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Changes in Prostate Cancer Grade on Serial Biopsy in Men Undergoing Active Surveillance

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ABSTRACT

Purpose
Active surveillance is now considered a viable treatment option for men with low-risk prostate cancer. However, little is known regarding changes in Gleason grade on serial biopsies over an extended period of time.

Patients and Methods
Men diagnosed with prostate cancer between 1998 and 2009 who elected active surveillance as initial treatment, with 6 or more months of follow-up and a minimum of six cores at biopsy, were included in analysis. Upgrading and downgrading were defined as an increase or decrease in primary or secondary Gleason score. Means and frequency tables were used to describe patient characteristics, and treatment-free survival rates were determined by life-table product limit estimates.

Results
Three hundred seventy-seven men met inclusion criteria. Mean age at diagnosis was 61.9 years. Fifty-three percent of men had prostate-specific antigen of 6 ng/mL or less, and 94% had Gleason score of 6 or less. A majority of men were cT1 (62%), had less than 33% of biopsy cores involved (80%), and were low risk (77%) at diagnosis. Median number of cores taken at diagnostic biopsy was 13, mean time to follow-up was 18.5 months, and 29% of men had three or more repeat biopsies. Overall, 34% (129 men) were found to have an increase in Gleason grade. The majority of men who experienced an upgrade (81%) did so by their second repeat biopsy.

Conclusion
A proportion of men experience an upgrade in Gleason score while undergoing active surveillance. Men who experience early upgrading likely represent initial sampling error, whereas later upgrading may reflect tumor dedifferentiation.

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INTRODUCTION

Active surveillance has emerged as an initial treatment option for men with early stage, low-grade prostate cancer. This approach offers the ability to delay or altogether avoid definitive treatment, thereby minimizing patient morbidity. Studies to date have shown that this seems to be achieved without compromising long-term outcomes (progression-free survival) in appropriately selected patients.[1,2]

Currently, timing of intervention after diagnosis is based on variables such as prostate-specific antigen (PSA) kinetics, Gleason grade progression on follow-up biopsy, patient preference, and/or clinical or radiographic evidence of disease progression.[3,4] Increase in Gleason grade in particular is predictive of time to active treatment.[5] This may be in part a reflection of tumor biology, which suggests that grade provides an important tool in risk strati-

fication. Grade is known to correlate with outcome; however, there are little published data regarding changes in Gleason grade on serial biopsies in men who have remained on surveillance over an extended period of time.

In 2008, Epstein et al[6] studied 241 men with localized prostate cancer (T1c) and initial Gleason score of 6 or less who were observed expectantly for approximately 3 years. Grade progression occurred in 19% of men, and more than one half were within 2 years of diagnosis. Interestingly, a similar grade increase has been reported on immediate repeat biopsy (27%) in men enrolled onto an active surveillance protocol as well as in radical prostatectomy specimens (20%) procured shortly after diagnostic biopsy.[7] This short time span in comparison with the long natural history of prostate cancer suggests that sampling error, rather than true tumor progression, is the primary source of upgrading in

this setting. We aim to further characterize the behavior of Gleason grade on serial biopsies over time in men undergoing active surveillance.

PATIENTS AND METHODS

Men diagnosed with prostate cancer between 1998 and 2009 who elected active surveillance as initial treatment were identified through the University of California at San Francisco Urologic Oncology Database. This study was approved by the institutional review board to prospectively collect clinical data on patients who consented to research. Additional inclusion criteria included at least 6 months of follow-up, a minimum of six cores taken at diagnostic biopsy, at least one repeat biopsy, and no treatment before enrollment or within 6 months of diagnosis. We identified 377 men who met all inclusion criteria with complete clinical information.

