Prostate cancer after initial high-grade prostatic intraepithelial neoplasia and benign prostate biopsy

Premal Patel, MD,[1] Jasmir G. Nayak, MD,[1,2] Zlatica Biljetina, MD,[4] Bryan Donnelly, MD[3], Kiril Trpkov, MD[4]

[1]Section of Urology, University of Manitoba, Winnipeg, Manitoba, Canada
[2]Department of Urology, University of Washington Medical Center, Seattle, Washington, USA
[3]Division of Urology, Alberta Health Services, Calgary, Alberta, Canada
[4]Calgary Laboratory Services and University of Calgary, Calgary, Alberta, Canada

PATEL P, NAYAK JG, BILJETINA Z, DONNELLY B, TRPKOV K. Prostate cancer after initial high-grade prostatic intraepithelial neoplasia and benign prostate biopsy. *Can J Urol* 2015;22(6):8056-8062.

Introduction: *Limited data exist on long term pathological outcomes in patients with initial prostate biopsies showing either high-grade intraepithelial neoplasia (HGPIN) or benign findings, who are subsequently diagnosed with prostate cancer.*

Materials and methods: *Preoperative characteristics of patients showing either HGPIN or benign initial prostate biopsies were investigated and compared in patients with and without a subsequent diagnosis of prostate cancer. We also compared the biopsy and prostatectomy findings in patients with prostate cancer in both groups.*

Results: *We evaluated 161 and 85 patients with initial HGPIN and benign prostate biopsies, respectively, who underwent a subsequent biopsy. After a median follow up of 11 years, prostate cancer was detected in 26.7% patients after HGPIN and in 22.3% patients after initial benign biopsy. Ninety-eight percent of positive biopsies after initial HGPIN demonstrated either Gleason score (GS) 3 + 3 (86%) or GS 3 + 4 (12%). In the benign group, 100% of patients demonstrated prostate cancer on biopsy with either GS 3 + 3 (58%) or GS 3 + 4 (42%). Of 35 patients who underwent prostatectomy (22 after initial HGPIN biopsy and 13 after initial benign biopsy), all had node negative, organ-confined disease; 86% and 54% patients had GS6 disease, with ≤ 5% tumor volume found in 91% and 62% of the HGPIN and benign group, respectively.*

Conclusions: *Patients with initial HGPIN or benign biopsies preceding a diagnosis of prostate cancer usually show favourable pathology on positive biopsy and prostatectomy, most commonly exhibiting low volume and low grade disease. These findings may help clinicians risk-stratify patients who may benefit from conservative management options.*

Key Words: high-grade prostatic intraepithelial neoplasia, HGPIN, radical prostatectomy, prostate biopsy, insignificant prostate cancer

Introduction

High-grade prostatic intraepithelial neoplasia (HGPIN) is a preneoplastic lesion characterized by atypical cells lining the architecturally benign prostatic acini and ducts.[1,2] According to the literature review by Epstein and Herawi, the incidence of HGPIN on extended prostate needle biopsy with 10 or more cores ranged between 2.5% and 20.2%.[1] Following an initial diagnosis of HGPIN, the risk of prostate cancer on repeated extended prostate biopsy was between 2.3% and 44.7%.[1,3-6] To determine whether there is a true increased risk for prostate cancer in patients initially diagnosed with HGPIN, requires a comparison to patients with initial benign biopsies, who are subsequently diagnosed with prostate cancer. The majority of studies that compared the cancer risk for patients with an initial HGPIN and benign biopsy demonstrated no significant cancer risk difference between the groups.[5,7-10]

Accepted for publication September 2015

Acknowledgment
We thank James Zhang, MSc, who assisted with the statistical analysis.

Address correspondence to Dr. Kiril Trpkov, Department of Pathology and Laboratory Medicine, Calgary Laboratory Services and University of Calgary, Rockyview General Hospital, 7007 14 Street, Calgary, AB T2V 1P9 Canada

There is also a paucity of literature describing the final pathological outcomes in patients with an initial HGPIN biopsy, who are diagnosed with prostate cancer on follow up biopsy and ultimately undergo radical prostatectomy.[5,6,11-13] Similarly, the clinical significance of initial benign biopsy is unclear regarding the final pathological outcomes. Certainly, it is not uncommon for patients to undergo a repeat biopsy after an initial negative biopsy, often for changes in prostate specific antigen (PSA) kinetics or abnormal rectal exam findings; yet the impact of the initial negative biopsy on outcomes is unclear.

