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## Prostate Cancer

# Prostate Cancer Detection Rate in Patients with Repeated Extended 21-Sample Needle Biopsy

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### Abstract

**Background:** Prevalence of prostate cancer (PCa) after a negative first extended prostate needle biopsy protocol is unknown.

**Objective:** To evaluate the prevalence of significant PCa in patients who have had a negative first extended prostate biopsy protocol.

**Design, setting, and participants:** Between March 2001 and May 2007, 2500 consecutive patients underwent an extended protocol of 21 biopsies. Of 953 patients who had a negative first extended prostate biopsy procedure, 231 patients underwent a second or more set of 21-core biopsies. Indications for repeated biopsies were persistently elevated prostate-specific antigen (PSA), PSA increase during the follow-up, or prior prostatic intraepithelial neoplasia (PIN), or atypical small acinar proliferation (ASAP).

**Intervention:** All participants underwent at least two extended prostate needle biopsy protocols.

**Measurements:** Clinical and pathologic factors (age, PSA, PSA doubling time, PIN, ASAP, digital rectal exam [DRE]) were analyzed for their ability to predict positive biopsy, and tumour parameters were assessed in patients undergoing radical prostatectomy.

**Results and Limitations:** Second, third, and fourth extended 21-sample biopsy procedures yielded a diagnosis of PCa in 18%, 17%, and 14% of patients respectively. Patients with prior PIN had 16% risk of prostate cancer; patients with ASAP had a 42% risk. The mean number of positive cores was 2.19. Prostate volume and PSA density were statistically significant predictors of positive biopsy ( $p < 0.05$ ). For the 43 patients who underwent radical prostatectomy, pathologic findings revealed mean Gleason score of 6.7 (6–8), pT2a–c in 72%, pT3a in 16%, and pT4 in 7%. Mean cancer volume was 1.15 cc and 85.2% of tumours were clinically significant (tumour volume  $>0.5$  cc, Gleason  $\geq 7$  and/or pT3).

**Conclusions:** Negative first extended biopsies should not reassure a patient of not having PCa. However, prostate cancers detected after two or more sets of extended procedures, appear to be localized (intracapsular disease) and well-differentiated prostate cancers, although they are still clinically significant.

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### 1. Introduction

Despite efforts to improve the prostate cancer (PCa) detection rate using prostate biopsies, there exists a challenging cohort of patients with substantial risk factors for PCa who had a first negative biopsy set. If PSA increases and stays elevated or if atypical small acinar proliferation (ASAP) is found on biopsies, the scientific societies suggest repeat prostate biopsies, and a significant proportion of patients with PCa will be diagnosed on the second, third, or fourth set of biopsies [1,2]. Several authors suggest increasing the number of biopsies for this second set, with an extended or saturation protocol in order to increase the PCa detection rate [3–12].

Since 2001, our group has performed 21-needle prostate biopsies on every patient referred to us with an elevated PSA and/or an abnormal digital rectal exam (DRE) [12,13]. This protocol can be performed safely, and with minimal patient discomfort in the office using local anesthesia. A statistically significant increase of prostate cancer detection was observed [12].

However, for patients with a negative first extended biopsy protocol, the risk of missing a cancer is unknown: Can these patients be reassured of not having prostate cancer? What is the risk of having an aggressive disease after an extended protocol that is supposed to evaluate all prostate zones? The goal of this article is to focus on patients who had a negative first extended protocol and who were candidates for repeated biopsies. The risk of having PCa and the aggressiveness of these cancers were evaluated.

