White Paper

American Urological Association, Inc. Advancing Urology

AUA/Optimal Techniques of Prostate Biopsy and Specimen Handling

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INTRODUCTION / BACKGROUND

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 or NPV), limited detection of clinically insignificant cancers, and good concordance with whole-gland surgical pathology results to allow accurate risk stratification for treatment selection. 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.

A typical transrectal sextant biopsy involves samples from the parasagittal plane on the right and left sides of the base, midzone, and apex, with each site arbitrarily assigned by the operator (1). In the early 1990s, it was demonstrated that lateral displacement of the sextant resulted in an increased cancer detection rate (CDR), suggesting that core location could affect biopsy outcomes (2).

Early studies demonstrated that sextant biopsies had acceptable CDRs, but a considerable number of secondary cancers were detected on repeat biopsy following sextant biopsy (3). Several investigators demonstrated that sampling more cores improved CDR without increasing morbidity (4). As a result, today's biopsy protocols typically involve extracting 10–12 cores per biopsy, often from the standard sextant and other areas of the peripheral, transition, or anterior zones (5, 6). Despite these observations, controversy exists about the optimal strategy for prostate biopsy with regard to core number, location, labeling, and pathologic processing (6, 7).

Although increasing the number of biopsy cores has led to increased prostate cancer detection rates, many cancers diagnosed on extended sampling are small, low grade, and potentially indolent. A growing concern about the overtreatment of indolent or non-lethal prostate cancer is that "over-biopsies" might lead to over-detection. In addition, although increasing the number of cores can help detect indolent disease, this strategy can still miss clinically significant or potentially lethal cancers. Finally, increasing the number of cores has led to increased costs for specimen processing, pathologic evaluation, and cancer therapy. As a result, an optimal biopsy strategy includes an adequate number of cores to provide confidence in a negative finding while limiting the number of cores and pathologic specimens sufficiently to avoid over-detection and cost escalation.

EXPERT RECOMMENDATIONS

Expert panels in the United States, Canada, and Italy generally recommend initial prostate transrectal ultrasound (TRUS)-guided biopsy protocols involving 10–12 cores in men with an abnormal digital rectal examination (DRE) finding or a high prostate-specific antigen (PSA) level (7-10). The experts define high PSA level slightly differently—the National Comprehensive Cancer Network (NCCN) advises clinicians to consider an initial prostate biopsy in men with a PSA level higher than 2.6 ng/mL, while the Italian panel recommends an initial biopsy in men with a PSA of 4.0 ng/mL or of 2.5 ng/mL in men with a family history of prostate cancer, an abnormal DRE finding, or a PSA ratio of less than 10% (7, 8). The American Urological Association (AUA) does not recommend a single threshold PSA value to prompt a prostate biopsy because some risk exists at any PSA level, although the risk rises along a continuum of PSA levels (10).

The NCCN panel suggests an "extended-pattern 12-core biopsy" that includes the standard sextant; peripheral base, mid-gland, and apex; and lesion-directed palpable nodules or suspicious images (8). The other panels do not specify the regions of the prostate to sample, although the Italian panel recommends biopsy protocols directed to the peripheral-lateral zone (7). Only the Italian guidelines address biopsy specimen labeling with a recommendation to package biopsy specimens from different sides and different areas (e.g., base, mid-gland, and apex) in separate containers; however, core specimens from the same area should be packaged in the same container. This group also suggests that specimens from different sides and areas be labeled and that no more than two or three specimens be placed in the same container.

PURPOSE OF THIS REVIEW

We undertook a review of the literature to address the following primary objectives:

1. Define the optimal number and location of biopsy cores during primary prostate biopsy among men with suspected prostate cancer. In doing so, we address the CDR, NPV, detection of clinically insignificant cancer, and pathologic concordance with radical prostatectomy (RP) pathology results for each biopsy strategy.

2. Define the optimal method of labeling prostate biopsy cores for pathologic processing that will provide relevant and necessary clinical information for all potential clinical scenarios.

3. Determine the maximal number of prostate biopsy cores allowable within a specimen jar that would not preclude accurate histologic evaluation of the tissue.

Several indications for prostate biopsy exist, including primary biopsy at the time of suspicion of cancer; repeat biopsy for persistent suspicion or premalignant/atypical findings; surveillance biopsy for low-risk cancer; and staging biopsy for therapeutic planning or, most recently, focal ablation. Because the desired outcome of each biopsy indication is distinct, we focus our efforts on the primary (initial) biopsy among men with suspected prostate cancer due to elevated PSA, abnormal DRE results, or both. Although this review does not include studies involving a repeat biopsy, we do include studies that used an initial biopsy to locate the cancer for later verification and staging through a repeat biopsy. We also did not evaluate the additional value of nodule-directed or image-directed biopsies for this analysis. Given the lack of a community standard for image-directed biopsy, we assume that these additional samples are warranted and should be labeled and processed separately.

METHODS

We searched PubMed for English-language articles published between January 1, 1990, and December 31, 2011, with some targeted searches of articles published in January and February of 2012. We used combinations of the following key terms: prostatic neoplasms, biopsy methods, cores, saturation, sextant, clinical trial, meta-analysis, practice guideline, comparative study, consensus development conference, evaluation study, and multicenter study. This search yielded approximately 550 articles. We reviewed each of these articles to determine whether they met our inclusion criteria of describing a prostate biopsy protocol, availability of data on patients who had not had a previous prostate biopsy, indication of entry site, and availability of data on patients who underwent TRUS only if the study included TRUS and another biopsy entry site. We carried out additional searches to identify studies that used different biopsy strategies, including region-based and core number-specific sampling strategies.

Forty-five studies initially met the inclusion criteria for this review. We categorized these articles based on which of the three objectives of this review the articles addressed. We then extracted relevant data from each of these 45 articles, including details on biopsy protocol(s) used (such as number of cores and prostate regions from which cores were extracted), number and percentage of cancers found, average Gleason score for cancers found, specimen packaging and labeling techniques used, and outcomes of packaging and labeling protocols. We analyzed data from these studies to determine the influence of core number, core location, and saturation technique on CDR, NPV, surgical pathology concordance, and detection of insignificant cancers. We evaluated data regarding specimen processing to determine the influence of location-based labeling of cores on risk stratification, therapeutic planning, and assessment of biopsy adequacy.

