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Disease reclassification risk with stringent criteria and frequent monitoring in men with favorable-risk prostate cancer undergoing active surveillance

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Abstract

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Objective—To determine the frequency of disease reclassification and to identify clinicopathologic variables associated with it in patients with favorable-risk prostate cancer undergoing active surveillance.

Patients and Methods—We assessed 191 men selected by what may be the most stringent criteria used in active surveillance studies yet conducted who enrolled in a prospective cohort active surveillance trial. Clinicopathologic characteristics were analyzed in a multivariate Cox proportional hazards regression model. Key features were an extended biopsy with a single core positive for Gleason score (GS) 3+3 (<3 mm) or 3+4 (<2 mm) and a prostate-specific antigen (PSA) level <4 ng/mL (adjusted for prostate volume). Biopsies were repeated every 1–2 years and clinical evaluations every 6 months. Disease was reclassified when PSA level increased 30% from baseline or when biopsy tumor length increased beyond the enrollment criteria, more than one positive core was detected, or any grade increased to a dominant 4 pattern or any 5 pattern.

Results—Disease was reclassified in 32 (16.8%) patients (median follow-up time among survivors, 3 years [interquartile range, 1.9–4.6 years]), including upgrading to GS 4+3 in 5 (2.6%). Overall, 13 of the 32 (40.6%) had incremental increases in GS. Tumor length (hazard ratio [HR], 2.95; 95% confidence interval [CI], 1.34–6.46; $P=0.007$) and older age (HR, 1.05; 95% CI, 1.00–1.09; $P=0.05$) were identified as, respectively, significant and marginally significant predictors of disease reclassification. Disease remained stable in 83.2% of patients.

Conclusion—Needs persist for improvements in risk stratification and predictive indicators of cancer progression.

Clinical trial information—NCT00490763

Keywords

active surveillance; biopsy; prostate; prostate cancer; tumor; watchful waiting

Introduction

In the era of PSA screening in the United States, despite evidence supporting the use of active surveillance (AS), most men with low-risk prostate cancer receive curative treatment. As data emerge challenging this status quo interventional response [1, 2], the management paradigm is shifting away from immediate intervention toward active surveillance with curative treatment delayed until disease progression occurs [3]

The prospective AS study with the longest follow-up [4, 5], in general, including patients with mostly low-risk and some intermediate-risk prostate cancer, demonstrated the feasibility of AS. Application of AS to a wider cohort of men with early stage prostate cancer, however, is limited by currently available clinicopathologic tools (Gleason grading and prostate-specific antigen level). As shown by surgical series of low-risk prostate cancer cases selected for immediate surgical intervention, about a third of men are found to have radical prostatectomy specimen pathology characterized by increased disease volume, grade, and disease extension beyond the prostate [6, 7]. Additionally, prostate cancer's widely variable heterogeneous biology and the absence of a clear definition of early progression remain unmet challenges in managing early stage prostate cancer by active surveillance.

Aggregate studies [8, 9] have demonstrated three central and evolving concepts integral to AS, including selection criteria, surveillance interval and tools, and the trigger (or triggers) for treatment recommendation.

In 2006, to test the hypothesis that a systematic strategy of AS could shelter patients from unnecessary intervention yet detect tumor progression when disease remained curable, we initiated a multiyear prospective cohort study. Our aim was to determine the rate of disease reclassification of clinically organ-confined prostate cancer, including the most stringently selected favorable-risk cases, and compare it to rates in other AS series [8, 10].

PATIENTS AND METHODS

This single-institution prospective cohort study, conducted by a multidisciplinary team of urologic surgeons, radiation oncologists, and medical oncologists, was approved by The University of Texas MD Anderson Cancer Center (MDACC) Institutional Review Board. All patients signed an informed consent.

Patients with early stage prostate cancer were stratified to AS groups I (favorable risk), II (patient's choice), or III (therapy prevented by comorbidities). For the favorable-risk group, inclusion criteria, based on previous work at MDACC that established clinical predictors of LV/LG disease [11], required that patients have a biopsy no more than 6 months before enrollment of 10 cores showing either a 3+3 Gleason score (GS) in one core (tumor focus, <3.0 mm) or a 3+4 GS in one core (tumor focus, <2.0 mm). The study entry PSA had to be <4 ng/mL or adjusted for volume [12]. Patients with a 3+3 GS or 3+4/4+3 GS, not meeting the criteria for group I were considered group II. Patients in group III had comorbidities precluding local therapy, as determined by the managing physician. In June 2007, the protocol was amended to include a confirmatory biopsy onsite at enrollment or within six months of diagnosis, unless MDACC performed the diagnostic biopsy.

