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Delayed radical prostatectomy after a period of active surveillance is not associated with the use of secondary treatments compared with immediate prostatectomy

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Abstract

Background: We evaluated the use of secondary treatments in men with grade group (GG) 1 PC following a period of active surveillance (AS) compared with men undergoing immediate radical prostatectomy (RP) to evaluate what is potentially lost in terms of cancer control, if a patient trials AS and transitions to treatment.

Methods: We reviewed the Michigan Urological Surgery Improvement Collaborative (MUSIC) registry for men with GG1 PC undergoing RP from April 2012 to July 2018. Men were classified into groups based on time from diagnosis to RP: immediate (surgery within 1 year of diagnosis) and delayed RP (surgery >1 year after initiation of AS). Time to secondary treatment was estimated using Kaplan–Meier curves and compared using the log-rank test. A multivariable Cox proportional hazards model was fit to assess the association between timing of RP and use of secondary treatments. A chi-squared test was used to assess the association between delayed RP and adverse pathology.

Results: We identified 1878 men that underwent an RP during the study period, of which 1489 (79%) underwent immediate RP and 389 (21%) underwent delayed RP. The incidence of adverse pathology was higher in men with delayed versus immediate RP (49% vs. 36%, $p < 0.0001$, respectively). However, we noted only a small absolute difference in the estimated 24-month secondary treatment-free probability between men with delayed versus immediate RP (93% and 96%, respectively). On multivariable analysis, delayed RP was associated with increased use of secondary treatments (hazard ratio = 1.94, 95% confidence interval = 1.23–3.06, $p = 0.004$).

Conclusions: The use of secondary treatment after RP in men with GG1 PC undergoing immediate or delayed prostatectomy was rare. These data suggest that the burden of treatment is near equivalent in patients who progress to treatment on AS compared with those who underwent immediate RP.

KEYWORDS

active surveillance, prostate cancer, radical prostatectomy

1 | INTRODUCTION

The majority of patients with newly diagnosed prostate cancer in the United States are treated with radical therapies such as radiation and surgery.[1,2] Recent randomized trial data suggest that men undergoing radical prostatectomy (RP) and radiation have similar overall prostate cancer mortality compared with men managed on an observational strategy, particularly in patients with low-risk disease.[3] While radical treatments provide excellent oncologic control, the potential for long-term impairment of urinary and sexual function make them less attractive options for patients with indolent disease when weighing the oncological benefit of treatment against decline in quality of life.[4] As a result, active surveillance (AS) has emerged as a primary management strategy for very low-risk, low-risk, and certain patients with low volume, favorable intermediate-risk prostate cancer, allowing for preservation of functional outcomes while maintaining the ability to treat and cure the patient of their cancer when, or if, warranted.[5–7]

Some men initially managed on AS will convert to treatment due to anxiety, grade reclassification, or volume progression. Ideally, AS affords these men the same opportunity for cure as those men who elect to undergo immediate RP.[8,9] Following surgery, some men undergoing immediate or delayed prostatectomy after a period of AS may harbor adverse pathology or develop early biochemical recurrence (BCR) requiring secondary treatments, such as radiation therapy (RT) and/or androgen deprivation therapy (ADT). The oncologic benefits of secondary treatments (ADT/RT) following primary treatment come at the cost of worse urinary function, sexual function, and overall quality of life (QoL).[10,11] Thus, the risk of secondary treatment with delayed RP after an initial period of AS versus the risk of secondary treatment if a patient underwent immediate RP could affect decision-making in patients with newly diagnosed prostate cancer.

Herein, we compared the use of post-RP secondary treatments (Adjuvant/Salvage RT and/or ADT) in men undergoing delayed RP after a period of AS compared with immediate RP to help quantify what is "lost" in terms of cancer control for men that start on AS and then progress to treatment. Understanding the risk of additional secondary treatments—or conversely, the lack thereof—with delayed RP after an initial period of AS versus the risk of secondary treatment if a patient underwent immediate RP could affect decision making in patients with newly diagnosed prostate cancer consider management options.