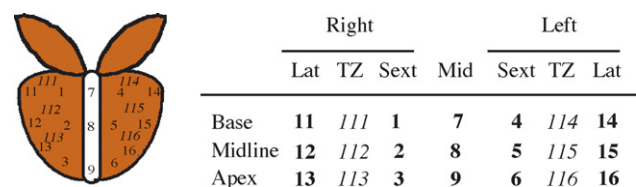
### 2. Materials and methods

Between March 2001 and May 2007, 2500 consecutive patients underwent an extended protocol of 21 biopsies. All patients were included prospectively in the clinical database. Of 953 patients who had a negative first extended prostate biopsy procedure, 231 patients underwent second, third, or more sets of 21-core biopsies of prostate. Indications for repeated biopsies were patients with high risk of PCa with prior PIN or ASAP on previous 21-core biopsies, prostate-specific antigen (PSA) persistently elevated (greater than 4ng/ml), increase of PSA during the follow-up, and persistent prostatic nodule on DRE. Clinical and pathologic data, including patient age, PSA, PSA density, transrectal ultrasound measured (TRUS) prostate volume, Gleason score, the number and location of positive cores, were analyzed using our computerized data base. PSA doubling time was calculated with the following method:  $PSADT = \log 2 \times dT / (\log B - \log A)$  where A and B are the initial (A) and final (B) PSA measurements, and dT is the time difference between the calendar dates of the two PSA measurements [14].

The prostate needle biopsy procedure has been described previously [12]. Briefly, patients were prescribed enemas 1 d and 3 h before the procedure. A fluoroquinolone antibiotic was prescribed for 7 d, starting the day before the procedure. All patients were adequately informed of the mode of execution of the procedure and its potential complications. All patients received local anesthesia using a 22-gauge spinal needle that was passed through the biopsy guide channel and 10 cc 1% lidocaine was injected into each neurovascular bundle. Ultrasound prostate volume calculations were then performed. A total of 21 biopsies were taken, using 18-gauge biopsy needles and a spring-loaded biopsy gun, providing 17 mm length tissue cores. The patients were allowed to leave the hospital 2 h after the procedure. The biopsies were performed in the following order: First, six sextant medial biopsies at a standard 45° angle (numbers 1–6), then three biopsies in each lateral zone from base to apex at an 80° angle (numbers 11–16). Next, three biopsies were taken in each transitional zone from base to apex (numbers 111–116). Finally, three biopsies in the midline peripheral zone (numbers 7–9) (Fig. 1). Each prostate core was given a specific number according to the biopsy protocol and was analyzed separately [5]. For each patient with abnormal DRE or hypoechoic lesions, our 21-biopsy protocol included these areas, although we did not specifically biopsy these anomalies. A board-certified pathologist interpreted all slides. Dedicated uropathologists were involved in daily practice for prostate needle biopsy diagnosis.

For patients undergoing radical prostatectomy, tumour grade, positive surgical margins, and extracapsular extension were assessed. Prostate specimens were serially sectioned and totally submitted. Tumour volume in cm<sup>3</sup> was calculated for every prostatic specimen as a summation of all tumour nodules using. We defined clinically significant tumours according to Epstein et al as a tumour volume of greater than 0.5 cm<sup>3</sup> or less than 0.5 cm<sup>3</sup> plus a Gleason score of 7 or greater and/or pT3 [6].

Statistical analysis was performed using Statview 5.0 (SAS Institute, Cary, NC). Continuous covariates (age) were compared using Student’s t test and covariates without normal distribution (PSA, prostate volume, PSA density) were compared using nonparametric tests (Mann-Whitney U test, Kruskal-Wallis test). In all analyses, two-sided hypothesis testing was carried out with probability values less than 0.05 deemed significant. Cox proportional-hazard regression was used to carry out the multivariate analysis.



**Fig. 1 – Mondor Hospital’s 21-sample needle biopsy protocol including sextant biopsy, six biopsies in far lateral peripheral zone, six biopsies in transitional zone, and three in the middle peripheral zone.**

