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Pathological Outcome following Radical Prostatectomy in Men with Prostate Specific Antigen Greater than 10 ng/ml and Histologically Favorable Risk Prostate Cancer

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Abstract

Purpose—Active surveillance is now the treatment of choice in men with low risk prostate cancer. Although there is no consensus on which patients are eligible for active surveillance, prostate specific antigen above 10 ng/ml is generally excluded. In an attempt to determine the validity of using a prostate specific antigen cutoff of 10 ng/ml to counsel men considering active surveillance we analyzed a multi-institution database to determine the pathological outcome in men with prostate specific antigen greater than 10 ng/ml but histologically favorable risk prostate cancer.

Materials and Methods—We queried a prospectively maintained database of men with histologically favorable risk prostate cancer who underwent radical prostatectomy between 2003 and 2015. The cohort was categorized into 3 groups based on prostate specific antigen level, including low—less than 10 ng/ml, intermediated—10 or greater to less than 20 and high—20 or greater. Associations of prostate specific antigen group with adverse pathological and oncologic outcomes were analyzed.

Results—Of 2,125 patients 1,327 were categorized with histologically favorable risk disease. However on multivariate analyses the rates of up staging and upgrading were similar between the

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intermediate and low prostate specific antigen groups. In contrast compared to the intermediate prostate specific antigen group the high group had higher incidences of up staging ($p = 0.02$) and upgrading to 4 + 3 or greater disease ($p = 0.046$). Biochemical recurrence-free survival rates revealed no pairwise intergroup differences except between the low and high groups.

Conclusions—Patients with preoperatively elevated prostate specific antigen between 10 and less than 20 ng/ml who otherwise had histologically favorable risk prostate cancer were not at higher risk for adverse pathological outcomes than men with prostate specific antigen less than 10 ng/ml.

Keywords

prostatic neoplasms; prostate-specific antigen; watchful waiting; risk; outcome assessment (health care)

While the advent of PSA has revolutionized the detection of PCa, its predictive ability has decreased in recent years.¹ As a result the over diagnosis of clinically insignificant PCa has led to overtreatment and associated complications, including erectile dysfunction and urinary incontinence.^{2,3} With the understanding that many of these cancers have an indolent course AS has emerged as the favored choice in men with lower risk PCa.⁴ In patients who elect AS quality of life has been shown to be significantly better than that of men who underwent definitive treatment.⁵

Despite these advantages of AS there are no universally accepted inclusion and exclusion criteria. However establishing AS eligibility criteria remains a clinically complex process. Under lenient criteria patients harboring high risk features may progress during AS and miss the therapeutic window of treatment.⁶ Conversely overly stringent criteria may exclude patients based on an isolated finding that is not entirely representative of the tumor characteristics, subjecting them to potentially unnecessary treatment. Therefore multiple investigators have made efforts to refine the eligibility criteria for AS using various clinical parameters, including biopsy GS, clinical stage, preoperative PSA, PSAD and estimated measures of tumor burden (number of positive cores and tumor involvement in each core).

Of the mentioned parameters PSA remains a nonspecific biomarker that may not correlate with disease severity.⁷ Moreover although PSA less than 10 ng/ml is a frequently required condition under which many AS protocols operate,⁸⁻¹¹ the current guideline may predispose patients at lower risk with incongruently elevated PSA to aggressive and potentially unnecessary therapies. Specifically urologists infrequently encounter patients with PSA greater than 10 ng/ml but in whom biopsy demonstrates relatively lower risk PCa. Therefore we hypothesized that AS may be a viable option in some men with histologically favorable risk PCa and serum PSA greater than 10 ng/ml.

To answer this question we investigated the rate of adverse oncologic features, specifically upgrading, up staging and biochemical recurrence, in men with serum PSA greater than 10 ng/ml but with biopsy findings consistent with indolent disease. In particular the aim of our study was to assess the risks of poor oncologic outcomes in men with serum PSA between

10 and 20 ng/ml by comparing them to risks in men with lower PSA (less than 10 ng/ml) and higher PSA (20 ng/ml or greater).