2 | MATERIALS AND METHODS

2.1 | Study design

This is a retrospective cohort study of men with newly diagnosed, grade group 1 (GG1) prostate cancer in the Michigan Urological Surgery Improvement Collaborative (MUSIC) registry from April 2012 to July 2018. MUSIC is a physician-led state-wide quality improvement collaborative funded by Blue Cross Blue Shield of Michigan. Approximately 95% of urologists in the state of Michigan, including academic, private practice, and hospital-employed groups participate in MUSIC. Trained data abstractors review the primary medical records at each clinical site at fixed intervals and enter pertinent clinical, demographic, surgical, and pathological parameters into a web-based registry. Approval to participate in MUSIC was obtained by each practice's or institution's Institutional Review Board (IRB). This study was deemed exempt by the Wayne State University IRB.

2.2 | Study population

Men with GG1 prostate cancer on the diagnostic biopsy that subsequently underwent RP were included in this study. Both men that underwent an immediate RP (within 12 months of diagnosis) and delayed RP (>12 months after initiation of AS) were included. For men on AS, date of diagnosis was considered the date of initiation of AS. AS is affirmatively annotated within the registry as the primary management strategy, and not defined as deferred definitive treatment. MUSIC does not provide strict guidelines for transition off AS, but rather provides a framework to conduct informed and shared decision-making with patients.[12] The decision to undergo delayed RP was at the discretion of the treating clinician and patient. Follow-up and interval of prostate-specific anti (PSA) testing after RP was individualized for each patient according to their urologist. Men with a GG1 prostate cancer and a PSA > 10, any volume NCCN intermediate or high-risk disease on the diagnostic biopsy, or any other treatments before RP (such as ADT or RT) were excluded from this study.

2.3 | Study objectives

The primary objective of our study was to test for an association of delayed prostatectomy with the use of secondary treatments. Secondary treatments were defined as the use of adjuvant or salvage radiation or ADT post-RP, regardless of the PSA at the time of secondary treatment. The secondary objective was to test for an association of delayed RP with adverse pathology, which was defined as the presence of one or more of the following: primary Gleason pattern 4, extra-prostatic extension (EPE), seminal vesicle invasion (SVI), positive surgical margin (PSM), and lymph node-positive disease.

2.4 | Statistical analysis

Clinical and demographic parameters were reported as counts, medians, and interquartile ranges (IQRs) when appropriate. Categorical measures were compared with the chi-squared test and continuous measures were compared using the Wilcoxon rank-sum test. For our primary outcome, we used the Kaplan–Meier method to estimate the unadjusted secondary treatment-free probability between men undergoing immediate versus delayed RP. Freedom from secondary treatment was defined as the period from the date of RP to the date of initiation of secondary treatment; follow-up was

censored at the date of last clinical contact for patients without secondary treatment. Kaplan–Meier curves were compared using the log-rank test. We fit a multivariable Cox proportional hazard model to assess the association between delayed RP and time to use of secondary treatments. The multivariable model was adjusted for baseline PSA, maximal percent of a single core involved with cancer, number of cores positive for cancer, clinical T stage (cT1 vs. ≥cT2), family history of prostate cancer, and age. The model also included random effects for surgeons to account for within-surgeon correlation. For the secondary outcome, we compared the proportion of patients with adverse pathology between those undergoing an immediate and delayed RP using chi-squared test. We then fit a multivariable logistic regression model, where the same set of covariates and random effects for surgeons were used for adjustment, to assess for the association of delayed RP and adverse pathology. All statistical tests were two-sided with significance set at 0.05, and statistical analysis was performed with SAS.

