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Standards for prostate biopsy

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Abstract

Purpose of review—A variety techniques have emerged for optimization of prostate biopsy. In this review, we summarize and critically discuss the most recent developments regarding the optimal systematic biopsy and sampling labeling along with multiparametric MRI and MR targeted biopsies.

Recent findings—The use of 10–12-core extended-sampling protocols increases cancer detection rates compared to traditional sextant sampling and reduces the likelihood that patients will require a repeat biopsy, ultimately allowing more accurate risk stratification without increasing the likelihood of detecting insignificant cancers. As the number of cores increases above 12 cores, the increase in diagnostic yield becomes marginal. However, limitations of this technique include undersampling, over-sampling, and the need for repetitive biopsy. MRI and MR-targeted biopsies have demonstrated superiority over systematic biopsies for the detection of clinically significant disease and representation of disease burden, while deploying fewer cores and may have applications in men undergoing initial or repeat biopsy and those with low risk cancer on or considering active surveillance.

Summary—A 12-core systematic biopsy that incorporates apical and far-lateral cores in the template distribution allows maximal cancer detection, avoidance of a repeat biopsy, while minimizing the detection of insignificant prostate cancers. MRI guided prostate biopsy has an evolving role in both initial and repeat prostate biopsy strategies, as well as active surveillance, potentially improving sampling efficiency, increasing detection of clinically significant cancers, and reducing detection of insignificant cancers.

Keywords

prostate biopsy; multiparametric MRI; MRI targeted biopsy; MR-US fusion; Visual estimation TRUS-guided biopsy

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Introduction

Biopsy of the prostate to diagnose or exclude cancer is performed nearly one million times annually in the U.S., frequently as a result of an elevated PSA.[1] Most biopsies are conducted under ultrasound guidance by a transrectal approach. Using this technique, tissue cores are obtained systematically throughout the prostate, most commonly in an extended 12-core biopsy template, which is supported by the American Urological Association.[2] A variety of biopsy techniques have emerged for optimizing these attributes, including computerized and image-guided techniques, but systematic sampling with variable core numbers remains the standard in practice.

Recent evidence suggests that multi-parametric MRI along with MR-targeted biopsies could improve the accuracy of diagnostic assessment in prostate cancer. Specifically MRI with targeted biopsies could reduce unnecessary biopsies, avoid false negative biopsies, reduce the number of cores required, and improve selection of low risk men for surveillance. This review addresses the current standards in prostate biopsy, its limitations, along with the contemporary use of multiparametric MRI and MR-targeted prostate biopsies.

Limitations of Contemporary Biopsy Technique

The contemporary systematic prostate biopsy strategy relies on sampling efficiency for cancer detection and is consequently subject to sampling error including a false negative biopsy or incorrect risk stratification due to undersampling, detection of clinically insignificant disease as a result of over-sampling, and the necessity for repetitive biopsy. Undersampling of the prostate occurs in up to 30 % of cases in which systematic template biopsies leads to clinically significant tumors being missed on initial biopsy.[3],[4] The overall false negative rate of a 12-core extended biopsy exceeds 30% in some series.[4] This is not greatly improved by increasing core numbers to greater than 12 cores.[2] Undersampling also leads to incorrect risk stratification. Non-targeted prostate biopsies might only sample a cancer lesion at its periphery, which may reveal a small length of tumor in a biopsy core with a low Gleason score when in fact, a clinically significant lesion may exist adjacent to the biopsy site. This sampling error intrinsic in ultrasound-guided prostatic biopsy[5] has been shown to undergrading of disease in a substantial proportion of patients. Interestingly, increasing core number, as done in saturation or repeat biopsy techniques, does not appear to greatly reduce the risk of undersampling and incorrect risk classification. [2]

