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When serial prostate biopsy is recommended: most cancers detected are clinically insignificant

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What's known on the subject? and What does the study add?
Many patients undergo serial biopsy with a low rate of detection of prostate cancer, and the rate of detection declines as more biopsies are pursued. Furthermore, the clinical significance of detected cancer appears to decline as well. It is important to follow all possible methods to detect cancer; however, there should be a parallel consideration for the clinical value for detection of these tumours with low malignant potential.

The present study investigated in detail the total rate of cancer detection in serial biopsy and how many of these were deemed clinically insignificant. Moreover, it addressed the impact of detecting premalignant lesions on further detection of cancer in serial biopsy.

OBJECTIVE

- Many patients pursue serial prostate biopsies after two consecutive negative biopsy sessions. The objective of this study is to determine the indications of serial prostate biopsy and to compare outcomes, including the risk of detecting clinically insignificant cancer using different biopsy protocols in this highly selected population.

PATIENTS AND METHODS

- Most cases of prostate cancer are detected on initial or one repeat biopsy, but persistent suspicion of prostate cancer occasionally leads to serial biopsy, which we define as more than two biopsy sessions. We recently showed that transrectal saturation biopsy (sPBx) significantly increases cancer detection when compared with extended schemes (ePBx) in the initial repeat biopsy (second overall biopsy) population, and that most cases identified are clinically significant.
- In the past decade, 479 men underwent 749 repeat prostate biopsies after two prior negative biopsy sessions.
- The ePBx group included 347 biopsies with 10–14 cores.
- The sPBx group included 402 biopsies with >20 cores.
- We analysed overall cancer detection and risk of detecting clinically significant vs insignificant tumours.

RESULTS

- Prostate cancer was detected in 15.9% of 749 serial biopsies, representing a cumulative prostate cancer detection rate of 24.8% (119/479 patients).
- The sPBx group had a significantly higher detection rate per biopsy session (18.6% vs 12.7%, $P = 0.026$).
- Nevertheless, most positive biopsies 75/119 (63%) revealed clinically insignificant cancer, including 74.6% of cancers detected by sPBx.

CONCLUSION

- In men with two prior negative prostate biopsies, prostate cancer detection remains low regardless of clinical indication or transrectal biopsy protocol; most cancers identified are clinically insignificant, suggesting the threshold to repeat biopsy after more than one negative session should be very high.

KEYWORDS

prostate biopsy, saturation, extended, serial, prostate cancer

INTRODUCTION

Laterally directed extended prostate biopsy (ePBx) significantly enhances the diagnosis of prostate cancer compared with conventional sextant biopsy [1,2]. However, the false-negative rate remains substantial [3]. Urologists are frequently faced with the dilemma of managing patients with a high suspicion for unrecognised prostate cancer despite negative PBx. This suspicion is usually based on either clinical or pathological indicators, e.g. abnormal DRE, elevated PSA level, or a previous biopsy showing high-grade prostatic intraepithelial neoplasia (HGPIN) and/or atypical small acinar proliferation (ASAP). Several studies have shown significant cancer detection

rates of repeat biopsies in those patient populations [3,4].

Among all serial repeat biopsies that a patient may undergo, the initial repeat (second overall) biopsy possesses the highest chance for prostate cancer detection, being positive in 25–30% in most series, although the likelihood of identifying clinically insignificant cancer also increases during this biopsy session [4–7]. Consequently, a negative initial repeat biopsy increases complexity of decision making because most of those patients do not have unrecognised significant prostate cancer. Nevertheless, it remains unknown which patients merit further investigation, or when the serial biopsy cascade should stop.

Based on the referral nature of our practice, we are frequently consulted on patients for suspicion of prostate cancer despite one or more negative biopsies. As biopsy can be highly variable among practitioners, we cannot assume that the entire gland has been adequately assessed, and multiple publications have shown a high concentration of 'missed' cancers in the anterior gland and extreme apex [8,9].

Various indications and tools have been proposed to aid in the prediction of prostate cancer after initial negative biopsy sessions [10–12]. Several series have suggested both safety and superior prostate cancer detection rates of sPBx in repeat biopsy population [13–15]. Based on our favourable experience with transrectal saturation biopsy (sPBx), many of these patients are recommended to undergo sPBx in the hope of providing potential finality in their diagnostic journey, during which many have had as many as seven prior biopsy sessions.