3 | RESULTS

The final analytic cohort consisted of 1878 men with GG1 prostate cancer, of which 1489 men underwent immediate RP and 389 underwent delayed RP after initially choosing AS (Figure 1). Median length of follow-up since surgery was 34.3 months (IQR = 18–51 months). Median time from diagnosis to RP in the immediate and delayed RP groups was 3.3 and 21.1 months, respectively. Of the 389 men that underwent delayed RP, 247 underwent a surveillance biopsy resulting in upgrading to GG2 or greater pathology before RP. Men who underwent an immediate RP tended to be younger at the time of diagnosis, have a slightly higher number of positive cores and highest greatest percent positive of an individual core length of cancer at the diagnostic biopsy compared with men who underwent a delayed RP (Table 1).

In the entire cohort, only 116 (6.2%) men had a secondary treatment following RP. The unadjusted Kaplan–Meier curves of secondary treatment-free survival demonstrated a small difference in the use of secondary treatments for patients with immediate versus delayed RP (Figure 2, $p = 0.0023$). Patients with an immediate RP had an estimated 24-month secondary treatment-free probability of 96% compared with 93% for patients with a delayed RP. After adjustment, delayed RP remained associated with increased use of secondary treatments (hazard ratio = 1.94, 95% confidence interval [CI] = 1.23–3.06, $p = 0.004$; Table 2). Among those individuals that underwent secondary treatment, salvage treatment with EBRT was the most commonly utilized secondary treatment (Table S1).

We found a significantly higher proportion of adverse pathology in men undergoing a delayed RP compared with men undergoing immediate RP (48% vs. 36%, $p < 0.001$; Table 3A). This difference in adverse pathology was largely accounted for by the increased proportion of patients upgraded to primary pattern 4 (23% vs. 6.9%, $p < 0.001$) and extraprostatic extension (19% vs. 13%, $p = 0.005$) in the delayed RP group compared with immediate RP group. We noted patients undergoing immediate and delayed RP had a similar proportion of PSM (25% vs. 26%, respectively, $p = 0.656$), node-positive disease (0.27% vs. 0.26%, respectively, $p > 0.9$), and SVI (2.6% vs. 3.6%, respectively, $p = 0.263$. On multivariable analysis, delayed RP was associated with increased odds of adverse pathology after adjusting for clinical and demographic differences (odds ratio = 1.70, 95% CI = 1.32–2.18, $p < 0.0001$; Table 3B).

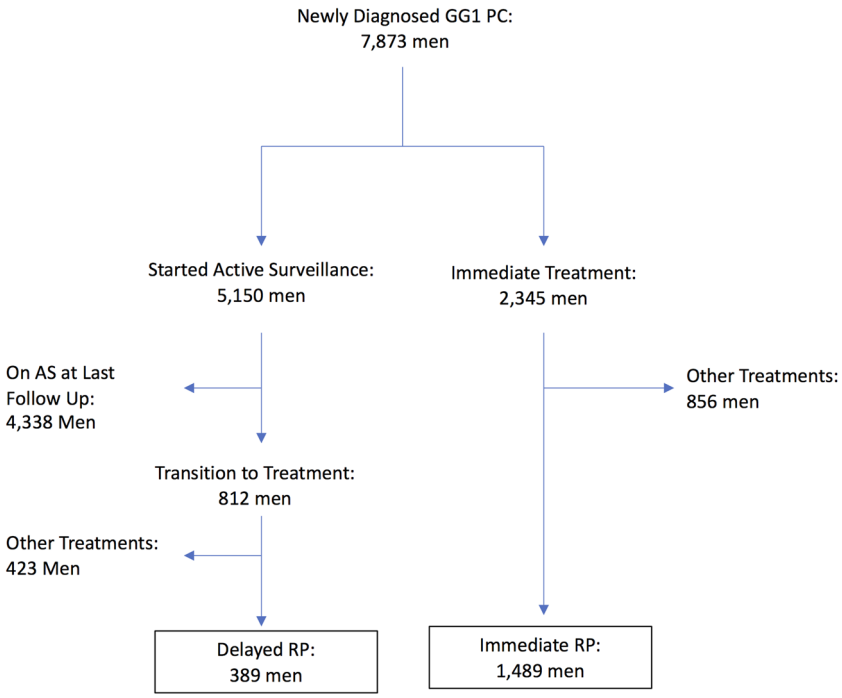

FIGURE 1 Flow diagram depicting the generation of study cohort [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Clinical, demographic, and oncological characteristics of 1878 patients with GG1 prostate cancer treated with immediate or delayed RP

