

## SYSTEMATIC SEXTANT BIOPSIES IN 420 PATIENTS REFERRED FOR PROSTATE EVALUATION

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### ABSTRACT

**Purpose:** We present the results of our series of six systematic sextant transrectal ultrasound guided biopsies in a prostate cancer detection program. **Material and Methods:** A total of 420 men referred to the outpatient clinic of our department to exclude prostate cancer, underwent examination with transrectal ultrasound and transrectal ultrasound guided systematic sextant biopsy. The reasons for referral were, increased serum prostate specific antigen (PSA) level, finding of a palpable nodule on digital rectal examination or greater firmness of one prostatic lobe. **Results:** One hundred eighteen of 420 patients (28%), who underwent systematic sextant biopsies of the prostate, had prostatic carcinoma. The percentage of well differentiated prostate cancers decreased with increasing PSA level. Cancer was found more than twice as often in patients with hypoechoic peripheral zones compared to those with isoechoic zones. Twenty nine percent of all cancer detected was in an isoechoic prostate. **Conclusion:** Overall, 28% of patients who underwent systematic sextant biopsies of the prostate had prostatic carcinoma. Although the transrectal ultrasound guided sextant biopsy technique is the gold standard for the detection of prostate cancer, the true false-negative rate is unknown.

**Key Words:** Biopsy, Prostate Cancer, Ultrasonography.

### INTRODUCTION

Except for skin cancer, prostate cancer is the most common type of cancer and the second leading cause of death due to cancer among men in the United States. The American Cancer Society estimated that 179,300 men were diagnosed with and 37,000 died of prostate cancer in the United States during 1999 (1).

Transrectal ultrasound (TRUS) and TRUS-guided biopsy have become the method of choice for the detection of prostate cancer, especially

when curative treatment is planned. Isoechoic cancers are frequent (23% to 25%); therefore, sampling cannot be restricted to hypoechoic or hyperechoic lesions (2, 3).

Systematic sextant biopsy of the prostate under transrectal ultrasound guidance was introduced in 1989 and has revolutionised the ability to detect carcinoma of the prostate (4). As originally described, 6 biopsies were obtained in the parasagittal line halfway between the lateral border and midline of the prostate on the right and left sides from the base, midgland and apex.

Later Stamey recommended shifting biopsies more laterally to sample the anterior horn of the peripheral zone better (5).

Several groups have proposed new biopsy strategies, often increasing the number of biopsies and the sectors to be sampled or performing biopsies more laterally, but controversial data have also been reported about the real advantage of these new techniques (6-8).

We present the results of our series of six systematic sextant TRUS-guided biopsies in a prostate cancer detection program.

#### **MATERIAL AND METHODS**

From February 1996 through June 2000, a total of 420 men who were referred to the outpatient clinic of our department to exclude prostate cancer, underwent examination with TRUS and TRUS-guided biopsy. Patient age ranged from 50 to 77 years. The reasons for referral were increased serum prostate specific antigen (PSA) level, finding of a palpable nodule on digital rectal examination or greater firmness of one prostatic lobe.

Before any digital or ultrasonographic examination of the prostate, blood serum was obtained for PSA determination using the Hybritech method (Hybritech, Inc., San Diego, California). Patients with a medical history of finasteride use and urethral catheter due to urinary retention were excluded from the study. Digital rectal examination (DRE) was performed with the patient in the knee-elbow position, and the results were reported as normal (including benign prostatic hyperplasia [BPH]), firm or nodular. The Bruel and Kjaer Type 2001 was used for the ultrasound examinations, with a multiplane 7.5 MHz probe. All digital rectal and transrectal ultrasound examinations were performed by the same urology team. All patients underwent biopsy mapping of the prostate with six systematic sextant ultrasonography guided biopsies with an 18 gauge Tru-Cut biopsy needles, as described by Hodge et al (4). The transrectal biopsies were performed at the apex, middle and base of the right and left prostatic lobes in the parasagittal plane. If a hypoechoic area in the peripheral zone was diagnosed with transrectal ultrasound, a biopsy of that area was also performed. Prostatic cancer was histologically graded according to the Gleason

system (9). All patients took a three to five day course of a fluoroquinolone antibiotic (or appropriate alternative in those with fluoroquinolone allergy) the night before and a pre-examination enema was given. Patients with prosthetic devices (artificial joints or mechanical heart valves) or a diagnosis of mitral valve prolapse with regurgitation and/or thickened valve received additional prophylactic amoxicillin or erythromycin before biopsy. Patients were instructed not to take aspirin or nonsteroidal antiinflammatory agents for at least 5 days before the procedure.