Patients were evaluated at baseline and every 6 months by clinical examination (digital rectal examination) and laboratory studies (serum PSA, testosterone). Additionally, information on concomitant medications, including 5 α -reductase inhibitors, was recorded as was body mass index (BMI) at each follow-up. All biopsies were performed with the transrectal ultrasound-guided technique using the 11-core multisite-directed biopsy scheme (sextant locations, one posterior midline, and two each laterally directed and designated as left and right anterior horn) [13]. Prostate biopsies were repeated every 1–2 years; if the biopsy was negative, then the following year's biopsy was omitted, unless requested by the patient.

Disease was reclassified when change in biopsy findings or PSA level was significant. The threshold for a significant change was detecting an increase in tumor length in a positive core beyond study entry criteria, more than one positive core at biopsy, or an upgrade to a dominant Gleason grade 4 or any Gleason grade 5 component. If the location of disease on repeat biopsy (including contralateral location) otherwise met criteria, it was not reclassified. The threshold for a significant change in PSA level was finding a >30% increase, which had to be confirmed within a month of laboratory results or three months after biopsy.

Patients who declined repeat prostate biopsies were allowed to remain on protocol, provided their treating physician agreed, and were included in the analysis as not having had disease reclassified. Since patients' compliance with long-term surveillance was also of interest, patients were allowed to remain on protocol unless they requested to go off, met the criteria for disease reclassification, or were diagnosed with a second malignancy.

PSA Metrics During AS

PSA velocity (PSAV) was computed by fitting a linear regression model on PSA values over time. The American Urological Association [14] suggests that a correct measurement of PSAV requires at least three PSA measurements after diagnosis over at least 18 months. PSA doubling time (PSADT) was calculated by regressing the $\ln(\text{PSA})$ over time to obtain the slope (m), and the PSADT was defined as $\ln(2)/m$.

Statistical Methods

Patient characteristics were summarized using median and range for continuous variables and frequency with percentage for categorical variables. Disease reclassification was defined by prespecified pathologic criteria and/or an increase in PSA value, and an unadjusted disease reclassification probability was estimated [15]. A log-rank test was performed to compare the time to disease reclassification between patients with and without delayed treatment. Cox proportional hazards models [16] were fit to assess the association between disease reclassification and baseline patient characteristics, including age, race, BMI, clinical stage, total PSA, testosterone level, total prostate volume by transrectal ultrasound, tumor length, and first-degree family history. PSA density (PSAD) was excluded from this model because in our unique cohort with stringent criterion for PSA, it was highly correlated with PSA and tumor length. However, in several other AS series, PSAD has been shown to be an important predictor of AS biopsy disease reclassification [17].

P values < 0.05 were deemed statistically significant. All analyses were performed in S-PLUS (TiBCO Spotfire S+ S.2 for Windows, Palo Alto, CA).

RESULTS

Between February 2006 and February 2012, 575 men were enrolled and one patient was deemed ineligible: 191 men entered group I; 369, group II; and 14, group III. We describe results for those in group I, all of whom had at least 6 months of follow-up. Among survivors, the median follow-up time was 3 years (interquartile range, 1.9–4.6 years), and the mean follow-up time was 3.2 years (Fig. 1 and Table 1). Of 191 patients, 150 enrolled after confirmatory biopsy onsite became mandatory at study entry or within 6 months of diagnosis, including 23 whose diagnostic extended biopsy was performed at MDACC within 6 months of study registration. Of the 41 enrolled beforehand, 15 underwent rebiopsy prior to study entry per treating physicians' preference. Based on the stratification criteria for group I, patients were required to have no tumor on rebiopsy prior to study entry or confirmatory biopsy. There was no significant difference in the rate of disease reclassification between the patients who enrolled before and after confirmatory biopsy became mandatory (data not shown).

Disease reclassification occurred in 32 (16.8%) patients, exclusively driven by repeat biopsy findings. The 3-year and 5-year freedom from the reclassification rate was 82.3% (95% CI: 76.2%–88.8%) and 69.8% (95% CI: 59.4%–82.2%), respectively. Disease reclassification was documented at first occurrence on repeat biopsy. Of the 32 patients with reclassified disease, 19 (59.4%) had increases in tumor volume, including 12 (37.5%) who had an increase in the number of cores with tumor, 6 (18.8%) who had increases in tumor length, and 1 (3.1%) who had both. Of the remaining 13 (40.6%), 3 (9.4%) had increases in tumor grade only, and 10 (31.3%) had increases in tumor grade plus increases in tumor volume (tumor length and/or tumor positive cores). All 13 increases in tumor grade were to GS 7: 3+4, n=8; 4+3, n=5. Therefore, although the overall rate of disease reclassification was 16.8%, the rate of *biologically concerning* disease reclassification occurred in 5 (2.6%), that is, in those cases in which GS was upgraded to 4+3.

