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Initial High-grade Prostatic Intraepithelial Neoplasia With Carcinoma on Subsequent Prostate Needle Biopsy: Findings at Radical Prostatectomy

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Abstract

There are only a few small studies on men with an initial biopsy showing high-grade prostatic intraepithelial neoplasia (HGPIN) who later have cancer on repeat biopsy and then undergo radical prostatectomy. It is unknown whether this scenario impacts the prognosis of subsequent radical prostatectomy. We compared radical prostatectomy findings in 45 men with an initial diagnosis of HGPIN who subsequently were diagnosed with cancer with 18,494 men diagnosed with cancer who lacked an earlier diagnosis of HGPIN. All cases were retrieved from our institution between 1993 and 2008. The mean patient age was 60.2 years, and the mean serum prostate-specific antigen value was 9.0 ng/mL. For the 45 men with an initial HGPIN diagnosis, 21 of 45 (46.7%) men were found to have cancer within 6 months and 29 of 45 (64.4%) within 1 year after the diagnosis of HGPIN. Cancer involved a single core in 32 of 45 (71.1%) cases, and the maximum tumor volume was 5% in 57.8% of the 45 cases. Men with initial HGPIN had 84.4% organ-confined cancer, whereas cases without HGPIN had 65.4% organ-confined cancer ($P=0.007$) at radical prostatectomy. For the RPs performed in men with an earlier diagnosis of HGPIN followed by cancer on biopsy, the mean and median tumor volumes were 0.3 cm³ and 0.12 cm³ (0.003 cm³ to 1.46 cm³). Favorable pathologic stage was maintained even when we restricted the analysis to men with only Gleason score 6 cancer on biopsy. In men with Gleason score 6 cancer on biopsy, men with an initial diagnosis of HGPIN had 88.9% organ confined versus 73.2% for men with no earlier biopsy diagnosis of HGPIN, ($P=0.03$). At radical prostatectomy, although men with an earlier HGPIN diagnosis had less adverse findings in terms of Gleason score, surgical margin involvement, seminal vesicle involvement, and lymph node metastasis, the differences did not reach statistical significance. This was possibly due to the relatively small number of positive events in the men with no earlier HGPIN and due to the relatively small number of cases with earlier HGPIN. Prostatic adenocarcinomas discovered after an initial HGPIN diagnosis on biopsy are more likely to be organ confined, yet of similar grade, compared with cases diagnosed as cancer on the first biopsy. These findings likely reflect cancers associated with HGPIN, in which the cancers were missed on the initial biopsy as a result of smaller size.

Keywords

prostatic intraepithelial neoplasia; prostate cancer; needle biopsy

High-grade prostatic intraepithelial neoplasia (HGPIN) is defined as architecturally benign prostatic ducts and acini lined by atypical cells with prominent nucleoli. The estimated mean incidence of HGPIN on needle biopsy is 7.7%.¹ HGPIN has been associated with an increased risk of cancer on subsequent needle biopsy in several studies, especially in men with multifocal (>1 core) HGPIN on biopsy.^{1,3,6,8,10}

However, only a few small studies have been published on men with an initial biopsy showing HGPIN who later have cancer on a repeat biopsy and then undergone radical prostatectomy. It is unknown whether this scenario correlates with prognostic findings in the subsequent radical prostatectomy specimen. In this study, we investigate clinical and pathologic features at radical prostatectomy in men who initially had HGPIN on biopsy, then developed prostatic adenocarcinoma on repeat prostate needle biopsy, and then underwent radical prostatectomy.

