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Contemporary Role of Systematic Prostate Biopsies: Indications, Techniques, and Implications for Patient Care

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Abstract

Context: Prostate cancer (PCa) screening to detect early stage PCa has resulted in increased identification of small-volume, low-grade PCa, many of which meet criteria for clinically indolent disease. Nevertheless, there remains some degree of underdetection of high-risk PCa in substantial numbers of men despite current diagnostic strategies. **Objective:** To discuss the contemporary role of prostate biopsy (PB), focusing on the indications, techniques, and limitations of current PB techniques and evolving techniques affecting patient care.

Evidence acquisition: A comprehensive Medline search was performed using the medical subject heading search terms *prostate cancer*, *detection*, *prostate biopsy*, *significant cancer*, and *diagnosis*, with restriction to the English language. Emphasis was given to publications within the past 5 yr.

Evidence synthesis: Because abnormal digital rectal examination (DRE) and prostate-specific antigen (PSA) tests alone lack specificity for cancer, there is no universal indication for PB. This lack has inspired exploration for a cancer-specific biomarker and prediction tools such as risk calculators. Indication for biopsy should involve a balance between the underdiagnosis of high-risk cancers and the potential risks for the overdiagnosis of clinically insignificant cancers as well as biopsy-related morbidity. Evidence supports the inclusion of laterally directed cores during transrectal ultrasound (TRUS) PB in addition to the traditional sextant pattern, which significantly improves cancer detection without a demonstrable increase in morbidity. These data indicate that such PB templates, typically 12 cores, represent the optimal template in initial PB. Optimised techniques and templates for repeat PB remain controversial. However, debate continues regarding indications, sampling number, and location as well as on

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the potential of modern image-guided approaches or three-dimensional (3D) mapping biopsy in this unique setting. Additional limitations of repeat PB techniques include associated procedural risks if general anaesthesia is required and inherent sampling errors of template-based techniques that are not targeted to the specific tumour site. **Conclusions:** Current data support the utility of extended PB templates for initial TRUS PB intended to detect clinically significant PCa. Repeat PB in the setting of prior negative PB on the grounds of clinical suspicion or for risk-stratified approaches to management of low risk PCa requires balancing overdetection of low-risk cancer with the potential to miss significant cancer. Several options, including modern image-guided targeting, biomarker development, transrectal saturation PB, and 3D template mapping PB, are changing the clinical paradigms for evaluation and management. Evidence to support adopting approaches other than the current established standards should be tested through appropriately designed prospective studies.

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1. Introduction

Recent efforts towards the earlier detection of prostate cancer (PCa) have resulted in the discovery of earlier, smaller-volume, lower-grade PCa that are often described as clinically insignificant, with a 10-yr relative survival rate comparable to the general population. However, there is still *underdiagnosis* (defined as failure to detect cancers that are high grade, pathologically non-organ confined, or have positive surgical margins if resected) of high-risk PCa, even in patients with low prostate-specific antigen (PSA) values [1–3]. Despite downward stage migration of newly detected PCa in the past two decades, underdiagnosis continues to occur in 25–30% of cases.

In contrast, *overdetection* (frequently defined as detection of cancers with a pathologic volume ≤ 0.5 ml, pathologically organ-confined disease with no Gleason pattern 4 or 5) occurs in 1.3–7.1% of patients found to have PCa, and the possibly consequent overtreatment is one of the main concerns in prostate oncology [1,4]. Current unresolved issues include the lack of accurate cancer-specific predictors of tumour behaviour within the context of competing risk models and the limitations associated with currently available clinical variables such as tumour biomarkers or biopsy tissue samples.

The role of prostate biopsies (PBs) has changed. Their importance has evolved from pure cancer detection to assisting clinical patient management. Biopsy as a critical part of active surveillance (AS) protocols emphasises the necessity of reproducible and standardised staging and grading strategies. The increase in sampled tissue may achieve a more complete picture of the disease burden.

The historical likelihood of missing clinically significant cancers because of sampling error during sextant PB led to the introduction of extended-core PB strategies [5–10]. Extended or transrectal saturation PB have been advocated to detect cancers that standard biopsies miss and also to better characterise PCa volume and prognosis [11–14]. Finally, a number of prediction models, imaging techniques, and template mapping biopsies have arisen for more complex scenarios.

To improve PCa diagnosis and management, this review identifies the importance of considering individual risk factors and patient-specific goals at various points in the patient's care in determining the indication and techniques of PB.

2. Evidence acquisition

A nonsystematic, comprehensive Medline search was performed using the medical subject heading search terms *prostate cancer*, *prostate biopsy*, *detection*, *diagnosis*, and *significant cancer*. We included original articles, review articles, and editorials, with restriction to the English language, up to 31 July 2012. We reviewed the abstracts of the retrieved records and selected those most pertinent to the objectives of the present analysis. Among a retrieved total of 975 articles, the articles analysing indications, techniques, limitations, and implications on patient care for PB were selected based on title and abstract. Further searches were performed based on manual selection of the reference lists of the articles, with an additional search of guidelines available online. The articles were selected with preference to original articles, publications within the past 5 yr, and those with the highest level of evidence. Eventually, 156 articles in total were listed in the references.

3. Evidence synthesis

3.1. Indications

3.1.1. Indications for initial biopsy

The indication to perform initial PB has traditionally been based worldwide on abnormal digital rectal examination (DRE) and/or elevated or high PSA values.

3.1.1.1. Digital rectal examination. Abnormal DRE identifying any suspicion of a tumour usually indicates an initial PB regardless of PSA level. Among approximately 36 000 men who participated in the Washington PCa screening study, 3568 (10%) had positive PBs [15]. Among the 6% ($n = 2233$) of those screened who underwent radical prostatectomy (RP), 303 (14%) were diagnosed by DRE alone. Another 1426 (64%) underwent prostatectomy for cancer diagnosed on PSA alone and 504 (22%) because of abnormalities on both tests. Of the cancers detected by DRE alone, 60 (20%) were non-organ confined, and 56 (20%) had a Gleason score ≥ 7 . Gleason score ≥ 7 cancers detected at PSA levels < 1.0 , 1.0 – 2.0 , 2.0 – 3.0 , and 3.0 – 4.0 ng/ml were present in 10%, 22%, 14%, and 35% of cases, respectively, indicating that a substantial population of cancers detected by DRE at a PSA level < 4.0 ng/ml were clinically important.

3.1.1.2. Prostate-specific antigen. The debate regarding the pros and cons of PSA-based screening continues despite two randomised controlled trials (RCTs) [16,17]. The North American trial did not find a benefit in a group of men randomised to screening compared to those randomised to not screening, but cross-contamination of this study was immense, limiting interpretation. In contrast, the European trial demonstrated a clear reduction in the risk of PCa death, particularly after a 10-yr duration and especially when considering only those men screened compared to those not screened instead of the cross-contaminated intent-to-screen analysis.

Recommendations for the indication for PB in various organisations' published guidelines vary (Table 1). However, throughout the two RCTs as well as the organisations' recommendations, there is an argument that once a patient has made a decision to undergo screening for PCa, the indication to undergo PB is typically made on the basis of PSA, with no absolute cut-off defining an abnormal level.

In the past decade, PB has been extensively performed with a lowering of the PSA threshold to reduce underdiagnosis of high-risk cancer. This practice has led to increased detection of "insignificant cancer," especially when coupled with another historical change—an increased core number in the PB technique. The clinical dilemma is based on the fact that there is no absolute threshold PSA value to exclude high-grade cancers. The Prostate Cancer Prevention Trial reported 2950 men in the placebo arm who underwent sextant PB in 85% of the participants; the prevalence of Gleason score >7 cancer was observed in 2.3% (67 of 2950) of men with PSA levels ≤ 4.0 ng/ml [2]. However, the majority (10.2% [361 of 2950] of men biopsied) of cancers in men with PSA levels of < 4.0 ng/ml were Gleason score < 6 .