**Table 1 – Patient characteristics**

No patients	231
Mean age (yr)	63.4 ( $\pm 6.4$ )
Mean PSA (ng/ml)	7.26 ( $\pm 7.97$ )
Mean PSA density (ng/ml/ml)	0.180 ( $\pm 0.15$ )
Mean prostate volume (ml)	46.1 ( $\pm 25.8$ )
Mean months interbiopsy interval	10 ( $\pm 6$ )
Mean interval Between (ranges):	
1st and 2nd biopsy	8 ( $\pm 6.4$ )
2nd and 3rd biopsy	11 ( $\pm 7.6$ )
3rd and 4th biopsy	24 ( $\pm 7.2$ )
4th and 5th biopsy	34 ( $\pm 7.66$ )
Result on rebiopsy	
Benign	142 (61.5%)
PIN	20 (8.6%)
ASAP	11 (4.9%)
Cancer	58 (25.1%)
DRE (digital rectal exam)	
Normal	202 (88%)
Abnormal	29 (22%)

### 3. Results

A total of 231 patients underwent repeated 21-core prostate biopsies. The baseline characteristics of the cohort are seen in Table 1. The mean number of repeated 21-core biopsies procedures was 2.4. Only eight (3.4%) of the 231 patients reported adverse events after the repeat extended 21-sample procedure, with fever and prostatitis in three patients, acute urinary retention in four patients, and rectal bleeding in one patient.

#### 3.1. Pathological findings

PCa detection rate was 25.1%, PIN 8.6%, and ASAP 4.9%. Cancer was detected in 42 of 231 patients (18%) in the second biopsy set; 13 of 76 (17%) in the third biopsy set; and 3 of 21 patients (14%) in fourth biopsy procedure (Table 2).

#### 3.2. Patients with prior PIN or ASAP on the first extended protocol

PCa prevalence was 16% for patients who had on the first set of biopsies a PIN lesion (Table 2). Of the

seven patients with ASAP on the first set of biopsies, three had PCa on the second set of biopsies (42%); the four remaining patients underwent a third set of biopsies and one of them was found to have PCa (Table 2).

#### 3.3. Patients with negative first extended protocol

For patients with a first negative (with no PIN or ASAP) set of biopsies, the risk of having PCa was 17% (Table 2) and if repeated biopsies were performed, the risks on the third, fourth, and fifth sets of biopsies were 16%, 14%, and 0% respectively.

According to the PSA level, PCa rates were 21% for patients with PSA < 4 ng/ml, 16% for PSA between 4–10 ng/ml, 12.9% for PSA between 10–20 ng/ml, and 30.7% for PSA > 20 ng/ml.

#### 3.4. Site of positivity

Cancer was diagnosed in 30 of 58 patients (51.7%) in medial peripheral zone (sextant biopsy), in 51 patients (88%) in peripheral zone (sextant + lateral biopsies). In seven of 58 patients (12.1%), only transition and/or midline peripheral zone were positive for cancer (Table 2). One case (1.7%) was identified from the transition zone (TZ)-only cores. Overall, the repeat 21-sample biopsy procedure yielded a diagnosis of PCa in 25.1% of patients compared with 13% and 22.1% of patients on the basis of six biopsies (sextant biopsies only) and 12 biopsies (sextant + 6 far lateral biopsies) respectively. Thus, the repeated 21-sample biopsies improved also the diagnostic yield by 93.3% and 13.7% compared to sextant biopsies (medial peripheral zone) and 12 biopsies (sextant + 6 lateral biopsies) respectively.

#### 3.5. Predictors on positive re-biopsies

Table 3 shows characteristics of 58 diagnosed cancers. The mean PSA in the group with cancer was 7.8 ng/ml (range 3–89.6). The mean Gleason score was 6.1 (range 5–8). Forty-four patients (76%)

**Table 2 – Prevalence of positive biopsies according to the set and to the PIN or ASAP**

	Positive biopsy (%)			
	2nd biopsy	3rd biopsy	4th biopsy	5th biopsy
Total	42/231 (18%)	13/76 (17%)	3/21 (14%)	0/4 (0%)
Prior PIN on the first procedure	3/18 (16%)			
Prior ASAP on the first procedure	3/7 (42%)	1/4 (25%)		
Benign on the first procedure	36/206 (17%)	12/72 (16%)	3/21 (14%)	0/4 (0%)