MATERIALS AND METHODS

Study Cohort

Under institutional review board approval we reviewed prospectively maintained databases of patients who underwent radical prostatectomy for localized PCa between November 2003 and January 2015 at 3 participating institutions, including Rutgers Cancer Institute of New Jersey, New Jersey, and Samsung Medical Center, Seoul and Seoul National University Bundang Hospital, Bundang, Republic of Korea. Men with histologically favorable risk PCa were categorized into 3 groups using the PSA cutoff values 10 and 20 ng/ml, including LP—less than 10 ng/ml, IP—10 or greater to less than 20 and LP—20 or greater.¹²

Definitions

Histologically favorable risk PCa was defined as 1) biopsy GS 6 or less, 2) 3 or fewer positive cores, 3) 50% or less cancer involvement in each core and 4) clinical stage T2a or less. This definition coincides with our institutional inclusion criteria for AS with the absence of PSA requirement. The terms very low risk and low risk were not used as it may interfere with the formal definition provided by NCCN® (National Comprehensive Cancer Network®).¹³

Up staging was defined as any change from clinical stage T2a or less to pathological stage T3-T4. Upgrading was defined as any increase in GS from biopsy to pathological specimen. Upgrading was divided into 2 groups, including any upgrading (GS 3 + 4 or higher) and stricter upgrading (GS 4 + 3 or higher).^{14,15} BCR was defined as rising PSA on 2 consecutive measurements with the last one greater than 0.2 ng/ml. PSAD was calculated in 683 patients using known pathological prostate weights with adjustment using the formula, (preoperative serum PSA/ [pathological prostate weight in gm — 7 gm for seminal vesicles]) as a proxy for volume measured by transrectal ultrasound.^{16,17} A PSAD threshold of 0.15 ng/ml/gm was used for risk stratification.¹³

Clinicopathological Parameters

Patient demographics (age, race, height and weight), preoperative parameters (serum PSA, derived PSA density, biopsy GS, number of positive cores, maximum percent of cancer in core and clinical stage) and postoperative parameters (pathological stage, pathological GS, positive surgical margins and followup PSA) were reviewed.

Statistical Analysis

The groups were compared using the chi-square test for categorical variables, and the t-test and ANOVA for continuous variables. Multivariate logistic regression analyses were performed using preoperative PSA and other relevant clinicopathological variables. Generalized linear mixed models with logit link and random intercept were used to account for the cluster effect of each participating institution. BCR was analyzed by the Kaplan-

Meier method with the log-rank test. All statistical analyses were done with SPSS®, version 21 SAS®, version 9.4 with 2-sided $p = 0.05$ considered significant.

RESULTS

A total of 1,327 patients were determined to have histologically favorable risk PCa. The patients included 354, 331 and 642 from Rutgers Cancer Institute of New Jersey, Samsung Medical Center and Seoul National University Bundang Hospital, respectively. There were 1,154 men in the LP group, 135 in the IP group and 38 in the HP group. Demographically the IP group was comparable to the LP group except the IP group had higher median age, lower BMI and a greater proportion of Asian patients. The IP and HP groups were similar in all demographic characteristics (supplementary table 1, <http://jurology.com/>).

Pathological Gleason score upgrading to 3 + 4 or greater was more frequently observed in the IP group than in the LP group (60.7% vs 49.5%, $p = 0.008$, table 1). However the rate of clinically significant Gleason score upgrading to 4 + 3 or greater did not significantly differ between the LP and IP groups (6.3% vs 8.1%, $p = 0.26$). In addition the rate of up staging did not differ significantly between the LP and IP groups. In contrast the HP group had a greater proportion of upgrading to Gleason score 4 + 3 or greater (21.1% vs 8.1%, $p = 0.03$) as well as up staging (pT3 or greater 21.1% vs 7.4%, $p = 0.02$) compared to the IP group. At a median followup of 32 months the BCR rate in the LP, IP and HP groups was 3.6%, 7.2% and 11.4%, respectively.

Univariate and multivariate logistic regression models adjusted for center effects were constructed based on age, race, BMI, the number of positive cores and PSA ranges. Supplementary table 2 (<http://jurology.com/>) shows that on univariate logistic regression analysis the number of positive cores, maximum percent of cancer involvement and PSA 20 ng/ml or greater were associated with up staging. In regard to upgrading to 3 + 4 or greater many variables had significant predictive value, including age, race, number of positive cores and maximum percent of cancer involvement. However, only age and PSA 20 ng/ml or greater had a significant association with upgrading to 4 + 3 or greater. None of these clinical variables predicted BCR.

The multivariate model revealed that higher age was predictive of upgrading to 3 + 4 or greater (OR 1.04, 95% CI 1.02-1.06, $p < 0.0001$) and to 4 + 3 or greater (OR 1.06, 95% CI 1.02-1.09, $p = 0.003$, table 2). Nonwhite race was also predictive of upgrading to 3 + 4 or greater (OR 2.03, 95% CI 1.22-3.40, $p = 0.007$). In addition having 3 positive cores was predictive of up staging (OR 2.56, 95% CI 1.61-4.08, $p < 0.0001$) and upgrading to 3 + 4 or greater (OR 1.75, 95% CI 1.27-2.41, $p = 0.001$). In the context of PSA only serum levels 20 ng/ml or greater were predictive of an adverse pathological outcome (table 2). Specifically compared to the IP the HP group had a higher incidence of up staging (OR 3.27, 95% CI 1.17-9.15, $p = 0.02$) and significant upgrading (4 + 3 or greater, OR 2.77, 95% CI 1.02-7.57, $p = 0.046$). In contrast compared to the LP group the IP group had a similar rate of upgrading and up staging. In terms of PSAD 128 of 135 men (97.7%) in the IP group and all 38 (100.0%) in the HP group had PSAD 0.15 ng/ml/gm or greater. These findings suggest