We sought to evaluate the biopsy and prostatectomy pathological characteristics of prostate cancer in patients with an initial biopsy showing either HGPIN or benign findings. Additionally, we compared the preoperative biopsy and other findings in these patients to those who did not exhibit prostate cancer on follow up biopsy.

Materials and methods

During a 24 month period (July 2000 to June 2002), we identified 161 patients with an initial diagnosis of HGPIN on prostate biopsy and 85 patients with initial benign biopsy findings. All included patients were consecutive patients in which a diagnosis of 'HGPIN' only or 'benign' was rendered on needle biopsy and all patients underwent at least one repeat biopsy at our institution. None of the patients with HGPIN showed either atypical or suspicious biopsy findings. For patients with initial HGPIN on biopsy, our institutional practice at that time was to repeat the biopsy (usually within 12-24 months), but strict protocol regarding the timing of the repeat biopsy was not followed and was at the discretion of the urologist. In patients with an initial benign biopsy, the indication for repeat biopsy was typically due to changes in PSA kinetics or changes in the clinical exam findings; however, no strict criteria were used to trigger the follow up biopsy. During the study period, the annual volume of prostate biopsies performed in our institution with centralized regional urology service was between 1200-1400 biopsies. Both the initial and the repeat biopsies were performed using a transrectal ultrasound guidance with a standard 10-core sampling with site-specific submission (2 cores from the base and mid zones, 1 core from the apex, bilaterally), by four dedicated radiologists. The biopsies were reported using a site-specific synoptic template, by four dedicated surgical pathologists with interest in genitourinary pathology. Patient age, gland volume, PSA, PSA density, number of biopsy sites/locations with HGPIN, biopsy Gleason score (GS), number of positive cores, percentage of cancer involvement, and pathology findings on prostatectomy were extracted from the reports, retrieved from the electronic data records. In patients who had radical prostatectomy, the glands were sampled completely and were also reported using a synoptic format. The study was undertaken after receiving Institutional Review Board approval.

The biopsy and other variables for patients with initial HGPIN and benign biopsy were compared in those with and without prostate cancer on follow up biopsy. Biopsy and prostatectomy findings in patients with prostate cancer were compared between those with initial HGPIN and benign biopsies. Subject characteristics were presented as means with standard deviations and inter-quartile ranges for continuous variables, and frequencies and percentages for categorical variables. Differences in patient demographic, clinical and pathologic characteristics between the groups with initial HGPIN (cancer versus no cancer) and benign biopsy (cancer versus no cancer) were compared using the Wilcoxon rank-sum test for continuous variables and Chi-square test for categorical variables. All analyses were conducted using SAS (version 9.3; SAS Institute Inc, Cary, NC, USA).

Results

Prostate cancer was found in 26.7% (43/161) of repeat biopsies in patients with initial HGPIN and in 22.3% (19/85) biopsies in patients with initial benign biopsy. These patients had a mean follow up of 8.9 and 9.3 years (medians, 11.4 and 11.1 years), respectively. Patients with initial HGPIN, diagnosed with prostate cancer on follow up biopsy, compared with those without prostate cancer, were older (63.8 years versus 60.8 years, $p = 0.039$) and had a higher PSA at the time of the initial biopsy (8.6 ng/mL versus 6.7 ng/mL; $p = 0.041$), as shown in Table 1. Gland volume, PSA density and the number of sextant sites exhibiting HGPIN in the initial biopsy did not differ between the patients with and without prostate cancer on follow up biopsy. Patients with initial benign biopsies and subsequent prostate cancer, compared with patients without prostate cancer, had smaller glands (45.4 cc versus 63.7 cc, $p = 0.012$), but other preoperative variables, including the age, PSA and PSA density did not differ between the groups.

