CAN BIOPSY BE A RELIABLE PREDICTOR OF SPATIAL DISTRIBUTION OF PROSTATE CANCER? COMPARISON OF A NOVEL BIOPSY REGIMEN WITH RADICAL PROSTATECTOMY FINDINGS

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ABSTRACT

Objectives. To obtain accurate spatial information on cancer distribution with a novel prostate biopsy regimen.

Methods. From 2003 to 2005, 265 patients underwent a three fan-shaped biopsy (3FSB) technique of 12 to 14 cores and sextant biopsy (SB) simultaneously. When both techniques had positive findings, and radical prostatectomy was performed, the concordance among the positive biopsy locations of the SB, 3FSB, and the combination of both (the reference standard biopsy [RSB]), the proven locations of cancer, and the presence of extracapsular extension and positive surgical margins was calculated.

Results. A total of 41 patients were selected, and 74 locations (left and right apex, left and right lobe) had cancer. Of these, 61 were confirmed by RSB, 58 by 3FSB, and 43 by SB with a sensitivity of 95%, 78%, and 58%, respectively. The sensitivity at the apical location was consistently greater for the 3FSB at 68% (19 of 28) compared with 40% (11 of 28) for all proven apical positive localizations and 100% (19 of 19) compared with 58% (11 of 19) for the RSB. The receiver operating characteristic analysis showed 78% accuracy for 3FSB and 68% accuracy for SB compared with the RSB. At the apex, the 3FSB and SB revealed positive surgical margins with a sensitivity of 1 and 0.4, specificity of 0.067 and 0.4, positive predictive value of 0.263 and 0.182, and negative predictive value of 1 and 0.667, respectively.

Conclusions. The 3FSB had a great ability to find cancer in the gland, especially at the apex.


Biopsy is recognized as the standard procedure for the diagnosis of prostate cancer but also provides useful information regarding disease grade and extent. Overall, the side-specific and site-specific percentages of cores found with cancer are predictors of positive surgical margins (PSMs), extracapsular extension (ECE), and final tumor volume. However, it is known that positive biopsy findings frequently do not detect tumor bilaterally. Moreover, the presence of tumor at the prostate apex is frequently underestimated. This lack of information undermines the potential prognostic value of the procedure and can lead to disease extent underestimation when planning treatment.

To date, a variety of biopsy schemes have been proposed to increase the detection rate, but the accuracy for detecting the anatomic location of prostate cancer has rarely been considered. Therefore, we present a novel biopsy technique that provides a fan-shaped sampling of the apex and posterolateral regions of the prostate. This biopsy regimen is called the three fan-shaped biopsy technique (3FSB). It was developed according to the well-known pathways of cancer spread in the gland and from a previously described biopsy technique.

MATERIAL AND METHODS

From June 2003 to June 2005, 265 patients provided written informed consent and agreed to undergo the 3FSB and sextant biopsy (SB) simultaneously. The procedures were performed by three surgeons (C.I., A.N., and G.V.). In the 265 patients, 84 cases of prostate cancer were detected (32%).
even-numbered sections were not stained but were used for 7, 9, 11, 13, and 15) were stained with hematoxylin-eosin. The consecutive sections of 5

FIGURE 1. 3FSB scheme (gray). Adjunctive cores of 3FSB scheme for prostate greater than 50 cm³ (white). SB scheme shown in black.

33 cases (63%), both techniques disclosed tumor. In 29 (35%), only the 3FSB was diagnostic. Only 2 cases were uniquely identified by SB (2%). Overall, 3FSB had a 31% detection rate (82 of 265) and SB a 21% detection rate (55 of 265). Of 84 patients, 47 underwent radical prostatectomy, and 41 had had positive biopsy findings from both techniques and underwent additional evaluation.

**BIOPSY TECHNIQUE**

The prostate was imaged in real time using a type 2102 Hawk BK Medical ultrasound scanner and model 8808, 5 to 7.5-MHz biplanar probe. Transrectal ultrasound-guided systematic biopsies were performed with an end-firing technique during sagittal scanning using an 18-gauge biopsy needle driven by a spring-loaded biopsy gun. SB was performed first. Two containers were provided to the pathologist, one for the left and one for the right side. Apical cores were recognizable because they were inked at the distal side. In 3FSB (Fig. 1), the prostate was divided into four regions: the left and right apex and the left and right posterolateral zones. Medial and lateral biopsy cores from the apex were taken, about 30° and 60° from the midline in the transverse scan. On sagittal scanning, the needle was directed nearly parallel to the rectal surface because, at the apex, the vertical growth is limited. The posterolateral aspects of the gland were then sampled. Four cores (five for glands greater than 50 cm³ in volume) were taken from each lobe. The probe was angulated 45° laterally and rotated until the lateral aspect of the prostate was reached in the frontal scan. Moving to the base, the probe was progressively inclined anteriorly, increasing the vertical extension. A total of 12 to 14 cores (when the prostate volume was greater than 50 cm³) were obtained. Four containers, one each for the left and right posterolateral zone, right posterolateral zone, right apex, and left apex were provided.

