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The Natural History of Untreated Biopsy Grade Group Progression and Delayed Definitive Treatment for Men on Active Surveillance for Early-Stage Prostate Cancer

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Study Need and Importance: Little is understood about the characteristics and oncologic outcomes of patients on active surveillance (AS) who experience grade group (GG) upgrade on biopsy and continue AS. Our goal was to better characterize these patients and compare short- to intermediate-term oncologic outcomes among patients who underwent early vs delayed radical prostatectomy (RP) following GG upgrade.

What We Found: Our analytical cohort included 531 patients on AS initially diagnosed with clinically localized GG1 disease who experienced GG upgrade and continued AS with median followup since diagnosis of 85 months (IQR 56–123). Among them, 40% (214) continued AS and remained untreated within 5 years after upgrade, 36% (192) underwent early RP (within 6 months of upgrade) and 24% (125) underwent late RP (6 months to 5 years after upgrade). Untreated patients were older (64 vs 62 vs 60 years old, p <0.01) with lower prostate specific antigen density (0.13 vs 0.15 vs 0.14, p <0.01) than early and late RP groups, respectively. The early vs late RP groups had similar distribution of GG (p=0.15), adverse pathology rates (55% vs 53%, p=0.74) and 3-year recurrence-free survival (RFS; 80% vs 87%, log-rank p=0.64) after RP (see figure). Early vs late RP was not associated with risk of RFS in multivariable models.

Limitations: This study was conducted in a large, single-institution cohort so results are most likely representative of outcomes at tertiary care, referral centers. There was limited post-surgical followup, which resulted in reporting of 3-year RFS and does not reflect long-term oncologic outcomes.

Interpretation for Patient Care: A large proportion of patients continued on AS after GG upgrade. Eventually, 60% underwent treatment within 5 years of upgrade. Early oncologic outcomes were comparable among patients who underwent early vs late RP after upgrade, suggesting select patients can possibly safely delay treatment. Further work is needed to quantify long-term oncologic outcomes as followup matures.

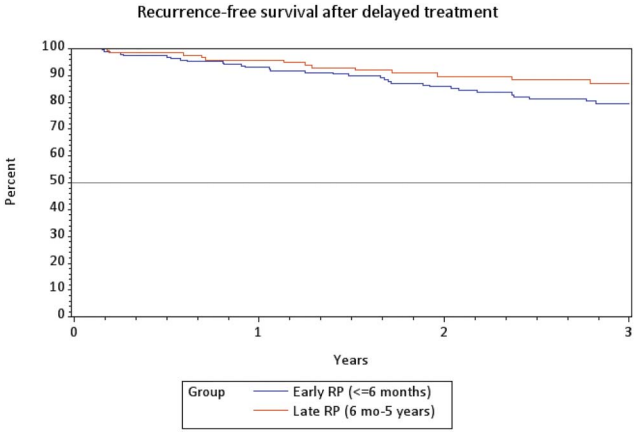

Figure. Biochemical recurrence or secondary treatment-free survival following RP in early vs late RP for 317 men who underwent RP after AS at University of California, San Francisco.

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The Natural History of Untreated Biopsy Grade Group Progression and Delayed Definitive Treatment for Men on Active Surveillance for Early-Stage Prostate Cancer

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Abbreviations and Acronyms

AS = active surveillance
CAPRA = Cancer of Prostate Risk Assessment
CAPRA-S = post-surgical Cancer of Prostate Risk Assessment
GG = grade group
MRI = magnetic resonance imaging
PSA = prostate specific antigen
PSAD = prostate specific antigen density
RFS = recurrence-free survival
RP = radical prostatectomy
TRUS = transrectal ultrasound
UCSF = University of California, San Francisco

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Purpose: For men with clinically localized prostate cancer outcomes of continuing active surveillance (AS) after biopsy progression are not well understood. We aim to determine the impact of continuing AS and delayed definitive treatment after biopsy progression on oncologic outcomes.

