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Original Article

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The current recommendation for the management of isolated high-grade prostatic intraepithelial neoplasia

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Abstract

Objective

To analyse the current predictive value of isolated high-grade prostatic intraepithelial neoplasia (HGPIN) for clinically significant prostate cancer (csPCa) detection in repeat biopsies.

Patients and Methods

A cohort of 293 men with isolated HGPIN detected in previous biopsies performed without multiparametric magnetic resonance imaging (mpMRI), and who underwent repeat biopsy within 1 to 3 years, was analysed. Pre-repeat biopsy mpMRI and guided biopsies to suspicious lesions (Prostate Imaging – Reporting and Data System [PI-RADS] ≥3) and/or and systematic biopsies were performed. Persistent prostate cancer (PCa) suspicion, defined as sustained serum prostate-specific antigen level >4 ng/mL and/or abnormal digital rectal examination, was present in 248 men (84.6%), and was absent in 45 men (15.4%). A control group of 190 men who had no previous HGPIN, atypical small acinar proliferation or HGPIN with atypia who were scheduled to undergo repeat biopsy due to persistent PCa suspicion were also analysed. csPCa was defined as tumours of Grade Group ≥2.

Results

In the subset of 45 men with isolated HGPIN, in whom PCa suspicion disappeared, only one csPCa (2.2%) and one insignificant PCa (iPCa) were detected. csPCa was detected in 34.7% of men with persistent PCa suspicion and previous HGPIN, and in 28.4% of those without previous HGPIN (P =0.180). iPCa was detected in 12.1% and 6.3%, respectively (P =0.039). Logistic regression analysis showed that the risk of csPCa detection was not predicted by previous HGPIN: odds ratio (OR) 1.369 (95% confidence interval [CI] 0.894–2.095; P =0.149); however, previous HGPIN increased the risk of iPCa detection: OR 2.043 (95% CI 1.016–4.109; P =0.006).

Conclusion

The risk of csPCa in men with isolated HGPIN, in whom PCa suspicion disappears, is extremely low. Moreover, in those men in whom PCa suspicion persists, the risk of csPCa is not influenced by the previous finding of HGPIN. However, previous HGPIN increases the risk of iPCa detection. Therefore, repeat prostate biopsy should not be recommended solely because of a previous HGPIN.

Keywords

high-grade intraepithelial neoplasia, clinically significant prostate cancer, insignificant prostate cancer, multiparametric MRI, repeat prostate biopsy

Introduction

In 1986, McNeal and Bostwick [1] initially described intraductal prostatic dysplasia as a premalignant lesion, while Bostwick and Brawer [2] subsequently coined the name prostatic intraepithelial neoplasia (PIN). The poor reproducibility of low-grade PIN and its lack of association with prostate cancer (PCa) meant that, after a while, only high-grade PIN (HGPIN) was reported. In addition, isolated HGPIN appeared to be more associated with future detection of PCa, specifically when multifocal, which occurs when three or more cores contain the lesion [3-5]. The initial incidence of isolated HGPIN ranged from 0.6% to 24%, but this decreased after the application of more aggressive biopsy schemes. The current risk of PCa detection following isolated HGPIN is ˜20–30%, which is not significantly higher than detection after a benign biopsy [5,6]. Currently, the European Association of Urology (EAU) PCa guidelines recommend repeating prostate biopsy within 1 to 3 years after a finding of multifocal HGPIN [7].

The current challenge regarding early detection of PCa has changed. Currently, the goal is to detect the maximum amount of clinically significant PCa (csPCa), reducing the overdetection of insignificant PCa (iPCa), and saving unnecessary prostate biopsies [7,8]. Pre-biopsy multiparametric MRI (mpMRI) and guided biopsies have improved the early detection of PCa, and they are the current strategy for early detection of csPCa [7]. Recent evidence suggests that the majority of tumours detected in repeat biopsies after isolated HGPIN are low-grade tumours. However, the impact of this new strategy for detecting csPCa is unknown [6,8,9,10,11,12,13].

The main aim of the present study was to evaluate the current recommendation of repeating prostate biopsy after isolated HGPIN detection, by assessing the risk of csPCa and iPCa in such men, based on the persistence of PCa suspicion, based on serum PSA, and DRE evolution.