**Table 3 – Characteristics of cancer detected on repeated extended biopsy protocol**

No cancer diagnosed	58 (25.1%)
Mean PSA (ng/ml)	7.8 (±7.6)
PSA ≤ 4	4 (6.9%)
4 < PSA ≤ 10	38 (65.5%)
10 < PSA ≤ 20	12 (20.7%)
PSA > 20	4 (6.9%)
Mean PSA density (ng/ml/ml)	0.242 (±0.14)
Biopsy Gleason score	
5 (2+3)	1 (1.8%)
5 (3+2)	3 (5.2%)
6	44 (75.9%)
7 (3+4)	6 (10.3%)
7 (4+3)	3 (5.2%)
8	1 (1.8%)
Mean positive cores (/21)	2.19 (±1.5)
Anatomical location	30 (51.7%)
Medial peripheral zone (sextant biopsy)	51 (88%)
Peripheral zone	1 (1.7%)
Transition zone only*	4 (6.9%)
Midline zone only*	7 (12.1%)
Transition and/or Midline peripheral zone only*	

\* These patients had prostate cancer detected only in the TZ or midline PZ zone.

had a Gleason score of 6, and a Gleason score of 7 or greater was noted in 10 patients (17%).

We analyzed in univariate and multivariate analyses whether any prebiopsy characteristics were associated with positive second set of biopsies (Table 4). In multivariate analysis, ASAP, prostate volume, and PSA density were found to be a predictive parameter of positive biopsies.

**3.6. PCa characteristics on radical prostatectomy specimens**

A total of 43 patients (74.1%) underwent radical prostatectomy. Table 5 shows pathologic findings at

**Table 5 – Pathologic findings on radical prostatectomy specimens**

Radical prostatectomy	43
No Gleason score	
6	13 (30.2%)
7 (3+4)	25 (58.1%)
7 (4+3)	2 (4.7%)
8	1 (2.3%)
No stage	
No cancer (PIN only)	2 (4.7%)
pT2a	7 (16.3%)
pT2b	9 (21%)
pT2c	15 (34.9%)
pT3a	7 (16.3%)
pT4	3 (7%)
Mean cancer volume (cm <sup>3</sup> )	1.15 (±1.2)

prostatectomy. The mean Gleason score was 6.7 (range 6–8) versus 6.12 at biopsy ( $p = 0.11$ ). In 28 patients (65.1%), Gleason score was seven or greater versus 17.2% at positive biopsy. Pathologic stage was pT2a–c (organ-confined disease) in 31 of 43 patients (72.1%), pT3a in 7 (16.3%), and pT4 in 3 (7%). No cancer (only PIN) was detected in two patients (4.7%). These two patients had one or two positive biopsy cores, PSA less than 10 ng/ml, and Gleason score of 6 at biopsy. Tumour volume was 0.3 to 3.4 cm<sup>3</sup> (mean = 1.15 cm<sup>3</sup>). Of the 43 tumours, 85.2% were clinically significant (Tables 5 and 6).

**4. Discussion**

The ideal strategy for prostate biopsy procedure has yet to be fully elucidated. The sextant biopsy (medial peripheral zone) proposed by Hodge et al is associated with a significant false-negative rate [15]. The prevalence of false-negative sextant biopsy ranges between 20% and 33% [15,17]. Recent studies

**Table 4 – Comparisons of patients’ characteristics with and without cancer after the second biopsy set**

	Univariate analysis			Multivariate analysis*		
	Cancer (n = 42)	No cancer (n = 189)	p	Relative risk*	95% Confidential intervals	p
PSA (ng/ml)	10.3 ± 12.59	8.1 ± 6.58	0.759			
Prior PIN	10.5%	89.5%	0.747			
Prior ASAP	37.5%	62.5%	0.130	3.65	1.09–12.29	0.036
Abnormal DRE (image Echo)	8.0%	92.0%	0.390			
PSA density (ng/ml/ml)	0.32 ± 0.31	0.21 ± 0.13	0.045	24.70	6.13–99.47	<0.0001
Age (yr)	65.2 ± 5.69	63.7 ± 6.75	0.212			
Prostate volume (ml)	(<50) 21.7% (≥50) 6.6%	(<50) 78.3% (≥50) 93.4%	0.004	0.34	0.13–0.91	0.031
PSA doubling time	2.05 ± 13.28	–6.95 ± 54.99	0.809			

Data presented as the mean ± SD.  
\* Cox regression with relative risks adjusted for age.