We then conducted a second comprehensive search of PubMed using the following search terms: cancer detection rate, repeat biopsy, negative predictive value, pathology

concordance, insignificant cancer, apex, transition zone, lateral, extracapsular extension, surgical margin, and labeling. We did not limit publication dates for this second search. We screened the articles that resulted from this search to find studies not identified in the initial search and maximize inclusion of pertinent data, with an emphasis on clinical studies that address the three objectives of this analysis. We carefully examined all additional studies identified through this search to extract data that were relevant to prostate biopsy.

This report summarizes the results of our literature review and the data we extracted from the articles that met our eligibility criteria. We also provide recommendations based on this literature review and our clinical experience.

RESULTS

Numbers of Cores

Comparison of Standard Sextant to Extended-Core (10-12 Cores) Biopsy Protocols

Cancer Detection Rates

Comparisons of CDRs between standard sextant biopsy protocols and extended-core biopsy protocols (involving 10–12 cores) have demonstrated an overall trend of increasing CDRs with greater numbers of cores.

In a study comparing sextant biopsies to an 11-core approach (n=362), Babaian et al. reported a 33% increase in CDR (11). Durkan et al. (n=493) and Singh et al. (n=179) found similar trends, reporting CDR increases of 19% and 31%, respectively, when they used an extended 12-core prostate biopsy scheme as opposed to the standard sextant biopsy scheme (12, 13). In a large study of community-based urologists who performed the 12-core extended biopsy (n=2,299), Presti et al. confirmed the findings of academic centers that had reported that extended biopsies increased the CDR by 22% compared to the sextant strategy (14). When Elabbady et al. randomly assigned patients to a sextant (n=113) or 12-core biopsy scheme (n=176), they observed an 11.6% higher CDR with the extended-core strategy (24.8% vs. 36.4% for the sextant scheme, p=0.039) (15).

Gore and colleagues collected data on 396 consecutive patients (mean age 61.4 years, range 56–67 years) who underwent systematic sextant biopsy (16). Of these patients, 178 underwent systematic 12-core biopsies and 264 had not previously undergone prostate biopsy. The 12-core biopsies detected cancer in 43% of patients undergoing a first biopsy compared to 31% of patients for standard sextant cores. Philip et al. collected data on 445 new consecutive patients (mean age 64.5 years) undergoing biopsy and found CDRs of 23% and 32% for sextant and 12-core biopsies, respectively (17). Shim et al. evaluated 516 Korean men aged 40–79 years (mean age 64.1±7.8 years) who had not previously undergone prostate biopsy (18). The CDR for the standard sextant approach was 22%, compared to 28% for the 12-core approach. In a large review of 87 studies involving 20,698 patients, Eicher et al. found that an increased number of cores was significantly associated with a higher cancer yield (19). A 12-core biopsy scheme that included

laterally directed cores had a 31% higher relative predictive rate than the sextant scheme.

These data, taken together, demonstrate that extended prostate biopsy schemes increase CDRs compared to sextant biopsies by more efficiently sampling the prostate.

Negative Predictive Value: Avoidance of Repeat Biopsy

In addition to detecting cancer, the goal of a biopsy scheme should be to reduce the likelihood of a positive biopsy result in repeat sampling by increasing the NPV and reducing the number of false-negative results from the initial biopsy. Sextant biopsies have false-negative rates of 15–34% based on repeated biopsies and computer simulations (4, 20-24).

Simply by performing a second sextant biopsy during the same office visit, Levine et al. (n=137) increased the number of cancers detected by 30% (4). Hong and colleagues (n=218) demonstrated that prostate CDRs on repeat biopsy vary as a function of the extent of the initial biopsy (25). If a prior negative biopsy involved a sextant scheme, the CDR was 39% with a repeat extended biopsy, whereas if a prior negative biopsy involved an extended scheme, the CDR of the repeat biopsy decreased to 28%. Singh et al. evaluated 841 patients who had had an initial 12-core biopsy (13). Of these patients, 99 underwent a repeat 12-core biopsy after the initial biopsy result was negative because a physician continued to suspect that the patient had prostate cancer, and the CDR for these repeat biopsies was 21.2%.

Pathology Concordance

Several studies have demonstrated that extended biopsy schemes improve biopsy concordance with prostatectomy specimens. Concordance rates when an extended biopsy scheme is used range from 56% to 76%, compared to 41% to 63% with a sextant biopsy (26-29). When Mian et al. reviewed prostatectomy specimens (n=426) for biopsy concordance, the overall accuracy rates of the extended and sextant schemes were 68% and 48% ($P<0.001$), respectively (26). Upgrading of the Gleason score was significantly less likely with the extended scheme (17% vs. 41% for the sextant scheme, $P<0.001$). The sextant biopsy result was more likely to be upgraded for a Gleason score of 6 or less (44% vs. 25% for the extended scheme, $P<0.002$) and a Gleason score of 7 (14% vs. 3%, $P<0.02$) (26).

San Francisco et al. observed a similar concordance rate of 76% for extended needle biopsies (10 or more cores, n=126) compared with 63% for needle biopsies involving 9 or fewer cores (n=340, p=0.08) (28). Only 14% of the prostate cancers detected using extended biopsy schemes were under-graded compared to 25% of cancers detected using sextant schemes (p=0.01).

King et al. also reported improved biopsy grade concordance with a 10-core biopsy, which resulted in upgraded results for only 13% of patients who had undergone a prostatectomy, vs. 25% of patients who had a sextant biopsy (p=0.045), and in

downgraded results for 24% vs. 13% of patients, respectively (p=0.06) (30). Subset analysis by Gleason score demonstrated that for patients with a biopsy Gleason score of 6, a clinically significant upgrading occurred in 66.7% of cases with a sextant biopsy and 36.8% of cases with a 10-core biopsy (p=0.068). The primary Gleason grade was upgraded from 3 to 4/5 in 41.8% of sextant biopsy cases and only 25.5% of 10-core biopsy cases (p=0.078). When Elabbady et al. evaluated concordance rates of Gleason scores from biopsies and prostatectomies (n=289), they found an 85.2% agreement rate using a 12-core biopsy scheme compared to a 50% agreement rate using a sextant biopsy scheme (p=0.026) (15).

These data demonstrate that prostate cancer grading by extended needle biopsy is a better predictor of the final Gleason score than sextant needle biopsy.

Insignificant Cancer Detection

A potential drawback of the extended-core biopsy scheme and the resulting increased CDR is the increased likelihood of detecting insignificant prostate cancers. In a study of 179 prostatectomy specimens from men who underwent a 12-core extended biopsy, Singh et al. observed that the rate of clinically insignificant prostate cancer was 11.9% higher than with the sextant biopsy scheme (13).