Four of 10 patients treated after disease reclassification underwent radical prostatectomy. One had pT3a GS 4+3 with a focal positive margin, two had organ-confined GS 7 (one 3+4 and the other 4+3), and one was further upgraded to organ-confined GS 4+5. The last of the four had a GS 6 tumor (1-mm focus in one core biopsy) at study entry, had reclassification of tumor on repeat biopsy at year 5 to GS 4+3 (4.5-mm focus in one core biopsy), and had further upgrading at prostatectomy to organ-confined GS 4+5. The tumor was at the apex (Fig. 2). All patients are disease free with limited follow-up. Two patients without disease reclassification who opted for radical prostatectomy had organ-confined GS 3+3 disease. Potential predictors of disease reclassification included higher PSA velocity ($P=0.04$), increasing number of repeat surveillance biopsies ($P<0.0001$), and increasing tumor length ($P=0.03$) (Table 2). In a multivariable Cox proportional hazards regression model in which PSA kinetics and PSAD were excluded, tumor length (hazard ratio [HR], 2.95; 95% confidence interval [CI], 1.34–6.46; $P=0.007$) and age at study enrollment (HR, 1.05; 95% CI: 1.00–1.09; $P=0.05$) remained significant or marginally significant (Table 3).

The time to disease reclassification was estimated by the Kaplan-Meier method and has been depicted for all patients (Fig. 3A) and by treatment status (Fig. 3B). Among all 191 patients, the median time to disease reclassification had not been reached after a median follow-up time of 3 years (Fig. 3A). The 3-year freedom from disease reclassification rate was 82.3% (95% CI: 76.2%–88.8%). Among the 17 treated patients, 10 (58.8%) experienced disease reclassification, and the median time to reclassification was 23.7 months (95% CI: 12.9 to an unestimable value). Among the 174 untreated patients, only 22 (12.6%) had disease that was reclassified, and the median time to reclassification had not been reached. There was a significant difference between these two groups in terms of the median time to disease reclassification ($P<0.0001$, log-rank test, Fig. 3B).

Reclassification for patients was not based in any case on an increase in serum PSA level. PSAV and PSADT measurements using baseline and at least three PSA follow-up values over at least 18 months from baseline was feasible in 124 (64.9%) of 191 patients. The median PSAV was 0.1 (range, –2.0–8.4). The median PSADT was 3.4 years (PSA range, –67.9–351). As the negative values in the ranges indicate, some patients' PSA levels decreased after starting AS.

DISCUSSION

Among 191 men with favorable-risk prostate cancer who met stringent criteria as compared to any other series for AS, 32 (16.8%) were reclassified at a median follow-up of 3 years, and 5 (2.6%) had biologically concerning upgrading to GS 4+3. Biopsy findings determined reclassification, most often by incremental changes in GS and/or length. Of 32 patients with reclassified disease, 10 (31.3%) chose treatment; the remainder continued surveillance. Three patients undergoing subsequent radical prostatectomy had findings of high-grade disease (GS, 7 [4+3]), two had confined disease, and the other had nonconfined disease.

PSA level, which was included in our protocol based on 2005 knowledge, had minimal impact on outcomes. To more specifically delineate each case, we adjusted PSA by prostate volume. In a previous study by our group, we had derived a nomogram predicting low-volume/low-grade (LV/LG) prostate cancer based on findings from 258 men with untreated early stage prostate cancer who underwent radical prostatectomy. We found age, PSA density, and tumor length in a biopsy core to be predictive of LV/LG cancer [18]. We adjusted PSA by simply multiplying the total prostate volume on transrectal ultrasound by a factor of 0.12 [12]. Among the total 191 patients, 63 had PSA \leq 4 ng/mL, and among the 32 patients who had disease reclassification, 9 had a PSA value \leq 4 ng/mL. Given that none of the cases reclassified were reclassified because of the preset PSA criterion, this attempt to refine PSA's value had no effect on the conclusion of the study. Other authors have found similar limitations in correlating PSA with adverse pathology and/or triggers for intervention [5, 19, 20].

