Prostate cancer detection after a negative prostate biopsy: Lessons learnt in the Cleveland Clinic experience

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Abstract: Urologists are often faced with the dilemma of managing patients with a negative initial prostate biopsy in whom clinical or pathological risk for prostate cancer still exists. Such real-life challenging scenarios might raise questions such as: Who should undergo further biopsies? What are the optimal predictors for prostate cancer on subsequent biopsies? What is the optimal biopsy protocol that should be used? When to stop the biopsy cascade? The last decade has witnessed numerous studies that have analyzed factors conferring a significant risk for cancer discovered on repeat biopsies. We and others have developed predictive models to aid decision-making regarding pursuing further biopsies. For decades, high-grade prostatic intraepithelial neoplasia has been considered a strong risk indicator for subsequent cancer. However, it has been recently shown that only through segmentation of this heterogeneous population does the real risk profile emerge. Biopsy templates underwent modification regarding the number and location of cores with emergence of the transrectal or brachytherapy grid transperineal saturation biopsy. However, the best biopsy protocol remains controversial. We have refined the initial biopsy template to a 14 core initial biopsy template that optimizes cancer detection, and have shown that transrectal saturation biopsy significantly improves cancer detection for repeat biopsy. Another concern is the overdiagnosis of clinically insignificant cancer on repeat biopsies, so we explored ways to limit this, and to deal with its ramifications. Through carrying out a Medline literature search, we critically evaluated pertinent articles together with emphasis of our own journey in this arena to assist in the decision-making process for repeat biopsy population.

Key words: nomogram, pathological findings, prostate-specific antigen, repeat biopsy.

Introduction

Currently, the use of extended, laterally directed templates for transrectal ultrasound (TRUS)–guided prostate biopsy (PBx) is considered the gold standard, because it significantly enhances the diagnosis of prostate cancer (PCa) compared with conventional sextant protocols.1

However, even with the widespread application of such extended prostate biopsy (ePBx) protocols, the false negative rate remains substantial.2 It has been shown that 12 biopsy cores using an 18-gauge needle allow histological examination of just 0.04% of a prostate with a typical volume, with a high incidence of sampling errors.3 With the inability of negative initial PBx to firmly exclude the presence of PCa, the need for repeat biopsies continues to rise.

Indications for repeat biopsies include sustained suspicion of PCa as a result of clinical and/or pathological findings.4 Some studies showed that rate is not a predictor for PCa on repeat biopsy; however, risk factors, such as African American race or family history of PCa, often impact urologists’ decisions.5 Patient anxiety about the possibility of PCa is another common, but difficult, indication to determine for repeat biopsy.

Impact of the initial PBx protocol

The first step in the evaluation is to assess the adequacy of initial PBx. In total, 70% of PCa is detected on initial PBx; therefore, we believe that optimization of the initial PBx intuitively reduces the likelihood of facing a “repeat biopsy dilemma”.6 The PCa detection rate on repeat biopsies varies as a function of how many cores were obtained on initial PBx. In the Stanford series, the PCa detection rate was 39% following a negative sextant biopsy compared to 28% when ePBx was adopted as the initial biopsy scheme.7 Eskicorapci et al. showed that 14-core repeat biopsy detected PCa in 36.1% and 18.7% of the patients who had a previous sextant biopsy and 10-core biopsy protocol, respectively (P = 0.005).8

As defined by the National Comprehensive Cancer Network, ePBx is essentially a sextant template with at least four additional cores from the lateral peripheral zone.9 Sampling of the prostate lateral horn increases the detection rate by approximately 25%.10 Wright and Ellis showed that the
most common unique site of cancer was the anterior apex, where 17% of cancers would have been missed by standard peripheral zone biopsies.11

This can be attributed by the fact that the entire apex is comprised of the peripheral zone tissue, which is most likely to harbor cancer and can be difficult to palpate by digital rectal examination (DRE).12 In addition, apical biopsy is widely recognized as being more painful than biopsy of the remainder of the gland, so urologists are likely to avoid this area to minimize pain.13

Recently, we published our experience regarding the yield of apical biopsies using the standard 12-core biopsy scheme plus two additional cores taken from the extreme anterior apex. The apical cores (three on each side) achieved the highest cancer detection rate (73.6% of all cancers), and the additional extreme anterior apical cores (one on each side) achieved the highest rate of unique cancer detection.14

In contrast, routine biopsy from the transitional zone (TZ) has not been found to be valuable by most authors.15 Furthermore, in a study on patients undergoing repeat saturation PBx (sPBx; ≥20 cores) at our institution, we found no exclusive TZ cancers in patients diagnosed with PCA.16 However, some studies showed that approximately 20% of PCA cases were detected only from the anterior aspect of the TZ through transperineal route, which is being used in a considerable number of institutes, especially in Japan.17,18

