Using Biopsy to Detect Prostate Cancer

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Transrectal ultrasound-guided systemic biopsy is the recommended method in most cases with suspicion of prostate cancer. Transrectal periprostatic injection with a local anesthetic may be offered as effective analgesia; periprostatic nerve block with 1% or 2% lidocaine is the recommended form of pain control. On initial biopsy, a minimum of 10 systemic, laterally directed cores is recommended, with more cores in larger glands. Extended prostate biopsy schemes, which require cores weighted more laterally at the base (lateral horn) and medially to the apex, show better cancer detection rates without increasing adverse events. Transition zone biopsies are not recommended in the first set of biopsies, owing to low detection rates. One set of repeat biopsies is warranted in cases with persistent indication. Saturation biopsy (≥20 cores) should be reserved for repeat biopsy in patients who have negative results on initial biopsy but who are still strongly suspected to have prostate cancer.

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Prostate cancer rarely causes symptoms until it is advanced. Thus, suspicion of prostate cancer resulting in a recommendation for prostatic biopsy is most often raised by abnormalities found on digital rectal examination (DRE) or by serum prostate-specific antigen (PSA) elevations. Although there is controversy regarding the benefits of early diagnosis, it has been demonstrated that an early diagnosis of prostate cancer is best achieved using a combination of DRE and PSA.

Transrectal ultrasound (TRUS)–guided, systematic needle biopsy is the most reliable method, at present, to ensure accurate sampling of prostatic tissue in men considered at high risk for harboring prostatic cancer on the basis of DRE and PSA findings. In very rare circumstances, a biopsy of a metastatic site (bone lesion) or a suspicious lymph node may be easier and more advantageous. There are also circumstances in which the usual transrectal route is not feasible (eg, status post–anteroposterior resection of the rectosigmoid; see Tissue Diagnosis in Patients with No Rectal Access section, below). As nearly universal as the approach, as nearly universal is the technique, namely a TRUS-guided biopsy using an 18-gauge needle to obtain a tissue core. To be certain, the same biopsy device and needle may be used to perform a finger-guided biopsy, but this is reserved for unusual circumstances (eg, TRUS imaging not available, finger-guided directed biopsy of suspicious nodule not seen on TRUS). Last, whereas in decades past physicians in many countries performed fine-needle aspiration of the prostate, today this technique is less and less often used, although advocates claim that it is cheaper, faster, easier to perform, and results in lower morbidity than any other technique developed to date. Appropriate training in performing transrectal fine-needle aspiration of the prostate and in interpreting the smears is, of course, essential.[1] Fine-needle aspiration plays a major role in the aforementioned situations in which diagnosis is established from nonprostatic tissue sources, such as lymph nodes and others.[2,3]

Since the landmark study by Hodge and colleagues[4] demonstrating the superiority of TRUS guidance compared with digitally guided biopsy, the TRUS-guided biopsy technique has become the worldwide accepted standard in prostate cancer diagnosis. Statistical performance (sensitivity, specificity, positive and negative predictive values) of all other diagnostic tests (eg, DRE and PSA assay) is calculated according to the assignment (cancer present vs absent) made by prostate biopsy. Recognizing the fact that all sampling procedures, including prostate biopsies, incur the risk of returning false-negative results (ie, cancer is present but missed by the biopsies), calculation of the statistical performance characteristics of all other tests using biopsy outcomes as the gold standard are inherently incorrect and biased. Similarly, when comparing the statistical performance of various biopsy strategies, usually the most extensive strategy is chosen as the gold standard to define disease presence or absence, and the performance of all other strategies is calculated on the basis of that particular strategy, again incurring a significant bias due to the remaining false-negative rate of even the most extensive sampling strategy.

Likelihood of Missing Cancer

The question of how often a prostate biopsy will produce false-negative results is therefore of clinical as well as statistical importance. Computerized biopsy simulations on a series of mapped whole-mount sections of radical prostatectomy specimens showed that the chance of missing a cancer by sextant biopsy is estimated at approximately 25%.[5] A repeat sextant biopsy of the prostate performed in 118 men with biopsy-proven state cancer failed to identify cancer in 27 men, or 23%.[6] Although the repeat biopsy-negative patients tended to have lower PSA values and larger glands, none of the differences in clinical or pathologic parameters or PSA relapse rates were significant. Svetec and colleagues[7] performed an ex vivo sextant biopsy on 90 prostates removed for biopsy-proven cancer, which was negative in 41 prostates (46% of cases). Depending on the presenting characteristics (eg, age and serum PSA level), the risk of a false-negative result on re-biopsy varied widely. Although one might argue that the ex vivo biopsy of a removed prostate significantly differs from an in vivo TRUS biopsy, the results clearly validate the concept of false-negative biopsy results and their impact on detection and statistical performance characteristics. A similar but more extensive study was performed by Fink and coworkers,[8] who performed ex vivo sextant and 10-core biopsies on 91 radical prostatectomy specimens. The first sextant set found 60% and the second sextant set 75% of all cancer, whereas the 10-core biopsy sets found 78% and 90% of the cancers, respectively. Thus, even using 2 10-core biopsies, approximately 10% of the cancers were missed, of which 8 were significant according to a tumor volume of greater than 0.5 mL.

Patient Preparation

To avoid the presence of fecal material in the rectal vault, the administration of enemas before the biopsy is commonly recommended and was practiced by approximately 80% of participants in a survey,[9] although others dispute their benefit.[10] To avoid the collection of air in front of the ultrasound probe, interfering with sound-wave penetration and resolution, the patient is ideally positioned in the left lateral decubitus position, although some physicians prefer the lithotomy position.

The issue of the use of antibiotic prophylaxis has been settled by controlled trials. Two-hundred thirty-one patients were randomized into 3 groups receiving placebo, a single dose of ciprofloxacin 500 mg and tinidazole 600 mg, or the same

combination twice daily for 3 days. There was no significant difference among the 3 groups in noninfective complications (27, 29, and 31 in groups 1, 2, and 3, respectively), but the incidence of infective complications (19, 6, and 8, respectively) was significantly higher in group 1 ($P = .003$).[11] Isen and colleagues[12] investigated the efficacy of prophylactic use of single-dose oral ofloxacin and trimethoprim-sulfamethoxazole regimens in 110 men. In the ofloxacin, trimethoprim-sulfamethoxazole, and control groups, urinary infection was found in 2 (4.76%), 3 (6.66%), and 6 (26.08%) patients, respectively. Both of these antibiotic regimens produced a statistically significant reduction in urinary infection ($P < .02$, $P < .05$). Kapoor and associates[13] randomized 537 patients to receive either oral ciprofloxacin 500 mg or placebo before transrectal needle biopsy of the prostate. Six ciprofloxacin-treated patients (3%) and 19 placebo-treated patients (8%) had bacteriuria ($> 10^4$ colony-forming units per mL) after the procedure ($P = .009$). Six ciprofloxacin recipients (3%) and 12 placebo recipients (5%) had clinical signs and symptoms of a urinary tract infection ($P = .15$). Single-dose oral ciprofloxacin reduced bacteriuria after biopsy compared with placebo in patients undergoing transrectal prostatic biopsy and provided an economic advantage. In addition, this study established the actual rate of bacteriuria after transrectal needle biopsy of the prostate without antibiotic prophylaxis to be 8%, with a clinical rate of urinary tract infection of 5% and a hospitalization rate of 2%.

