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Widespread high grade prostatic intraepithelial neoplasia on biopsy predicts the risk of prostate cancer: A 12 months analysis after three consecutive prostate biopsies

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Summary

Purpose: *To evaluate the risk of prostate cancer (PCa) on a third prostate biopsy in a group of patients with two consecutive diagnoses of high grade intraepithelial neoplasia (HGPIN).*

Materials and methods: *From November 2004 to December 2007, patients referred to our clinic with a PSA ≥ 4 ng/ml or an abnormal digital rectal examination (DRE) were scheduled for trans-rectal ultrasound (TRUS) guided 12-core prostate biopsy. Patients with HGPIN underwent a second prostate biopsy, and if the results of such procedure yielded a second diagnosis of HGPIN, we proposed a third 12-core needle biopsy regardless of PSA value. Crude and adjusted logistic regressions were used to assess predictors of PCa on the third biopsy.*

Results: *A total of 650 patients underwent 12 cores transrectal ultrasound prostatic biopsy in the study period. Of 147 (22%) men with a diagnosis of HGPIN, 117 underwent a second prostatic biopsy after six months and 43 a third biopsy after other six months. After the third biopsy, 19 patients (34%) still showed HGPIN, 15 (35%) were diagnosed with PCa and 9 (21%) presented with chronic prostatitis. Widespread HGPIN on a second biopsy was significantly associated with PCa on further biopsy ($\chi^2 = 4.04$, $p = 0.04$). Moreover, the presence of widespread HGPIN significantly predicted the risk of PCa on crude and adjusted logistic regressions.*

Conclusions: *Widespread HGPIN on second biopsy is associated with the presence of PCa on a third biopsy. Nonetheless, the relationship between HGPIN and PCa remains complex and further studies are needed to confirm our findings.*

KEY WORDS: *Prostate cancer; High grade prostatic intraepithelial neoplasia; Biopsy; Gleason score; Widespread.*

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INTRODUCTION

High grade prostatic intraepithelial neoplasia (HGPIN) is a cytoarchitectural modification of the prostatic tissue, with pre-existing acini and ducts lined by cytologically atypical cells (1). It has long been considered the pre-neoplastic lesion of prostate cancer (PCa) (1, 2) and is considered a risk factor for PCa on subsequent biopsy (3-7). The prognostic value of HGPIN in prostate biopsy cores however has been questioned and controversy has arisen on whether patients with a diagnosis of HGPIN should undergo further biopsies (2, 8, 9). Widespread HGPIN, defined as ≥ 4 biopsy cores involved with the intraepithelial lesion, has been found to be significantly associated with PCa diagnosis on further biopsy by different investigators (6, 10-15), including our group (16). Other predictors of PCa on a subsequent biopsy in patients with isolated HGPIN, such as age, an abnormal digital rectal examination (DRE), an abnormal prostate volume, PSA, PSA ratio or PSA density values have been examined, yet no

consensus on their predictive role has been reached (5, 7, 14, 17). To date, the prognostic value of HGPIN, clinical markers (age, digital rectal examination, PSA, etc) and widespread HGPIN in men after multiple diagnoses of isolated HGPIN remains controversial, and little is available on long term follow-up of these patients.
Data confirming a positive association of widespread HGPIN and PCa diagnosis on repeat biopsy have already been published by our group (16). We now report the results after the third biopsy in men with two consecutive diagnoses of isolated HGPIN. We explored the association of HGPIN, widespread HGPIN and clinical markers (age, digital rectal examination, PSA, etc) and PCa risk on a third biopsy, in order to elucidate the potential predictive role of HGPIN on PCa and further help to indentify the correct clinical management for patients with HGPIN.

Materials and methods

From November 2004 to December 2007, after receiving institutional review board approval, patients referred to our clinic with a PSA ≥ 4 ng/ml or an abnormal digital rectal examination (DRE) were scheduled for trans-rectal ultrasound (TRUS) guided 12-core prostate biopsy after informed consent was signed. In every patient diagnosed with HGPIN, a second biopsy was proposed after 6 months regardless of PSA values. Finally, in patients with a second diagnosis of HGPIN a third and final biopsy was proposed 6 months after the second procedure, for a total of 12 months follow-up.
Biopsy was performed as an outpatient procedure and the methodology has been throughout fully described in previously published peer-reviewed manuscripts (16, 18). All biopsies were performed following the same 12-core scheme. Before each procedure, blood specimens were obtained and free and total PSA were measured. Prostate volume was calculated by TRUS. Patients on finasteride or dutasteride and men who had undergone prostate surgery were excluded from the study.
A single uro-pathologist performed the histological evaluation for all biopsy series. The histological/architectural threshold used to assign the various diagnoses was that proposed by the WHO (19, 20). In areas suspicious for ASAP or HGPIN, immunohistochemical staining of sequential sections was used to confirm the eventual loss of basal cells using a mix of anti-p63 and 34βE12 cytokeratin antibodies. As defined by Netto and Epstein, widespread HGPIN was defined as 4 or more cores involved with HGPIN (21).

