High Grade PIN in prostate biopsies and cancer detection on re-biopsy. The cancer found is significant on the pathological point of view. By the " Italian Group for Definition of Guide Lines on Prostatic Biopsy".

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Abstract

Objectives Repeat biopsy (re-biopsy) has been advocated following the diagnosis of High-grade prostatic intraepithelial neoplasia (HGPIN) found in prostate biopsy specimens. Previous studies of repeat prostate biopsy for HGPIN that report cancer detection rates of 40-70%, are based on the sextant biopsy scheme. Currently, extended prostate biopsy schemes that incorporate lateral/anterior peripheral zone are routinely utilized at most centres because of the associated increased cancer detection rate when compared to sextant biopsy. Our objective was to determine the prognostic value of HGPIN in men who underwent prostate biopsy with a major number of samples .

Methods We retrospectively evaluated 6196 transrectal ultrasound guided prostate biopsies done for elevation of PSA (between 4 and 10 ng/ml) from January 1998 to December 2002 in 8 Italian Urologic departments. All patients who had the initial pathological finding of High Grade PIN were selected and cancer detection rate was determined in follow-up biopsies. We also compare the pathological stage of the cancer detected with or without the diagnosis of HGPIN.

Results The overall detection rate of isolated High Grade PIN lesions was 3.38% (209 patients). Of 209 patients with isolated High Grade PIN on initial biopsy 182 (88%) underwent re-biopsy up to three times. The total incidence of cancer detection rate was 41% (79 patients). 85% after the first re biopsy, 15% after the 2^{nd}.

There were no differences at the pathological stage after radical prostatectomy between the group of patients who had cancer after detection of HGPIN or at the first biopsy.

Conclusions Our results suggest that for patients with a PSA between 4 and 10 ng/ml, whose initial biopsy contains HGPIN but not cancer, the presence of PIN alone is an indication to re-biopsy. Up to the 3rd re-biopsy prostate cancer could be detected.

Timing for re-biopsy, how many sample taken on re-biopsy, and how many times re-biopsy are still problems to solve. However the cancer found was pathological significance and did not differ from the prostatic carcinoma found after the first biopsy.

Keywords: prostatic neoplasms; prostatic intraepithelial neoplasia; biopsy

INTRODUCTION

High grade prostatic intraepithelial neoplasia (HGPIN) is characterized by glands and ducts with epithelial cell crowding and stratification, nuclear enlargement with some nuclear size and shape variation, increased chromatin density and clumping, and occasional to frequent large prominent nucleoli. Between 4.4% and 25% of men will have high grade prostatic intraepithelial neoplasia on transrectal needle biopsies performed for increased prostate specific antigen (PSA) or abnormal digital rectal examination (1). High grade prostatic intraepithelial neoplasia is often a multifocal lesion and has been found to coexist with cancer in radical prostatectomy specimens in more than 85% of cases (2). Prostatic intraepithelial neoplasia is currently considered by many investigators to be a precursor lesion of adenocarcinoma of the prostate (1-5). It has been postulated that intraepithelial neoplasia may precede the development of prostate cancer by several years (5). Studies suggest that it shares many his pathological, morphometric and genetic features with prostate cancer (6). It is difficult to determine precisely the natural history of a single high grade prostatic intraepithelial neoplasia lesion since it is not feasible to follow up with precision the exact areas of abnormality on repeat biopsy. Since the natural history of prostatic intraepithelial neoplasia has not been elucidated, current recommendations for serial repeat biopsy have not been validated by evidence based medicine, many studies have demonstrated that finding high grade prostatic intraepithelial neoplasia on prostate biopsy merits an immediate repeat biopsy since 27% to 100% of men will have prostate cancer on repeat biopsy (7-10).

The reported incidence of prostatic intraepithelial neoplasia in needle biopsy specimens varies from 8 to 31%, and it has been identified in 59 to 100% of surgical specimens of patients with localized prostate cancer. (11-14)

Davison et al noted a 15-fold increase in the relative risk of prostate cancer on repeat biopsy if high grade neoplasia was found in the initial biopsy (14).

Based on this evidence, a biopsy finding of high grade prostatic intraepithelial neoplasia is generally considered to require further investigation in candidates for curative treatment of localized prostate cancer. Followup at 6-month intervals for 2 years and thereafter at 12-month intervals has been suggested (15-17).