Our observations suggest that even with stringent AS selection criteria and frequent monitoring, inherent limitations of the tools available may allow biologically significant cases to go undetected. Our study did not demonstrate a zero risk of biologically concerning disease reclassification. With biopsy, that rate was 2.6%; with prostatectomy, it was 1%—a rate confounded by exclusion of treatments other than prostatectomy at disease reclassification. These rates are certainly low, but the exact interpretation for key decision points will vary by patients and physicians (a young patient may view such odds as too risky; an older patient, as very favorable).

The observed low incidence of higher-grade disease in our cohort suggests two interesting areas for future research and discussion. First, our cohort should have less occult high-grade disease than any similar population that is unbiopsied. For example, in the placebo arm of the Prostate Cancer Prevention Trial, 4,888 men with a PSA level \leq 4 ng/mL who underwent biopsy were observed to have high-grade prostate cancer incidence of 3.2% [21]. Yet the biologic significance of upgrading in this multibiopsied cohort remains unclear, in part, because so many upgraded patients are ultimately treated. Recently Hussein et al. [22] reported on a cohort of active surveillance patients who were upgraded (3+4 or greater) on follow-up biopsy, and they found that 69% were treated with radical prostatectomy; however, among men who deferred treatment further, only 6% were later upgraded and 34% downgraded. Significant follow-up will be required to correlate the positive predictive value of upgrading to metastatic progression and cancer-specific mortality, and we should keep an

open mind to the possibility that the biology of these patients is different (favorable) from that of men with higher grade disease initially undergoing biopsy.

The study design reflects knowledge about AS in 2005. During protocol design, it was well known that PSA screening led to increased prostate cancer detection; but no consensus existed, and no evidence linked it with a decline in mortality [23]. Therefore, the hypothesis that PSA screening led to overdetection of clinically insignificant tumors was widely accepted, but how to segregate tumors using clinically available testing (staging, biopsy, PSA) remained challenging. Albertsen et al. [24] demonstrated a very small risk of prostate cancer disease-specific mortality among men with low-grade disease, even after 20 years of follow-up.

Two prospective series were reported [4, 25] that specifically studied PSA-era patients selected for AS with predefined inclusion, monitoring, and reclassification (IMR). However, these studies demonstrate the difficulty in making advances when studies use different criteria. The Carter et al. [25] series emphasized yearly biopsies and minimal use of PSA metrics; the Klotz et al. [4] series emphasized PSA metrics but biopsies only every 3 to 4 years. Guidelines developed in this era [20] considered AS a standard option for all risk categories of clinically localized disease, but they did not specify parameters for IMR. Therefore, the stringent criteria used are both a strength and limitation in this study, as is the avoidance of protocol updates (other than entry repeat biopsy) during study follow-up. This protocol is meant to address a specific question in a small cohort of patients, whereas other series are meant to be for larger cohorts of patients, and they, therefore, evolve techniques over time [5]. The Klotz series [5], for example, contained multiple methodology updates after its 1995 inception: 2000, biopsy inclusion criteria changed; 2003, mandatory informed consent discontinued; 2009, PSA discontinued as sole trigger for intervention. A separate arm of our surveillance program will report on the outcomes of men with more heterogeneous entry criteria.

For our series to achieve the goal of defining a favorable-risk cohort, we utilized internal studies that sought to predict, using the criteria of Epstein et al. [26] levels of insignificant cancer from pretreatment factors [11]. Thus, patients with one core of GS 3+3 <3 mm or 3+4 <2 mm had the highest likelihood of harboring a total tumor volume of <0.5 mL³. In 2010, we reported a retrospective study of radical prostatectomies that met these same criteria, except PSA was <10 ng/mL [27]. Of 66 cases studied, 6% were upgraded to GS 4+3, and all were organ confined. Total tumor volume was <0.5 mL³ in 71% of cases, but in undersampled disease, the transition zone was a common location. We found that even subtle changes in inclusion criteria, such as those identified by Griffin et al. [28] and Chun et al. [29], were associated at radical prostatectomy with significant increases in extraprostatic extension and upgrading.

By contrast, the series of Carter et al. [25] showed 31% met criteria at a median follow-up of 1.2 years. In the Klotz et al. [4] series, inclusion criteria were much more liberal in comparison to those of the current study (cT2b or lower, PSA <15 ng/mL, and GS ≤ 7). Monitoring included a schedule of PSA and repeat biopsies, and thresholds for included PSA metrics such as a PSADT of less than 2 years, clinical progression, or histologic

progression to a GS 8. At a median follow-up of 4.6 years, 60% remained on surveillance, and disease-specific survival was 97.2%. AS programs under way in North America, using variable IMR, have reported that 14%–41% of men move from surveillance to active treatment [30]. At least six additional series with defined IMR [10] [30–34] and two recent high-profile reviews [8], [9] compare differences in IMR and outcomes. Mandatory repeat biopsy onsite at study entry or within six months of diagnosis, in addition to stringent selection criteria, may be responsible for our study's low rate of disease reclassification. This requirement often reveals higher volume or grade of disease that could significantly alter the appropriateness of surveillance. In screening after the protocol amendment requiring confirmatory biopsy, we observed approximately 15% disease reclassification (data not shown). Adamy et al. [34] demonstrated the importance of a confirmatory biopsy in 531 low-risk cases: 35% were excluded.