Statistical analysis

Widespread HGPIN on the second biopsy was examined as a categorical variable. The presence or absence of cancer on the third biopsy specimens defined our main categorical outcome variable. We performed chi-square test to evaluate the association between widespread HGPIN on the second biopsy and the diagnosis of PCa on the subsequent biopsy. Crude and adjusted logistic regressions were used to evaluate the association of clinical and pathological predictors and the risk of PCa on the third biopsy. However, given the small number of events in our model, we executed separate multivariate analyses for each predictor other than widespread HGPIN: multivariate analyses constantly included the presence of widespread HGPIN on the second biopsy (categorical) plus a second term as age, PSA, TRUS volume, DRE, PSA ratio and PSA Density. Due to non-parametrical distribution, PSA values and derivates (PSA ratio and density) were logarithmically transformed in the multivariate logistic regression tests. Mann-Whitney test was used to explore differences in age, prostate volume, PSA concentration, PSA ratio and PSA density across our two outcome groups and between men with and without widespread HGPIN at second biopsy. Wilcoxon signed rank sum test was used to evaluate significant modifications of PSA concentration, ratio and density between the second and third biopsy. Statistical analysis was performed using STATA 11 (*StataCorp, College Station, TX*).

Results

During the study period 650 men underwent primary prostate biopsy. Of these, 147 (22%) were diagnosed with HGPIN. As 30 men refused further procedures, a second biopsy was performed in 117 men, six months later. Data regarding the second biopsy have already been published (16). Out of 117 re-biopsies, 75 (64%) yielded a second diagnosis of HGPIN and to these men a third prostate biopsy was proposed, 6 months after the second biopsy. 22 of these patients refused to undergo the third biopsy and 10 underwent prostate surgery for bladder outlet obstruction; no cancer was found in any of the pathological specimens examined after surgery in these 10 patients. 43 men were therefore available for final analysis. Patients characteristic are illustrated in Table 1. After the third biopsy, 19 patients (44%) still showed HGPIN, 15 (35%) were diagnosed with PCa and 9 (21%) presented with chronic prostatitis. A flow chart (figure 1) clearly illustrates the results of the biopsies. The 10 men who underwent prostate resection for bladder outlet obstruction were all diagnosed with benign prostatic hypertrophy.

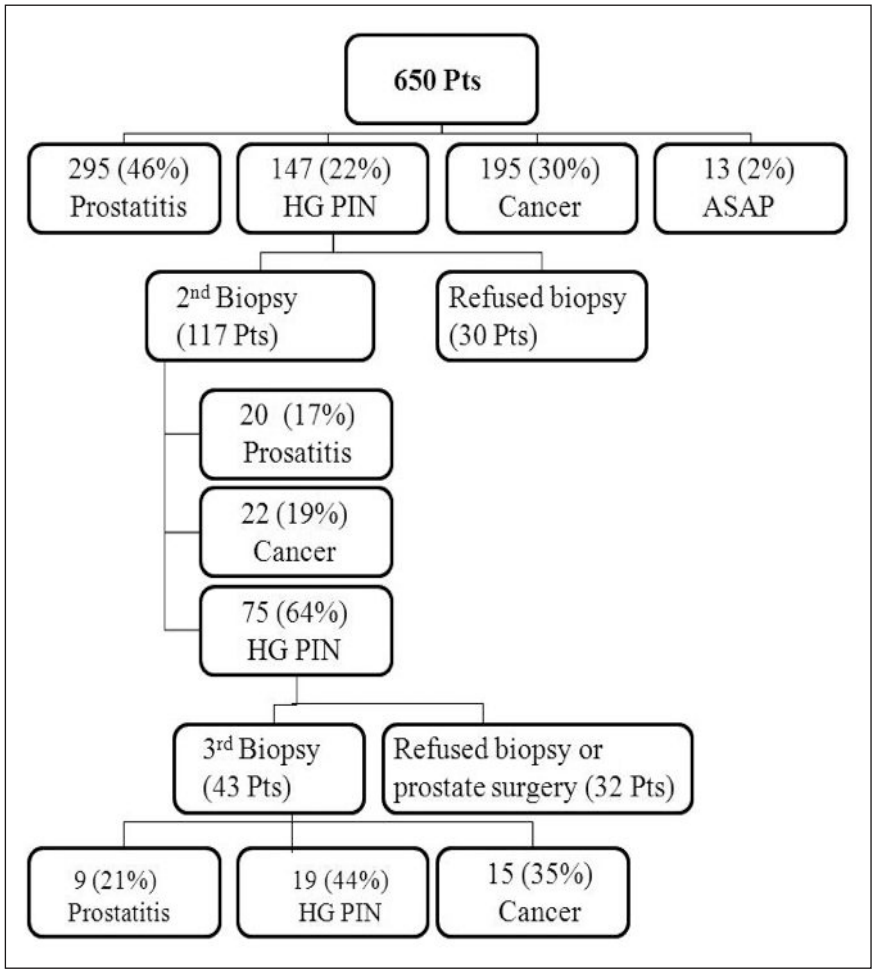
Table 1.