It might be intuitive that adding cores can enhance the detection of PCA over the routinely carried out ePBx; however, this has not been supported by multiple trials in the setting of initial biopsy.19 We previously showed that 24 cores yielded no higher detection rate than 10 cores (44.6% vs 51.7% respectively, P > 0.9).20 Lane et al. reported the follow-up study of our initial negative sPBx on 59 patients with a PCA detection rate of 24%.21

**Prostate-specific antigen indices as indications for repeat PBx**

An elevated or persistently rising prostate-specific antigen (PSA) level is generally considered the commonest indication for repeat PBx; however, a controversy exists regarding the cut-off level that warrants repeat PBx.4 A recent observation suggested that, after a negative PBx, PSA was of no use in assessing patient risk for PCA.22 In contrast, Thompson et al. showed that the performance of PSA is well maintained in repeat PBx populations.23

A persistent PSA >10 ng/mL is traditionally agreed on as a clear indication for repeat PBx.24 Considering a PSA cut-off of 4 ng/mL as a discriminator of PCA has been challenged by detection of PCA at lower PSA values.25 In 315 men with PSA level between 2–4 ng/mL, Djavan et al. detected PCa in 24% and 13% on first and second biopsy, respectively, with comparable biochemical and pathological features between both groups.26

PSA levels between 4 ng/mL and 10 ng/mL represent a common range among a repeat PBx population. An important limitation is derived from the considerable overlap between PCa and other benign conditions through this range. In the European Prostate Cancer Detection Study (EPCDSS) of men with a total PSA level of 4 ng/mL to 10 ng/mL, PCa was detected in 10% of the 820 patients after an initial negative PBx.27

**Percent free PSA**

Historically, an inverse relationship exists between PCa detection rate and percent free PSA (%fPSA) value. Catalona et al. showed that %fPSA cut-off of less than 25% corresponded with the highest PCA detection rate and the least number of unnecessary biopsies among men seeking an initial PBx.28 Subsequently, the predictive role of %fPSA was similarly suggested for a repeat PBx population.29

Djavan et al. recommended a %fPSA < 30% as an accurate predictor of a positive repeat PBx. Furthermore, the predictive value of %fPSA outperformed that of PSA density (PSAD), PSAD-TZ or total PSA.24 Morgan et al. showed that a %fPSA <10% was a strong predictor for PCa, even after two negative prior biopsies with a sensitivity of 91% and a specificity of 86%.30 Rodriguez et al. reported that %fPSA < 18% had a sensitivity of 90% and a specificity of 20% when used as a predictor for PCa on repeat biopsy population.31

Recently, we evaluated the performance of %fPSA on 683 repeat biopsies. The area under the receiver–operator curve (AUC) for %fPSA was 0.65 for men who underwent one repeat biopsy and 0.72 for men who underwent more than one repeat biopsy. A %fPSA cut-off of 11% achieved 85% and 86% specificity in both categories, respectively (Lee B et al., unpublished data).

**PSAD**

PSAD has been popularized by Benson et al. in its ability to distinguish between PSA elevations resulting from PCa versus benign prostatic hyperplasia.23 Keetch et al. showed that using a value of 0.13 misses 35% of PCa detection on repeat biopsies. However, in conjunction with a PSA velocity (PSAV) > 0.75, they had a detection rate of 46% on repeat biopsy versus just 13% when both values were below the suggested cut-off.33

Djavan et al. introduced the value of PSAD-TZ. Using a value of 0.13 for PSAD, the authors reported a sensitivity of 74% and a specificity of 44%; for a value of 0.26 for PSAD-TZ, they reported a sensitivity of 78% and a specificity of 52%.24 Similarly, Singh et al. showed that PSA-TZ was associated with higher risk of PCa detection after an initial negative 12-core biopsy (P = 0.05).34

Recently, Okada et al. showed that a PSAD > 0.33 was an independent predictor of positive repeat PBx. Furthermore,
a combination of this cut-off value, PSAV > 0.48 and abnormal DRE findings reduced 31% of unnecessary biopsies while missing 8% of low volume, low grade PCa.35

**PSAV**

Although the PSAV has been a useful marker for identifying men at risk of aggressive PCa, its utility to predict PCa on repeat biopsies remains debatable.36 Keech et al. reported that PSAV > 0.75 would reduce the number of patients who required repeat biopsies, but that velocity alone would have missed 40% of cancers without the use of other parameters (i.e. PSAD).33 However, Borboroglu et al. found that a PSAV > 0.75 was the only statistically significant risk factor for PCa detection on repeat biopsy.37

Loeb et al. showed that the median PSAV was significantly greater in men with high-grade prostatic intraepithelial neoplasia (HGPIN) who were subsequently diagnosed with PCa. Furthermore, a PSAV threshold of 0.75 predicted which men with HGPIN would ultimately be diagnosed with PCa.38 Okada et al. found that PSAV > 0.48 was a statistically significant predictor of PCa in 140 repeat PBx men (P = 0.001).35