**Table 6 – Pathologic characteristics of diagnosed cancers**

	2nd positive biopsy (n = 42)	3rd positive biopsy (n = 13)	4th positive biopsy (n = 3)	p value
Mean age (yr)	64.3 ± 6	65.6 ± 5.9	61.3 ± 4.7	0.5268
Mean prostate volume (ml)	41.7 ± 29.4	36.3 ± 22	42.3 ± 13.6	0.5032
Mean PSA (ng/ml)	7.8	7.8	7	0.7733
Mean PSA density (ng/ml/ml)	0.233	0.338	0.287	0.5263
Mean Gleason score at biopsy	6.1 ± 0.53	6.2 ± 0.44	6 ± 0	0.7184
Mean Gleason score at prostatectomy	6.7 ± 0.45	6.7 ± 0.75	6.67 ± 0.58	0.772
Mean cancer volume (cm <sup>3</sup> )	1.94 ± 0.12	1.70 ± 0.34	1.27 ± 0.37	0.423
T stage (%)	n = 33	n = 7	n = 3	
pT2	24 (73%)	5 (72%)	2 (67%)	
pT3	6 (18%)	0	1 (33%)	
pT4	2 (6%)	1 (14%)	0	
PIN	1 (3%)	1 (14%)	0	
Insignificant cancer	3 (9%)	2 (28.6%)	1 (33.3%)	

suggest that modifications of the standard sextant biopsy technique by increasing the number of cores obtained or expanding the number of regions sampled may improve the detection of PCa at biopsy. Eskew et al observed that a five-region biopsy method that incorporated lateral and mid-line biopsy with traditional sextant cores improved the diagnostic yield by 35% [3]. Presti et al investigated a 12-core biopsy strategy, including sextant biopsies and laterally directed sextant biopsies, in a multipractice community study involving 2299 men. The laterally directed sextant biopsies detected 83% of cancers [4]. For urologists, there is a not yet clear recommendation for the follow up of patients with negative prostate biopsies. In this study, we repeated prostate biopsies for young patients with PSA progression or elevated PSA, for whom in multivariate analysis ASAP, prostate volume, and PSA density were predictors of cancer risk. However, a prospective study with a long follow-up should be conducted to answer this question.

In this study, we analyzed the performance of repeated extensive biopsies in 231 patients who had negative 21-sample biopsy procedure and who were at increased risk for PCa. Our overall diagnostic yield was 25.1%, which is similar to the 13.5% to 34% yield in other series [5,16]. Selection of high-risk patients at the discretion of the physician represents a bias of this study. However, an important difference is that these other series included patients who had only prior sextant or 12-sample biopsies. In our series, all patients underwent prior extensive 21-sample biopsies. We noted yields of 13% and 22.1% when 6 and 12 cores were taken respectively. In the literature, there is a debate on the TZ biopsies. In our repeated biopsies, we found that 12% of positive biopsies were on the transitional zone or on midline

peripheral zone. This also leads us to propose these additional biopsies.

In terms of determining the ideal number of cores to obtain in difficult diagnostic cases, in our series, 88% of cancers were identified in the peripheral zone (1 biopsies). One case (1.7%) was identified from the TZ-only cores and the indication of TZ biopsies alone could be discussed. According to published reports, PCa is diagnosed on the basis of TZ biopsies only in 1.8% to 8% of cases [7–10]. In these studies, TZ biopsies were indicated in patients with prior negative biopsy procedures and elevated serum PSA levels associated with an enlarged, non-nodular prostate [7]. The prevalence of positive TZ biopsies was 1.5% in 274 men who underwent sextant plus TZ biopsies for elevated PSA levels, but this rate increased to 9.5% in the 116 patients who previously had negative sextant biopsies [7]. The latter prevalence was slightly lower in our study (1.7%), in which TZ biopsies were systematically performed since the first biopsy procedure. Recently, Walz et al [23] reported a high PCa detection rate of 41% with a 24-core protocol. Similarly to the initial biopsy protocol, it has been proven that more time and effort should be spent on lateral biopsies, which increase the cancer detection rate, whereas parasagittal biopsy provides a low yield on repeat biopsy [24].