**PATHOLOGIC EXAMINATION**

**Biopsy Specimens.** Each core was stretched and put in a labeled tissue cassette between two nylon sponges and subsequently fixed in 10% buffered formalin. After dehydration, the core biopsies were embedded in paraffin wax. During embedding, the histotechnologist attempted to put the whole length of the biopsy in the same plane. Each paraffin block was serially sectioned using a conventional microtome, obtaining 15 consecutive sections of 5 μm. Odd-numbered sections (1, 3, 5, 7, 9, 11, 13, and 15) were stained with hematoxylin-eosin. The even-numbered sections were not stained but were used for successive immune phenotypic analysis such as p63 and keratin 34βE12.12-14

**Radical Prostatectomy Specimens.** The entire surface of the specimen was inked using two different colors for each side and fixed by immersion into a moldant. The specimen was then injected with 10% neutral-buffered formalin solution and immersed in 300 to 400-mL formalin solution to fix for 24 hours. The seminal vesicles were removed from the specimen and analyzed by taking a section through the base of the seminal vesicle at which the seminal vesicle joins the prostate. The prostate specimen was step-sectioned at 4-mm intervals perpendicular to the long axis (apical to basal) of the gland. Serial coronal sections, parallel to an initial en face section of the apex, were taken until the junction of the seminal vesicles was approached. The whole mount sections were identified in a consecutive manner. The cut specimen was dehydrated in graded alcohols, cleared in xylene, embedded in paraffin, and examined histologically as 5-mm-thick, whole-mount, hematoxylin-eosin-stained sections. For the final report, the prostate gland was divided into four zones: the left and right lobe and left and right apex. The biopsy cores were grouped accordingly.

**COMPARISON OF BIOPSY CORES WITH RADICAL PROSTATECTOMY SPECIMENS**

**Cancer Location.** No false-positive biopsy locations were found. To calculate the sensitivity, the sum of all positive proven localizations was divided with the sum of all biopsy positive localizations obtained by the combination of the two techniques, the reference standard biopsy (RSB), and then the sum of all biopsy-positive localizations of the 3FSB and SB techniques. To better compare the biopsy regimens, an additional analysis was performed.

For each radical prostatectomy specimen, the sum of the proven localizations with a correspondent positive biopsy core was divided with the sum of proven positive localizations. This was repeated for the SB, 3FSB, and RSB. Thus, for each patient, we had a corresponding fraction for SB, 3FSB and RSB, with six possible values corresponding to a six-point scale (grade) of accuracy: one fourth (1), one third (2), one half (3), two thirds (4), three fourths (5), and one (6).

When the fraction attributed to the RSB was one, we designated the case as truly positive. When the fraction was less than one or the cancer volume was less than 0.5 cm³, the case was designated as truly negative. Truly negative and positive cases were challenged with the resulting grade of accuracy of both techniques, and receiver operating characteristic analysis was then performed.

**PSMs and ECE.** The sensitivity, specificity, positive predictive value, and negative predictive value of each technique for PSMs were determined for all four locations together and at the apex. The sensitivity, specificity, positive predictive value, and negative predictive value were also calculated for lobar ECE.

**RESULTS**

The median age of the 41 patients examined was 62 years (range 48 to 72). The median prostate-specific antigen level was 7.94 ng/mL (range 3.1 to 19.8). The mean biopsy Gleason score was 5.6 (median 6, range 4 to 9). Nine patients (22%) had Stage pT2a prostate cancer, 8 had T2b (20%), 10 had T2c (24%), 12 had T3a (29%), and 2 had Stage T3b (5%). Three patients had nodal metastasis (7%), and seven had at least one PSM (17%). The mean definitive Gleason score was 6.5 (median 6,
range 4 to 9). Of the 41 patients, 21 had a Gleason score of 4 to 6 (51%), 11 had a Gleason score of 7 (27%), and 9 had a Gleason score of 8 to 10 (22%). The median prostate volume was 35.1 cm³ (range 15.8 to 90.7), the median cancer volume was 2.8 cm³ (range 0.4 to 13.2), and the fraction of prostate cancer found with cancer ranged from 0.7% to 24.9% (median 9.9%, mean 11%). One patient had a prostate cancer volume of less than 0.5 cm³, and the definitive Gleason score was 6. Only 2 cases of multicentric carcinomas were detected.

The cancer was located in the left lobe in 24 radical prostatectomy specimens, in the right lobe in 22, in the right apex in 13, and in the left apex in 15. Right and left ECE was present in 9 and 3 cases, respectively. PSMs were present in 3 cases in the left lobe, in 3 in the right lobe, in 2 in the left apex, and in 3 in the right apex.