In contrast to these findings, a previous systematic review found little direct evidence of the predictive value of PSAV.39 Vickers et al. assessed 2579 repeat biopsies from the European Randomized Screening study of Prostate Cancer (ERSPC) and showed a low predictive accuracy for the PSAV (AUC 0.55).40 These results were consistent with their previous study that failed to show a role for PSAV in predicting the result of an initial biopsy.41

Bittner et al. found no significant association between PSAV and PCa diagnosis (P = 0.84), Gleason score (P = 0.78), the percentage of positive cores (P = 0.37) or tumor location, although patients underwent three or more PSA measurements in the year before biopsy.42 Similarly, a recent study showed that PSAV was the only PSA variable that did not significantly predict PCa on repeat PBx.43

**PSA doubling time**

PSA doubling time (PSADT) has similarly shown more utility in the prediction of PCa aggressiveness than as an indicator for repeat PBx. Consequently, most of the studies focused on its role in active surveillance, disease recurrence and in androgen-independent PCa.44 However, Shimbo et al. have reported that only PSADT was of statistical significance (P = 0.035) regarding repeat PBx outcome.45 Similarly, Garzotto et al. retrospectively examined 373 patients undergoing repeat PBx and found that PSADT was the best independent predictor for positive results and high-risk disease (Gleason > 7).46

In conclusion, many PSA indices have been suggested as predictors of PCa on repeat PBx without a consensus regarding the best single index. Several investigators have concluded that no single PSA parameter is adequate to indicate the need for repeat biopsies. The guidelines failed to show the validity of PSA-related indices to select candidates for repeat PBx, therefore repeat biopsy strategy is still left to the discretion of each screening facility.

**Impact of initial pathological findings**

**High grade prostatic intraepithelial neoplasia**

The reported incidence of HGPIN on needle biopsies varies considerably at 0.6–24% (mean 7.7%).47 In the early 1990s, the risk of finding PCa after diagnosis of HGPIN was thought to be higher, with most studies citing a probability of ≈50%.47 However, in recent years, the premalignant potential of HGPIN has been questioned.

In a recent review, Epstein and Herawi noticed that, when comparing studies published between 2000 and 2005, the risk of cancer on repeat PBx within 1 year of a diagnosis of HGPIN (18.1%) was not sufficiently different from the same risk after a benign diagnosis (23.0%).47 This could be as result of the shift from the sextant PBx to the routinely applied ePBx protocols that can detect more cancers associated with HGPIN.48

The number of HGPIN foci now appears to have a clear impact on both the prognosis and the suggested management protocols. Merrimen et al. showed that unifocal HGPIN had no more likelihood of PCa detection than a benign diagnosis.49 Similarly, Godoy et al. found that after confirming the adequacy of initial PBx (at least 10 cores), isolated HGPIN does not warrant any further PBx.50

The original report from our institution showed that individuals with multifocal HPGIN versus isolated HGPIN on initial SPBx had 80% versus 0% incidence of PCa on repeat PBx, respectively.51 We recently published our report on 328 men who underwent a second PBx after HGPIN diagnosis. HGPIN alone on initial PBx had a significant effect on the subsequent diagnosis of PCa (hazard ratio 1.89; 95% CI 1.39, 2.55; P < 0.0001). Stratifying HGPIN into multifocal and bilateral disease significantly increased the hazard ratios to 2.56 (95% CI 1.83, 3.6) and 2.2 (95% CI 1.51, 3.21), respectively.52

Furthermore, multifocal HGPIN might be an excellent target for chemoprevention. Data from the Prostate Cancer Prevention Trial (PCPT) showed a statistically significant decrease in the diagnosis of HGPIN from 11.7% to 8.2% when given placebo or finasteride, respectively.53 The Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial showed a decreased volume of HGPIN in a randomized trial of 46 patients who underwent radical prostatectomy that approached statistical significance at P = 0.052.54 Selective estrogen receptor modulators also show promise in prevent-
ing the progression of HGPIN to PCa. In a large phase IIB clinical trial, men with HGPIN who were given 20 mg toremifene had a decreased incidence of PCa at 24.4% versus 31.2% with placebo at 1 year. We do not routinely use 5-alpha reductase inhibitors for chemoprevention; however, we believe that men motivated to decrease PCa risk might benefit from such therapy.

**Atypical small acinar proliferation**

Unlike HGPIN, atypical small acinar proliferation (ASAP) indicates the presence of suspicious glands with insufficient cytological or architectural atypia for a definitive diagnosis of PCa. It indicates a situation of diagnostic uncertainty, detectable in a mean of 5% of biopsies with a PCa detection rate of 34–60% on repeat biopsies.

We previously reported that the risk of cancer on repeat biopsy is in that same range, even after sPBx. Additionally, we have shown that the presence of inflammation can increase the likelihood of the histological diagnosis of ASAP, creating another avenue by which inflammation can stimulate the carrying out of unnecessary repeat biopsies.