Clinically insignificant cancers are often identified by chance during a systematic biopsy approach, contributing, in part, to the problem of over-detection and over-treatment of indolent prostate cancers.[6, 7] The recent trend of overcoming sampling error through increasing core number, or repeating biopsies, further escalates the risk of identifying small, indolent cancers in addition to escalating costs.[2] Several studies have shown that when serial biopsies are indicated, most cancers detected are clinically insignificant[8] and the rate of indolent cancer detection increases.[6, 7] Furthermore, increasing the number of cores beyond the extended template only has a marginal increase in overall detection rate while it appears to increase the rate of insignificant cancer detection.[2]

Optimal Prostate Biopsy

An optimal prostate biopsy in clinical practice is based on a balance between adequate detection of clinically significant prostate cancers (sensitivity), assuredness regarding the accuracy of negative sampling (negative predictive value), limited detection of clinically insignificant cancers, and good concordance with whole-gland surgical pathology results to allow accurate risk stratification for treatment selection.[2] This strategy incorporates an appropriate biopsy core number and core location. The use of 10–12-core extended-sampling protocols increases cancer detection rates compared to traditional sextant sampling methods and reduces the likelihood that patients will require a repeat biopsy by increasing negative predictive value, ultimately allowing more accurate risk stratification without increasing the likelihood of detecting insignificant cancers (Table 1).

As the number of cores increases above 12 cores, the increase in diagnostic yield becomes marginal. La Taille et al. (n=303) found that the cancer detection rates using sextant, extended 12-core, 18-core, and 21-core biopsy schemes were 22.7%, 28.3%, 30.7%, and 31.3%, respectively.[18] Diagnostic yield improved by 24.7% when the number of cores increased from 6 to 12, but only by 10.6% when the number of cores increased from 12 to 21. Only limited evidence supports the use of initial biopsy schemes involving more than 12 cores or saturation. Although increasing core number may risk increasing the detection of insignificant cancers, the majority of reports found no significant differences in the detection rate of insignificant cancers between sextant and extended biopsy schemes.[24] In a large database study (n=4,072), Meng and colleagues found that increasing the number of biopsy cores did not result in the identification of a disproportionate number of lower-risk tumors. [24] However, increasing the number of cores beyond the extended biopsy strategy appears to increase insignificant cancer detection.

Apical and laterally directed sampling of the peripheral zone increases cancer detection rates, reduces the need for repeat biopsies, and predicts pathological features on prostatectomy while transition-zone biopsies do not. Babaian et al. evaluated an 11-core biopsy strategy in 362 patients, including 85 (23%) who were undergoing a first biopsy.[12] The cancer detection rates for patients undergoing an initial biopsy was 34%, and 9 cancers were uniquely identified by non-sextant sites. Of the cancers identified uniquely by cores from non-sextant sites, 7 were identified by anterior-horn biopsies and 2 by transition-zone biopsies. Because the entire apex is composed of peripheral zone, biopsies performed at the apex or lateral apex might not sample the anterior apex. In a study evaluating individually labeled, preoperative apical core biopsies and corresponding prostatectomy specimens, Rogatsch et al. determined the positive predictive value (PPV) for identifying the tumor location correctly was 71.1%, while the lack of cancer in the apical biopsy had an NPV of 75.5%.[25] Concordance rates when an extended biopsy scheme is used are as high as 85%, compared to 50% with a sextant biopsy.[13, 26, 27] Upgrading of the Gleason score has been shown to be significantly less likely with the extended scheme (17% vs. 41% for the sextant scheme, $p<0.001$).[26] The results of biopsy schemes involving saturation biopsies (more than 12 cores) appear to have a higher concordance rate with results from prostatectomy (59%) than a scheme involving fewer than 12 cores (47%, $p=0.05$).[28] The role of lateral sampling of the prostate was evaluated by Singh et al. who showed that

laterally directed cores were independent predictors of pathological features at prostatectomy.[29]