that PSAD has little discriminatory power in men with PSA greater than 10 ng/ml who are considering AS (table 3).

Finally when the BCR-free rate was analyzed with the Kaplan-Meier curve, a significant difference was observed when all 3 cohorts were assessed simultaneously ($p = 0.02$, see figure). However only the comparison between the HP and LP groups revealed a statistically significant difference ($p = 0.02$). Pairwise comparisons between the LP and IP groups, and between the IP and HP groups demonstrated no significant difference in the BCR-free rate ($p = 0.10$ and 0.97 , respectively).

DISCUSSION

In our study we attempted to characterize postoperative pathological and oncologic outcomes in men with histologically favorable risk PCa and serum PSA 10 ng/ml or greater. Our results demonstrated that the risk of up staging and significant upgrading was similar in patients with PSA 10 or greater but less than 20 (IP group) and those with PSA less than 10 ng/ml (LP group). However in patients with PSA 20 ng/ml or greater (HP group) the rates of up staging and significant upgrading were significantly higher than in the IP group (OR 3.27, 95% CI 1.17-9.15, $p = 0.02$ and OR 2.77, 95% CI 1.02-7.57, $p = 0.046$, respectively). Simultaneously pairwise comparisons demonstrated that the BCR-free rate was significantly lower in the HP group than in the LP group ($p = 0.02$).

Results of the current study advocate increasing the PSA cutoff to 20 ng/ml in men with lower risk PCa who are considering AS. To define low risk PCa in the context of AS a PSA cutoff value of 10 ng/ml is an almost universally accepted criterion. Yet elevated PSA in men with histologically favorable risk PCa may be due to concurrent prostatitis while benign prostatic hyperplasia may also cause an elevation.^{7,18} Indeed our results further support the notion that higher PSA may be attributable to subclinical benign prostatic hyperplasia because prostate weight between the LP group (PSA less than 10 ng/ml) and the IP plus HP groups (PSA 10 ng/ml or greater) was significantly different (41 vs 47 gm, $p = 0.007$, data not shown). Therefore while a PSA upper limit of 10 ng/ml provides a convenient diagnostic threshold for clinicians, it should not be a rigid requirement. PSA level should be considered an additional component of the AS protocol to allow for flexibility in selecting patients. When the overall clinical picture indicates low risk disease, patients with isolated and incongruent PSA increases up to 20 ng/ml should still be offered AS.

To improve PSA specificity PSAD has been extensively studied and validated across various AS criteria as a derived construct of PSA.¹³ In fact a group at The Johns Hopkins Medical Institutions used PSAD 0.15 ng/ml to select candidates for AS.¹⁹ In particular Faisal et al found that derived PSAD 0.15 ng/ml/gm or greater can be used to stratify individuals with more adverse oncologic characteristics in the group of patients with incongruently elevated PSA between 10 and 20 ng/ml.²⁰ Our study results indicate that the cutoff point of 0.15 ng/ml/gm was not sensitive for stratifying patients in the IP and HP groups. Given this lack of validation, a higher PSAD cutoff value may be more accurate to identify men with PSA greater than 10 ng/ml who are at greater oncologic risk.

Incongruently increased preoperative PSA in men with otherwise favorable risk PCa should not be an indication for invasive procedures. Similarly some experts have argued that AS should be expanded to include select patients with Gleason score 3 + 4.²¹ For example in cases of low volume Gleason 3 + 4 cancer with minimal (less than 5%) Gleason 4 involvement the biological cancer aggressiveness is comparable to that of Gleason 3 + 3 disease.²² While to our knowledge the definitive clinical benefit of such expansion remains to be determined, we have used upgrading to 3 + 4 or greater and to 4 + 3 or greater to assess the adverse pathological characteristics of different PSA groups. In fact in the PRIAS (Prostate Cancer Research International Active Surveillance) study 5-year BCR-free survival rates were similar for pathological GS 3 + 3 (94.4%) and 3 + 4 (92.2%).²³ While no statistical associations were observed in upgrading to 3 + 4 or greater between the PSA groups in our study, compared to the IP group the HP group was predictive of showing more incidences of upgrading to 4 + 3 or greater (OR 2.77, 95% CI 1.02-7.57, $p = 0.046$).