In a recent study limited to initial repeat PBx population, we showed that sPBx significantly enhances prostate cancer detection when compared with ePBx [16]. We have also shown that despite assumptions to the contrary, sPBx is not associated with higher morbidity than ePBx [17], so several of our urologists use the technique for all repeat biopsy sessions regardless of clinical indication.

The aim of the present study was to determine indications for serial biopsy and to compare outcomes, including the risk of detecting clinically insignificant cancer using these protocols in highly selected, mostly external referral patients who pursue serial prostate biopsies after two consecutive negative biopsy sessions.

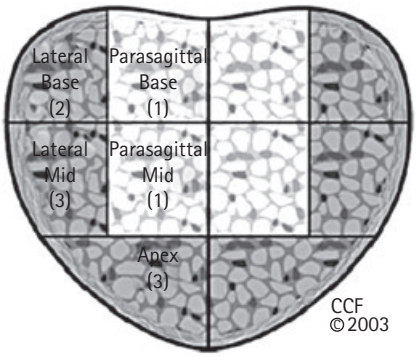
PATIENTS AND METHODS

Between March 2000 and April 2010, 479 men underwent 749 repeat TRUS-guided PBx after two biopsy sessions negative for prostate cancer. We included only patients with complete data for all prior biopsy schemes and pathology findings. Patients were not randomized, but were prospectively evaluated for these outcomes in our Institutional Review Board (IRB)-approved, Health Insurance Portability and Accountability Act-compliant, PBx database. To avoid confusion about biopsy sessions, we use the term 'initial repeat biopsy' for the second biopsy session, and 'serial biopsy' to describe a third or greater biopsy when this is recommended.

The indications for serial biopsy in this highly selected population comprised suspicious pathological findings and/or clinical indicators. Suspicious pathological findings included either ASAP (with or without HGPIN) or HGPIN alone. The clinical indications for repeat biopsies encompassed persistently rising PSA level, abnormal DRE and/or a persistent very high PSA level. Most of the patients adhering to the latter indication were referred specifically requesting definitive biopsy.

We recommend routine delayed interval biopsy every 2–3 years after HGPIN detection in young healthy men, based on studies showing significant cancer diagnosis at these intervals [18]. For patients with ASAP, we recommend repeat biopsy within 6 months. For patients with initial completely normal or benign biopsy findings, the time for further biopsy was tailored according to the risk indicators encountered with each individual case, based on clinical decisions with the staff physician. As noted, for many of these patients, the indication was consultation for definitive diagnosis by a referring urologist. Some of the prior biopsies were performed outside the institution, but all TRUS-guided serial prostate biopsies reported herein were performed at our institution in an office-based setting with periprostatic block being safely and effectively used since 2002 [19].

FIG. 1. The most common protocol for 20-core scheme in sPBx.



The attending urologist's practice pattern was the major factor determining the PBx scheme.

Serial biopsies were divided into two groups: 347 TRUS-guided biopsies included 10–14 cores (ePBx) and 402 biopsies comprised of ≥20 cores (sPBx). The 10–14 core template obtained medial and lateral cores on each side from the base, mid-gland, and apex, with a few recent patients having an additional core on each side of the extreme apex. Our most common technique for sPBx obtains 20 cores as previously published (Fig. 1).

Clinically insignificant cancer was defined as having Gleason score <7, positive cores ≤3 and maximum percentage involvement of cancer in any positive core ≤50%; otherwise it was considered as a clinically significant cancer per a previously reported definition [16,20].

For demographics, mean, median and range were given for continuous variables, and frequency and percentage were given for categorical variables. The demographics of the biopsy groups were compared by two-sided *t*-test for continuous variables and by chi-square test for categorical variables.

The detection rate of overall prostate cancer and clinically insignificant cancer was compared between the groups by chi-square test. The conditional association of prostate cancer detection and biopsy group adjusting for patients who had previous suspicious lesions and for those who had benign previous biopsies was also explored. Cochran–Armitage trend statistics was used

to test trend of cancer detection rate in different biopsies. Statistics were considered significant at the level of 0.05.

RESULTS

An ePBx was used in 441/479 (92%) patients for their first PBx; in the initial repeat biopsy, 53.4% and 46.6% had undergone ePBx and sPBx, respectively (Table 1). Serial biopsies were performed during a median (range) follow-up of 1.8 (0.5–3.4) years after the previous biopsy session. Most clinical and demographic variables were comparable between the groups as shown in Table 2. However, the percentage free/total PSA (%fPSA) and central prostate volumes were higher in the sPBx group.