Demographic	Immediate RP, *n* = 1489		Delayed RP, *n* = 389		*p*
	n/median	%/IQR	n/median	%/IQR	
Time to RP (months)	3.3	2.3–5.2	21.1	16.1–31.3	
Age (years)	61	56–66	64	59–69	<0.001
Family history					0.011
Unknown	110	7.4%	18	4.6%	
Yes	558	38%	126	32%	
No	821	55%	245	63%	
Clinical stage					<0.001
T1c or less	1307	88%	367	94%	
T2a or above	182	12%	22	5.7%	
Risk strata					<0.001
Low risk	1200	81%	272	70%	
Very low risk	289	19%	117	30%	
Median # of positive cores	3	2–5	2	1–3	<0.001
Median greatest % of individual core involvement	20	10–41	11.5	5–30	<0.001
Median PSA	5.0	4.0–6.3	5.3	4.1–6.7	0.009

Abbreviations: GG, grade group; IQR, interquartile range; PSA, prostate-specific antigen; RP, radical prostatectomy.

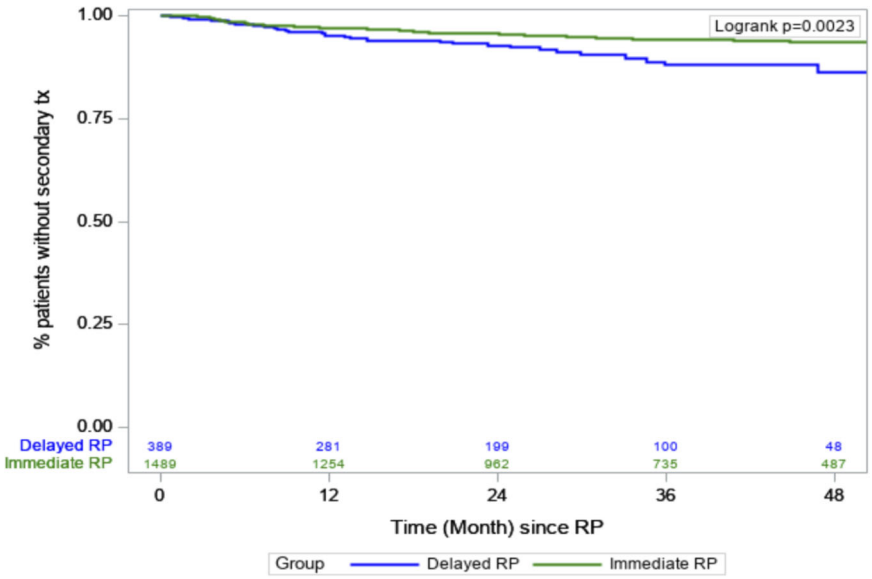

FIGURE 2 Kaplan–Meier estimates of secondary treatment-free survival for men undergoing immediate RP (green) and delayed RP (blue). RP, radical prostatectomy [Color figure can be viewed at wileyonlinelibrary.com]

4 | DISCUSSION

AS is a management strategy designed to mitigate over-treatment of otherwise indolent prostate cancer without compromising cure. After a period of AS, men who convert to treatment on the basis of repeat imaging or biopsy are inherently enriched with worse disease which could compromise oncological outcomes. Yet, it remains unknown if men who initially were managed with AS and underwent a delayed RP have compromised oncology outcomes and incur a higher treatment burden and use of secondary treatments compared with men who underwent immediate RP. In our study, we found men who underwent delayed RP had a slightly increased use of secondary treatment compared to men with immediate RP; and, after adjustment in our multivariable model, the use of secondary treatment remained associated with delayed RP. Despite statistical significance, the absolute difference in the use of secondary treatment between the immediate and delayed RP group was only ~3%, suggesting a small overall clinical impact.

