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High-grade prostatic intraepithelial neoplasia and atypical small acinar proliferation on initial 21-core extended biopsy scheme: incidence and implications for patient care and surveillance

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saturation biopsy

ABSTRACT

PURPOSE:

To evaluate the incidence of high-grade prostatic intraepithelial neoplasia (HGPIN) and atypical small acinar proliferation (ASAP) in initial 21-core extended biopsy scheme and to determine the prostate cancer detection rate in the repeated biopsy.

METHODS:

Between 2002 and 2008, 2,006 patients underwent a first 21-core extended biopsy scheme. Incidences of cancer, ASAP and HGPIN were studied. Cancer detection rate in the repeated 21-core extended biopsy for ASAP and HGPIN was reported and compared with those obtained on repeated biopsy for clinico-biological indications.

RESULTS:

Incidences of HGPIN and ASAP were 1.7% and 1.1%, respectively. The 6-core and 12-core biopsy schemes detecting HGPIN would have missed the diagnosis of cancer in 10% and 3.6% of cases, compared to a 21-core biopsy protocol, respectively. The cancer detection rate on repeated biopsy for HGPIN was 19% and not significantly different compared with the detection rate on repeated biopsy for clinico-biological indications (16.8%, $p=0.77$). Seven prostate cancers were found among the 17 re-biopsies for ASAP revealing a detection rate of 41.2% ($p=0.01$). All detected cancers were organ-confined. No clinico-pathological data was independent predictor of cancer on repeated biopsy.

CONCLUSION:

Our report demonstrates the different risk profiles for HGPIN and ASAP in a 21-core extended biopsy scheme. Presence of HGPIN does not imply a higher risk for cancer detection at immediate re-biopsy compared to other patients for who repeated biopsies were indicated for increasing or persistently increased PSA levels. Repea biopsy is warranted when ASAP is diagnosed because of a high risk of prostate cancer.

INTRODUCTION

In most of the cases, results of prostate biopsies are currently dichotomized and the urologist can inform the patient about the presence or absence of cancer in his prostate. In some cases, results that are neither benign nor cancer, are diagnosed such as high-grade prostatic intraepithelial neoplasia (HGPIN) and atypical small acinar proliferation (ASAP).

HGPIN refers to architecturally atypical cells which share morphologic and genetic changes with cancer but do not invade the basement membrane of prostatic glands [1]. ASAP, also referred to as atypical focus suspicious but not diagnostic of malignancy, contains a small group of glands that harbour some but not all the features needed for definitive diagnosis of adenocarcinoma [2].

Combination of these two distinct entities is also reported [3].

Clinical management of these lesions and indication of repeated biopsy have been often debated, especially in case of diagnosed HGPIN [4,5,6]. The prostate cancer detection rate on repeated biopsy after initial diagnosis of HGPIN or ASAP largely varies among the literature, from 2.3% to 100% after diagnosis of HGPIN and from 17% to 70% after diagnosis of ASAP [5,7]. The literature recommends that all men with initial ASAP need repeated biopsy within 3 to 6 months [5,6,7,8,9]. The prognostic value of HGPIN has recently been questioned since the development of extended peripheral zone biopsy schemes [5]. Increased needle core biopsy sampling (from sextant to 12-core extended biopsy scheme) appeared as a major contributing factor of the decreased incidence of cancer after an initial diagnosis of HGPIN [8,11,12]. Moreover, the gain of a 21-core extended biopsy technique as initial strategy compared to 12-core protocol was demonstrated in terms of prostate cancer detection rate in a previous study [13].

The aim of the present series was to evaluate the incidence of HGPIN and ASAP in an initial 21-core extended biopsy scheme and to study the prostate cancer detection rate on the repeated biopsy after HGPIN or ASAP diagnosis.