Materials and Methods: Participants in our prospective AS cohort (1990–2018) diagnosed with grade group (GG) 1, localized prostate cancer, with prostate specific antigen <20 who were subsequently upgraded to ≥GG2, and underwent further surveillance (biopsy/imaging/prostate specific antigen) were identified. Patients were stratified by post-progression followup into 3 groups: continue AS untreated, pursue early radical prostatectomy (RP) ≤6 months, or undergo late RP within 6 months to 5 years of progression. Patients receiving other treatments were excluded. We compared characteristics between groups and examined the associations of early vs late RP with risk of adverse pathology (AP) at RP and recurrence-free survival (RFS) after RP.

Results: Of 531 patients with biopsy progression and further surveillance 214 (40%) remained untreated, 192 (36%) pursued early RP and 125 (24%) underwent late RP. Among patients who underwent early vs late RP, there was no difference in GG (p = 0.15) or AP (55% vs 53%, p = 0.74) rate at RP, or 3-year RFS (80% vs 87%, log-rank p = 0.64) after RP. In multivariable models, only Cancer of Prostate Risk Assessment post-surgical score was associated with risk of RFS (HR = 1.42 per point, 95% CI 1.24–1.64).

Conclusions: Among patients continuing AS after biopsy progression, 60% underwent surgery within 5 years. Delayed surgery after progression was not associated with higher risk of AP or RFS. This suggests select patients may be able to safely delay treatment after progression.

Key Words: disease progression, prostatectomy, prostatic neoplasms, time-to-treatment, watchful waiting

For men with low-risk or favorable intermediate-risk localized prostate cancer, active surveillance (AS) provides a treatment strategy to avoid adverse effects associated with potentially unnecessary definitive treatment.[1–3] The hallmark of AS protocols is close followup with serial biopsies to monitor for disease progression, which serves as a trigger to pursue definitive treatment.[4] Prior work demonstrates approximately 30% of patients on AS will experience

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disease progression and pursue definitive treatment within 4–5 years of diagnosis.[5,6] While several studies have focused on identifying factors associated with an increased risk of biopsy progression,[7,8] there is little known about outcomes for patients who do not pursue immediate treatment after biopsy progression.

This group may represent a sizeable cohort of patients on AS, as a prior study from our group demonstrated approximately 30% of patients who experienced biopsy progression to Gleason grade group (GG) 2 or higher continued on AS without treatment.[9] It remains unclear which sociodemographic factors or clinical characteristics impact the decision to continue AS for these patients. Additionally, there is little known about whether delaying treatment after disease progression in this cohort is associated with worse oncologic outcomes when the decision is finally made to undergo delayed radical prostatectomy (RP). Therefore, we aim to further characterize the cohort of patients who continue on AS after biopsy progression and determine the impact of continuing on AS after biopsy progression on short- to intermediate-term oncologic outcomes after early vs delayed RP.

MATERIALS AND METHODS

Patient Cohort

Data were obtained prospectively for men enrolled on AS at University of California, San Francisco (UCSF). We identified men diagnosed from 1990–2018 with localized (clinical stage T1-T2), GG1 prostate cancer with prostate specific antigen (PSA) <20 mg/mL at diagnosis who experienced progression of disease on a subsequent biopsy but continued AS (fig. 1). Progression was defined as an increase from GG1 to ≥GG2 on subsequent biopsy. Continuing AS was defined as having any additional biopsy, imaging or PSA tests after disease progression. While we have patients diagnosed with >GG1 disease on AS at our institution, we chose to limit inclusion criteria to only GG1 on diagnosis to create a more homogenous cohort for comparison of outcomes after progression. Additionally, AS is most commonly employed in this group of patients. We excluded patients on finasteride. All participants provide informed consent to participate in research under supervision by the UCSF institutional review board (Study No. 11-05226).

AS Protocol

The AS protocol includes PSA testing at 3-month intervals, transrectal ultrasound (TRUS) and digital rectal examination every 6–12 months, and TRUS guided biopsies every 1–2 years. All patients undergo confirmatory biopsy approximately 1 year following diagnostic biopsy, and subsequent biopsies are performed on average every 1–2 years with exact schedule tailored to each patient. Biopsies include at least 14 cores with 2 from each sextant and 1 anterior biopsy bilaterally. Although not a formal requirement for biopsy, magnetic resonance imaging (MRI) has been incorporated into biopsy techniques in recent years. The use of MRI is left to the discretion of the provider and not a formal requirement of the AS protocol.

