



Faith Krucina. *Tribute to Grover*. Acrylic on canvas, 48" × 36". Courtesy of Artistic Images by Faith, Dunedin, Fla.

*Transrectal ultrasound is
a vital component of
systematic biopsy procedures
for suspected prostate cancer.*

Transrectal Ultrasound and Biopsy in the Early Diagnosis of Prostate Cancer

*Jeffrey C. Applewhite, MD, Brian R. Matlaga, MD, MPH,
David L. McCullough, MD, and M. Craig Hall, MD*

Background: *Historically, the prostate was evaluated for cancer by simple digital rectal examination, and biopsy to obtain a tissue diagnosis of cancer was performed blindly. The advent of ultrasound technology offered a new way to evaluate the prostate, and biopsy techniques were soon developed to incorporate ultrasound guidance.*

Methods: *The authors review the role of transrectal ultrasound (TRUS) of the prostate and ultrasound-guided biopsy of the prostate in the diagnosis of prostate cancer. These techniques are traced from their origins to the current standards of care, with attention paid to developments and controversies in recent literature.*

Results: *Early experience with TRUS led to the description of "classic" sonographic findings of prostate cancer. To obtain a tissue diagnosis of cancer, these regions were initially targeted in ultrasound-guided biopsies. Concomitant with the development of TRUS, though, was the development of the prostate-specific antigen (PSA) assay. Over the past decade, there has been a profound stage migration due to earlier detection of prostate cancer. Most patients now diagnosed with prostate cancer have no palpable abnormality or specific sonographic findings. In response, ultrasound-guided biopsies have become more systematic, rather than lesion-specific, in nature.*

Conclusions: *TRUS continues to play an important role in the evaluation of the prostate when malignancy is suspected. Although the optimal method of prostate biopsy is controversial, ultrasound is critical in ensuring accurate sampling of the gland.*

From the Department of Urology and Comprehensive Cancer Center, Wake Forest University Baptist Medical Center, Winston-Salem, NC.

Address reprint requests to M. Craig Hall, MD, Department of Urology, Wake Forest University Baptist Medical Center,

Medical Center Blvd, Winston-Salem, NC 27157-1094. E-mail: mchall@wfubmc.edu

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Introduction

Prostate cancer is the most commonly diagnosed cancer in American men, making this disease a significant public health issue. Unfortunately, the anatomic location of the prostate does not lend itself to straightforward examination. Historically, digital rectal examination has been the principal method of examination of the prostate. However, this technique has its own inherent limitations. The advent and refinement of ultrasound technology have provided a new, important method to examine the prostate. Transrectal ultrasound with prostate biopsy, a generally well-tolerated outpatient procedure, in conjunction with the development of serum assays for prostate-specific antigen (PSA), has resulted in an impressive change in the manner of diagnosis and stage presentation of men with prostate cancer.

Before Ultrasound: Digital Rectal Examination

Digital rectal examination (DRE) is the primary method of examination of the prostate. This technique allows the examiner to appreciate the gland's morphology, including any irregular, nodular, or indurated areas, that may be suspicious for malignancy. In 1971, Gilbertson¹ published a series of 5,856 men who underwent annual DRE as a screening for prostate cancer from 1948 through 1964. This study was the first of its type to document a survival advantage to DRE screening.

As a subjective examination, however, DRE has limitations. Not all prostatic malignancies are palpable on DRE.² When DRE findings are correlated to pathologic evaluation, understaging and overstaging are often found.³ Ultimately, DRE fails to detect a significant number of malignancies, and of those that it does detect, a significant number are at an advanced stage.

History of Transrectal Ultrasound

Transrectal ultrasound (TRUS) was initially described as a technique to evaluate rectal pathology.^{4,5} In 1963, Takahashi and Ouchi⁶ were the first to describe the use of TRUS to evaluate the prostate. However, medical ultrasound was rather primitive at this time, so the images created with this array were of such poor quality that they carried little medical utility.^{6,7} The first clinically applicable images of the prostate obtained with TRUS were described in 1967 by Watanabe et al.⁸ They used a 3.5 MHz transducer, which at that time was considered to be state of the art, to obtain images that were clinically meaningful. As ultrasound technology

has become more refined, the use of TRUS in the evaluation of prostatic disease has increased. By the mid 1980s, the 7 MHz ultrasound probe, which more clearly delineated the architecture of the prostate, had become a standard diagnostic instrument of the urologist.