Patients and Methods

Study cohort

A cohort of 483 men scheduled to undergo repeat prostate biopsy between 1 January 2015 and 31 December 2019, who previously had 12-core systematic biopsy without pre-biopsy mpMRI, were selected. Men with a previous PCa diagnosis, atypical small acinar proliferation, HGPIN with atypia (PINATYP), undergoing 5-α-reductase inhibitor treatment, and who had incomplete datasets were previously excluded. The institutional review board approved the study (PR/317/2017).

A total of 293 men with previous HGPIN were prospectively followed and re-biopsied within 1 to 3 years. Pre-repeat biopsy mpMRI and guided biopsies to Prostate Imaging – Reporting and Data System (PI-RADS) lesions ≥3 and/or 12-core systematic biopsies (if negative mpMRI) were always performed. Multifocal HGPIN, defined as detection of ≥3 cores with HGPIN [3,4,8,12,13], was found in 192 men (65.6%). Persistent PCa suspicion, defined as sustained serum PSA level >4 ng/mL and/or abnormal DRE, was present in 248 men (84.6) and not in the remaining 45 men (15.4%). A control group of 190 men without previous HGPIN and persistent PCa suspicion, who were previously subjected to systematic biopsies without mpMRI, and were scheduled to undergo pre-repeat biopsy mpMRI and guided and/or systematic re-biopsies during the same period were also selected.

Repeat biopsy procedure

The EAU PCa guidelines and recommendations for repeating prostate biopsies were strictly followed [7]. A 3-Tesla mpMRI (Magneton Trio; Siemens Medical Solutions, Erlangen, Germany) was performed according to the guidelines of the European Society of Urogenital Radiology [14]. After November 2015 and, retrospectively, before this date, two expert radiologists (S.R. and R.M.) used the PI-RADS v2 scoring system [15]. An expert urologist (A.C.) performed all repeat biopsies according to the EAU PCa guideline recommendations [7]. A minimum of two-cores TRUS-guided biopsies were obtained, through MRI–ultrasonography cognitive fusion, from the lesions with PI-RADS lesions >3 [16], and 12-core TRUS systematic biopsy was performed alone when no suspicious lesions were detected on mpMRI [17]. A BK Focus 400 ultrasonography scanner with a triplane endorectal probe 8881 (BK Medical Company Inc., Herlev, Denmark), and an 18-gauge, 25-cm, automated biopsy needle (Bard Monopty; Bard Medical Inc, Covington, GA, USA) were used. Two expert uropathologists (I.M.d.T. and M.E.S.) analysed the biopsy material. The tumour grading was reported using Grade Groups (GGs), which were initially proposed by authors led by Dr Epstein at Johns Hopkins Hospital [18]. These were validated in a large multi-institutional study [19], and subsequently endorsed by the 2014 International Society of Urological Pathology Consensus Conference [20], whereby GG1 = Gleason score ≤6, GG2 = Gleason score 3+4=7, GG3 = Gleason score 4+3=7, GG4 = Gleason score 8, and GG5 = Gleason score 9–10 [18-20]. GG ≥2 tumours were classified as csPCa, while GG1 defined iPCa [21,22].

Statistical Method

The main outcome variables were csPCa and iPCa. Quantitative variables were denoted by medians and interquartile range, while qualitative variables were denoted by numbers and rates. Associations between categorical

variables were assessed with chi-squared or McNemar´s tests, while the Mann–Whitney *U*-test, Kruskal–Wallis test and median test were used to assess quantitative variables. Multivariate analysis, using binary logistic regression, was performed to predict PCa, csPCa, or iPCa; the odds ratios (ORs) and 95% CIs were calculated. Two-sided statistical tests were evaluated, and *P* values <0.05 were taken to indicate statistical significance. This analysis was performed using the Statistical Package for the Social Sciences (SPSSv.24; IBM Corp., Armonk, NY, USA).

