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ORIGINAL ARTICLE

Predicting prostate cancer at rebiopsies in patients with high-grade prostatic intraepithelial neoplasia: a study on 546 patients

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The aim of this study was to analyse the factors that predict the diagnosis of prostate cancer (PCa) after high-grade prostatic intraepithelial neoplasia (HGPIN). Data from 546 patients with HGPIN submitted up to a 6-month series of three rebiopsies, according to an institutional protocol, were reviewed. PCa has been found in 174 cases (31.8%), in 116 cases at the first and in 58 cases at a further rebiopsy. The risk of finding PCa at the first rebiopsy was correlated with the PSA value and with an anomalous digital rectal examination (DRE) at the time of the initial biopsy; the risk at a subsequent rebiopsy was correlated to the number of cores with HGPIN, with a cutoff of four, and to the ratio with the total number of cores ('PIN density'), with a cutoff of 50%, at the time of initial biopsy. A tailored protocol of controls can be suggested: (a) higher PSA value and/or anomalous DRE: early extended or saturation rebiopsy; (b) number of cores with HGPIN $\geqslant 4$ and/or PIN density $\geqslant 50\%$: delayed rebiopsy; and (c) no risk factors: PSA and DRE controls.
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Keywords: high-grade prostatic intraepithelial neoplasia; prostate carcinoma; prostate biopsy; rebiopsy

Introduction

High-grade prostatic intraepithelial neoplasia (HGPIN)—defined as the presence of architecturally benign ducts and acini lined by abnormal secretory cells with morphological changes similar to those observed in prostatic cancer (PCa)[1]—is generally considered a precursor lesion of PCa. However, if compared with the first reports, the cancer detection rate at a rebiopsy has been definitely lowered by the current adoption of a more extended bioptic sampling scheme, which have surely allowed one to spare some of the diagnoses previously missed by the first biopsy. Although HGPIN is a common finding with an incidence of up to 24% of all prostatic biopsies,[2] its surveillance protocol is still debated with inconsistent opinions among experts.

This paper reviews our experience in patients with HGPIN submitted to a bioptic follow-up to find out which of the data available at the initial biopsy could be predictive for the diagnosis of cancer at rebiopsy to outline a tailored protocol of controls.

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Materials and methods

There are no screening programs for PCa based on PSA in Italy, even its dosage is commonly suggested by general practitioners and urologists in asymptomatic male subjects older than 40–50 years. At our institute, prostatic biopsy is indicated for a PSA value higher than $4\,ng\,ml^{-1}$ or suspicious prostatic digital rectal examination (DRE) or transrectal prostatic ultrasound. The procedure is performed using a transperineal approach with local anaesthesia. From 2001 to 2005, the sampling scheme at the first biopsy generally provided for 8/10 cores of the peripheral zone, but later it was increased up to a minimum of 12 cores; suspicious areas at DRE or transrectal prostatic ultrasound have been separately sampled; the transition zone has been usually sampled only at the rebiopsies.

After the diagnosis of HGPIN in all the patients eligible for radical therapy (life expectancy longer than 10–15 years), it has been recommended that the patients be submitted to three rebiopsies at a 6-month interval and later to periodical clinical controls of DRE and PSA value; in patients unfit for radical therapy, the series of rebiopsies was recommended but stopped if a benign histology was found. All the specimens have been evaluated only by a single experienced uropathologist (RT).

For this study, all the cases with a diagnosis of HGPIN observed from 2001 to 2009 and submitted to at least one rebiopsy have been reviewed. The cases with an

associated diagnosis of atypical small acinar proliferation or small foci of PCa have been excluded. The occurrence of PCa at the first rebiopsy or at a further rebiopsy has been separately analysed considering clinical (age, PSA, DRE transrectal prostatic ultrasound —at each biopsy), bioptic and pathological data. DRE and transrectal prostatic ultrasound findings other than normal have been defined as abnormal (that is, including into this definition the cases regarded as ambiguous by the examiners). Among bioptic data, the ratio between the number of cores with HGPIN and the total number of cores sampled was defined as 'PIN density'.