History of TRUS-Guided Prostate Biopsy

Ferguson⁹ performed the first prostate needle biopsy in 1930. He described a transperineal approach with an 18-gauge needle in which he aspirated a sample of prostate tissue. Astraldi¹⁰ performed the first transrectal biopsy in 1937. In the mid 1980s, a transperineal ultrasound array was fitted with biopsy apparatus to allow direct correlation of the sonographic appearance of focal prostatic lesions with the histology of these lesions. Several years later, a spring-loaded core biopsy device was developed that operated via a TRUS probe.

In 1987, the first literature appeared describing the use of TRUS with transrectal biopsy. Since then, as ultrasound technology has become more refined, this technique has been described as a superior method of performing a core biopsy of the prostate.¹¹

Since the initial reports of TRUS of the prostate by Wild and Reid,⁴ substantial technologic advances have improved the diagnostic capabilities of this modality. The current state-of-the-art TRUS probe is a 5-8 MHz hand-held, high-resolution probe with multiaxial planar imaging capabilities, which has the capacity for both transverse and sagittal imaging of the prostate in real time. This probe can be fitted with an adapter that accepts the needle of a spring-loaded biopsy gun, thus allowing multiple cores of tissue to be easily obtained. The visualization provided by the new higher resolution transducers, coupled with the ability to direct the biopsy needle into various regions of interest and to provide uniform spatial separation of the areas to be sampled, has helped to make TRUS-guided prostate biopsy a standard technique in the diagnosis of prostate cancer.

Other Modalities: Transperineal and Transabdominal Prostatic Ultrasound

Although TRUS is the current standard for ultrasound imaging of the prostate, other modalities are available. Transabdominal ultrasound can image the prostate, as well as other abdominal organs. The primary advantage of this technique is that it is noninvasive and thus does not require special patient preparation. Similarly, transperineal ultrasound can image the prostate, is noninvasive, and does not require any spe-

cial patient preparation. Despite their advantages, these techniques have fallen out of favor as tools with which to image the prostate, except in unusual cases (eg, a patient without a rectum after an abdominoperineal resection). These techniques provide images inferior to TRUS, primarily because of the anatomic consideration that the prostate is physically closer to the TRUS probe than it is to the probe in either of these other two methods.

New Technology: Doppler Ultrasound and Intravenous Contrast Agents

TRUS technology has limits in specificity and sensitivity, which has led investigators to explore the potential use of color Doppler imaging with and without intravenous contrast administration. Doppler sonography is based on the principle that the frequency of a sound beam changes when that beam is reflected by a moving target. In the case of Doppler sonography of the prostate, the transducer generates the sound beam, and the moving target is blood. This technique allows real-time visualization of blood flow. The utility of color Doppler ultrasound rests on the theory that tumors in general, and prostate tumors in particular, have different blood flow characteristics from the surrounding normal tissue. Recent literature, however, fails to support this technique as being superior to traditional gray-scale imaging in the diagnosis of prostate cancer.¹²

Recognizing that traditional Doppler ultrasound is limited in its ability to display small, deep, and low-volume-flow blood vessels, such as those of the prostate, the addition of intravenous contrast agents have been used to promote vascular visualization. Ultrasound scanning using contrast agents has been performed extensively in the heart, liver, and kidney, with good results.¹³ Preliminary studies suggest that employing sonographic contrast agents enhances the visualization of neovascularity associated with prostatic cancer.¹⁴

Indications for Prostate Biopsy

Elevated Serum PSA

The most common indication for prostate biopsy is an elevated serum PSA. Although a level greater than 4 ng/mL is considered elevated, age-adjusted normal PSA values have been established (Table). Oesterling et al¹⁵ demonstrated an 8% increase in the number of biopsies and organ-confined cancers detected in men with a normal DRE aged 50 years or less when these age-specific reference ranges were used. A rising PSA over time, though still less than 4 ng/mL, may also be an indication

Age-Specific Reference Ranges for Serum PSA

	Age (years)			
	40-49	50-59	60-69	70-79
Serum PSA (ng/mL)	0.0-2.5	0.0-3.5	0.0-4.5	0.0-6.5

Adapted from Oesterling JE, Jacobsen SJ, Chute CG, et al. Serum prostate-specific antigen in a community-based population of healthy men: establishment of age-specific reference ranges. *JAMA*. 1993;270:860-864.

for biopsy, especially in high-risk groups. Carter et al¹⁶ demonstrated that a change in PSA, or PSA velocity, of more than 0.75 ng/mL per year was a specific marker for the presence of prostate cancer. Furthermore, in their study, men diagnosed with cancer had significantly more rapid rates of a rise in PSA than men without prostate cancer when the PSA levels were normal.