Limited data are available on how high grade prostatic intraepithelial neoplasia may affect serum total and percentage of free prostate specific antigen (PSA) (18-20).

We try to understand insight into the natural history of HGPIN by studying the follow up of a population after the initial diagnosis of HGPIN regardless of change in PSA or digital rectal examination.

MATERIALS AND METHODS

We retrospectively evaluated 6196 transrectal ultrasound guided prostate biopsies done for elevation of PSA (between 4 and 10 ng/ml) from January 1998 to December 2002 in 8 Italian Urologic departments. All patients who had the initial pathological finding of High Grade PIN were selected and cancer detection rate was determined in follow-up biopsies. We also compare the pathological stage of the cancer detected within the first repeat biopsy after diagnosis of HGPIN and the following.

Biopsies were performed because of elevated total serum PSA. Our study group consisted of 6196 men with a mean age of 67.4 ± 7.8 years.

Repeat biopsy 3 months later was recommended to all HGPIN men to rule out concurrent prostate cancer. Of the men XX (79%) had 2 or more biopsies (mean 2.2 per patient since the first biopsy that showed prostatic intraepithelial neoplasia, range 1 to 5).

There was no significant difference in mean percentage of PSA . We process the value of free Psa.

Prostate biopsies were performed transrectally with an 18 gauge needle using a Biopty gun with ultrasound guidance. Regardless of biopsy technique, targeted biopsies of hypoechoic or palpably abnormal areas of the prostate were not done.

All biopsy specimens were evaluated by the institution's referee genitourinary pathologist
The diagnosis of high grade prostatic intraepithelial neoplasia was established using the criteria of Bostwick and Brawer. (2)
Statistical analyses. Statistical analyses were performed using computer software. Student´s t test was used to compare continuous variables and Fisher´s exact test was used to compare categorical variables. The significance of relationships between various parameters was assessed with the Pearson correlation.

All cases with an original diagnosis of high grade prostatic intraepithelial neoplasia detected via transrectal ultrasound guided needle biopsy in a total of.

RESULTS

The overall detection rate of isolated High Grade PIN lesions was 3.38% (209 patients). Of 209 patients with isolated High Grade PIN on initial biopsy 182 (88%) underwent re-biopsy up to three times. The total incidence of cancer detection rate was 41% (79 patients). 85% after the first re biopsy, 15% after the 2^{nd}.

There were no differences at the pathological stage after radical prostatectomy between the group of patients who had cancer after detection of HGPIN at the first biopsy or at later biopsies.

Of the men with high grade prostatic intraepithelial neoplasia XX underwent an initial 12-core biopsy to exclude coexisting prostate cancer, and all were eligible for our repeat biopsy study.

Of these men underwent followup interval biopsy 3 years after detection of prostatic intraepithelial neoplasia. Characteristics of the study population at the time of initial diagnosis are presented in table 1

Mean age biopsies 63.4 yrs (52-72)
Mean age HGPIN 61.2 yrs (52-71)
Mean PSA value 6.1 ng/ml (4.1-10)
Mean PSA HGPIN 5.7 ng/ml (4.1-10)

Table 1. *Baseline characteristics of study population*

Mean PSA for the HGPIN group and men with or without cancer on repeat biopsy are shown in table 2..

The change in PSA level was statistically significant for the group without cancer and not statistically significant for the group with cancer on repeat biopsy. Of the 31 men who underwent 3 year followup biopsy 8 (25.8%) had prostate cancer, 11 (35.5%) had high grade prostatic intraepithelial neoplasia only and 12 (38.7%) had no tumor or prostatic intraepithelial neoplasia. Average Gleason score for those men with prostate cancer was 6.4.

Mean PSA HGPIN no cancer (4.1-10)	Table 2 PSA and diagnosis of cancer in HGPIN pts
Mean PSA HGPIN + cancer (4.1-10)	

Using univariate linear regression analysis, no significant correlation ($p > 0.10$) was found between differences in serum PSA and the diagnosis of prostate cancer on the follow up biopsies (table 2).

Overall, the men with HGPIN but no cancer on follow up had less than a 1.0 unit increase in serum PSA during the followup. Nothing is possibly to say about the men diagnosed with prostate cancer because we performed the biopsies indipentently by the value of PSA so we have not the registration of this variable.