In a recent study from our institute, most of the PCa detected after initially diagnosed ASAP are proved to be clinically significant (69.8%). Several authors proposed different risk predictors for PCa after ASAP detection. Borboroglu et al. showed that mean PSA V was the only significant predictor of positive repeat PBx. A recent study showed that the combination of HGPIN and ASAP in the same biopsy is even more predictive of subsequent cancer (58%) than isolated ASAP (35%).

According to current evidence, the presence of ASAP warrants a repeat biopsy within 3–6 months with increased sampling of atypical site and adjacent areas. If no PCa is found, the National Comprehensive Cancer Network recommends close follow up with PSA, DRE and periodic extended-pattern biopsy; however, the optimum schedule is poorly defined.

**What is the optimal repeat PBx protocol?**

The initial report was published by Borboroglu et al., but the term “saturation biopsy” was coined by Stewart et al. Since then, the concept of sPBx became feasible with the advent in anesthesia techniques. We previously showed that it can be effectively carried out in the office. Furthermore, multiple reviews confirmed its safety when compared with the ePBx protocols. We recently published two studies that discussed morbidity after TRUS-guided PBx. We encountered no statistically significant impact of biopsy cores number and the incidence of different postbiopsy complications. Similarly, there was no correlation between the adopted PBx protocol and the emergence of quinolones-resistant Escherichia coli.

The sPBx scheme has witnessed a number of modifications, both numerically and geometrically. However, to date, there is no clear recommendation regarding the optimal number of cores that sPBx should comprise. We originally used a 24-core transrectal template with cores concentrated laterally and apically based on the preponderance of cancer in these locations. Based on our experience with site-specific labeling, it soon became clear that the lateral sectors (dark shading) were the site of all unique tumors. As a result, we reduced sampling from two cores to one core per medial sector (midgland and base), resulting in a 20-core template for patients undergoing repeat biopsy (Fig. 1).

As mentioned, the apex is the most likely site for missing PCa, so focus of at least three cores is made at that level, especially during repeat biopsy. We showed that the pain of apical biopsy can be avoided by using the rectal sensation test to bypass anal pain fibres.

According to the 2010 European Association of Urology (EAU) guidelines, TZ biopsy should be considered for men undergoing a repeat biopsy for suspicion of PCa. Recently, Ploussard et al. have shown that TURP significantly increased the PCa detection rate by 28.5% (P = 0.035) when used with a 21-core scheme repeat PBx. Although we showed that sPBx did not increase cancer detection as an initial biopsy strategy, our own and several other series suggested that sPBx enhances cancer detection in a repeat PBx population. This can 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, might increase the diagnostic yield by 30% to 35%.

Recently, we retrospectively compared sPBx and ePBx in 1056 patients undergoing their first repeat PBx for different indications. The sPBx had a statistically significant higher
detection rate when compared with the ePBx (32.7% vs 24.9%, P = 0.0075). For patients with benign initial biopsy, sPBx showed a significantly greater PCa detection (33.3% vs 25.6%, P < 0.027; Zaytoun et al., unpublished data). Table 1 shows studies that evaluated the performance of sPBx in different biopsy settings.

What is the best time interval between repeat biopsies?

There is no consensus or clear recommendations regarding the optimum repeat PBx scheduling. However, it has been suggested that PCa detection might be influenced by the interval between biopsies.10,19 This can be attributed by giving adequate time for premalignant lesions to progress into overt adenocarcinoma.

In absence of guidelines regarding the best intervals between biopsies, it seems reasonable that the optimal interval should be tailored according to the risk indicators encountered in each individual case. After a negative PBx session, we usually wait 1 year, unless ASAP was detected. Risk of detection of insignificant cancer; how many sessions are enough?

Several studies have shown that the chance of PCa detection drops with serial repeat biopsies.2,87,88 This dilemma could be approached by determining both the rate and clinical behavior of the PCa that might be detected on repeated biopsies. The ERSPC showed PCa detection rates on first, second, third and fourth biopsies of 22%, 10%, 5% and 4%, respectively. On comparing the pathological characteristics of PCa detected on the first biopsy and that detected on the second biopsy, no differences were noted with respect to organ confinement (P = 0.15) and extra-prostatic capsular extension (P = 0.22). Meanwhile, PCa detected on third and fourth biopsies had a lower grade, stage and volume compared with that on first and second biopsies.87 Consequently, the authors recommended one repeat biopsy in all cases of a negative biopsy, reserving further biopsies for patients with a high suspicion of cancer based on rising PSA and/or poor prognostic factors on first or second biopsy.89

Table 1  Previous studies evaluating saturation prostate biopsy in different biopsy settings

