Subsequent prostate cancer detection in patients with prostatic intraepithelial neoplasia or atypical small acinar proliferation

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Abstract

Introduction: To evaluate the predictors of prostate cancer in follow-up of patients diagnosed on initial biopsy with high-grade prostatic intraepithelial neoplasia (HGPIN) or atypical small acinar proliferation (ASAP).

Methods: We studied 201 patients with HGPIN and 22 patients with ASAP on initial prostatic biopsy who had subsequent prostatic biopsies. The mean time of follow-up was 17.3 months (range 1–62). The mean number of biopsy sessions was 2.5 (range 2–6), and the median number of biopsy cores was 10 (range 6–14).

Results: On subsequent biopsies, the rate of prostate cancer was 21.9% (44/201) in HGPIN patients. Of these, 32/201 patients (15.9%), 9/66 patients (13.6%) and 3/18 patients (16.6%) were found to have cancer on the first, second and third follow-up biopsy sessions, respectively. In ASAP patients, the cancer detection rate was 13/22 (59.1%), all of whom were found on the first follow-up biopsy. There was a statistically significant difference between the cancer detection rate in ASAP and HGPIN patients ($p < 0.001$). Multivariate analysis showed that the independent predictors of cancer were the number of cores in the initial biopsy, the number of cores (> 10) in the follow-up biopsy and a prostate specific antigen (PSA) density of ≥ 0.15 (odds ratio 0.77, 3.46 and 2.7,8 respectively; $p < 0.04$). Conversely, in ASAP patients none of these variables were found to be associated with cancer diagnosis.

Conclusion: ASAP is a strong predictive factor associated with cancer when compared with HGPIN. The factors predictive of cancer on follow-up biopsy of HGPIN are number of cores on initial biopsy, more than 10 cores in rebiopsy and elevated PSA density. As the cancer detection rate on repeated biopsy of HGPIN patients is the same as that of patients without HGPIN, perhaps the standard of repeat biopsy in all patients with HGPIN should be revisited.

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Owing to the widespread use of prostate specific antigen (PSA) as a screening tool for prostate cancer associated with increasing use of transrectal ultrasound (TRUS) guided prostate needle biopsy and the increasing number of sampling cores per biopsy, the histological findings of high-grade prostatic intraepithelial neoplasia (HGPIN) and atypical small acinar proliferation (ASAP) has also increased.

The detection rate of HGPIN in TRUS-guided needle biopsies performed owing to an elevated PSA level or an abnormal digital rectal examination (DRE), was found to be between 4% and 25% of patients[1–4] and the cancer detection rate on repeated biopsy was reported from 2% to 47% of patients.[1,3,5–7] Conversely, the rate of ASAP on initial biopsy was reported to range from 2.4% to 3.7%[3,8,9]; the cancer detection rate on repeated biopsy was found to be as high as 52% in isolated ASAP[3,8,10] and 72% in ASAP associated with HGPIN.[3,11]

The management of patients found to have HGPIN on initial biopsy varies considerably, ranging from immediate rebiopsy to close observation at varying intervals.[12–15] Our aim was to examine our experience with prostatic rebiopsy in patients with HGPIN, ASAP or both.

Methods

We reviewed the clinical, transrectal ultrasonographic and pathological reports of 2265 patients who underwent TRUS-guided prostatic biopsy at the McGill Prostate Cancer Detection Clinic in Montréal, Que., between January 2000 and May 2006. The indication for biopsy was either abnormally elevated PSA or rising PSA and suspicious DRE (or both). For the purposes of this study, we selected patients who had HGPIN or ASAP and who underwent rebiopsy in the same clinic.

On initial biopsy, there were 537 patients (23.7%) with isolated HGPIN, 57 patients (2.5%) with isolated ASAP and 32 patients (1.4%) with ASAP associated with HGPIN. TRUS-guided biopsy was performed via standard approach with a median of 10 cores

as described elsewhere.[16] All biopsies were examined by the same uropathologist. We created univariate and multivariate logistic regression models to study the independent predictors of cancer in patients with HGPIN or ASAP. The variables we examined included age, serum PSA, PSA density, PSA velocity, prostate volume, abnormal DRE, number of biopsy cores in the initial biopsy and also in rebiopsy sessions, and the number of cores with HGPIN or ASAP. The mean of follow-up biopsy sessions and duration of follow-up were 2.5 sessions (range 2–6) and 17 months (range 1–62), respectively. All statistics were performed using STATA 9.2 (Stata Corp., College Station, Tex.).