In patients diagnosed with prostate cancer, those with initial HGPIN compared with those with benign biopsy, were older (63.8 years versus 59.4 years, $p = 0.032$) and had a shorter time to prostate cancer diagnosis (1.5

TABLE 1. **Preoperative variables for patients with initial HGPIN and benign biopsies**

HGPIN **Variable**	**Total** **(n = 161)** **Mean (SD)** **IQR**	**No cancer** **(n = 118)** **Mean/SD** **IQR**	**Cancer** **(n = 43)** **Mean (SD)** **IQR**	**p value**
Age, years				0.039
	61.6 (8.9)	60.8 (8.9)	63.8 (8.6)	
	54.5-68.2	52.9-67.2	58.7-68.9	
Gland volume				0.687
(cc)	54.1 (33.0)	54.7 (35.2)	52.3 (25.8)	
	31.9-67.4	31.6-67.4	33.9-67.7	
PSA				0.041
(ng/mL)	7.2 (5.4)	6.7 (4.5)	8.6 (7.3)	
	4.5-8.4	4.3-8.2	5.3-9.4	
PSA density				0.149
(ng/mL)	0.2 (0.1)	0.2 (0.1)	0.2 (0.2)	
	0.1-0.2	0.1-0.2	0.1-0.2	
Number of HGPIN sites				0.879
1	79 (49)	57 (48)	22 (51)	
2	46 (29)	35 (30)	11 (26)	
3 or more	36 (22)	26 (22)	10 (23)	
Benign **Variable**	**Total** **(n = 85)** **Mean (SD)** **IQR**	**No cancer** **(n = 66)** **Mean/SD** **IQR**	**Cancer** **(n = 19)** **Mean (SD)** **IQR**	**p value**
Age, years				0.696
	59.8 (6.9)	59.9 (6.9)	59.4 (6.9)	
	54.4-65.8	54.9-65.9	53.7-63.4	
Gland volume				0.012
(cc)	59 (31.2)	63.7 (33)	45.4 (20)	
	38.1-74.6	41.8-77.3	32.6-63.5	
PSA				0.183
(ng/mL)	7.4 (3.6)	7.7 (3.8)	6.3 (2.5)	
	5.2-9.1	5.4-9.5	4.6-8.1	
PSA density				0.673
(ng/mL)	0.1 (0.1)	0.1 (0.1)	0.2 (0.1)	
	0.1-0.2	0.1-0.2	0.1-0.3	

years versus 2.5 years, $p < 0.001$), as shown in Table 2. In contrast, patients with initial benign biopsies showed greater change of the PSA (at initial biopsy versus at positive biopsy). Gland volume, PSA, Gleason score, number of follow up biopsies, percentage of cancer involvement, and number of positive cores were not found to be significantly different between the groups. Of note, 98% (42/43) of positive biopsies after initial HGPIN demonstrated either Gleason score (GS) 3 + 3 (86%) or GS 3 + 4 (12%). In the benign group, 100% of patients demonstrated prostate cancer on biopsy with either GS 3 + 3 (58%) or GS 3 + 4 (42%).

Of patients diagnosed with prostate cancer, 51% (22/43) with initial HGPIN biopsy and 68% (13 of 19) with initial benign biopsy, underwent radical prostatectomy. The remaining patients diagnosed with prostate cancer were treated with different modalities including active surveillance, radiation, or a

TABLE 2. **Variables in patients with prostate cancer after initial HGPIN or benign biopsy**