Anesthesia Issues

Traditional finger-guided biopsy of the prostate was performed either without any or under spinal or general anesthesia, depending on physician preferences. With the introduction of the TRUS-guided biopsy, most practitioners used either no analgesia/anesthesia and/or oral pain medications. With the recognition that more than 6 biopsies might be advantageous in the diagnosis of cancer, more and more practitioners have explored the use of various methods of achieving analgesia/anesthesia during the biopsy.

The results with intrarectal lidocaine gel (2%) versus placebo have been controversial. Some investigators, such as Desgrandchamps and colleagues[14] in a randomized study of 109 patients, found no improved pain control when comparing intrarectal lidocaine gel with simple hydrophilic gel. In contrast, Issa and associates[15] found a significantly lower median pain score with use of intrarectal lidocaine than with placebo in 50 randomized patients. In a recent meta-analysis of 5 studies involving 466 patients,[16] Tiong and colleagues found that intrarectal local anesthesia was associated with pain reduction compared with placebo, but the effect size was not statistically significant.

Several randomized studies have recently shown that intrarectal local anesthesia is inferior to periprostatic nerve block with lidocaine injection.[17-22] For example, Alavi and colleagues[17] randomized 150 patients undergoing TRUS biopsy to either 2% lidocaine gel intrarectally or periprostatic infiltration with 1% aqueous lidocaine. The mean pain scores were 3.7 versus 2.4 ($P < .001$) in favor of the infiltration.

The results of periprostatic nerve block with aqueous lidocaine have been positive in randomized controlled trials. Bulbul and associates[23] performed 12-core biopsies in 25 patients without and in 47 matching patients with 2% lidocaine periprostatic infiltration and found no discomfort in 48% of the control patients, compared with 70% of the lidocaine patients ($P < .05$). Moderate-to-severe discomfort was reported by 32% of the control patients, compared with 11% of the lidocaine patients. Randomized and sham controlled studies performed in series of 152,[24] 90,[25] 132,[26] and 157 patients[27] all found less discomfort and pain with the infiltration of lidocaine. Given these data, at present periprostatic infiltration with 1% or 2% lidocaine is the recommended form of pain control and comfort management during TRUS-guided prostate biopsy.

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Although the efficacy of periprostatic nerve block is established, the optimal dosage and technique remain controversial. Various infiltration sites have been described, including the apex only, bilateral neurovascular bundle regions only (defined variously as basolateral, posterolateral, periprostatic nerve plexus, prostate-vesicular junction injections), apex and neurovascular bundle, three locations (base, mid, and apex) posterolaterally, and lateral to the tip of the seminal vesicles. A study using a placebo and groups of escalating doses of 1% lidocaine infiltration (2.5, 5, and 10 mL) demonstrated that the best pain relief was obtained with 10 mL of lidocaine infiltrated solely at the neurovascular bundle region (single site) or to the neurovascular bundle and apical regions (double site).[28] Therefore, the investigators recommended single-site, 10-mL infiltration

in the region of the neurovascular bundle. Even if infiltration of the neurovascular bundle region seems essential for effective anesthesia, apical infiltration alone has been reported to provide significant pain relief.[29] However, the combination of neurovascular bundle and periapical local anesthesia is not superior to neurovascular bundle block alone in reducing pain during prostate biopsy.[30]

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The issue of whether periprostatic nerve block should be associated with intrarectal lidocaine or oral medication remains an open question. Pendleton and colleagues[31] recently reported that oral administration of 75 mg tramadol/650 mg acetaminophen 3 hours before periprostatic nerve block seems to provide more effective pain control than periprostatic nerve block alone, without causing any additional complications.

The introduction of periprostatic nerve block has allowed extended prostate biopsy to be performed easily in the office and the number of biopsies taken to be increased without increasing patient discomfort and pain. Despite the variability of location and dosage of infiltration, at present the periprostatic nerve block is the most effective method to reduce pain during TRUS biopsy. It remains controversial whether periprostatic nerve block should be associated with intrarectal lidocaine or oral medication.

Complications of TRUS-Guided Biopsies

TRUS-guided prostate biopsy is in general a safe procedure. Aside from infectious complications and pain, the majority of complaints center on the issues of urethral and rectal bleeding, as well as hematospermia. In a contemporary series,[32] the morbidity of 1000 patients undergoing a TRUS-guided biopsy was compared with the morbidity of a second biopsy performed in 820 of these patients in whom the initial biopsy results were negative for cancer. Immediate morbidity was minor and included rectal bleeding (2.1% vs 2.4% for first vs second biopsy, respectively; $P = .13$), mild hematuria (62% vs 57%; $P = .06$), severe hematuria (0.7% vs 0.5%; $P = .09$), and moderate-to-severe vasovagal episodes (2.8% vs 1.4%; $P = .03$). Delayed morbidity of first and re-biopsy included fever (2.9% vs 2.3%; $P = .08$), hematospermia (9.8% vs 10.2%; $P = .1$), recurrent mild hematuria (15.9% vs 16.6%; $P = .06$), persistent dysuria (7.2% vs 6.8%; $P = .12$), and urinary tract infection (10.9% vs 11.3%; $P = .07$). Major complications were rare and included urosepsis (0.1% vs 0) and rectal bleeding that required intervention (0 vs 0.1%). Roberts and colleagues[33] reviewed 2258 biopsies performed in Olmsted County (Minnesota) from 1980 to 1997 and found an overall complication rate of 16.7%, which was remarkably constant from the first period (1980-1986; 16.9%) to the last period (1993-1997; 16.5%). Gross hematuria was by far the most common complication in the last period (12.8%), and major complications occurred in only 1.9% of cases.

