The clinical and pathological history of prostate cancer progression in men with a prior history of high grade prostatic intraepithelial neoplasia

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Objectives: *The natural history of high grade prostatic intraepithelial neoplasia (HGPIN) is incompletely understood limiting evidence based recommendations regarding screening and repeat biopsy intervals. Our objective was to evaluate the natural history of HGPIN to better assess the time frame to disease progression and the pathological findings at the time of progression to cancer.*
Methods and materials: We retrospectively reviewed 74 consecutive patients with an initial diagnosis of HGPIN. The number and timing of all biopsies leading to the diagnosis of cancer were assessed. Clinical and pathological features of those patients with eventual disease progression were evaluated.

Results: *The mean number of biopsies performed before subsequent cancer diagnosis was 5 (range: 3-13). The mean time to the diagnosis of cancer was 29 months (range: 7-83). Men with a history of HGPIN had lower percent positive biopsies at the time of cancer diagnosis ($p < 0.001$) and smaller volume tumors on final pathology ($p = 0.041$) compared to men without a history of HGPIN.*
Conclusions: *Patients with an initial diagnosis of HGPIN on transrectal ultrasound (TRUS) guided biopsy progressed to cancer at a mean of 29 months. The vast majority of patients that progressed to prostate cancer had low volume disease at the time of diagnosis and definitive treatment. Our data indicate the importance of re-evaluation in HGPIN patients and suggest a trend toward low volume disease in carefully followed patients. Prospective data is warranted to adequately define an evidence based biopsy regimen in men with HGPIN.*

Key Words: prostate cancer, prostatic intraepithelial neoplasia, tumor volume

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Introduction

Prostatic intraepithelial neoplasia (PIN) consists of cytologically atypical cells within a preserved ductacinar architecture and was first described in 1987.[1] PIN is classified either as low grade (LGPIN) or high grade (HGPIN) based on microscopic analysis. Several studies have suggested a link between HGPIN and

the subsequent development of prostate cancer based on the findings of HGPIN more commonly in the peripheral zone of the prostate, microscopic foci of prostate cancer arising adjacent to areas of HGPIN, similar biomarker expression between HGPIN and prostate cancer, and the multifocal nature of both HGPIN and prostate cancer.[2-4]

HGPIN at the time of prostate needle biopsy is a widely accepted risk factor for the subsequent diagnosis of prostate cancer.[5-7] Early studies estimated the risk of prostate cancer to be as high as 27%-79% in men with a prior history of HGPIN.[8] More recent studies have demonstrated the risk of prostate cancer with a prior history of HGPIN to be between 25%-30%, calling into question the exact significance of the diagnosis of HGPIN.[8-10] In light of these most recent studies, formal recommendations for the timing and need for repeat biopsies in men with an initial diagnosis of HGPIN have become less clear. The objective of this study was to evaluate the antecedent natural history of HGPIN in a well documented radical prostatectomy data base to better assess the time frame to disease progression and the pathological findings demonstrated with the evolution of frank prostate cancer.

Materials and methods

With institutional review board approval, we retrospectively reviewed the University of Pennsylvania radical prostatectomy series for those patients who demonstrated a diagnosis of HGPIN on initial biopsy. This database consists of 2117 patients who underwent radical prostatectomy from 1991-2005 for clinically localized prostate cancer. Of the 2117 patients in this database, 53 (2.5%) were identified who had an initial diagnosis of HGPIN prior to the development of prostate cancer. Twenty-one additional patients with an initial diagnosis of HGPIN who went onto develop prostate cancer, but were not treated surgically were also included in the HGPIN cohort, (13 treated with radiation, 8 with no treatment) for a total of 74 evaluable patients. All patients with HGPIN underwent repeat 12 core biopsy within 3 months of their initial biopsy to exclude a missed diagnosis of prostate cancer at the time of original HGPIN diagnosis. Indication for initial prostate biopsy in all cases was either an elevated prostate-specific antigen (PSA) or abnormal digital rectal exam.