<table>
<thead>
<tr>
<th>Reference</th>
<th>Biopsy session</th>
<th>Route</th>
<th>Patient no.</th>
<th>Total PCa detection (%)</th>
<th>No. cores (mean), [median]</th>
<th>Clinically insignificant PCa (%)</th>
<th>Setting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Borboroglu et al.37</td>
<td>Repeat</td>
<td>Transrectal</td>
<td>57</td>
<td>30%</td>
<td>(22.5)</td>
<td>7%</td>
<td>Clinic</td>
</tr>
<tr>
<td>Stewart et al.63</td>
<td>Repeat</td>
<td>Transrectal</td>
<td>224</td>
<td>34%</td>
<td>14–45 [23]</td>
<td>14.3%</td>
<td>OR</td>
</tr>
<tr>
<td>Pryor et al.69</td>
<td>Repeat</td>
<td>Transrectal</td>
<td>35</td>
<td>20%</td>
<td>14–28 [21]</td>
<td>0%</td>
<td>OR</td>
</tr>
<tr>
<td>Fleschner et al.70</td>
<td>Repeat</td>
<td>Transrectal</td>
<td>37</td>
<td>13.5%</td>
<td>32–38</td>
<td>NA</td>
<td>OR</td>
</tr>
<tr>
<td>de la Taille et al.71</td>
<td>Initial and repeat</td>
<td>Transrectal</td>
<td>303</td>
<td>31.3%</td>
<td>21</td>
<td>NA</td>
<td>Clinic</td>
</tr>
<tr>
<td>Rabets et al.72</td>
<td>Repeat</td>
<td>Transrectal</td>
<td>116</td>
<td>29%</td>
<td>20–24 [22.8]</td>
<td>0</td>
<td>Clinic</td>
</tr>
<tr>
<td>Pinkstaff et al.73</td>
<td>Repeat</td>
<td>Transperineal</td>
<td>210</td>
<td>37%</td>
<td>(21)</td>
<td>0</td>
<td>OR</td>
</tr>
<tr>
<td>Sato et al.74</td>
<td>Repeat</td>
<td>Transperineal</td>
<td>128</td>
<td>22.7%</td>
<td>22</td>
<td>NA</td>
<td>OR</td>
</tr>
<tr>
<td>Bott et al.75</td>
<td>Repeat</td>
<td>Transperineal</td>
<td>60</td>
<td>38%</td>
<td>(24)</td>
<td>NA</td>
<td>OR</td>
</tr>
<tr>
<td>Moran et al.76</td>
<td>Repeat</td>
<td>Transperineal</td>
<td>180</td>
<td>38%</td>
<td>[41]</td>
<td>NA</td>
<td>OR</td>
</tr>
<tr>
<td>Walz et al.77</td>
<td>Repeat</td>
<td>Transrectal</td>
<td>161</td>
<td>41%</td>
<td>18–32 [24.2] [24]</td>
<td>15.6%</td>
<td>Clinic</td>
</tr>
<tr>
<td>Jones et al.20</td>
<td>Initial</td>
<td>Transrectal</td>
<td>139</td>
<td>44.6%</td>
<td>24</td>
<td>15.8%</td>
<td>Clinic</td>
</tr>
<tr>
<td>Pepe et al.78</td>
<td>Initial and repeat</td>
<td>Transrectal</td>
<td>189</td>
<td>33.8%</td>
<td>24–37 [29],</td>
<td>NA</td>
<td>Clinic</td>
</tr>
<tr>
<td>Merrick et al.79</td>
<td>Repeat</td>
<td>Transperineal</td>
<td>102</td>
<td>42%</td>
<td>(51.1) [50]</td>
<td>7.1</td>
<td>OR</td>
</tr>
<tr>
<td>Li et al.80</td>
<td>Initial</td>
<td>Transperineal</td>
<td>303</td>
<td>37.6%</td>
<td>11–44 [23.7]</td>
<td>NA</td>
<td>Clinic</td>
</tr>
<tr>
<td>Sajadi et al.81</td>
<td>Repeat</td>
<td>Transrectal</td>
<td>82</td>
<td>19.5%</td>
<td>24–40 [24]</td>
<td>NA</td>
<td>Clinic</td>
</tr>
<tr>
<td>Simon et al.82</td>
<td>Repeat</td>
<td>Transrectal</td>
<td>40</td>
<td>45%</td>
<td>39–139 [64]</td>
<td>NA</td>
<td>OR</td>
</tr>
<tr>
<td>Campos-Fernandes83</td>
<td>Repeat</td>
<td>Transrectal</td>
<td>231</td>
<td>25.1%</td>
<td>21</td>
<td>NA</td>
<td>Clinic</td>
</tr>
<tr>
<td>Novara et al.84</td>
<td>Repeat</td>
<td>Transperineal</td>
<td>143</td>
<td>26%</td>
<td>24</td>
<td>NA</td>
<td>Clinic</td>
</tr>
<tr>
<td>Ahayi et al.85</td>
<td>Repeat</td>
<td>Transrectal</td>
<td>540</td>
<td>39.4%</td>
<td>18–41 [25] [25]</td>
<td>NA</td>
<td>Clinic</td>
</tr>
<tr>
<td>Pepe et al.86</td>
<td>Repeat</td>
<td>Transrectal</td>
<td>423</td>
<td>19.4%</td>
<td>[23]</td>
<td>NA</td>
<td>Clinic</td>
</tr>
<tr>
<td>Zaytoun et al. [unpublished data]</td>
<td>First repeat</td>
<td>Transrectal</td>
<td>663</td>
<td>32.7%</td>
<td>20–32 (20.7)</td>
<td>40.1%†</td>
<td>Clinic</td>
</tr>
</tbody>
</table>