**Cancer Location.** The sum of all proven positive localizations was 74. The sensitivity was 82% (61 of 74) for RSB, 78% (58 of 74) for 3FSB, and 58% (43 of 74) for SB. With respect to RSB, the sensitivity of 3FSB and SB was 95% (58 of 61) and 70% (43 of 61), respectively. The sensitivity at the apical location was consistently greater for 3FSB at 68% (19 of 28) compared with 40% (11 of 28) for all proven apical positive localizations. It was 100% (19 of 19) compared with 58% (11 of 19) for RSB.

The receiver operating characteristic (ROC) analysis showed 78% accuracy for detecting the anatomic location of prostate cancer using 3FSB, with 85.2% sensitivity and 64.3% specificity for RSB. The fitted ROC area was 0.913, the empiric ROC area was 0.877. The accuracy of the SB was 68.3%, with 55.6% sensitivity and 92.9% specificity; the fitted ROC area was 0.88 and the empiric ROC area was 0.844.

**PSM Status.** Considering all the locations together, 3FSB and SB had a sensitivity of 0.727 and 0.364, specificity of 0.206 and 0.381, positive predictive value of 0.138 and 0.093, and negative predictive value of 0.813 and 0.774, respectively.

At the apex, 3FSB and SB had a sensitivity of 1 and 0.4, specificity of 0.067 and 0.4, positive predictive value of 0.263 and 0.182, and negative predictive value of 1 and 0.667, respectively.

**ECE Status.** The 3FSB and SB techniques had a sensitivity of 0.917 and 0.417, specificity of 0.118 and 0.235, positive predictive value of 0.268 and 0.161, and negative predictive value of 0.800 and 0.533, respectively.

**COMMENT**

Prostate biopsy is expected to have the greatest detection rate of clinically significant prostate cancer; however, in the case of a histologically con-firmed diagnosis, it should also give an idea of the real disease extent and the biologic behavior. Overall, the side-specific and site-specific percentage of cores found with cancer are predictors of PSMs, ECE, and final tumor volume. A negative finding for an SB core had a high negative predictive value for ECE. However, prostate biopsy frequently fails to ascertain the tumor location in the gland. The distribution of prostate cancer in the gland has a great prognostic affect and aids in treatment planning but is frequently underestimated. The analysis of the side-specific and site-specific percentage of cores found with cancer has been extensively studied and was not the object of the present study. We studied a biopsy protocol to increase the spatial information given by the procedure on the basis of the assumptions previously reported. McNeal et al. found that the cancer spread in the prostate was not random but was largely an expression of the interaction between the tumor and organ stroma, which follows a predictable pattern. The dominant growth is toward the base from the apex in a transverse direction. Spread along the capsule characterizes most of the cancer located in the peripheral zone. In contrast, transitional zone cancers tend to invade the anterior fibromuscular stroma in the early phases, owing to their location in the anterior-mid part of the zone. Vertical growth is, in an initial phase, limited and increases, moving toward the base. Therefore, the apex and posterior zone of the prostate are the sites most likely to harbor cancer. Takashima et al. found that prostate cancer extended to the distal half/apex of the prostate in 85% of cases when it was not palpable. Accordingly, Gore et al. concluded that biopsy regimens that include cores from the lateral apex are associated with the greatest detection rate. Presti et al. and Chon et al. demonstrated that biopsies directed laterally when moving closer to the base, sampling the lateral mid gland and lateral base, should be included in an optimal biopsy scheme. Moreover, no rationale seems to exist for routine biopsy of the transitional zone of the prostate or seminal vesicles. In our biopsy regimen (Fig. 1), the prostate is divided into four regions: the left and right apex and left and right posterolateral zone. The apex is sampled using the fan-shaped scheme. The posterolateral regions are sampled in a fan-shaped fashion, increasing the inclination of the probe anteriorly moving toward the base; the probe is always extra rotated and the needle directed laterally. Our scheme follows the routes of cancer spread among the gland and was expected to have a detection rate comparable to that of more recent biopsy regimens but also to give an exact idea of the location of the prostate cancer in the gland.
We selected 41 patients with positive biopsy findings from SB and 3FSB who subsequently underwent radical prostatectomy. In this subgroup of patients, the accuracy of 3FSB for finding all cancer locations in the gland was significantly greater than that of the SB, 78% versus 68%, with respect to the RSB. The negative predictive value for PSM and ECE was always greater for 3FSB; considering the apex only, the negative predictive value was 1 for the PSM.

The use of the 3FSB was very informative, especially at the apex. However, the present study had limits. First, the number of patients examined was low. Second, we compared the 3FSB technique to the SB, which has a low detection rate and can no longer be considered the standard biopsy. However, which modern scheme can be considered standard? We are also not sure that an increased detection rate corresponds with increased accuracy in determining prostate cancer location. A recent report showed that a 10-core biopsy scheme failed to find tumor bilaterally in 78% of cases when a single, well-differentiated microfocal cancer was detected.17

CONCLUSIONS

Just as with more recent biopsy regimens, 3FSB increases the detection rate of prostate cancer by about 30% with respect to SB and, more importantly, has a great ability to determine the cancer location in the gland, resulting in improved prognostic impact, particularly at the apex.

REFERENCES