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Pathological Outcomes in Men with Low Risk and Very Low Risk Prostate Cancer: Implications on the Practice of Active Surveillance

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Abstract

Purpose—We assessed oncologic outcomes at surgery in men with low risk and very low risk prostate cancer who were candidates for active surveillance.

Materials and Methods—In a prospectively collected institutional database, we identified 7,486 subjects eligible for active surveillance who underwent radical retropubic prostatectomy. Candidates were designated as being at low risk (stage T1c/T2a, prostate specific antigen 10 ng/ml or less, and Gleason score 6 or less) or very low risk (stage T1c, prostate specific antigen density 0.15 or less, Gleason score 6 or less, 2 or fewer positive biopsy cores, 50% or less cancer involvement per core) based on preoperative data. Adverse findings were Gleason score upgrade (score 7 or greater) and nonorgan confined cancer on surgical pathology. The relative risk of adverse findings in men at low risk with very low risk disease was evaluated in a multivariate model using Poisson regression.

Results—A total of 7,333 subjects met the criteria for low risk disease and 153 had very low risk disease. The proportion of subjects at low risk found to have Gleason score upgrade or nonorgan confined cancer on final pathology was 21.8% and 23.1%, respectively. Corresponding values in those at very low risk were 13.1% and 8.5%, respectively. After adjusting for age, race, year of surgery, body mass index, and prostate specific antigen at diagnosis, the relative risk of Gleason score upgrade in men with low risk vs very low risk disease was 1.89 (95% CI 1.21–2.95). The relative risk of nonorgan confined cancer was 2.06 (95% CI 1.19–3.57).

Conclusions—Men with very low risk prostate cancer were at significantly lower risk for adverse findings at surgery compared to those with low risk disease. These data support the stratification of low risk cancer when selecting and counseling men who may be appropriate for active surveillance.

Keywords

prostate; prostatic neoplasms; risk; disease progression; treatment outcome

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Study received Johns Hopkins Medical Institutions institutional review board approval.

Since the early 1990s, the number of prostate cancer deaths occurring annually in the United States has fallen by approximately 40%.[1] Despite this, prostate cancer remains the second leading cause of cancer mortality in American men. Furthermore, improvements in mortality have come with significant costs. In recent years, multiple studies have demonstrated the increasing prevalence of men who are diagnosed with cancers that would not have become life threatening or otherwise problematic during their lifetime.[2,3] This over diagnosis often leads to unnecessary treatment, which may be associated with significant side effects and reduced quality of life.[4]

To address these concerns, attention has shifted to AS with curative intent as an alternative to immediate intervention.[5,6] This approach involves closely monitoring men with LR cancer using serial examinations, PSA measurement, and prostate biopsy, with treatment recommended at the first signs of higher risk disease.[7] Several institutions have reported their initial experiences with AS, and results have been largely encouraging.[8] Indeed, no report published to date has demonstrated a decreased likelihood of cure in men initially treated with surveillance compared to similar men who underwent immediate treatment.[9–11]

While AS appears to be a reasonable approach in some men with LR cancer, its widespread acceptance remains limited by a lack of consensus in defining appropriate candidates, an area that was identified by the National Institutes of Health as an important research question.[12] Current guidelines from the National Comprehensive Cancer Network® consider AS an option for otherwise healthy men with VLR or LR prostate cancer.[13]

However, there are limited data on whether VLR and LR classifications are associated with different pathological phenotypes that warrant consideration when counseling men regarding management. Using a prospectively collected institutional database, we compared pathological and prognostic outcomes in men with VLR and LR prostate cancer who underwent radical prostatectomy.

MATERIALS AND METHODS

Since January 1975, data have been prospectively collected on all subjects who underwent radical prostatectomy for prostate cancer at our institution. Complete or partial data were obtained on a total of 18,899 men, and stored in our institutional database. This study protocol was approved by the institutional review board at the Johns Hopkins Medical Institutions.

Subjects with VLR or LR cancer based on preoperative characteristics, including clinical stage, PSA, and prostate biopsy findings, were identified. Criteria for VLR disease were described previously by Epstein et al,[14] including stage T1c, PSA density 0.15 ng/ml/gm or less, GS 6 or less on biopsy, 2 or fewer positive cores on biopsy, 50% or less involvement of any core with cancer, and 12 or fewer cores sampled. Subjects with LR disease met certain criteria, including stage T1c/T2a, PSA 10 ng/ml or less, and GS 6 or less on biopsy.

