# Risk of Prostate Cancer on First Re-Biopsy Within 1 Year Following a Diagnosis of High Grade Prostatic Intraepithelial Neoplasia is Related to the Number of Cores Sampled

**Mehsati Herawi, Hillel Kahane, Christina Cavallo and Jonathan I. Epstein***

*From the Departments of Pathology (MH, JIE), Urology (JIE) and Oncology (JIE), The Johns Hopkins University School of Medicine, Baltimore, Maryland, and Dianon Systems Inc. (HK, CC), Stratford, Connecticut*

**Purpose:** We determined the influence of the extent of needle biopsy sampling on the detection rate of cancer on first biopsy within 1 year following a diagnosis of HGPIN.

**Materials and Methods:** We identified 791 patients with HGPIN on the initial biopsy who had a followup biopsy within 1 year of their diagnosis. The mean interval from diagnosis of HGPIN to re-biopsy was 4.6 months. In the initial biopsy with HGPIN, 323 men had 8 or more cores (median 10, range 8 to 26) and 332 men had 6 core biopsies.

**Results:** In the 6 core initial sampling group, the risk of cancer on re-biopsy was 20.8% compared to only 13.3% following an initial 8 core or more sampling ($p = 0.011$). With 6 core biopsies for both the initial and re-biopsy the risk of cancer was 14.1% (group 1). With an initial 6 core biopsy and 8 core or more biopsy on followup, the risk of cancer was 31.9% (group 2). With 8 core or more biopsy sampling for both initial and repeat biopsies, the risk for cancer was 14.6% (group 3). The differences between groups 1 and 3 as compared to group 2 were statistically significant ($p = 0.001$ and $p < 0.0001$, respectively).

**Conclusions:** With relatively poor sampling (6 cores) on the initial biopsy, associated cancers are missed resulting in only HGPIN on the initial biopsy, and with relatively poor sampling on re-biopsy there is also a relatively low risk of finding cancer on re-biopsy (group 1). With poor sampling on the initial biopsy and better sampling on re-biopsy, some of these initially missed cancers are detected on re-biopsy yielding a higher detection of cancer (group 2). Sampling more extensively on the initial biopsy detects many associated cancers, such that when only HGPIN is found they often represent isolated HGPIN. Therefore, re-biopsy even with good sampling does not detect many additional cancers (group 3). Our study demonstrates that the risk of cancer on biopsy within 1 year following a diagnosis of HGPIN (13.3%) is not that predictive of cancer on re-biopsy if good sampling (8 or more cores) is initially performed. For patients diagnosed with HGPIN on extended initial core sampling, a repeat biopsy within the first year is unnecessary in the absence of other clinical indicators of cancer.

*Key Words: prostatic neoplasms, prostatic intraepithelial neoplasia, biopsy*

Since the formal description of HGPIN by McNeal and Bostwick in 1986, several studies have reported on the positive predictive value of isolated HGPIN for cancer on subsequent prostate needle biopsy, ranging from 2.3% to 100%.[1–3] Recommendations for following men with initial isolated HGPIN on biopsy varies widely from re-biopsy immediately, to re-biopsy at 3 to 6 months, 6 to 12 months, or at 3 years.[4–6] The most aggressive re-biopsy protocol is followup biopsies at 3 to 6 months intervals for 2 years followed by 12 months intervals for life.[2]

While many studies have documented that increased biopsy sampling can improve the detection rate of prostate cancer, few works have addressed its influence on the predictive value of HGPIN for cancer on subsequent biopsy.[7–10] In this retrospectively conducted study, we aimed to determine how the number of biopsy cores sampled, both on initial and repeat prostate biopsy, influences the predictive value of HGPIN for the detection of cancer on subsequent biopsy. We restricted our analysis to men who had a repeat biopsy within 1 year after initial diagnosis of HGPIN. Biopsies performed farther out are more likely to be done because of changing clinical signs and/or symptoms, such as increasing serum prostate specific antigen or development of an abnormality on digital rectal examination rather than as a routine re-biopsy for HGPIN.

## MATERIALS AND METHODS

The patient database of a single pathology laboratory (Dianon Systems, Stratford, Connecticut) from 1/1/97 until 12/31/01 was searched for men who satisfied the criteria of 1) diagnosis of only HGPIN on initial biopsy (patients who in addition to HGPIN had a focus of atypical glands those suspicious for cancer were excluded from analysis), 2) minimum of 6 core sampling, 3) followup biopsy performed within 1 year of HGPIN diagnosis and 4) number of cores could be assessed on initial and repeat biopsy. As the previous biopsy history of these patients was not known, the first biopsy for these patients processed and interpreted by Dianon Systems was considered initial biopsy. A total of 791

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* Correspondence: Department of Pathology, The Johns Hopkins Hospital, 401 N. Broadway St., Room 2242, Baltimore, Maryland 21231 (telephone: 410-955-5043; FAX: 443-287-3818; e-mail: jepstein@jhmi.edu).

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TABLE 1. *Risk of cancer following a diagnosis of HGPIN*

| No. Cores 1st Biopsy | No. Ca on Re-Biopsy/Total (%) |
|---|---|
| Any | 139/791 (17.6) |
| 6 | 69/332 (20.8) |
| 8 or More | 43/323 (13.3) |

men fulfilled these criteria and were considered for this analysis. In a subset of 602 of 791 (76.1%) cases, we were able to determine whether 1 or more than 1 core had HGPIN. Data were analyzed using the statistics graphic data measurement software program (STATA).

## RESULTS

Of the 791 men in the study, the mean age was 67.2 years (range 39 to 87) with no statistical difference in the mean age between men with and without cancer on repeat biopsy ($p = 0.25$). The mean initial prostate specific antigen value in men with cancer on followup was 9.3 ng/ml (median 6.5, range 0.7 to 82.4) and without cancer 7.5 ng/ml (median 6.3, range 0.6 to 41). This difference did not reach statistical significance ($p = 0.24$) using the rank sum test comparing medians.