Clinically Significant Cancer

The original TRUS-guided technique was described as a sextant biopsy performed both in a randomized and systematic fashion.[4] Many modifications to this scheme have been proposed, and in general the more cores are taken, the greater is the diagnostic yield of cancer. Given the considerations above, we must assume that more cores will find more cancer and that we will never be able to find all cancer. The key, therefore, is to determine the most appropriate number of biopsies for any individual patient, which ensures with the greatest statistical probability that all clinically significant cancers will be found.

The very term *clinically significant cancer*, however, is the crux of the matter, because there is very little information available to determine what constitutes clinical significance. Stamey and coworkers[34] examined prostates after 139 consecutive unselected cystoprostatectomies from patients with bladder cancers in whom prostate cancer status was unknown. Prostate cancer was found in 55 patients (40%); the volume of the largest cancer in each specimen was determined by morphometry. The largest 11 of the 55 cancers represented 7.9% of the total 139 samples. These cancers ranged in volume from 0.5 to 6.1 mL, representing only 20% of all patients with prostate cancer. Prostate cancers larger than 0.5 mL seem to correspond to the 8% of men who will be diagnosed with a clinically significant carcinoma, and the investigators

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concluded that these represent "clinically significant" cancer. Epstein and colleagues,[35] in a series of prostatectomy patients, found that tumors smaller than 0.2 mL had no capsular penetration or progression over 5 years, whereas tumors of 0.2 to 0.5 mL had extracapsular penetration or progression in 13% of cases, suggesting that the smallest tumors were clinically insignificant. Crawford and associates,[36] on the basis of computer modeling, defined insignificant cancers as smaller than 0.25 mL, with a Gleason score of 7 or less.

Vashi and colleagues[37] determined significance by the size at time of diagnosis, taking into consideration the age of the patient as well as the doubling time of the cancer—an intuitively appealing process, although it confounds the calculation with the uncertainty of the doubling time as well as the patient's life expectancy. A doubling time of 3 to 6 years was assumed for the calculations.[38] A study by Bostwick and associates[39] demonstrated a 10% probability of metastasis for 5-mL tumors, 50% at 13 mL, and 87% at 20 mL. Using these assumptions and life tables from the US Department of Health and Human Services, the following formula can be used to determine life-threatening tumor volume at time of diagnosis:

$$V_0 = V_D/2^{LE/DT} = 20\ mL/2^{LE/DT}$$

where V_0 is life-threatening volume at time of diagnosis, V_D is critical tumor volume at time of death, LE is life expectancy, and DT is doubling time.

According to these assumptions, a life-threatening tumor volume may range from 0.05 mL in a 50-year-old man, assuming a doubling time of 3 years, to 6.7 mL in a 75-year-old man, assuming a doubling time of 6 years. Depending on prostate size, the investigators then calculated the number of cores needed to ensure 90% certainty of cancer detection stratified by tumor volume, and finally the recommended number of cores stratified by prostate gland volume and age of patients, taking into consideration the volume of life-threatening tumor for each age group. The number of cores needed ranged from 2 (75-year-old man with a 10-mL prostate) to 23 (50-year-old man with a 30-mL prostate).

Initial Prostatic Biopsy: Results of Different Biopsy Strategies (Number and Location of Cores)

Recently there has been increasing interest in defining more efficient biopsy schemes for prostate cancer detection. Intuitively, adding more biopsies to prostatic areas not sampled by standard sextant schemes should increase the detection rate for prostate cancer. However, it is not clear whether the increased detection rate is simply due to the additional biopsies or to the location from which the cores are taken. Moreover, the number of biopsies required for the optimal detection of clinically significant prostate cancer remains controversial. One thing is established, however: biopsies of the transitional zone add little to cancer detection and should therefore not be sampled during the initial biopsy.[40] Moreover, the necessity of biopsying single hypoechoic lesions no longer seems to be necessary because a visible lesion itself is as likely to be the source of cancer as the next adjacent area.[41]

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Although the diagnostic yield of sextant biopsies varies depending on the population studied, in general between 20% and 35% of patients are found to have cancer using the original description by Hodge and colleagues.[4] Several researchers have evaluated the diagnostic yield of lateral biopsies within an extended prostate biopsy scheme. Most of the studies have demonstrated that extended prostate biopsy is superior to the sextant protocol in cancer detection, without significant morbidity and without increasing the number of insignificant cancer cases.[42] The addition of laterally directed biopsies, which are aimed at also sampling the lateral horn, has been shown to yield an approximately 5% to 35% increase in sensitivity.[40,43-46] The vast majority of the extra cancers were detected in the far-lateral mid-lobar region, an area well sampled by the technique of laterally directed sextant biopsy. In addition to the number of cores, the direction of the biopsies may be just as important. The apex and the base of the peripheral gland are the sites at which prostate cancer is most likely located and at which the biopsies should be directed, whereas midline biopsies have been demonstrated to have the lowest probability of showing positive results.[40,43-46]

Eskew and coworkers[46] demonstrated that the 5-region biopsy protocol with 13 to 18 cores increased the detection rate by 35% when compared with standard, mid-lobar sextant biopsies. Ravery and associates[47] performed TRUS-guided biopsies in 303 men with DRE and PSA abnormalities, using either 10 or 12 cores (if total prostate volume >50 mL) and found cancer in 38%, which represents a 6.6% increase in the cancer detection rate compared with sextant biopsy. The increase was

particularly pronounced in patients with a PSA value of less than 10 ng/mL and/or a total prostate volume of greater than 50 mL.

Presti and colleagues[48] performed sextant biopsies in 483 men with abnormal DRE or PSA findings and added 4 lateral cores at the base and mid-gland. If total prostate volume was greater than 50 mL, 2 additional mid-lobar, parasagittal transition zone biopsies were taken. The overall cancer detection rate was 42%, and the sextant technique missed 20%.

Babaian[49] evaluated an 11-core multisite directed biopsy scheme incorporating the anterior transition zone, midline peripheral zone, and inferior portions of the anterior horn in the peripheral zone in 362 patients and compared it with sextant biopsy.[49-51] The additional sites were identified on the basis of computer simulations. Overall, a 33% increase in cancer detection (36 of 110 patients) was observed when the biopsy technique included the alternate areas ($P = .0021$). The anterior horn was the most frequently positive biopsy site, followed by the transition zone and midline sites. The 11-core technique had significantly better cancer detection rates when DRE and TRUS findings were normal in men with serum PSA values between 4.1 and 10 ng/mL.