Statistical analysis

Cutoff values were defined as the lowest value of a continuous variable that could discriminate two groups making the difference of the considered variable statistically significant.

Nominal variables have been compared by Pearsons's χ^2 test and, if applicable, Fisher's exact test and continuous variables by the Mann–Whitney *U*-test or, if applicable, by Student's *t*-test.

All the analyses have been carried out by using the software SPSS (version 17, SPSS, Chicago, IL, USA).

Results

A total of 546 patients were analysed, with a mean age of 64.9 (range 45–87) years submitted to a median number of 3 biopsies per patient (2–6 biopsies per patient), with a mean number of 10.8 cores per biopsy (6–23 cores per biopsy) at the initial biopsy and 12.9 cores per biopsy (6–37 cores per biopsy) at rebiopsies, a mean interval between consecutive biopsies of 5.1 (1–39.5) months and a mean 'bioptic' follow-up time of 14.8 (2–102) months.

PCa was found in 174 patients (31.8%), in 116 (21.2%) at the first rebiopsy, at a mean interval of 7.8 months, and in 58 (10.6%) after a median of two rebiopsies at a mean interval of 21.6 months. At statistical analysis, the detection of PCa at the first rebiopsy was significantly related only to the PSA value and abnormal DRE referred to the initial biopsy; for the PSA value, it was identified at a cutoff of 7 ng/ml (Table 1). Conversely, the diagnosis of PCa at a further rebiopsy was related to the number of cores with HGPIN and to the PIN density at the initial biopsy and it was possible to identify the cutoff values of four cores with HGPIN and of 50% for PIN density (Table 2). Grouping the patients on the basis of these cutoff values could discriminate with high specificity the risk of finding PCa at the first or at a further biopsy (Table 3).

These results were confirmed at a subanalysis among the 251 patients sampled with at least 12 cores: PCa was found in 48 patients at the first rebiopsy (19.1%, mean latency 7.8 months) with a significant correlation with PSA value (8.4 vs 7.2 ng ml^{-1}, $P=0.034$) and abnormal DRE (28.8 vs 15.0%, $P=0.015$) at the initial biopsy, whereas PCa at a further rebiopsy was found in 21 patients (8.3%, mean latency 15.0 months) with a correlation with the number of cores with HGPIN (4.75 vs 2.89, $P=0.025$) and the PIN density (0.3238 vs 0.2051, $P=0.031$) at the initial biopsy. Also the cutoffs of PSA, number of PIN cores and PIN density could be applied to this subset of patients.

Table 1 Comparison of features of initial biopsy in patients with cancer and no cancer diagnosis at the first rebiopsy

Features of initial biopsy	*Findings at first re-biopsy*		P-*value*
	Cancer	*No cancer*	
PSA value	8.617 ng ml^{-1}	7.202 ng ml^{-1}	**0.004**
PSA value <7	16.9%	83.1%	**0.003**
PSA value ⩾7	28.1%	71.9%	
Difference of PSA value with first re-biopsy	−0.0811 ng ml^{-1}	0.2244 ng ml^{-1}	0.617
Normal prostatic rectal examination	18.8%	81.2%	**0.014**
Anomalous prostatic rectal examination	29.8%	70.2%	
Normal prostatic ultrasound	21.2%	78.8%	0.456
Anomalous prostatic ultrasound	22.0%	78.0%	
No. of cores	10.55	10.89	0.368
No. of cores with PIN	2.57	2.39	0.617
No. of cores with PIN <4	19.4%	80.6%	0.425
No. of cores with PIN ⩾4	24.0%	76.0%	
PIN density	0.2768	0.2537	0.296
PIN density <50%	19.6%	80.4%	0.455
PIN density ⩾50%	24.0%	76.0%	
Latency of first rebiopsy	7.85 mesi	7.08 mesi	0.648

Abbreviation: PIN, prostatic intraepithelial neoplasia.
Bold values represent *P*-value of comparison reaching statistical significance.