Clinical characteristics of the cohort (43 patients).

	Median (IQR)
Age (yrs)	65 (61-70)
Prostate volume (ml)	56 (42-64)
PSA (ng/ml)	7.53 (5.87-10.8)
PSA ratio (%)	15 (12-22)
PSA Density (ng/ml^2)	0.14 (0.10-0.22)
DRE	
Negative	37 (86%)
Positive	6 (14%)
Widespread HGPIN at second biopsy (≥ 4 cores)	17/43 (40%)

Figure 1.

Study design.



Of the 15 patients with PCa, 9 had a low grade Gleason 6 (3 + 3) adenocarcinoma, 4 men had a Gleason 7 (3 + 4) tumor, while only one Gleason 8 (4+4) and one Gleason 9 (4 + 5) cancers were diagnosed. A single core was involved in 10 of the men with cancer, with a 15% median core cancer extension. Of these, 7 were Gleason 6 (3 + 3) and the remaining 3 were Gleason 7 (3 + 4). Two cores were positive for cancer in 4 patients with a median extension of 15%. In one patient, diagnosed with a Gleason 8 (4 + 4), 4 cores were involved with cancer, for a maximum of 60% of their length.

No significant difference in the distribution of age, PSA, prostate volume, DRE, PSA ratio and PSA density (at the time of third biopsy) was found across the two outcome groups (Table 2).

Widespread HGPIN on a second biopsy was significantly associated with PCa on further biopsy ($\chi 2$ = 4.04, p = 0.04) (Table 2). Moreover, the presence of widespread HGPIN significantly predicted the risk of PCa on crude logistic regression (OR 3.75, 95%CI 1.00-14.02, p = 0.049). Widespread HGPIN remained a significant predictor of PCa on all

Table 2.

Clinical and pathological differences across groups.

	No Cancer	Cancer	p-value[1]	< 4 cores involved	≥ 4 cores involved (Widespread HGPIN)	p-value[1]
Number of patients	28 (65%)	15 (35%)	—	26 (60%)	17 (40%)	—
Age (yrs) **Median (IQR)**	66 (60-70)	65 (61-71)	0.86	66 (62-71)	64 (57-70)	0.30
Prostate volume (ml) **Median (IQR)**	58 (43-65)	51 (38-64)	0.31	57 (40-65)	51 (45-63)	0.80
DRE negative positive	25 (89%) 3(11%)	12 (80%) 3 (20%)	0.402	22 (85%) 4 (15%)	15 (88%) 2 (12%)	0.74[2]
PSA (ng/ml) **Median (IQR)**	6.86 (5.66-9.3)	8.84 (6.75-13.5)	0.14	7.8 (5.88-11.7)	6.86 (5.87-8.89)	0.39
PSA ratio (%) **Median (IQR)**	16 (12-24)	15 (10-19)	0.27	16 (12-25)	15 (12-20)	0.72
PSA Density (ng/ml^2) **Median (IQR)**	0.13 (0.10-0.21)	0.15 (0.1-0.26)	0.24	0.145 (0.10-0.23)	0.14 (0.10-0.18)	0.57
Widespread HGPIN	8/28 (29%)	9/15 (60%)	0.042	—	—	—
Prostate cancer	—	—	—	6/26 (23%)	9/17 (53%)	0.042

[1] Mann-Whitney test.
[2] χ^2 test.