In the Klotz et al. [4] series, only five patients died of prostate cancer after initial surveillance and, in the authors' opinion, had lethal disease at the outset [35]. Some did not pursue early curative therapy when disease was reclassified to high risk. Three other series confirmed this conclusion [30, 36, 37], indicating that errors in diagnosis are unlikely to lead to early mortality. In a 2015 report covering 15 years of follow-up, Klotz et al. [5] found that 2.8% of men in the study were diagnosed with metastatic disease and 1.5% had died of prostate cancer. In their study, men were 9.2 times more likely to die of other causes than they were of prostate cancer. Given such a low rate of mortality in patients undergoing AS, even when the most liberal criteria for selection are used [4], the number of men considered candidates for AS should be increased. Our study represents the other end of the spectrum in using the most stringent criteria to help define a framework for AS, but the important question of how liberal patient selection criteria for AS may be without compromising patient safety remains unanswered.

A significant burden rests on the patient in AS who undergoes tests and biopsies repeatedly. We found increasing tumor length to be predictive and older age to be marginally predictive of disease reclassification. Others also have shown older age to be predictive of pathological progression [38], and higher risk of upgrading and upstaging in men who met AS criteria undergoing prostatectomy [39]. Given that prostate carcinogenesis and progression represent a multistep and multiyear process, older men harboring small indolent tumors may find with time the tumors become clinically significant. It is of note that in our unique cohort in which the majority of patients (78.5% using the standard extended biopsy scheme) had negative confirmatory biopsy within six months of study entry, the extent of tumor on diagnostic biopsy was still predictive of disease reclassification. Biopsies themselves carry an infection risk, and some studies have raised the concern of a biopsy-related decline in sexual function [40, 41]. Urgently needed is a more rational approach to biopsy frequency and triggers for treatment, especially in patients with LV/LG disease. Researchers are hoping the Prostate Testing for Cancer Treatment (ProtecT) trial, a phase III study comparing active monitoring, radiotherapy, and radical prostatectomy, reveals answers about early diagnosis and active treatment in LV/LG disease [42]. Results are expected in 2016.

Upstream of the overdiagnosis and overtreatment dilemma, improved screening methods are needed to indicate when LV/LG disease could be safely ignored. We remain confident that

improvement in accuracy of risk assessment and determination of biological potential of the disease based on integration of imaging and biomarkers will one day reduce or eliminate the uncertainty in prostate cancer AS that today prompts unnecessary therapy with adverse effects on quality of life. Finally, we can suggest from our study and from aggregate literature [43] that when patients approach ages 75–80 years and beyond with disease characteristics matching our stringent criteria that monitoring and reclassification thresholds be reduced to a plan more closely resembling traditional watchful waiting.