Results

Comparison between the characteristics of men without prior HGPIN and those with unifocal or multifocal HGPIN in the previous negative biopsy

The characteristics of the study population are summarized in Table 1. The study highlights that 60.5% of men scheduled for repeat prostate biopsy had previous HGPIN, 34.4% had unifocal and 65.6% had multifocal tumours. Among the men scheduled for repeat prostate biopsy, 91.3% had PCa suspicion, which was based on persistent serum PSA elevation and/or abnormal DRE, while 45 men (8.7%) had previous multifocal HGPIN, which was the only indication for repeating prostate biopsy. The overall rate of PCa detection was 38.1%, including 29.2% of csPCa and 8.9% of iPCa. Table 2 summarizes the general characteristics of men based on the finding of isolated HGPIN in the previous negative prostate biopsies and its type, unifocal or multifocal. The rate of negative mpMRI ranged between 24.2% and 32.8% in men with HGPIN, while the rates of PI-RADS score 5 ranged between 4.0% in men with unifocal HGPIN and 5.7% in those with mHGPIN. The overall PI-RADS distribution between men without previous HGPIN and those with unifocal and multifocal HGPIN was similar (*P* =0.292).

Table 1 Demographics of the study population

Characteristic	Value
Sessions, *n*	483
Median (IQR) age, years	67 (62–73)
Median (IQR) PSA, ng/mL	7.5 (5.2–12.0)
Positive DRE, *n* (%)	95 (19.7)
Median (IQR) prostate volume, mL	56 (40–76)
Median (IQR) PSA density, ng/mL/mL	0.13 (0.09–0.23)
PCa family history, *n* (%)	83 (17.2)
Median (IQR) number of previous biopsies	1 (1–2)
Median (IQR) interval between last two biopsies, months	23 (14–36)
Previous HGPIN, *n* (%)	293 (60.5)
Unifocal HGPIN, *n* (%)	101 (34.4)
Multifocal HGPIN, *n* (%)	192 (65.6)
Persistent PCa suspicion based on PSA and/or DRE, *n* (%)	441 (91.3)
mpMRI, *n* (%)	
PI-RADS 1–2	136 (28.6)
PI-RADS 3	182 (37.7)
PI-RADS 4	135 (28.0)
PI-RADS 5	28 (5.8)
PCa detection, *n* (%)	184 (38.1)
csPCa detection, *n* (%)	141 (29.2)
iPCa detection, *n* (%)	43 (8.9)

csPCa, clinically significant prostate cancer; HGPIN, high-grade prostate intraepithelial neoplasia; iPCa, insignificant prostate cancer; IQR, interquartile range; mpMRI, multiparametric MRI; PCa, prostate cancer; PI-RADS, Prostate Imaging – Reporting and Data System.

PCa detection rate in men with previous multifocal HGPIN in whom the suspicion of PCa, based on PSA and DRE, had not persisted after the previous negative biopsy

In 45 men with previous multifocal HGPIN and no currently suspected PCa, based on their PSA and DRE, a repeat prostate biopsy was only recommended based on the previous finding. PCa was found in two men (4.4%): csPCa in one (2.2%) and iPCa in the other. The man with iPCa had a PI-RADS score of 3 and the man with csPCa had a PI-RADS score of 4. By contrast, among the 248 men who had previous HGPIN and persistent PCa suspicion, the overall detection rate of PCa was 46.8% (*P* <0.001): 34.7% for csPCa (*P* <0.001) and 12.1% for iPCa, as shown in Table 3.

PCa detection rates in men with persistent PCa suspicion according to the finding of HGPIN in the previous negative biopsy, and based on PSA and DRE

Among the 248 men with previous HGPIN and persistent serum PSA elevation and/or abnormal DRE, PCa was detected in 43.6% of 101 men with previous unifocal HGPIN, and in 49.0% of the 147 men with multifocal HGPIN (*P* =0.438). The csPCa detection rate was 34.7% in both men with unifocal HGPIN and those with multifocal HGPIN (*P* = 1.000). The iPCa detection rates were 8.9% and 12.1%, respectively (*P* =0.238; Table 4). Logistic regression analysis showed that the previous HGPIN had an OR of 1.701 (95% CI 1.139–2.539) to predict overall PCa (*P* =0.009), while PCa suspicion had an OR of 11.992 (95% CI 2.786–51.623; *P* <0.001), and mpMRI had an OR of 3.579 (95% CI 2.247–5.966; *P* <0.001). The risk of csPCa was only significantly predicted by PCa suspicion, with an OR of 12.699 (95% CI 3.240–12.829; *P* <0.001), and mpMRI with an OR of 6.447 (95% CI 1.676–92.204; *P* <0.014). Finally, the risk of iPCa detection was only predicted by the finding of previous HGPIN, with an OR of 2.043 (95% CI 1.016–4.1.09; *P* =0.006 [Table 5]).