Table 3.

Multivariate logistic regressions: exploring the risk of prostate cancer on third biopsy.

	OR	95% CI	p-value
Widespread HGPIN	3.75	1.00-14.02	0.04
Age [1]	1.04	0.93-1.15	0.51
PSA [1, 2]	3.98	0.83-19.02	0.08
Prostate volume [1]	1.00	0.97-1.04	0.81
DRE [1]	2.53	0.39-16.19	0.98
PSA ratio [1, 2]	0.37	0.10-1.35	0.13
PSA Density [1, 2]	2.89	0.84-9.94	0.09

[1] *Due to the small number of events separate regressions were performed, adding each single term to the initial model with our main predictor variable (widespread HGPIN) (see text).*
[2] *PSA, PSA ratio and PSA density were log-transformed due to non-parametrical distribution.*

multivariate models (all $p < 0.05$). All clinical parameters evaluated, such as age, PSA, DRE, prostate volume and PSA ratio were not significant predictors of cancer at the time of the third prostate biopsy (Table 3). No significant differences in age, prostate volume, DRE, PSA, PSA ratio and PSA density were found between men with and without widespread HGPIN (Table 2). PSA concentration was not significantly modified between the second and third biopsy (median [IQR]: 7.83 [5.34-10.50] vs. 7.53 [5.87-10.80], $p = 0.34$). The presence or absence of widespread HGPIN on the second biopsy did not significantly differ across patients with chronic prostatitis and patients with HGPIN on third biopsy ($p = 0.12$).

Finally, of the 43 patients who underwent the full set of three biopsies, 12 had a diagnosis of widespread HGPIN at the time of the first biopsy. Of these, 9 (75%) were rediagnosed with widespread HGPIN on the second biopsy, while the remaining 3 (25%) had focal HGPIN at that time. Cancer was found on third biopsy only in the first 9 patients (those with widespread lesions on both biopsies, in particular in 5 of these 9 men (56%), while none of the 3 patients with widespread HGPIN only on the first biopsy had a diagnosis of PCa on the third biopsy.

Discussion

HGPIN is a common pathological finding on prostate biopsy and has been associated with an increased risk of PCa on subsequent biopsies (3-6, 9). Initially this risk was estimated around 50% (4), however studies performed after 2000, in the era of extended prostate biopsy, have shown that this risk is approximately 23%, compared to a 19% risk of detecting cancer after a benign diagnosis (2). The impact of HGPIN on the need for further biopsies has thus been redimensioned, and numerous studies have explored pathological features of HGPIN in order to predict PCa on subsequent biopsies (2, 21). In this context, the denomination of widespread or multifocal HGPIN has arisen, defined by Netto and Epstein as ≥ 4 cores involved with HGPIN (21). This pathological entity has been positively associated with a significantly increased risk of PCa in numerous studies (6, 7, 10-14, 16), ranging from 36% to 39%. To date only few studies (12, 14, 22-25) have explored the risk of cancer following multiple biopsies (> 2 procedures) diagnosing HGPIN; moreover only two manuscripts have examined the cancer risk at third biopsy after diagnosing multiple cores involved with HGPIN on a second prostate biopsy (12, 14). In this manuscript we addressed this issue by conducting a prospective trial with a minimum 12 month follow-up, during which men with two consecutive diagnoses of HGPIN underwent a third prostate biopsy. Widespread HGPIN on the second biopsy was significantly associated with the risk of PCa. No clinical parameter such as age, DRE, prostate volume, PSA, PSA Density or PSA ratio was able to significantly predict cancer. If validated, these results strengthen the prognostic value of widespread HGPIN, with impact on the need for further oncologic surveillance in patients with such diagnosis.