†Clinically insignificant cancer was defined as having Gleason score <7, positive cores ≤3 and maximum percentage involvement of cancer in any positive core ≤50%. NA, non-assessed data; OR, operative room; PCa, prostate cancer.
It is still recognized that just 70% of PCa cases are detected during the initial biopsy and that the second biopsy can detect an additional 20% of PCa cases. Therefore, on analysis of repeat biopsies, we believe to consider them as two different categories; second overall biopsy as one group and all other biopsies afterwards in another group. In addition to comprising a more homogenous group of patients, the second biopsy is characterized by the highest chance for PCa detection among all serial biopsies that the patient might undergo after a negative PBx. In contrast, the latter group comprises a more heterogeneous population in which multiple biopsies might be needed to achieve much lower PCa detection rates. Furthermore, we previously found that the incidence of low-grade PCa was 62% of patients identified with two or more negative PBx.

Both diagnosis of clinically insignificant PCa on repeat PBx and its association with the number of biopsy cores are issues of considerable argument. To date, it must be recognized that there is not a universally accepted definition of “clinically insignificant PCa” on the basis of biopsy findings. Furthermore, detection of clinically insignificant PCa is an inevitable risk of either initial or repeat biopsy. Singh et al. reported that the risk increased from 22.7% to 33.5% by increasing the number of cores from six to 12. The CaPSURE database shows that taking more cores improves cancer detection and does not appear to increase the risk of detecting clinically insignificant cancer.

Although the increased number of cores in sPBx might theoretically harbor an increased risk of detection of clinically insignificant cancer, the original sPBx studies had conflicting findings with most reports, suggesting that sPBx does not increase the detection of clinically insignificant tumors. Borboroglu et al. found that 12 out of 13 sPBx patients undergoing prostatectomy had clinically significant cancer. Similarly, of four patients who had a prostatectomy in the series by Rabets et al., all were deemed clinically significant; with volumes of >0.5 mL, and three of the four were Gleason 7.

In conclusion, the concern of overdetection must be weighed against the risk of missing clinically significant malignancy. Regarding detection of small, potentially insignificant cancers, it is our strong belief that detection and treatment of PCa should always be considered independent processes as advocated by Carroll, and we actively pursue less rigorous management options, such as active surveillance or focal therapy, for patients with tumors that appear clinically insignificant.

Models for prediction of positive prostate biopsy

Different models have been created to predict PCa detection after a negative PBx.

The basic concept of these models is that incorporation of different clinical and pathological parameters in a single model outperforms using any of these parameters individually. Also, patient counselling requires the integration of various prognostic factors to arrive at a single prediction for the individual. O’Dowd et al. pioneered a logistic regression model for repeat PBx ($n = 813$). Their model showed 70% accuracy, but was subjected to neither internal nor external validation. In 2003, Lopez-Corona et al. published a nomogram that was corrected for predicting a positive repeat PBx based on 343 patients. Although their nomogram included eight predictors, the PSA level in their nomogram has a negative coefficient and it is difficult to calculate the corresponding value for PSA slope. Yanke et al. applied this nomogram to a validation dataset of 230 patients, and found that the calibration was good and that the AUC was 0.71.

Since then, several alternative predictive models have emerged. In 2010, we published our experience regarding the development and validation of a nomogram to predict the outcome of repeat PBx. In this, 408 men were included for creating the model and another 470 men for the validation purpose. The concordance index of the nomogram was 0.72, which was greater than any single risk factor. In the validation group, the AUC was 0.62. Table 2 shows a comparison between different published nomograms for prediction of PCa in a repeat PBx population.

**Impact of prostate volume on the detection of PCa on repeat PBx**

Similar to initial PBx, sampling accuracy of repeat PBx tends to progressively decrease when the prostate increases in size. In the ERSPC, Rietbergen et al. found that the most important factor responsible for failure to diagnose PCa at the primary screening was a large prostate volume. Interestingly, Sajadi et al. found a much lower PCa detection rate with repeat sPBx in large prostates compared with smaller glands. Walz et al. yielded a greater cancer detection rate in larger glands.

Nevertheless, the published data do not support obtaining more than 20 cores, so we routinely use a 20-core biopsy as described earlier for all repeat biopsies, regardless of indication or prostate volume. This is supported by a preliminary report that showed no correlation between the TRUS-determined prostate volume or pathological weight and the number of biopsies needed for PCa; therefore, taking more biopsies in larger prostates has no benefit.