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Abbreviations

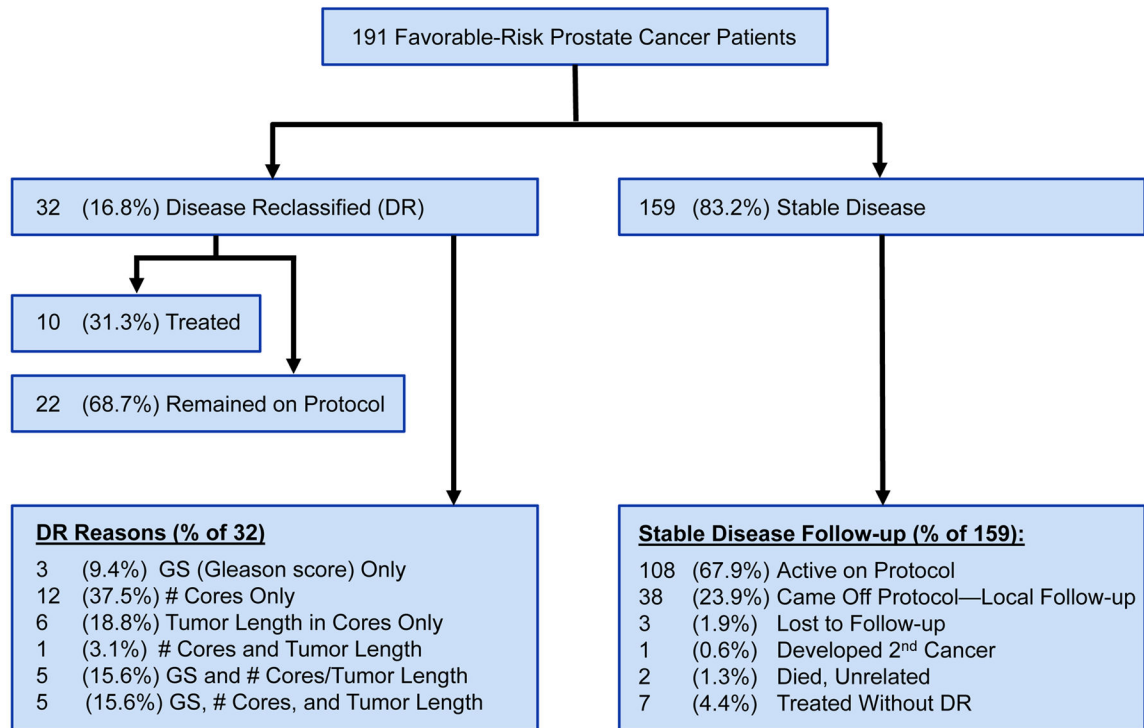
PSA prostate-specific antigen

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**Fig. 1.**

Disposition of cohort in active surveillance: patients with favorable-risk prostate cancer (Gleason score ≤ 6 [3 + 3] with no more than 1 positive biopsy core [tumor, <3 mm] or Gleason score 7 [3 + 4] with no more than 1 positive biopsy core [tumor, <2 mm] and PSA level <4 ng/mL).