PIN and ASAP in the initial biopsy were associated with a positive repeated biopsy rate of 6% and 42% in our patients, respectively. This rate is consistent with those in other series of repeated biopsy in which initial biopsy findings indicated PIN or ASAP. It is also important to note that patients with PIN detected on a first extended protocol have the same risk as men with a benign (no PIN or ASAP) biopsy of having PCa on the repeated biopsies (16% vs 17%) [18]. Consequently, some authors conclude that

there is no need to perform repeat biopsy within the first year on men with PIN unless there are other factors worrisome for cancer, such as PSA increase [2]. Moreover, the small number of patients with PIN or ASAP is a limitation in our study. We are unable to assess whether presence of PIN and/or ASAP represents a risk factor for PCa on extended biopsy.

When we analyzed factors that may be associated with positive biopsy in our group, PSA density (PSAD) was found to be a strong predictor. Some authors have reported that larger prostates have a decreased rate of cancer detection. In our series, cancer was detected in only 14% of prostates larger than 60 cc, compared with 27% in those with less than 40 cc. Many larger prostates have elevated PSA, which is not secondary to a malignant process but rather a reflection of increased size, and in particular TZ size. While undersampling of larger prostates may explain this discrepancy, it is also possible that there is a lower prevalence of cancer in these large organs composed mostly of benign tissue [6]. Another possibility is the use of nomogram: Karakiewicz's group reported several nomograms to predict the risk of PCa in extended repeat biopsies and the risk of positive biopsies in the TZ [19,20]. These powerful and attractive statistical models seem very useful for clinicians but their uses are not widely accepted.

Some authors suggested that increasing the number of biopsies can lead to a treatment of 3% to 27% of clinically insignificant tumours [21,22]. In our series, 85.2 % of cancers diagnosed by repeated 21-core biopsy were significant (tumour volume >0.5 cc, Gleason  $\geq$ 7, and/or pT3). It appears that in our series the detection of clinically insignificant cancers with repeated saturation biopsy is similar to that in other series in which the diagnosis of PCa was made with fewer biopsy cores (6–18 cores). Thus, it does not appear to increase the detection of insignificant cancers. Moreover, different studies have demonstrated that the use of the extended biopsy procedure has been beneficial in the pre-treatment decision-making process, because an increased number of biopsies increase the Gleason concordance. In our study, no significant difference existed between the biopsy and prostatectomy Gleason (6.1 vs 6.7). Different authors [25,26] have demonstrated that, with a more extended biopsy procedure, the risk of significant upgrading decreases because of higher sampling density and more accurate pathologic biopsy evaluation. The two largest published cohorts [27,28] showed a rate of overall Gleason sum upgrading of 29.3% and 32.6% and a rate of significant upgrading of 32% and 28.2%,

respectively. Prospective studies are needed for the evaluation of the aggressiveness of PCa detected on extended repeat biopsies in terms of progression and overall survival.

Djavan et al reported in 2001 an original work on the risk of PCa on repeated biopsies performed 6 wk after a negative set [29]. They found that cancer detection rates on biopsies 1, 2, 3, and 4 were 22% (231 of 1051), 10% (83 of 820), 5% (36 of 737) and 4% (4 of 94), respectively, and that 58.0%, 60.9%, 86.3%, and 100% of patients who had a radical prostatectomy had organ-confined disease on biopsies 1, 2, 3, and 4, respectively. There are some differences between this study and the present report: First the delay between the first and the subsequent biopsies is different; second, the definition of clinically significant PCa was not used. Finally, one question remains unanswered: what is the evolution of PCa detected at the biopsy 3, 4, or 5. We need more data on the aggressiveness of PCa detected on extended repeat biopsies in terms of progression and overall survival. Probably, the use of repeated extended biopsies can lead to detection of intracapsular PCa for which active surveillance can represent a potential option instead of radical treatment.