Optimal Sample Labeling

The optimal method of labeling prostate biopsy cores for pathologic processing that provides relevant and necessary clinical information for all potential clinical scenarios has recently been addressed.[2] There is limited data to suggest that knowing the exact site of an individual positive biopsy core provides meaningful clinical information. However, determining laterality of cancer on biopsy may be helpful for both predicting sites of extracapsular extension and therapeutic planning. Taneja et al retrospectively compared the results of the diagnostic biopsies of 243 men undergoing radical prostatectomy with their final surgical pathology results and concluded that packaging cores in individual containers is substantially more expensive than packaging samples in just two containers without providing much clinical benefit. [30] Few other studies have evaluated the relationship between biopsy location and ECE location, but several studies have integrated site-specific core data into predictive models.[31].[32] Similarity, other researchers have individual labeled cores but identifying the exact position may have limited benefit.[33] The importance of base and apical positive core sampling have also been investigated.[34] In a study of 371 men, a positive biopsy at the apex was not predictive of a positive apical surgical margin or extra prostatic extension, but a positive biopsy at the base was predictive of a positive basal surgical margin and extra prostatic extension.[35] A positive SM, in turn, correlated with extra prostatic extension on final pathology.

Potential for MRI to Correct Shortcomings of Contemporary Biopsy

With the increasing challenge in preferentially detecting higher-grade prostate cancer while avoiding lower-grade tumors, noninvasive imaging may offer a means of selective disease localization. The use of MRI to evaluate the prostate and subsequently guide biopsy location has gained considerable momentum as it offers sufficient spatial resolution for disease localization and novel functional parameters for non-invasive risk assessment.[36, 37] Recent advances employ functional and physiologic MRI techniques, in combination with the established morphologic imaging with T1-weighted and T2-weighted sequences, creating a multiparametric approach.[36] The ability to detect and localize prostate using these MRI techniques has led to the development of MRI-guided prostate biopsy strategies, which aim to improve the diagnostic performance of prostate biopsy. MRI-targeted biopsy has been proposed as a way to improve detection rates and risk stratification, as well as reduce the number of cores. The benefits of MRI may address the shortcomings of contemporary prostate biopsy including improved sensitivity of biopsy for intermediate to high risk cancer, more accurate assessment of tumor grade and volume, reduced over-detection of low risk cancer, potential avoidance of biopsies in low risk men, and reduction in the number of cores per biopsy session. A recent systematic review concluded that MRI-guided biopsy detects significant prostate cancer in an equivalent or higher number of men to standard biopsy, using fewer cores with less complications and less diagnosis of insignificant cancer.[37]

Potential Applications of MRI Targeting in Prostate Biopsy

MRI targeted prostate biopsy has potential applications among men with no previous, biopsy, among men with a previous negative biopsy, and among men with low risk cancer.

Among men with no previous biopsy

Recent studies have demonstrated the beneficial role of MRI before initial biopsy. In a study evaluating 555 patients with high a PSA or abnormal DRE, Haffner et al performed a 10-core TRUS-biopsy plus cognitive transrectal ultrasound guided (TRUS) biopsy of MRI suspicious regions.[38] If only targeted cores had been performed in place of a standard TRUS biopsy, 37% of biopsies would have been avoided, a mean of 3.8 instead of 10 cores would have been needed, 13% of insignificant cancers would not have been over-detected, and detected cancers would have had more accurate grading (16% more high grade cancers detected) and volume assessment. In a randomized controlled trial Park et al evaluated 85 biopsy naïve men with clinical suspicion of prostate cancer. The visual estimated TRUS-guided biopsy group, compared to the systematic TRUS biopsy group, had a three-fold higher cancer detection rate (29.5% vs 9.8%) [OR 3.9 (95% CI 1.1–13.1, $p=0.03$)] and a four-fold higher positive core rate (9.9% vs 2.5%) [OR 4.2 (95% CI 2.2–8.1, $p<0.01$)] suggesting more accurate detection and risk stratification.[39] In another prospective study on 351 consecutive patients with elevated PSA, Numao et al. reported that the frequency of significant cancer in men with a positive MRI versus negative MRI was much higher (43-50% versus 9-13%) in the low risk group and higher (68-71% versus 47-51%) in the high risk group.[40] A important finding of this study demonstrates that in the low risk group, defined as men with PSA < 10ng/ml and normal DRE, the negative predictive value of a combination of negative MRI and prostate volume < 33ml for significant cancer was 95.1-97.5%, suggesting that a third of men with negative MRI and small prostate volume could avoid biopsy.