Abnormal DRE

An abnormal finding on DRE is an indication for prostate biopsy regardless of the patient's PSA value. Abnormalities include a discrete nodule, focal induration, a diffusely hard prostate and, in some cases, asymmetry.

TRUS in Practice

Patient Preparation

Full informed consent that outlines alternatives, consequences, and complications of biopsy is obtained prior to the procedure. Patients routinely receive either preprocedural enemas or a formal polyethylene glycol bowel preparation. Administration of prophylactic antibiotics around the time of biopsy has become standard of care. At our institution, we routinely use a 3-day course of a quinolone antibiotic beginning the day before biopsy. Patients with valvular heart disease are administered parenteral antibiotics as outlined by the American Heart Association.¹⁷ Furthermore, patients are taken off anticoagulants and antiplatelet drugs for an appropriate time period.

There has been recent interest in techniques to reduce the morbidity associated with TRUS and prostate biopsy. A recent trial from Emory University¹⁸ concluded that the use of intrarectal lidocaine gel is simple, safe, and efficacious in providing satisfactory anesthesia in men undergoing transrectal prostate biopsy. At our institution, patient comfort is provided by injecting a solution of 1% lidocaine (Xylocaine) along the neurovascular bundles of the prostate, beginning at the seminal vesicles and moving outward to the apex. This is accomplished with a 20-gauge spinal needle, and

the injection is performed under TRUS guidance. This procedure is simple and inexpensive, and patients describe good anesthetic results.

Imaging Techniques

A DRE is performed prior to insertion of the probe. The reason for this is 2-fold: (1) It rules out any rectal pathology that would contraindicate insertion of the probe, and (2) it allows the identification of any palpable prostatic abnormalities to which special attention could be paid during ultrasound examination.

The probe is introduced and the contrast of the console is adjusted to provide a uniform mid-gray image of the normal peripheral zone. The shading of the peripheral zone should be the homogenous gray standard by which other areas of the prostate are classified as hyperechoic, hypoechoic, or isoechoic. Imaging of the gland is then carried out, first in a transverse fashion. The right and left seminal vesicles are viewed, followed by the bladder neck, mid gland, and apex. After complete transverse imaging, the transducer is configured to provide for sagittal imaging, and the right, mid, and left aspects of the prostate are visualized. During this part of the examination, particular attention is paid to any regions that are hypo- or hyper-echoic when compared to the peripheral zone of the prostate.

The console is reconfigured for volume measurement of the prostate. First, in the transverse view, an image of the prostate at its largest diameter is obtained, and this diameter is recorded. Then, in the sagittal view, the greatest cephalo-caudal and anterior-posterior dimensions of the prostate are recorded. These measurements are used to calculate the volume of the prostate. The volume of the prostate is based on the assumption that the gland is an ellipsoid.¹⁹ Thus, the formula for the prostate's volume is: (transverse diameter) \times (cephalo-caudal diameter) \times (anterior-posterior diameter) \times ($\pi/6$). With the volume of the gland and the patient's PSA level, PSA density (PSAD) can be calculated (PSA divided by gland volume). PSAD recognizes that PSA originates not only from prostate cancer cells, but also from normal prostate epithelial cells, so it is not specific to prostate cancer. The concept of PSAD assumes that for any prostate volume, there is a finite number of normal prostate epithelial cells that can occupy that volume and thus an upper limit to PSA of benign origin. Once this critical PSA level has been passed, nonbenign epithelial cells must occupy the prostate gland; this is prostate cancer.²⁰ A PSAD of 0.15 has been proposed as a threshold for recommending prostate biopsy in men with mildly elevated PSA (4-10 ng/mL) and no suspicion of cancer on DRE or TRUS.²¹

Sonographic Findings

The normal prostate gland has a homogenous, uniform echo pattern. The seminal vesicles are visualized at the base of the bladder and are hypoechoic compared with the remainder of the prostate. In contrast to the homogenous appearance of the normal prostate, a prostatic malignancy may take on unique ultrasound findings. Most ultrasound-detected lesions found to be carcinoma are described as hypoechoic regions with irregular borders. However, this is not a rule, and the appearance of carcinoma on ultrasound is variable.²²