However, several other authors found no significant differences in the detection rate of insignificant cancers. In a study comparing a 5-region, 13-core biopsy scheme to a sextant biopsy scheme (n=21), Eskew et al. found no difference in the rate of insignificant cancers detected by the two biopsy strategies (31). In a study to determine whether increased needle biopsy sampling detects a higher number of potentially insignificant cancers, Chen et al. reported that a 12-core biopsy scheme and the sextant strategy resulted in equivalent proportions of clinically insignificant cancers (32). 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 (33). When Siu et al. compared an extended-pattern biopsy scheme (10 or more cores) to the standard sextant scheme (n=740), they found no association between numbers of clinically insignificant prostate cancers detected and extended-pattern vs. standard sextant biopsy approaches (34).

Conclusions Regarding 12-Core Approaches

The use of 10–12-core extended-sampling protocols increases CDRs compared to traditional sextant sampling methods and reduces the likelihood that patients will require a repeat biopsy by increasing the NPV. More accurate grade concordance with RP is observed, thereby allowing more accurate risk stratification among men with cancer diagnosed by 12-core protocols. The use of 12-core extended-biopsy protocols does not appear to increase the likelihood of detecting insignificant cancers compared to traditional sextant methods.

<u>Comparison of Protocols Involving More than 12 Cores with 12-core Protocols</u>

Cancer Detection Rates

The improved CDRs that result from extended biopsy schemes compared to standard sextant approaches have prompted evaluations of whether even higher numbers of initial biopsy cores would increase CDRs even more. For the purpose of this document, saturation biopsy was performed using the transrectal approach.

For example, several researchers have evaluated the utility of an 18-core or saturation biopsy as an initial biopsy strategy. Scattoni et al. (n=1,684) did not observe a difference in the overall CDR of an 18-core biopsy scheme (n=1,776) (39.9%) compared to a 12-core biopsy strategy (38.5%, p=0.37) (35). They did, however, find that an 18-core prostate biopsy strategy detects a significantly higher number of cancers only in patients with a prostate volume of 55 cc or greater. De La Taille et al. (n=303) found that the CDRs using sextant, extended 12-core, 18-core, and 21-core biopsy schemes were 22.7%, 28.3%, 30.7%, and 31.3%, respectively (36). 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. Similar results were reported by Pepe et al. (n=189), who found that the CDR for an initial 12-core biopsy scheme (39.8%) was not significantly different from the CDR for a saturation biopsy with a median of 29 cores (49.0%, p=0.6) or an 18-core biopsy (39.8%, p=0.3) (37).

When Jones and colleagues studied the utility of an office-based saturation biopsy for initial biopsy in sequential cohorts, CDRs were similar in patients undergoing a 24-core saturation scheme (45%) compared with a 10-core scheme (52%, $p \geq 0.9$) (38). This trend was corroborated in a large study by Guichard et al. (n=1,000), who also found no significant gain in CDR when a 21-core biopsy scheme (42.5%) was chosen over an 18-core or a 12-core biopsy scheme (41.5 and 38.7%, respectively) (39). When Ploussard and colleagues compared CDRs in 2,753 consecutive patients, CDRs using sextant, 12-core, and 21-core schemes were 32.5%, 40.4%, and 43.3%, respectively (40). The 12-core procedure improved the CDR by 19.4% (p=0.004) compared to the sextant approach, and the 21-biopsy scheme improved the CDR by 6.7% overall ($p<0.001$). In a large review of 87 studies of 20,698 patients, Eichler et al. determined that taking more than 12 cores did not significantly improve cancer yield (19).

These data demonstrate that increasing the number of cores taken during prostate biopsy has a trend toward increasing CDRs but the increase in yield is not significant after the number of cores reaches 10 to 12.

Negative Predictive Value: Avoidance of Repeat Biopsy

Extended-core biopsies have been used for both initial and repeat biopsies for cancer detection. Researchers have also examined saturation biopsy schemes as an initial strategy to increase CDR after a negative extended biopsy in patients whose physicians still suspect that they have prostate cancer and after an initial saturation biopsy.

Singh et al. reviewed 841 patients who underwent an initial extended 12-core biopsy with a CDR of 37.1% (13). Of these patients, 99 underwent a repeat extended 12-core biopsy after the initial biopsy results were negative. The CDR for the repeat 12-core biopsy was 21.2%. Lane et al. (n=257) evaluated their experience with patients who underwent a repeat saturation biopsy (24 cores) for persistently elevated PSA or abnormal DRE after an initial saturation biopsy (41). The CDR was 24%, which was similar to the CDR of 29% for biopsies following an initial sextant biopsy (p=0.08). The authors concluded that the false-negative rate for repeat prostate biopsies after an initial saturation biopsy is equivalent to that following traditional biopsy and they recommended against saturation prostate biopsies as an initial strategy.

Pathology Concordance

Biopsy schemes involving more than 12 cores have been evaluated with the goal of increasing prostatectomy concordance.

Kahl et al. evaluated the concordance of results from prostatectomy and biopsy schemes involving more than 12 cores (n=185) and 12 or fewer cores (n=55) in 240 patients (42). They found that a biopsy scheme using more than 12 cores better predicted the final Gleason score (59%) than a scheme involving fewer than12 cores (47%, p=0.05) In a similar study, Antunes et al. found no differences in the concordance rates of biopsy specimens using schemes involving 6, 8, and 10 or more cores with prostatectomy specimens (P=0.18) (43). A subset analysis found an increase in concordance in men with a prostate volume of less than 50 cm^3 (p=0.03). Delongchamps and colleagues compared the results of a 36-core saturation biopsy scheme with those from autopsied prostate glands (n=48) and determined that saturation biopsies might overestimate the final Gleason score on whole-mount analysis (44).

Insignificant Cancer Detection

Ploussard et al. (n=2,753) compared the results of a 21-core biopsy scheme for the first set of biopsy specimens to sextant and 12-core schemes (40). The rates of detection of insignificant cancers were 4.2%, 7.2%, and 8.3% for sextant, 12-core, and 21-core approaches, respectively. The 21-core protocol significantly increased the rate of prostate cancers eligible for active surveillance (62.5% vs. 48.4%, p=0.036) compared to the rate detected by a 12-core scheme without significantly increasing the rate of insignificant prostate cancers detected (p=0.503). When Haas et al. performed 18-core needle biopsies on autopsied prostates (n=164) from men without a history of prostate cancer, they showed that an extended-biopsy 18-core strategy increased the detection rate of insignificant prostate cancers by 22% (45).