METHODS

Between January 2001 and February 2008, 2,006 patients underwent a first set of prostatic biopsies for increased PSA levels (>4 ng/ml), free to total PSA ratio $<10\%$ or abnormal digital rectal examination (DRE) at the Department of Urology, Hospital Henri Mondor, Créteil, France. A high PSA velocity was also an indication for biopsies. Characteristics of patients are shown and compared in Table 1 according to pathological results. The minority of the patients (18%) had a abnormal DRE. The inclusion criterion was the use of a 21-core extended biopsy scheme: all the patients underwent a 21-core biopsy protocol for the initial and the repeated biopsies.

The 21-core biopsy protocol was previously described and performed by 3 senior urologists (ADLT, LS, CCA) [13,14]. This biopsy protocol included prostate ultrasound examination to evaluate the prostate volume using the prolate ellipsoid formula. The biopsies were performed in the following order: first, six sextant biopsies (standard 45° angle), then 3 biopsies in each peripheral zone at an 110° angle from base to apex, next 3 biopsies in each transition zone from base to apex, and finally 3 biopsies in the midline peripheral zone. All patients tolerated complete 21-core biopsy scheme obtaining the planned numbers of cores. All the cores were mapped for location and submitted in 21 separate containers for pathology. Two senior uropathologists (YA, SA) performed the analysis. Before rendering a diagnosis of ASAP, immunostains were performed.

The same procedure was performed in case of repeated biopsy after initial ASAP or HGPIN. Mean interval between the two biopsies was 5.9 months (range: 1 to 16) in case of ASAP and 12.4 (range: 2 to 66) in case of HGPIN. During the same period, 345 patients with no history of pre-malignant lesions had undergone second 21-core biopsy scheme for increasing or persistently increased PSA levels, free to total PSA ratio $<10\%$, abnormal digital rectal examination (DRE) or a high PSA velocity.

Incidences of benign prostatic hyperplasia, cancer, ASAP and HGPIN were studied according to the site of positive cores. Cancer detection rate on repeated biopsy for ASAP or HGPIN was reported and compared with those obtained on repeated biopsy for clinico-biological indications. Criteria of re-biopsy were HGPIN, ASAP and/or clinico-biological indications.

The qualitative data were tested using a ANOVA test. A Kruskal-Wallis test was used for variables with no normal distribution. The limit of statistical significance was defined as $p<0.05$. SPSS 13.0 (Chicago, Illinois) software was used for analysis.

RESULTS

Incidence at the first biopsy.

The prostate cancer detection rate was 43.2% (n=866). Prostate cancer was associated with lesions of HGPIN in 30 patients. Only 34 patients had lesions of HGPIN with no cancer on biopsies (1.7%). The incidence of ASAP was 1.1% (23 patients).

According to positive cores site, atypical lesions (HGPIN and ASAP) were detected by sextant biopsies (6 cores) in 35.7% of cases, by 6 additional posterolateral biopsies (12 cores) in 28.6% of cases and by transition zone or midline peripheral zone (21 cores) in 35.7% of cases. Table 2 and Table 3 showed the site of positive cores according to a 6-core, 12-core or 21-core biopsy scheme. The use of a 12-core biopsy protocol would have missed HGPIN or ASAP in 35.3% and 39.1% of cases, respectively.

When HGPIN was detected on the first 6 sextant biopsies (n=30), extended lateral peripheral zone (12 cores) cores and transition zone and midline cores (21 cores) revealed adenocarcinoma in 2 and 1 cases, respectively. A 6-core and 12-core biopsy scheme detecting HGPIN would have missed the diagnosis of cancer in 10% and 3.6% of cases, respectively. Gleason score was 6 in these 3 cases and mean tumor length was 3.2 mm.

Risk of cancer on repeated biopsies.

Pathological results of repeated biopsy according to the initial pathological diagnosis are listed in Table 4. The prostate cancer detection rate on repeated biopsy for clinico-biological indications was 16.8%. In case of repeated biopsy in patients with no history of ASAP or HGPIN (clinico-biological indications only), a mean of 2.46 cores was positive. Mean total tumor length and mean percent of core invasion was 7.2 mm and 15.9% in this group. Nineteen percent of cancers detected in control group were graded Gleason 7 or more.