Prostate cancer was detected in only 119 of 749 (15.9%) sPBx sessions. Nevertheless, the cumulative risk of prostate cancer detection was 24.8% (119/479 patients). Transrectal sPBx had a statistically significant higher prostate cancer detection rate when compared with ePBx (18.6% vs 12.7%, respectively, $P = 0.026$) (Table 2).

Table 3 shows the overall cancer yield according to previous biopsy findings. For patients with benign first and initial repeat biopsies, prostate cancer was detected in only 9% of biopsy sessions. No significant difference was identified between sPBx compared with ePBx (10.2% vs 7.6%, $P = 0.4$). By contrast, the prostate cancer detection rate was significantly higher in the sPBx group for patients with previous suspicious lesion(s) (ASAP and/or HGPIN; 27.6% vs 17.5%, $P = 0.021$).

Nevertheless, of 119 positive biopsies, 75 (63%) showed clinically insignificant prostate cancer according to the predetermined criteria, which was higher in sPBx group (74.6% vs 56.8%, $P = 0.044$; Table 4).

Table 5 shows the incidence of significant and insignificant prostate cancer according to prior biopsy findings. Both patients with previous benign biopsies and those with HGPIN had a higher incidence of clinically insignificant tumours ($P < 0.001$ and $P = 0.03$, respectively). There appeared to be a trend for more insignificant cancer detection in patients with previous ASAP but this did not reach statistical significance ($P = 0.6$).

TABLE 1 Biopsy schemes applied in the initial two negative biopsies

Biopsy scheme	Biopsy one: number of patients (%)	Biopsy two: number of patients (%)
ePBx	441 (92)	256 (53.4)
sPBx	38 (8)	223 (46.6)
Total	479	479

TABLE 2 Baseline clinical characteristics of the study population with comparison between the ePBx and sPBx

Variables	Biopsy Group Total	ePBx	sPBx	*P*
Mean (median, range):				0.31
Age, years	64.7 (65, 42–86)	65.1 (65, 42–81)	64.4 (64, 45–86)	
N (%):				
Race:				0.26
African-American	55 (7.3)	19 (5.5)	36 (9.0)	
Asian	6 (0.8)	4 (1.2)	2 (0.5)	
Caucasian	662 (88.4)	310 (89.3)	352 (87.6)	
Hispanic	2 (0.3)	1 (0.3)	1 (0.3)	
Unknown	24 (3.2)	13 (3.8)	11 (2.7)	
Mean (median, range):				
PSA level, ng/mL	11.4 (7.8	13.1 (7.9	10.0 (7.7	0.22
%fPSA	17.1 (16	15.9 (15	17.7 (16.5	0.05
PSA density, ng/mL^2	0.21 (0.15	0.24 (0.16	0.20 (0.13	0.14
Number of previous biopsies	2.6 (2	2.6 (2	2.7 (2	0.26
Number of biopsy cores	16.5 (20	11.5 (12	20.8 (20	<0.001
Total prostate volume, mL	56.9 (50	54.3 (44.7	58.5 (53	0.16
Central prostate volume, mL	34.1 (28	23.3 (20.9	36.1 (30	<0.001
N (%):				
DRE:				0.43
no abnormality	669 (91.6)	305 (90.8)	364 (92.4)	
yes	61 (8.4)	31 (9.2)	30 (7.6)	
Pathological feature in initial two biopsies:				
HGPIN	253 (33.8)	124 (35.7)	129 (32.1)	0.3
ASAP ± HGPIN)	120 (16)	53 (15.2)	67 (16.7)	0.6
benign	376 (50.2)	170 (49.1)	206 (51.2)	0.54
+ve biopsies/total biopsies	119/749 (15.9)	44/347 (12.7)	75/402 (18.6)	0.026
Cumulative +ve patients/total patients	119/479 (24.8)	–	–	–

Notably, the incidence of clinically significant cancer was almost doubled in patients with previous suspicious lesion(s) when compared with those having prior benign biopsies (42.4% vs 23.5%, $P = 0.055$).

As expected, prostate cancer detection became less likely with each biopsy session (biopsies three, four, five and six were positive in 17.2%, 14.5%, 13.8% and 8.7%, respectively; Table 6).

