Prostate Cancer Detection in Patients with Elevated and/or Rising Serum Prostate-Specific Antigen Values and Negative Initial Prostate Biopsy: Value of Repeat Saturation Prostate Biopsy.

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Abstract: Introduction: Patients with elevated values of serum total prostate-specific antigen (PSA) without clinical evidence of prostate carcinoma (PCa) on digital rectal examination (DRE) has to have prostate biopsy (PB) for the diagnosis of PCa. When PB results are negative there are controversies exist over further assessment either by antibiotic therapy. Repeat saturation biopsy (SPBx) with 30 cores, detection rate of PCa in repeat SPBx is 11-28%.The study aimed at detection of PCa in patients with negative initial prostate biopsy with an elevated or rising PSA. **Method:** A retrospective observational and prospective study was done to evaluate the diagnostic values of repeat saturation prostate biopsy in the detection of PCa with an initial negative PB. Inclusion criteria were patients who had evaluated had persistently increased trend of serum PSA of 4-20 ng/mL. Their initial prostate biopsy of 10 cores taken through trans-rectal ultrasound (TRUS) was negative for PCa, prostatic intraepithelial neoplasia (PIN), or atypical small acinar proliferation (ASAP). Eighty seven patients 87/115(75.6%) had benign prostatic hyperplasia (BPH), 28 patients 28/115(24.3%) had inflammation of the prostate in histopathological assessment, whom they received antibiotic for 7 days. As PSA was elevated or rising, 64 patients approved to have had repeat PB with saturation prostate biopsy with 30 cores. **Results:** 115 patients with elevated PSA, had initial PB that that negative for PCa, PIN, or ASAP. 87 patients (75.6%) had (BPH). 28 patients (34.4%) had different degrees of inflammation for which they received antimicrobial therapy with quinolone for one week. These 115 patients had elevated PSA in 68 and rising in 47 after the initial PB. All were offered to have repeat biopsy. 64 patients agreed to have SPBx . Eleven patients 11/64 (17.2%) had PCa in the repeat prostate biopsy. **Conclusion:** Elevated and or rising PSA values in presence of initial negative prostate biopsy indicate repeat saturation prostate biopsy with 30 cores. Proven aggressiveness of inflammation evident with pathological findings would explain the elevated PSA without PCa. Repeat SPBx was positive for PCa in 17.2% patients.

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1. Introduction:

Prostate cancer(PCa) is the most common tumour with about 340,000 new diagnoses per year in the European Union(1).Men with early stages of PCa are usually asymptomatic. The symptoms are identical with benign prostatic hyperplasia (BPH). Lower urinary tract symptoms (LUTS) are identical with early PCa symptoms. There is a link between LUTS and PCa, screening for PCa is recommended for men with LUTS (2).

While the mortality of PCa has greatly declined in many developed countries, it is increasing in less developed regions worldwide. Digital rectal examination (DRE), prostate biopsies (PB), serum prostate-specific antigen (PSA), and trans-rectal ultrasound (TRUS) are techniques used for early detection. PSA has been considered to be the best tool so far. But in other conditions such as BPH and prostatitis, PSA can also be elevated. The specificity of PSA is not very good for early interventions. In patients with PSA between 2 and 4 ng/ml, only 25% have PCA (3).In most cases, PCa causes no symptoms. The two most commonly used tests are digital rectal examination (DRE) which is of low sensitivity and specificity, and serum prostate-specific antigen (PSA). A total serum PSA >4.0 ng/ml has traditionally been used as a threshold for considering prostate biopsy, and large programs for early detection have shown that almost 70% of cancer cases can be detected using such PSA cut-off. Lowering the PSA threshold to 2.o ng/ml increased the detection rate of PCa (4).

Large prostate volume is associated with BPH and concomitant release of non-cancer related PSA into the serum, which interferes with cancer detection.