All biopsy slides and radical prostatectomy specimens were reviewed at our institution under the direction of a genitourinary pathologist. HGPIN was diagnosed according to our institution's protocol, which is in line with standard accepted criteria.[11] The percentage of positive biopsies with prostate cancer was calculated by dividing the number of positive biopsies by the total number of biopsies and then multiplied by one hundred. Final estimated tumor volume in each radical prostatectomy specimen was calculated according to our institution's previously published protocol.[12] The number of cores sampled could not be determined for three patients in the HGPIN cohort, which excluded the evaluation of percent of positive biopsies in those patients. Evaluated clinical features included age, number of biopsies between HGPIN diagnosis until prostate cancer diagnosis, time from HGPIN diagnosis until prostate cancer diagnosis, biopsy and final Gleason score, presence of extracapsular extension, margin status and lymph node status.

The percent of positive biopsy cores were compared between the 74 patients with a prior history of HGPIN and those without a prior history. Final tumor volume at the time of radical prostatectomy in the HGPIN patients who subsequently developed prostate cancer and underwent a radical prostatectomy were compared to those without a prior history of HGPIN. Biopsy and pathological Gleason score were not available in 39 and 29 patients in the control population. Percent of positive biopsy and estimated tumor volume data were not available in 344 and 104 patients respectively in the control population, excluding them from analysis. The Chi-squared test was used to compare final tumor volumes and percent of positive biopsies for patients with prostate cancer and a history of HGPIN versus those without a prior history of HGPIN. P-values of < 0.05 were considered statistically significant. Statistical analysis was performed using Stata version nine (StataCorp LP 1996-2007, College Station, Texas).

TABLE 1. **Clinical features of 74 HGPIN patients who progressed to prostate cancer**

Age	
HGPIN, years (range)	62 (44-82)
Prostate cancer, years (range)	64 (44-83)
Race	
Caucasian	59 (79.7%)
African American	8 (10.8%)
Other	7 (9.5%)
BMI, (range)	27.4 (21.5-40.2)
Family history	
Yes	14 (19%)
No	60 (81%)
PSA	
HGPIN, (range)	6.7 (1.2-22.3)
Prostate cancer, (range)	8.8 (0.4-42.0)

Values reported as means

Results

The clinical features of the 74 patients with a history of HGPIN are illustrated in Table 1. Of the 74 patients included in our study, mean age at the time of HGPIN diagnosis was 62 years (range: 44-82) and 64 years (44-83) at the time of prostate cancer diagnosis. Median follow up was 60 months. Patients with a prior history of HGPIN that progressed to prostate cancer did so at a mean of 29 months (range: 7-83). The mean number of biopsies between the initial diagnosis of HGPIN and prostate cancer was 5 (range: 3-13). The mean PSA at the time of HGPIN diagnosis was 6.4 ng/ml (range: 1.2-22.3) compared to 8.8 ng/ml (range: 0.4-42.0) at the time of prostate cancer diagnosis ($p = 0.03$). The serum PSA at the time of prostate cancer diagnosis was lower than the PSA at the time of HGPIN diagnosis in 16 (22%) men. Ten (13.5%) additional men had an absolute PSA increase of ≤ 1.0 ng/ml at the time of prostate cancer diagnosis.

Sixty-four (86%) patients were diagnosed with Gleason score 6 prostate cancer on prostate needle biopsy, with only nine (12%) patients having Gleason score 7 or greater prostate cancer at the time of needle biopsy. Of the 53 patients that went on to radical prostatectomy, a significant percentage were upgraded to higher Gleason scores. Thirty-six (68%) patients had Gleason score 6 or less prostate cancer on final pathology and 17 (32%) had Gleason score 7 or greater prostate cancer, Table 2. Seven (13%) patients had extracapsular extension evident on final pathological review and six (11%) patients had a positive surgical margin.

An overwhelming majority of the patients with a prior history of HGPIN had low volume disease. Sixty-seven (91%) patients had $\leq$16.6% positive biopsy cores at the time of cancer diagnosis, and no patient had > 33.3% positive biopsies. In contrast, prostate cancer patients without a prior history of HGPIN had a significantly higher rates of percent

TABLE 2. **Pathologic characteristics of patients with a history of HGPIN and those without a history of HGPIN prior to radical prostatectomy**