To compare the CDRs of extended-core and saturation biopsy schemes on repeat prostate biopsy, Zaytoun et al. evaluated 1,056 men who underwent prostate biopsy after a negative initial biopsy (46). In this study, 393 men underwent an extended repeat biopsy (12–14 cores) and 663 men underwent a saturation repeat biopsy (20–24 cores). Saturation repeat biopsy detected almost one third more cancers than extended repeat

biopsy (32.7% vs. 24.9%, p=0.0075). In patients with a benign initial biopsy, saturation biopsy identified significantly more prostate cancers (33.3% vs. 25.6%, p=0.027). Saturation biopsy revealed clinically insignificant cancer in 40.1% of the 315 men in whom repeat biopsy detected prostate cancer compared to 32.6% in men who had an extended biopsy (p=0.2).

Conclusions Regarding Biopsies Involving More than 12 Cores

As the number of cores increases, the diagnostic yield becomes more marginal. Only limited evidence supports the use of initial biopsy schemes involving more than 12 cores or saturation. CDRs do not appear to increase significantly, and likewise, NPV does not appear to increase when more than 12 cores are sampled. The results of biopsy schemes involving more than 12 cores or saturation biopsies appear to have a higher concordance rate with results from prostatectomy, but they also appear to increase the rate of insignificant cancer detection.

CORE LOCATION

Several studies have evaluated the effect of core location on CDR. Much of this literature has focused on samples from the far-lateral region, apex, and transition zone. Studies of anterior prostate cancer distribution in RP specimens demonstrate that tumor frequency is highest in the mid-gland (85.5%), followed closely by the apex (82.3%) (47). Because these regions are common locations for missed cancers on repeat biopsy, we evaluated the independent effects of primary biopsy cores from these regions on CDR.

Apex

Cancer Detection Rates

Several investigators have reported on various extended biopsy schemes involving cores from the apex. Babaian et al. evaluated an 11-core biopsy strategy in 362 patients, including 85 (23%) who were undergoing a first biopsy (11). The biopsy scheme included cores from the standard sextant, bilateral anterior horn (far-lateral region), bilateral transition zone, and midline. The CDR for patients undergoing an initial biopsy was 34%, and 9 cancers were uniquely identified by non-sextant sites (increasing CDR by 31%). 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. Meng et al. (n=255) studied a 12-core scheme involving the standard sextant and lateral mid-gland, lateral base, and anterior apex (48). Cores from the anterior apex contributed uniquely to cancer detection in 6% of men with a normal DRE and a prostate size of 50 cc or smaller. A study by Orikasa et al., which had similar results, found that 5.2% of 252 men with a positive extended 12-core biopsy result had cancer exclusively in the anterior apical peripheral zone cores (49). When Wright and Ellis evaluated the location of prostate cancers found using a 12-core biopsy scheme, the most common site of isolated disease was the anterior apex; 17% of

cancers in this site would have been missed if these areas had not been biopsied (50). Moussa et al. (n=181) prospectively evaluated men undergoing a 12-core biopsy with 2 additional cores from the extreme anterior apex (51). The apical cores achieved the highest CDR (73.6% of all cancers), and the additional extreme anterior apical cores (one on each side) achieved the highest rate of unique cancer detection (P=.011).

Negative Predictive Value: Avoidance of Repeat Biopsy

To determine the benefit of sampling the anterior apical peripheral zone on repeat biopsy, Orikasa et al. evaluated extended 12-core repeat biopsies, including 6 anterior apical peripheral zone cores sites, in 118 men (49). The repeat 12-core biopsy identified 9 men (36.0%) with cancer exclusively in the anterior apical peripheral zone cores. The CDR from the anterior apical peripheral zone sites was significantly higher in the repeat biopsies than in the initial biopsies ($P<0.01$), suggesting a predominance of missed cancers in this location. Based on their finding that apical cores achieved the highest CDR (73.6% of all cancers) and the additional extreme anterior apical cores achieved the highest rate of unique cancer detection (P=.011), Moussa et al. concluded that apical cores, especially the extreme apical cores, increase CDR and minimize the potential for misdiagnosis and need for repeat biopsy (51).

Pathology Concordance

There is a paucity of data on concordance rates of Gleason scores from apical needle biopsies and final prostatectomies. Rogatsch et al. evaluated 240 individually labeled, preoperative apical core biopsies and corresponding prostatectomy specimens from 120 patients who underwent RP for clinically localized prostate cancer (52). 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%. In this context, the predictive value of an individual positive apical core biopsy was only 28.8% for surgical margin (SM) positivity at the apex.

Insignificant Cancer Detection

When Wright and Ellis evaluated the benefit of apical core biopsies (n=164), they observed that the most common unique site of cancer was the anterior apex (50). In this study, which included initial and repeat biopsies, 16.7% of anterior/apical biopsy specimens had a Gleason score of less than 6, 66.7% had a Gleason score of 6, 16.7% had a Gleason score of 7, and no specimens had a Gleason score of 8–10.

Conclusions

The apex is a common site of cancers detected by traditional biopsy and of missed cancers found on repeat biopsy. For this reason, apical sampling appears to increase CDR and reduce the need for repeat biopsies. Furthermore, apical sampling predicts a high likelihood of apical disease on radical resection.

Transition Zone

Cancer Detection Rates

The rationale for transition-zone biopsies stems from the observation is that 15–25% of prostate cancers are located anteriorly within the transition zone (53-55). In the late 1980s, McNeal et al. reported a 24% cancer rate in the transition zone in a study of 104 prostatectomy glands (53). Biopsy results, however, have not reflected this rate of cancer detection. Bazinet et al. (n=847) reported that only 2.9% of their patients had cancer exclusively in the transition zone on first biopsy (56). The remaining 97.1% had one or more positive peripheral-zone biopsies and these cancers would have been detected without additional systematic transition-zone biopsies. Fleshner and Fair did not identify any cancers exclusive to the transition zone on initial biopsy (57). Other researchers have also found that initial diagnostic transition-zone biopsies have a low CDR (58-61). These results were corroborated in a retrospective analysis of data from a PSA screening study in which only 1.8% of prostate cancers originated exclusively from the transition zone (62). However, in a prospective study of 1,000 men, Guichard et al. did find a significant improvement in CDR (by 7.2%, p=0.023) with the addition of transition-zone biopsies to a 12-core scheme, for an overall CDR of 41.5% (39).

