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RESEARCH

Patients with Persistently Elevated PSA and Negative Results of TRUS-Biopsy: Does 6-Month Treatment with Dutasteride can Indicate Candidates for Re-Biopsy. What is the Best of Saturation Schemes: Transrectal or Transperineal Approach?

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Abstract To identify patients who actually need a re - biopsy, based on alterations in PSA readings after 6-month treatment with Dutasteride. We also sought to bring out the most beneficial re-biopsy scheme. We have reviewed the records of patients with persistently elevated PSA and at least one set of TRUS biopsies. Patients who were treated with alpha - blockers/Dutasteride combination were considered as the study group, while patients in control received alpha-blockers alone. Patients in both groups underwent re-biopsy 6 months later. The two protocols of re-biopsies were used at that time: 20-24 cores saturation transrectal (ST)) and ≥40 cores saturation transperineal template-guided (STT) biopsies. One hundred thirty-three patients were included in this study. In 86.7 % of the patients in the study group mean PSA decreased from 7.4±2.69 to 4.037±1.53 (p-0.001). The overall cancer detection rate was 29 % (n-39: 19 v/s 20, control and study groups, respectively). In the study group PSA decreased to 26.73±11.26 % in patients with cancer, compared with 40.54±13.3 % in patients without. It must be emphasized that STT-biopsies detected significantly more cancers (38.46 v/s 20.59 %, p- 0.005). Mean cores number got to 21±2.45 and 45±5.65 in ST and STT biopsies, respectively. Six-month treatment with Dutasteride decreases PSA readings in 86.7 % of the patients. A PSA decline of less than 40% (cutoff) should be considered as an indicator for re-biopsy. Transperineal template-guided biopsies had a higher cancer detection rate.

Keywords Prostate cancer · Biopsy · Elevated PSA · Dutasteride

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Introduction

Among patients with previous negative biopsies the incidence of PCa (prostate cancer) at repeat biopsy is approximately 20 %, accordingly novel predictors for better estimation of an individual's risk for PCa are essential [1]. In this context, it should be reminded that in patients with benign prostatic hyperplasia (BPH) Dutasteride suppresses PSA levels, therefore, a rise in PSA under this treatment might be indicative of aggressive PCa and could be used as the indicator for biopsies [2]. In order to pick and choose possible candidates for re-biopsy, previous studies validated how the above mentioned treatment can affect PSA nadir and kinetics in the patients with previous negative biopsies and persistently elevated PSA [3–5]. Even so, it is still not clear what could be used as an indicator for re-biopsy and which type of re-biopsy protocol is better for these patients. Although different studies used extended, transrectal saturation as well as transparently template-guided biopsies for the latter purpose, only some of them showed that transrectal saturation biopsies had a higher cancer detection rate than extended scheme [6–9]. It also must be emphasized that only one study had compared transrectal

with transperineal template-guided scheme in a face to face manner [10].

In this retrospective study, we evaluated the ability of Dutasteride to diminish the rate of unnecessary re-biopsies and overdiagnosis of PCa in the patients with persistently elevated PSA after negative TRUS-biopsies. For this purpose, we evaluated and compared PSA kinetics in patients who were treated with alpha-blockers /Dutasteride combination and alpha-blockers alone. We also compared two different variants of re-biopsies, which were performed ≥6 months after previous negative biopsies.

Patients and Methods

After obtaining approval from the ethics committee of our hospital (0077-13 BRZ) we have reviewed in a retrospective manner the records of patients who were treated in our outpatient clinics for LUTS from 2009 to 2013. The main inclusion criterion was persistently elevated PSA obtained ≥3 months after at least one set of negative TRUS-biopsies, as well as patients' agreement to undergo re-biopsies. The exclusion criteria were age >70 years, PSA >10 ng/ml, high PIN, history of *5-α reductase inhibitors* before previous biopsies, rejection of re-biopsy, open or transurethral resection of the prostate, as well as patients with indwelling catheters.

As a part of our policy at that period, we used to postpone re- biopsies for at least 6 months since the last post-biopsy PSA evaluation. In the meantime, patients with LUTS were treated with alpha-blocking agents, Dutasteride and the combination of the alpha-blockers plus Dutasteride. In all patients we returned to the PSA before re-biopsies . Patients, who were treated with Dutasteride or its combination with alpha – blockers were considered as the study group, while the control group comprised patients who received alpha-blocker alone.

At that period, we used two protocols for re-biopsies: 20-24 cores saturation transrectal (ST) and transperineal template-guided (STT) TRUS biopsies, which were done under local and general anesthesia, respectively. In the latter, we used to take biopsies according to the template-guide every 5 mm. After thorough explanation patients chose each protocol according to their preference. Clinical significant disease was defined as cancer of Gleason score 6, involving 50 % of any core and seeing in ≥3 cores in addition to all Gleason 7-10 cancer [11, 12].