	HGPIN (n = 53)	**RRP (n = 2064)**
Biopsy Gleason score		
5	1 (1.4%)	282 (13.9%)
6	64 (86.5%)	1158 (57.2%)
7	7 (9.5%)	464 (22.9%)
8	1 (1.4%)	89 (4.4%)
9	1 (1.4%)	31(1.5%)
10	0 (0%)	1 (0.05%)
RRP Gleason score		
5	2 (3.8%)	194 (9.5%)
6	34 (64.2%)	885 (43.5%)
7	13 (24.5%)	796 (39.1%)
8	2 (3.8%)	86 (4.2%)
9	2 (3.8%)	71 (3.5%)
10	0 (0%)	3 (0.15%)
Percent positive biopsies		
< 16.67%	**67 (91%)**	**677 (39.4%)**
16.67%-33.3%	**7 (9%)**	**478 (27.8%)**
33.3-50%	**0 (0%)**	**304 (17.7%)**
> 50%	**0 (0%)**	**261 (15.2%)**
Estimated tumor volume (RRP)		
< 2%	21 (40%)	405 (20.7%)
2%-10%	17 (32%)	758 (38.6%)
11%-25%	8 (16%)	511 (26.1%)
26%-50%	7 (14%)	229 (11.7%)
> 50%	0 (0%)	58 (2.9%)

HGPIN = high grade prostatic intraepithelial neoplasia; RRP = radical retropubic prostatectomy

positive biopsies at the time of diagnosis with only 41% having ≤ 16.6% positive biopsies and 15% having > 50% positive biopsies at the time of TRUS sampling ($p < 0.001$). Forty-three (86%) men with a prior history of HGPIN had estimated tumor volumes of less than 25% on final pathological review and no patient had an estimated tumor volume of > 50%, Table 2. Patients with a prior history of HGPIN had significantly smaller estimated tumor volumes in their RRP specimens than those without a prior history of HGPIN ($p = 0.041$).

Discussion

The exact significance of HGPIN diagnosed by prostate needle biopsy continues to be debated in the literature. Initial studies had estimated the likelihood of finding prostate cancer on repeat biopsy as high as 79% in some series.[8,13] Larger and more recent studies suggest the risk of prostate cancer to be closer to 23%-32%.[9,10,13-15] Furthermore, several studies have demonstrated no significant risk of prostate cancer on repeat biopsy.[8,16] Increased tissue sampling at the time of TRUS guided biopsy has most likely accounted for the decreasing cancer rates in repeat biopsy samples.[5,10,17] This increased tissue sampling at the time of initial biopsy (with ≥ 12 cores) theoretically decreases the risk of under sampling and thus missing cancers in proximity to areas of HGPIN at the time of initial biopsy.[5,10,18,19] Additionally, the number of repeat biopsies performed and the timing of biopsies varies from series to series which could also potentially have had an impact on cancer detection rates between series.

There currently is no evidence based recommendation regarding a follow up strategy in patients with HGPIN. Our series of patients progressed to prostate cancer after an initial diagnosis of HGPIN at a mean time of 29 months. Additionally, a mean number of five biopsies were required before a progression to cancer was detected. We believe this data highlights the importance of follow-up in this patient population beyond an early single repeat biopsy. Data supporting the limited utility of an early repeat biopsy in patients adequately sampled at the time of initial biopsy has been reported by Lefkowitz et al, who found only a 2.3% cancer detection rate on immediate repeat biopsy in men diagnosed with HGPIN who initially underwent a 12 core biopsy.[20] In a separate publication, the same authors reported a 25.8% positive biopsy rate for men with a history of HGPIN who underwent repeat biopsy at 3 years from initial diagnosis.[21] The question of the exact timing and number of biopsies remains unanswered, but it appears that if an initial 12 core biopsy is performed, subjecting patients to multiple biopsies within the first 2 years is unnecessary and likely adds morbidity. Although a repeat biopsy within the first year of diagnosis of HGPIN is likely unnecessary, our findings and that of Lefkowitz et al suggest a repeat biopsy between 24 and 36 months is likely warranted. Further evidence for follow-up beyond an initial repeat biopsy has also recently been demonstrated by Gokden et al who found that three biopsy sessions were required to detect 88% of the carcinomas following a diagnosis of HGPIN.[10] A prospectively validated biopsy regimen with regard to both the timing and number of subsequent biopsies in patients with a history of HGPIN is needed. Eliminating unnecessary biopsies in this subset of men would reduce patient anxiety, morbidity and overall cost to the health care system.

