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PROSTATE CANCER DETECTION IN REPEAT EXTENDED PROSTATE BIOPSY IN MEN WITH PREVIOUS NEGATIVE BIOPSY FINDINGS

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SUMMARY – The purpose of this report is to show our own results of repeat transrectal ultrasound guided biopsies, with special reference to the prevalence of newly diagnosed carcinoma in the transition zone of the prostate. Transrectal ultrasound guided repeat biopsies (six cores laterally plus two cores from transition zones) were performed in 64 patients. Indications for repeat biopsy were persistently elevated prostate specific antigen (PSA) levels of 4.0 ng/ml or more, premalignant lesions noted in previous biopsy result (PIN, prostatic intraepithelial neoplasia; ASAP, atypical small acinar proliferation; and AAH, atypical adenomatous hyperplasia), PSA velocity of 0.75 ng/ml *per* year or more, PSA density of 0.15 ng/ml/ccm or more, and free/total PŠA ratio less than 18%. Twenty-one (32%) patients had positive biopsies for prostate cancer, and the rest of 43 (68%) patients were diagnosed as having benign prostate hyperplasia, inflammation, normal prostate tissue, or suspect lesions. When stratified according to anatomic location of positive cores, 19.1% of patients had isolated transition zone tumors on repeat biopsy, and 28.6% had both transition and peripheral zone tumors. A total of 23 (35.93%) patients with premalignant lesions on initial biopsy were also included. Of these, repeat biopsy pathologic specimens indicated malignancy in nine (39.1%) patients. There is a significant false-negative rate for initial transrectal ultrasound guided biopsy. Therefore, repeat biopsy is recommended in all patients who meet the criteria for transrectal ultrasound guided biopsy and in those in whom initial biopsy is negative. Also, classic sextant biopsy laterally plus two cores from each transition zone of the prostate is recommended to reduce the false-negative rate in repeat biopsies due to the high detection rate of cancer in the transition zone of the prostate. Recent literature on the topic is reviewed and discussed.

Key words: *Prostatic neoplasms – diagnosis; Prostatic neoplasms – pathology; Prostate – pathology; Biopsy – methods*

Introduction

Prostate cancer is a significant cause of morbidity and mortality. The natural aging of the population as well as the widespread use of diagnostic tests such as prostate specific antigen (PSA) have led to an increase in the incidence of men diagnosed with localized prostate cancer. The majority of prostate cancers are currently diagnosed *via* transrectal ultrasound (TRUS) guided prostate needle biopsy. Indications for this procedure in patients who are candidates for therapy are well established, including suspect digitorectal examination or abnormal serum PSA levels[1]. The sextant biopsy technique has been widely accepted, however, some recent studies suggest that standard sextant biopsy may underestimate cancer[2-4]. Since the introduction of sextant biopsies, the average number of biopsies performed *per* patient has risen, the cancer detection rate has fallen, and the repeat biopsy rate has increased[5]. This is largely due to the growing rate of false-negative biopsies. Repeat TRUS biopsies should be recommended for patients in whom the initial set of biopsies has not revealed cancer but have a high risk of the pres-

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ence of malignancy based on clinical staging tools. Such patients include those with persistent or elevating PSA level, those with a family history of prostate cancer, those with positive digital rectal examination, and finally those with premalignant lesions on previous biopsy. Clinicians are commonly faced with a dilemma of treating a patient with abnormal digital rectal examination or elevated PSA level but negative TRUS biopsy. This paper deals with the prevalence and localization, especially in the transition zone of the prostate, of newly diagnosed prostate carcinoma in patients with previously negative biopsies.

Patients and Methods

From January 1999 to December 2002, a total of 64 patients with previously negative TRUS guided biopsies were admitted to our department for evaluation and submitted to repeat TRUS guided biopsies. These patients are included in this report and were entered in the study in a prospective fashion. The patients were 43 to 81 years old. The indications for biopsy were persistently elevated PSA of 4.0 ng/ml or greater, abnormal digital rectal examination with or without elevated PSA, premalignant lesions noted in previous biopsy result (PIN, prostatic intraepithelial neoplasia; ASAP, atypical small acinar proliferation; and AAH, atypical adenomatous hyperplasia), PSA velocity of 0.75 ng/ml *per* year or more, PSA density of 0.15 ng/ml/ccm or more, and free/total PŠA ratio less than 18%. All ultrasound examinations were performed by one urologist on a Siemens SI 400 diagnostic ultrasound machine with 7.5 MHz biplanar probe. Eight needle cores (classic sextant plus bilateral transition zones) were routinely obtained with 18 gauge needle and automatic biopsy gun. In patients with previously abnormal pathologic findings (PIN, ASAP, AAH) one extra core was obtained from the suspect sector. All biopsy material was classified according to the Gleason scoring system. All patients were administered antibiotic prophylaxis (fluoroquinolone) for five consecutive days, starting one day prior to biopsy. Serum PSA value was measured by the DPC ELISA method. PSA density was obtained by dividing PSA by prostate volume (0.52 x height x width x length). PSA velocity was obtained by subtracting PSA value at repeat biopsy from that on initial biopsy and dividing the result by the inter-biopsy interval standardized to one year.