## 5. Conclusion

A negative first extended biopsy protocol should not reassure a patient of not having prostate cancer: second, third, and fourth extended 21-sample needle procedures led to a cancer detection rate of 18%, 17%, and 14% respectively. Cancer detected at these sets of biopsies appeared to be intracapsular disease in 75% of the cases. These were considered as significant cancer, mostly due to a Gleason score greater or equal to 7 in 85%.

**Author contributions:** Alexandre de la Taille had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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### Editorial Comment on: Prostate Cancer Detection Rate in Patients with Repeated Extended 21-Sample Needle Biopsy

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Currently, an extended prostate biopsy scheme consisting of at least 10 cores has been generally accepted as the diagnostic gold standard [1]. It has been shown to improve detection rates without increasing the rate of insignificant prostate cancers [2]. With this paper ( $n = 231$ ), further evidence is added to the sequential use of an extended biopsy scheme [3]. Indeed, it is the first report in the literature that describes detection rates based on subsection to initial, second, third, and even fourth sets of an extended biopsy scheme consisting of 21 cores. The results demonstrate that even after a fourth set of an extended prostate biopsy, the prostate cancer detection rate remains high at 14%. Thus, a negative extended prostate biopsy, even after sequential subsections, does not reassure the clinician that significant disease has not been detected. This suggestion is further elucidated by the authors' pathological findings, as a more important clinical end point, from 43 men who underwent radical prostatectomy after a positive repeat, third, or fourth positive extended biopsy. These pathological findings exhibit significant disease defined according to the Epstein criteria [4] in the majority of cases, ranging between 91% and 66.7% after a second and a fourth extended biopsies, respectively.

From a clinical viewpoint, it remains unclear which biopsy strategy should be followed after an initial negative extended biopsy. Whether one or two negative extended biopsy sets should be followed by a saturation biopsy, for example, needs to be further and prospectively investigated. Inter-

estingly, overall Gleason sum upgrading from 6 to 7 was noted regardless whether it was the second, the third, or even the fourth positive extended biopsy set [3]. These data confirm the current diagnostic problem, even in the era of extended biopsy schemes, that approximately 40% of Gleason score assignments at biopsy will eventually be upgraded at final pathology.

The authors' findings [3] are especially interesting in the light of a potential active-surveillance recommendation. All men were subjected to the extended biopsy scheme; the mean number of positive cores after the second biopsy set was 2, prostate-specific antigen (PSA)  $<10$  ng/ml, PSA density 0.2, and the mean intervals between biopsy sets 1 and 2 and sets 2 and 3 were 8 mo and 11 mo, respectively. Even with these characteristics, the mean tumor volume was 1.9 cc and 1.7 cc, and 24 and 14% demonstrated non-organ-confined disease after the second and third biopsy sets, respectively. It may be allowed to hypothesize that this rate of unfavorable pathologic outcome is even higher if all Gleason scores would have been tabulated. Therefore, these data further corroborate the need for a critical appraisal of current active surveillance criteria [5] based on biopsy information even after subsection to sequential 21 core prostate biopsy sets.

Taken together, this study demonstrates non-negligible disease detection as well as significant disease detection even after a second or third sequential extended prostate biopsy.