Table 2 Comparison of features of initial biopsy in patients with cancer and no cancer diagnosis at the second or further rebiopsy

Features of initial biopsy	*Findings at second (or more) re-biopsy*		P-*value*
	Cancer	*No cancer*	
PSA value	7.435 ng ml^{-1}	6.993 ng ml^{-1}	0.235
PSA value <7	18.9%	81.1%	0.283
PSA value ⩾7	24.5%	75.5%	
Normal prostatic rectal examination	23.2%	76.8%	0.198
Anomalous prostatic rectal examination	14.5%	85.5%	
Normal prostatic ultrasound	21.6%	78.4%	0.878
Anomalous prostatic ultrasound	20.2%	79.8%	
No. of cores	9.98	10.84	0.156
No. of cores with PIN	3.23	2.44	0.085
No. of cores with PIN <4	15.2%	84.8%	**0.013**
No. of cores with PIN ⩾4	34.1%	65.9%	
PIN density	0.3602	0.2626	**0.036**
PIN density <50%	16.1%	83.9%	**0.025**
PIN density ⩾50%	34.4%	65.6%	
Mean latency between biopsies	5.95 mesi	6.49 mesi	0.836

Abbreviation: PIN, prostatic intraepithelial neoplasia.
Bold values represent *P*-value of comparison reaching statistical significance.

Among the cases that were submitted to at least two rebiopsies, the histological findings of the first rebiopsy were not related to the risk of a subsequent diagnosis of PCa: indeed, the detection rate of PCa was 15.7% in the cases with a benign histology and 21.7% in those with a persistence of HGPIN ($P=0.444$).

Cancers found at the first rebiopsy showed a higher aggressiveness when compared with the ones found at a further rebiopsy. In particular, they had a significantly higher prevalence of bioptic Gleason score ⩾7 (16.0 vs 5.3%, $P=0.049$) and among the 88 patients who underwent radical prostatectomy, a higher prevalence of pathological Gleason score ⩾7 (27.9 vs 16.7%, $P=0.404$) and a higher

Table 3 Risk stratification for the diagnosis of PCa at the first or further rebiopsy

	Rate of cancer diagnosis			
	First rebiopsy		*Second (or more) rebiopsy*	
PSA value $<7\,ng\,ml^{-1}$ and normal rectal examination	13.9%	$P<0.001$	21.0%	$P=1.000$
PSA value $\geqslant 7\,ng\,ml^{-1}$ and/or anomalous rectal examination	28.0%		21.2%	
No. of PIN cores <4 and PIN density $<50\%$	20.1%	$P=1.000$	14.6%	$P=0.015$
No. of PIN cores $\geqslant 4$ and/or PIN density $\geqslant 50\%$	20.4%		30.9%	

Abbreviations: PCa, prostate cancer; PIN, prostatic intraepithelial neoplasia.

rate of pT3a (10.9 vs 0.0%, $P=0.183$); in all the cases, no lymph nodal metastasis was detected.

Discussion

HGPIN was described in 1969 by McNeal,[3] but its current definition was formulated in 1987 by Bostwick and Brawer[4] and formalised during a consensus conference on prostatic preneoplastic lesions in 1989. There are some evidences supporting the hypothesis that HGPIN is a preneoplastic lesion:[5] is multifocal, similar to PCa; is more frequent in patients with PCa; has an age distribution equal to PCa; may degenerate into PCa with a progressive transition.[6–9] However, some clinical studies showed that patients with HGPIN have a low risk of further cancer diagnosis but not higher than that observed in cases with a benign diagnosis.[10–14] In any case, after the introduction of extended bioptic schemes with 10/12 samples, the rate of cancer diagnosis after HGPIN decreased from the values up to 80% of the sextant biopsy era to the current 20–30%; probably, owing to a wider sampling, the diagnoses at rebiopsy that were previously not detected at the initial biopsy were avoided.[15] Therefore, it is still debated whether it is really necessary to repeat a biopsy for all the patients with HGPIN and EAU guidelines,[16] generically suggest an early rebiopsy only for multifocal HGPIN. Several studies, indeed, have ascertained that the number of cores with HGPIN at a sextant[17] or extended biopsy[18–20] correlates with the risk of finding PCa at rebiopsy, although there are also data against this conclusion.[21,22] Among the studies supporting the correlation between multifocality of HGPIN and the risk of PCa, different cutoff values in the number of cores with HGPIN have been reported: two cores in Merrimen *et al*.[23] in a population study on 564 cases, and four cores in Netto and Epstein[24] in an institutional study on 41 cases in which such a condition, worsened by a risk reaching approximately 40%, was formally defined as 'widespread PIN'. Again, also with regard to the timing of rebiopsy, the literature reports heterogeneous opinions from controls every 6 months for 2 years and then yearly[25] to one single rebiopsy after 36 months.[26]