Because these men were originally biopsied for increased serum PSA, it is difficult to make conclusions about a relationship between the finding of HGPIN in men with abnormal PSA and the development of prostate cancer.

There were no significant differences in mean age among men with high grade prostatic intraepithelial neoplasia, prostate cancer or BPH.

DISCUSSION

The finding of high grade prostatic intraepithelial neoplasia without concomitant prostate cancer is not

uncommon. (8).

The detection rate of isolated HGPIN , at our institutions is lower to that reported previously in the literature (11-13) this is due, by our opinion to the increasing number of samples obtained by our institutions in each biopsy respect to the early series (11-13), performing a wider mapping of the prostate is more easy to find cancer associated or not to HGPIN.

After this experience we begin to accept the concept that there are two different scenario about HGPIN: a) the association with prostate cancer (21) and b) the possibility of a cancer that may developed years after the diagnosis of HGPIN (5-7).

The former possibility is in a someway proved obtaining a increasing number of core samples during the biopsy. In this way we could find HGPIN and cancer simultaneously in different part of the prostate. This what was happening by repeating a sextant biopsy or with immediate 12 or more core samples performed every biopsy.

The latter is a kind of curse for the patients with isolated HGPIN, if after the first re biopsy, since further sampling with repeat biopsy is usually recommended for those with HGPIN, we do not find cancer, the patient is put under high surveillance and new biopsies are performed at regular interval with a much trouble for the unlucky patients .

To fight this doctrine of without ending biopsies there are a few alternative, wait for changing of PSA or try some form of clinical trials to prevent the development of HGPIN into cancer with chemo preventive treatment, such as hormonal therapy. (22).

In our experience none of the patients underwent treatment, and we performed the follow up biopsies only for the conditions to be HGPIN positive.

The probability of cancer on a second biopsy following an initial benign biopsy varies from 10 to 26%. (23-27) Studies have also presented findings on men diagnosed with cancer on needle biopsy, although repeat biopsy did not reveal carcinoma. (28-31).

Although these studies (23-31) are not comparable to studies like our evaluation of patients with a HGPIN needle biopsy, the issues are pregnant.
Also in cases with a totally benign initial biopsy the possibility to have cancer in a repeat biopsy is high (from 10 to 25%) (23-27) and is true also the contrary scenario in proven needle cancer on repeat biopsies is possible to find nothing (28-31).
These issues make things more complicated. It is true that in almost all series patients with atypical findings suspicious for cancer or HGPIN on initial biopsy have a destiny associated with an increased risk

of cancer on follow up biopsies and should not be considered with cases with an entirely benign initial biopsy.(32,33).

But there are some voices like Fowler et al. on the opposite opinion, for them HGPIN was not a predictor of repeat biopsy cancer detection and PSA functions were similar among men without cancer who did and did not have HGPIN in 1 or more benign biopsies, for them percent free PSA was the most powerful predictor of cancer.. This finding suggests that HGPIN may not be a reliable indicator of clinically significant existing prostate cancer. (34) The elevation of PSA could be the reason of concomitant or follow up cancer.

Evidence of if and in case how high grade prostatic intraepithelial neoplasia affects total serum PSA levels is conflicting. Brawer et al studied the relationship between serum PSA levels and prostate diseases in men who underwent simple prostatectomy for presumed benign prostate enlargement (35). They reported an intermediate value for mean serum PSA in patients with prostatic intraepithelial neoplasia between that for benign tissue and carcinoma. However, their patients underwent open enucleation or transurethral resection of the prostate, which makes it difficult to exclude cancer from diagnosis.

Similar results were reported by Lee et al (36). Conversely, in recent studies based on radical prostatectomy specimens Ronnett et al reported that high grade prostatic intraepithelial neoplasia did not correlate with serum PSA (19). Similarly, in a study of 194 completely embedded radical prostatectomy specimens Alexander et al noted that intraepithelial neoplasia did not appear to contribute significantly to serum PSA (20).