Fluctuations resulting from the presence of a urinary tract infection (UTI), prostatitis, or prostate trauma often cause a false-positive result, and a majority of PSA values in the 2.5–10.0 range are high based on benign rather than malignant changes. Most guidelines recommend repeating an abnormal PSA value prior to making the decision to perform PB if the DRE is normal.

3.1.1.3. Prostate-specific antigen derivatives, new markers, and imaging. To develop strategies to reduce the number of unnecessary PBs while still detecting most clinically significant cancers, an individualised algorithm using other available information in addition to prebiopsy PSA could result in a considerable reduction in potentially unnecessary biopsies [18]. Most studies assessing potential new diagnostic markers have been based on a study population already screened and selected by an abnormal PSA test. However, new biomarkers (including urine PCa antigen 3 [PCA3] and serum kallikrein) show promise for the indication of PB [18,19]. There are multiple factors to consider in proceeding to biopsy, potentially including PSA velocity, percent free PSA (%fPSA), prostate size (PSA density), age (age-referenced PSA), family history, ethnicity, comorbidities, and validated nomograms, which have been listed in various guidelines (Table 1).

It is intuitive that rapidly rising PSA suggests a high risk of cancer. Carter et al. demonstrated a significant correlation between PSA velocity and survival among patients diagnosed with PCa in the Baltimore Longitudinal Study of Aging project, suggesting a PSA velocity threshold of 0.35 ng/ml per year for detection of potentially lethal cancer within the window of curability [20]. Based on this finding, the National Comprehensive Cancer Network (NCCN) recommendation includes the threshold value of PSA velocity (≥ 0.35) for the indication of initial biopsy in men with PSA ≤ 2.5 ng/ml [21]. Nevertheless, one systematic review of PSA velocity and doubling time reported that no article used decision analytic methods to examine the clinical value of PSA kinetics as a predictor of PB outcomes [22]. Future research on PSA kinetics would require avoiding verification bias, for example, avoiding defining men not undergoing PB as proven to be cancer free.

The NCCN guideline recommends the use of %fPSA as an alternative indication of initial biopsy, especially for selected men who had normal PSA, a PSA level between 4 and 10 ng/ml, and a relative contraindication to PB (such as the use of anticoagulants or another comorbidity), with the intention of avoiding unnecessary biopsy. In the selected case, this measure could be used to indicate biopsy by $\leq 10\%$, consider PB intermediate ($> 10\%$ to $\leq 25\%$), and no PB by $> 25\%$ [21,23]. PSA density [24,25] and age-referenced PSA [26,27] has been investigated but is controversial [21].

Emerging serum-based and urine-based biomarkers include human kallikrein markers and PCA3. A panel of four kallikrein markers (total PSA, free PSA, intact PSA, and kallikrein-related peptidase 2) appears to be more predictive of biopsy outcomes than PSA [28,29]. These authors suggested that for every 1000 men with a total PSA level > 3 ng/ml, the model would classify as high risk 131 of 152 (86%) of the cancer cases diagnosed clinically within 5 yr; 421 men would be classified as low risk by the panel and recommended against PB [30]. Because proPSA is the precursor form of PSA and [-2]proPSA is the prevalent form in cancer cells more than in benign cells, the %[-2]proPSA (percent of [-2]proPSA to %fPSA) and Beckman Coulter Prostate Health Index (PHI) were developed from a mathematical formula combining total PSA, %fPSA, and [-2]proPSA [31–33]. In a PSA range of 2–10 ng/ml, the studies reported that %[-2]proPSA and PHI are significant predictors of PCa at initial extended PB [33]. Its impact on detecting significant PCa is ongoing in a European clinical trial.

PCA3 is a highly overexpressed gene in PCa cells and is independent of total PSA, DRE findings, and prostate volume [34,35]. There are increasing data to suggest that the use of PCA3 for predicting initial PB outcomes may be better than PSA, PSA density, and %fPSA [36,37]. However, current guidelines suggest that using PCA3 as an indication for initial PB at a single-patient level remains experimental [21,38].

A suspicious lesion on imaging is a relative indication for targeted PB in addition to systematic random biopsy. Transrectal ultrasound (TRUS)-directed biopsy-proven

Table 1 – Summary of guideline recommendations for the indication of the initial prostate biopsy

Document or organisation	Recommendation		Reference
	Regards PSA cut-off and DRE	Factors to consider	
European Association of Urology Guidelines on Prostate Cancer, 2012 update	<ul style="list-style-type: none"> • An abnormal DRE or elevated PSA (no exact cut-off value for normal PSA) • For young men, PSA values <2–3 ng/ml are often used • The first elevated PSA level should not prompt an immediate biopsy, to be verified after a few weeks by the same assay under standardised conditions 	<ul style="list-style-type: none"> • Biologic age, potential comorbidities (ASA index and CCI), and therapeutic consequences • Risk stratification: important tool for reducing unnecessary biopsies • Standardised condition of the verified PSA: no ejaculation and no manipulations, such as catheterisation, cystoscopy, or TUR, and no UTI 	Heidenreich, Eur Urol 2011;59:61–71 (2012 update: www.uroweb.org)
American Urological Association PSA Best Practice Statement: 2009 update	<ul style="list-style-type: none"> • Based on PSA and DRE results, but no longer recommending a single threshold value of PSA 	<ul style="list-style-type: none"> • Free and total PSA, patient age, PSA velocity, PSA density, family history, ethnicity, prior biopsy history, and comorbidities 	Greene, J Urol 2009;182:2232–41
American Cancer Society Guideline for the Early Detection of Prostate Cancer: Update 2010	<ul style="list-style-type: none"> • PSA without DRE (when PSA >4 ng/ml) or with DRE (when PSA 2.5–4.0 ng/ml) 	<ul style="list-style-type: none"> • PSA level ≥ 4.0 ng/ml: remains a reasonable approach for men at average risk • PSA levels 2.5–4.0 ng/ml: need to consider an individualised risk for high-grade cancer • Risk factors include African American race, family history, increasing age, and abnormal DRE 	Wolf, CA Cancer J Clin 2010;60:70–98
NCCN Guideline Version 2012 Prostate Cancer Early Detection	<ul style="list-style-type: none"> • Abnormal DRE (regardless of PSA): biopsy • PSA ≤ 2.5 ng/ml and PSA velocity ≥ 0.35 ng/ml per year: consider biopsy • PSA 2.6–4.0 ng/ml: consider biopsy • PSA 4–10 ng/ml: biopsy (preferred) or in select patients where risk of biopsy or diagnosis and treatment is outweighed by co-morbid conditions • PSA 4–10 ng/ml and percent free PSA $\leq 10\%$: biopsy • PSA ≥ 10 ng/ml: biopsy 	<ul style="list-style-type: none"> • Age (men >75 yr of age should be considered individually), comorbid conditions, percent free PSA, prostate exam/size, strength of family history, and African American ethnicity 	www.nccn.org
National Institute for Health and Clinical Excellence, United Kingdom Clinical Guideline 58, Prostate Cancer 2008	<ul style="list-style-type: none"> • PSA level alone should not automatically lead to a prostate biopsy 	<ul style="list-style-type: none"> • DRE, estimate of prostate size, comorbidities, age, and black African and black Caribbean ethnicity • To give information, support, and adequate time for men and their partners or careers to decide whether they want to undergo biopsy • The information includes an explanation of the risks of the diagnosis of clinically insignificant PCa and benefits of prostate biopsy • Nomograms can be used, with an explanation of the reliability, validity, and limitations of the prediction 	www.nice.org
Updated Japanese Urological Association Guideline on PSA-based Screening for Prostate Cancer in 2010	<ul style="list-style-type: none"> • The cut-off of PSA test level for the biopsy indication is recommended at 4.0 ng/ml • Alternative cut-offs for the biopsy indications are age-specific reference ranges of PSA 	<ul style="list-style-type: none"> • Age-specific reference ranges of PSA, which are set at 3.0, 3.5, and 4.0 ng/ml in the age ranges of 50–64, 65–69, and ≥ 70 yr of age, respectively 	Int J Urol 2010;17:830–8
Australian Cancer Network. Localized Prostate Cancer: A Guide for Men and Their Families in 2010	<ul style="list-style-type: none"> • The absolute level of PSA at which a biopsy may be recommended varies for each patient and depends on risk factors 	<ul style="list-style-type: none"> • Age, prostate size, family history, change in PSA over time, and (crucially) and DRE • Two online risk calculators are available that bring these factors together into a single risk estimate (need to be used with caution and in discussion with the physician) 	www.cancer.org.au
Systematic Development of Clinical Practice Guidelines for Prostate Biopsies: A 3-Year Italian Project	<ul style="list-style-type: none"> • Recommended when the diagnosis leads to a treatment that will improve both the patient's quantity or quality of life and when total PSA is >4 ng/ml • Total PSA cut-off may be lowered to 2.5 ng/ml when indicated by other risk factors 	<ul style="list-style-type: none"> • Familiarity (at least one first-degree relative ≤ 60 yr of age affected by PCa) or abnormal DRE or low ratio of free to total PSA (<10%) • In PSA range of 4–10 ng/ml, ratio of free to total PSA • In evaluating patients treated for at least 3 mo with finasteride or dutasteride, total PSA values must be doubled or values discharged and considered as pretreatment values only 	Anticancer Res 2007;27:659–66
Prostate Cancer: European Society for Medical Oncology Clinical Practice Guidelines for Diagnosis, Treatment, and Follow-up	<ul style="list-style-type: none"> • PSA should be measured and DRE performed in appropriately counselled patients in whom there is clinical suspicion of PCa or in those who want to be screened 	<ul style="list-style-type: none"> • Free PSA, PSA velocity and PSA density, DRE findings, prostate size, ethnicity, age, and comorbidities 	Ann Oncol 2010;21(Suppl 5):v129–33