Of the 18,899 records with complete or partial data, 7,552 men did not meet LR or VLR criteria and were excluded from the study. Of the 7,552 men who did not meet inclusion criteria, 5,006 (66.3%) had GS greater than 6, 2,493 (33.0%) had PSA greater than 10 ng/ml, and 2,333 (30.9%) had disease stage greater than T2a. Of the 11,347 remaining men, 2,324 could not be categorized by risk due to incomplete data. Baseline comparison of these subjects to the 9,023 with complete risk data revealed no significant difference in race or BMI. Men with incomplete data were slightly older (58.1 vs 57.5, $p < 0.001$), and had a later date of surgery (2001.3 vs 2001.8, $p = 0.002$) and higher PSA at diagnosis (5.9 vs 5.1, $p < 0.001$). Of the 9,023 subjects with complete risk data, an additional 1,537 lacked complete demographic data (race or BMI) and were excluded from the final study cohort.

A total of 7,486 subjects had complete data for baseline variables (year of surgery, age, race, PSA at diagnosis and BMI) and outcomes (GS upgrade and NOCC). Of these men, 153 (2.0%) and 7,333 (98.0%) were classified as having VLR and LR disease, respectively. Subjects classified with LR disease met all LR criteria and could be definitively excluded from VLR classification based on at least 1 criterion (ie number of biopsy cores obtained, number of positive biopsy cores, percent cancer involvement per biopsy core and/or PSA density). In such cases, these subjects did not require data on all VLR criteria. GS upgrade was defined as a change from GS 6 or less on biopsy to GS 7 or greater on surgical pathology.

Statistical Analysis

Study group characteristics were compared between the VLR and LR groups using the t test in cases of equal variance or the t test with the Satterthwaite approximation for df in cases of unequal variance. Race was treated as a dichotomous variable (white and nonwhite) and compared between risk groups using the chi-square test. The primary outcomes assessed were adverse pathological features, defined as GS upgrade and NOCC.

The proportion of patients with GS upgrade or NOCC after surgery was calculated for the VLR and LR groups, and compared using the Fisher exact test. Multivariate models were constructed using Poisson regression to assess the relative risk of adverse pathological outcomes (GS upgrade and NOCC) in the LR vs VLR group after adjusting for year of surgery, age, race, PSA at diagnosis, and BMI. All statistical tests were 2-sided and $p < 0.05$ was considered statistically significant.

RESULTS

Table 1 lists demographic characteristics for the overall cohort and risk classification groups. The majority of subjects were white (89.5%), while 10.5% were nonwhite. Compared to VLR subjects, LR subjects had a similar mean PSA at diagnosis ($p = 0.085$) and BMI ($p = 0.200$). However, LR subjects were significantly younger ($p = 0.004$) and more commonly white ($p = 0.035$) than VLR subjects. Also, men with VLR disease underwent surgery significantly later than LR subjects, with a mean year of surgery of 2005.4 and 2000.6, respectively ($p < 0.001$).

Table 2 lists the number and proportion of men who were found to have adverse pathological outcomes after surgery. GS upgrade (GS 7 or greater) was observed in a significantly higher proportion of men with LR disease than those with VLR disease (21.8% vs. 13.1%, $p = 0.010$). Of those with GS upgrade, 86.7% were upgraded to GS 3 + 4 = 7. This proportion was similar between the LR and VLR groups (86.6% vs 90.0%, $p = 1.000$). Notably, 57 men (0.8%) from the LR group were upgraded to GS 8 and 29 (0.4%) were upgraded to GS 9, while no men from the VLR group were upgraded to GS 8 or 9. With regard to organ confined disease, a higher proportion of men considered at LR were found to have NOCC compared to the VLR group (23.1% vs 8.5%, $p < 0.001$).

In a multivariate model of GS upgrading, the relative risk of upgrading increased with more recent year of surgery as well as increased age, PSA at diagnosis, and BMI, while white subjects were less likely to undergo upgrading. After adjustment for these variables, patients with LR disease were 1.89 times more likely to undergo pathological GS upgrading than men with VLR disease (table 3).

In the multivariate model for NOCC, the relative risk of NOCC was higher with increasing age, PSA at diagnosis, and BMI. However, more recent year of surgery was associated with a decreased risk of NOCC. After adjustment for these covariates, LR disease was associated

with a 2.06 times greater likelihood of finding NOCC on pathological evaluation compared to men with VLR disease (table 3).