TABLE 2 Multivariable Cox proportional hazard model of clinical, demographic, and oncological factors associated with the use of secondary treatment post-RP

	HR	95% CI	p
Delayed versus immediate RP			
Immediate RP	Ref	Ref	Ref
Delayed RP	1.94	(1.23, 3.06)	0.004
Family history of prostate cancer			
No	Ref	Ref	Ref
Yes	0.73	(0.48, 1.11)	0.138
Unknown	0.96	(0.46, 2.03)	0.923
Clinical T stage			
≤cT1	Ref	Ref	Ref
≥cT2	1.05	(0.56, 1.96)	0.873
No. of positive cores	1.02	(0.93, 1.12)	0.724
Greatest % cancer involvement	1.01	(1.00, 1.02)	0.015
Age	1.01	(0.98, 1.03)	0.660
PSA (log)	3.45	(1.95, 6.11)	<0.001

Abbreviations: CI, confidence interval; HR, hazard ratio; PSA, prostate-specific antigen; RP, radical prostatectomy.

TABLE 3A Proportion of patients undergoing immediate and delayed RP with adverse pathology, primary pattern 4, extraprostatic extension, seminal vesicle invasive, positive surgical margin, and pathological N+ disease

	Immediate RP (%)	Delayed RP (%)	p
Adverse pathology	36	49	<0.001
Primary pattern 4	6.9	23	<0.001
Extraprostatic extension	13	19	0.005
Seminal vesicle invasion	2.6	3.6	0.263
Positive surgical margin	25	26	0.656
Pathologic N+	0.27	0.26	>0.9

TABLE 3B Multivariable logistic regression model of factors associated with adverse pathology

	OR	95% CI	p
Delayed versus immediate RP			
Immediate RP	Ref	Ref	Ref
Delayed RP	1.70	(1.32, 2.18)	<0.0001
Family history of prostate cancer			
No	Ref	Ref	Ref
Yes	1.22	(0.99, 1.50)	0.067
Unknown	1.06	(0.90, 1.98)	0.148
Clinical T stage			
≤cT1	Ref	Ref	Ref
≥cT2	1.06	(0.77, 1.48)	0.709
No. of positive cores	1.06	(1.00, 1.11)	0.039
Greatest % cancer involvement	1.01	(1.00, 1.01)	0.003
Age	1.02	(1.00, 1.03)	0.014
PSA (log)	1.90	(1.48, 2.43)	<0.0001

Abbreviations: CI, confidence interval; OR, odds ratio; PSA, prostate-specific antigen; RP, radical prostatectomy.

To our knowledge, this is the first study to use secondary treatment as an intermediate outcome in men with prostate cancer in a surveillance cohort. Due to the protracted natural history of prostate cancer progression following RP, previous AS study cohorts, including MUSIC, have used the intermediate outcome of adverse pathology at the time of RP to infer oncological differences between patients undergoing immediate and delayed RP.[8,13–15] Strong evidence to suggest that the adverse pathology translates into worse oncological outcomes, such as BCR, metastasis, or death, in men with GG1 prostate cancer on AS is lacking.[9] In our study, we demonstrate that more men undergoing a delayed prostatectomy had adverse pathology (48%) compared with men undergoing an immediate RP (36%). This finding is understandable as men who undergo a delayed RP after a period of AS are inherently enriched with men with higher grade disease, as evident by the majority of men in the delayed RP cohort were upgrading to ≥ GG2 disease on surveillance biopsy before RP. Despite this finding, only 4.4% and 7.3% of men undergoing a delayed and immediate RP underwent a secondary treatment within 2 years of their prostatectomy. Utilization of adverse pathology alone as a surrogate endpoint over-estimates the oncological risk of delayed RP after a period of AS. Given the impairments of quality of life associated with secondary treatments of adjuvant or salvage ADT and/or RT, the use of secondary treatment-free survival is a more clinically relevant and meaningful way to judge the success or failure of AS beyond AP or BCR. We propose the concept of utilizing a secondary treatment—failing to clinically cure the patient with the initial surgery—as a clinically meaningful endpoint for patients with GG1 prostate cancer.