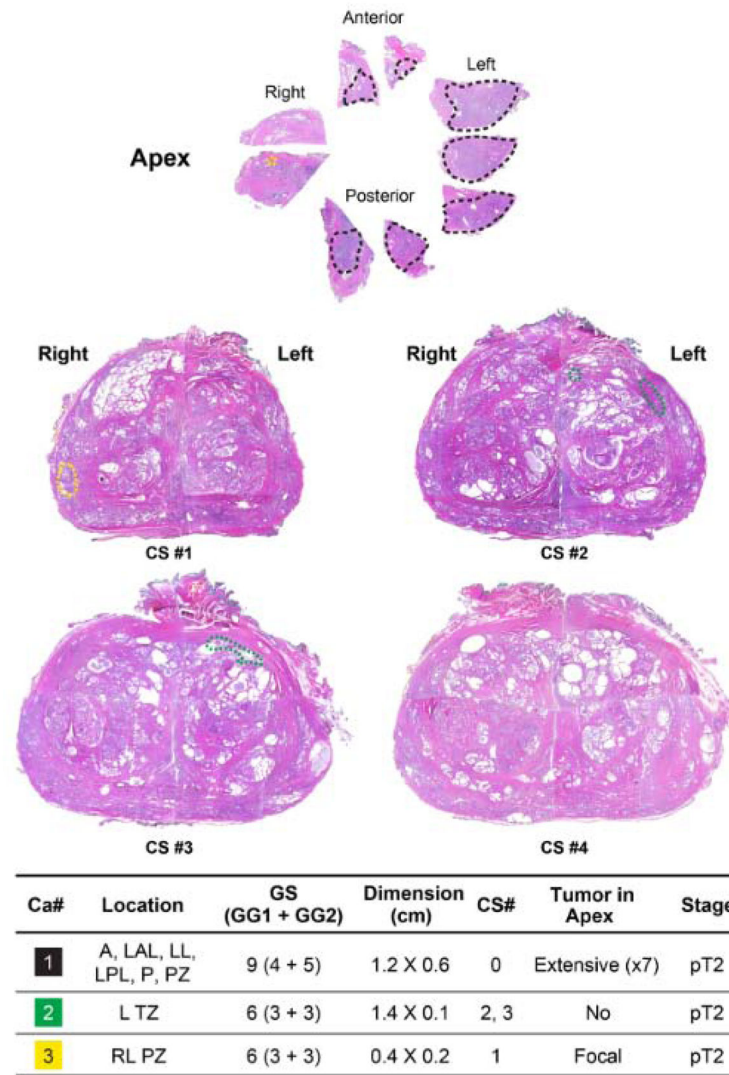


Fig. 2. Cross-sectional analysis of the prostatectomy specimen of a patient who had Gleason 6 tumor at study entry, had reclassification of tumor on repeat biopsy at year 5 to Gleason 4 + 3, and had a further upgrade at prostatectomy to organ-confined Gleason 4 + 5 tumor in the apex. The apex and the four cross sections (CS#1-CS#4) are depicted. Three tumor foci (two in the peripheral zone and one in the transition zone) are indicated with black, yellow, and green dots). All tumor foci are confined to the prostate. The location and Gleason score/grades and dimensions for each tumor focus is listed at the bottom. (A = anterior; LAL = left anterior lateral; LL = left lateral; LPL = left posterolateral; P = posterior; PZ = peripheral zone; L = left; TZ = transition zone; RL = right lateral; GS = Gleason score; GG = Gleason grade; Ca#1 = Gleason 4 + 5 tumor at the apex.)

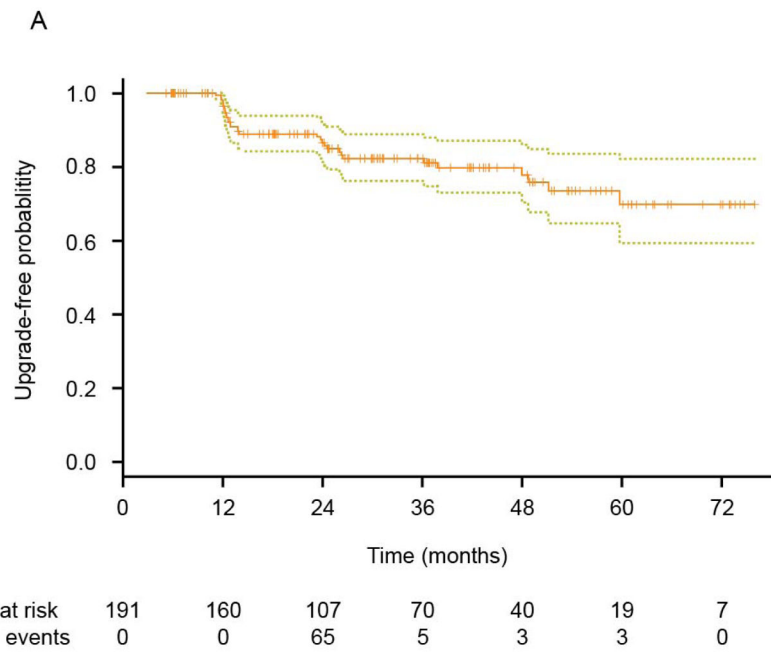


Figure 3a

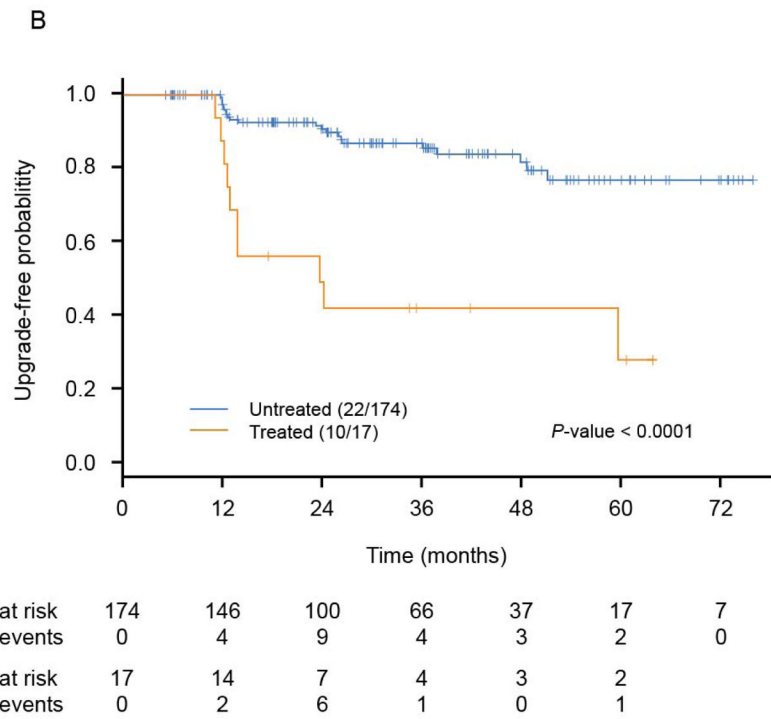


Figure 3b

Fig. 3. Kaplan-Meier estimates. Kaplan-Meier estimates for time to disease reclassification by the Kaplan-Meier method are illustrated in *A* and estimates for time to disease reclassification

by treatment status are illustrated in B (patients untreated after reclassification = 22; patients treated after reclassification = 10).