PSA = prostate-specific antigen; DRE = digital rectal examination; ASA = American Society of Anaesthesiologists; CCI = Charlson Comorbidity Index; TUR = transurethral resection; UTI = urinary tract infection; NCCN = National Comprehensive Cancer Network; PCa = prostate cancer.

cancers are likely to be of higher grade and volume and may be missed without the additional targeted biopsy [39,40]. One recent Canadian clinical setting study ($n = 982$) reported that logistic regression analysis revealed that a TRUS-visible lesion is the most important independent predictor of PCa (odds ratio [OR]: 2.47; 95% confidence interval [CI], 1.91–3.2), followed by DRE (OR: 2.29; 95% CI, 1.72–3.06; $p < 0.01$) as well as high-grade cancer [41]. An obvious limitation of conventional TRUS is that the definition of TRUS-visible or suspicious lesions is highly dependent on the operator and ultrasound technology used. Recently, substantial efforts have been made to introduce evolving imaging modalities, especially magnetic resonance imaging (MRI), to potentially visualise all clinically significant cancers [42]. With radiologic expertise [43,44], the diagnostic accuracy of multiparametric MRI is high in detecting and excluding high-grade cancers $>0.5 \text{ cm}^3$ in volume, with a sensitivity of 93% and a negative predictive value of 98%. In 2012, the European Society of Urogenital Radiology developed prostate MRI guidelines offering clinical indications and minimal and optimal imaging acquisition protocols for multiparametric MRI; the organisation also proposed a structured reporting system for scoring criteria [45]. However, MRI expertise remains limited in the broader urologic community.

3.1.1.4. Family history and ethnicity. A family history of PCa and ethnicity should always be assessed when deciding whether to perform PB. Based on the population-based Prostate Cancer Database ($n = 22\,511$) in Sweden, men who had at least one brother and a father with PCa had increased PCa standardised incidence ratios of 3:1 (95% CI, 2.9–3.3) [46]. Recent data from the Reduction by Dutasteride of Prostate Cancer Events study demonstrated that family history is a significant risk factor for cancer, with biopsy positive in 32% versus negative in 24% among a total 3407 men in a placebo group [47]. Interestingly, further analysis revealed that family history was not associated with an increased risk in North American men (OR: 1.02; 95% CI, 0.73–1.44), whereas family history was significantly related to positive PB outside of North America (OR: 1.72; 95% CI, 1.38–2.15; $p = 0.01$) [48].

Yanke et al. reported that in 9473 patients undergoing initial PB, African American race remains an independent predictor of PCa detection in men undergoing initial PB [49]. Hemmerich et al. suggested that because African American race more often affected the likelihood of PCa, an informational discussion of PCa risk is essential at the time of PB [50].

3.1.1.5. Predictive models. Several predictive models have been developed to drive indication for PB. However, many of these lack external validation, and when validation was available, the benefits were predictably lower in the external population than in the model population [51]. For reducing unnecessary biopsies while still detecting most clinically important cancers, recently the most popular risk calculators that had been externally validated include those from the Prostate Cancer Prevention Trial

(PCPT) and the European Randomised Study of Screening for Prostate Cancer (ERSPC). Variables used in the PCPT model are PSA, age, family history, race, DRE, and prior negative biopsy [52]. The ERSPC model also uses TRUS-estimated prostate volume and the presence of hypoechoic lesions [18].

The PCPT model was developed from an un-referred cohort defined by PSA $< 3 \text{ ng/ml}$ and negative DRE at study entry. Most patients underwent traditional sextant biopsy, which may underestimate actual cancer risk [53–55]. Furthermore, these men were prescreened, and all were ≥ 55 yr of age, limiting the study's applicability to current practice, as has been shown in subsequent external validation studies in the clinical setting. Multiple validation studies of the ERSPC model have revealed significant superiority to the PCPT model or clinical decisions based on PSA and/or DRE [41,56,57]. A threshold $\geq 20\%$ probability on the ERSPC risk calculator could be reasonable for recommending a PB based on identification of most high-grade cancers [57].

The following risk calculators are available online:

- ERSPC risk calculator (<http://www.prostatecancer-risk-calculator.com>) [18]
- PCPT risk calculator (<http://deb.uthscsa.edu/URORiskCalc/Pages/uroriskcalc.jsp>) [52]
- Montreal nomogram (<http://www.nomogram.org>) [58]
- Sunnybrook nomogram (http://sunnybrook.ca/content/?page=OCC_prostateCalc) [59]
- Cleveland Clinic nomogram (http://www.clevelandclinic.org/health/interactive/proassess_risk.asp) [60].

3.1.2. Indications for repeat biopsy

3.1.2.1. Repeat biopsy after an initial negative biopsy. When a patient has an initial negative PB and there is persistent clinical suspicion of cancer from DRE, PSA, or suspicious pathologic findings (such as atypical small acinar proliferation of prostate [ASAP] or multifocal high-grade prostatic intraepithelial neoplasia [HGPIN]) in initial PB specimens, repeat PB may be warranted (Table 2) [38]. Because any technique involves a significant sampling error, a *repeat PB dilemma* occurs in a large number of patients. An important consideration is adequacy of the initial PB, taking into account the number of cores taken and anatomical sites sampled, length of each core, and quality of the tissues sampled. Most studies of repeat PB following extended initial PB indicate that up to 30% of patients have cancers that were not previously identified, so repeat PB is a consideration in any patient in whom PSA values remain suspicious after a single negative PB [61,62].

Modern imaging studies (including multiparametric MRI, multiparametric TRUS, or an MR/US fusion technique) might have an even more relevant role in visualising clinically significant cancers to facilitate precise sampling from a suspicious area in the repeat PB setting [63–66]. Sampling locations of elusive anterior cancer might be further enhanced using emerging MRI and TRUS techniques [67,68].