Table 1: The criteria of high grade prostatic intraepithelial neoplasia and atypical small acinar proliferation

Variable	No. (and %) of patients* HGPIN (n = 201)	ASAP (n = 22)
Age, yr		
< 60	66 (32.8)	8 (36.4)
60–70	115 (57.2)	10 (45.5)
> 70	20 (10)	4 (18.2)
Mean (and SD)	62.6 (6.5)	63.2 (6.6)
Range	46–77	50–75
Serum PSA, ng/mL		
≤ 4	42 (20.9)	2 (9.1)
> 4–10	120 (59.7)	14 (63.6)
< 10	39 (19.4)	6 (27.3)
Mean (and SD)	7.6 (32.1)	7.5 (5.3)
Range	0.22–86	1.2–24
Prostate volume, cm^3		
Mean (and SD)	60.5 (28.8)	59.7 (38.5)
Range	15–175	20–148
Suspicious DRE	65 (32.3)	6 (27.3)
Cores in initial biopsy		
6 and 7	74 (36.8)	9 (40.9)
8 and 9	32 (15.9)	4 (18.2)
≥ 10	95 (47.3)	9 (40.9)
HGPIN or ASAP cores		
Median (and range)	2 (1–7)	1 (1–2)
Time between initial and last biopsy, mo		
Mean (and SD)	15.7 (14.8)	10.4 (7.7)
Range	1–62	1.5–31
Cancer on re-biospsy	44 (21.9)	13 (59.1)
Gleason score		
Median (and range)	6 (5–9)	6 (5–8)

HGPIN = high grade prostatic intraepithelial neoplasia; ASAP = atypical small acinar proliferation; SD = standard deviation; PSA = prostate specific antigen; DRE = digital rectal examination.
*Unless otherwise indicated.

Results

Of patients included in the analyses, 201 were diagnosed with HGPIN and 22 patients were diagnosed with ASAP. The rate of cancer detection in the HGPIN group was 21.9% (44/201). The rate of cancer detection in each subsequent biopsy session was 32/210 (15.9%), 9/66 (13.6%, 4.5% of total) and 3/18 (16.6%, 1.5% of total) in the first, second and third sessions, respectively. The rate of cancer detection in the isolated ASAP group was 59.1% (13/22), all of which were detected in the first follow-up biopsy. We found a statistically significant difference between the rates of cancer detection in both groups using the Pearson chi-squared test ($p < 0.001$). Table 1 shows the clinical and pathological characteristics of both groups. Of cancer foci found in follow-up biopsies, 38.6% (17/44) were found in the same sites as previous HGPIN, while 53.8% (7/13) of the cancer foci were found in the same sites as previous ASAP. There was no correlation between the original site of HGPIN or ASAP and the site of subsequent cancer.

Univariate analysis (Table 2) and forward and backward stepwise logistic regression (Table 3) revealed that the independent predictors of prostate cancer in HGPIN patients were the number of cores in the initial biopsy (odds ratio [OR] 0.77, 95% confidence interval [CI] 0.64–0.99, $p = 0.04$), the number of cores in the follow-up biopsy (> 10 cores) (OR 3.49, 95% CI 1.05–11.59, $p = 0.041$) and a PSA density ≥ 0.15 (OR 2.78, 95% CI 1.31–5.90, $p = 0.008$). There was no independent predictor of cancer in the ASAP group.

Discussion

The cancer detection rate on subsequent biopsies in patients previously diagnosed with HGPIN is progressively decreasing with the increasing use of extended biopsy techniques at the outset, as shown in recently published series.[17–20] Herawi and colleagues demonstrated that the cancer detection rate in rebiopsy in patients previously diagnosed with HGPIN depends on the number of cores in the initial biopsy; they found it was 20.8% and 13.3% if the initial number of cores were 6 and 8 or more, respectively.[17] The overall rate of can-

cer detection on rebiopsy without HGPIN or ASAP in a series of 218 patients who underwent extended biopsy was 35%. The rate was 39% for patients with prior standard sextant biopsy and 28% with prior extended biopsy.[21]

In the current study, the rate of isolated HGPIN on initial biopsy was 23.7%, which is concordant with the literature.[1–4] The cancer detection rate in subsequent biopsies of HGPIN cases was 21.9%. When individualized by follow-up biopsy session, the detection rate was about 15%. This appears to be about one-half of the detection rate for repeated biopsy in patients without HGPIN or ASAP (39% with prior standard sextant biopsy and 28%