Gore and colleagues[40] studied 396 consecutive patients who underwent biopsy of the lateral peripheral zone in addition to standard sextant biopsy. The cancer detection rate for each biopsy core was calculated. The sensitivity of different combinations of biopsy cores was compared with those of standard sextant biopsies and with a 12-core biopsy protocol that combined the standard sextant biopsy with a complete set of laterally directed cores. Cancer was detected in 160 of 396 patients (40.4%). Of the possible combinations of biopsy cores, a strategy that included laterally directed cores at the base, mid-gland, and apex of the prostate with mid-lobar base and apical cores detected 98.5% of cancers. The detection rate of this 10-core biopsy regimen was significantly better than that of the standard sextant protocol ($P \leq .001$) and was equivalent to that of the 12-core biopsy. The investigators recommend using a 10-core biopsy regimen that combines laterally directed cores at the base, mid-gland, and apex of the prostate with mid-lobar biopsy cores at the base and apex.

Despite the use of an extended protocol, sampling error still can occur in some patients, especially those with large prostate glands. It is well known that prostate volume is one of the factors that may influence the prediction of cancer at first biopsy and that a significant inverse relationship exists between the cancer detection rate and prostate volume. Therefore, some investigators have advocated even more aggressive biopsy schemes, with more than 12 cores up to a saturation biopsy ($\geq$ 20 cores), and have reported even higher cancer detection rates.[44,46] A recent study demonstrated that a scheme with 8 cores is only appropriate in patients with prostates smaller than 30 mL.[52] On the other hand, in prostates larger than 50 mL, an extended procedure with more than 12 to 14 cores was necessary to detect cancer. In accordance with these findings, Inahara and associates[53] have shown that a 14-core protocol is superior to an 8-core protocol for patients with prostate volumes of 30 to 40 mL. In a study of 303 patients comparing 6-, 12-, 18-, and 21-core protocols in the same patient, de la Taille and coworkers[44] found that a 21-sample needle biopsy scheme increases the prostate cancer detection rate. The investigators reported a prostate cancer detection improvement of approximately 25% and 11% when 12- versus 6-core and 21- versus 12-core protocols were compared, respectively. Interestingly, they have demonstrated that the improvement was most marked in patients with a prostate volume greater than 40 mL.

On the other hand, in a recent meta-analysis, Eichler and colleagues[54] studied the efficacy and adverse effects of various biopsy schemes and concluded that a 12-core extended biopsy scheme strikes a balance between adequate cancer detection and an acceptable level of adverse effects. There seemed to be no significant benefit in taking more than 12 cores, and methods requiring 18 or more cores had a poor side-effect profile. In agreement with these findings, Jones and associates[55] demonstrated that the saturation technique with more than 20 cores as an initial prostate biopsy strategy does not improve cancer detection. They suggested that saturation biopsy should be reserved for repeat biopsy in patients with negative results on initial biopsy but who are still strongly suspected to have prostate cancer.

Recognizing the findings of these and other investigators, as well as the various computer simulation and

Recognizing the findings of these and other investigators, as well as the various computer simulation and mathematic models, it seems reasonable to recommend (1) taking at least 10 biopsy cores; (2) focusing the biopsies laterally and at the areas listed above; and (3) adjusting the number of cores taken according to prostate volume.

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Repeat Biopsy

For men who have a prostate biopsy that shows only benign tissue but for whom there is continued suspicion of prostate cancer on the basis of DRE findings, repeated PSA measurements, or other PSA derivatives (ie, percentage of free PSA, complexed PSA, PSA density, PSA velocity), a repeat prostate biopsy should be considered.[56] Clearly, the yield of the repeat biopsy depends on the population studied, the particular features of a given patient (eg, PSA value, DRE, prostate volume), the type of biopsy previously performed, and the type of biopsy performed during the repeat TRUS-guided biopsy. In the second set of biopsies, a detection rate of approximately 10% to 35% has been reported in cases with a negative first set of biopsies.[57-67]

Even patients who have undergone more extensive biopsies may still have a significant detection rate at repeat biopsy.[57,68,69] Moreover, a third biopsy has been shown to identify nearly 10% of cancers.[58] At present there is no proven biopsy scheme that omits the need for re-biopsy in the case of a persistent indication. However, more than 90% of prostate cancers are detected by the performance of 2 sextant biopsies,[70] and therefore with the biopsy approaches currently preferred it is unlikely that 2 extended biopsies would miss a life-threatening cancer. Indeed, 2 sets of biopsies have been shown to detect most clinically significant cancers.[58]

Biopsy of the transition zone of the prostate, although not recommended at initial biopsy, should be considered for men undergoing a repeat biopsy and for whom suspicion of a missed cancer anteriorly is high.[56]

For men who have high-grade prostatic intraepithelial neoplasia found at the time of an extended prostate biopsy, the risk of cancer on a repeat biopsy is similar to the risk of cancer on repeat biopsy if the initial biopsy results are negative.[66,71] Thus, a repeat biopsy is not indicated for men with high-grade prostatic intraepithelial neoplasia if the original biopsy technique was adequate.[56] A prostate biopsy that reveals atypical glands that are suspicious but not diagnostic of cancer should be repeated because the chance of finding prostate cancer on a repeat biopsy is 40% to 50%.[56,72,73]

Recently, investigators have suggested that treatment with 5-alpha-reductase inhibitors may unmask prostate cancer by preferential suppression of benign prostate hyperplasia–derived PSA. Kaplan and colleagues[74] have suggested that after 1 year of finasteride treatment, prostate cancer detection is more likely in men with a smaller decrease in PSA levels. This hypothesis is supported by a meticulous analysis of the Prostate Cancer Prevention Trial, which found that accuracy for detecting prostate cancer was greater in the finasteride group compared with the placebo group.[75]

Saturation Biopsy

The concept of increasing the number of cores and/or repeating the biopsy can be taken further with the idea of a saturation or mapping biopsy, in which 20 or more cores are obtained in a systematic fashion. Jones and colleagues[55] have demonstrated that saturation biopsy does not offer benefit as an initial biopsy technique. However, saturation biopsy may serve as a follow-up strategy in men with negative findings on initial office biopsy.[76,77] The results of saturation biopsy studies are shown in Table 1. For example, Stewart and associates[67] performed TRUS-guided saturation biopsy (mean number of cores 23; range, 14-45) in 224 men with negative results on previous biopsies (mean, 1.8) in an outpatient surgical setting. They detected cancer in 77 patients (34%). The number of previous negative sextant biopsies was not predictive of subsequent cancer detection by saturation biopsy. At prostatectomy, median cancer volume was 1.04 mL, and 85.7% of removed tumors were clinically significant, assuming a 3-year doubling time. Complications and risk of diagnosing clinically insignificant cancer using saturation biopsy after a prior negative biopsy are reported to be no higher than with routine sextant or extended core biopsy unless general or regional anesthesia is used, whereas the detection of clinically significant cancer is higher.[78] Although initial investigators used regional or general anesthesia, periprostatic block has now allowed several investigators to report routinely performing this procedure in the office setting. This seems to overcome the increased risk of urinary retention related to systemic anesthesia. One useful application of saturation biopsy is to predict the likelihood of finding insignificant cancer at the time of prostatectomy, thus allowing the selection of men for a watchful waiting or surveillance