Our study has several important limitations. 1) Our retrospective design introduced selection bias and had a limited role in establishing causality. 2) A multicenter study spanning 3 institutions may have compromised consistency across subcohorts, although a generalized mixed linear model was used to compensate for the cluster effects present in a multi-institution study. Similarly the complicated interplay among age, race and BMI was not well explored since the discussion of these variables would be beyond the scope of our study. To account for the effect of race we performed race adjusted logistic regression analyses. 3) Our study cohort included 30 patients from 1 institution whose prostate specimens were analyzed based on the old scoring system prior to the modified 2005 ISUP (International Society of Urological Pathology) scoring system, introducing a source of systemic error. However given the small sample size of pre-2005 ISUP scores, this would have been unlikely to influence the result of the overall analysis. 4) Because our cohort consisted of patients with lower malignant potential who had a relatively short followup, only a small number of BCR events were projected to develop. Therefore it is feasible that any existing oncologic differences among the PSA groups may not have been captured in the current study.

With a growing population electing AS as management of lower risk PCa the benefits and limitations of preoperative PSA should be further clarified. Our study deals with a clinically practical concept but large-scale, prospective, randomized clinical trials are needed to validate our findings for clinical application.

CONCLUSIONS

Men with isolated elevation of preoperative PSA between 10 and 20 ng/ml who are otherwise considered to have histologically favorable risk PCa are not at a higher risk for adverse pathological and oncologic outcomes compared to men who qualify for AS. Therefore AS may be extended to carefully selected individuals with incongruently increased PSA between 10 and 20 ng/ml.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Abbreviations and Acronyms

AS	active surveillance
BCR	biochemical recurrence
BMI	body mass index
GS	Gleason score
HP	high PSA
IP	intermediate PSA
LP	low PSA
PCa	prostate cancer
PSA	prostate specific antigen
PSAD	PSA density

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Figure.

Kaplan-Meier analysis of BCR-free survival in LP, IP and HP groups

Table 1

Up staging, upgrading and BCR in patients with LP, IP and HP

	No. Pts (%)	No. LP (%)	No. IP (%)	No. HP (%)	p Value	
					LP vs IP	IP vs HP
Up staging (T3a or greater)	96 (7.2)	78 (6.8)	10 (7.4)	8 (21.1)	0.44	0.02
Upgrading:						
3 + 4 or Greater	680 (51.2)	571 (49.5)	82 (60.7)	27 (71.1)	0.008	0.17
4 + 3 or Greater	92 (6.9)	73 (6.3)	11 (8.1)	8 (21.1)	0.26	0.03
BCR *	53 (4.2)	40 (3.6)	9 (7.2)	4 (11.4)	0.05	0.31

* 1,266 patients with minimum 3-month followup.

Table 2
Multivariate logistic regression analysis of relevant parameters predicting up staging or upgrading

	Up staging		Upgrading to 3 + 4 or Greater		Upgrading to 4 + 3 or Greater	
	OR (95% CI)	p Value	OR (95% CI)	p Value	OR (95% CI)	p Value
Age	1.02 (0.99–1.05)	0.29	1.04 (1.02–1.06)	<0.0001 *	1.06 (1.02–1.09)	0.003 *
Race:						
White	Referent	–	Referent	–	Referent	–
Other	0.74 (0.42–1.30)	0.30	2.03 (1.22–3.40)	0.007 *	1.06 (0.45–2.51)	0.89
BMI	0.97 (0.90–1.04)	0.35	1.02 (0.98–1.06)	0.27	1.04 (0.97–1.11)	0.32
No. pos cores:						
1 or 2	Referent	–	Referent	–	Referent	–
3	2.56 (1.61–4.08)	<0.0001 *	1.75 (1.27–2.41)	0.001 *	1.50 (0.89–2.54)	0.13
Preop PSA:						
LP	0.93 (0.47–1.87)	0.84	0.75 (0.51–1.10)	0.14	0.73 (0.37–1.43)	0.35
IP	Referent	–	Referent	–	Referent	–
HP	3.27 (1.17–9.15)	0.02 *	1.38 (0.61–3.10)	0.44	2.77 (1.02–7.57)	0.046 *

* Statistically significant.

Table 3

PSAD

	No. PSAD (%)		Total No.
	Less Than 0.15 ng/ml/gm	0.15 ng/ml/gm or Greater	
LP	710 (61.6)	442 (38.4)	1,152
IP	7 (5.2)	128 (94.8)	135
HP	0	38 (100)	38
Totals	717	608	1,325