Exposure

Patients who experienced biopsy progression and continued AS were stratified based on post-progression followup: Group 1—no definitive treatment after biopsy progression (untreated), Group 2—underwent RP within 6 months of biopsy progression (early RP) or Group 3—underwent RP within 6 months to 5 years after biopsy progression (late RP). Six months was chosen as the cutoff between early vs late RP as recent studies have suggested patients can safely delay definitive treatment for clinically localized intermediate- and high-risk prostate cancer without adverse outcomes.[10,11] The decision to undergo early vs later RP was the outcome of shared decision making between the provider and patient. Patients in the untreated group were censored at 5 years followup. Patients who underwent nonsurgical definitive treatment were excluded from analyses.

Independent Variables

Sociodemographic data included age at diagnosis, race/ethnicity and relationship status (single/widowed, married/partnered). Clinical characteristics collected at the time of diagnosis included PSA, prostate volume, PSA density (PSAD) and Cancer of Prostate Risk Assessment (CAPRA) score. For patients who had genomic testing (Oncotype Dx®, Prolaris® or Decipher®) performed on a biopsy sample, a composite genomic classifier variable was created. For each patient, the first genomic test score was evaluated and a score higher than mean+standard deviation was categorized as a high score. Pathological Gleason grade, T stage, N stage and surgical margin status were reported for men who underwent RP. Adverse pathology (AP) at RP was defined as GG ≥3, pathology T stage ≥pT3a or node positive (pN1+) disease.

Outcomes

Our primary outcome was time to recurrence following RP, defined as PSA failure (2 consecutive PSA tests >0.2 ng/ml at least 8 weeks after RP) and/or receiving additional treatment (radiation therapy and/or androgen deprivation therapy). Secondary outcomes were development of metastases and death.

Statistical Analysis

Baseline sociodemographic and clinical characteristics, and biopsy progression factors were compared between the 3 groups using Chi-squared and Kruskal-Wallis tests as appropriate. Further analyses were completed in the subset of patients who underwent RP to determine the effect of delaying RP after biopsy progression on oncologic outcomes. Surgical pathology features and the rates of adverse pathology were compared between the 2 groups using Chi-squared tests. Kaplan-Meier curves were used to model recurrence-free survival (RFS) between the 2 groups and were compared using the log-rank test. Univariable and multivariable Cox proportional hazards models were used to determine if continuing AS for a longer time after biopsy progression (late vs early RP) was associated with worse RFS following RP. Variables in the multivariable model were chosen *a priori*. Given the small number of patients