Negative Predictive Value: Avoidance of Repeat Biopsy

Because relatively few cancers are found uniquely in the transition zone, it is unlikely that repeat biopsies would be avoided by routine transition-zone sampling. To evaluate the role of transition-zone sampling on initial and repeat biopsy, Terris et al. compared 736 consecutive patients undergoing routine sextant biopsy with 161 men subsequently biopsied with sextant, transition-zone, and seminal vesical sampling (58). The results showed no difference in the number of men from each group requiring a repeat biopsy (3.3% vs 2.5%, p=0.601). Interestingly, only one cancer was identified in the transition zone uniquely.

Pathology Concordance

Few studies have evaluated the concordance of tumor grade from prostate needle biopsies of the transition zone and prostatectomy specimens. Some studies have, however, reported low rates of concordance between cancers in the transition zone detected by needle biopsy and final prostatectomy. Two studies in which the only cancer detected on needle biopsy was in the transition zone showed that cancer was isolated to the transition zone upon final prostatectomy evaluation in very few cases (62, 63). When Haarer et al. compared the results of transition zone-directed needle biopsies with those of corresponding RP specimens from 61 men, cancer concordance rates ranged from 21% to 39.5% (64). Cancers identified in transition zone-directed needle biopsy cores were not

from the transition zone or did not reflect a dominant transition-zone lesion in almost 80% of cases. Cancers identified in a left or right transition zone-directed needle biopsy did not predict ipsilateral transition-zone cancer in almost 50% of cases.

Insignificant Cancer Detection

Because transition-zone biopsies have a low CDR, they have a low probability of detecting insignificant cancers. Fleshner et al. reported that 8 of 156 patients (16%) had an isolated transition-zone tumor based on a repeat prostate biopsy that included transition-zone cores after a prior negative peripheral biopsy (57). Of the tumors in these 8 men, one had a Gleason score of 7 and one had a Gleason score of 8. Similarly, Bazinet et al. found that the median Gleason score was 7 for isolated transitional tumors in 8 of 277 patients with cancer (2.9%) who had a single positive core, and 51.6% of the core was carcinoma (8 of 847 overall) (56).

Conclusions

Taken together, these findings indicate that transition-zone biopsies do not improve prostate CDR at initial extended biopsy and do not appear to reduce clinical NPV. Pathology concordance and the significance of detected cancers have not been well studied but these issues have little relevance because of the low CDR of transition-zone sampling.

Far-Lateral Zone

Cancer Detection Rates

Based on the observation that laterally directed sextant cores result in higher CDRs (2), Presti and colleagues (n=483) and Ravery et al. (n=303) examined the extended 12-core approach (65, 66). Both studies found that the addition of laterally directed biopsies of the base, mid-gland, and apex resulted in a 14–17% increase in the CDR (65, 66).

Chang et al. (n=273) found that the CDR increased by 14% when they added 4 lateral biopsies to the standard sextant, and the lateral biopsies detected 70% of the cancers found (67). When Presti et al. sampled the lateral peripheral zone at the base and mid-gland in addition to the sextant, they found that the lateral sextant approach outperformed the traditional mid-lobar sextant approach (88.6% vs. 79.7%, respectively, p=0.027) (66). Gore and colleagues evaluated a 12-core biopsy scheme in 396 patients that included a complete set of laterally directed cores (16). In the 264 (67%) patients undergoing a first biopsy, the CDR was 42%, and standard sextant biopsies would have detected only 71% of the cancers in this group. The lateral sextant biopsy scheme along with the apical and base biopsies from the standard sextant scheme detected all of the cancers in this subgroup. A laterally directed 12-core extended biopsy also detected 31% more cancers than the sextant scheme in a large review (19). Guichard et al. corroborated these findings

in a prospective study of 1,000 men that found that the CDR increased from 31.7% with the sextant biopsy to 38.7% when lateral-directed biopsies were added ($p<0.0001$) (39).

Negative Predictive Value: Avoidance of Repeat Biopsy

Few studies have evaluated the NPV of far-lateral sampling of the prostate. However, lateral sampling appears to improve clinical NPV because several cancers are identified only in the lateral sample.

Pathology Concordance

To determine the role of lateral sampling of the prostate, Singh et al. studied 178 consecutive men whose prostate cancer was diagnosed during an initial systematic 12-core biopsy and who subsequently underwent RP (68). The authors analyzed subsets of the 6 traditional sextant cores, 6 laterally directed cores, and complete 12-core set. Multivariate analysis showed that laterally directed cores were independent predictors of pathological features at prostatectomy. The authors concluded that the addition of 6 systematically obtained, laterally directed cores to the traditional sextant biopsy improved the ability to predict pathological features at prostatectomy by a statistically and prognostically significant margin.

Insignificant Cancer Detection

Presti et al. demonstrated that the majority of cancers detected by lateral biopsies of the peripheral zone were not significant, although they did not describe all of the parameters of these tumors (66). In a study that evaluated cores from the anterior lateral horns of the peripheral zone, Miyake et al. found that the rates of insignificant cancers detected were similar, regardless of whether the specimens came from the sextant, anterior lateral horn of the peripheral zone, or both (69). The authors concluded that sampling biopsy cores from the anterior lateral horns does not appear to increase the detection of potentially insignificant cancers.

Conclusions

Laterally directed sampling of the peripheral zone improves CDR and clinical NPV because several cancers are identified only in the lateral sample. In addition, laterally directed sampling of the peripheral zone improves the ability to predict pathological features on prostatectomy and does not increase the rate of insignificant cancers detected.

SUMMARY OF BIOPSY RECOMMENDATIONS

The differences in populations studied makes comparing the results from the studies of protocols involving different numbers of cores challenging. Patient age, serum PSA, ethnicity,

and family history all influence CDR for any biopsy strategy. What can be concluded from the literature is that increasing core number increases CDR and sextant biopsy results in an unacceptably high likelihood of false-negative results, leading to underdetection of clinically significant cancers. Increasing core numbers using saturation techniques might identify cancers missed on extended core sampling but this strategy also increases the risk of overdetection of indolent cancers without significantly improving CDR or pathology concordance.

In selecting locations for sampling, clinicians should use templates that incorporate adequate sampling of the apex or anterior apex; the far-lateral region, including the base, mid-gland, and apex; and the traditional sextant sites. Transition-zone sampling does not have a substantial impact on CDR, NPV, or predictive ability. The use of a 12-core sampling strategy that incorporates apical and far-lateral cores appears to be optimal for CDR, NPV, and pathology concordance.