Variable	HGPIN (n = 43) Mean (SD) IQR	Benign (n = 19) Mean (SD) IQR	p value
Age, years			0.032
	63.8 (8.6)	59.4 (6.9)	
	58.7-68.9	53.7-63.4	
Gland volume			0.295
(cc)	52.3 (25.8)	45.4 (20.1)	
	33.9-67.7	32.6-63.5	
PSA (ng/mL)			0.196
	8.6 (7.3)	6.3 (2.5)	
	5.3-9.4	4.6-8.1	
PSA change from baseline			0.026
(ng/mL)	2.7 (12.6)	3.3 (3.9)	
	-0.7-1.7	0.7-6.4	
Gleason score 3 + 3	37 (86%)	11 (58%)	
Gleason score 3 + 4	5 (12%)	8 (42%)	
Gleason score 4 + 4	1 (2%)		
Time to prostate cancer diagnosis, years			< 0.001
	1.5 (2.2)	2.5 (1.5)	
	0.3-1.6	1.4-3.2	
Number of follow up biopsies			0.633
	1.4 (0.6)	1.5 (0.5)	
	1-2	1-2	
Total % of cancer on biopsy			0.628
	2.4 (3)	2.3 (2.4)	
	0.5-4.5	0.5-2.5	
Number of positive cores			0.368
	1.4 (0.6)	1.7 (0.9)	
	1-2	1-2	

TABLE 3. **Prostatectomy findings after initial HGPIN and benign biopsy**

Variable	HGPIN n = 22 (%)	Benign n = 13 (%)
Pathologic stage		
pT2	22 (100)	13 (100)
Lymph node involvement	0	0
Positive margins	2 (9)	0
Tumor volume		
≤ 5%	20 (91)	8 (62)
> 5%	2 (9)	5 (38)
Gleason score		
6 (3 + 3)	19 (86)	7 (54)
7 (3 + 4 and 4 + 3)	2 (9) and 1 (5)	4 (31) and 1 (7.5)
8	0	1 (7.5)

combination of radiation and hormones. Prostatectomy findings for both groups are summarized in Table 3. All patients who had surgery demonstrated organ-confined and node negative disease (pT2 N0). Limited volume of prostate cancer (≤ 5%) was found in 91% (20/22) of patients with initial HGPIN and in 62% (8/13) patients with initial benign biopsy. In patients with initial HGPIN, 97% (21/22) patients had either GS 3 + 3 (n = 19) or GS 3 + 4 (n = 2) on prostatectomy; only one patient had GS 4 + 3 disease. In patients with initial benign biopsy, 85% (11/13) patients had either GS 3 + 3 (n = 7) or GS 3 + 4 (n = 4) on prostatectomy; 15% (2/13) patients had prostate cancer with adverse pathologic findings, including GS 4 + 3 and GS 4 + 4 (one patient each).

Discussion

In the contemporary era of prostate cancer, limited data exist on long term pathological outcomes in patients with initial extended prostate biopsies showing either HGPIN or benign findings, who are subsequently diagnosed with prostate cancer. We found a similar risk of prostate cancer on repeat biopsy after an initial HGPIN and benign biopsy of 26.7% and 22.3%, respectively. Regarding the final pathology, both groups exhibited favorable cancer findings with organ-confined and node negative disease, and showed similar pathology findings, which may likely indicate that in both groups the cancers were small and not sampled on the initial biopsy. We also found that the preoperative clinical and biopsy findings did not discriminate sufficiently those patients who were subsequently diagnosed with prostate cancer. The patients with initial HGPIN and a diagnosis of prostate cancer on a subsequent biopsy, were slightly older and had higher initial PSA values than those not diagnosed subsequently with prostate cancer, after the initial HGPIN biopsy. The patients with initial benign biopsy and subsequently diagnosed with prostate cancer, differed only by the lower gland volume, compared with those with initial benign biopsy but without a subsequent prostate cancer. This may highlight the inherent sampling error associated with a transrectal ultrasound guided biopsy, with a higher likelihood of finding limited prostate cancer disease in a smaller gland, using the same number of cores. When comparing the initial clinicopathologic features in patients with prostate cancer following HGPIN or benign biopsy, the patients in the HGPIN group were slightly older and were diagnosed with prostate cancer earlier that those with initial benign biopsy. A likely explanation is that patients with initial HGPIN biopsy would have been followed more closely, with repeat biopsies initiated earlier, relative to those with an initial benign biopsy. Conversely, patients with initial benign biopsies may have been subject to a higher threshold for rebiopsy, based on more significant changes of PSA kinetics or clinical exam findings. While many of these patients had surgery, in the current practice, many would have been offered a conservative management option with active surveillance.