The core biopsy specimens were kept in labelled, separate containers, and a notation was made when the specimen was taken from a lesion. All specimens were fixed in 10% neutral buffered formalin and stained with hematoxylin and eosin. All biopsy samples were examined by the same pathology team.

#### **RESULTS**

Overall, 118 of the 420 patients (28%) who underwent systematic sextant biopsies of the prostate had prostatic carcinoma (Table 1). Among the 14% of the patients with prostate cancer who had a normal prostate on DRE, the PSA level had some impact on the detection rate. For men with a PSA level between 4-10ng/ml, the positive biopsy rate was 12%, whereas it was 21% for men with a PSA level greater than 10ng/ml.

The percentage of well-differentiated prostate cancers decreased with increasing PSA levels (Table 2). In 60% of men with positive biopsy who had a PSA level lower than 4ng/ml, the cancer was well-differentiated (Gleason score < 7), compared to 28% in those with biopsy proven cancer and a PSA level of 4 to 10ng/ml, and 20% in those with a PSA level greater than 10ng/ml (Table 2).

Of 133 patients with a firm, nonnodular prostate on DRE, 28 (21%) had prostate cancer. For those with a PSA level of less than 4, 4 to 10 and greater than 10ng/ml, the positive biopsy rates were 11%, 18% and 29% respectively (Table 1). For those with a nodular prostate and PSA levels of less than 4, 4 to 10 and greater than 10ng/ml, the positive biopsy rates were 14%, 35% and 61%, respectively.

Table 1: Results of systematic, sextant TRUS-guided biopsies in 420 men according to DRE and PSA concentration.

PSA Findings				
DRE	0-3.99ng/ml n(%)	4-10ng/ml n(%)	>10ng/ml n(%)	Total n(%)
Normal	-	8/69 (12)	6/29 (21)	14/98 (14)
Firm	3/28 (11)	9/50 (18)	16/55 (29)	28/133 (21)
Nodular	7/50 (14)	22/62 (35)	47/77 (61)	76/189 (40)

Values are expressed as the number of patients with proven prostate cancer/total (percent).

Table 2: Results of histological grading of 118 patients with biopsy proven prostate cancer according to PSA concentration

PSA Findings				
Gleason score	0-3.99ng/ml n(%)	4-10ng/ml n(%)	>10ng/ml n(%)	Total n(%)
<7	6/10 (60)	11/39 (28)	14/69 (20)	31/118 (26)
=7	3/10 (30)	18/39 (46)	35/69 (51)	56/118 (48)
>7	1/10 (10)	10/39 (26)	20/69 (29)	31/118 (26)

Values are expressed as the number of patients/total (percent).

Table 3: Results of transrectal ultrasound in 420 men according to digital rectal examination findings.

Prostate Cancer According to TRUS Findings		
DRE	Hypoechoic No/Total (%)	Normal No/Total (%)
Normal	7/29 (24)	7/69 (10)
Firm	23/82 (28)	5/51 (10)
Nodular	54/108 (50)	24/81 (30)
Total	84/219 (38)	34/201 (17)

For patients with a firm and nodular prostate the positive biopsy rate increased with increasing levels of PSA (Table 1). It should be emphasised that 10 of the 78 patients (13%), with PSA levels less than 4ng/ml but suspicious (firm or nodular) DRE findings, had prostate cancer.

Cancer was found more than twice as often in patients with hypoechoic peripheral zones (38%) compared to those with isoechoic zones (17%) (Table 3). Overall, 29% of all detected cancer was in an isoechoic prostate. It is important to note

that the positive biopsy rate increased with increasing abnormality of the prostate (normal to firm to nodular) regardless of the echogenicity of the prostate (Table 3).

Three hundred and two of 420 patients (72%) demonstrated negative results in prostate biopsy. Patients having pathological sonographic results, increased serum PSA levels or a palpable nodule on digital rectal examination were reevaluated in another biopsy.