Table 2: Results of univariate analysis

	HGPIN			ASAP		
Variable	No cancer; no. (and %)*	Cancer; no. (and %)*	*p* value	No cancer; no. (and %)*	Cancer; no. (and %)*	*p* value
No. of patients	157	44		9	13	
Mean age, yr (and SD)	62.2 (6.5)	64 (6.5)	0.09	62.6 (4.5)	63.4 (7.4)	0.21
Mean PSA, ng/mL (and SD)	6.6 (3.6)	8.8 (12.6)	0.70	9.4 (6.7)	8.6 (5.5)	0.46
PSA density						
< 0.15	115 (83.3)	23 (16.7)		5 (38.5)	8 (61.5)	
≥ 0.15	42 (66.7)	21 (33.3)	0.009	4 (44.4)	5 (55.6)	0.86
PSA velocity, ng/mL/yr†						
< 0.75	93 (80.2)	23 (19.8)		7 (53.8)	6(46.2)	
≥ 0.75	57 (75)	19 (25)	0.43	2 (28.6)	5 (71.4)	0.15
Mean prostate volume, cm^3 (and SD)	59.9 (27.1)	51.2 (20.9)	0.05	59.2 (22.4)	62.8 (34.0)	0.8
DRE						
Abnormal	49 (75.4)	16 (24.6)		3 (60)	2 (40)	
Normal	108 (79.3)	28 (20.7)	0.53	6 (35.3)	11 (64.7)	0.69
Mean no. of initial biopsy cores (and SD)	8.5 (2.0)	8.0 (2.0)	0.18	8.9 (2.4)	7.9 (3.2)	0.43
No. of re-biopsy cores						
≤ 10 cores	147 (79.5)	38 (20.5)		7 (36.8)	12 (63.2)	
> 10 cores	10 (62.5)	6 (37.5)	0.12	2 (66.7)	1 (33.3)	0.4
Mean no. of cores with HGPIN or ASAP (and SD)	1.9 (1.2)	2.2 (1.4)	0.14	1.2 (0.9)	1.1 (0.9)	0.86
Mean time of follow up, mo (and SD)	17.7 (14.1)	15.7 (14.9)	0.42	16.2 (25.2)	10.4 (7.7)	0.41

HGPIN = high grade prostatic intraepithelial neoplasia; ASAP = atypical small acinar proliferation; SD = standard deviation; PSA = prostate specific antigen DRE = digital rectal examination.
*Unless otherwise indicated.
†7 patients in HGPIN group and 2 patients in ASAP group had only 1 PSA value.

Table 3: The results of logistic regression multivariate analysis

Independent predictor	Odds ratio	*p* value	95% CI
No. of initial biopsy cores	0.77	0.04	0.64–0.99
No. of re-biopsy cores > 10	3.49	0.041	1.05–11.59
PSA density ≥ 0.15	2.78	0.008	1.31–5.90

CI = confidence interval; PSA = prostate specific antigen.

with prior extended biopsy).[17,21] The independent predictors for cancer on rebiopsy in HGPIN cases were a lower number of cores in the initial biopsy, more than 10 cores in rebiopsy and a PSA density of ≥ 0.15.

The relation between the number of cores either in the first biopsy or in the rebiopsy and cancer detection has been previously reported in patients with HGPIN and ASAP.[17,21] Age, PSA density and the number of cores with HGPIN were found to predict cancer in another series of HGPIN patients.[22] Although multifocality of HGPIN was inconclusive in predicting cancer,[22,23] it was not an independent predictor in the current study. With respect to the relation between the site of HGPIN and the subsequent cancer site, we found that only 38.6% of cancer found on follow-up biopsy was at the same site as the original cancer. This is similar to other investigators who reported 20% of cases had cancer in the same locations as previous HGPIN.[24]

Of further interest, some have shown that the presence of HGPIN is not a predictor of cancer in subsequent biopsy.[23,25] It is conceivable that having HGPIN on initial biopsy is no greater risk for cancer detection than rebiopsy of cases with normal histology on initial biopsy. Obviously, the amount of sampling on initial biopsy affects the outcome of subsequent sampling. Although we could not find a number-of-core cutoff on initial biopsy, our data suggest that a less than 10 core initial biopsy is suboptimal for men found to have HGPIN.

Conversely, in ASAP cases the cancer detection rate was 59.1%, which is higher than the reported rates for isolated ASAP[3,8,10] making it a more significant histological finding, compared with HGPIN. We did not find any predictors for cancer detection in ASAP patients, nor did we find a correlation between the original sites of the ASAP and the sites of subsequent cancer. This differs from what was reported by Park and colleagues, where age and abnormal DRE were independent predictors for cancer detection in patients diagnosed with ASAP on initial biopsy.[26] Perhaps our small number of cases with ASAP precluded finding significant associated variables.

Our study, unfortunately, suffers from potential selection bias; specifically because only 223 of the 626 HGPIN and ASAP cases were rebiopsied in our clinic and the outcome of the remaining cases is unknown. Additionally, since the reasons for rebiopsy were not standard, it is possible that other variables may be important in cancer detection.

Nevertheless, we suggest that among patients with HGPIN, the recruitment of PSA density and the number of cores in the initial biopsy may help in selecting patients who benefit from rebiopsy and spare those who would not. On the other hand, rebiopsy of patients with ASAP should always be considered in all patients.

Conclusion

Our study found that, in patients with HGPIN on initial prostatic biopsy, subsequent biopsy identifies cancer in 21.9% of cases. We suggest that among patients with HGPIN the decision to rebiopsy may be individualized. In patients with a greater than 10 core initial biopsy and in whom PSA density is < 0.15 it is reasonable to defer rebiopsy until PSA kinetics, PSA density or DRE findings become suspicious. In patients with a less than 10 core initial biopsy, repeat biopsy should be considered. In patients with ASAP, rebiopsy relatively soon is warranted.

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