Table 2 – Summary of guideline recommendations or comments for repeat prostate biopsy

Document or organisation	Recommendation or comment		Reference
	Indication or technique	Complementary	
European Association of Urology Guidelines on Prostate Cancer, 2012 update	<ul style="list-style-type: none"> • Indication: (1) rising and/or persistently elevated PSA, (2) suspicious DRE, (3) ASAP, and (4) extensive (multiple biopsy sites) HGPIN. • One set of repeat biopsies is warranted in cases with rising or persistent PSA, suspicious DRE, and ASAP of the prostate. 	<ul style="list-style-type: none"> • Optimal timing of repeat biopsy is still uncertain. • MRI may be used to investigate the possibility of an anteriorly located cancer, followed by TRUS- or MRI-guided biopsies of the suspicious area. • Overall recommendation for further (≥ 3) sets of biopsies cannot be made; the decision must be made based on an individual patient. • PCA3 urine test may indicate repeat biopsy, but cost-effectiveness remains to be shown. 	Heidenreich, Eur Urol 2011;59:61–71 (2012 update: www.uroweb.org)
NCCN Guideline Version 2012 Prostate Cancer Early Detection	<ul style="list-style-type: none"> • ASAP in biopsy: extended pattern repeat biopsy (within 6 mo), with increased sampling of the ASAP site and adjacent areas. • HGPIN multifocal (≥ 2 cores): extended pattern biopsy within the first year. • Patients with prior negative biopsies, yet persistently rising PSA values should undergo repeat biopsy based on risks and benefits discussion. • Extended pattern repeat biopsy: number of cores, sextant (6); lateral PZ (6); and lesion targeted at palpable nodule or suspicious image. 	<ul style="list-style-type: none"> • PSA velocity, adequacy of initial biopsy (number of cores, prostate size), age (men > 75 yr of age should be considered individually), comorbid conditions, percent free PSA, prostate exam/size, strength of family history, and African American ethnicity. • Additional MRI imaging (T2w plus DWI) may help identify regions of cancer missed on prior biopsies and should be considered in selected cases. • For high-risk men with multiple negative biopsies, saturation biopsy may be considered. • Particular attention should be given to apical sampling, including the anterior apical horn, which is comprised of the PZ, and TZ biopsy can be considered. 	www.nccn.org
National Institute for Health and Clinical Excellence, Clinical Guideline 58, Prostate Cancer 2008	<ul style="list-style-type: none"> • Men should decide whether to have a rebiopsy following a negative biopsy, having had the risks and benefits explained to them. 	–	www.nice.org
Systematic Development of Clinical Practice Guidelines for Prostate Biopsies: A 3-Year Italian Project	<ul style="list-style-type: none"> • It is recommended that a biopsy be repeated after a prior negative biopsy when (1) the prior sampling is inadequate (< 6 cores sampled, no prostatic tissue, and in the case of thin or bad readable cores); (2) PSA persistently > 10 ng/ml; (3) PSA velocity > 0.75–1 ng/ml per year; or (4) ASAP or HGPIN at first biopsy. 	<ul style="list-style-type: none"> • The biopsy should be repeated within 6–12 mo. • Repeat biopsies following the second biopsy should be considered in select patients. • TURP is not considered a rebiopsy method. • A rebiopsy setting should include an increased number of cores relative to the previous biopsy and sampling of the TZ. 	Anticancer Res 2007;27:659–66
Canadian Urological Association Guidelines 2010 on Prostate Biopsy Methodology	<ul style="list-style-type: none"> • ASAP lesions are cancerous until proven otherwise and should undergo repeat biopsy. • Repeat biopsy may no longer be indicated for HGPIN lesions in the era of extended core biopsy, unless the patient has an increase in PSA or change on DRE. • Saturation biopsy may be considered in high-risk cases (eg, rising PSA, abnormal DRE, persistent ASAP) with at least two previous negative extended biopsies. 	–	Can Urol Assoc J 2010;4:89–94

PSA = prostate-specific antigen; DRE = digital rectal examination; ASAP = atypical small acinar proliferation; HGPIN = high-grade prostatic intraepithelial neoplasia; MRI = magnetic resonance imaging; TRUS = transrectal ultrasound; PCA3 = prostate cancer antigen 3; NCCN = National Comprehensive Cancer Network; PZ = peripheral zone; T2w = T2-weighted imaging; DWI = diffusion-weighted imaging; TZ = transition zone; TURP = transurethral resection of prostate.

The US Food and Drug Administration (FDA) recently approved the ProgenSA PCA3 assay [69], which uses a PCA3 score (a ratio of PCA3 RNA to PSA RNA) with a cut-off value of 25 [70] in post-DRE (attentive) first-catch urine. The cut-off value remains debatable, as some studies have used 35 as the cut-off of *abnormal*. The ProgenSA PCA3 assay is indicated for use in conjunction with other patient information to aid in the decision for repeat PB in men ≥ 50 yr of age who have had one or more previous negative

PBs and for whom a repeat PB would otherwise be recommended by a urologist. However, FDA has included a black-box warning not to use the assay in men with ASAP [71–76]. In the largest repeat PB cohort, in which 1072 men underwent two sets of 10-core repeat PBs at 2-yr and 4-yr follow-up, sensitivity and specificity of a PCA3 score of 35 were 48.4% and 78.6%, respectively. Cancer detection increased from 6% at PCA3 score < 5 to 57% at a score ≥ 100 , with significant correlation to biopsy Gleason score

($p = 0.00017$) [75]. A multi-institutional external validation study of 621 men who underwent ≥ 10 -core biopsy indicated that a median PCA3 score of biopsy-negative versus biopsy-positive men was 20 versus 48, and an area under the curve of a PCA3 score of 35 was 0.74 [74,76]. The superiority of the PCA3 score compared to %fPSA was also demonstrated, indicating that a lower PCA3 score may potentially prevent unnecessary repeat PB [72,75,77]. However, in 127 patients who had multiple repeat PB sessions, PCA3 appeared to have a role in reducing unnecessary PB at first repeat PB but not at second or more repeat PB sessions [78].

Suspicious pathologic findings, including HGPIN and ASAP (or an alternative: atypical glands suspicious for cancer) in prior biopsy may be an indication for repeat PB [79,80]. Initial PB identifies a median of 15–20% for HGPIN and 5% for ASAP [79,81–83]. Cancer detection following these pathology findings ranges from 20% to 80%. A finding of a single core with HGPIN does not warrant immediate repeat PB, and it is controversial whether repeat PB should be performed 2–3 yr later. A single focus of HGPIN appears to be relatively unrelated to PCa risk, but multifocal HGPIN indicates a 40% risk of cancer on repeat PB, which some authors recommend within 1 yr of the initial PB [84]. Godoy et al. have demonstrated a continued risk of PCa development in these patients and propose a “delayed-interval” biopsy approximately every 3 yr in healthy patients, although their patient population has not been tested with newer modalities such as PCA3, so it is not known whether new molecular markers could determine which of these patients require that protocol [85]. ASAP is an almost certain clinical indication for repeat biopsy, as approximately 40% of patients who undergo repeat PB are found to have cancer that was not identified during initial PB. The timing for repeat PB within 3–6 mo in this setting is, however, untested, and there appears to be no reason to wait beyond the time that can be conveniently scheduled.

3.1.2.2. Repeat biopsy after initial positive biopsy

3.1.2.2.1. Immediate repeat biopsy at entry into active surveillance. Patient-selection criteria for AS are generally based on diagnostic biopsy outcomes suggesting a high likelihood of indolent cancer, using tumour extent and Gleason grade [86]. However, when diagnosis is made of apparently low-grade or low-volume cancer, the patient faces the dilemma of a lack of reliable predictors to define clinically significant cancer. Currently available clinical variables, including biopsy results, inherently give only a sampling of the tumours. To reduce misclassification on the initial diagnostic PB, repeat PB at 3–18 mo from entry into AS have been suggested [87–89].