It is known that the percentage of free PSA is lower in men with prostate cancer than in those with BPH, and that measurements of free PSA can help distinguish between hyperplasia and cancer. Catalona et al reported that median percentage of free PSA was 9.2% in men with cancer and a normal-sized gland, 15.9% in men with cancer and an enlarged gland, and 18.8% in men with BPH (37). However, there is limited information about how high grade prostatic intraepithelial neoplasia can affect the percentage of free PSA. Tarle and Kraljic compared the percentage of free PSA in patients with intraepithelial neoplasia, BPH and prostate cancer (38). They found an intermediate mean value of percentage of free PSA in patients with high grade prostatic intraepithelial neoplasia (16.9 ± 9%) compared to that for BPH (29.1 ± 13%) and prostate cancer (14.4 ± 10%). However, 50% of the patients with prostatic neoplasia were subsequently diagnosed with prostate cancer and, therefore, probably had concomitant prostate cancer that influenced the earlier percentage of free PSA results.

Our patients with cancer had not a significantly lower percentage of free PSA than those with high grade prostatic intraepithelial neoplasia and there was no difference in mean total serum PSA or the percentage of free PSA between those with high grade neoplasia and those with biopsy proved benign findings (20.8 ± 7.1 versus 20.1 ± 7.3%).

The observation that repeat biopsy had the greatest yield with increasing time from detection of prostatic intraepithelial neoplasia supports the notion that it is a precursor of cancer and suggests that interval follow up biopsy may be advisable but how many biopsies we have to performed and how long follow up ?.

The fact that not all biopsies of the men with high grade prostatic intraepithelial neoplasia were evaluated by the same pathologist could introduce a potential bias to our study because of interobserver variability in the diagnosis of this condition. However, this is a spontaneous study and reflect the real situation in most institutions, we know that there is good agreement about HGPIN definition and diagnostic criteria within pathologists (39).

We have enough element to affirm according by Djavan et al that after the third biopsy the percentage of possibility to find cancer in the prostate is very low, and cancer found during the forth biopsy is different from these found early (low grade – low stage, perhaps indolent or latent cancer (40), so we think that

after the third biopsy is reasonable give a stop to the biopsies, almost until new events occurs. The timing of the biopsies after the first re biopsy is controversy too.

It is likely that, despite extensive sampling of the prostate, a number of patients with high grade prostatic intraepithelial neoplasia will have cancer missed at baseline due to limitations in our biopsy ability. It is intuitive that small undetectable cancers would be detected at a delayed interval as they continue to grow.

In addition to those cancers missed at baseline, if one believes that prostatic intraepithelial neoplasia is a premalignant lesion, some men with no cancer at baseline are likely to have prostate cancer during follow up. Once again, it is unclear that PSA can detect this progression in longitudinal follow up.

While the incidence of cancer in the series of HGPIN has varied due to pre-biopsy PSA level and suspicion of cancer in the biopsy cohort, the majority of studies have suggested a cancer detection rate up to 50% at the time of immediate repeat sextant biopsy. (13,14) Therefore, it has long been concluded that an immediate repeat biopsy is mandatory to exclude coexisting prostate cancer in men with high grade prostatic intraepithelial neoplasia on a sextant biopsy. The optimal site and number of additional core biopsies required to exclude coexisting prostate cancer have more recently been studied.

Borboroglu et al examined the repeat biopsy strategy for patients with high grade prostatic intraepithelial neoplasia or atypia. (16). Of their patients 73% had repeat biopsy within 12 months and the rate of prostate cancer on repeat sampling for patients with high grade prostatic intraepithelial neoplasia was 44%. They concluded that repeat biopsy should include bilateral and transition zone sampling.

Rosser et al reported the detection of high grade prostatic intraepithelial neoplasia and rates of cancer diagnosis on repeat biopsy using a 5-region biopsy technique, which includes a variable number of cores (mean 14) targeting the traditional sextant as well as the far lateral and midline regions (41). Repeat biopsy in this series at a mean interval of 9.2 months revealed prostate cancer in 8 (33%) cases, 5 of which were diagnosed outside the midsagittal plane which is sampled by traditional sextant biopsy. In fact, the detection rates in these series do not appear to be significantly greater than those noted for repeat sextant biopsy in earlier series.

Keetch et al showed that the detection rate of cancer in a screening population re-biopsied every 6 months for 5 years diminishes after the second biopsy (8). Borboroglu et al previously reported on the cancer detection rate of repeat biopsy using an extensive sampling biopsy technique (mean of 22.5 cores). (42). In men diagnosed with high grade prostatic intraepithelial neoplasia on initial biopsy the cancer detection rate using this extensive repeat biopsy technique was 47%, comparable to detection rates reported for a simple repeat sextant biopsy.