Patients who have elevated PSA levels or abnormal findings on a digital rectal examination (DRE) but whose biopsy results are negative pose a problem in PC screening. When the result of a DRE is normal and PSA is lower than 10 ng/ml, prostate biopsies fail to detect PC in 80% of men. However,

PSA is not a cancer-specific marker, and various benign processes also affect PSA concentrations (6-7). Elevated PSA due to benign conditions PBH and prostatitis are most directly underscores the difficulty in making a decision about repeat biopsy. The question remains as to the nature of the relationship between PSA and subclinical prostatic inflammation. Histological inflammation is a frequent finding in prostate biopsies that are performed on men without PCa (8). Several studies have investigated the relationship between PSA levels and the morphology of prostatic inflammation. The results are controversial. Although it is known that acute prostatitis can contribute to lack of total PSA (tPSA) specificity, major disagreement remains over the effect of asymptomatic inflammation on free PSA (fPSA) and percentage of free PSA (f/tPSA) values(9). An elevated PSA in the absence of any abnormality on DRE or symptoms is indicated for prostate biopsy (10)

Many studies advocated combination of systematic sextant biopsy and laterally directed biopsy which is the 10-11 cores biopsy scheme that included the standard sextant biopsy regimen obtained halfway between the lateral border and midline of the prostate on both right and left sides, but also obtained 2 biopsies from each lateral aspect of the prostate, and 3 biopsies from the midline at the apex, mid-gland, and base. In their initial report on 119 patients, the overall cancer detection rate was 40%, much higher than the 20% to 25% typically seen in sextant biopsy series (11-15).

The combination of sextant and lateral biopsies, for a total of 10 peripheral zone biopsies, detected 96% of all cancers detected. Only4% were detected by the lesion-directed biopsies, or the transition zone biopsies. It was concluded that: traditional sextant biopsies may miss over 20% of cancers; a lateral sextant regimen (apex, lateral mid, lateral base) outperforms the traditional mid lobar sextant regimen (89% vs 80%, respectively; variations in cancer detection rates were most pronounced in patients with PSA levels < 10 ng/mL or in patients with prostate sizes ≥ 50 cc.(10)

Patients whose initial PB indicated a negative result for PCa they showed non-cancer lesions as benign prostatic hyperplasia (BPH), prostatic intraepithelial neoplasia(PIN), atypical small acinar proliferation(ASAP), and prostatic inflammation that had been reported to be present in is present in 1.5-24% of needle biopsies, the cancer detection rate in repeat biopsies of these cases with vary between 19-38% (16-17).

Pepe and associate showed that repeat prostate biopsy with saturation prostate biopsy (SPBx) with median 30 cores, in patients with PSA values between 4.1 ng/mL-10 ng, all patients had negative DRE and median PSA was 7.9 ng/mL, and negative initial PB, Prostate cancer was found in 28% patients(18). Repeat saturation biopsy in detection of PCa would be equal to pelvic phased-array multiparametric MRI (20).

2. Patients and Methods

A retrospective analysis of data of patients who had negative initial prostate biopsy with elevated or rising PSA were enrolled in the study. Between January 2010 to May 2014, retrospective and prospective analysis of data of 115 consecutive patients aged 63-76 years (median 65.7 years) underwent initial prostate biopsy with 10 cores. 64 patients had repeat saturation biopsy with 30 cores. All of the men had negative digital rectal examination and the indications for biopsy were, 85 patients had PSA >10 ng/ml, 30 patients had PSA 4.1-10 ng/ml. The initial prostate biopsy was 10 cores, and the repeat saturation biopsy was 30 cores. The prostate needle biopsy was performed under the guidance of transrectal ultrasonography using tru-cut 18 gauge needle under sedation and local anesthesia, and antibiotic prophylaxis for three days beginning the day before biopsy.

Exclusion criteria were the finding in histopathological examination of the initial prostate biopsy the presence of PCa, prostatic intraepithelial neoplasia (PIN), or atypical small acinar proliferation (ASAP).