Among men with previous negative biopsy

In patients with a prior negative biopsy, MRI targeted prostate biopsy can guide treatment decisions by helping overcome diagnostic uncertainty as imaging may assist in localizing an area of suspicion, such as the 30% of men with prostate cancer whose tumor originates in the anterior or transitional zone. Lawrentschuk and Fleshner analyzed combined data from 215 men across six prospective studies of MRI prior to repeat biopsy for rising PSA, and found that in those who had both standard and MRI-directed biopsies that 54% had prostate cancer detected only by MRI-directed cores.[41] In a related study involving MR-US fusion biopsy on 105 patients with prior negative biopsy and elevated PSA, Sonn et al. found a cancer detection rate of 34% (36/105), with 72% of these 36 cancers being clinical significant. On multivariate analysis, a highly suspicious MRI lesion was the most significant predictor of significant cancer with an odds ratio of 33, with 12/14 (86%) patients found to have clinically significant cancer.[42] Multiparametric MRI is now recommended according to National Comprehensive Cancer Network and the European Association of Urology guidelines for men with a rising PSA and suspicion of cancer despite multiple negative biopsies.

Among men with low risk cancer

MRI targeted biopsy may be a valuable tool in men with prostate cancer on active surveillance due to its high negative predictive value for intermediate-high risk prostate cancer. Vargas et al evaluated a cohort of 388 consecutive men with low risk prostate cancer on initial biopsy who underwent MRI followed by initial surveillance and a confirmatory biopsy within 12 months, a negative MRI (score of 1–2 out of 5) had a 98% specificity and negative predictive value for ruling out Gleason upgrading, while a positive MRI (score of 5 out of 5) was 93% sensitive for Gleason upgrading (20% of the cohort showed Gleason upgrading at first surveillance biopsy).[43] In a series of 66 men who had MRI then repeat biopsy within 3 months of active surveillance enrollment, Berglund and colleagues evaluated pathological upgrading and up staging and found 27% of men had suspicion of extra capsular extension on MRI, 39% of whom were risk-upgraded on repeat biopsy; none of the 73% with a normal MRI were risk-upgraded at repeat biopsy.[44] Recently multiparametric MRI with confirmatory biopsy was associated with reclassification of men who may have been eligible for active surveillance highlighting its role in the decisions making process when considering active surveillance.[45]

Technique of MR-Targeted Biopsy

The technique of MR-targeted biopsies employed one of three main categories of navigational systems including in-bore MRI targeting, visual estimation TRUS-guided biopsy, MRI–Ultrasound (US) fusion. When conducting in-bore MRI targeting the biopsy is performed under MRI guidance within the MRI magnet. This technique is time consuming and expensive, but allows for accurate localization of the needle. Visual estimation TRUS-guided biopsy allows the urologist to sample a visually estimated location on ultrasound that corresponds to the MRI-suspicious region. The technique does not require specialized equipment and can easily incorporated into the office setting. However, the manual biopsy may not guarantee sampling of the MRI suspicious region. Kasivisvanathan et al evaluated 182 consecutive men with an MRI-suspicious lesion underwent transperineal free-hand MRI-targeted biopsy followed by a systematic template transperineal mapping biopsy MRI-targeted biopsy had a much higher proportion of positive cores (38% vs 14%) and a significantly lower rate of over diagnosis of insignificant cancer (9% vs 17%, $p = 0.024$), together with avoidance of the high complication rate of transperineal mapping biopsy.[46] MRI-US fusion biopsy potentially overcomes the limitation of cognitive fusion through reproducible methods for identification of MR lesions on ultrasound. A number of commercial platforms have become available. These applications utilize different hardware platforms for aligning the biopsy with the co-registered image. MRI/US fusion biopsy potentially has greater reproducibility due to less operator dependence and by providing real time feedback of actual biopsied locations. MR targeted TRUS –biopsy fairly accurate sampling of the region of interest is achieved, although slight deformations of the prostate due to the TRUS probe and biopsy gun are not accounted for with existing technology. Several studies have evaluated the role of MR targeted TRUS-biopsy and found increasing cancer detection rates with increase MR suspicions score.[42, 47-49] High suspicion lesions were found to harbor prostate cancer in up to 96% of cases.[48] In a study of MR-US fusion biopsy in 85 men with a rising PSA, previously negative TRUS biopsy and a positive MRI,