In 104 men who had an initial diagnosis on a biopsy done elsewhere, repeat, extended 14-core PB within 3 mo of the diagnostic PB was negative for cancer in 27 patients (26%), positive for cancer with no upgrade in 49 patients (47%), and upgraded in 28 patients (27%) [87]. Porten et al. [88] reported immediate repeat PB outcomes in 377 men who elected AS, with a median of 13 cores at initial diagnostic PB,

including 29% of men who had three or more repeat PBs; 34% ($n = 129$) were upgraded during a median follow-up of 18.5 mo. Bul et al. [89] reported that in 757 men after a median follow-up of 1.03 yr, the immediate repeat PBs were negative for cancer in 277 patients (37%), favourably low risk in 317 patients (42%), and upgraded in 67 patients (9%); an increase in positive biopsy cores >2 was found in 130 patients (17%). Analysis showed that the upgrade to high risk was significantly influenced by the number of initial diagnostic positive cores (OR: 1.8; $p = 0.002$) and higher PSA density (OR: 2.1; $p = 0.003$) [89]. Thus, approximately 1 of 3 of patients considered candidates for AS actually have more significant disease than is recognised on diagnostic PB, so repeat PB is highly valuable in determining reasonableness for enrolment in AS protocols.

PCA3 may also be a useful marker for improving selection for AS. PCA3 score appears to be strongly indicative of tumour volume and insignificant PCa [90–92]. When the impact of MRI in the reclassification of men under AS was evaluated in 60 consecutive men, the MRI findings failed to identify biopsy-proven cancer in 60% and were concordant with biopsy-positive location in 40% [93]. The introduction of imaging in an AS program is still experimental but has the potential to enhance reclassification of biopsy-proven cancers as well as false-negative lesions in the initial diagnostic image-blinded biopsy and also may direct restaging targeted biopsy to confirm adequacy for entry into AS.

3.1.2.2.2. Follow-up surveillance biopsy under active surveillance. AS protocols ideally involve periodic follow-up PB to determine potential disease progression. In 16 AS cohorts, routine follow-up PBs were performed initially within 6–18 mo after enrolment, and then at intervals of every year to every 3–4 yr. Progression was defined by criteria such as upgrading or an increase in the number of biopsy cores positive for cancer (≤ 3 or ≤ 4) [94]. In a series of men who progressed on AS and underwent RP, the large tumours that the biopsy protocol missed had a marked tendency to involve the transition zone (TZ) [95]. Given that percentage involvement of a biopsy core by tumour is often used as an inclusion criterion for AS, it is crucial that the biopsy be able to determine the amount of tumour in the anterior zone with reasonable accuracy. Based on the current study data, these authors recommend that the repeat surveillance biopsy protocol for AS include anterior zone sampling.

Conventional systematic biopsy techniques are suboptimal when considering the sampling error from the same or adjacent tissue of low-volume cancer foci. When cancer volumes were assessed in 399 men on AS with at least two repeat PBs, the cancer volume increased and decreased at a similar rate of 10% per biopsy [96]. In this study, the majority of men on AS had fewer than three positive cores and $<33\%$ of total positive cores at diagnostic biopsy. An important limitation of current techniques of surveillance staging biopsy is that it lacks the ability to reliably revisit the location of previously discovered cancer foci, resulting in the risk of understaging even in the false diagnosis of the absence of cancer. This also occurs during template

mapping biopsy at rates of approximately 20%. In contrast, annual biopsies have been reported to be associated with an increased risk of erectile dysfunction in men on AS [97].

PSA kinetics or PCA3 score are thus far considered unreliable triggers for clinical decision-making during an AS programme [98–100]. With regard to the concept of an emerging *image-based mapping* biopsy technique, the development of geographically tracking biopsy trajectories in the diagnostic or entry repeat PB may have a role in reliably retargeting the known cancer to refer the recorded geographical location at the time of follow-up surveillance biopsy, although results are preliminary at the moment and more study is needed [101–103]. The indication, PB scheme, and interval of follow-up biopsies in current protocols vary, and criteria on triggers for intervention also vary in study protocols.

3.2. Techniques

Prospective randomised trials using extended 12-core schemes revealed no differences between the transrectal and transperineal approach in terms of cancer detection in initial PB [104,105]. Similarly, in the repeat biopsy setting, both approaches have a similar detection rate in men undergoing saturation biopsy [106]. A retrospective analysis of 1132 RP specimens revealed that cancers previously detected by transrectal ($n = 718$) or transperineal ($n = 414$) PB are similar in tumour size (2.0 vs 1.8 cm³, respectively). Furthermore, the rate of insignificant cancer (defined as size <0.5 cm³, Gleason ≤ 6 , organ confined) is 5.1% for both [107]. Both methods identify the majority of clinically significant cancer (94.9%). Nevertheless, the transperineal approach detected more anterior tumours (16.2%) than the transrectal approach found (12%) [107].

3.2.1. Number of cores and sampling locations

It is difficult to compare the diagnostic accuracy of PB techniques, because men with a negative biopsy never undergo RP. Thus, there is no proof of biopsy accuracy in the clinical setting, leading to potential verification bias. As a result, the only way to compare schemes regarding number and location of cores depends on detection rates in biopsy series, recognising that there is no way of knowing how many cancers were missed on any of the series. Computerised models have been used to assess techniques, but their *ideal state* modelling ignores the fact that the real biopsy needle takes an imprecise path through the prostatic tissue that may or may not reflect the three-dimensional (3D) sampling that the models predict.

When mathematically considering the limited sampling volume of a single biopsy core in comparing it to the entire prostate volume, an optimal PB scheme would be theoretically achieved not only by increasing core numbers but also by sampling proper geographical locations. In an analysis of 164 autopsies, in which 18-core biopsy (12 extended scheme plus an additional 6 sextant cores from the TZ or central zone) was performed in patients who had not previously undergone clinical biopsy (similar to the setting of initial biopsy), step-section analysis revealed that the

12-core technique detected the majority of clinically significant cancers with 80% sensitivity [108]. The authors concluded that the ability to detect cancer was related more to the sampling location than to the number of biopsy cores taken and that the peripheral zone (PZ) tissue where PCa preferentially occurs is more adequately sampled with lateral and apical cores.

3.2.1.1. Initial biopsy. The accuracy of initial PB schemes depends on several factors. Sampling accuracy tends to progressively decrease with increasing prostate volume [80]. Furthermore, PSA, %fPSA, and DRE influence the detection rate.

Substantial modifications from the original sextant PB approach have resulted in the contemporary acceptance of an extended PB scheme (defined as the traditional sextant template plus at least four and up to eight laterally directed samplings from the PZ) as an initial diagnostic PB [21,38,80]. The 12-core biopsy scheme (sextant template plus laterally directed sampling from each sextant template) has become the most widely accepted method in recent years, with some authors adding a core from the extreme apex on each side based on the observation that this is the most common site where cancer is missed during initial biopsy [109]. The debate continues as to whether there is value in adjusting the number of cores based on age or prostate volume. Until now, data have not demonstrated a clear value to image-guided initial biopsy, but emerging experience has the potential to change that.

Several clinical studies have demonstrated that extended biopsy has a significantly superior detection rate compared to sextant biopsy [10,110]. The Vienna nomogram suggested a minimum number of cores (range: 8–18) based on patient age and gland volume in the PSA 2–10 ng/ml range to ensure 90% certainty of cancer detection; for example, in men with a prostate size of 50–60 ml, 16, 14, 12, or 10 cores were prescribed for patients aged <50, 50s, 60s, or 70s, respectively [111]. Nevertheless, most initial biopsy studies have shown that a further increase of the number of biopsy cores >12–14 or a saturation template has no significant benefit and does not decrease the positive biopsy rate during subsequent biopsy [112,113].