Evaluation of the prostate by TRUS requires a comprehensive knowledge of the anatomy of the prostate, as the current PSA-era phenomenon of stage migration has made most tumors nonpalpable at diagnosis. In 1968, McNeal²³ proposed that the prostate is composed of three distinct glandular zones (Fig 1). The transition zone surrounds the urethra and extends from the ejaculatory ducts proximally. The transition zone is surrounded by a discrete fibromuscular band of tissue, and it is the site of origin of benign prostatic hyperplasia. The peripheral zone encompasses the posterolateral aspect of the prostate from the base (superior) to the apex (inferior), and it accounts for the majority of the volume of the prostate. The majority (70%-80%) of prostate can-

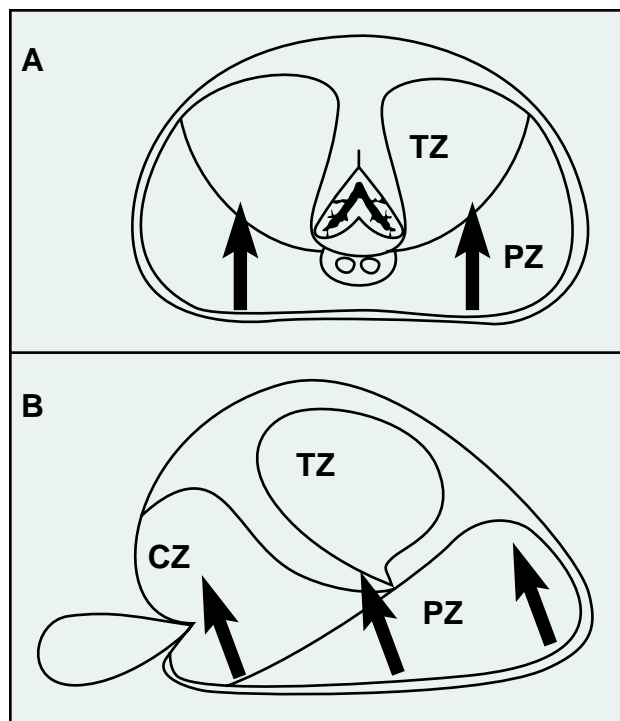


Fig 1. — Schematic depiction of the transition zone (TZ), peripheral zone (PZ), and central zone (CZ) in transverse (A) and sagittal (B) planes. The arrows represent the path of sextant biopsy needles. From Terris MK, McNeal JE, Stamey TA. Detection of clinically significant prostate cancer by transrectal ultrasound-guided systematic biopsies. *J Urol*. 1992; 148:829-832. Reprinted with permission.

cers arise from the peripheral zone. The central zone is composed of tissue immediately surrounding the ejaculatory ducts, and it expands inferiorly.

The anatomic distinction between the central and peripheral zones is generally not appreciated by ultrasound. In a normal man, these two zones are seen as a homogenous, isoechoic area in the posterior section of the prostate. Their normal echo pattern is used as a reference for defining other structures as hypoechoic or hyperechoic.²⁴ The normal transition zone in a young man comprises only a small percentage of the gland and thus is difficult to image. In an older man with benign prostatic hyperplasia, the transition zone expands, compressing its surrounding fibromuscular band of tissue. This compressed tissue gives rise to the "surgical capsule" of the prostate, which is a sonographic landmark of zonal demarcation. The transition zone itself is moderately hypoechoic when compared to the central and peripheral zones.²⁵

Cancer of the prostate was initially thought to have a hyperechoic appearance on ultrasound. However, recent literature confirms that modern ultrasound technique displays prostate cancer as generally a hypoechoic area. Lee et al²⁶ reported that the most common sonographic appearance of prostate cancer was a hypoechoic peripheral-zone lesion. The highest predictive values for prostate cancer are seen in hypoechoic lesions that are well defined and are larger than 1 cm.⁷ The etiology of this hypoechogenicity is currently believed to be due to the replacement of the prostatic stroma with infiltrating glandular elements.⁵ However, not all hypoechoic regions in the peripheral zone are prostate cancer. Potential hypoechoic lesions also include prostatitis, prostatic infarction, dilated glands, smooth muscle bundles, scarring, and prostatic intraepithelial neoplasia.⁷ Studies following Lee's work reported that a significant number of prostate carcinomas are isoechoic.²⁷ The average yield of a biopsy of a peripheral-zone hypoechoic lesion has been 30%-50%.⁷ With these limitations, the sonographer should be able to recognize more subtle findings such as irregularity or asymmetry, extension of hypoechoic areas from the central zone into the seminal vesicle, or any area corresponding to an abnormality on DRE.