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Table 1
Prostate Cancer Detection Rates Using a Saturation Scheme in a Re-Biopsy Setting

Reference	Route	Number of Patients	Cancer Detection Rate (%)	Number of Previous Cores	Number of Patients With Initial Biopsy	Number of Cores	Clinically Insignifiant Cancer (%)
de la Taille A et al.[44]	TR	303	31.3	NR	188	21	NR
Rabets JC et al.[76]	TR	116	29	Mixed	0	20-24; mean, 22.8	0
Walz J et al.[115]	TR	161	41	8 +	0	24.2	15.6
Jones JS et al.[55]	TR	139	44.6	NA	139	24	15.8
Pryor MB et al.[116]	TR	35	20	6	0	14-28; median, 21	0
Stewart CS et al.[67]	TR	224	34	6	0	14-45; mean, 23	14.3
Borboroglu PG et al.[64]	TR	57	30	6	0	Mean, 22.5	7
Fleshner N et al.[117]	TR	37	13.5	Mixed	0	32-38	NR
Pinkstaff DM et al.[118]	TP	210	37	NR	0	Mean, 21	0
Bott SR et al.[119]	TP	60	38	8	0	Mean, 24	
Satoh T et al.[120]	TP	128	22.7	8 +	0	22	NR
Moran BJ et al.[121]	TP	180	38	12 median	0	Median, 41	NR

NA, not applicable; NR, not reported; TP, transperineal; TR, transrectal.

strategy.[79] The role and appropriate number of cores for saturation biopsy continue to be defined, but a threshold of 20 cores with emphasis on the lateral areas and apex is supported by the literature.

Tissue Diagnosis in Patients With No Rectal Access

In patients with no rectal access (eg, status post–anteroposterior resection) there are several ways to obtain a tissue diagnosis. The most commonly used route is a transperineal biopsy. We have found that this often results in cores obtaining no prostate tissue but rather fibromuscular or adipose tissue only, and we have resorted to performing such biopsy under cystoscopic guidance. The cystoscope with a 0° or 12° lens is situated at the verumontanum, and an assistant advances the needle through the perineum until the needle tip hits the prostate capsule. This is clearly noted as a movement of the prostate cystoscopically. The biopsy gun is then fired, and again a motion and sometimes even the needle become visible. In our hands, this has resulted in a relevant tissue diagnosis in 100% of cases, with the vast majority of all cores containing prostate tissue.

Other options include image-guided biopsy through the perineum (magnetic resonance imaging, computed tomography, or ultrasound; see next section) or transurethral resection of the prostate, with its inherent limitation of obtaining mostly transition zone tissue.

Transrectal Versus Transperineal Biopsy

In the United States transperineal biopsy is seldom performed. In contrast, in some European and Asian centers, it is the standard technique. Theoretically, the direction of the transperineal biopsies might be better than the transrectal route because of the longitudinal sampling of the peripheral zone. Initially the transperineal route was demonstrated to be less accurate than the transrectal route in terms of identifying hypoechoic lesions[80] and systematic sextant-directed detected cancer.[81] However, in a simulation experiment, Vis and collegues[82] have shown that the 2 approaches did not differ in terms of prostate cancer detection. Moreover, Emiliozzi and associates[83] reported that sextant transperineal biopsy is superior to transrectal biopsy for detecting prostate cancer in humans. On the other hand, 2 studies have shown that the overall cancer detection rate did not differ between the 2 approaches when the same number of cores was used.[84,85] Indeed, 12-core transperineal prostate biopsy is superior to 6-core biopsy, and the number of cores may have a greater impact on cancer detection than the route of the prostate biopsy.[83,86] In the last few years the concept of extended biopsies has been equally applied to

the transperineal approach, with results similar to those achieved with the transrectal approach.[84,85]

The Role of Doppler Imaging as an Aid for Cancer Detection

Standard gray-scale TRUS technology has limited specificity and sensitivity for prostate cancer detection because of its inability to detect isoechoic neoplasms. To increase its accuracy and utility, researchers have investigated a number of alternatives, including color Doppler TRUS, Power Doppler imaging with and without intravenous contrast administration, and recently, elastography. Increased microvascularity accompanies cancer growth, and neovascularity may be detectable by color Doppler TRUS and Power Doppler TRUS because of abnormal blood flow patterns in larger feeding vessels.

However, several studies have shown that color Doppler TRUS does not add significant information to gray-scale TRUS in detecting early stages of prostate cancer.[87,88] Overall, the sensitivity of color Doppler TRUS for the diagnosis of prostate cancer ranges between 49% and 87%, and specificity ranges between 38% and 93%.[87,88]

Power Doppler TRUS is considered the next generation of color Doppler imaging because it has the advantage of increased sensitivity for detecting small, low-flow blood vessels. Halpern and Strup[89] have shown that Power Doppler TRUS may be useful for targeted biopsies when the number of biopsy passes must be limited, but that there is no substantial advantage of Power Doppler over color Doppler. Remzi and colleagues[90] have recently reported a normal Power Doppler TRUS signal might exclude the presence of a prostate cancer.

Contrast-enhanced color Doppler is an ultrasound-based technology for imaging of the prostate that is used after intravenous administration of gas-encapsulated microbubbles. This methodology allows for better prostate cancer visualization and for targeted biopsies to isoechoic areas that generally become hypervascular after contrast infusion. Halpern and associates[91] have reported significantly improved sensitivity, from 38% to 65%, for detecting prostate cancer with preserved specificity at approximately 80%. Recently, different investigators have demonstrated that targeted biopsy with contrast-enhanced color Doppler detects a number of tumors equal to that of systematic biopsies with less than half the number of cores.[91-94] Unfortunately, the poor discrimination of benign from malignant tissue, which is due to the contrast-enhanced color Doppler ultrasound signal arising from areas of benign disease (eg, benign prostatic hyperplasia), has diminished the specificity of this technology. Thus contrast-enhanced color Doppler has not yet gained popularity because of its low specificity, complexity, and high cost.