Eighty seven patients 87/115(75.6%) had benign prostatic hyperplasia (BPH), 28 patients 28/115(24.3%) had inflammation of the prostate in histopathological assessment, whom they received antibiotic for 7 days. As PSA was elevated or rising, 64 patients agreed to have had repeat PB with saturation prostate biopsy with 30 cores. The histopathological results of all 115 patients with initial prostate biopsy with 10 cores, and the consequent 64 patients who had repeat saturation prostate biopsy were assessed.

3. Results

Patient characteristics are presented in Table 1. The mean age of the patients was 65.7 years; their mean PSA levels before the initial and repeat biopsy sets were 9.2 and 12.8 ng/ml, respectively. The 115 patients enrolled in this study had a negative initial PB where serum PSA was 4-20 ng/ml and they had no definite abnormality in DRE. Results of the initial PB were: 87 patients 87/115(75.6%) had benign prostatic hyperplasia (BPH), 28 patients 28/115(24.3%) had inflammation of the prostate in histopathological assessment, whom they received antibiotic for 7 days (21). As PSA was elevated or

rising, 64 patients agreed to have had repeat PB with saturation prostate biopsy with 30 cores. Prostate cancer was detected in eleven patients 11/64 (17.2%), inflammation of the prostate in 21/64 (32.8%), BPH in 29/64 (45.3%), and 15/64 (23.4%) had normal prostate tissue. The eleven patients with proven PCa on 30 cores saturation biopsy were evaluated clinically, five patients underwent radical prostatectomy, and 3 patients had locally advanced disease and bone metastases and were on hormonal therapy. Three patients were on active surveillance.

Table 1. Patient characteristics.

Variable	Initial prostate biopsy	Repeat prostate biopsy
	Extended biopsy 10 cores	Saturation biopsy 30 cores
No. of patients	115	64
Age+-SD	65+-7	67+-4
PSA(ng/ml)mean+-SD	9.2+- o.3	12.9+-0.4
BPH	87/115(75.6%)	29/64(45.3%)
Prostate cancer	0(0%)	11/64(17.2%)

PSA: Prostate specific antigen; SD: standard deviation; BPH: Benign prostate hyperplasia

4. Discussion

Patients who present with an initial negative biopsy, a repeat biopsy should be performed as the clinical suspicious of prostate cancer is existing, elevated PSA or rising PSA. Prostate cancer detection rate in repeat saturation biopsy range from 19-38% (16-17). In the present cohort of the retrospective prospective observational study the prostate cancer detection in repeat saturation biopsy was 17.2%. The presence of inflammation of the prostate in the initial biopsy indicated the administration of antibiotic for one week (21). In the present study prostate inflammation was reported in 24.3% in the initial prostate biopsy, the PSA level did not decreased following antimicrobial therapy, which indicated non related PSA rising. These patients underwent a repeat saturation biopsy. It has been reported that minor or prominent disorders were similar in initial or repeat prostate biopsies (22). In the present stud the side effects of initial and repeat biopsies were similar. Some patients had refused the repeat biopsy 51/115 (44.3%) due to either the risk of side effects or the concept that it is an invasive procedure. The finding in the present study that 17.2 % of patient who underwent repeat biopsy proved to be prostate cancer is an alarming finding that urologist try to convince the patient with an initial negative biopsy and elevated PSA to accept a repeat prostate biopsy.in the current study the adoption of technique of 10 cores initial PB and 30 cores repeat saturation biopsy avoided sampling error and in adjusted to other studies that practiced the same policy (11-17).

5. Conclusion

the present study demonstrated that indicated that repeat saturation prostate biopsy with 30 cores increased detection rate of prostate cancer in patients with elevated and/or rising PSA whose initial Prostate biopsy with 10 cores were negative. The detection rate of PCa in repeat biopsy in our study is relatively high (17.2%), which is near to other studies that was reported to be 19-38%.

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