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Baseline demographic and clinical characteristics and surveillance PSA metrics of study participants in all patients and by reclassification status.

Table 1

Variable	All patients		No reclassification		Reclassification		P
	No.	%	No.	%	No.	%	
No. of patients	191	100	159	100	32	100	
Age (years)	64 (57–69)		63 (57–69)		65.5 (59.5–70)		0.18
Race or ethnicity (n = 190)							0.36
White	155	81.6	131	84.5	24	15.5	
Black	17	8.9	15	88.2	2	11.8	
Hispanic	15	7.9	11	73.3	4	26.7	
Asian	3	1.6	2	66.7	1	33.3	
Body mass index	29.1 (26.1–31.8)		29.2 (26.2–31.8)		27.9 (25.1–32.6)		0.5
PSA level (ng/mL)							
PSA	3.3 (2.2–4.3)		3.3 (2.1–4.4)		3 (2.4–4.2)		0.68
PSA density	0.1 (0.1–0.1)		0.1 (0.1–0.1)		0.1 (0.1–0.1)		0.67
PSA velocity (n = 124)	0.1 (–0.1–0.6)		0.1 (–0.2–0.5)		0.4 (0–0.7)		0.04
PSA doubling time (n = 124)	3.4 (–3.4–7.2)		2.7 (–4–7.1)		4.5 (1.4–7.7)		0.34
Testosterone (ng/dL)	379 (295–479)		379 (290–469)		389 (323–494)		0.44
Transrectal ultrasound, total (mL)	43.9 (29.7–56.3)		44 (29.5–57.5)		43.5 (33.6–53.2)		0.81
Gleason score							1.00
5*	1	0.5	1	100	—	—	
6	189	99	157	83.1	32	16.9	
7	1	0.5	1	100	—	—	
Clinical stage							0.86
cT1a*	5	2.6	4	80	1	20	
cT1c	164	85.9	137	83.5	27	16.5	
cT2a	20	10.5	16	80	4	20	
cT2b	1	0.5	1	100	—	—	
cT2c	1	0.5	1	100	—	—	
Number of surveillance biopsies (n = 183)							<.0001
0	33	18	33	100	—	—	

Variable	All patients		No reclassification		Reclassification		P
	No.	%	No.	%	No.	%	
1	72	39.3	62	86.1	10	13.9	
2	44	24	37	84.1	7	15.9	
3	25	13.7	17	68	8	32	
4	8	4.4	2	25	6	75	
5	1	0.5	—	—	1	100	
Tumor length (mm) (n = 185)							
< 0.5	10	5.4	8	80	2	20	0.03
0.5-< 1	84	45.4	77	91.7	7	8.3	
1-< 2	68	36.8	52	76.5	16	23.5	
2-< 3	23	12.4	17	73.9	6	26.1	
5-alpha-reductase inhibitor: current or history of treatment							
No	159	83.2	130	81.8	29	18.2	0.3
Yes	32	16.8	29	90.6	3	9.4	
Family history, first degree (n = 190)							
No	139	73.2	114	82	25	18	0.66
Yes	51	26.8	44	86.3	7	13.7	
Family history, second degree (n = 190)							
No	161	84.3	136	84.5	25	15.5	0.29
Yes	30	15.7	23	76.7	7	23.3	

Table 2 Univariate and multivariable Cox proportional hazards regression model for disease reclassification.

	Univariate Cox Models			Multivariable Cox Model		
	Hazard ratio	95% Confidence Interval	P	Hazard ratio	95% Confidence Interval	P
Age at registration	1.04	0.99 – 1.08	0.12	1.05	1.00 – 1.09	0.05
Race						
Black (vs. White)	1.97	0.27 – 14.65	0.51			
Hispanic (vs. White)	0.79	0.19 – 3.35	0.75			
Asian (vs. White)	2.03	0.70 – 5.86	0.19			
BMI	0.98	0.90 – 1.07	0.61			
Clinical stage (cT2 vs. cT1)	0.84	0.12 – 6.18	0.87			
Tumor length of 1 mm (vs. < 1 mm)	2.80	1.29 – 6.08	0.009	2.95	1.34 – 6.46	0.007
PSA—total	1.01	0.81 – 1.26	0.95	0.94	0.75 – 1.19	0.62
Testosterone level/100	1.07	0.86 – 1.33	0.56			
Transrectal ultrasound(total)	1.00	0.98 – 1.01	0.60			
First-degree family history—Yes (vs. No)	0.86	0.37 – 1.99	0.72	0.75	0.32 – 1.76	0.5