MATERIALS AND METHODS

We compared radical prostatectomy findings in 45 men with an initial diagnosis of HGPIN who subsequently were diagnosed with prostatic adenocarcinoma on repeat biopsy with 18,494 men diagnosed with prostatic adenocarcinoma on needle biopsy but lacking an initial diagnosis of HGPIN. Only a minority of these 18,494 men had earlier negative biopsies. All of our cases of HGPIN lacked coexisting small atypical glandular proliferations. All cases were retrieved from 1993 to 2008 at The Johns Hopkins Hospital. The groups with and without initial HGPIN were compared for differences in age, serum prostate-specific antigen (PSA) values, maximum percentage of cancer per core, number of positive cores, surgical margins, and pathologic stage. Favorable pathologic stage was defined as being organ confined. Each index tumor nodule was circled and the volume was calculated using the grid method. Areas of the nodules were photocopied over a paper containing 1 mm squares. The number of the squares that the tumor nodule occupied was counted. The volume in cubic millimeter was recorded with a correction factor for fixation-related shrinkage: index tumor nodule volume = number of squares involved by tumor $\times$ 3 mm (thickness of the tissue block) $\times$ 1.12 (formalin shrinkage factor). Cubic millimeter was then converted to cubic centimeter. Statistical tests were conducted using STATA (College Station, TX). *T* test of the equality of means was used to compare differences between the groups in terms of age, grade, and serum PSA values. χ^2 test assessed differences in stage, surgical margins, single positive core, and maximum percentage of cancer per core ($\leq 5\%$) between the groups. Statistical significance was defined as $P < 0.05$.

RESULTS

The clinicopathologic findings at biopsy are summarized in Table 1. Multifocal HGPIN (HGPIN present on > 1 core) was present in 14 of 45 (31.1%) cases. Men with earlier HGPIN were slightly older than men without HGPIN ($P=0.04$). Similarly, men with earlier

HGPIN had slightly higher mean serum PSA levels than men without earlier HGPIN ($P=0.03$). For the 45 men with an earlier HGPIN diagnosis, 21 (46.7%) men were found to have cancer within 6 months and 29 (64.4%) within 1 year after the diagnosis of HGPIN (range from 1 to 62 mo). Cancer involved a single core in 71.1% and 34.1% of cases with and without earlier HGPIN, respectively ($P < 0.0001$). In the majority of cases with earlier HGPIN, the maximum tumor volume per core was 5%. In contrast, only 6.9% of cases without earlier HGPIN had 5% maximum tumor volume per core ($P < 0.0001$). There was no significant difference in Gleason score at biopsy between the 2 groups. The mean total number of biopsy cores at the time of diagnosis of HGPIN was 13.3 (median, 14; range, 6 to 18). At the time of repeat biopsy, a mean of 14.6 (median, 15; range, 6 to 25) cores was sampled.

At radical prostatectomy, men with earlier HGPIN had 84.4% (38 of 45) organ-confined cancer, whereas men without earlier HGPIN had 65.4% (12,075 of 18,461) organ-confined cancer ($P=0.007$) (Table 2). For the RPs performed in men with an earlier diagnosis of HGPIN followed by cancer on biopsy, the mean and median tumor volumes were 0.3 and 0.12 cm³ (0.003 to 1.46 cm³). Favorable pathologic stage was maintained even when we restricted the analysis to men with only Gleason score 6 cancer on biopsy. In men with Gleason score 6 cancer on biopsy, men with an earlier diagnosis of HGPIN, tumor at radical prostatectomy was organ confined in 88.9% of cases compared with 73.2% for men with no earlier biopsy diagnosis of HGPIN, ($P=0.03$). At radical prostatectomy, although men with an earlier HGPIN diagnosis had less adverse findings in terms of Gleason score, surgical margin involvement, seminal vesicle involvement, and lymph node metastasis, the differences did not reach statistical significance. This was possibly due to the relatively small number of positive events in the men with no earlier HGPIN and due to the relatively small number of cases with earlier HGPIN.

DISCUSSION

Men with HGPIN on biopsy are at a greater risk of subsequent diagnosis of prostatic adenocarcinoma.^{1,3,6,8,10} In particular, it has been shown that men with multifocal HGPIN involving 2 and more cores on extended prostate needle biopsy are at a greater risk of subsequent prostatic adenocarcinoma than those with unifocal HGPIN. Although the risk of cancer after the diagnosis of HGPIN on 1 core is similar to that after a benign biopsy, it increases to 30% to 40% when HGPIN is found on >1 needle biopsy core.^{6–8}

However, only a few small studies have been published on men with an initial HGPIN who later developed cancer and then underwent radical prostatectomy. San Francisco et al⁹ reported that 5 of 47 patients with HGPIN developed cancer, and all 5 had organ-confined cancer. In 1995, Keetch et al⁵ reported that 23 of 58 men with prostatic intraepithelial neoplasia developed cancer; 19 occurred in men with HGPIN. Seventeen of these 23 men elected to undergo radical prostatectomy, 16 of whom had pathologically organ-confined tumors. Only 1 patient with HGPIN had pathologic stage pT3a tumor. Most of the biopsies in Keetch et al⁵ study had only 4 to 6 needle biopsy core sampling. Similar findings have been reported by Izawa et al⁴ study in which 7 of 21 patients with initial HGPIN developed cancer and all had organ-confined disease.