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### Editorial Comment on: Prostate Cancer Detection Rate in Patients with Repeated Extended 21-Sample Needle Biopsy

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The authors should be congratulated for the present study, which represents the largest published series of men submitted to repeat extended prostate biopsy after first negative extended biopsy [1]. The most notable finding is that cancer detection rate remains high (approximately one in four patients), with most cancers being clinically significant, even when a 21-core multisite template is adopted. This finding suggests that the sampling strategy on initial prostate biopsy should be revisited, which may be theoretically attained by either increasing further the number of cores or by modifying their geographical distribution. The former option may be fuelled by a contemporary trend witnessed by the shift from conventional sextant through extended to saturation templates [2]; however, evidence has begun to accumulate supporting the idea that where and how to take the cores is more important than how many cores to take [3–5]. To my mind, this latter notion is likely a reflection of the inherent limitations of the current biopsy technique regarding both the sampling route and the materials used. These limitations lead to the result that certain prostate regions are inevitably excluded from adequate sampling and would be excluded even if the number of cores became “supersaturated.” It is, in fact, plausible that by combining transrectal sampling with transperineal sampling [5], coupling ultrasound probe firing with different angles of needle sampling, or simply using longer core needles [6], a real optimisation of cancer detection rate may be achieved.

This consideration holds particularly true for large-sized prostates, which are traditionally associated with a lower detection rate [7]. Given that growing prostate volume is solely due to an enlarging transition zone (TZ), TZ biopsy has initially been recommended on an intuitive basis to enhance diagnostic accuracy. Most recent studies have demonstrated that cancer is rarely harboured exclusively in the TZ. The low detection rate appears to be due to the largely inadequate sampling of the peripheral zone (where cancer most commonly arises), because of its compression and lateral displacement caused by enlarging TZ, with the

current biopsy technique. As confirmed in the present paper, the benefit of TZ biopsy, at least in the repeat biopsy setting, seems negligible because only 1 out of 58 cancers was exclusively detected with TZ cores [1]. Conversely, the site of positivity still concentrates in the peripheral zone, mostly the lateral and apical anterior regions [1,3].

Until the optimal strategy for initial biopsy is found, identifying patients at higher risk for positive repeat biopsy appears to be highly desirable, and this should be done by incorporating established predictors into the most reliable statistical models [8,9]. On the other hand, additional research should address the issue of whether insisting on the biopsy cascade is worthwhile since no solid data are currently available on the biological characteristics and ultimate outcome of cancers detected on repeat biopsy.

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### Editorial Comment on: Prostate Cancer Detection Rate in Patients with Repeated Extended 21-Sample Needle Biopsy

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This paper [1] adds important data about the prevalence and significance of cancers detected in men who are negative by a “good” first biopsy, that is, extended number of cores (21 in this paper) and in the right areas (mostly lateral). The reasons for the subsequent up-to-four biopsy sessions were the usual ones: persistent positive digital rectal examination (DRE), prostate-specific antigen (PSA) >4, and rising PSA. The essential data are not surprising in revealing 25% cancers overall and sequential biopsy rates of 18%, 17%, 14%, and 0%. In multivariate analysis, prostatic volume <50 cm<sup>3</sup>, atypical small acinar proliferation of prostate (ASAP), and PSA density were predictive. In those having surgery, 82% had “significant” cancer.

One obvious conclusion from this data is that one good biopsy session is probably not enough if the patient subsequently has classic suspicious findings. But how many more are needed—one, two, or what? Probably three biopsy sessions are appropriate, but there will be exceptions.

This paper does not definitively provide us with a complete biopsy scheme. There are many unanswered questions, particularly now that the Prostate Cancer Prevention Trial (PCPT) data [2] show us that there are many men with cancer and some with significant cancer who have no

suspicious findings and very low PSA. The specific questions and references are legion and need not occupy space here.

So, what should we do about repeating the biopsies when the first is negative? I believe we still need to practice from a well-informed position, that is, consider the individual patient and, in most cases, be aggressive in trying to find out whether cancer exists. In most cases, I perform at least one good repeat biopsy if the original indications were appropriate (PSA >2.5, life expectancy >10 yr). Factors that heighten my aggressiveness are the extent and positions of the original biopsy; race; family history; the true DRE findings; PSA density; a small cancer; and of course, PSA changes over time (eg, PSA velocity >0.5 ng/ml per year). I have painfully learned that diligent follow-up is important and that I need to be flexible in my indications as more data are revealed.

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