TRUS evaluation of the prostate is not without its weaknesses. Carter et al²⁸ were the first to suggest a relative lack of sensitivity with TRUS when they observed that only 54% of carcinomas identified on the nonclinically suspicious side of the prostate could be visualized with ultrasound. Another study found that in radical prostatectomy specimens, only 36% of nonpalpable tumors were visualized on ultrasound.²⁹ Others have also reported that up to 40% of prostate cancers are

isoechoic on ultrasound and therefore "invisible" to TRUS. This number is probably much higher today with the stage-migration seen at presentation of prostate cancer.^{27,28,30,31} The specificity of the classic hypoechoic ultrasound finding of prostate cancer is low; a hypoechoic lesion can reflect anything along the continuum from normal prostate to prostatitis to infarct to prostatic intraepithelial neoplasia.³²

TRUS-Guided Prostate Biopsy Techniques

Systematic Sextant Prostatic Biopsy

The limitations in cancer detection based on sonographic appearance and the stage migration during the PSA era have been driving forces in the evolution of TRUS and prostate biopsy. Patients are presenting earlier in the disease process, when tumors are more likely to be nonpalpable and isoechoic. The true utility of ultrasound in the modern era, therefore, is to enable sampling of all relevant areas of the prostate, including those that appear normal on sonography.

Hodge et al³³ published the landmark paper demonstrating the efficacy of systematic sampling of the prostate during TRUS-guided biopsy. They were the first to report that systematic sampling of the prostate guided by TRUS improved the detection rate of prostate cancer over merely sampling hypoechoic or other lesions. By taking sextant biopsies from the mid lobe (parasagittal) of each side of the prostate at the apex, middle, and base, the cancer detection rate was superior to lesion-directed biopsies in 136 men with palpable abnormalities. This technique was accepted at the time as the standard of care and helped to emphasize that TRUS was more useful for biopsy than for imaging (Fig 2).

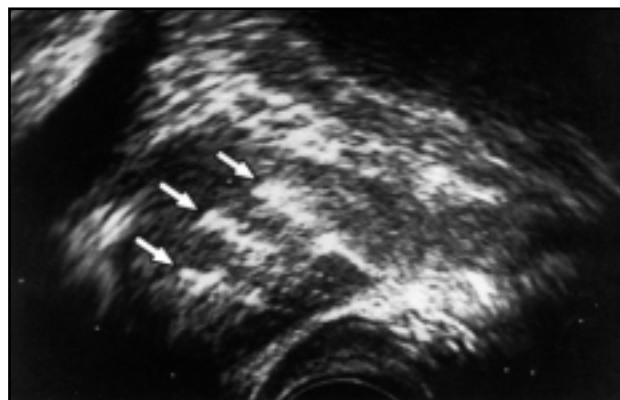


Fig 2. — Transrectal ultrasound in sagittal plane demonstrating hyperechoic biopsy tracts (arrows) evenly spaced throughout the gland. From Eskew LA, Bare RL, McCullough DL. Systematic 5 region prostate biopsy is superior to sextant method for diagnosing carcinoma of the prostate. *J Urol.* 1997;157:199-203. Reprinted with permission.

More recent evidence, however, demonstrates that this technique may no longer be the standard of care. The sextant technique was recommended based on biopsies of men with palpable abnormalities. In the current PSA era, though, most men who are undergoing prostate biopsy do not have palpable abnormalities or hypoechoic lesions. Furthermore, mapping of radical prostatectomy specimens has shown that the majority of nonpalpable lesions lie in the far lateral peripheral zone of the prostate, which is not routinely sampled by the sextant technique. Literature has demonstrated undersampling by the sextant technique, notably in a study by Levine et al³⁴ in which 137 men underwent two consecutive sets of parasagittal sextant biopsies in a single setting. The initial biopsy revealed cancer in 30 men (22%), while 13 (10%) had cancer diagnosed only on the second set of biopsies.

Optimizing Biopsy Methods

Increasing numbers of investigators are modifying the number and the areas of the prostate sampled. Based on cancer mapping of radical prostatectomy specimens, Stamey³⁵ suggested that biopsies near the middle or the base should be directed laterally into the anterior lateral crescent of the peripheral zone. As much as 75% of all prostate cancer originates from the peripheral zone. However, the standard sextant technique samples a limited portion of the peripheral zone and does not take advantage of the common extension of peripheral-zone cancers into the anterior lateral aspect of the peripheral zone.