Recently, Scattoni et al. presented a flowchart to utilize the lowest core number to detect 95% of cancers that would have been detected with 24 cores. For patients who were DRE negative, had a prostate volume ≤60 and aged >65 years, or were DRE negative and had a prostate volume >60, two different combinations of a 14-core biopsy were
<table>
<thead>
<tr>
<th>Reference</th>
<th>Prediction form</th>
<th>Patient no.</th>
<th>Median no. previous biopsies</th>
<th>Risk factors</th>
<th>No. cores range (mean)</th>
<th>PCA detection, (%)</th>
<th>Accuracy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Repeat PBx</td>
<td></td>
<td></td>
<td></td>
<td>Age, FH of PCa, DRE, PSA, PSA slope, months from initial PBx, No. of previous –ve cores, HGPIN and/or ASAP</td>
<td>6–22 (9.15)</td>
<td>20%</td>
<td>0.70</td>
</tr>
<tr>
<td>Lopez et al.</td>
<td>Nomogram development and internal validation</td>
<td>343</td>
<td>2.92</td>
<td>Age, FH of PCa, DRE, PSA, PSA slope, months from initial PBx, No. of previous –ve cores, HGPIN and/or ASAP</td>
<td>6–12</td>
<td>33.9%</td>
<td>0.71</td>
</tr>
<tr>
<td>Yanke et al.</td>
<td></td>
<td>230</td>
<td>2.56</td>
<td>Age, FH of PCa, DRE, PSA, PSA slope, months from initial PBx, No. of previous –ve cores, HGPIN and/or ASAP</td>
<td>20.0–32.0 (24.5)</td>
<td>44.3%</td>
<td>0.72</td>
</tr>
<tr>
<td>Walz et al.</td>
<td>External validation of Lopez Corona et al.</td>
<td>115</td>
<td>2.48</td>
<td>Age, FH of PCa, DRE, PSA, PSA slope, months from initial PBx, No. of previous –ve cores, HGPIN and/or ASAP</td>
<td>10–24 (11)</td>
<td>30%</td>
<td>0.76</td>
</tr>
<tr>
<td>Chun et al.</td>
<td>Nomogram development and internal validation</td>
<td>721</td>
<td>1.5</td>
<td>Age, FH of PCa, DRE, PSA, PSA slope, months from initial PBx, No. of previous –ve cores, HGPIN and/or ASAP</td>
<td>12–24 (12)</td>
<td>31%</td>
<td>0.856</td>
</tr>
<tr>
<td>Benecchi et al.</td>
<td>Nomogram development and internal validation</td>
<td>590</td>
<td>1</td>
<td>Age, FH of PCa, DRE, PSA, PSA slope, months from initial PBx, No. of previous –ve cores, HGPIN and/or ASAP</td>
<td>10–24 (11)</td>
<td>31%</td>
<td>0.696</td>
</tr>
<tr>
<td>Rochester et al.</td>
<td></td>
<td>63</td>
<td>1</td>
<td>Age, FH of PCa, DRE, PSA, PSA slope, months from initial PBx, No. of previous –ve cores, HGPIN and/or ASAP</td>
<td>8–34 (20)</td>
<td>31.6%</td>
<td>0.72</td>
</tr>
<tr>
<td>Moussa et al.</td>
<td>Nomogram development and internal validation</td>
<td>419</td>
<td>NA</td>
<td>Age, FH of PCa, DRE, PSA, PSA slope, months from initial PBx, No. of previous –ve cores, HGPIN and/or ASAP</td>
<td>8–26 (20)</td>
<td>58.3%</td>
<td>0.62</td>
</tr>
<tr>
<td>Mixed: initial and repeat</td>
<td>Probability nomogram development split sample validation</td>
<td>87</td>
<td>1</td>
<td>Age, PSA, %fPSA, PSAD, PSATZ, PV, TZV, No. previous PBx, No. –ve cores</td>
<td>8–12</td>
<td>39.1%</td>
<td>0.747</td>
</tr>
<tr>
<td>Stephan et al.</td>
<td>Probability nomogram development split sample validation</td>
<td>23</td>
<td>NA</td>
<td>Age, PSA, %fPSA, PSAD, PSATZ, PV, TZV, No. previous PBx, No. –ve cores</td>
<td>10–35 (15)</td>
<td>41.1%</td>
<td>0.70–0.73</td>
</tr>
<tr>
<td>Chun et al.</td>
<td>Probability nomogram development split sample validation</td>
<td>408</td>
<td>NA</td>
<td>Age, PSA, %fPSA, PSAD, PSATZ, PV, TZV, No. previous PBx, No. –ve cores</td>
<td>≥10</td>
<td>0.73–0.75</td>
<td></td>
</tr>
<tr>
<td>Auprich et al.</td>
<td>Nomogram development and internal validation Set of probability nomogram development and validation</td>
<td>393</td>
<td>NA</td>
<td>Age, DRE, PSA, %fPSA, No. previous –ve biopsies, sampling density</td>
<td>DRE, %fPSA, PSAD, PSATZ, PV, TZV, No. previous PBx, No. –ve cores</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Artificial neural network and internal validation Set of probability nomogram development and validation</td>
<td>809</td>
<td>NA</td>
<td>Age, DRE, PSA, %fPSA, No. previous –ve biopsies, sampling density</td>
<td>DRE, %fPSA, PSAD, PSATZ, PV, TZV, No. previous PBx, No. –ve cores</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>External validation to Chun et al.</td>
<td>621</td>
<td>NA</td>
<td>Age, DRE, PSA, %fPSA, No. previous –ve biopsies, sampling density</td>
<td>DRE, %fPSA, PSAD, PSATZ, PV, TZV, No. previous PBx, No. –ve cores</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ASAP, atypical small acinar proliferation; BMI, body mass index; DRE, digital rectal examination; FH, family history; %fPSA, percent free prostate-specific antigen; HGPIN, high grade prostatic intraepithelial neoplasia; PCa, prostate cancer; PCA3, prostate cancer antigen 3; PSA, prostatic-specific antigen; –ve, negative; PSAD, PSA density; PSATZ, PSA density of transitional zone; PSAV, PSA velocity; PV, prostate volume; TZV, transitional zone volume.
the most advantageous. However, based on its simplicity, tolerability and reproducibility, we continue to use the 20-core template in our institute with variable prostate volumes.