A summary of contemporary recommendations (Table 3) supports a 10- to 12-core extended PB scheme, with additional cores from areas suspected by DRE or TRUS. Figure 1 indicates the recommended biopsy location and direction of a typical transrectal 12-core biopsy template to maximise the sampling from the PZ (without the distal end of the needle into the TZ).

3.2.1.2. Repeat biopsy. Recognising the inherent potential for a systematic biopsy to miss (usually) small-volume cancers, a significant number of men will undergo repeat PB. The indication may be based on either persistently or increasingly elevated PSA levels, suspicious %fPSA or PCA3 or initial biopsy findings such as multifocal HGPIN or ASAP. Approximately one-half to one-third of patients who undergo repeat biopsy are found to have cancer in most extended biopsy series.

Table 3 – Summary of guideline recommendations for prostate biopsy techniques

Document or organisation	Recommendation		Reference
	Regards core number or location	Complementary	
European Association of Urology guidelines on Prostate Cancer, 2012 update	<p>Initial biopsy:</p> <ul style="list-style-type: none"> • TRUS-guided systemic 10- to 12-core biopsy, with a sample site as far posterior and lateral into the PZ, is recommended. • Additional cores from suspect areas by DRE or TRUS. <p>Repeat biopsy:</p> <ul style="list-style-type: none"> • Additional TZ biopsies are confined to repeat biopsy (not recommended in the initial biopsy). 	<ul style="list-style-type: none"> • Under local anaesthesia (TRUS-guided periprostatic block is state of the art). • Oral or IV antibiotics are state of the art. Optimal dosing and treatment time vary. Quinolones are the drugs of choice, with ciprofloxacin superior to ofloxacin. • Low-dose aspirin is not an absolute contraindication. • For repeat biopsy, the detection rate of saturation repeat biopsy (>20 cores) depends on the number of cores sampled during earlier biopsies • MRI may be used to investigate the possibility of an anterior-located cancer, followed by TRUS or MRI-guided biopsies of the suspicious area. • TURP instead of repeat biopsies is a poor tool. 	Heidenreich, Eur Urol 2011;59:61–71 (2012 update: www.uroweb.org)
NCCN Guideline Version 2012 Prostate Cancer	<ul style="list-style-type: none"> • Initial and repeat: extended pattern biopsy (12 cores). • Number of cores: sextant (6), lateral PZ (6), and lesion targeted at a palpable nodule or on a suspicious image. • Anterior directed biopsy is not supported in routine biopsy. However, the addition of a TZ biopsy to an extended biopsy protocol may be considered in a repeat biopsy. 	<ul style="list-style-type: none"> • After two negative extended TRUS biopsies, PCa is not commonly found at repeat biopsy. • Additional MRI imaging (T2w plus DWI) may help identify regions of cancer missed on prior biopsies and should be considered in selected cases. • Local anaesthesia can decrease pain and discomfort associated with PB. • For high-risk men with multiple negative biopsies, consideration can be given to a saturation biopsy strategy. 	www.nccn.org
The Prostate Cancer Risk Management Programme Guide No 1 (United Kingdom, 2006)	<p>Initial biopsy:</p> <ul style="list-style-type: none"> • The scheme used at first biopsy should be a 10- to 12-core pattern that samples the mid-lobe PZ and the lateral PZ of the prostate only. • Directed cores should also be sampled from any hypoechoic areas identified during the procedure. <p>Repeat biopsy:</p> <ul style="list-style-type: none"> • Additional anterior or TZ samples may be appropriate at a repeat biopsy. 	<ul style="list-style-type: none"> • In cases where a locally advanced PCa has been identified, the operator may want to perform a limited number of cores from a prognostic viewpoint rather than the full 10- to 12-core pattern. 	www.cancerscreening.Nhs.uk
Systematic Development of Clinical Practice Guidelines for Prostate Biopsies: A 3-Year Italian Project	<ul style="list-style-type: none"> • The optimal sampling technique should include 8 to 12 cores more peripheral or laterally directed. 	<ul style="list-style-type: none"> • Doubling the sextant scheme by the transrectal approach is not sufficient to improve diagnostic accuracy. • Focused biopsies on hypoechoic areas or on suspected areas detected on Doppler if at least 10 cores are taken are not recommended. • Evidence supports the sampling of a number of cores in relation to the prostate volume. • Sampling from the TZ or the central part of the prostate is reasonably indicated in the presence of a prior negative biopsy or of a high PSA level. 	Anticancer Res 2007;27:659–66
Canadian Urological Association Guidelines 2010 on Prostate Biopsy Methodology	<ul style="list-style-type: none"> • An extended biopsy scheme of 10–12 cores is recommended to optimise the ratio of cancer detection to adverse postbiopsy events. • Lesion-guided biopsy can be added to further optimise cancer detection. 	<ul style="list-style-type: none"> • Mathematical formulas that account for prostate size, patient age, and PSA range are not required provided an extended biopsy scheme is applied. • TZ biopsies are seldom necessary and add little to the overall detection rate of an extended biopsy scheme. 	Can Urol Assoc J 2010;4:89–94
Updated Japanese Urological Association Guideline on PSA-based Screening for Prostate Cancer in 2010	<ul style="list-style-type: none"> • Systematic PB must be carried out by TRUS guidance. • The optimal number of biopsy cores is uncertain at present but should be at least six cores. 	<ul style="list-style-type: none"> • A multiple-core biopsy, which takes around 12 cores, is an alternative option for PB. 	Int J Urol 2010;17:830–8
Prostate Cancer: European Society for Medical Oncology Clinical Practice Guidelines for Diagnosis, Treatment and Follow-up	<ul style="list-style-type: none"> • PB should be performed with a minimum of eight cores obtained. 	<ul style="list-style-type: none"> • PB should be performed under antibiotic cover with TRUS guidance. 	Ann Oncol 2010;21(Suppl 5):v129–v133

TRUS = transrectal ultrasound; PZ = peripheral zone; DRE = digital rectal examination; TZ = transition zone; IV = intravenous; MRI = magnetic resonance imaging; TURP = transurethral resection of prostate; NCCN = National Comprehensive Cancer Network; PCa = prostate cancer; T2w = T2-weighted imaging; DWI = diffusion-weighted imaging; PB = prostate biopsy; PSA = prostate-specific antigen.

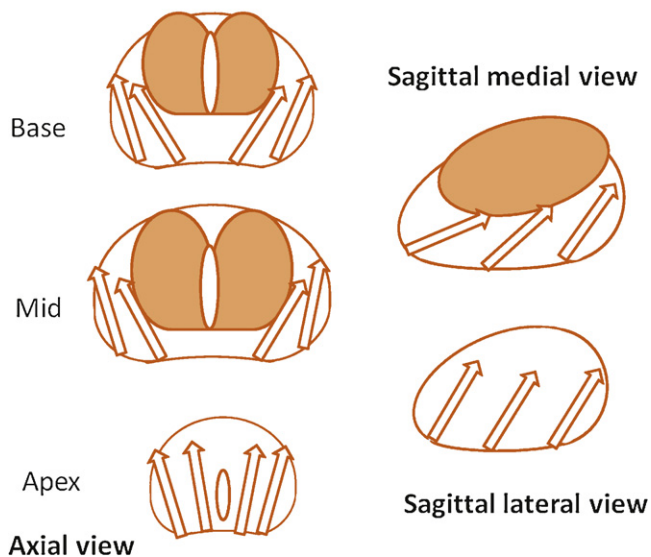


Fig. 1 – Recommended scheme for initial prostate biopsy. A lateral and medial sextant pattern with 12 cores (extended) covers the entire peripheral zone (PZ) of the prostate to maximise diagnosis of the most frequent cancer located in the PZ.