Active surveillance was offered to men with Gleason score of 6 or less, PSA less than 10 ng/mL, less than 33% of biopsy cores involved, and clinical T1 or T2a tumor. However, some men chose to undergo active surveillance with disease characteristics outside these criteria; they were included in the present study population. Biopsies performed at other institutions underwent slide review by an in-house genitourinary pathologist. The active surveillance regimen consisted of digital rectal examination, serial PSA testing at 3-month intervals, and repeat prostate biopsies (10 or more cores) at 12- to 24-month intervals performed at our institution. Repeat biopsies were taken from each sextant (medial and lateral cores) and included anterior gland sampling. Most men had one additional core taken at a site previously positive for cancer. A patient was considered to have an upgrade if there was an increase in primary or secondary Gleason score (eg, 3 + 3 to any pattern 4, or 3 + 4 to 4 + 3). Downgrades on repeat biopsy were defined as a decrease in primary or secondary Gleason score (eg, 4 + 3 to 3 + 4, or 3 + 4 to 3 + 3). No patient experienced a downgrade lower than Gleason 3 + 3, but a proportion had negative findings on repeat biopsy.

Means and frequency tables were used to describe diagnostic age, PSA, Gleason grade, number of biopsy cores taken and percentage positive, Cancer of the Prostate Risk Assessment score, and the D'Amico classification system.[8] Life-table product limit estimates were used to determine rates of treatment-free survival during surveillance. All analyses were performed using SAS 9.1 for Windows (SAS Institute, Cary, NC).

RESULTS

Of 649 men undergoing active surveillance, a total of 377 men met all inclusion criteria. Mean age at diagnosis was 61.9 years (range, 40 to 85 years; standard deviation, 7.48 years). At diagnosis, 200 men (53%) had PSA of 6 ng/mL or less (median, 5.74 ng/mL; range, 0.30 to 37.9 ng/mL). A majority of men were clinical stage T1 (234 men; 62%) and had less than 33% of biopsy cores involved (302 men; 80%) at diagnosis. Median number of cores taken at diagnostic biopsy was 13 (mean, 13.3 cores; range, six to 43 cores). Only 29 men (7%) had fewer than 10 cores at diagnostic biopsy. Additionally, a majority of patients (356 men; 94%) had initial Gleason score of 6 or less, and 20 men (6%) had Gleason score of 7 (3 + 4, 5%; 4 + 3, 1%). Using the D'Amico classification system, 291 patients (77%) were classified as low risk, 77 (20%) were intermediate risk, and nine (2%) were high risk at diagnostic biopsy. Using the Cancer of the Prostate Risk Assessment classification system, a relatively similar proportion of patients were in each risk category (Table 1).

Mean time to follow-up after diagnostic biopsy was 54 months (median, 47 months), and 13 (3%) patients were lost to follow-up. Figure 1 depicts change in Gleason grade on serial biopsy over time. Two hundred five men (54%) had two or more repeat biopsies

Table 1. Patient Characteristics at Time of Diagnosis

Variable	No.	%
PSA (ng/mL)		
≤ 4	72	19
4.1-6	128	34
6.1-10	124	33
> 10	53	14
PSA density		
≤ 0.08	79	21
0.081-0.12	94	25
0.121-0.18	106	28
> 0.18	98	26
Gleason grade		
2-6	356	94
7 (3 + 4)	17	5
7 (4 + 3)	3	1
8-10	1	< 1
Positive cores (%)		
< 33	332	88
33-66	41	11
> 66	4	1
CAPRA risk group		
0-2	316	84
3-5	54	14
6-10	2	1

Abbreviations: CAPRA, Cancer of the Prostate Risk Assessment; PSA, prostate-specific antigen.