In this study, we reviewed a larger group of 45 men with an initial diagnosis of HGPIN who subsequently developed prostatic adenocarcinoma and underwent radical prostatectomy. This group was compared with a control group of 18,494 men who lacked initial HGPIN on biopsy. We found that men with an initial HGPIN diagnosis were slightly older than men without earlier HGPIN and were more prone to have slightly higher serum PSA levels. Despite higher PSA values, men with an earlier HGPIN diagnosis had more favorable pathologic stage (organ-confined cancer) on radical prostatectomy than men without earlier HGPIN. As 64.4% of the men with initial HGPIN were found to have cancer within 1 year, these cancers most likely were present at the time of initial HGPIN biopsy. They were likely missed on the initial biopsy as a result of their smaller size as opposed to cancers detected on the initial biopsy. Although we did not measure the tumor size for over 18,000 control cases, the tumor volume for the cases with earlier HGPIN was very minimal with a median tumor volume of 0.12 cm³. It is likely that these findings would be analogous to cases in which the initial biopsy was benign and cancer was subsequently found on repeat biopsy. In some cases in which cancer was detected at a later interval after initial HGPIN diagnosis, the more favorable findings at radical prostatectomy could reflect that these men were followed more closely and their cancers were detected at an earlier stage.

A potential weakness of this study is that the cases spanned from 1993 until 2008, over which time there has been some evolution both in terms of Urology and Pathology practice. Starting around 2005, most urologists had changed their practice from performing sextant biopsies to more extended biopsy schemes. In addition, Gleason grading had evolved in the hands of urological pathology experts, culminating in the codification of these changes in a consensus conference published in 2005.² If we had restricted our analysis to cases occurring only after 2005, we would have had only one half of our cases for evaluation which would have prohibitively limited statistical analysis. However, as 59.2% and 51.1% of the control and HPIGN cases, respectively, occurred before 2005, any differences in sampling or grading should have been equally distributed between the groups.

In summary, prostatic adenocarcinomas discovered after an initial HGPIN diagnosis on biopsy are more likely to be organ confined compared with cases diagnosed as cancer on the first biopsy. These findings likely reflect cancers associated with HGPIN, in which the cancers were missed on the initial biopsy as a result of their smaller size.

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TABLE 1**Clinicopathologic Findings at Biopsy**

	Earlier HGPIN	No Earlier HGPIN	<i>P</i>
Age (mean, years)	60.2	58.2	0.04
Serum PSA (mean)	9.0ng/mL	7.0 ng/mL	0.03
Single positive core	32/45 (71.1%)	2939/8622 (34.1%)	<0.0001
Maximum cancer per core (≤ 5%)	26/45 (57.8%)	585/8591 (6.9%)	<0.0001
Gleason score			0.5
6	38/45 (84.4%)	13,565/18,396 (73.7%)	
7 (3+4)	4/45 (8.9%)	2912/18,396 (15.8%)	
7 (4+3)	1/45 (2.2%)	1145/18,396 (6.2%)	
8–10	2/45 (4.4%)	774/18,396 (4.2%)	

TABLE 2

Pathologic Findings at Radical Prostatectomy

	Earlier HGPIN	No Earlier HGPIN	<i>P</i>
Gleason score			
6	36/45 (80%)	10,907/18,346 (59.5%)	0.3
7 (3+4)	2/45 (4.4%)	4594/18,346 (25%)	
7 (4+3)	2/45 (4.4%)	1628/18,346 (8.9%)	
8–10	5/45 (11.1%)	1217/18,346 (6.6%)	
Surgical margin involvement	4/45 (8.9%)	2673/18,470 (14.5%)	0.3
Organ confined	38/45 (84.4%)	12,075/18,461 (65.4%)	0.007
Seminal vesicle involvement	0/45 (0%)	990/18,494 (5.3%)	0.1
Lymph node metastasis	0/45 (0%)	448/18,494 (2.4%)	0.6