Miyagawa et al reported 35% had prostate cancer detected only by fusion biopsy, compared to 14% by standard biopsy.[50] Recently Wysock et al recently reported on a prospective, blinded comparison of MRI-US fusion and visual estimation or 125 consecutive men.[51] The authors concluded that MRI-US fusion was more often histologically informative than visual targeting but did not increase cancer detection. A trend toward increased detection with fusion biopsy was observed across all study subsets, suggesting a need for a larger study size. Fusion targeting improved accuracy for smaller lesions. Collectively, the published literature suggests that overall detection is decreased by MR-targeted biopsy, but significant cancers are detected with fewer cores, and insignificant cancers are detected less often.

Conclusions

A 12-core systematic biopsy that incorporates apical and far-lateral cores in the template distribution allows maximal cancer detection, avoidance of a repeat biopsy, while minimizing the detection of insignificant prostate cancers. MRI guided prostate biopsy has an evolving role in both initial and repeat prostate biopsy strategies, potentially improving sampling efficiency, increasing detection of clinically significant cancers, and reducing detection of insignificant cancers. Among men with low risk cancer contemplating surveillance, MR-targeted approaches improve risk stratification and potentially reduce the need for repetitive biopsy in follow-up.

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None

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Papers of particular interest, published within the annual period of review, have been highlighted as:

*of special interest

**of outstanding interest

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Key Points

- A 12-core systematic biopsy that incorporates apical and far-lateral cores in the template distribution allows maximal cancer detection, avoidance of a repeat biopsy, while minimizing the detection of insignificant prostate cancers.
- MR-targeted prostate biopsy has an evolving role in both initial and repeat prostate biopsy strategies, potentially improving sampling efficiency, increasing detection of clinically significant cancers, and reducing detection of insignificant cancers.
- Among men with low risk cancer contemplating surveillance, MR-targeted approaches improve risk stratification and potentially reduce the need for repetitive biopsy in follow-up.

Table 1

Cancer detection rates by number of prostate biopsy cores

No. prostate biopsy cores Study	Cancer Detection Rate				
	6	10-12	18	20-21	24
Eskew et al[9]	26.1%	40.3%*			
Naughton et al[10]	26%	27%			
Presti et al[11]	33.5%	39.7%			
Babaian et al[12]	20%	30%			
Elabbady et al[13]	24.8%	36.4%			
Gore et al[14]	31%	43%			
Philip et al[15]	23%	32%			
Shim et al[16]	22%	28%			
Scattoni et al[17]		38.5%	39.9%		
De La Taille et al[18]	22.7%	28.3%	30.7%	31.3%	
Pepe et al[19]		39.8%	39.8%		49.0%**
Jones et al[20]		52%			45%
Guichard et al[21]		38.7%	41.5%	42.5%	
Ploussard et al[22]	32.5%	40.4%		43.3%	

* 13 core extended biopsy strategy

** 29 core saturation biopsy strategy

Adapted from Bjurlin MA, Wysock JS, Taneja SS. Optimization of Prostate Biopsy: Review of Technique and Complications. Urologic Clinics of North America. In Press. [23]