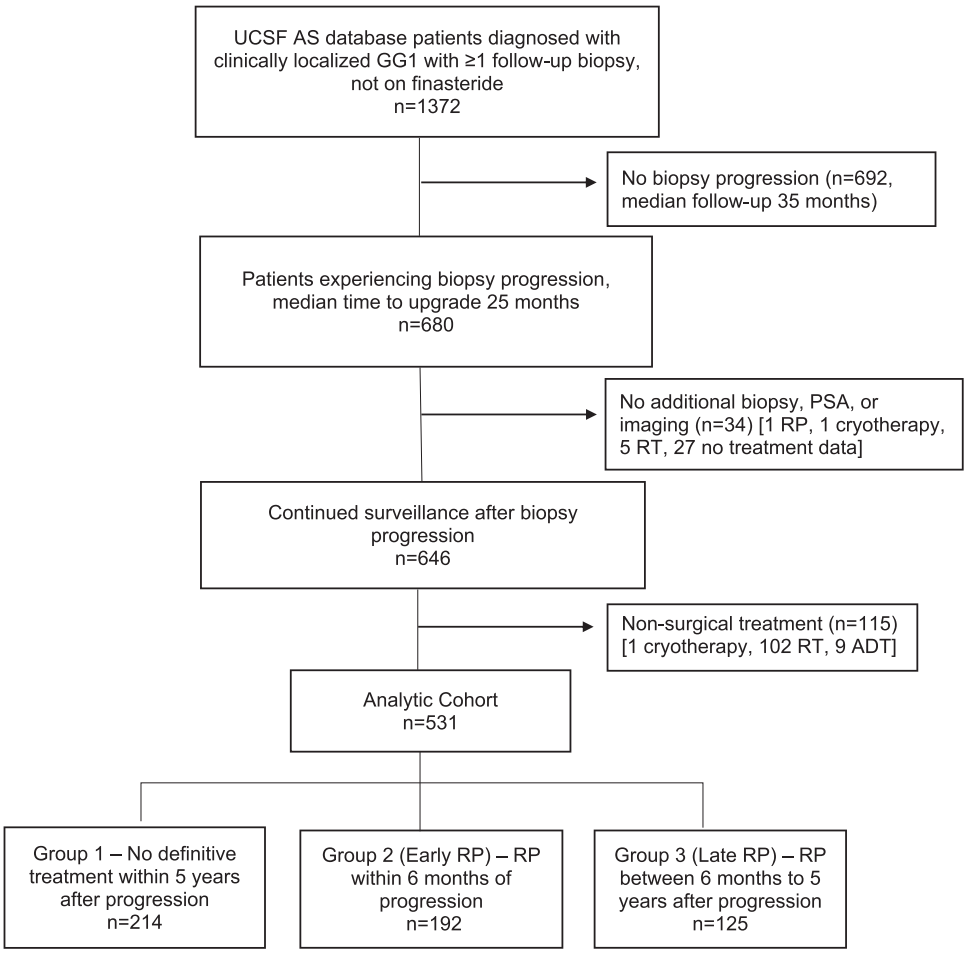

Figure 1. CONSORT (Consolidated Standards of Reporting Trials) diagram of analytical cohort of men on AS at UCSF. *ADT,* androgen deprivation therapy. *RT,* radiation therapy.

who developed metastases or died, no further survival analyses were conducted. Statistical analyses were performed used SAS version 9.4 (SAS, Cary, North Carolina) with $p < 0.05$ considered statistically significant.

RESULTS

Within the cohort of 1,372 patients diagnosed with clinically localized GG1 prostate cancer with ≥1 biopsies performed on AS, 49.6% (680) patients experienced biopsy progression at a median of 25 months (IQR 12–54). For the 692 patients without progression median followup was 35 months (IQR 16–69 months). Among patients with biopsy progression, 95% (646) underwent additional biopsies, imaging or PSA tests after progression (fig. 1). The final analytical cohort consisted of 531 patients, as 115 patients were excluded as they pursued nonsurgical management. Of 531, 40% were in the untreated group, 36% in the early RP group and 24% in the late RP group. Median year of diagnosis was 2010 (IQR 2007–2013). Median duration of followup since diagnosis was 85 months (IQR 56–123).

At the time of initial diagnosis, patients in the untreated group were older (64 years vs 62 and 60, $p < 0.01$), had lower PSAD (0.13 ng/ml^2 vs 0.15 and 0.14, $p < 0.01$), and had fewer high-risk genomic scores than the early RP and late RP groups (5% vs 13% and 8%, $p < 0.01$), respectively (table 1). The 3 groups did not differ significantly with respect to other demographics and clinical characteristics.

Biopsy Progression Characteristics

The median time to biopsy progression in the total cohort was 25 months (IQR 12–54). Patients in the early RP group had the shortest median time to upgrade (18 months) vs late RP and untreated groups (25 and 38 months, respectively, $p < 0.01$; table 2). There were no differences in the 3 groups with regard to the types of biopsies (systematic vs MRI fusion vs TRUS targeted) at diagnosis and confirmatory biopsy, and PSA at the time of progression (table 2). Patients in the early RP group had higher GG and higher CAPRA score at progression than the late RP and untreated groups. As expected, patients in the untreated group had more

Table 1. *Sociodemographic and clinical characters by post-progression followup group for 531 men on AS at UCSF*