## DISCUSSION

The cancer detection rate in this study cannot be compared with those in other early detection programs because most of our patients had been referred for further diagnosis of the prostatic status and thus, they were biased.

Hodge et al (4) standardized the TRUS-guided biopsy procedure in 1989. In this widely used protocol, the biopsy angle was set at 45° and three biopsy specimens were taken from the centre of each lobe from the apex, middle and base of the prostate, equidistant from the midline and the lateral border of the gland and located approximately 1 cm apart. In taking three biopsies at points 1 cm apart, these authors were anticipating detection at least of tumors over 1 cm<sup>3</sup> in volume. They also recommended that additional biopsies should be performed, directed at specific hypoechoic areas. The sextant method has been the gold standard of systematic prostate biopsy. However, the optimum number of prostate biopsy cores needed for detection of prostate cancer is unknown.

Eskew et al reported a biopsy protocol ranging between 13 and 18 prostate biopsies performed under ultrasound guidance (7). The biopsies included the sextant cores described by Hodge et al (4), with additional biopsies of the transitional and lateral peripheral zones. The detection rate of adenocarcinoma of the prostate increased by 35% if more than 6 biopsies were performed. A concern of the 5 region method is that this more extensive biopsy detects cancers that would otherwise remain clinically insignificant (10). Later, Eskew et al demonstrated no significant difference in tumor volume, DNA ploidy status, Gleason score or final pathological tumor stage between tumors diagnosed using the 5 region versus sextant biopsy techniques (11). In addition to all of these biopsy protocols, most authors recommend that routine transition zone biopsies should be performed in patients in whom prior negative systematic sextant biopsies failed to reveal cancer, but whose PSA is markedly elevated or rapidly increasing (12,13).

Table 1 indicates that patients with an abnormally firm prostate, either symmetrical or asymmetrical, should undergo systematic sextant biopsies regardless of the level of PSA, since a

positive biopsy rate of 11% in patients with a PSA level of less than 4ng/ml appears to be cost-effective. These positive biopsy rates increase precipitously with increasing levels of PSA and this finding is even more dramatic in patients with a nodular prostate on DRE. While hypoechoic areas in abnormally firm and nodular prostates were associated with a much higher incidence of cancer than isoechoic prostates (Table 3), 29 cancers would have been missed if these isoechoic, abnormal prostate had not been thoroughly biopsied.

Overall, approximately 29% of all cancer will be missed if hypoechogenicity is used as a transrectal ultrasound criterion for biopsy. Vallencien et al (14) performed systematic sextant biopsies in 100 men with benign prostatic hyperplasia. Of the 14 cancers detected, 12 were isoechoic. Of the 18 hypoechoic areas, only 2 were positive for prostate cancer. These differences serve to emphasise the subjectivity of hypoechoic lesions on transrectal ultrasound, which is also true for the digital rectal examination, a subjectivity that confirms the usefulness of systematic sextant biopsies almost regardless of what is seen or felt on transrectal ultrasound and digital rectal examination.

In screening studies, most men with elevated serum PSA concentrations have PSA levels in the 4 to 10 ng/ml range and may have enlarged, palpably benign prostate glands on DRE. Overall, only one quarter of these men have cancer detected by an initial prostatic needle biopsy (15). Two studies from Turkey about this concept revealed that the biopsy guided prostate cancer detection rate is disappointingly low (17.5% regardless of DRE findings, 7.5% with normal DRE) in the PSA ranges between 4 to 10ng/ml. (16,17). Our cancer detection rate was 12% in patients with PSA between 4-10ng/ml and normal DRE findings, which correlates with the previous studies from Turkey.

Although the TRUS-guided sextant biopsy technique is the gold standard for the detection of prostate cancer, the true false-negative rate is unknown. In this study, overall 28% of patients who underwent systematic sextant biopsies of the prostate had prostatic carcinoma. Therefore, 72% of patients had negative biopsy results. Other authors have reported on their experience concerning the yield of carcinoma on ultrasound

guided biopsy, following a negative biopsy (18). If a patient has pathological sonographic findings, high PSA level and abnormal digital rectal examination we suggest a repeat biopsy. Future attempts to improve the sextant biopsy technique will have to take factors such as prostate volume, free PSA, PSA density and PSA density of the transition zone into account.

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