**Role of magnetic resonance imaging targeted biopsy**

The strategy of biopsies targeted to magnetic resonance imaging (MRI)-suspicious areas has been proposed as a potential strategy to improve repeat PBx results, including detection of significant tumors with the used of the least number of biopsy cores to obtain such data. This concept was advocated by Ahmed et al. Hambrock et al. has shown that MRI-targeted biopsies can detect PCA in areas outside the peripheral zone or locations not biopsied in normal schemes, in particular the anterior part of the gland. In that study, they utilized MRI to localize PCA-suspicious areas followed by a median of four cores. They could definitely diagnose PCA in 40 out of 68 patients (59%). Of those 40 patients, 37 (93%) were considered to could definitely diagnose PCA in 40 out of 68 patients (59%). Of those 40 patients, 37 (93%) were considered to

**Lessons from Cleveland Clinic experience**

For most of the past decade, we have utilized the ePBx scheme as the initial biopsy protocol in approximately 1600 patients every year. Among these men, PCA is diagnosed in 49% on initial setting, whereas approximately one-third of men pursuing subsequent biopsies prove to have PCA. These recommendations are based on our own experience and our pertinent studies.

The first step in approaching the problem is simply trying to avoid it. The utmost efforts should be paid to maximally optimizing the yield of the first PBx. The ePBx is the gold standard and sextant PBx is obsolete. We recommend a 14-core protocol with the “additional” cores being in the critical area of the apex. We do not recommend additional cores from either a hypoechoic lesion on TRUS or a palpable nodule, although it seems reasonable to do so if there is doubt about whether these lesions have been included in the biopsy.

- There is no defined cut-off value of PSA to indicate repeat PBx. No single PSA-derived index is adequate. We found that %fPSA cut-off of 11% and PSAV more than 0.75 are valuable clinical indicators in our repeat PBx population, so strongly recommend biopsy if these conditions exist.
- Consistent with recent reports, multifocal HGPIN is associated with a significantly higher risk of PCA on repeat biopsies. Therefore, we recommend “delayed interval” repeat PBx every 2–3 years for this high-risk category. By contrast, focal HGPIN does not substantially increase the risk of developing PCa, so does not factor into our decision to recommend repeat biopsy.
- ASAP is a “red flag”; we recommend repeat PBx within 3–6 months after its initial diagnosis. Even if the repeat PBx did not detect PCa, this category should always be under closer follow up and a periodic sPBx should be considered if PSA findings are suspicious.
- We recommend sPBx for all repeat biopsy sessions, whatever the indication, based on higher detection rates and comparable complication rates. It can be carried out as a clinical procedure with effectively applied periprostatic block. We recommend the 20-cores template (as described earlier) as the sPBx scheme of choice, regardless of the biopsy indication or the prostate volume. Focus on the apex is vital, as this is the most common site of “missed” cancers.
- We just updated our guidelines regarding optimum pre-biopsy preparation protocol to a single dose ciprofloxacin plus gentamicin without enemas, regardless of initial or repeat biopsies.
- The first repeat PBx has the highest yield after the first biopsy. If this session proved to be negative for PCa, consider further biopsies only for high-risk men. It is critical to apply this role only after confirmation of the adequacy of the first (ePBx) and the second (sPBx) sessions.

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