Twenty-one re-biopsies were performed for HGPIN and prostate cancer was noted in 4 cases (19.0%).

This rate did not differ significantly from the detection rate on repeated biopsy for clinico-biological

indications ($p=0.77$). Mean tumor length was 1.9 mm (range: 0.5 to 3). Gleason score was graded 6 in all cases. Tumor was located on ipsilateral side in 75% and was bilateral in 50%. Tumor was noted in the area of the atypical focus in 50% of biopsies.

Seven prostate cancers were found among the 17 re-biopsies for ASAP revealing a detection rate of 41.2%. Difference with the detection rate on repeated biopsy for clinico-biological indications was statistically significant ($p=0.01$). Mean tumor length was 5.0 mm (range: 1.1 to 15.6). Mean number of positive cores was 2.8 (range: 2 to 6). Gleason score 7 (3+4) was noted in one case. Side concordance between the first and the second biopsies was 100%. Tumor was noted in the area of the atypical focus in 71% and bilateral in 57% of cases.

Patients who underwent re-biopsies after an initial diagnosis of ASAP were comparable to patients who underwent re-biopsies for clinico-biological indications, according to the PSA level and DRE ($p=0.69$ and 0.12, respectively). Patients who underwent re-biopsies for HGPIN were comparable to patients who underwent re-biopsies for clinico-biological indications, according to the PSA level and DRE ($p=0.48$ and 0.18, respectively).

None of the studied parameters including interval between biopsies, PSA level, age, volume, plurifocality of pre-malignant lesions were predictive of prostate cancer on re-biopsy. Cancer on repeated biopsy after an initial diagnosis of ASAP was more frequent in larger prostate (mean volume 63.0 mL) but difference did not reach significance ($p=0.20$). In case of ASAP plurifocality on initial biopsy (2 patients), cancer was systematically found in repeated biopsy, but difference failed to reach significance.

Five patients underwent radical prostatectomy after repeated biopsies. Prostate cancer was organ-confined in each case and graded Gleason 6 except in one case (Gleason 7=3+4).

DISCUSSION

High-grade prostatic intraepithelial neoplasia (HGPIN) has been traditionally related to prostate cancer and considered as a precursor of adenocarcinoma [15]. Diagnosis of atypical small acinar proliferation (ASAP) denotes a focus of atypical glands suspicious for cancer but with insufficient cytological or architectural atypia for a definitive carcinoma diagnosis. Both ASAP and HGPIN on biopsy were considered as a high risk of positive repeated biopsies and for this reason systematical re-biopsy were recommended 3-6 months after the first one [6]. These recommendations were based essentially on men who underwent standard sextant biopsy. It has been demonstrated that an increased number of biopsies allowed a prostate cancer detection improvement compared to the original Hodge sextant biopsy protocol [10,14]. Recently, contradictory data have been reported regarding the risk of associated cancer and necessity of early subsequent biopsies in case of HGPIN even after extended biopsy scheme [4,5]. Our aim was to determine the incidence of HGPIN and ASAP and the risk of cancer detection at repeated extended 21-core biopsy scheme in men diagnosed with HGPIN or ASAP on first 21-core extended biopsy scheme.

The incidence of HGPIN on the initial needle biopsy varied markedly in the literature from 0% to 24.6%. Mean and median values reported in recent reviews were 7.7% and 5.2%, respectively [4,5]. Similarly, the incidence of ASAP ranged from 0.7% to 23.4% with an average of 5%. Technical factors relating to the biopsy specimens processing, subjective nucleolar size quantification, immunostaining or interobserver reproducibility are potential explanations for this observed variation. However, no relationship between the number of cores sampled and the incidence of pre-malignant lesions appeared in previous studies. In our series, the use of a 21-core extended biopsy scheme did not increase the overall incidence of HGPIN and ASAP on needle biopsy compared with previous studies. The 21-core biopsy technique does not imply HGPIN or ASAP over-diagnosis.