For an optimisation repeat biopsy model, Kawakami et al. proposed a unique 3D 16-core biopsy scheme, with a combination of 8 transrectal cores plus 8 transperineal cores [114]. This combination was derived from the optimisation of the initial 26-core template, which is a unique combination of 12-core transrectal and 14-core transperineal biopsy schemes. This template included sampling from both anterior and posterior parts of the prostate apex, which conventional sextant biopsy is likely to miss, and crossover of the angle of biopsy direction by this combination of two approaches. Nevertheless, if general anaesthesia is required for the transperineal cores, increased morbidity is to be expected, as discussed below, so this technique has not been widely adopted. Recently, Scattoni and colleagues developed an optimal repeat transrectal biopsy scheme that varies according to the clinical characteristics of the patients [115]. The model revealed that for patients with previous ASAP, the best model was a 14-core biopsy without TZ sampling. For patients with no previous ASAP and %fPSA $\leq 10\%$, the best model was a 14-core biopsy, including four TZ cores. Finally, patients with no previous ASAP and %fPSA $> 10\%$ were shown to benefit from a 20-core pattern, including four TZ cores. Both groups used a mathematical optimisation model (ie, *recursive partitioning analysis* [classification and regression tree analysis]) that consisted of a nonparametric statistical technique that can select and calculate interactions between core numbers and locations in the optimal biopsy scheme that are most important in determining the cancer detection rate [114,115].

Computer-based geographical analysis of all cancer foci based on reconstructed RP specimens can also simulate the clinical scenario of biopsy outcomes. A historical report demonstrated that sampling errors missing clinically

significant cancer were most likely in the medial apex of the PZ, the anterior horn of the lateral PZ, and the TZ [116]. These computerised geographical maps of cancer foci have been recently updated by morphometric analysis by Villers and colleagues [117,118]. With regard to cancers < 4 ml in volume in the TZ/anterior fibromuscular stroma (AFMS), 50% and 70% were located in the anterior third and inferior half of the TZ and/or AFMS, respectively [119]. Similarly, with regard to anterior horn PZ cancers > 2 ml, the width of the PZ is reduced and the cancers partially spread into the TZ or AFMS [118].

Ideally, the sampling location after negative PB should be different from the previous negative PB session to find tumours that were not in the original needle paths. An exception occurs after multifocal HGPIN or ASAP, in which the same or an adjacent location with previous suspicious pathology findings should be sampled either separately or as part of a systematic approach. The risk of finding cancer in patients with ASAP is location specific; in approximately 50% of patients, when cancer is found, it is in the same location as ASAP. This trend does not apply to HGPIN, which is a general risk factor for carcinoma throughout the gland [119,120]. An optimal, efficient biopsy could be achieved not only by identifying the optimal increase in the number of cores but also the technique for refining the sampling location to focus on the areas where missed significant cancers could be present but were not discovered in the previous biopsy session.

Aiming for the potential detection of all clinically significant cancers, contemporary researchers have introduced transperineal template mapping techniques with the use of an external 5-mm grid [121,122]. Onik et al. reported the role of an external (5-mm grid) template-based 3D mapping biopsy (median: 50 cores), with unilateral cancer diagnosed initially by systematic biopsy to better characterise the known cancer for possible improvement of management. 3D mapping biopsy was positive for cancer in only 80% (144 of 180) of patients with previously proven cancer. Bilateral disease was demonstrated in 61%, and only 34 patients (19%) were confirmed to have only unilateral disease [121]. Thus, the false negative rate is 20%, even with this aggressive transperineal technique in men who were known to be positive for cancer at initial biopsy. One-fourth of the patients had an increase to ≥ 7 in Gleason score. They concluded that 3D mapping biopsy may change management in 69.4% (125 of 180) of men with unilateral cancer diagnosed initially by systematic biopsy [121]. Also, detection of anterior cancer would be enhanced using this technique [122]. However, template-based biopsy is significantly more involved and invasive. Template biopsy also risks biopsy-related morbidity, including an approximately 10% urinary retention rate and the potential for oversampling of clinically insignificant cancer, which often results in overtreatment. In addition, the prostate is mobile, deformable, and swells during multiple needle passes, so template-based biopsy still involves real-time sampling errors in vivo, which are not adequately modelled using *ideal state* mathematical simulations. The specific clinical indication of this relatively invasive procedure, which

requires general anaesthesia with additional costs, remains under debate, and its use is limited in most centres.

In a repeat PB setting, to minimise sampling error, the office-based transrectal saturation biopsy technique with a number of biopsy cores ≥ 20 has gained interest in some academic circles to enhance the detection of PCa by approximately 30%. Complication rates have not been higher than for standard biopsy [61,62,10,123].

The optimal repeat PB technique is more controversial than initial PB, requiring further consideration of the risk for clinically significant versus insignificant cancer based on the results of initial biopsy as well as biopsy-related morbidity. Contemporary recommendations for the technique of repeat prostate biopsy (Table 3) suggests that a repeated 10- to 12-core extended biopsy scheme remains the most frequently used technique, with additional cores from suspected areas by modern imaging or the anterior/TZ. Figure 2 indicates the recommended consideration of PB sites by transrectal approach (including anterior horn PZ, anterior apical PZ, and anterior TZ) that are most likely missed with the conventional transrectal biopsy fired from the posterior surface of the prostate.

3.2.2. Image-guided prostate biopsy

Imaging potentially improves the process of PCa detection through the ability to visualise and characterise lesions and to guide precise, targeted biopsy. A higher prevalence of image-targeted biopsy-proven cancers in suspicious areas has been reported using evolving imaging modalities such as advanced TRUS technologies or multiparametric MRI

[40,64,65,124–126]. Contemporary series of image-guided PBs have increasingly demonstrated the significant superiority of image-guided targeted biopsy, with a better characterisation of identified cancers compared to image-blinded random biopsy. Recent studies to introduce modern imaging, such as elastography or contrast-enhanced TRUS, demonstrated the positive impact of TRUS image-targeted biopsy on improving cancer detection in the initial biopsy setting [127,128]. A prospectively randomised study compared cancer detection of targeted biopsy using real-time elastography ($n = 178$) to grey-scale ultrasound ($n = 175$) in patients undergoing a 10-core prostate biopsy. The study included a single targeted biopsy from stiffer blue or hypoechoic lesions; if there was no suspicious area in US images, all 10 cores were taken systematically. Overall sensitivity and specificity were 61% and 68% for real-time elastography versus 15% and 92% for grey-scale US, respectively [127]. Sano et al. reported that targeted biopsy using contrast-enhanced US significantly enhanced cancer detection compared to systematic biopsy (27.3% vs 9.5%; OR: 3.4, $p = 0.013$) [128]. Pathologic specimens of targeted initial biopsy-proven cancer have significantly greater volume and a higher Gleason score compared to those diagnosed from random biopsy [40,64]. MR-directed targeted biopsy can also enhance determination of aggressiveness as well as the detection of cancers that were missed in previous random, systematic biopsy [124,125].