SPECIMEN PROCESSING FOR ANALYSIS

In processing prostate biopsies for pathologic analysis, urologists must choose the number of cores to place in each specimen container and the optimal method of labeling these cores to indicate the prostate site from which the cores were extracted. Several factors can have an impact on urologists' decisions, including the influence of cancer location on therapeutic planning and surveillance, quality of pathology analysis when multiple cores are placed in a single container, and assurance of biopsy quality through identification of core location. The first two factors can be critically assessed from the existing urologic and pathologic literature.

For the latter factor, the importance of individually labeling core location might only be meaningful if individual cores are deemed non-informative or substandard for processing. If cores are grouped together, urologists cannot determine whether any region of the prostate was under-sampled. Because the importance of apical and far-lateral sampling is well demonstrated in the existing literature, assessment of biopsy adequacy would seem to require, at least, demonstration of adequate sampling of these regions.

Importance of Clinical Information Derived from the Labeling of Cores

Prediction of Extracapsular Extension (ECE)

Taneja et al. retrospectively compared the results of the diagnostic biopsies of 243 men undergoing RP with their final surgical pathology results (70). In this study, 103 men had individually labeled cores for specimen processing and only the right and left cores from the remaining 141 were labeled. The presence of cancer in an individually labeled core was associated with an 8.9±2.2% PPV and 96.9±1.4% NPV for the ECE location compared to a PPV of 12.9 ±3.0% and NPV of 95.8±1.8% when cores were packaged in two containers. The authors concluded that packaging cores in individual containers is substantially more expensive than packaging samples in just two containers without providing much clinical benefit.

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. Naya et al. demonstrated that the number of positive ipsilateral cores, ipsilateral biopsy Gleason score, a positive core at the basal region, and cancer core volume higher than 50% or a maximum tumor length of at least 7 mm increased the likelihood that ECE was present at the posterolateral region on that side (71). Multivariate analysis showed that maximum tumor length of at least 7 mm and positive basal core location were the strongest independent predictors of ECE on a side ($p<0.0001$ and 0.002, respectively). In a review of 2,660 cases, Tsuzuki et al. demonstrated that the percentage of side-specific cores with tumor (greater than 33.3% vs. 33.3% or less) and average percent involvement of each positive core (greater than 20% vs. 20% or less) were independent predictors of neurovascular bundle penetration in multivariate analysis (72). Ohori et al. demonstrated that a nomogram constructed with biopsy core laterality only could accurately predict the laterality of ECE (73).

In a study of 124 patients who underwent RP for clinically localized cancer diagnosed using individually labeled sextant cores, Tombal et al. concluded that the topography of the positive biopsies was predictive of ECE (74). In patients with 2 or 3 positive sextants, a greater likelihood of organ-confined disease was observed if the cores were from adjacent locations ($p<0.01$). However, the number and topography of positive sextants and the percentage of positive cores correlated almost linearly, suggesting on first analysis that identifying the exact position of the biopsy has no benefit. In a separate study of 223 men undergoing RP, the best predictors of the risk of ECE on a side were an average percentage of biopsy cores positive for cancer overall of 15 or greater (odds ratio 8.4, $p<0.0001$) and an average from 3 ipsilateral biopsies of 15 or greater (odds ratio 7.4, $p<0.0001$) (75). The sextant-specific percentage of biopsy cores positive for cancer predicted risk of ECE in a sextant (odds ratio 2.5, $p<0.020$).

Other researchers have evaluated the importance of base and apical positive core sampling. Badalament et al. demonstrated that, in decreasing order, quantitative nuclear grade, preoperative PSA, total percent tumor involvement, number of positive sextant cores, preoperative Gleason score, and involvement of more than 5% of a base and/or apex biopsy were significant ($p \leq 0.006$) for predicting disease organ confinement status (76). Kamat et al. showed that a core tumor length of 7 mm and a positive basal biopsy core of any tumor length and tumor grade predict ipsilateral extraprostatic extension (EPE) (77). In a separate study of 371 men, a positive biopsy at the apex was not predictive of a positive apical SM or EPE, but a positive biopsy at the base was predictive of a positive basal SM and EPE (78). A positive SM, in turn, correlated with EPE on final pathology. A positive basal SM correlated with EPE in 75% of cases, whereas a positive apical SM showed EPE in only 33% of cases ($P<0.02$).

Prediction of Surgical Margin Status

The location of cancer can influence the likelihood of a positive SM at the time of resection. The ability of a positive biopsy location to predict the risk of SM violation probably depends on the predictive accuracy of the biopsy with regard to location. Rogatsch et al. evaluated the presence of apical prostate cancer in the final surgical

specimens of 240 men with individually labeled, preoperative apical core biopsies from a 10-core extended biopsy conducted prior to RP (52). The PPV of a single positive apical core for identifying tumor location correctly in the prostatectomy specimen was 71.1%, whereas the absence of cancer in the apical biopsy had an NPV of 75.5%. Sensitivity was 44.5% for a positive biopsy core. In this context, the predictive value of an individual positive apical core biopsy was only 28.8% for SM positivity at the apex. In a study of 280 RP specimens by Malavaud et al., positive apical biopsies were strongly linked to the occurrence of positive margins ($p<0.001$) (79).

Tigrani et al. demonstrated that men with three or more positive biopsies had a higher risk of a positive SM (P=0.009) (80). Also, only on univariate analysis, patients with bilateral positive biopsies in the prostate base and mid-gland had a higher frequency of a positive SM than those who had 0 or 1 positive biopsy in those regions (P=0.045 and P=0.015, respectively).

In a study of 242 men who underwent sextant biopsy prior to RP, multivariate logistic regression analysis was used to develop models for predicting positive bladder neck, apical, and right and left posterior margins (81). Patients with 3 or more positive cores who did not receive neoadjuvant androgen deprivation therapy had a higher incidence (24%) of positive apical margins. A nomogram incorporating pretreatment serum PSA, number of ipsilateral positive cores, and whether androgen deprivation therapy was used identified patients at high risk of positive posterior margins. In this study, the location of a positive biopsy core did not predict positive SM. Similarly, Huland et al. demonstrated that decisions about unilateral nerve sparing are most appropriately based on negative ipsilateral cores in cases of contralateral palpable disease (82). Others have also shown that biopsy laterality is a predictor of the ipsilateral positive SM (83).