The previous studies comparing cancer risk for patients with initial HGPIN and benign biopsies with at least 10 cores, are summarized in Table 4.[5,7-10] Four of the five previous studies failed to show a significant difference in cancer risk between the groups, suggesting that a routine repeat biopsy may not be warranted in patients with an initial HGPIN. The volume of HGPIN may also influence this clinical decision, as shown in some studies in which an increased risk for prostate cancer was found, if HGPIN was present in > 1 biopsy core.[3,4,7,11,14] However, this was not a uniform finding.[5,9,10] The current study did not show that the higher number of HGPIN involved sites on the initial biopsy was associated with a higher risk of subsequent diagnosis of prostate cancer. This may be partially due to the fact that we did not analyze

TABLE 4. **Cancer detection after initial HGPIN and benign extended prostate biopsy**

	No./total no. (%)		No. biopsy cores		
Reference	**HGPIN**	**Benign**	**Initial**	**Repeat**	**p value**
Current study	43/161 (26.7)	19/85 (22.3)	10	10	NS
Merrimen et al[7]	14/105 (13.3)	25/120 (20.8)	Minimum 10	Minimum 10	NS
San Francisco e al[5]	5/21 (23.8)	1/43 (2.3)	10 or greater	10 or greater	0.01
Naya et al[10]	4/42 (9.5)	13/75 (17.3)	10-11	10-11	NS
Gallo et al[9]	14/65 (21.5)	15/65 (23)	12-20	12-20	NS
Adamczyk et al[8]	6/19 (31.5)	4/40 (10)	10-12	10-12	NS

the exact number of cores showing HGPIN, but only the number of HGPIN involved sites (bilateral apex, base mid). Although this is a study limitation, the number of involved sites may be roughly equated to the number of cores involved, because the biopsy site submission included only 1 or 2 cores sampled per each site (apex = 1 core; base, mid = 2 cores).

Al-Hussain and Epstein compared 45 patients who underwent radical prostatectomy after an initial biopsy demonstrating HGPIN, with prostate cancer on a subsequent biopsy, to 18,494 patients diagnosed with prostate cancer who lacked an earlier diagnosis of HGPIN.[12] The initial clinicopathologic findings were not different regarding the age, mean serum PSA and GS. Single core positivity and a maximum cancer per core percentage of ≤ 5% was found to be more common in patients with an initial HGPIN ($p < 0.0001$). Organ confined disease was also more common in patients with an initial biopsy demonstrating HGPIN ($p = 0.007$). The final pathology on prostatectomy showed no significant differences between the GS, margin positivity, seminal vesicle involvement and lymph node metastasis. A small study by Izawa et al consisted of 21 patients with an initial biopsy demonstrating HGPIN, of which 7 had prostate cancer on follow up biopsy and underwent radical prostatectomy, showing organ-confined disease.[13] A limitation of both studies represents the lack of use of standardized extended needle biopsies. In another study with an initial diagnosis of HGPIN, which required at least 10 biopsy cores, 5 of 21 (24%) patients with repeat biopsies were subsequently diagnosed with prostate cancer.[5] Only 3 of the 5 patients underwent radical prostatectomy and were found to have an organ-confined node negative disease. Although a limited number of patients were analyzed in the previous studies, with initial HGPIN biopsies and a subsequent diagnosis of cancer, including the present one, the results indicate that a vast majority showed favorable pathologic outcomes on prostatectomy with low grade and low volume, node negative disease. Therefore, patients diagnosed with prostate cancer after an initial HGPIN or benign biopsy in the current practice may be considered candidates for conservative management. Favorable biopsy findings alone however are insufficient to predict favorable pathologic outcomes after prostatectomy. It is well known that limited cancer on biopsy does not automatically indicate that prostatectomy will show prostate cancer with favorable grade and stage, which limits the predictive power for the individual patient. Certainly, the biopsy findings are but one of the elements to be considered when determining the final patient management.

The limited sample size and the retrospective design are also limitations of the current study. This study also did not follow a specific protocol regarding the frequency and the timing of follow up biopsies, which was reflective of the practice at the time of the study. However, given the favorable outcomes in both groups, and in concordance with previously published data, we suspect that results would not have been significantly different, even if a protocol was followed.