Table 1. Gleason score grades in positive repeat biopsy specimens (n=21)

Gleason score grade	n	%
2-4	4	19
5-6	10	47.6
7	4	19.1
8-10	3	14.3

Table 2. Results of repeat biopsies in patients with premalignant lesions on initial biopsy

	Initial biopsy		Repeat biopsy – PC	
	n	%	n	%
PIN	16	69.6	6	66.66
ASAP	5	21.8	2	22.22
AAH	2	8.6	1	9.99

PC=prostate cancer; PIN=prostatic intraepithelial neoplasia; ASAP=atypical small acinar proliferation; AAH=atypical adenomatous hyperplasia

Results

As mentioned above, TRUS guided repeat biopsies were performed in 64 patients, mean age 68.4 (range 43-81) years, mean PSA 10.75 ng/ml, mean PSA velocity 1.18 ng/ml *per* year, mean PSA density 0.38 ng/ml *per* ccm of prostate tissue, and mean free to total PSA ratio 14.08%. In patients with premalignant lesions, repeat TRUS biopsy was performed after 6 weeks and all others were diagnosed within three years of initial biopsy. Twenty-one (32%) patients were pathologically diagnosed as having prostatic cancer, and the remaining 43 (68%) patients as having benign prostate hyperplasia, inflammation, normal prostate tissue or suspect lesions. Pathologic specimens from the initial biopsy were benign in 41 (64.06%) patients, whereas premalignant lesions were detected in other patients. Gleason score grades in repeat biopsy specimens are shown in Table 1. Twenty-three (35.93%) patients with premalignant lesions (PIN in 16 (69.6%), ASAP in 5 (21.8%) and AAH in 2 (8.6%) patients) on initial biopsy

Table 3. Anatomic localization of malignant lesions (positive cores) in repeat biopsies (n=21)

Localization	n	%
Peripheral zone	11	52.3
Peripheral and transition zone	6	28.6
Transition zone	4	19.1

were also included. Of these, repeat biopsy pathologic specimens were diagnosed as malignant in nine (39.1%) patients (Table 2). When stratified according to anatomic location of positive cores, 11 (52.3%) patients had positive peripheral zone biopsies, six (28.6%) had combined positive transition zone and peripheral zone biopsies, and four (19.1%) had isolated transition zone tumors (Table 3).

Discussion

None of the available tests can exclude the diagnosis of prostate cancer with certainty. PSA testing along with TRUS guided needle prostate biopsy has revolutionized the evaluation of men with prostate carcinoma. The overwhelming majority of men diagnosed with prostate carcinoma are diagnosed on the basis of systematic sextant TRUS guided prostate biopsies. There is ever more evidence in the recent literature suggesting a high false-negative rate of initial sextant biopsies. The false-negative rate of standard sextant biopsy has been reported to be as high as 15% to 31%[2-4]. So, standard sextant prostate biopsies may underestimate cancer in men in whom clinical findings are suspect of localized prostate cancer. Numerous studies suggest that modifications of the standard sextant biopsy technique by increasing the number of cores obtained or expanding the number of regions sampled may improve the detection of prostate cancer at TRUS guided biopsy[2-4]. Of our patients with negative initial TRUS guided biopsies, 32% had positive repeat biopsies. Similar results have been reported by Fleschner *et al.*[6]. In their study, PSA levels exceeding 20 ng/ml and hypoechoic lesions on prostate sonography were found to significantly predict positive biopsy. There are many explanations for the high false-negative rate associated with TRUS guided prostate biopsy. Conventional sextant biopsy samples a small proportion of the prostate gland. As seen in our results, almost 20% of cancers detected on repeat biopsy were localized in the transition zone of the prostate gland. Thus, if standard sextant biopsy is performed laterally, a significant proportion of prostate cancers are missed. The increasing number of patients with impalpable tumors may also be a contributing factor, as these small tumors are extremely difficult to detect[2]. Also, prostate cancers are multifocal in nature and have a relatively high prevalence. All these factors make the potential finding of prostate cancer on repeat biopsy possible by chance alone. Catalona *et al.* report that 41% of men with PSA levels greater than 10 ng/ml had positive second biopsies[7]. On the other hand, in a large study by Keech *et al.* positive repeat biopsies were found in only 19% of patients[8]. In this study, PSA and PSA velocity were significant risk factors for positive repeat biopsies. One of the reasons for these discrepancies is the fact that transition zone biopsies were not routinely done in the former study.