Table 6 [10,25-31] provides a summary of the main characteristics and findings of published studies that included more than 50 men who had previous HGPIN and were subjected to repeat biopsy.

Table 2 Characteristics according to the previous finding of high-grade prostate intraepithelial neoplasia and type

Characteristic	Without HGPIN	Unifocal HGPIN	Multifocal HGPIN	*P*
Sessions, *n* (%)	190 (39.3)	101 (20.9)	192 (39.8)	-
Median (IQR) age, years	68 (63–73)	68 (63–74)	68 (61–73)	0.389
Median (IQR) PSA, ng/mL	7.3 (5.8–13.5)	7.6 (5.7–13.8)	7.0 (3.2–9.4)	0.238
Positive DRE, *n* (%)	37 (19.5)	22 (23.8)	34 (17.5)	0.367
Median (IQR) prostate volume, mL	59 (44–93)	57 (46–85)	58 (37–78)	0.187
Median PSA density, ng/mL/mL	0.13 (0.09–0.22)	0.12 (0.08–0.20)	0.12 (0.07–0.18)	0.749
PCa family history, *n* (%)	24 (12.6)	66 (15.8)	28 (14.6)	0.587
Median (IQR) previous biopsies	1 (1–2)	1 (1–2)	1 (1–2)	0.756
Median (IQR) months between last two biopsies	22 (15–42)	23 (13–38)	21 (14–30)	0.268
Persistent PCa suspicion based on PSA and/or DRE, *n* (%)	190 (100)	101 (100)	147 (76.6)	0.001
mpMRI, *n* (%)				
PI-RADS 1–2	46 (24.2)	29 (28.7)	63 (32.8)	0.292
PI-RADS 3	68 (35.8)	40 (39.6)	74 (38.5)	
PI-RADS 4	63 (33.2)	28 (27.7)	44 (22.9)	
PI-RADS 5	13 (6.8)	4 (4.0)	11 (5.7)	
PCa detection, *n* (%)	66 (34.7)	44 (43.6)	74 (38.5)	0.332
csPCa detection, *n* (%)	54 (28.4)	35 (34.7)	52 (27.1)	0.382
iPCa detection, *n* (%)	12 (6.3)	9 (8.9)	22 (11.5)	0.211

csPCa, clinically significant prostate cancer; HGPIN, high-grade prostate intraepithelial neoplasia; iPCa, insignificant prostate cancer; IQR, interquartile range; PCa, prostate cancer; mpMRI, multiparametric MRI; PI-RADS, Prostate Imaging – Reporting and Data System.

Table 3 Prostate cancer detection rates in men with previous high-grade prostate intraepithelial neoplasia, with and without persistently suspected prostate cancer, based on serum PSA and/or DRE, at the time of repeat prostate biopsy

Type of PCa	PCa suspicion		*P*
	Yes (*n* =248)	No (*n* =45)	
Overall PCa	116 (46.8)	2 (4.4)	<0.001
csPCa	86 (34.7)	1 (2.2)	<0.001
iPCa	30 (12.1)	1 (2.2)	0.031

csPCa, clinically significant prostate cancer; iPCa, insignificant prostate cancer; PCa, prostate cancer.

Table 4 Prostate cancer detection rates in men scheduled to repeat prostate biopsy due to previous high-grade prostate intraepithelial neoplasia (HGPIN) and persistent prostate cancer suspicion based on serum PSA elevation and/or abnormal DRE, according to the type of HGPIN.

Type of PCa	Type of HGPIN		*P*
	Unifocal (*n* =101)	Multifocal (*n* =147)	
Overall PCa	44 (43.6)	116 (46.8)	0.438
csPCa	35 (34.7)	72 (34.7)	1.000
iPCa	9 (6.3)	21 (14.3)	0.238

csPCa, clinically significant prostate cancer; iPCa, insignificant prostate cancer; PCa, prostate cancer.