Some investigators reported the use of sonography with manual compression of the prostate gland with the transrectal probe to generate elastograms.[88] The basis for improved detection of cancer is that the elasticity of the neoplastic tissue is less compared with normal prostate. There are only limited data available regarding the ability of elastography to detect prostate cancer. Investigators have shown that a targeted biopsy detects as many cancers as a systematic biopsy, with less than half the number of biopsy cores.[88] However, more clinical trials are needed to assess this technology before widespread use.

Several studies have shown that color Doppler TRUS does not add significant information to gray-scale TRUS in detecting early stages of prostate cancer.

Overdiagnosis and Insignificant Cancer

Clearly, the critical question is whether the cancer detected in sequential biopsies or saturation biopsies with increasing numbers of cores is clinically significant. There is mounting evidence that a substantial proportion of men with screen-detected prostate cancer would otherwise have not known about the disease during life in the absence of screening. In these men cancer treatment is not beneficial. Identifying the patients with newly diagnosed prostate cancer who have indolent disease for which surveillance or expectant management may be an appropriate alternative to immediate curative intervention is a timely and important issue. There is currently no marker of biologically indolent cancer. Although life expectancy and comorbidity are as important as pathologic characteristics of the cancer, most investigators have defined indolent disease according to pathologic stage, tumor volume, and cancer grade (organ-confined tumor less than 0.5 mL with no Gleason pattern 4 or 5; Table 2).

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Table 2
Preoperative Parameters Predicting the Presence of Insignificant Prostate Cancer Defined as Tumor < 0.5 mL and a Gleason Score < 4 and 5 on Final Pathology

Reference	Location	Percentage Insignificant Cancer	Biopsy Protocol	Preoperative Variables Predicting Insignificant Cancer
Epstein JI et al[35]	United States	26	Sextant	• Gleason sum ≤ 6 • Adenocarcinoma present in fewer than 3 of 6 cores • No more than 50% malignancy involvement in each positive biopsy core • PSA density < 0.15 ng/mL/g
Goto Y et al[122]	United States	10	Sextant	• Quantitative analysis of the extent of cancer • PSA, PSA density, and grade
Carter HB et al[123]	United States	17	Sextant	• PSA density • Quantitative histology (number of cores involved with cancer and percentage of cancer within the core)
Epstein JI et al[124]	United States	30	Sextant	• Needle biopsy findings • Free/total PSA levels
Kattan MW et al[125]	United States	20	≥ 6	• Nomogram incorporating pretreatment variables (clinical stage, Gleason grade, PSA value, and the amount of cancer in a systematic biopsy specimen)
Ochiai A et al[126]	United States	22	10 or 11 cores	• Combination of tumor length < 2 mm, Gleason score 3 + 4 or less, and prostate volume > 50 mL
Augustin H et al[127]	Europe	6	Sextant	• PSA density • Percentage cancer per biopsy core
Chun FK et al[128]	Europe	6	≥ 6	• Preoperative nomograms (predictor variables: PSA value, clinical stage, biopsy Gleason scores, core cancer length, and percentage of positive biopsy cores)
Steyerberg EW et al[129]	Europe	49	Sextant	• Updated Kattan nomogram[125] in screening setting
Miyake H et al[130]	Japan	14	8	• Gleason score < 7 • Percentage positive biopsy cores < 15%

PSA, prostate-specific antigen.

The issue of nonsignificant prostate cancer is becoming even more important with the advent of extended biopsy schemes. Indeed, several studied have shown that extended biopsy increases the likelihood of detecting smaller-volume tumors of little clinical relevance. There is no doubt that the recent stage migration of prostate cancer has been witnessed by regular increases in the proportion of patients with moderately differentiated low-volume tumor and a significant decrease in the volume of the cancers removed at surgery.[95] Recently Master and colleagues[96] demonstrated that a higher number of biopsy cores was associated with smaller tumor volumes at radical prostatectomy. Boccon-Gibod and associates[97] reported that 30% of patients with microfocal prostate cancer on extended biopsy have the risk of having insignificant tumor and of being overtreated. Unfortunately, no parameter was able to identify on an individual basis the patients harboring a prostate cancer potentially amenable to surveillance with delayed therapy. In contrast to these studies, Siu and coworkers[42] have demonstrated that it is possible not only to enhance tumor detection using an initial extended biopsy scheme but also to ultimately lead to the finding of clinically significant disease. Similarly, several investigators reported no association between more extensive biopsy schemes and number of lower-risk tumors identified.[98,99]

Even if the use of extended biopsy is recommended, the risk of detecting insignificant tumor should not be

neglected. Saturation biopsies and rebiopsies, which are now used as part of active surveillance protocols, have recently proved to provide helpful information about quantitative and qualitative histology to predict the clinical significance of prostate cancer.[79,100] The concern of overdetection must be weighted against the risk of missing clinically significant malignancy, and cancer detection does not need to trigger treatment immediately because men with low-volume and low-grade diseases may also be managed expectantly. Avoiding undertreatment of men with larger-volume, higher-grade cancer requires treatment in a large proportion (50% or more) of those with small-volume, low-grade disease. In time our current methods of assessing the biologic behavior of prostate cancer on the basis of needle biopsy may be augmented or replaced by molecular profiles or panels of biomarkers that predict life-threatening prostate cancer.

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The Role of Nomograms as Decision-Making Tools for Prediction of Biopsy Outcome

Traditionally, physician judgment has formed the basis for risk estimation, patient counseling, and decision making. However, humans have difficulty with predicting outcomes, owing to the biases that exist at all stages of the prediction process.[101-104] First, clinicians do not recall all cases equally; certain cases can stand out and exert an unsuitably large influence when predicting future outcomes. Second, clinicians tend to be inconsistent when processing their memory and tend to resort to heuristics (rules of thumb) when processing becomes difficult.[105] When it is time to make a prediction, they tend to predict the preferred outcome rather than the outcome with the highest probability.[103] Third, it is difficult to integrate the multitude of predictive variables that have been shown to be of importance in clinical judgment.[106,107] Finally, clinicians have difficulty weighing the relative importance of each of these factors when formulating predictions of outcome. Therefore, to obtain more accurate predictions, researchers have developed decision aids based on statistical models.[108] Decision aids consist of the Kattan-type nomograms,[109] risk groupings, artificial neural networks, probability tables, and classification and regression tree analyses. In general, these predictive models have been shown to perform as well as or better than clinical judgment when predicting probabilities of outcome.[107] That said, physician input is obviously essential and crucial for the measurement of variables that are used in the prediction process and for the entire decision-making process.