DISCUSSION

Since the introduction of PSA based screening, there has been increasing concern regarding the over diagnosis of nonthreatening prostate cancers.[15] Previous studies indicated that preventing 1 death due to prostate cancer may require active treatment of 12 to 48 men diagnosed.[16,17] AS with curative intent is a management strategy that may help reduce the number of men unnecessarily treated. Multiple institutions have reported their experiences with surveillance, and aggregate data reveal prostate cancer specific survival ranging from 97% to 100% after short-term to intermediate term followup.[18,19] However, identifying appropriate candidates for surveillance remains controversial, as existing programs vary in criteria for enrollment.[19]

Accurate measurement and assessment of risk is critical to the practice of AS. The vast majority of published surveillance cohorts use some proxy for the biological potential of the cancer, for example histological grade (ie GS) and tumor volume (ie number of positive biopsy cores and percent of tumor involvement within each core), in addition to other factors, when identifying the level of risk. There is general agreement that surveillance should be limited to men with low grade cancers, and the vast majority of programs exclude otherwise healthy men with GS 7 or higher disease. More recently, a distinction has been made among low grade cancers, identifying VLR and LR disease as separate entities.[20] This distinction draws attention to the possibility that men with GS 6 or less prostate cancer have significant differences in the risk of subsequent adverse outcomes.

Among men enrolled in AS (GS 6 or less), we previously noted that those meeting VLR criteria were less likely than patients at LR to be reclassified with higher risk disease during followup biopsy and less likely to undergo treatment.[9] Further evidence that men with VLR disease may be safer candidates for surveillance, as judged by the rate of upgrading on surveillance biopsies, is seen throughout the literature.[8] In our program, which emphasizes VLR, the rate of GS upgrading on serial biopsies was found to be less than 10% annually. In a separate cohort including mostly LR disease, the rate of upgrading ranged from 20% to 30% per biopsy.[21] Similar differences were observed in long-term outcomes. In AS patients who ultimately underwent treatment, the proportion of men experiencing biochemical recurrence in our program was lower than that of cohorts without an emphasis on VLR disease.[18,22] Indeed, it appears that an emphasis on VLR disease may result in a lower rate of adverse outcomes during followup. We believe that this distinction is important in the selection of candidates, especially when attempting to assess the safety of surveillance in a man with a 15 to 20-year life expectancy or more whose preference is to avoid the complications of prostate cancer treatment.

The proportion of men with VLR disease in our cohort who were found to have GS upgrade was 13.1%. This is less than the 23% observed by Conti et al in their cohort of 42 men who met the VLR criteria.[23] Variation between these cohorts is accounted for by the limited sample size, as few men are diagnosed with VLR disease and still fewer elect surgery. However, the proportion of men found to have NOCC was similar between these 2 cohorts. We observed that 8.5% of men had NOCC, while their cohort reported 7% with extracapsular extension and 2% with seminal vesical invasion. As additional data emerge, the likelihood of adverse pathological findings in men with VLR disease can be more accurately projected.

Given the prolonged time course from prostate cancer diagnosis to death,[24] we propose that pathological upgrade after surgery may serve as a proxy for long-term outcomes in patients eligible for AS. Indeed, we found that men with VLR disease had lower rates of GS upgrading and NOCC on final pathological findings compared to those with LR disease. Considering year of surgery, age, race, PSA at diagnosis, and BMI, men with LR disease were approximately twice as likely to have pathological GS upgrade or NOCC compared to those with VLR. Furthermore, although upgrade to GS 8 or 9 was extremely rare in each risk group, a small proportion of men at LR had GS 8 or 9, while no men from the VLR group had GS greater than 7. It is important to note that, although GS upgrade and NOCC are associated with long-term outcomes, these factors are not surrogates for prostate cancer specific survival and, thus, they should be interpreted with caution.[25] With appropriate followup in AS programs, subjects initially classified as at LR due to under sampling can be identified as at higher risk before surgery, thus, avoiding compromising surveillance outcome data.