The mean interval from diagnosis of HGPIN to re-biopsy was 4.6 months with a median interval of 4.0 months (range 1 to 52 weeks). The overall rate of cancer detected on repeat biopsy was 17.6% (139 of 791, table 1). In the initial biopsy resulting in a diagnosis of HGPIN, 332 men had 6 cores, 136 men had 7 cores, and 323 men had 8 or more core sampling (median 10, mean 10.7, range 8 to 26). Without taking into account the number of cores on re-biopsy, the risk of cancer on re-biopsy in the 6 core initial sampling group was 20.8% (69 of 332), whereas in the initial 8 cores or more group the risk of cancer was 13.3% (43 of 323, $p = 0.011$, table 1). There was no statistical difference in the risk of subsequent cancer stratified by 1 core with HGPIN (16.7%) as compared the risk of cancer with greater than 1 core with HGPIN (22.2%, $p = 0.13$).

To compare routine sextant biopsy sampling to a more extended biopsy, cases with 6 cores and 8 or more cores on either the initial and/or the repeat biopsy were compared. Cases with 7 cores on either the initial and/or repeat biopsy were then placed in the 6 core group and alternately into the 8 or more core group and analyzed to see how that would affect the risk of cancer on re-biopsy. Tables 2 to 4 show the risk of cancer following an initial diagnosis of HGPIN stratified by the number of cores on the first and repeat biopsy. The differences between groups 2 as compared to groups 1 and 3 were statistically significant ($p = 0.001$ and $p < 0.0001$, respectively). Comparable results were obtained if the cases with 7 cores were combined with 6 cores or were combined with 8 or more cores (table 2).

TABLE 3

| Group | No. Cores 1st Biopsy | No. Cores Re-Biopsy | No. Risk of Ca/ Total (%) |
|---|---|---|---|
| 1 | 6–7 | 6–7 | 49/295 (16.6) |
| 2 | 6–7 | 8 or More | 47/173 (27.2) |
| 3 | 8 or More | 8 or More | 37/253 (14.6) |
| 4 | 8 or More | 6–7 | 6/70 (8.6) |

Group 2 vs 1 $p = 0.006$; 2 vs 3 $p = 0.0001$; 2 vs 4 $p = 0.001$ and group 1 vs 3 $p = 0.53$; 1 vs 4 $p = 0.091$; 3 vs 4 $p = 0.19$.

## DISCUSSION

The detection rate of cancer after an initial diagnosis of HGPIN has decreased compared to the initial data reported in the early 1990s. The strength of positive predictive value of HGPIN and the clinical significance of repeat biopsy immediately or shortly after a diagnosis of isolated HGPIN have therefore become debatable. The reported rate of cancer following an initial diagnosis of HGPIN on biopsy has consistently decreased since the first studies on this issue appeared in the early 1990s. Whereas the average risk of cancer following a diagnosis of HGPIN on biopsy in initial studies was 50%, in some studies the risk reached 100%.[1,2] In most recent studies, cancer detection rates on re-biopsy after sextant sampling showing HGPIN range from 20% to 30%, similar to our 20.8% rate for cases with initial sextant sampling.[1] However, only a few studies have taken into account how the number of needle biopsy samples could affect the results.

The importance of sampling for detecting cancer on prostate biopsies in general has been extensively documented. Whereas the sextant biopsy technique in the past was the standard procedure, subsequent studies have documented that increased biopsy sampling can improve the detection rate of prostate cancer.[7–10] Presti et al demonstrated that with sextant biopsies 20% of cancers were missed, as opposed to an 8 core biopsy scheme where only 5% of cancers went undetected.[8] Based on this data, we chose 8 or more core sampling as the requirement for our extended biopsy cohort which also maximized the numbers of patients in this group. The mean and median number of cores in this group was 10.7 and 10 cores, respectively, which reflects an extended biopsy scheme that differentiates it from the sextant group. In the current study, the significance of adequate sampling at the initial biopsy was demonstrated in men who had a relatively poor initial sampling (6 cores), where a sufficient core sampling (8 or more cores) on followup biopsy

TABLE 2. *Combined influence of numbers of cores in initial and repeat sampling*

| Group | No. Cores 1st Biopsy | No. Cores Re-Biopsy | No. Risk of Ca/ Total (%) |
|---|---|---|---|
| 1 | 6 | 6 | 20/142 (14.1) |
| 2 | 6 | 8 or More | 36/113 (31.9) |
| 3 | 8 or More | 8 or More | 37/253 (14.6) |
| 4 | 8 or More | 6 | 4/44 (9.1) |

Group 2 vs 1 $p = 0.001$; 2 vs 3 $p < 0.0001$; 2 vs 4 $p = 0.003$ and group 1 vs 3 $p = 0.93$; 1 vs 4 $p = 0.37$; 3 vs 4 $p = 0.33$.

TABLE 4

| Group | No. Cores 1st Biopsy | No. Cores Re-Biopsy | No. Risk of Ca/ Total (%) |
|---|---|---|---|
| 1 | 6 | 6 | 20/142 (14.1) |
| 2 | 6 | 7 or More | 49/190 (25.8) |
| 3 | 7 or More | 7 or More | 55/359 (15.3) |
| 4 | 7 or More | 6 | 15/100 (15.0) |

Group 2 vs 1 $p = 0.009$; 2 vs 3 $p = 0.003$; 2 vs 4 $p = 0.035$ and group 1 vs 3 $p = 0.73$; 1 vs 4 $p = 0.84$; 3 vs 4 $p = 0.94$.