(three biopsies total), 109 (29%) had three or more, 48 (13%) had four or more, 23 (6%) had five or more, 11 (2%) had six or more, four (1%) had seven or more, and one had eight. Median time between biopsies ranged from 12 to 16 months. Eighty-one men (21%) were upgraded at their first repeat biopsy. Of 198 (53%) men whose Gleason grade remained unchanged after first repeat biopsy, only 24 (12%) demonstrated upgrading after second repeat biopsy. Sixty-nine men showed no change in Gleason grade until the third repeat biopsy (fourth biopsy total), when six men (9%) experienced an upgrade. Conversely, 91 (24%) men with initial diagnosis of Gleason 6 disease were downgraded to negative findings on first repeat biopsy. Of these men, 19 (21%) of 91 were found
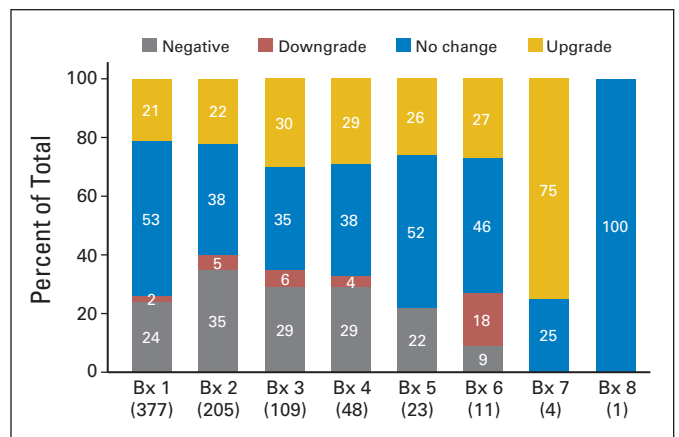

Fig 1. Change in Gleason grade with repeat biopsy (Bx) over time. Number in parentheses represents number of patients.

Table 2. Detailed Overview of Gleason Grade on Serial Biopsy Over Time

Serial Biopsy (No. of Patients)					
First (diagnostic)→ Second		Second→ Third		Third→ Fourth	
Upgrade	81	Upgrade	1		
		No change/downgrade	15	Upgrade	1
				No change/downgrade	4
				Negative finding	1
No change/downgrade*	205	Upgrade	25	No change/downgrade	7
				Upgrade	6
		No change/downgrade	73	No change	27
				Negative finding	7
		Negative finding	29	Upgrade	10
				Negative finding	9
Negative finding	91	Upgrade	19	Upgrade	3
				No change/downgrade	6
				Negative finding	3
		Negative finding	43	Upgrade	13
				Negative finding	12
Total	377		205		109

*Only seven men experienced downgrading (from Gleason 3 + 4 to Gleason 3 + 3) on first repeat biopsy. One man was subsequently upgraded to Gleason 3 + 4 on second repeat biopsy and underwent treatment.

to have cancer on second repeat biopsy, and 13 (30%) of 43 were eventually found to have cancer on third repeat biopsy (Table 2). There was no significant difference (t-test $P = .67$) in mean number of biopsies in men with and without cancers who were upgraded. Overall, of the 129 men who experienced grade progression, 98% were upgraded to Gleason 3 + 4 disease. Median percentage of Gleason 4 found on repeat biopsy in these men was 15% (interquartile range, 10 to 25; range, 1% to 40%), and median number of cores involved was one (interquartile range, one to two cores; range, one to five cores).

In 102 men with a mapped diagnostic biopsy who experienced an upgrade, 37% (38 men) did so at a sextant site not previously cancerous. Thirty-four men (33%) had upgrading mostly found at sites of previously detected cancer ($>$ 75% of upgraded areas were in location of known tumor on prior biopsy). Thirty men (29%) had partial match (ie, 25% to 75% of upgraded areas were in location of known tumor on prior biopsy) between cores that had cancer upgrade and cores that previously contained lower-grade cancer (Table 3). Because of unmapped diagnostic biopsy, 27 men were excluded from this analysis.