A prospective study³⁶ from our institution assessed the yield of a 5-region biopsy method in which cores are obtained by ultrasound guidance from the far lateral peripheral zone and midline in addition to the standard sextant biopsies (Fig 3). By obtaining at least 13 cores (18 cores in glands greater than 50 g by ultrasound), the authors demonstrated a significant increase in prostate cancer detection over sextant biopsies. The overall cancer detection rate was 40%, with 35% of the cancers diagnosed by the additional regions only. The benefit of this technique was most notably seen in patients with a PSA <10 ng/mL where 54% of the cancers diagnosed were found in the additional regions only. In a subsequent study,³⁷ the authors demonstrated no statistically significant difference in the tumor volume, Gleason's score, or pathologic stage between tumors diagnosed by the 5-region technique or those diagnosed by standard sextant biopsies. Ongoing data accrual has demonstrated this technique to be durable after 256 biopsy sessions.³⁸ Furthermore, other authors using clinical studies as well as computer-generated models have demonstrated results consistent with the increased yield of the 5-region technique.

Chang et al³⁹ prospectively evaluated the usefulness of adding four lateral biopsies of the peripheral zone to the routine sextant biopsy regimen for prostate cancer. Lateral biopsies of the peripheral zone were obtained just medial to the lateral border of the prostate, in addition to the routine lesion-directed and systematic sextant regimen in 273 patients. Forty-four percent of patients had cancer on biopsy. Routine sextant biopsies detected 82% of cancers, while the combination of sextant and lateral biopsies detected 96% of the cancers diagnosed. They concluded that the addition of lateral peripheral-zone biopsies increases the sensitivity for cancer detection while virtually eliminating the need for lesion-directed biopsies. Looking specifically at 6-core biopsy combinations, the regimen with greatest sensitivity was the combination of the two apical biopsies of routine sextant and four addi-

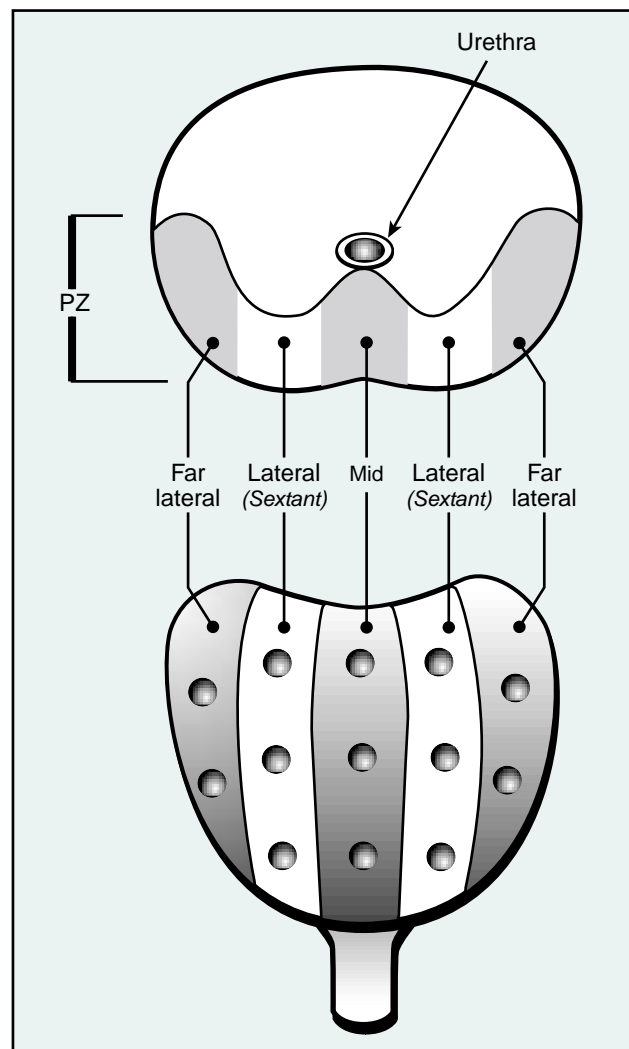


Fig 3. — Transverse and posterior views of the prostate showing the peripheral zone (PZ) and areas of biopsy. Shaded areas represent the additional regions of the 5-region biopsy technique. From Eskew LA, Woodruff RD, Bare RL, et al. Prostate cancer diagnosed by the 5-region biopsy method is significant disease. *J Urol.* 1998;160:794-796. Reprinted with permission.

tional lateral cores. Their findings emphasized the importance of not only increasing the number of biopsies, but also specifying location.