Baseline Characteristics	No Definitive Treatment	Early RP	Late RP	p Value
No. pts	214	192	125	
Median yrs age at diagnosis (IQR)	64 (58–68)	62 (57–66)	60 (55–65)	<0.01
Median ng/ml PSA at diagnosis (IQR)	5.3 (4.4–6.9)	5.6 (4.6–7.1)	5.4 (4.3–7.2)	0.52
Median ng/ml^2 PSAD at diagnosis (IQR)	0.13 (0.09–0.18)	0.15 (0.11–0.23)	0.14 (0.10–0.18)	<0.01
Median % pos biopsy cores at diagnosis (IQR)	15 (8–25)	17 (8–25)	15 (8–25)	0.47
Median yr of diagnosis (IQR)	2010 (2006–2013)	2011 (2009–2014)	2010 (2008–2013)	<0.01
No. race/ethnicity (%):				0.77
White	178 (92)	161 (91)	101 (92)	
Black/African American	4 (2)	6 (3)	5 (5)	
Native American	1 (1)	0 (0)	0 (0)	
Asian/Pacific Islander	10 (5)	7 (4)	4 (4)	
Mixed	1 (1)	2 (1)	0 (0)	
Missing	20	16	15	
No. relationship status (%):				0.36
Single/widowed	34 (17)	38 (22)	27 (23)	
Married/partnered	163 (83)	138 (78)	88 (77)	
Missing	17	16	10	
No. clinical T stage (%):				0.63
T1	101 (47)	98 (51)	65 (52)	
T2	113 (53)	94 (49)	60 (48)	
No. genomic classifier (%):				<0.01
Low risk	98 (46)	82 (43)	72 (58)	
High risk	10 (5)	24 (13)	10 (8)	
No testing	106 (50)	86 (45)	43 (34)	
Median Oncotype Dx score (IQR)	22 (15–32)	26 (19–34)	26 (20–34)	0.05
Median Prolaris score (IQR)	27 (17–40)	35 (33–65)	30 (20–50)	0.13
Median Decipher score (IQR)	0.43 (0.35–0.58)	0.56 (0.38–0.78)	0.39 (0.39–0.39)	0.59
No. CAPRA clinical risk (%):				0.63
Low	182 (90)	163 (90)	107 (87)	
Intermediate	20 (10)	18 (10)	16 (13)	
Missing	12	11	2	

post-progression biopsies performed than the other 2 groups (table 2).

Pathology: Early vs Late RP

The median time from upgrade to RP was 17 months (IQR 8–28) in the late RP group and 3.5 months (IQR 2–4) in the early RP group. The distributions of pathological T stage, GG at time of RP, and positive margin rate were similar for the early and late RP groups (table 3, all $p > 0.05$). Although the post-surgical CAPRA (CAPRA-S) score was higher in the early RP (42% intermediate, 10% high) than the late RP (44% intermediate, 2% high, $p = 0.04$) group, rates of adverse pathology were similar between groups.

Survival Outcomes: Early vs Late RP

Among the 317 patients who underwent early or late RP, a total of 45 patients experienced a recurrence in the 3-year followup time period. The median followup in the cohort after RP was 34 months (IQR 16–54). The 3-year RFS was comparable among the early RP vs late RP groups (80% vs 87%, $p = 0.6$ respectively; fig. 2).

Undergoing late RP was not associated with worse RFS in either univariable (HR = 0.90, 95% CI 0.57–1.41) or multivariable models (HR = 1.04, 95% CI 0.64–1.68; table 4). The only predictor of higher risk of recurrence identified in the multivariable model was higher CAPRA-S score at surgery (HR = 1.42 per point, 95% CI 1.24–1.64). Additionally, in the multivariable model stratified by group, CAPRA-S was associated with higher risk of recurrence in both the early RP (HR = 1.42 per point, 95% CI 1.20–1.67) and late RP groups (HR = 1.43 per point, 95% CI 1.07–1.90). Additional sensitivity analyses of multivariable models including only clinical variables available prior to surgery (excluding CAPRA-S and using clinical CAPRA instead of CAPRA-S) showed no significant associations of clinical variables with RFS.

There were 4 patients who developed metastases following RP at a median time of 44 months (IQR 18–87), and 3 of these patients were in the early RP group. In the total cohort 3 patients died with a median followup of 115 months (IQR 53–179). There were no patients who developed metastases or died in the no definitive treatment group.