Treatment-free survival rates at 5 years after diagnosis were 40% for those who were upgraded and 80% for those with no upgrade

(log-rank $P < .01$; Fig 2). Of the 129 men who had any upgrade on biopsy, 76 (59%) elected to undergo definitive treatment: 39 underwent radical prostatectomy, 30 chose radiation, and seven received androgen deprivation therapy. Of 37 men who decided to proceed with active treatment despite no change in Gleason grade on serial biopsy, 23 underwent surgery, 12 received radiation, and two received androgen deprivation therapy. Of the 62 men combined who were treated with surgery (either because of upgrade on biopsy or preference for definitive treatment), 12 (20%) were downgraded on final pathology, 37 (59%) showed no change, and 13 (21%) showed further upgrade in Gleason score. Of the men who were upgraded from Gleason grade 6 on biopsy, eight (65%) of 13 had 3 + 4 disease, and two (18%) of 13 had 4 + 3 disease on final pathology. Additionally, two men had Gleason grade 3 + 4 on biopsy and were upgraded to 4 + 3 at surgery, and one man had Gleason grade 4 + 4 disease and was upgraded to 4 + 5 at surgery. The remaining 46 men (36%) who experienced upgrading continue to undergo active surveillance (patient preference). They are vigilantly monitored at our institution with serial 3-month PSA testing, 6-month transrectal ultrasound imaging, and
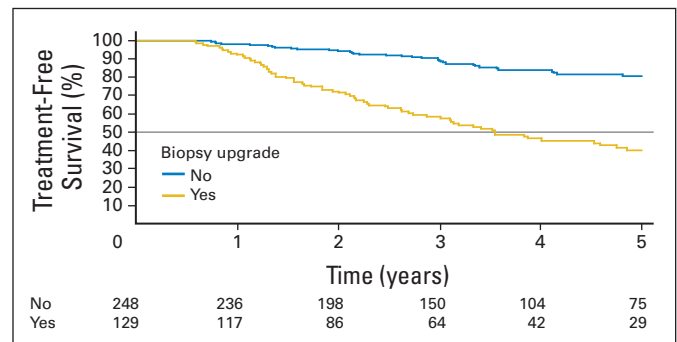
Table 3. Reproducibility of Tumor Location in Men Who Experienced Upgrading

Degree of Site Match	Upgrading < 1 Year		Upgrading > 1 Year	
	No.	%	No.	%
No (< 25%)	28	39	10	33
Partial (25%-75%)	25	35	5	17
Yes (> 75%)	19	26	15	50

No	248	236	198	150	104	75
Yes	129	117	86	64	42	29

Fig 2. Treatment-free survival during active surveillance.

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low threshold for planned early repeat biopsy ($<$ 12 months) if these clinical parameters worsen.

DISCUSSION

In our series, an increase in Gleason grade was found in 34% (129 of 377) of men undergoing active surveillance on serial biopsies. A majority of patients who experienced an upgrade (105 men; 81%) did so at their first or second repeat biopsy, within 30 months of initial diagnosis. With each serial biopsy, upgrading occurred less often (20% to 30% of each patient group), at an interval of approximately 13 months. A majority of men (94%) in our cohort entered with Gleason 3 + 3 disease, and a majority of grade progression (98%) was to Gleason 3 + 4 disease.

These findings generally confirm observations reported by others. Epstein et al[6] examined 241 patients enrolled onto an active surveillance program and noted an increase in grade in 19%, with 53% showing grade progression within 24 months of initial diagnosis. This suggests that in many instances, upgrading reflects undersampling by the original biopsy rather than true dedifferentiation of the prostate cancer. It is well documented that approximately 30% of men who undergo radical prostatectomy for low-grade disease are upgraded on final pathology.[9] Sampling error is also a well-described phenomenon in many surveillance cohorts. Berglund et al[7] found upgrading in 27% of men undergoing immediate restaging biopsy. These results were confirmed by Eggener et al[10] in a multi-institutional cohort; the authors found a 30% rate of upgrade on restaging biopsy before initiation of surveillance-based treatment. Van den Bergh et al[11] also reported a 22% rate of upgrading with rebiopsy at 1 year in a large cohort of more than 500 men undergoing active surveillance. We also noted that 91 men (24%) underwent downgrading to no cancer on first repeat biopsy, which is comparable to previously reported studies (rates of 14% to 34%).[11,12] Overall, we observed a negative biopsy rate of approximately 25% to 30% with each subsequent biopsy until patients reached sixth repeat biopsy (one of 11 men; 9%). The smaller negative biopsy rate seen as biopsy number increased may be a result of small sample size, chance, or reduced likelihood of undersampling.