The detection of prostate cancer on follow up interval biopsy up to 3 years after the initial finding of high grade prostatic intraepithelial neoplasia was independent of changes in PSA. The change in mean PSA was not significantly different between those men with and without prostate cancer at the time of repeat biopsy. Of the men diagnosed with prostate cancer 75% had a PSA change of less than 1.0 ng./dl. This finding has tremendous implications with regard to the use of longitudinal serum PSA measurement for following men with high grade prostatic intraepithelial neoplasia.

Additionally, it implies that those individuals with high grade prostatic intraepithelial neoplasia should undergo followup interval biopsy regardless of the absence of changes in the serum PSA. Certainly, individuals with rapidly increasing PSA or markedly altered digital rectal examination may need to be considered for sooner interval biopsy but this conclusion cannot be made from our data.

The optimal timing of followup interval biopsy in men with high grade prostatic intraepithelial neoplasia requires further investigation. It must represent a balance between unnecessary negative biopsies (due to biopsying too early) and missing the opportunity to cure the detected cancer (due to biopsying too late).

Of those men diagnosed with prostate cancer at follow up biopsy 85% underwent radical prostatectomy we compare the pathological results of the cancer with diagnosis after the first re-biopsy with those

diagnosticated during the second and third re biopsy. While the number of patients undergoing surgery is going smaller and smaller, so is difficult have a statistically real significance, the results does not show a difference by a pathological point of view, this observation strongly suggests that, although progression to clinical prostate cancer may occur at an earlier interval, early detection of prostate cancer at a curable stage can be achieved with followup interval biopsy.

Several caveats of our study deserve mention. The study is retrospective based on transrectal needle biopsy findings, which limits our ability to exclude cancer from diagnosis and estimate the impact of an undetected cancer on the percentage of free PSA. Additionally, although none of the men with HGPIN after the third biopsy has been subsequently diagnosed with cancer, they have not been followed for a long time (mean 20 ± 12 months) and, therefore, it is possible that some may later have prostate cancer.

CONCLUSIONS

A high proportion of men with high grade prostatic intraepithelial neoplasia will have prostate cancer, independent of changes in PSA and number of sampling following initial diagnosis. Our study reaffirms the approach that men with high grade prostatic intraepithelial neoplasia and no evidence of coexisting cancer should be followed and re-biopsied to exclude prostate cancer. Our longitudinal data in men with high grade prostatic intraepithelial neoplasia strongly support the concept that it is a risk factor for the development of prostate cancer, thereby further validating the lesion as a target for chemopreventive and therapeutic agents. We recommend a prolunged followup in men with high grade prostatic intraepithelial neoplasia, regardless of change in serum PSA.

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Can the number of cores with high-grade prostate intraepithelial neoplasia predict cancer in men who undergo repeat biopsy?

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OBJECTIVES: To evaluate whether the presence of, or the number of cores containing, high-grade prostatic intraepithelial neoplasia (PIN) found in men who underwent initial extended multisite biopsy could predict which men would have prostate cancer on subsequent repeat biopsies. METHODS: Between June 1997 and January 2003, 1086 men underwent initial prostate biopsy for early detection of prostate cancer using an extended multisite biopsy scheme. Of these, 175 men without cancer underwent at least one repeat biopsy (range one to three; median interval between biopsies, 3 months). Among these 175 patients, 47 had high-grade PIN on initial biopsy. RESULTS: The initial extended biopsy identified cancer in 33.8% (367 of 1086) and high-grade PIN in 20.8% (226 of 1086). The incidence of high-grade PIN only in patients found to have cancer on initial biopsy was 29.7% (109 of 367). The presence of high-grade PIN was associated with concurrent prostate cancer at the initial biopsy ($P < 0.0001$). Overall, repeat biopsy identified cancer in 18.3% of the 175 men. Of the 47 men with high-grade PIN, 5 (10.6%) were found to have cancer on repeat biopsy. The number of biopsy specimens positive for high-grade PIN on initial biopsy was not associated with the likelihood of prostate cancer on repeat biopsy. Multivariate logistic regression analysis showed that neither the presence of high-grade PIN nor the number of cores containing high-grade PIN on initial biopsy were predictors for prostate cancer on repeat biopsy. CONCLUSIONS: The number of cores positive for high-grade PIN was not predictive for cancer on repeat biopsy.