DISCUSSION

In our effort to better understand treatment patterns after biopsy progression on AS, we found at our institution approximately 65% of patients with biopsy progression from GG1 disease continued on AS (untreated or late RP groups). Among these patients, 37% eventually decided to undergo late RP within 6 months to 5 years after biopsy progression. Importantly, delaying surgery >6 months from biopsy progression was not associated with higher rates of adverse pathology or

Table 2. *Biopsy characteristics by post-progression followup group for 531 men on AS at UCSF*

Biopsy Characteristics	No Definitive Treatment		Early RP		Late RP		p Value
No. pts	214		192		125		
Median ng/ml PSA at upgrade (IQR)	5.5 (3.9—8.4)		6.1 (4.3—8.9)		5.7 (4.2—7.8)		0.15
Median mos to upgrade from diagnosis (IQR)	37 (14—66)		18 (11—39)		25 (12—47)		<0.01
No. targeting at diagnostic biopsy (%):							0.12
Systematic only	130	(68)	90	(57)	72	(68)	
Systematic+MRI fusion	28	(15)	39	(25)	17	(16)	
Systematic+TRUS targeted	33	(17)	29	(18)	17	(16)	
Missing	23		34		19		
No. targeting at confirmatory biopsy (%):							0.90
Systematic only	165	(90)	140	(92)	96	(92)	
Systematic+MRI fusion	5	(3)	2	(1)	2	(2)	
Systematic+TRUS targeted	13	(7)	11	(7)	6	(5)	
Missing	31		39		21		
No. type of progression (%):							<0.01
Upgrade	145	(68)	92	(48)	76	(61)	
Upgrade and increase on vol	69	(32)	100	(52)	49	(39)	
No. Gleason Grade at upgrade (%):							<0.01
GG2	176	(82)	115	(60)	104	(83)	
GG3	29	(14)	56	(29)	19	(15)	
GG4—5	9	(4)	21	(11)	2	(2)	
No. % cores pos at upgrade (%):							<0.01
≤33	145	(68)	92	(48)	76	(61)	
34—45	34	(16)	52	(27)	23	(18)	
46—60	22	(10)	27	(14)	19	(15)	
>60	13	(6)	21	(11)	7	(6)	
No. change in CAPRA at upgrading (%):							<0.01
No change or decrease	49	(24)	34	(19)	37	(30)	
Low to intermediate risk	140	(70)	106	(59)	71	(58)	
Low to high risk	9	(4)	32	(18)	9	(7)	
Intermediate to high risk	3	(1)	8	(4)	5	(4)	
No. any neg biopsy during surveillance (%):							0.65
No	191	(89)	175	(91)	110	(88)	
Yes	23	(11)	17	(9)	15	(12)	
No. post-progression biopsies (%):							<0.01
1	50	(42)	13	(100)	46	(61)	
2	30	(25)	0		25	(33)	
3	22	(18)	0		3	(4)	
4	7	(6)	0		1	(1)	
5+	11	(9)	0		0		

worse RFS. Additionally, there was a very low rate of metastatic disease in this cohort. These findings suggest some patients may be able to safely delay definitive management after biopsy progression.

While biopsy progression on AS is often thought to trigger immediate treatment, we demonstrate 65% of patients continue on AS (untreated or late RP groups) after progression at a rate similar to a

Table 3. *Pathological findings at time of RP by post-progression followup group for 317 men who underwent RP after AS at UCSF*

Pathology Variable	Early RP	Late RP	p Value
No. pts	192	125	
No. Gleason Grade at prostatectomy (%):			0.15
GG1	10 (5)	14 (11)	
GG2	126 (66)	83 (67)	
GG3	40 (21)	20 (16)	
GG4/5	16 (8)	7 (6)	
Missing	0	1	
No. pathological T stage (%):			0.54
pT2	107 (56)	74 (59)	
≥pT3	85 (44)	51 (41)	
No. surgical margins (%):			0.41
Neg	146 (76)	100 (80)	
Pos	46 (24)	25 (20)	
No. CAPRA-S surgical risk (%):			0.04
Low	92 (48)	67 (54)	
Intermediate	81 (42)	54 (44)	
High	19 (10)	3 (2)	
Missing	0	1	
No. adverse pathology GG ≥2 or pT3/4 or pN1 (%)	105 (55)	66 (53)	0.74