From a single-institution population of $\sim$5500 patients who were submitted to a fine-needle prostatic biopsy during a period of 9 years evaluated by a single experienced pathologist, the present study retrospectively reviews the data of 546 patients with isolated HGPIN, all subjected to at least one rebiopsy after a short interval of time (6 months) and, in a proportion of 65% (278/430) of cases, monitored with at least two rebiopsies.

Unlike what has been previously reported,[18–22] we found a significant correlation between the cancer detection rate at the first rebiopsy and PSA value and DRE at the time of the initial biopsy: considering the short interval between biopsies, and that HGPIN can justify neither the increased values of PSA nor the anomalous DRE,[27] it is reasonable to suspect that in these cases a PCa already present was missed by the first sampling. On the contrary, in cases in which the diagnosis of PCa has occurred at a subsequent rebiopsy, a statistically significant correlation was identified with the number of cores positive for HGPIN and with the PIN density of the initial biopsy. In these patients, the fact that the diagnosis of PCa was reached after a longer time, and after at least two rebiopsies, makes it more reasonable that PCa was not present at the time of the initial biopsy and that a true transition from HGPIN to PCa occurred, as it should be indirectly confirmed by the lower aggressiveness of these cancers.

An accurate risk stratification was possible on the basis of cutoff values (see Table 3). In our cohort of patients, a PSA cutoff of $7\,ng\,ml^{-1}$ and an anomalous prostatic DRE defined a group with a twofold risk (28.0 vs 13.9%) of finding PCa at the first rebiopsy. Conversely, four or more cores with HGPIN and 50% or more in PIN density doubled the risk (30.9 vs 14.6%) of the diagnosis at a further rebiopsy.

Our experience also confirms that the rate of PCa diagnosis after HGPIN is $\sim$30%, but, once the diagnoses probably missed by the first biopsy as discussed above are excluded, the actual risk of diagnosis of PCa after HGPIN would be reduced to 10%. Such an exiguous rate can support the criticisms of several authors about the real need of an indiscriminate bioptic control in all HGPIN cases.

The main limitation of the study is its retrospective design; indeed, even if bioptic controls followed a well-codified internal protocol, some biases, especially in the number of cores per biopsy—there is a proportion of 13% of patients who were not initially submitted to an extended biopsy—and intervals between biopsies, come from the fact that the patients were not formally enrolled in a perspective study.

To conclude, three conditions deserving different control modalities can be identified:

(a) higher PSA value and/or anomalous DRE, in which an extended or saturation rebiopsy is indicated after $\sim$2/4 months, that is, the time required for the recovery from the bioptic damage in order not to invalidate pathological evaluation;
(b) number of cores with HGPIN $\geqslant 4$ and/or PIN density $\geqslant 50\%$, in which a rebiopsy is indicated after at least 24 months; the finding of less aggressive

cancers in such conditions allows to delay the control in order to increase the rate of diagnosis without losing the chance of a radical therapy;

(c) no risk factors, in which it is advisable to carry out just a clinical and PSA monitoring to eventually indicate the repetition of the biopsy.

Conflict of interest

The authors declare no conflict of interest.

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