Table 5 Logistic regression analysis for the prediction of overall prostate cancer (PCa), clinically significant PCa and insignificant PCa detection in repeat prostate biopsies, according to the previous finding of high-grade prostate intraepithelial neoplasia, persistent PCa suspicion based on serum PSA elevation and/or abnormal DRE, and previous multiparametric MRI

Predictor	Odds ratio (95% CI)	*P*
For overall PCa		
Previous HGPIN (ref.: no previous HGPIN)	1.70 (1.139–2.539)	**0.009**
PCa suspicion (ref.: no PCa suspicion)	11.99 (2.786–51.623)	**<0.001**
mpMRI (ref.: PI-RADS 1–2)	3.58 (2.247–5.966)	**<0.001**
For csPCa		
Previous HGPIN (ref.: no previous HGPIN)	1.37 (0.894–2.095)	0.149
PCa suspicion (ref.: no PCa suspicion)	12.70 (3.240–12.829)	**<0.001**
mpMRI (ref.: PI-RADS 1–2)	6.45 (1.676–92.204)	**<0.014**
For iPCa		
Previous HGPIN (ref.: no previous HGPIN)	2.04 (1.016–4.1.09)	**0.006**
PCa suspicion (ref.: no PCa suspicion)	6.99 (0.895–53.680)	0.064
mpMRI (ref.: PI-RADS 1–2)	0.75 (0.373–1.516)	0.426

csPCa, clinically significant prostate cancer; iPCa, insignificant prostate cancer; mHGPIN, multifocal high-grade prostate intraepithelial neoplasia; mpMRI, multiparametric MRI; PCa, prostate cancer; PI-RADS, Prostate Imaging – Reporting and Data System.

Discussion

The current effectiveness of using HGPIN detection in negative prostate biopsy to predict the risk of csPCa is unknown, especially after the recent recommendation for pre-biopsy mpMRI and guided biopsies [6]. The present study focused on the two clinical scenarios derived from HGPIN detection in the negative prostate biopsy, according to the current recommendations included in the EAU PCa guidelines for repeating prostate biopsy [7].

The first scenario occurs when there is a normalization of serum PSA and/or DRE after the detection of multifocal HGPIN. Here, EAU guidelines recommend repeating prostate biopsy between 12 and 36 months after the negative result

Table 6 Summary of characteristics and results of repeat biopsies in men with isolated high-grade prostate intraepithelial neoplasia; selected studies had more than 50 men subjected to repeat biopsy.

Study (year)	Reference population (*n*)	Repeat biopsy in HGPIN (%)	Age, years	PSA, ng/mL	Biopsy cores	MRI	PCa, *n* (%)	Gleason score ≤ 6, *n* (%)	Gleason score ≥ 7, *n* (%)
Girasole et al. (2006) [25]	Previous HGPIN (1,293)	358 (28)	68	NR	≥ 6	No	79 (22)	NR	NR
López (2007) [26]	Previous HGPIN (125)	96 (77)	72	NR	6-8	No	21 (22)	15 (71)	5 (24)
Singh et al. (2007) [27]	Previous HGPIN (88)	67 (76)	68	8.5	12	No	28 (42)	18 (64)	10 (36)
He at al. (2012) [28]	NR	94 (NR)	64	NR	13	No	36 (38)	39 (27)	16 (29)
Taneja et al. (2013) [29]	Previous HGPIN (802)	590 (73.5)	65	4.3	12	No	198 (33.6)	157 (79.3)	41 (20.7)
Kim et al. (2015) [30]	Repeat biopsies (1,323)	149 (NR)	65	5.8	6-12	No	33 (22.1)	19 (57.6)	14 (42.4)
Wiener et al. (2017) [10]	Previous HGPIN (868)	208 (24.0)	62	5.2	NR	No	23 (15.7)	19 (82.6)	4 (17.4)
Oderda et al. (2021) [31]	Previous HGPIN, or ASAP, or PINATYP (384)	99 (NR)	NA	NA	12	No	33 (34.7)	15 (45.5)	18 (54.5)
Present study	Previous HGPIN (308)	293 (95.1)	68	7.3	12 + GB	Yes	118 (40.3)	31 (26.3)	87 (73.7)

ASAP, atypical small acinar proliferation; GB, guided-biopsies to PI-RADS lesions ≥3; HGPIN, high-grade prostatic intraepithelial neoplasia; NR, not reported; PINATYP, high-grade prostatic intraepithelial neoplasia with atypia.