The extended biopsy scheme corrected diagnosis in some cases when carcinoma was marginally or not sampled. Increasing the number of sampled cores detected many associated cancers on initial biopsy. In our series, a 6-core and 12-core biopsy scheme detecting HGPIN would have missed the diagnosis of

cancer due to sampling error in 10% and 3.6% of cases, respectively. The 21-core extended biopsy scheme improved the diagnostic yield of 35.3% and 39.1% for HGPIN and ASAP, respectively compared with the 12-core biopsy scheme. The sampling of the midline and transition zones increased by more than 1.3-fold the detection rate of HGPIN and ASAP. Moreover, 7.8% of cancers were detected only in midline and/or transition zone cores. The 21-core biopsy protocol implied a more accurate pathological assessment of prostatic gland concerning prostate cancer, ASAP and HGPIN, compared to 6-core and 12-core biopsy schemes.

The prostate detection rate on re-biopsy was 19.0% after an initial diagnosis of HGPIN and was statistically comparable to the detection rate of re-biopsy for clinical (abnormal digital rectal examination) or biological (increasing or persistently increased PSA levels, free to total PSA ratio<10%) indications (16.8%, $p=0.77$) [8,12,16,17,18].

After an initial diagnosis of ASAP, adenocarcinoma was found on repeated extended biopsy in 41.2%, which was significantly different of result of re-biopsies for clinico-biological indications ($p=0.01$). This result was comparable to data reporting in the literature [5,8,9,16]. Thus, the presence of ASAP on initial biopsy meant a high risk of cancer on re-biopsy and that repeated biopsy after ASAP was warranted, even with the use of an initial 21-core biopsy protocol. The high likelihood of cancer being found at the same sampled site (71%) and side (100%) implied that atypical focus on initial biopsy represented carcinoma. This concordance site is important. The repeated biopsy should include an increased sampling of the initial atypical site and adjacent sites. Thus, urologist should submit biopsy specimens in a manner in which the location of each core can be determined [5]. In all cases, cancer was organ-confined disease in line with published values.

The clinical and biological characteristics of patients with HGPIN or ASAP on initial biopsy corresponded more to those of patients with benign diagnosis than to those of patients with detected prostate cancer. Mean PSA elevation ranged from 7.4 to 8.6 ng/mL in HGPIN and ASAP group, respectively. Comparatively, mean PSA level was 7.3 ng/mL for patients with benign tissue and 21.9 ng/mL for patients diagnosed with prostate cancer. These data confirmed that HGPIN and ASAP by itself did not increase serum PSA.

No clinical or pathological parameter was shown to be predictor of cancer on re-biopsy in line with published studies [8,11,17]. Age, PSA level, free PSA, volume, digital rectal examination and interval between biopsies were not independent predictors of cancer in men with ASAP or HGPIN on first set of biopsies. The number of cores involved by HGPIN did not help to predict which men are at higher risk for cancer on repeated biopsy ($p=1.00$) in line with most published values [5].

The morbidity rate of our 21-sample prostate biopsy procedure has been demonstrated to be close to that reported with the 6-sample procedure, in terms of bleedings, infection and pain. Intra-rectal anesthesia and peri-prostatic nerve block were systematically used in the procedure [14]. The additional cost of the 21-core biopsy procedure compared with the 12-core biopsy scheme was 225 euros (25 euros per each additional core). This additional cost is significant and limits the generalization of the 21-core biopsy procedure in all first sets of biopsies. The benefit-cost ratio must be considered and the results of our study can help the urologist to appreciate it

One of the limitations of our study is the sample size. Thus, it was not possible to draw a conclusion concerning the extent of HGPIN as a predictor of cancer on re-biopsy (4 cases of plurifocal HGPIN). Data in the literature have shown that it is not enough to stratify HGPIN as unifocal versus plurifocal but rather extensive HGPIN (>2 cores) is predictive of cancer on re-biopsy [21,22]. Prostate cancer was found in the two patients with plurifocal ASAP on first biopsy but difference did not reach significance ($p=0.15$). Concerning ASAP, prostate cancer was found in larger prostate on re-biopsy (63.0 versus 36.0 mL, $p=0.20$). Thus, the clinical and pathological data did not help to stratify the patients with an initial diagnosis of HGPIN or ASAP, who are at increased risk for cancer.