In 2000, these same authors examined their 10-core biopsy regimen more closely as they performed a prospective trial of 483 consecutive patients in an attempt to identify the optimum systematic biopsy regimen to detect carcinoma of the prostate.⁴⁰ They believed that the biopsies of the base in the standard sextant regimen could be dropped without adversely affecting sensitivity. Eliminating these two cores would have decreased the cancer detection rates by only 1%-2%. Variations in cancer detection rates were most pronounced in patients with a PSA less than 10 ng/mL or prostate volume greater than 50 cc. The low yield from the mid lobar base may be due to the fact that this samples largely the central zone, where the incidence of cancer is low.

Chen et al⁴¹ sought to determine the optimum biopsy strategy based on a stochastic computer simulation model of ultrasound-guided biopsies using mathematically reconstructed radical prostatectomy specimens. Sextant biopsies reliably detected cancer in only 107 (73%) of 147 patients in whom the total cancer volume was greater than 0.5 cc. The authors demonstrated that a 10-core biopsy regimen that included the parasagittal base and apex, the inferior anterior horn (far lateral peripheral zone), the midline peripheral zone, and the anterior transition zone reliably detected 96% of cancers. They suggested that sampling of these additional areas be incorporated into an initial or repeat biopsy regimen. They emphasized that biopsy localization must be described in a highly specific way to facilitate further clinical study and confirmation, and this is heavily reliant on TRUS guidance for standardization.

In a subsequent paper, these authors used the same computer simulation to compare the ability of different biopsy regimens published in the literature to detect prostate cancer.⁴² The cancer detection rate for cancers greater than 0.5 cc in volume was highest for an 11-core multisite-directed scheme (94%) followed by the 5-region peripheral zone (18 cores, 87%) and 5-region peripheral zone (13 cores, 86%). The 11-core multisite-directed scheme consists of sextant, one posterior midline, two transition zone, and two inferior anterior horn biopsies. This is similar to the above-mentioned 10-core scheme and has similar detection rates. Again, cancer yield was not related solely to the number of cores; strategic sampling of multiple regions of the prostate under ultrasound guidance is also important.

Babaian et al⁴³ tested the 11-core multisite-directed prostate biopsy strategy of Chen and colleagues. Over-

all, a 33% increase in cancer detection over sextant in 362 patients was observed when this biopsy technique was utilized. The anterior horn was the most frequently positive biopsy site. This technique was significantly better in men whose DRE and TRUS were normal and in those with PSA between 4 and 10.

Another computer simulation by Bauer et al⁴⁴ comparing various published prostate biopsy regimens suggests that all the biopsy protocols using laterally placed biopsies based on the 5-region anatomic model are superior to the routinely used sextant prostate biopsy pattern. Of the lateral biopsy regimens, the authors suggest that the 10-core pattern that includes sextant plus far lateral mid and apical biopsies is the optimum. Lateral biopsies in the mid and apical aspects of the gland had higher yields than any other cores and, similar to reports by Chen and colleagues, sextant biopsies detected only 73% of cancers. Transition-zone biopsies added little to the detection rate, and the authors suggested that these biopsies are rarely required to detect cancer if lateral biopsies are used.

Interestingly, Naughton et al⁴⁵ recently reported a prospective, randomized trial to compare 6-core and 12-core biopsy protocols. Prostate cancer was found in 27% and 26% of patients after 6-core and 12-core biopsies, respectively. They concluded that the overall cancer detection was not improved by the addition of six additional laterally placed cores. However, 21% of men in the 12-core biopsy group would not have been detected without the addition of lateral biopsies. Furthermore, the authors acknowledge that there may have been a tendency to obtain the sextant biopsies alone a little more laterally, thus partially obscuring significant differences.

The Role of Transition-Zone Biopsies

Although approximately 20% of prostate cancers originate in the transition zone, isolated transition-zone tumors detected on prostate biopsy are uncommon. The addition of transition-zone biopsies to the initial biopsy strategy increases detection rates by only 1.8%-4.3 %, and there is little evidence to support the recommendation for routine transition-zone sampling.⁴⁶⁻⁴⁹ In men undergoing repeat biopsies, though, the yield of malignancy from the transition zone is 10%-13%.^{50,51} Thus, transition-zone biopsies may be indicated for patients in whom prior negative systematic sextant biopsies failed to reveal cancer but whose PSA is markedly elevated or rapidly increasing.⁴⁷

In men with previously negative biopsies, the important question is whether the undiagnosed cancer is in the transition zone. In their study of patients

undergoing repeat biopsy, Keetch and Catalona⁵⁰ found a yield of only 10% from transition-zone biopsies. However, certain subsets of patients may have a much higher incidence of transition-zone carcinoma. In repeat biopsies in men with a mean PSA of 32, a normal DRE, and a clinical picture suspicious for carcinoma, Lui et al⁵¹ found that 53% of cancers were detected in the transition zone only.