Conclusion

We compared the preoperative findings and the final surgical pathology in patients who were found to have prostate cancer after an initial biopsy demonstrating HGPIN and benign findings. Patients with initial HGPIN or benign biopsy, who were subsequently, diagnosed with prostate cancer, demonstrated favorable biopsy and prostatectomy findings. The great majority of patients showed low-risk or favorable intermediate risk disease that was low volume, organ-confined, and node negative. Initial HGPIN biopsy preceding a diagnosis of prostate cancer, should not preclude enrollment in conservative management protocols, and in fact, patients with initial HGPIN or benign biopsy, based on the data presented herein, may represent a patient group who can derive the greatest benefit from conservative treatment. □

References

1. Epstein JI, Herawi M. Prostate needle biopsies containing prostatic intraepithelial neoplasia or atypical foci suspicious for carcinoma: implications for patient care. *J Urol* 2006;175 (3 Pt 1):820-834.
2. Merrimen JL, Jones G, Srigley JR. Is high grade prostatic intraepithelial neoplasia still a risk factor for adenocarcinoma in the era of extended biopsy sampling? *Pathology* 2010;42(4):325-329.
3. Netto GJ, Epstein JI. Widespread high-grade prostatic intraepithelial neoplasia on prostatic needle biopsy: a significant likelihood of subsequently diagnosed adenocarcinoma. *Am J Surg Pathol* 2006;30(9):1184-1188.
4. Akhavan A, Keith JD, Bastacky SI et al. The proportion of cores with high-grade prostatic neoplasia on extended-pattern needle biopsy is significantly associated with prostate cancer on site-directed repeat biopsy. *BJU Int* 2007;99(4):765-769.
5. San Francisco IF, Olumi AF, Kao J et al. Clinical management of prostatic intraepithelial neoplasia as diagnosed by extended needle biopsies. *BJU Int* 2003;91(4):350-354.

6. Godoy G, Huang GJ, Patel T et al. Long-term follow-up of men with isolated high-grade prostatic intra-epithelial neoplasia followed by serial delayed interval biopsy. *Urology* 2011;77(3):669-674.
7. Merrimen JL, Jones G, Walker D et al. Multifocal high grade prostatic intraepithelial neoplasia is a significant risk factor for prostatic adenocarcinoma. *J Urol* 2009;182(2):485-490.
8. Adamczyk P, Wolski Z, Butkiewicz R et al. Significance of atypical small acinar proliferation and extensive high-grade prostatic intraepithelial neoplasm in clinical practice. *Cent European J Urol* 2014;67(2):136-141.
9. Gallo F, Chiono L, Gastaldi E et al. Prognostic significance of high-grade prostatic intraepithelial neoplasia (HGPIN): risk of prostatic cancer on repeat biopsies. *Urology* 2008;72(3):628-632.
10. Naya Y, Ayala AG, Tamboli P et al. Can the number of cores with high-grade prostate intraepithelial neoplasia predict cancer in men who undergo repeat biopsy? *Urology* 2004;63(3):503-508.
11. Roscigno M, Scattoni V, Freschi M et al. Monofocal and plurifocal high-grade prostatic intraepithelial neoplasia on extended prostate biopsies: factors predicting cancer detection on extended repeat biopsy. *Urology* 2004;63(6):1105-1110.
12. Al-Hussain TO, Epstein JI. Initial high-grade prostatic intraepithelial neoplasia with carcinoma on subsequent prostate needle biopsy: findings at radical prostatectomy. *Am J Surg Pathol* 2011;35(8):1165-1167.
13. Izawa JI, Lega I, Downey D et al. Do all patients with high-grade prostatic intraepithelial neoplasia on initial prostatic biopsy eventually progress to clinical prostate cancer? *BJU Int* 2005;96(3):320-323.
14. Schoenfield L, Jones JS, Reuther AM et al. The incidence of high-grade prostatic intraepithelial neoplasia and atypical glands suspicious for carcinoma on first-time saturation needle biopsy, and the subsequent risk of cancer. *BJU Int* 2007;99(4):770-774.