Tables 3 and 4 show the many models for prediction of prostate cancer presence on initial and repeat biopsy, respectively. A nomogram developed by Eastham and colleagues[110] for prediction of the probability of prostate cancer on initial biopsy in men with suspicious findings on DRE and serum PSA values less than 4.0 ng/mL yielded a predictive accuracy of 75%. Despite good accuracy, this nomogram suffers from limited generalizability. Unfortunately, the nomogram cannot be applied to men with unremarkable DRE findings and does not apply to patients with a PSA level greater than 4.0 ng/mL.

Recently, Garzotto and associates[111] developed a nomogram predicting prostate cancer on needle biopsy using routinely available clinical and transrectal ultrasound variables. Their model yielded a predictive accuracy of 73%. This model has 2 limitations: use of ultrasound-based input is highly impractical because men who undergo transrectal ultrasound are also likely to undergo ultrasound-guided needle biopsy, and the predictions of this nomogram are only applicable after transrectal ultrasound because transrectal ultrasound variables are necessary for risk estimation. Predictions based on input that does not require ultrasound findings are more practical and may be interpreted before planned ultrasound-guided biopsy.

Karakiewicz and colleagues[112] developed 2 nomograms for prediction of the probability of having prostate cancer. The first nomogram was based on patient age, DRE findings, and serum PSA value. Percentage free PSA was added as a predictor in the second nomogram. External validation of the nomograms with and without percentage free PSA yielded predictive accuracies of 77% and 69%, respectively. Unfortunately, these predictive models were based on sextant biopsy regimens, limiting their transportability to current biopsy strategies. Therefore, Chun and coworkers[113] updated these nomograms in 2900 men who underwent extended prostate biopsy. Moreover, they complemented the variables with sampling density (ie, ratio of gland volume and the number of planned biopsy cores). Internal validation of the new nomogram demonstrated 77% accuracy, and validation in

Table 3
Prostate Biopsy Nomograms for Prediction of Prostate Cancer Presence in Initial Biopsy Setting

Reference	Prediction Form	Number of Patients	Variables	Mean Number of Cores (Range)	Cancer Detection Rate (%)	Accuracy (%)	Validation
Babaian RJ et al.[131]	Risk group	151	Age, creatinine phosphokinase isoenzyme activity, prostatic acid phosphatase, PSA	6	24	74	Not performed
Eastham JA et al[110]	Probability nomogram development	700	Age, race, DRE, PSA (0-4 ng/mL)	6	9	75	Internal
Virtanen A et al[132]	Neural network	212	Percentage free PSA, DRE, heredity	Not available	25	81	Not performed
Finne P et al[133]	Neural network	656	Percentage free PSA, PSA, DRE, TRUS	Not available	23	Not available	Not performed
Horninger W et al[134]	Neural network	3474	Age, PSA, percentage free PSA, DRE, TRUS, PSA density, PSA density of transition zone, transition zone volume	Not available	Not available	Not available	Not performed
Kalra P et al[135]	Neural network	348	Age, ethnicity, heredity, IPSS, DRE, PSA, complexed PSA	6	Not available	83	Not performed
Garzotto M et al[111]	Probability nomogram development	1239	Age, race, family history, referral indications, prior vasectomy, DRE, PSA ($\leq$ 10 ng/mL), PSA density, TRUS findings	6.7 (6-13)	24	73	Not performed
Finne P et al[136]	Neural network	1775	DRE, percentage free PSA, TRUS, PSA	Not available	22	76	Not performed
Karakiewicz PI et al[112]	Probability nomogram development	6469	Age, DRE, PSA, percentage free PSA	6	35-42	77	Internal and external
Suzuki H et al[137]	Probability nomogram development	834	Age, PSA, percentage free PSA, prostate volume, DRE	$\geq$ 6	29	82	Internal
Chun FK et al[128]	Probability nomogram validation[112] and development	2900	Age, DRE, PSA, percentage free PSA, sampling density*	11 (10-20)	41	77	Internal and external
Porter CR et al[138]	Neural network	3814	Age, PSA, gland volume, PSA density, DRE, TRUS	6	27-42	72-75	Internal and external

*Sampling density = ratio of TRUS-derived total gland volume by the number of cores at biopsy.
DRE, digital rectal examination; IPSS, International Prostate Symptom Score; PSA, prostate-specific antigen; TRUS, transrectal ultrasound of the prostate.

Table 4
Prostate Biopsy Nomograms for Prediction of Prostate Cancer Presence in Other Than Initial Biopsy Setting

Reference	Prediction Form	Design	Number of Patients	Variables	Median Number of Previous Biopsy Sessions (Range)	Mean Number of Cores (Range)	Cancer Detection Rate (%)	Accuracy (%)	Validation
Repeat biopsy									
O'Dowd GJ et al[66]	Probability nomogram development	Repeat biopsy	813	Age, initial biopsy diagnosis, PSA, percentage free PSA	Not available	Not available	29	70	Not performed
Lopez-Corona E et al[114]	Probability nomogram development	Repeat biopsy	343	Age, DRE, number of previous negative biopsies, HGPIN history, ASAP history, PSA, PSA slope, family history, months from initial negative biopsy	2.9 (2-12)	9.2 (6-22)	20	70	Internal
Remzi M et al[139]	Neural network	Repeat biopsy	820	PSA, percentage free PSA, TRUS, PSA density, PSA density of the transition zone, transition zone volume	Not available	8	10	83	Not performed
Yanke BV et al[140]	Probability nomogram validation[114]	Repeat biopsy	230 (356 biopsies)	Age, DRE, number of previous negative biopsies, HGPIN history, ASAP history, PSA, PSA slope, family history, months from initial negative biopsy, months from previous negative biopsy	2.6 (2-7)	17.9 (12-54)	34	71	Internal
Chun FK et al[113]	Probability nomogram development	Repeat biopsy	2393	Age, DRE, PSA, percentage free PSA, number of previous negative biopsies, sampling density*	1.5 (1-7)	11 (10-24)	30	76	Internal and external
Saturation biopsy									
Walz J et al[115]	Probability nomogram development	Repeat saturation biopsy	161	Age, PSA, percentage free PSA, prostate and BPH volume, PSA doubling time, PSA density of the transition zone, number of previous biopsy sessions, number of cores at saturation biopsy	2.5 (2-5)	24.5 (20-32)	41	75	Internal
Mixed: Initial and repeat biopsy									
Snow PB et al[141]	Neural network	Initial and repeat biopsy	1787	Age, change on PSA, DRE, PSA, TRUS	Not available	6	34	87	Not performed

Table 4
(Continued)