We previously reported a greater frequency of Gleason upgrading at our institution on subsequent in-house biopsy among men who underwent their initial biopsy at another institution (26% v 16%).[3] Extended-pattern biopsies, especially those including anterior gland sampling, minimize the risk of undergrading at time of enrollment in an active surveillance program.[13] In the current study, in which many men were observed longer than previously reported, we show a higher cumulative incidence of grade progression. Although a proportion of upgrading seen in our cohort is attributable to undersampling because of limited biopsy strategies, this may not explain all of our findings, because a majority of men had multiple cores taken at biopsy (49% had 13 or more cores). In the subset of men who experienced grade progression (mainly to Gleason 3 + 4), the presence of Gleason pattern 4 tumor was limited; 75% of men had fewer than two cores or 25% of tissue involvement. We observed a low rate (2%) of upgrading to more extensive Gleason 4 + 3 on serial biopsy. Recent studies have reported a 6% to 8% rate of higher-grade cancer in men with low-risk disease who underwent prostatectomy either immediately or after a period of surveillance.[14,15] Anterior- or transition-zone cancer undersampling was the likely place for missed high-grade disease. We em-

ploy an extended-pattern biopsy template that included anterior-zone sampling in biopsies performed at our institution before enrollment in a surveillance program. This may account for the low rate of high-grade cancer, because such men are identified early and counseled to undergo immediate definitive treatment. Nevertheless, our findings, especially in those cases of upgrading occurring over a prolonged period of time, may represent true dedifferentiation or the development of separate areas of higher-grade tumor.

Adolfsson et al[16] found evidence supporting gradual prostate tumor dedifferentiation in 84 men with untreated cancer using serial fine-needle aspiration biopsies. Increased aneuploidy or decreased cytologic differentiation were observed over a time span of approximately 2 or more years in 23% of patients. More recently, Draisma et al[17] used statistical modeling in more than 2,000 men diagnosed with prostate cancer in the ERSPC (European Randomized Study of Screening for Prostate Cancer) trial to elucidate the natural history of dedifferentiation and its temporal relationship to prostate cancer screening. They found evidence to suggest that prostate tumors dedifferentiate during the screen-detectable preclinical phase, but they lacked long enough follow-up (approximately 5 years) to conclude whether screening or early treatment affected prostate cancer mortality. Interestingly, Whittemore et al[18] reported on low-grade, low-stage prostate cancers incidentally detected at autopsy. They compared tumor volume from autopsy findings adjusted for age and clinical parameters with men diagnosed with clinically detected prostate cancers to calculate a rate of tumor dedifferentiation. They found that 1 cm^3 of low-grade cancer may evolve into 0.024 cm^3 of high-grade cancer approximately 7 years later. A similar time course for tumor progression was found by Wheeler et al,[19] who noted that after radiation therapy, there were more cases of dedifferentiation as time to recurrence increased.