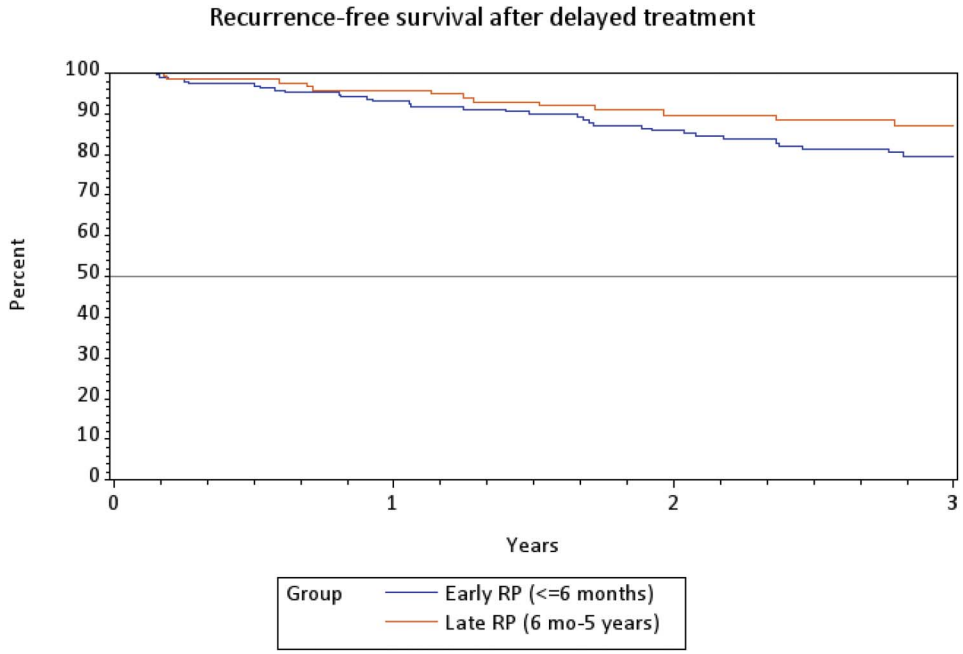

Figure 2. Biochemical recurrence or secondary treatment-free survival following RP in early vs late RP for 317 men who underwent RP after AS at UCSF.

prior study from our group.[9] These findings highlight the need for studies to further quantify risks of adverse outcomes for these patients so they can make well-informed decisions regarding their treatment after biopsy progression.

Among patients who decided to undergo treatment, patients undergoing early RP (within 6 months of progression) were slightly older (median age 62 vs 60) than patients undergoing late (6 months to 5 years after progression) RP, but all other sociodemographic factors and genomic tests were comparable between the groups. Additionally, as expected, GG was higher in patients who underwent early RP compared to late RP suggesting that most patients with GG $\geq$3 will choose to undergo early treatment. This is consistent with a prior study showing upgrade to GG $\geq$3 is associated with shorter time to treatment and consistent with National Comprehensive Cancer Network® guidelines that recommend treatment for GG $\geq$3 prostate cancer if life expectancy is $>$10 years.[9,12]

Among patients who initially delayed treatment but subsequently underwent RP within 5 years of progression, we found delaying RP beyond 6 months did not negatively impact oncologic outcomes. Adverse pathology and positive surgical margin rates along with RFS were comparable between patients who underwent early vs late RP and consistent with prior rates published.[9] Furthermore, in our multivariable model undergoing late RP was not predictive of worse RFS after controlling for patient and disease factors. These results suggest a subset of patients can safely delay treatment after biopsy progression, but of note does not help us

Table 4. *Univariable and multivariable Cox proportional hazards model for predictors of RFS for 317 men who underwent RP after AS at UCSF*

Parameter	p Value	Hazard Ratio	95% CI Lower Limit	95% CI Upper Limit
		Univariable model result		
Cohort Late RP (vs Early RP)	0.64	0.90	0.57	1.41
		Multivariable model result		
Cohort Late RP (vs Early RP)	0.85	1.05	0.65	1.69
Age at diagnosis (yrs)	0.51	0.99	0.95	1.02
Genomic classifier:*				
High risk vs no test	0.31	1.47	0.70	3.09
Low risk vs no test	0.87	1.04	0.63	1.73
PSA at upgrade (ng/ml)	0.96	1.00	0.95	1.06
Yr of surgery	0.41	1.03	0.96	1.09
CAPRA-S	$<$0.01	1.42	1.24	1.64