We found a significant association between widespread HGPIN on second biopsy and PCa ($\chi^2 = 4.04$, $p = 0.04$), and men with widespread HGPIN had a 4-fold, significant increase in risk of detecting PCa on subsequent biopsy compared to men with 3 or less cores involved with HGPIN. The overall cancer risk on the third biopsy for men with widespread HGPIN on second prostate biopsy was 53%, higher that the risk if widespread was present at the time of the first biopsy (36-39% risk). In line with these findings are the results reported by *Bishara et al,* who found a 50% cancer risk if multiple cores (≥ 2) involved with HGPIN had been found on second biopsy (12). *Abdel-Khaled et al.* reported a similar 58% risk in patients with multifocal HGPIN (14). Whether these results justify the need to perform an early re-biopsy (6 months) in patients with widespread HGPIN at the second biopsy cannot be fully determined by our data. However we feel that repeat biopsy should be advised after diagnosing widespread HGPIN on second biopsy, after adequately counseling patients on the risks and benefits of undergoing further prostate biopsies.

Moreover, we explored the prognostic value of other clinical and laboratory parameters on PCa. All parameters measured, including age, prostate volume, DRE, PSA, PSA ratio PSA density were not significant predictors of PCa on subsequent biopsy. Most studies have yielded similar results (5, 26-29), in that there does not appear to be any clinical parameter that helps identify men who are more likely to have cancer on further biopsies. Given these results, a finding of widespread HGPIN, especially on second biopsy, may be crucial in planning patients' future follow-up and should draw the urologist's attention, as it appears to be a significant predictor of PCa on further testing.

Of the neoplasms diagnosed on the third biopsy of our cohort, 9/15 (60%) were low-grade, Gleason 6 (3 + 3), 7 of which showed a single core, 10-15% core involvement. Thus, 7/15 (47%) of the tumors identified are probably clinically insignificant and of 43 biopsies only 6 men had PCa with Gleason score ≥ 7. It could be argued

therefore that performing a third biopsy in men all with two diagnoses of HGPIN it may not be legitimate, as too many biopsies should to be performed to find one clinically significant cancer. However, if we restrict the analysis to patients with widespread lesions on second biopsy (17 men of 43), 9 tumors were identified, of which 4 were Gleason ≥ 7. As such, 17 men underwent prostate biopsy to uncover 4 clinically significant high-grade cancers: these results in four men being biopsied to find one clinically significant cancer (4:1). These results suggests that, if not all men with two HGPIN biopsies should undergo further procedures, it may be appropriate to perform a repeat biopsy in men with widespread lesions on the second biopsy specimens, in order to uncover clinically significant prostate cancer.

It is correct to point out some limitations of this study as the small sample size (n = 43). Given the singularity of this group of patients, as it represents a second subset group of our initial study population, we believe that these results express the impact that widespread HGPIN on PCa. 10 patients who underwent prostate resection for bladder outlet obstruction were excluded from final analysis: given the different accuracy in PCa detection of TRUS-guided prostate biopsy vs. histologic analysis of resected specimen during transurethral prostatic surgery, we feel that such exclusion is justified (30). The follow-up period was limited to 12 months, time elapsed between the first and third biopsy: such period of time may seem inappropriate to evaluate the evolution of HGPIN on PCa, but patients are still under evaluation and the results of biopsies performed at 24 months will be soon available. Moreover, a significant number of patients failed to return for rebiopsy and unfortunately data on their follow-up was not available for analysis: however, if we consider these drop outs to be random, the results of this study should not have been significantly biased by such loss of data. This finding underlines the importance of patient follow-up after a diagnosis of HGPIN (3). Nevertheless, we must acknowledge that our study firstly confirmed in a homogeneous population that widespread HGPIN is associated with a significant higher risk of PCa even in patients with two previous biopsies. Furthermore another peculiar characteristics of our group is that our patients underwent three prostate biopsies in 12 months time regardless of PSA value, using the presence of HGPIN a mandatory indication for prostate biopsy. The lower cancer detection rate on initial biopsy and the high incidence of multiple isolated HGPIN areas may depend on our study population: our academic hospital operates under the Italian National Care System which does not support screening programs for PCa. Furthermore, our clinical facility opened in 2002, and we can assume that our patient population had limited access to PCa centers and screening programs in the past.

Conclusions

The results of our study suggest that HGPIN and in particular widespread HGPIN are associated with an increased risk of PCA on a repeat biopsy in men with two previous diagnoses of HGPIN. No clinical parameter evaluated such as age, PSA, prostate volume, DRE and PSA derivates was able to significantly predict PCa in this particular group of patients. Further studies are needed to confirm these findings in other populations and to evaluate which possible biological factors related to widespread HGPIN are responsible for the observed results.

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