TRUS is critical to ensure proper needle placement during biopsy of the transition zone. Imaging of the transition zone is not as reliable because the echo patterns are much more hypoechoic and heterogeneous, especially in the setting of benign prostatic hyperplasia. Fortunately, the posterior and posterolateral border of the transition zone is usually well seen on ultrasound and serves as an excellent marker for these biopsies. Chen et al⁴² found that the highest detection rate for transition-zone biopsies in a computer-generated model was observed when the biopsies were initiated near the prostatic apex and the needles were inserted to a depth of 3 cm before firing. Lower rates of detection were noted when the needles were inserted to a depth of 1-2 cm and as they were moved more toward the base of the gland.

The Impact of Prostatic Volume on Prostate Biopsy Technique

The most objective TRUS finding is prostatic volume. Calculating gland volume should be a routine part of every prostate biopsy session. Not only does prostatic volume have implications in future treatment planning in the setting of a positive biopsy and risk stratification using PSA density, but also an indirect relationship has been demonstrated between prostate size and the likelihood of finding prostate cancer. Recent studies have questioned the ability of the standard 6-core biopsy to provide optimal sampling in larger glands. The relative amount of gland that is sampled relies directly on the size of the gland, and thus the ideal number of cores to take may be dependent on the size of the gland calculated by TRUS.

Uzzo et al⁵² reported on cancer detection rates and their variation with prostate size using a systematic sextant core biopsy regimen. Using a sextant regimen, the cancer detection in glands greater than 50 g was 23% vs 38% in glands less than 50 g. Their data suggest that significant sampling error may occur in men with large glands, and more biopsies may be needed under these circumstances.

Karakiewicz et al⁵³ also evaluated the positive rate of sextant biopsy according to gland size. The positive biopsy rate for glands less than 20 cc was 40% vs 10%

for glands 80-90 cc. Their findings suggest that gland size represents an important determinant contributing to the yield of sextant biopsy in men at risk of harboring a nonpalpable, isoechoic cancer. They recommend an individualized approach to TRUS-guided biopsy based on prostate volume.

Levine et al³⁴ also contributed to the evidence of increased sampling error in larger glands. In their study population, cancer was detected in 43%, 27%, and 24% of men with prostate volumes of <30 cc, 30-50 cc, and >50 cc, respectively. Furthermore, data from our own institution⁵⁴ on the 5-region prostate biopsy method has also demonstrated a decreasing yield with increasing gland size. The cancer detection rate for glands <30 cc, 30-50 cc, and >50 cc was 49%, 42%, and 32%, respectively.

Vashi et al⁵⁵ created a mathematical model to determine the minimum number of cores necessary to detect clinically significant cancers in prostate glands 10-80 cc. Their data suggests that the sextant biopsy regimen optimally samples only a minority of prostate glands, and an approach to biopsy based on patient age and gland volume maximizes the detection of clinically significant cancer. They provided a table that indicates the number of cores to obtain based on patient age and gland volume. Their findings indicate that sextant biopsy does not provide adequate sampling of large prostate glands or the prostates of younger men who have normal or minimally elevated PSA.

Chen et al⁵⁶ used a computer-simulated model to compare the yield of the sextant technique in glands ≤50 g and >50 g. The yield was 67% and 48%, respectively. However, they also found that smaller volume cancers were more prevalent in the larger glands. They concluded that the lower biopsy rates in larger glands may be driven by elevations in PSA from benign prostatic tissue. Contrary to other studies, they felt that increasing the number of cores solely to compensate for an increase in prostate size risks a disproportionate increase in the detection of small-volume tumors with a low clinical likelihood of progression. However, most of the cancers detected in the large glands were still >0.5 cc and thus clinically significant.

Conclusions

TRUS maintains a critical role in the early diagnosis of prostate cancer. With the stage migration seen in the current PSA era, directed biopsies at lesions detected on ultrasound and DRE are becoming less common. However, ultrasound is essential in ensuring accurate sampling of the gland and can be helpful in tailoring

the number of cores and their distribution based on the size of the gland and patient risk stratification. Although the ideal number of cores is not clear, TRUS is an integral facet of prostate biopsy and will continue to contribute to our understanding of the optimum regimen for the diagnosis of prostate cancer. With more patients presenting earlier for biopsy as a result of PSA screening, together with potentially earlier diagnosis resulting from increased gland sampling, prostate cancer may be diagnosed at an earlier and more treatable point in the disease process.

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