The fact remains that 20% of cancers detected on repeat biopsy were localized in the transition zone of the prostate gland, and the overall detection of carcinoma on repeat biopsy was about 30%. Transition zone cancers are generally nonpalpable and have historically been diagnosed only by TURP. Many authors recommend transition zone biopsies plus sextant biopsies or even more extended biopsy protocols for all patients undergoing prostate tissue sampling[9,10]. Others suggest that routine performance of transition zone biopsies is not warranted[6,11]. However, most authors agree that transition zone biopsies are highly useful in patients undergoing repeat biopsies after prior negative sextant biopsies[8]. Transition zone biopsies should be performed near the midline, and as close as possible to the urethra and anterior fibromuscular stroma. Most authors obtain two cores from each lobe of the transition zone[6,8]. Also, recent studies report on an increased detection rate when far lateral directed biopsies are obtained. Biopsy tissue obtained in this far lateral plane is exclusively within the peripheral zone where most prostate cancers arise from. It is logical that more laterally directed biopsies may have improved detection rate as compared with standard sextant biopsies. In our patients, premalignant lesions on initial biopsy were associated with a positive repeat biopsy rate of 39.1%. This rate is consistent with those in another series of repeat sextant biopsy in patients in whom initial biopsy findings indicated prostatic intraepithelial neoplasia or atypical small acinar proliferation[12]. The rate of detection is somewhat increased in patients with premalignant lesions on previous negative biopsies.

Conclusion

Based on our data and recent literature review, it is concluded that the prevalence of false-negative TRUS guided biopsies is significant. In our series, 32% of patients had carcinoma on repeat biopsy. Also, more than 20% of these cancers were detected in the transition zone of the prostate gland, so transition zone biopsy is strongly recommended. We recommend repeat TRUS guided biopsy including transition zone assessment in all patients who meet the criteria for such biopsy and in whom initial biopsy was negative. The procedure is well tolerated to be suitable for outpatient setting and is associated with a minimal complication rate.

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Sažetak

OTKRIVANJE KARCINOMA PROSTATE U PONOVLJENIM BIOPSIJAMA PROSTATE U BOLESNIKA S PRETHODNO NEGATIVNIM NALAZOM

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U članku se opisuju vlastiti rezultati kod prve ponavljane, transrektalnim ultrazvukom vođene biopsije prostate, uz poseban osvrt na učestalost novodijagnosticiranog karcinoma u prijelaznoj zoni. Ponavljane transrektalnim ultrazvukom vođene biopsije prostate (6 cilindara lateralno i 2 iz prijelazne zone) učinjene su u 64 bolesnika. Indikacije za ponavljanu biopsiju prostate bile su tvrdokorno povišene vrijednosti za prostatu specifičnog antigena (PSA), brzina porasta PSA kroz godinu dana, gustoća PSA veća od 15 ng/ml/ccm i omjer slobodno i ukupnog PSA manji od 18%, prethodna biopsija s predmalignim lezijama, te sumnjivi digitorektalni nalaz. U 21 (32%) bolesnika na ponavljanoj biopsiji otkriven je karcinom prostate, a u ostalih 43 (68%) nalaz je bio upala, benigna prostatična hipertrofija ili predmaligna lezija. U 19,1% bolesnika na ponavljanoj biopsiji tumor je zabilježen u prijelaznoj zoni, a u 28,6% tumor je nađen u prijelaznoj i perifernoj zoni. U 23 (35,93%) bolesnika s predmalignim lezijama na inicijalnoj biopsiji učinjena je ponavljana biopsija, te je karcinom prostate otkriven u 9 (39,1%) bolesnika. Na inicijalnoj biopsiji prostate značajan je broj lažno negativnih nalaza. Ponavljana transrektalnim ultrazvukom vođena biopsija preporuča se u svih bolesnika koji zadovoljavaju kriterije za biopsiju prostate, te u kojih je inicijalna biopsija negativna. Također se preporuča učiniti klasičnu sekstant biopsiju lateralnije uz dva dodatna cilindra iz prijelazne zone prostate upravo zbog visoke razine otkrivanja karcinoma u prijelaznoj zoni. Prikazan je i kritički pregled novije literature o ovoj problematici.

Ključne riječi: *Neoplazme prostate – dijagnostika; Neoplazme prostate – patologija; Prostata – patologija; Biopsija – metode*