It is important to consider the study design while interpreting these results, as only men which underwent RP were included in this study. Of the 5150 men with GG1 prostate cancer in MUSIC who started AS, 4338 (84%) are still on AS and a free of a primary treatment, and therefore, are not included in this analysis. By only including men which transitioned from AS to treatment, we can help answer the common clinical question of what is "lost" in terms of cancer control if a man initially selects AS but eventually goes on to need treatment. Consider how this data would affect a hypothetical sample of 1000 men with newly diagnosed GG1 prostate cancer debating RP versus AS. If all 1000 men underwent immediate RP, 956 men would have a primary treatment, and 44 men (4.6% of the 1000 men which underwent an

immediate RP) would undergo a primary and secondary treatment. If all 1000 men instead choose AS and we assume that 50% will eventually undergo delayed RP,[16,17] 500 men would be spared any treatment, 463 men would have a primary treatment, and 37 men (7.3% of the 500 men which underwent a delayed RP) would undergo a primary and secondary treatment. Even if 68.5% of men transitioned to RP, the AS arm would get the same number of men receiving secondary treatment (7.3% of 685 = 50), but 315 men would still have avoided any definitive treatment. Despite the small additional risk of secondary treatment for those receiving delayed RP, for more men to actually receive more secondary treatments than if they had underwent immediate RP, the transition rate to definitive treatment after AS would have to exceed 68.5%. However, two of the largest AS cohorts with long-term follow-up have shown the risk of transition to treatment 15 years after diagnosis is approximate 45%–52%.[16,17]

These results may be extended to the recent revisions of the NCCN guidelines which no longer present AS as the preferred management strategy for men with low risk prostate cancer. Very little is lost in terms of cancer control if men with GG1 or low risk prostate cancer starts AS and progresses to treatment as seen by the similar uses of secondary treatments in men undergoing immediate and delayed RP.

There are several limitations of this study, inherent to this study design. First, despite adjusting for clinical, demographic, and oncological differences between men undergoing immediate and delayed RP, there remains the potential for residual and unaccounted confounding. Second, the reason for discontinuation of AS for RP was not explored in our study. Third, there was not a predefined threshold when to initiate a secondary treatment. Fourth, our study examined the short-term use of secondary treatment following RP. Further evaluation regarding the long-term use of secondary treatments is needed. Nevertheless, our study provides real-world outcomes of delayed RP on overall treatment incurred in a prospectively managed AS cohort.

5 | CONCLUSIONS

Despite an increase in adverse pathology, men undergoing delayed RP after initial period of AS had an overall small increase in the use of secondary treatments compared with men undergoing immediate RP. These results demonstrate very little is lost in terms of cancer control in men with GG1 prostate cancer that trial AS and go on to need treatment, suggesting AS should remain the preferred management strategy for men with GG1 prostate cancer.

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CONFLICT OF INTERESTS

Rohith Arcot – None; Michael L. Cher – None; Ji Qi – Salary support through MUSIC; Susan M. Linsell – Salary support through MUSIC; Rodney L. Dunn – Salary support through MUSIC; Arvin K. George – Salary support through MUSIC; James E. Montie – Salary support through MUSIC; Kevin B. Ginsburg – None.

DATA AVAILABILITY STATEMENT

Data is not available for public use. Statistical code can be shared and reviewed at the request of The Journal.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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