[7]. The second scenario is defined by the persistence of PCa suspicion due to previous HGPIN findings and based on PSA and/or DRE. Here, the rates of csPCa and iPCa that were found were similar to those observed in men without previous HGPIN. However, among the 45 men observed in the first scenario, where PCa suspicion no longer existed after the previous finding of multifocal HGPIN, the PCa detection rate was as low as 4.4%, with half of these being iPCa. These data have not been reported in previous studies. The present study suggests that this subset of men represents 15.4% of those with previous HGPIN and 23.4% of those with previous multifocal HGPIN. In those men, the incidence of csPCa potentially correlates with PSA levels, according to data reported from the control arm of the Prostate Cancer Prevention Trial [23]. In this scenario, it was also observed that 30% of mpMRI was negative. Therefore, this study suggests that mpMRI will avoid 30% of repeat prostate biopsies and 50% of iPCa overdiagnosis.

Among the published studies that included over 50 men with previous HGPIN subjected to repeat biopsy, the rate of men scheduled to repeat biopsy ranged from 24% to 95%. The median age ranged from 62 to 72 years, and the median PSA at repeat biopsy ranged from 4.3 to 8.5 ng/mL. The median number of cores obtained during repeat biopsy ranged from 6 to 13, and it is only in the present study that pre-repeat mpMRI and guided biopsies were carried out. The rate of PCa detection ranged from 22% to 40%, and overdetection of iPCa ranged between 26% and 82%. This overview suggests great variability among studies; however, there was a significant overdetection of iPCa, which was >25% in all of the studies.

The rate of men with isolated HGPIN with normalized PSA and/or DRE has not been previously reported in the literature, but it was approximately 15% in the present study. There were no observed differences between csPCa and iPCa detection rates among men with persistent suspected PCa, with and without previous HGPIN. Moreover, there was no observation of different rates of csPCa and iPCa detection between men with unifocal and those with multifocal HGPIN. Recent publications do not distinguish between men with unifocal and those with multifocal HGPIN [6,9,10,11]. The updated review by Epstein´s group in 2018 suggested that men with HGPIN in only one core should not be followed [8]. However, the multivariate analysis performed in this study was interesting. Previous HGPIN, current PCa suspicion based on PSA and DRE, and pre-repeat biopsy mpMRI information were included as predictors of overall PCa, csPCa, and iPCa rates. This led to interesting results that discriminate the confounders. This analysis showed that previous HGPIN did not predict an increased risk of csPCa in repeat biopsies, while it was the only significant predictor of the risk of iPCa overdetection. This finding aligns with recent evidence which suggests that previous HGPIN is mainly associated with iPCa [8,10,32,33,34].

The present study was limited by its retrospective design and the small size of the cohort, which comprised men with previous multifocal HGPIN with normalized PCa suspicion, based on serum PSA and/or DRE. The outcome for men without persistent PCa suspicion and previous unifocal HGPIN is unknown because EAU PCa guidelines do not recommend repeating biopsies for them. More precise definitions of csPCa and iPCa could be used. In addition, the

measurement of endpoint variables in biopsy specimens is always a limitation because they do not represent the true pathology of the whole prostate gland. Another limitation is the interobserver variability of HGPIN diagnosis. Finally, considering that the repeat biopsy scheme did not focus on the area where previous HGPIN was found, the results could be limited.

The results of the present study suggest that a repeat prostate biopsy should be based on the persistent suspicion of PCa, based on the evolution of PSA and DRE. Predictors of csPCa, such as mpMRI, PSA density, family history of PCa, and other markers may be helpful [7]. Lastly, isolated HGPIN does not appear to increase the risk of future csPCa when there is no suspicion of PCa.

In conclusion, in approximately 25% of men with previous multifocal HGPIN, serum PSA and/or DRE are normalized after the negative prostate biopsy. The risk of csPCa detection in repeat biopsies in such men appears to be identical to that reported in men with low PSA values. In men with persistent PCa suspicion, the risk of csPCa in repeat prostate biopsies, based on PSA and DRE, is independent of the previous finding of HGPIN; however, the risk of iPCa detection increases. Thus, the current recommendation to repeat prostate biopsy after HGPIN should be based on PSA and DRE evolution, and mpMRI findings.

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Abbreviatons: csPCa, clinically significant prostate cancer; EAU, European Association of Urology; GG, grade group; HGPIN, high-grade prostatic intraepithelial neoplasia; mpMRI, multiparametric MRI; OR, odds ratio; PCa, prostate cancer; PIN, prostatic intraepithelial neoplasia; PINATYP, high-grade prostatic intraepithelial neoplasia with atypia; PI-RADS, Prostate Imaging – Reporting and Data System; iPCa, insignificant prostate cancer.