As a result, 133 patients were included in this study. All patients underwent re-biopsies. We assessed the results of these biopsies, as well as the results of the final pathology in the cases when radical prostatectomy was done. We also compared different epidemiological and clinical data, as well as PSA reading and pathology reports in order to reveal a correlation between PSA dynamics under Dutasteride treatment and risk to diagnose potentially significant PCa. To delineate the population of the study, we used *T*-Test and Chi-Square test, while the logistic regression models with PCa as a dependent variable were used to assess the strongest predictor for cancer diagnosis. SPSS-13 software was used for these purposes.

Results

Study group comprised 60 patients v/s 73 men in the control group. Patients in the study group were older and had a higher BMI. Initial mean PSA and prostate volume were equal in both groups, however, they finally decreased significantly in the study group. Decrease in libido and potency didn't differ between both groups, while breast enlargement was detected only in one patient (Table 1).

After ≥6 months treatment with Dutasteride mean PSA in the study group decreased from 7.4±2.69 to 4.037±1.53 (*p*-0.001). This tendency was reported in 86.7 % of the patients, thus in 8 men, PSA didn't change significantly (*n*-5) or even rose (*n*-3). A strong correlation was revealed between pre-treatment PSA and PSA ≥6 months after Dutasteride treatment. There was no significant difference in PSA ratio in both groups, as well as its readings in the study group before and after Dutasteride treatment.

The overall cancer detection rate was 29 %, in particular 31.7 and 27.4 % in the study and control groups (*n*-39: 19 v/s 20, control and study groups, respectively). Three cases of insignificant cancer were found exclusively in the control

Table 1 Demographic, laboratory and clinical data

Group	Age	BMI	PSA initial	PSA final	Init.pro.V.	Fin. pro.V.	PCa det.rate	Decr. libido	Decr. potency	Atrophic changes	Inflam.
Study	65.1±4.9	29.7±5.1	7.4±2.6	4.48±1.9	61.8±9.2	56.8±9.5	31.7 %	54.9 %	66.7 %	47.6 %	14.8 %
Control	62±5.8	24.5±3.5	7.35±2.45	7.14±3.7	62.8±10.8	62.75±9.54	27.4 %	47.6 %	52.6 %	16.7 %	52.7 %
P=	*0.001*	*0.021*	*>0.05*	*0.001*	*>0.05*	*0.025*	*>0.05*	*>0.05*	*>0.05*	*0.001*	*0.003*

BMI, Body mass index, init. Pro. V – initial volume of prostate, fin. Pro.V – final volume of prostate, Pca det. rate – prostate cancer's detection rate, decr. Libido – decreased libido, decr. potency – decreased potency, atrophic changes – on pathologic data, inflame. – inflammation changes

Table 2 Saturation biopsies: transrectal v/s transperineal template-guided

Scheme	No.	age	PSA initial	Final pro.V	PCa det. rate	Cores No.	H-uria	H-chezia	AUR (n)
ST	68	63.5±3.8	7.28±3.2	61.4±6.7	20.59	21±2.45	23.5 %	32.6 %	0
STT	65	62±4.3	7.35±2.3	63.25±5.64	38.46	45±5.65	27.8 %	27.8 %	4
P=	*>0.05*	*>0.05*	*>0.05*	*>0.05*	*0.005*	*0.003*	*>0.05*	*>0.05*	

ST, Saturation transrectal biopsies; *STT*, saturation template-guided transperineal biopsies; *No*., number of patients, *H-uria*, hematuria; *H-chezia*, Haematochezia; *AUR*, acute urinary retention

group. After 6-month treatment with Dutasteride, PSA decreased for 26.73±11.26 % in patients with PCa, compared with 40.54±13.3 % in patients without PCa. It must be emphasized that significant PCa was detected in five of eight patients with stable or increased PSA under Dutasteride. It also might be worthwhile to emphasize that overall cancer detection rate in patients with BMI >30 cancer was significantly higher: 36.5 v/s 24.7 % (p – 0.03). Although, logistic regression analysis failed to reveal the strongest prognostic factor for cancer detection, among all data included in this analysis levels of PSA after ≥6 months treatment and BMI >30 showed weak statistical significance (p- 0.052 and 0.054, respectively).

ST-biopsies were done in 68 men, whereas 65 patients preferred STT-biopsies (Table 2). There was no statistically significant difference in biopsy-type distribution in the study and control groups. It must be emphasized that STT-biopsies detected significantly more patients with cancer, yet significantly more cores were taken with this technique. Except of acute urinary retention (4 v/s 0), complication rates didn't differ significantly between two groups. Thirty four patients with positive biopsies underwent radical prostatectomy and final pathology report agreed with biopsies in 25 patients: the final pathology showed higher and lower Glaeson score in seven and two patients, respectively. Re-biopsy and final pathology revealed atrophic changes in 47.6 v/s 16.7 % (p-0.001) in study and control groups, respectively, while chronic and acute inflammation was more frequently reported in the control group: 14.8 v/s 52.7 %, p – 0.003.