CONCLUSION

Our report demonstrates the different risk profiles for HGPIN and ASAP in a 21-core extended biopsy scheme. Presence of HGPIN detected on initial biopsy does not imply a higher risk for cancer detection at immediate re-biopsy. Repeated biopsy remains warranted when ASAP is diagnosed due to a high risk of prostate cancer, even with the use of a 21-core biopsy protocol. None of the clinical or pathological parameters were able to predict the presence of prostate cancer on repeated biopsy.

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LEGENDS

Table 1. Clinico-biological characteristics of patients undergoing first saturation biopsy according to pathological results.

Table 2. Site of positive cores and detection rate according to different biopsy schemes.

Table 3. Site of positive cores in case of diagnosis of HGPIN, ASAP and cancer, according to the different sampled zone.

Table 4. Pathological results of repeat biopsies according to the results of the initial biopsy.

	<i>Benign tissue</i> <i>n=1,083</i>	<i>Prostate cancer</i> <i>n=866</i>	<i>HGPIN</i> <i>n=34</i>	<i>ASAP</i> <i>n=23</i>	<i>Univariate</i> <i>analysis</i> <i>p</i>
PSA (ng/mL)	7.3 (\pm 5.8)	21.9 (\pm 125.2)	7.4 (\pm 3.2)	8.6 (\pm 4.3)	0.002
Free-to-total PSA (%)	17.8 (\pm 10.1)	13.4 (\pm 6.9)	16.0 (\pm 5.7)	16.1 (\pm 7.7)	<0.001
Age (years)	63.4 (\pm 7.2)	66.3 (\pm 8.3)	64.8 (\pm 6.8)	64.6 (\pm 7.7)	<0.001
Volume (mL)	48.6 (\pm 25.7)	40.6 (\pm 22.4)	41.1 (\pm 23.2)	47.5 (\pm 29.0)	<0.001
PSA density (ng/ml/gr)	0.175 (\pm 0.163)	0.515 (\pm 2.737)	0.194 (\pm 0.102)	0.210 (\pm 0.135)	0.002
Number of positive cores	-	6.4 (\pm 5.4)	1.9 (\pm 1.4)	1.2 (\pm 0.6)	<0.001

	<i>Sextant biopsies (6 cores)</i>	<i>Sextant + far lateral peripheral zone biopsies (12 cores)</i>	<i>Sextant + far lateral peripheral zone + middle line + transitional zone biopsies (21 cores)</i>
<i>Site of positive cores</i>			
Cancer	74.6%	17.6%	7.8%
HGPIN	38.2%	26.5%	35.3%
ASAP	30.4%	30.4%	39.1%
<i>Overall detection rate</i>			
Cancer	32.2%	39.8%	43.2%
HGPIN	0.6%	1.1%	1.7%
ASAP	0.3%	0.7%	1.1%

<i>Site of positive cores</i>	<i>Cancer (n=866)</i>	<i>HGPIN (n=34)</i>	<i>ASAP (n=23)</i>
Sextant (SXT) biopsies only	48	4	6
Lateral peripheral (PZ) zone only	89	7	6
Midline and transition zone (MTZ) only	68	12	9
SXT + PZ	76	2	0
SXT + MTZ	58	3	1
PZ + MTZ	63	2	1
SXT + PZ + MTZ	464	4	0

<i>Initial biopsy results</i>	<i>Benign tissue</i> <i>n=1,083</i>	<i>HGPIN</i> <i>n=34</i>	<i>ASAP</i> <i>n=23</i>
<i>Re-biopsy results</i>			
Benign tissue	273	17	10
HGPIN	5	0	0
ASAP	9	0	0
Cancer	58	4	7
Not done	738	13	6