* Genomic risk global classifier p=0.57.

further risk stratify this subset of patients. Prior studies have demonstrated genomic testing can identify patients on AS at risk for adverse pathology at RP and recurrence following RP.[13–15] However, in this study genomic classifier scores were not associated with risk of recurrence after RP in men who progressed on AS. These findings highlight that the risk stratification of patients on AS with biopsy progression is a potential area for further improvement in genomic testing to help improve treatment decision making while on AS. Potential areas for improvement include utilizing the heterogeneity of the tumor immune microenvironment found in both low- and high-risk prostate cancer to identify new biomarkers.[16,17] We feel this is a promising area of research and are hopeful upcoming studies will yield improved biomarkers for patients on AS which may help guide decision making after biopsy progression.

A major strength of this study is the large, institutional AS cohort used. However, this study also has limitations that must be acknowledged. The study design is retrospective in nature and the sample size was limited. Given this is an institutional cohort, the results are likely most representative of the practice patterns and outcomes of a tertiary care, referral center. Therefore, the results may not be generalizable to all practice settings. The limited post-surgical followup in our cohort resulted in reporting of 3-year RFS curves. This time point may not reflect long-term oncologic outcomes, which may diverge between early and late RP groups. Therefore, it will be important to report longer-term outcomes for this cohort in the future. Also, the cohort includes patients over a long period of time during which several new technologies (MRI, new biomarkers including genomic testing) have been adopted, which may bias our study to a null outcome as they likely improve risk stratification of patients on AS. Genomic testing on biopsy specimens was only conducted in approximately half of the cohort, which may limit our ability to draw conclusions on the utility of genomic testing in this patient population. Additionally, we may not have captured all factors influencing patient decision making. Since the decision to undergo biopsy is a shared decision-making process between patient and provider, it is impossible to ascertain the exact reasoning behind each biopsy to evaluate whether this would be related to pursuing early vs late RP in our cohort. However, at our institution most AS biopsies are performed based on timing instead of MRI or PSA results.

CONCLUSIONS

In this large AS cohort, a significant proportion of patients continue on AS after biopsy progression. During 5-year followup after biopsy progression, the majority of these patients will undergo RP. Delaying RP beyond 6 months after biopsy progression was associated with comparable adverse pathology rates and RFS. This suggests a subset of patients with biopsy progression can safely continue on AS. Further studies are needed to validate our findings and to identify biomarkers to improve the risk stratification of these patients moving forward.

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EDITORIAL COMMENT

Active Surveillance is a safe and preferred management strategy for Grade Group (GG) 1 patients. At least 30% will experience reclassification based on grade increase on surveillance protocol biopsies. Most of these will be GG2. Both patient and surgeon may be hesitant to automatically jump to definitive therapy based on this seemingly minor change and concerns about overtreatment. This is especially true at a time when we are increasingly exploring surveillance for newly diagnosed GG2 patients. In the current series, the authors found no difference in adverse pathology or 3-year biochemical recurrence rates for men who chose to remain on surveillance after reclassification to GG2 and had their radical prostatectomy up to 5 years later. If this holds up over time, it will support the concept that continuing surveillance after Gleason upgrading may be oncologically safe in select cases. This series does not help us understand how to select these men. Genomic classifiers did not show an association with outcome. This may indicate that these were already highly selected men with lower GG scores as they had chosen surveillance to begin with.

We need to be careful here as these outcomes were measured at a very early end point. The curves for recurrence-free survival after delayed treatment appear to separate but it will take several years to show differences in metastatic progression and survival.

In this series, 65% of the men reclassified to GG2 chose to stay on surveillance. This likely reflects positive discussions of options and risk between care provider and patient. How we frame the concept of risk in our interactions with patients and how we convey our own comfort with surveillance improves patient acceptance and adherence to active surveillance.[1,2] There is an opportunity here to study how we quantify and communicate risk and how it is perceived and interpreted by patients.

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