Conclusions Regarding Individual Labeling of Biopsy Cores

Most of the literature reviewed for this paper does not suggest that knowing the exact site of an individual positive biopsy core provides meaningful clinical information for determining the location of ECE or a potentially positive SM. Such information might be useful for directing ablative or radiation-based therapeutic modalities to selective regions of the prostate, but the value of these data are limited due to the variable methodologies employed to obtain core samples. The subjective nature of selecting base, mid-gland, and apical locations for biopsy probably contributes to the inability of core location to accurately predict disease location. The literature does strongly support the necessity of determining the laterality of cancer on biopsy for both predicting sites of ECE and therapeutic planning.

Influence of Core Number on Pathologic Analysis

A substantial literature suggests that placing more cores in a specimen container reduces the likelihood of cancer detection and the accuracy of cancer assessment, possibly because of tissue tangling, fragmentation, and inability to align tissue fragments at the time of sectioning (fig. 1).

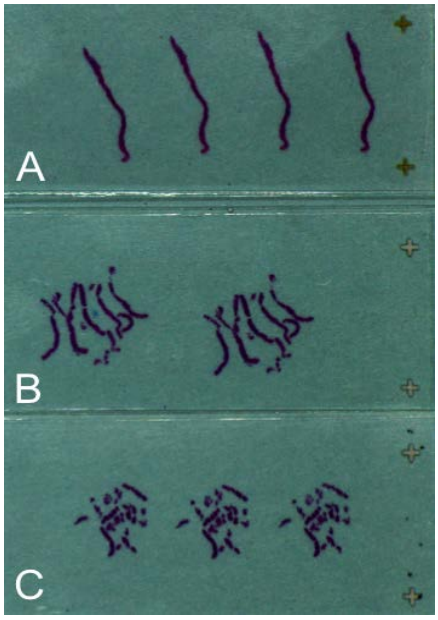

Figure 1.

One prostate biopsy core submitted in one specimen container and embedded in one cassette (A). Multiple prostate biopsy cores submitted in the same specimen container and embedded in one cassette (B, C). (Image courtesy of Ming Zhou MD, PhD, Department of Pathology, New York University).

In a retrospective analysis of data on 1,448 men who underwent a 6–12-core prostate needle biopsy, Gupta et al. compared 515 biopsy specimens submitted in 1 or 2 containers to 933 biopsy specimens submitted in 6–12 containers (84). Monthly equivocal diagnoses were less frequent in the 6–12-container group than in the 1–2-container group (2.8% vs. 6.0%, respectively, p=.003). The use of 6–12 containers also significantly reduced rates of atypical glands suspicious for adenocarcinoma (p=0.042) and high-grade prostatic intraepithelial neoplasia with adjacent atypical gland suspicious for adenocarcinoma (p=0.038) compared to the 1–2-container group.

Reis et al. demonstrated that pathologists often receive more cores than the number sampled by the urologist and suggested that these changes are due to core fragmentation (85). In their study, biopsies resulted in 21.54 (±3.56) cores, whereas pathologists examined 24.08 (±4.77, P<0.01) cores. Core numbers by all prostate gland areas (such as right and left base, mid-gland, and apex) were statistically different between biopsy and pathological examination reports (P<0.01).

Fajardo et al. also evaluated factors that can lead to core fragmentation (86). They examined 463 biopsies that contained prostatic adenocarcinoma in fragmented cores, as well as 200 control sets lacking fragmented cores. The mean number of cores per specimen container was significantly higher in the fragmented group than in the unfragmented group (2.6 vs. 2.1, respectively, P=0.004). The mean number of containers with cancer in the fragmented group was significantly higher, at 2.8 (1–13), than in the unfragmented group, at 1.6 (1–13, P < 0.001). Mean Gleason score was 6.6 (6–10) in the fragmented group and 6.2 (6–10) in the unfragmented group, P<0.001. The authors

concluded that the number of cores per container, presence of cancer, and increased Gleason score all contribute to the likelihood of tissue fragmentation.

Despite the observation that the placement of multiple cores in a single container compromises pathologic evaluation, no consensus opinion exists on how many cores can be safely placed in a container to allow adequate pathologic analysis. Researchers have demonstrated that simultaneously including 3 biopsy cores in the same cassette can lead to the loss of a mean length of 1.15 cm of assessable tissue, which corresponds to the average length of one prostate biopsy (87). In addition, computer simulation of a biopsy demonstrated that packaging multiple ipsilateral biopsies in a single container often entangles the specimens and can result in loss of 40% of the tissue surface area with only a 5-degree shift in the angle of the needle biopsy within the tissue block. This probably increases the rate of equivocal biopsies, resulting in the need for repeat biopsies (88).

Some authors have proposed alternative methods to overcome tissue entangling and fragmentation. Pre-embedding cores in multipacks led to a higher frequency of cancer diagnosis, reduction in the number of cases with atypical foci, and significantly lower number of cancers diagnosed in only one core (52). Firoozi et al. bundled two adjacent cores in a single container and marked the lateral core in each container with India ink (89). Thirteen of 64 (20%) men undergoing RP had ECE and 10 (15%) had a positive SM. The location of ECE and positive SM on whole-mount specimens correlated with a positive biopsy site in 70% and 60% of men, respectively. The tissue-labeling protocol used did not increase procedure time or introduce any tissue artifacts.

RECOMMENDATIONS

An optimized diagnostic prostate biopsy allows maximal cancer detection, avoidance of a repeat biopsy, and adequate information for both identifying men who need therapy and planning that therapy. Ideally, such a biopsy minimizes the detection of occult, indolent prostate cancers that are unlikely to reduce the patient's longevity.

In performing a biopsy, these goals appear to be best achieved through a 12-core systematic sampling methodology that incorporates apical and far-lateral cores in the template distribution. The results of our literature review suggest that collecting more than 12 cores or sampling the transition zone offer no benefit for initial diagnostic biopsies. However, such approaches might be useful for resampling following a negative biopsy, when indicated, and for planning the use of novel therapeutic approaches, such as focal ablation. In some cases, at the discretion of the individual urologist, less rigorous sampling might be indicated. Simple sextant biopsies might be sufficient to obtain tissue confirmation for a diagnosis in obvious locally advanced or metastatic disease.

The optimal methodology for processing and analyzing prostate biopsies allows adequate tissue evaluation, cost-effectiveness, and sufficient information regarding the location of cancer to support therapeutic planning and risk stratification. A recent criticism of individual labeling of site-specific biopsies has suggested that referrals of biopsy specimens by urologists to pathology

facilities in which they hold financial equity increases costs and numbers of specimens per biopsy without benefiting patients (90).