DISCUSSION

It is well recognised that PBx has a substantial false-negative detection rate due to sampling errors, so a negative PBx does not exclude cancer [2,3]. Early studies reported that one repeat PBx detects at least an additional 20% of prostate cancer cases and there was significant cancer detection even up to six biopsy sessions; nevertheless, the risk of identifying clinically insignificant cancers appropriately tempers enthusiasm for serial biopsy [3–7]. The aim of the present study was to assess contemporary outcomes for detection of overall cancer and clinically insignificant cancer during serial biopsy, and to compare ePBx to sPBx in this scenario.

Prostate cancer detection was significantly higher in the sPBx group, which may be intuitively attributed to both increasing the number of samples and varying the distribution of cores. Several series have shown that additional biopsy samples, particularly in the far lateral peripheral zone and extreme apex, may increase the diagnostic yield by 30–35% [21,22].

Cumulative prostate cancer detection after multiple serial biopsy sessions was 119/479 patients (24.8%). This may be interpreted that up to a quarter of patients referred for suspicious findings, including persistently elevated or rising PSA level, actually do harbour small unrecognised prostate cancer despite two prior negative biopsies. Nevertheless, this required up to eight biopsy sessions to reach that total yield. Again, we emphasise that most of these biopsy sessions were performed before referral to our centre, and once we had performed what we thought was one adequate repeat biopsy focusing on the lateral aspects, apex, and anterior tissue, we strongly encouraged patients to forego further biopsy in the absence of overwhelming suspicion of prostate cancer, with the exception being delayed interval biopsy for patients with HPGIN. Once we know that patients have undergone broad-based biopsy including the anterior prostate and extreme apex, we reassure them that the likelihood of significant cancer detection in the future is remote, and biopsy should only occur in unusually suspicious circumstances, which is a term necessarily vague based on limited data in that scenario.

*TABLE 3 Detection rates in patients with benign findings, PIN and ASAP on initial biopsy**

Indication	Total detection, *n*/*N* (%)	ePBx, *n*/*N* (%)	sPBx, *n*/*N* (%)	*P*
Benign biopsy	34/376 (9)	13/170 (7.6)	21/ 206(10.2)	0.4
Pathological findings:				
HGPIN	51/253 (20.1)	19/124 (15.3)	28/129 (21.7)	0.19
ASAP ± HGPIN)	34/120 (28.3)	12/53 (22.6)	26/67 (38.8)	0.06
Total	85/373 (22.8)	31/177 (17.5)	54/196 (27.6)	0.021

**If HGPIN or ASAP were detected on either of the first two biopsies, patients were considered positive for these.*

TABLE 4 Detection rates of clinically insignificant prostate cancer in both groups

Group	Total cancer detected, *n*	Insignificant cancer, *n*	% of insignificant cancer	*P*
ePBx	44	25	56.8	0.044
sPBx	75	56	74.6	
Total	119	75	63	

TABLE 5 Incidence of clinically insignificant cancer according to the initial pathological findings:

	Prostate cancer category			
Frequency, *n* (%)	Total	Clinically significant	Clinically insignificant	*P*
Previous benign findings	34	8 (23.5)	26 (76.5)	<0.001
Previous HGPIN	51	20 (39.2)	31 (60.8	0.03
Previous ASAP (+/– HGPIN)	34	16 (47)	18 (53)	0.6
Any pathological suspicion	85	36 (42.4)	49 (57.6)	0.046
Total	119	44 (37)	75 (63)	<0.001

TABLE 6 Cancer detection rate at different number of previous biopsy stratified by biopsy group

Number of repeat PBx session	Total, *n*/*N* (%)	ePBx, *n*/*N* (%)	sPBx, *n*/*N* (%)	*P*
3	82/479 (17.2)	32/227 (14)	50/252 (19.8)	0.09
4	23/158 (14.5)	8/75 (10.6)	15/83 (18)	0.18
5	9/65 (13.8)	2/25 (12)	7/40 (22.5)	0.12
6	2/23 (8.7)	1/11 (9.1)	1/12 (8.3)	0.9
7 and 8	3/24 (12.5)	1/9 (11.1)	2/15 (13.3)	0.6

We and others have shown that one repeat biopsy should be considered in patients with persistent suspicion of cancer after a single negative biopsy [3,4,20]. In a recent study in that setting, we showed that sPBx significantly enhanced prostate cancer detection compared with ePBx (32.7% vs 24.9%, $P = 0.008$) [16]. By contrast, the present data show that subsequent serial biopsies should be used uncommonly.