Discussion

Even after initial negative prostate biopsy, a dilemma of if and how to follow patients with persistently elevated PSA is still a challenge for urologists. To assist with a decision of re-biopsy, risk calculators have been proposed [13–15]. The main purpose of this tool is to assess the probability of cancer and distinguish between patients with potentially low and high risk (HR) cancer based on different patients' parameters, including PSA kinetics. However, even those models presume that potentially aggressive PCa might be missed [16]. On the other hand, data presented by Andriole et al. demonstrated that PSA alter in patients under Dutasteride treatment can be used as an indication for re-biopsy and detection of clinically significant and cancer [17].

In our study we found that a percentile decrease (less than 40 %) in PSA readings after 6-month treatment with Dutasteride might detect patients with potentially significant cancer. Indeed, PCa was found in patients with a mean PSA decline of 26.73±11.26 %, compared with a PSA drop of 40.54±13.3 % in the group with negative re-do biopsies. Thus, a PSA decrease of more than 40 % can identify patients with a low risk for PCa from potential candidates for re-biopsy. This cutoff will probably spare 60 % of patients with persistently elevated PSA from unnecessary biopsies. Although we performed biopsies after 6-month treatment, our results are in a full agreement with those described by Kaplan et al. who observed that most PCa were detected in the patients with a PSA decrease of less than 33 % after a one – year treatment with Finasteride [3].

Other studies also found a correlation between the magnitude of change in PSA velocity and density after 5-ARIs treatment and the probability of PCa detection [4, 5]. In particular, the results of the CombAT study showed an increased likelihood of PCa detection on re-biopsy in men with PSA growth under Dutasteride treatment [18]. We also found that patients with unchanged or elevated levels of PSA after a 6-month treatment with Dutasteride might benefit from early re - biopsy.

Another important finding of our study was a significantly higher rate of cancer detection in obese patients (BMI >30). It should be emphasized that patients in the study group had significantly higher BMI and showed an increased detection rate of significant cancer (all PCa in this group had features of clinical significant disease). In addition, eight of 13 patients with MBI ≥30 (61.5 %) had stable or elevated PSA despite Dutasteride. These results are in agreement with previous studies which found an increased detection rate of clinical significant and aggressive cancer in overweight patients [19, 20].

Although 5a-reductase inhibitors are indicated for the treatment of benign prostatic hyperplasia, there has been a growing interest in 5-ARIs for prostate cancer prevention. This interest is based on the ability of 5-ARIs to inhibit the conversion of testosterone to dihydrotestosterone, the process that affects

both benign and malignant growth of prostate tissue [21, 22]. In our study final pathology reported an increased rate of atrophic changes in the Dutasteride group, while inflammation was more frequently seen in the control group. We suggest that these processes are responsible for PSA drop in benign prostatic hypertrophy. Our study also showed that with exception of breast enlargement, the incidence of sexual adverse effects, such as impotence, reduced libido were equal in both groups. The same figures were reported by a previous study [23].

Although it is accepted that patients with persistently elevated and/or rising PSA after previous set of negative biopsies should undergo re-biopsy, it is still unclear what type of re-biopsy is the most beneficial for these purposes [8]. Previous studies had shared their experience with different kinds of the extended scheme of re-biopsy and emphasized (with some exceptions) an additional value of increased (≥20) number of biopsy cores [6–9]. Our practical standard in these circumstances was a saturation biopsy: transrectal or template-guided transperineal. At that period we, as well as the other authors [10], hesitated to give our preference to one of them. However, our results showed that STT scheme had detected significantly more cancers. The difference between our and previous results could be explained by the fact that we used a template-guide technique which allowed to take biopsies from every 5 mm of the prostate. The latter suggestion is supported by the results reported by Ekwueme et al. [6]. Except certain drawbacks of general anesthesia and acute urinary retention, this scheme had nearly the same rate of complications [24].

We accept several limitations of our study, such as retrospective nature and low-sampling volume. Patents in this study were not randomized for different schemes of re-biopsy and we presume that this fact might cause particular bias.

Conclusions

Six-month treatment with Dutasteride decreases PSA readings in 86.7 % of the patients and doesn't significantly affect libido and potency. Patients with PCa had persistent, increased PSA or PSA drop >40 % of original readings. The former is especially important for patients with BMI >30, and could be used as an indicator for re-biopsy. Transperineal template-guided approach has increased cancer detection rate and might be regarded as the preferred protocol for re-biopsy.

Ethical Statement This retrospective study was approved by ethical committee of our hospital: 0077-13 BRZ. Only after obtaining this authorization we reviewed in a retrospective manner the records of patients who were treated in our outpatient clinics for LUTS from 2009 to 2013.

Conflict of Interest The authors declare that they have no conflict of interest.

Authors' Contribution Kravchick - project development, data collection/management and manuscript writing.

Lobik - project development, data management and manuscript editing.

Cytron – project editing.

Kravchenko – data collection.

Ben Dor – manuscript editing.

Peled – data analysis and manuscript writing.

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