Site-specific labeling of biopsy cores, in theory, makes possible disease location assessment, assurance of biopsy adequacy, risk stratification, and, in some cases, collection of information that is important for planning therapy. Studies have shown that site-specific labeling of disease sites increases the likelihood of cancer detection during follow-up of men on active surveillance. Although this approach might detect occult high-risk disease, sampling of the remaining prostate through saturation might have the same detection ability.

It is evident from the existing literature that subjectivity in the selection of biopsy sites greatly lowers the predictive value of the biopsy with regard to cancer location. This literature review does not provide compelling evidence that individual site-specific labeling of cores benefits clinical decision making regarding the management of prostate cancer. Site-specific labeling does, however, provide some baseline data regarding the general location and extent of disease and evidence of the adequacy of the biopsy. Obtaining data regarding laterality appears to be essential for predictive nomograms and therapeutic planning.

Of all locations in the prostate, the existing literature suggests that disease in the apex, when present, is the most critical to detect. Apical sampling provides reliable data regarding cancer location and can suggest a greater likelihood of EPE. Base sampling can also suggest a greater risk of ECE. Information from these locations can influence both surgical and ablative treatment planning. Similarly, samples from far-lateral locations are important for some nomogram-based predictors of ECE and, when added to data from lateral zones, can influence decisions regarding nerve-sparing interventions. Importantly, when repeat biopsies are considered, assurance that the far-lateral region and the apical region were sampled appears to be essential because disease in these sites is frequently missed on first biopsy. For these reasons, labeling of these regions appears to be essential for clinical decision making.

The pathology literature suggests that increasing the number of cores in a specimen jar leads to increased tissue fragmentation, tangling of cores, and reduced tissue sampling, which can reduce CDRs and increase the likelihood of equivocal diagnoses (such as atypical small acinar proliferation). Although the literature does not identify the maximum number of cores that should be packaged in a single container, including fewer cores in each container appears to improve detection outcomes. We recommend packaging no more than two cores in each jar based on our assessment of the literature. Site-specific knowledge of disease location can be obtained by inking one of the two cores in the specimen without affecting the quality of the tissue assessment.

If cores are not individually labeled, specimen numbers per jar can be reduced using a strategy for grouping cores when submitting specimens. One potential labeling strategy when packaging up to two cores in each jar is to separate cores from the right and left lobe and label those from the base (one core), mid-gland (one core), apex (two cores, from the medial and lateral locations), and far-lateral zone (two cores, from the mid-gland and base) (fig. 2A). When this strategy is used, eight specimen jars containing no more than two cores per jar are submitted. An alternative methodology is to use six specimen containers, each containing two cores, for the

medial and lateral locations in the base, mid-gland, and apex on each side (fig. 2B). Inking the lateral core in each container can provide additional information. One core in the jar for orientation could, in fact, be inked when using any grouping method. Additional containers with image-directed samples or nodule-directed samples might be indicated in some cases.

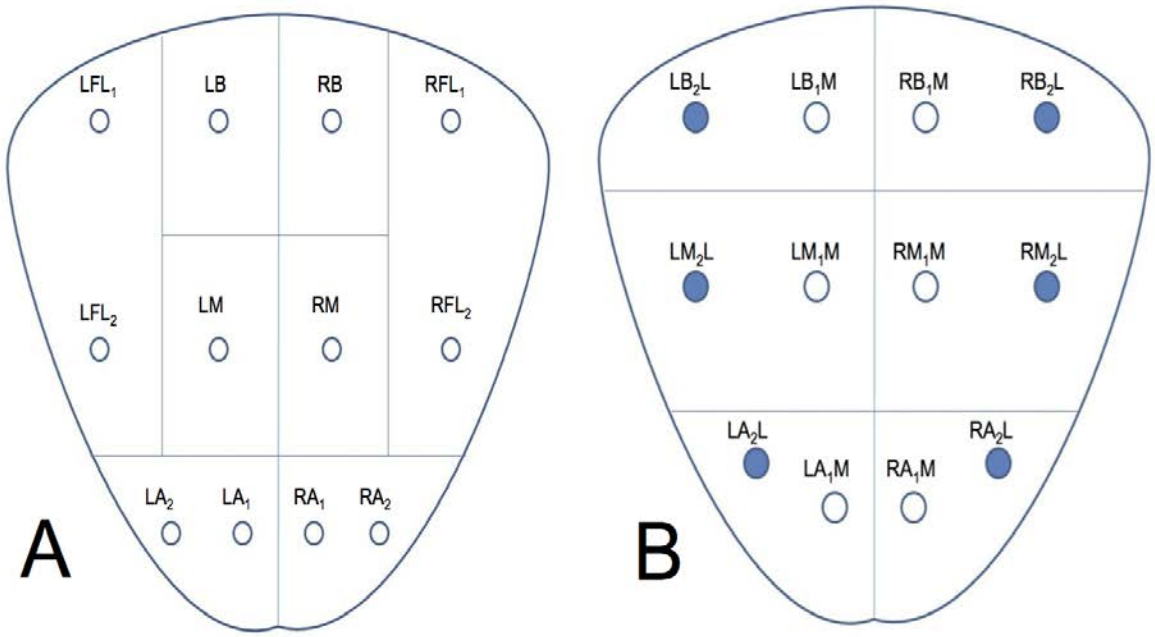

Figure 2.

Potential labeling strategies when packaging up to two prostate biopsy cores in a single specimen container using a total of either 8 (A) or 6 (B) containers. Inking the lateral core in each container can provide additional information regarding orientation (B). LFL; left far lateral, RFL; right far lateral, LB; left base, RB; right base, LM; left mid, RM; right mid, LA; left apex, RA; right apex, LBL; left base lateral, RBL; right base lateral, LML; left mid lateral, RML right mid lateral, LMM; left mid medial, RMM; right mid medial, LAL; left apex lateral, RAL; right apex lateral, LAM; left apex medial, RAM; right apex medial.

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ACRONYMS & ABBREVIATIONS LIST

CDR	Cancer detection rate
DRE	digital rectal examination
ECE	extracapsular extension
EPE	extraprostatic extension
NCCN	National Comprehensive Cancer Network
NPV	negative predictive value
PPV	positive predictive value
PSA	prostate-specific antigen
RP	radical prostatectomy
SM	surgical margin
TRUS	transrectal ultrasound

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