Despite the promise shown by AS programs to this point, the greatest risk remains the possibility of misclassification of the cancer or missing a high risk cancer due to under sampling on prostate biopsy. This is particularly worrisome in men with a life expectancy of greater than 10 to 15 years. In recent years, we have made progress toward identifying the best candidates for AS and decreasing the rate of misclassification. To reduce the risk of under sampling, we added transition zone sampling to our surveillance biopsy protocol beginning in 2009. Similarly, other programs have added repeat diagnostic biopsy or saturation biopsy to their protocol.[26,27] Furthermore, emerging data indicate that demographic factors such as race or BMI may help differentiate better candidates for surveillance.[28] Eventually, advances in imaging or biomarkers may play a role in improving patient selection and monitoring.[29]

There are limitations of this analysis. 1) A relatively small number of men had VLR disease. In addition to knowledge that VLR disease is less prevalent than LR disease among men diagnosed with prostate cancer, this can be explained by our belief that AS is particularly appropriate for men with VLR classification. Therefore, few men with VLR disease have undergone surgery at our institution, especially if older.[30] 2) Some men were excluded from the analysis because of missing data. Notably, men with and without missing data were similar with respect to key variables. 3) The overwhelming majority of patients were white, and our findings should be interpreted with caution in men of other races. 4) It is important to note that a contemporary pathology review was not performed. 5) As mentioned, longer term followup will be needed to verify whether our findings apply to cancer specific outcomes.

Ultimately, AS has shown great promise in reducing overtreatment of prostate cancer. While many patients with low grade disease may be appropriate for AS, it is important that we identify differences in risk among potential candidates so that we may inform patients fully and counsel them appropriately. This seems particularly relevant in younger men without comorbidities and a life expectancy of greater than 15 to 20 years, for whom a diagnosis of LR disease is not always associated with low volume, low grade disease.

CONCLUSIONS

The likelihood of a more aggressive pathological phenotype differs among men with LR and VLR prostate cancer who are eligible for AS. This may provide additional guidance in identifying subjects most appropriate for surveillance and counseling those men considering surveillance as an alternative to immediate curative intervention.

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Abbreviations and Acronyms

AS	active surveillance
BMI	body mass index
GS	Gleason score
LR	low risk
NOCC	nonorgan confined cancer
PSA	prostate specific antigen
VLR	very LR

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Table 1

Study group characteristics

	Overall	VLR	LR	p Value
No. men	7,486	153	7,333	
Mean ± SD age	57.3 ± 6.4	58.8 ± 6.0	57.3 ± 6.4	0.004
No. race (%):				0.035
White	6,699 (89.5)	129 (84.3)	6,570 (89.6)	
Nonwhite	787 (10.5)	24 (15.7)	763 (10.4)	
Mean ± SD surgery yr	2000.7 ± 5.2	2005.4 ± 3.2	2000.6 ± 5.2	<0.001
Mean ± SD BMI (kg/m^2)	26.9 ± 3.4	27.3 ± 3.3	26.9 ± 3.4	0.200
Mean ± SD PSA at diagnosis (ng/ml)	5.2 ± 2.2	4.9 ± 2.1	5.2 ± 2.2	0.085
Mean ± SD No. biopsy cores:				
Obtained	12.2 ± 3.6	12.7 ± 2.3	12.1 ± 3.8 (804 men)*	0.009
Pos	2.9 ± 2.0	1.4 ± 0.5	2.9 ± 2.0 (2,857 men)*	<0.001
Mean ± SD % Ca involvement/core	45.6 ± 28.7	20.1 ± 14.5	47.1 ± 28.7 (2,543 men)*	<0.001
Mean ± SD PSA density (units)	0.103 ± 0.054	0.081 ± 0.032	0.103 ± 0.054 (7,031 men)*	<0.001

*Sample size differs from that of total LR cohort since VLR disease specific data were not available on all men with LR disease.

Table 2

Adverse pathological outcomes

	No. VLR (%)	No. LR (%)	p Value
GS upgrade:			0.010
Yes	20 (13.1)	1,600 (21.8)	
No	133 (86.9)	5,733 (78.2)	
Disease:			<0.001
NOCC	13 (8.5)	1,693 (23.1)	
Organ confined	140 (91.5)	5,640 (76.9)	

Table 3

Multivariate model for GS upgrade and NOCC

	Relative Risk (95% CI)	p Value
GS upgrade:		
Surgery yr	1.02 (1.01–1.03)	<0.001
Age	1.04 (1.03–1.04)	<0.001
White race	0.81 (0.70–0.94)	0.006
PSA at diagnosis	1.12 (1.10–1.15)	<0.001
BMI	1.02 (1.00–1.03)	0.035
LR disease (vs VLR)	1.89 (1.21–2.95)	0.005
NOCC:		
Surgery yr	0.95 (0.94–0.95)	<0.001
Age	1.02 (1.01–1.03)	<0.001
White race	1.04 (0.88–1.23)	0.613
PSA at diagnosis	1.10 (1.08–1.12)	<0.001
BMI	1.04 (1.02–1.05)	<0.001
LR disease (vs VLR)	2.06 (1.19–3.57)	0.010