Unfortunately, serum PSA was not a reliable predictor of prostate cancer progression in our cohort. Although the 74 men in our HGPIN cohort had a statistically significant higher serum PSA as a group at the time of prostate cancer diagnosis, we believe this statistic is misleading. On closer analysis of the data more than a third of the patients (35.5%) had ≤ 1.0 ng/ml change in their serum PSA from the time of HGPIN diagnosis to prostate cancer progression. Furthermore 22% of the patients actually had a decrease in their serum PSA. This data highlights the short coming of using PSA kinetics as a sole indicator of repeat biopsy in this patient population. Although an increased PSA velocity should trigger a repeat biopsy in this patient population (as it would in a standard population), our data demonstrate the PSA stability alone does not correlate with freedom from progression to prostate cancer.

Histologically, there was a significant increase in the number of Gleason score 7 or greater cancers found at the time of radical prostatectomy. Of the 53 patients that went on to surgery 32% had Gleason score 7 disease or greater compared to only 12% at the time of prostate needle biopsy. This upgrading in Gleason score most likely represents a sampling error at the time of TRUS guided biopsy, but highlights the potential for high grade cancers in the HGPIN population. Interestingly, the vast majority of patients that progressed to cancer had low volume cancers either on the basis of percent of positive biopsy or estimated tumor volume on final pathology. No patient who progressed to cancer had a percent positive biopsy of > 33%. Percent of positive biopsies is a well documented surrogate for biochemical failure following definitive treatment for prostate cancer. Although due to the retrospective nature of this analysis it is impossible to draw any definitive

conclusions, one could speculate that close follow-up in patients with HGPIN could lead to detection of prostate cancers with smaller tumor burdens potentially increasing the likelihood of curing patients with definitive therapy. Eighty-six percent of the patients that went on to radical prostatectomy had estimated tumor volumes of < 25% on final pathology and no patient had an estimated tumor volume exceeding 50%. This data again suggests that with careful follow-up, patients with HGPIN may be diagnosed with prostate cancer at a more potentially curable stage. The exact timing and nature of follow-up in this patient population is currently unknown and requires further examination.

There are several limitations to this current study which merit attention. This is a retrospective analysis of a cohort of patients with a history of HGPIN who subsequently developed prostate cancer which in turn limits definitive conclusions. HGPIN patients were not followed prospectively in this series, and only data on those who developed prostate cancer was available therefore conclusions regarding the exact risk of prostate cancer in our patient cohort is impossible to surmise. Further prospective studies in men with HGPIN are needed in order to definitively characterize the absolute risk of prostate cancer and the appropriate timing of repeat biopsy. Despite these limitations, valuable information regarding the natural history of HGPIN can still be gleaned from this study population.

Conclusion

Patients with an initial diagnosis of HGPIN on TRUS guided biopsy progressed to cancer at a mean of 29 months. The vast majority of patients that progressed to prostate cancer had low volume disease at the time of diagnosis and definitive treatment. Our data indicate the importance of re-evaluation in HGPIN patients and suggest a trend toward low volume disease in carefully followed patients. Prospective data is warranted to adequately define an evidence based biopsy regimen in men with HGPIN. □

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EDITORIAL COMMENT

The inherent value of this paper is that it focuses attention on the problematic relationship between high grade prostatic intraepithelial neoplasia (HGPIN) and prostate cancer. This paper cannot resolve the question whether HGPIN is the harbinger of eventual prostate cancer, because, as the authors point out, it is NOT a prospective evaluation of all patients with the initial diagnosis of HGPIN.

The paper does conclude that men with a history of HGPIN have lower percent of positive biopsies and smaller tumor volumes at the time of the discovery of prostate cancer, compared to men whose cancer is detected at the initial biopsy. In order to find cancer, men were biopsied 3 to 13 times over a period of 7 to 83 months.

However, the reader should be cautioned against making too much of this relationship between HGPIN and the presence of lower volume disease on eventual discovery. The appropriate control group of men who are found to have prostate cancer on subsequent biopsy, when the original biopsy did NOT contain HGPIN, has not been included in this study. The observations described herein may be simply due to a selection bias: Men with higher volume disease are found on initial biopsy, whereas men with lower volume disease may need multiple biopsies to have their disease discovered, or simply progress with time to the point that their disease volume reaches the threshold of detection.

Simply put, if we biopsy any given patient often enough, with the passage of time, eventually we will find that elusive prostate cancer.

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