Subanalysing the outcomes, patient with previous benign biopsies (no HGPIN, no ASAP) showed a low chance (9%) of prostate cancer detection on serial biopsies. On the other hand, we found that patients with initial suspicious pathological findings, e.g. HGPIN and ASAP, had a higher likelihood of any given biopsy session being positive (22.8%), with a higher detection rate in sPBx group. In contrast to some studies [23–25], prostate cancer detection was significantly higher among patients with previous HGPIN (20.1%) compared with those with a benign history (9%) ($P < 0.001$). Nevertheless, most tumours detected in either group were clinically insignificant.

Moreover, we previously reported that the finding of multifocal HGPIN is the true risk factor for developing cancer on delayed interval biopsy, and that focal HGPIN was a negligible risk factor [26]. Unfortunately, we do not have complete data on which of these patients had multifocal compared with focal HGPIN, a limitation of the present report.

Prostate cancer was detected in 28.3% in the ASAP subgroup. Notably, most studies of repeat biopsy for ASAP considered only the initial repeat biopsy [2]. It is notable that the risk of cancer detection in the present patients with ASAP, even during multiple repeat biopsies, remains substantial and merits careful consideration. Furthermore, the incidence of clinically significant tumours in this subgroup doubles that encountered in patients with prior benign biopsies.

Detection of clinically insignificant prostate cancer is an inevitable risk of any biopsy, but appears to rise with saturation biopsy by 7.5% [16]. Based on the predetermined criteria in the present study, 63% of cancers were clinically insignificant, with higher detection using sPBx ($P = 0.044$).

There is no universally accepted definition of 'clinically insignificant cancer'. Repeat PBx patients are more likely to have indolent cancer and a more favourable prognosis [6,27]. Although a quarter of the present serial biopsy patients were eventually found to have cancer, most of these were clinically insignificant but we are unable to ascertain their ultimate clinical outcomes regarding survival.

The present study has other limitations. It is retrospective, based on data derived from an IRB-approved database. Instead of having mandated indications and biopsy templates, the attending urologist's preference, often influenced by request of an outside referring physician, was the main determinant. As previously reported, such patients may be ideal targets for chemoprevention strategies [7,28], but the present study cannot consider this issue. Moreover, both central prostate volume and the %fPSA were lower in ePBx patients, which might have skewed the risk of prostate cancer detection in this group upwards [10]. Furthermore, the number or percentage of positive cores may be a false surrogate for clinically insignificant cancer. Additionally, the discrepancy between biopsy and prostatectomy specimen findings would have intuitively decreased the percentage of men considered as having a clinically insignificant cancer, as the potential for upgrading or upstaging at prostatectomy was not considered. Finally, the data are from a highly selected referral population, so many comparable patients may not have undergone biopsy, which might have different outcomes.

The final philosophical issue to consider is whether patients referred for serial biopsy should undergo the procedure at the tertiary care centre. Our philosophy has been that there is significant potential variability in biopsy technique; without knowing whether the anterior prostate and lateral/apical areas have been adequately sampled, we are unable to reassure the patient or referring physician of benignity. After one prior negative biopsy, repeat biopsy appears to usually be justified, with detection rates of >30% [16]. After multiple prior negative biopsies, the data herein suggest that most patients do not have clinically significant cancers. Nevertheless, the onus is on the tertiary care centre to provide a definitive opinion, and we think that an office-based sPBx in experienced hands does so. If this is benign, assuming no change in normal DRE, we emphatically encourage the patient to forego future biopsy unless the PSA level at least doubles, or the %fPSA drops to very low levels (<12%). These indications are not derived from data, but from desire to help the patient avoid further unnecessary serial biopsies.

In conclusion, detection of clinically significant prostate cancer occurs in only a small percentage of men who undergo serial (more than two) prostate biopsies regardless of the biopsy protocol or indication for biopsy. The risk of detecting clinically insignificant cancers should be weighed against the risk of missing significant cases. Patients with clear indication to consider serial biopsies are those with ASAP, or multifocal HPGIN as part of a delayed interval biopsy protocol. Patients with truly benign findings are strongly encouraged to forego future serial biopsy in the absence of significant changes in clinical suspicion, including changes in DRE, doubling of PSA level or development of very low %fPSA.

CONFLICT OF INTEREST

None declared.

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Abbreviations: **(e)(s)PBx**, (extended) (saturation) prostate biopsy; **HGPIN**, high-grade prostatic intra-epithelial neoplasia; **ASAP**, atypical small acinar proliferation; **IRB**, Institutional Review Board; **%fPSA**, percentage free/total PSA.