The frequency of upgrading in our cohort was fairly stable (between 10% and 20%) over similar time intervals (approximately 13 months). One hypothesis is that with a continuous decline in sampling error on serial biopsies, tumor dedifferentiation may occur over a predictable time course. However, this statement would hold true if each biopsy core were taken from the same location at each repeat biopsy. At the present time, standardized biopsy templates are inherently imprecise, and true accuracy and precision of repeated biopsies is unknown. Alternatively, our findings could be purely the result of continuous sampling error. In our cohort, we found that 37% of men who experienced upgrading did so at a site that was previously not involved with carcinoma. When analyzed by time of upgrade, biopsies were more reproducible in men upgraded at greater than 1 year, which may be a result of initial undersampling in men upgraded at less than 1 year (on first repeat biopsy). In men with later upgrading, the increased reproducibility of upgrade at a site of previous tumor may point to the presence of tumor dedifferentiation (67%; 20 of 50 men). The small number of patients within this group limits this conclusion. Most importantly, our findings highlight the limitations of prostate biopsy in approximating true tumor burden and changes in tumor characteristics over time.

Our population included a small group of men with Gleason 7 or greater (16 men; 5%) on diagnosis who underwent repeat biopsies. Of these men with intermediate-risk disease, 11 had no change on first repeat biopsy, four experienced an upgrade, and one was downgraded. Of the men upgraded to Gleason 8 disease, two underwent treatment with external beam radiation, one underwent radical prostatectomy,

and one elected not to have treatment. In comparison, Klotz et al[20] observed 299 patients prospectively with active surveillance over 64 months and reported histologic progression in 16%, which is lower than many other institutions but is the result of more inclusive (grade) entry criteria.

The clinical significance of small-volume intermediate-grade disease after multiple biopsies is unknown. The natural history of these tumors is likely different from that in those of previously observed men with clinically detected disease in the pre-PSA era, such as those reported by Albertsen et al.[21] Furthermore, there is increasing evidence that patients with primary pattern 3 disease (including 3 + 3 and 3 + 4) have substantially different outcomes than those with primary pattern 4 to 5 disease (including 4 + 3 or any Gleason sum 8 to 10).[22] We are actively examining the significance of percentage of Gleason pattern 4 in biopsy specimens in men undergoing active surveillance. The biology of upgraded tumors during active surveillance may be different between those with predictable long-term interval grade changes or those with rapid, early-grade changes. Lapointe et al[23] have used advances in genomic profiling to better stratify patients with more aggressive prostate cancer. In the future, molecular markers may further refine our prediction of tumor biology to identify the best candidates for initiation, continuation, and termination of active surveillance.

Limitations of this study include those inherent to its observational design. Our cohort was heterogeneous and included a subset of higher-risk patients, which affects the ability to generalize our findings to other populations. Because different pathologists reviewed patient slides, there is the possibility of inter-observer variation with Gleason score assignment that would account for a proportion of upgrading on repeat biopsy. However, all slides underwent review by specialized genitourinary pathologists, and a previous study showed substantial agreement between experienced individuals, albeit at another institution.[24] Prostate biopsy is an imperfect surrogate for cancer detection, and sampling bias may have affected our reported results. There are still too few patients with a long duration of follow-up to assess whether outcomes are different between men who were upgraded and underwent surgery as compared with men who were treated immediately before grade progression was known, although initial assessment suggests that there is no difference.[25] Additionally, not all men who were upgraded chose to undergo definitive treatment, and longer follow-up is ongoing and necessary to determine their risk of significant progression and cure rates.

Among men with low-grade, low-stage disease managed with active surveillance, a proportion experiences an upgrade in Gleason score. Men who experience early upgrading more likely represent initial sampling error, whereas later upgrading may reflect tumor dedifferentiation. This is dependent on the limitation of prostate biopsy in the ability to reliably and accurately detect change in tumor volume and location. The natural history of a small volume of intermediate-grade disease after multiple biopsies is a key question for further research.

AUTHOR CONTRIBUTIONS

Conception and design: Sima P. Porten, Jared M. Whitson, Kirsten L. Greene, Maxwell V. Meng, Peter R. Carroll
Administrative support: Janet E. Cowan
Provision of study materials or patients: Matthew R. Cooperberg, Nannette Perez, Kirsten L. Greene, Maxwell V. Meng, Peter R. Carroll
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Manuscript writing: All authors
Final approval of manuscript: All authors

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