Routine PB in current practice may be called *image-blinded PB*. Because a biopsy through the centre of the cancer contains more tissue, which allows more accurate

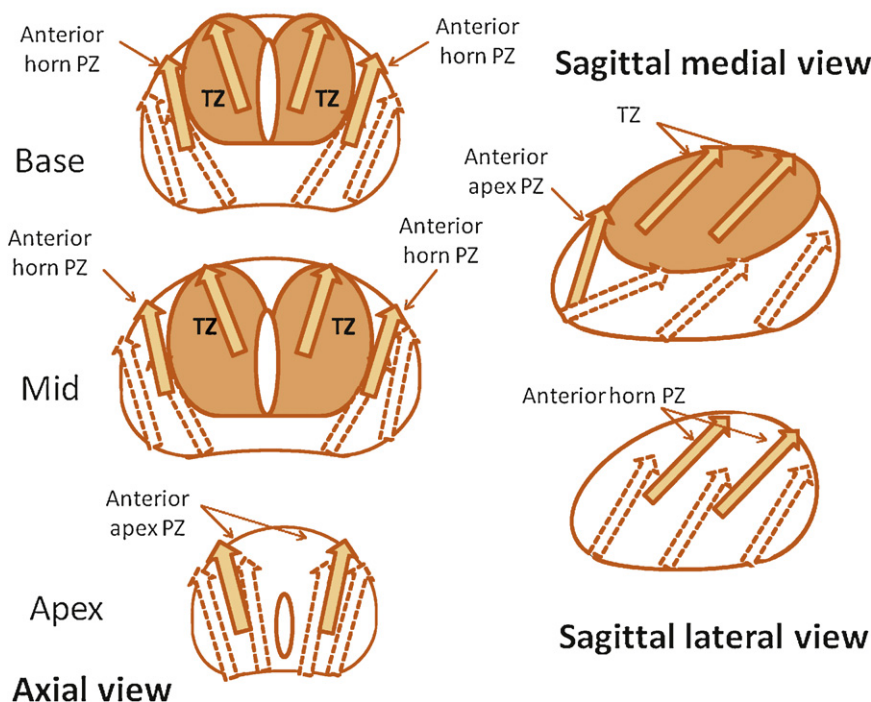


Fig. 2 – Recommended scheme for repeat prostate biopsy. The anterior apex peripheral zone (PZ), anterior horn PZ, and anterior transition zone are the recommended locations in which significant cancers likely missed on initial biopsy (dotted arrows) are potentially located. These anterior biopsies (yellow arrows) require the technique of needle placement into the middle of the prostate before firing the biopsy gun, with consideration of the advanced needle length of 22 mm (typically, including the proximal 17-mm part of the tissue sampling area and the distal 5-mm part, where the tissue is not sampled).

PZ = peripheral zone; TZ = transitional zone.

characterisation for pathologic interpretation [129,130], image visibility would help to obtain more cancerous tissue than the image-blinded procedure. Furthermore, the image visibility of cancer provides precise 3D localisation of the cancer, which could have an impact on per-lesion-based management. This would support the emerging strategy of focal therapy. The goal for focal therapy would be to selectively ablate known disease and preserve existing function, with the overall objective of minimising lifetime morbidity without compromising life expectancy [131,132]. A recent systematic review of image-guided PB using MRI-derived targets reported that cancer was detected in 30% of targeted cores (375 of 1252) versus 7% of systematic cores (368 of 5441). The efficacy (number of clinically significant cancers/number of men biopsied) of targeted sampling from MRI abnormalities appeared superior (70% vs 40%) to systematic sampling [133]. The authors suggested the possible benefits associated with an image-guided approach include fewer men undergoing biopsy overall, a greater proportion of men with clinically significant cancer undergoing biopsy, and fewer men being attributed a diagnosis of clinically insignificant cancer.

An important and obvious limitation of the image-guided PB technique is that it is operator dependent and requires significant radiologic expertise. As such, it should be noted that the recent promising accuracy of image-guided PB has been reported only by highly qualified radiologic experts and is not yet warranted for general practical use. For the further acceptance of image-guided PB in general practice, it seems essential to require significant cooperation with radiologic experts and standardisation of practical protocols.

A potential solution for MRI-guided PB available for urologists could be helped by the introduction of TRUS biopsy with MR/TRUS image fusion [66,134,135]. However, validation is needed to confirm reproducibility of the image fusion, because the prostate is a deformable organ and likely to have a shape in TRUS different from that in MRI. It is likely that this will require a nonrigid (elastic) image fusion technique [136].

Taken together, image-guided PB based on modern imaging techniques offers better characterisation of imaging-visible cancer for impact on per-lesion-based management of known disease as long as the imaging interpretation is supported by an expert in cooperation with uroradiologists or the use of a standardised, reproducible protocol. The education and standardisation of the modern imaging technique for urologic practice would be essential for enhancing the utility of image-guided PB.

Importantly, the learning curve for achieving efficient image guidance for PB is still undefined. It depends on the goal, which may include detection rate, appropriate distribution of biopsy, and reducing complications [137–139]. The goal of PB has evolved from pure cancer detection to better characterisation of the cancer to assist clinical management.

3.2.3. Minimising biopsy-related morbidity

Potential biopsy-related complications, including pain, infection, and bleeding, have implications on patient care.

Rosario et al. reported prospective evaluation of biopsy-related adverse events in 1147 men undergoing 10-core PB, indicating that 15% of men described moderate to severe pain during the biopsy procedure, 66% had blood in the urine, and 20% had a fever within 35 d after biopsy. Fewer men rated these symptoms as a major or moderate problem: 7.3% men for pain, 6.2% for haematuria, and 5.5% for fever, which was more likely in men with a previous history of UTI [140]. A prospective study of 820 men who had initial negative PB followed by repeat PB after 6 wk found that repeat PB can be performed with no significant difference in pain or morbidity [141]. The large ERSPC found that PB was not associated with excess mortality in 12 959 screening-positive men, and no patient died as an obvious complication of the biopsy [142]. Effective administration of prophylactic antibiotics and adequate local anaesthesia with prior consent for the biopsy-related complication should be standardised. Currently, the accepted standard for pain control during PB is local anaesthesia using periprostatic neural block [21,38], which may be enhanced in combination with perianal intrarectal anaesthetic cream [143,144].

Infection rates after PB have increased, leading to a hospital admission rate up to 4.3% during the past decade [140,145–149]. Recent researchers indicated that the use of enema had no significant impact on decreasing the incidence of infection or sepsis [148,149]. Several classes of antibiotics are effective for prophylaxis, with quinolone the best analysed class [147]. There are no definitive data to confirm that a longer course is superior to a short course or that multiple doses are superior to single-dose treatment [147]. Although antibiotic prophylaxis is effective in preventing infection, leading to a low incidence of sepsis [147,150], recently there have been increasing concerns of quinolone-resistant infection resulting from more frequent use of quinolones in the population overall, including at the time of transrectal PB [148,151–153]. In the contemporary era, some researchers suggest that targeted antimicrobial prophylaxis using rectal swab cultures [154] or additional use of aminoglycoside injection [155,156] could offer a more efficient regimen, with possible cost-effectiveness. However, these methods have not been broadly used and are difficult to apply to most clinical settings.

4. Conclusions

The significance of PB has evolved from pure cancer detection to better characterisation of clinically important cancer to assist the clinical management of patients. Recent data support the extended scheme (12–14 cores) for initial PB. Repeat PB after negative biopsy because of a continued risk of clinically important cancer requires balancing overdiagnosis of low-risk cancer with the potential for missing significant cancer. Although PSA and DRE remain at the centre of an indication for PB, their lack of cancer specificity has inspired the search for cancer-specific biomarkers and risk calculators. The threshold for performing second biopsy should be low because of significant cancer detection rates, but few patients are found to have

significant cancer following two negative adequate biopsies. Repeat PB should involve at least 12 cores, and several centres have shown that up to 20 transrectal cores provide additional value without increased complications.

Obtaining more adequate tissue sampling by increasing core numbers from the PZ and apex as well as sampling from suspicious areas by imaging would result in a better picture of the disease burden. Several options of PB technique, including modern image-guided targeting, biomarker development, transrectal saturation biopsy, and 3D mapping biopsy, are changing the clinical paradigms for evaluation and management. As the indication, biopsy scheme, and interval of the surveillance biopsy in an AS program vary, new PB techniques to reliably revisit the known cancer are awaited. Clearly, evidence to support adopting approaches other than the current, established standards should be tested through appropriately designed prospective studies.

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Acquisition of data: Ukimura.

Analysis and interpretation of data: Ukimura.

Drafting of the manuscript: Ukimura.

Critical revision of the manuscript for important intellectual content: Coleman, de la Taille, Emberton, Epstein, Freeland, Ginnarini, Kibel, Montironi, Plaussard, Scattoni, Jones.

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