Reference	Prediction Form	Design	Number of Patients	Variables	Median Number of Previous Biopsy Sessions (Range)	Mean Number of Cores (Range)	Cancer Detection Rate (%)	Accuracy (%)	Validation
Carlson GD et al[142]	Probability table	Initial and repeat biopsy	3773	Age, PSA, percentage free PSA	Not available	6	33	Not available	Internal
Djavan B et al[143]	Neural network	Initial and repeat biopsy	272	PSA density of the transition zone, percentage free PSA, PSA density, TRUS (PSA, 2.5-4.0 ng/mL)	Not available	8	24	88	Not performed
			974	PSA density of the transition zone, percentage free PSA, PSA velocity, transition zone volume, PSA, PSA density (PSA, 4.0-10.0 ng/mL)	Not available	8	35	91	Not performed
Stephan C et al[144]	Neural network	Initial and repeat biopsy	1188	Age, DRE, PSA, percentage free PSA, TRUS	Not available	Not available	61	86	Not performed
Porter CR et al[145]	Neural network	Initial and repeat biopsy	319	Age, PSA, gland volume, TRUS, DRE, previous negative biopsy, African American race	Not available	9.7 (6-10)	39	76	Not performed
Matsui Y et al[146]	Neural network	Initial and repeat biopsy	228	PSA density, DRE, age, TRUS	Not available	10-12	26	73	Not performed
Benecchi L[147]	Neural network	Initial and repeat biopsy	1030	Age, PSA, percentage free PSA	Not available	6-12	19	80	Not performed
Yanke BV et al[148]	Probability nomogram development	Initial and repeat biopsy	8851	Age, race, PSA, DRE, number of cores	Not available	6-13	27-38	75	Internal

*Sampling density = ratio of TRUS-derived total gland volume by the number of cores at biopsy.
ASAP, atypical small acinar proliferation of prostate; DRE, digital rectal examination; HGPIN, high-grade intraepithelial neoplasia; PSA, prostate-specific antigen; TRUS, transrectal ultrasound prostate.

external cohorts demonstrated 73% to 76% accuracy.

Accurate prediction of repeat biopsy would be helpful to spare men who do not have prostate cancer a negative repeat biopsy and to identify patients who need a re-biopsy to detect prostate cancer. O'Dowd and colleagues[66] used age, previous histologic findings, percentage free PSA, and total PSA to predict repeat biopsy results in 813 men. Their multivariate logistic regression model yielded 70% accuracy, but it was neither internally nor externally validated. Lopez-Corona and coworkers[114] developed a nomogram that predicts the probability of a positive repeat biopsy after 1 or more negative biopsies. The input variables of the nomogram were patient age, DRE findings, cumulative number of negative cores previously taken, histories of high-grade prostatic intraepithelial neoplasia and/or atypical small acinar proliferations, PSA value, PSA slope, and family history of prostate cancer. The nomogram yielded a predictive accuracy of 71%. However, the complexity of the nomogram makes it impractical in the clinical setting.

Finally, Chun and associates[113] developed and validated a nomogram for prediction of repeat biopsy outcome on the basis of systematic 10 or more cores. The model comprised patient age, DRE findings, PSA value, percentage free PSA, number of previous negative biopsy sessions, and sampling density (ie, ratio between prostate volume assessed at initial biopsy and the planned number of cores at repeat biopsy). Using 3 different cohorts of men, they reported predictive accuracies of 68% to 78% after external validation.

Interpretation of Biopsy Material

The most important task for the pathologist is to make the dichotomous determination of whether the biopsy material obtained contains any prostate cancer. Once this is established, some very relevant qualitative and quantitative assessments are of great utility to the clinicians ultimately counseling the patient regarding treatment options. To allow a pretreatment mapping of the prostate,

Main Points

- Abnormal results on digital rectal examination (DRE) or elevated serum prostate-specific antigen (PSA) value may indicate prostate cancer. The exact cutoff level of what is considered to be a normal PSA value has not been determined, but values of less than 2.5 ng/mL for younger men and slightly higher for older men are often used.
- The diagnosis of prostate cancer depends on histopathologic (or cytologic) confirmation. Biopsy and further staging investigations are only indicated if they affect the management of the patient.
- Transrectal periprostatic injection with a local anesthetic may be offered to patients as effective analgesia when undergoing prostate biopsies. Several types of local anesthesia are now available, but periprostatic nerve block with 1% or 2% lidocaine is the recommended form of pain control and comfort management during transrectal ultrasound-guided prostate biopsy.
- Transrectal ultrasound-guided systemic biopsy is the recommended method in most cases with the suspicion of prostate cancer. Transperineal biopsy is an up-to-standard alternative.
- On initial biopsy, a minimum of 10 systemic, laterally directed cores is recommended, eventually with more cores in larger glands.
- Extended prostate biopsy schemes, which require cores weighted more laterally at the base (lateral horn) and medially to the apex, show better cancer detection rates without increasing adverse events.
- Transition zone biopsies are not recommended in the first set of biopsies, owing to low detection rates.
- One set of repeat biopsies is warranted in cases with persistent indication (abnormal findings on DRE, elevated PSA value, abnormal PSA derivatives, and/or histopathologic findings suggestive of malignancy at the initial biopsy). Biopsy of the transition zone of the prostate should be considered for men undergoing a repeat biopsy for whom a suspicion of a missed cancer anteriorly is high. Overall recommendations for further (third or more) sets of biopsies cannot be made; the decision has to be made on the basis of the individual patient.
- A repeat biopsy is not indicated for men with high-grade prostatic intraepithelial neoplasia if the original biopsy technique was adequate. A prostate biopsy that reveals atypical glands that are suspicious for but not diagnostic of cancer should be repeated.
- Saturation biopsy ($\geq$ 20 cores) should be reserved for repeat biopsy in patients who have negative results on initial biopsy but who are still strongly suspected to have prostate cancer. Complications and risk of diagnosing clinically insignificant cancer using saturation biopsy after a prior negative biopsy are reported to be no higher than with routine sextant or extended-core biopsy unless general or regional anesthesia is used, whereas the detection of clinically significant cancer is higher.

the following prostate biopsy parameters should be reported to allow optimal decision making:

- Number and total length of all cores
- Number of cores with cancer and location (calculate percentage of biopsy cores involved with cancer: number of involved cores/total cores as percentage)
- Total length of biopsy cores involved with cancer (calculate percentage of biopsy core involved with cancer: millimeters involved with cancer/total length of core in millimeters)
- Number of cores with perineural invasion
- Number of cores with lymphovascular invasion
- Gleason score for each core with cancer
- Number and location of cores with atypical glands, suspicious for cancer
- High-grade prostatic intraepithelial neoplasia: extent and location
- Each core reported individually ■

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