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RESEARCH ARTICLE

WHAT IS THE PSA PREDICTIVE VALUE OF THE PATIENTS WITH ATYPICAL SMALL ACINAR PROLIFERATION (ASAP)? IS THE SECOND BIOPSY ALWAYS NECESSARY?

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ABSTRACT

Objective: The aim is to discuss the necessity of implementation of the second prostate biopsy on the patients atypical small acinar proliferation (ASAP) detected as a result of histopathologic examination and on the patients appliedprostate biopsy due to abnormal findings during the prostate specific antigen (PSA) height and/or digital rectal examination, and to detect necessity criteria of the second biopsy.

Materials and Methods: 2295 patients that transrectal ultrasonography-guided prostate biopsy was applied between January 2008 and January 2016 have been evaluated retrospectively. ASAP was detected on 228 of them following the histopathologic examinations. 217 patients, whose data were reached, are taken into the study. Re-biopsy was applied on 120 of 217 patients within a period of 3-6 months. Before the first and the second biopsy, total PSA, free PSA, free/total PSA rate, PSA density were calculated. Second biopsy results and changes in the data are compared. Data disagree with normaldistribution, and they are summarized by the median, minimum, and maximum values. To compare the first and the second biopsy, Wilcoxon signed rank test is used. The significance level is taken as 0,05 for all tests.

Results: The median age of 120 patients with ASAP who included this study was 63,06 (40-78). Prostate volume mean is 54,04 cc (10-140). Median total PSA value was detected as 8,63 ng/ml (0,9-32,5), free PSA value was detected as 1,59 ng/ml (0,0017-8,9), free/total PSA rate was determined as 19,77% (0,0014-0,79), PSA density was detected as 0,1959 ng/mL/cc (0,01-0,98). Average in 1,3 number (1-5) of the biopsy specimens, ASAP was detected. As a result of the second biopsies of 120 patients with ASAP, second biopsy result was reported as benign for 73 patients (60,8%), ASAP was reported for 24 patients (20%) and prostatic adenocarcinoma (PCa) was detected on 23 patients (19,2%). Although statistically significant decrease($p<0,001$) was determined on total PSA, free PSA and PSA density tests of the patients whose second biopsy was reported as benign, no difference on free/total PSA rates was available. For the group whose second biopsy showed ASAP again, there was no significant difference on any variable. While total PSA values of the patients whose second biopsy was PCa increased ($p=0,009$), there was no significant difference in free PSA values ($p=0,297$). Also, on PCa group free/total PSA value decreased ($p<0,001$) and PSA density values increased ($p=0,010$).

Conclusions: Total PSA, free PSA, free/total PSA rate and PSA density should be evaluated routinely in the patients with ASAP before the second biopsy, and before the second biopsy, the changes in these parameters should be considered and accordingly, a re-biopsy decision should be made. If there is a decrease in total PSA value, the decision for the second biopsy should not be hasted; however if there is an increase in total PSA value, the second biopsy should be done before it is too late.

INTRODUCTION

Prostate cancer is the most seen cancer type on the men above 70 years of age (1). One of the right markers of this cancer is serum prostate specific antigen (PSA) level. Although PSA is organ specific, it is not cancer specific. However, it is more vauable than digital rectal examination (DRE) and transrectal ultrasonography on diagnosing prostate cancer (2, 3). There is no consensus on PSA limit value issue yet. Apart from the high PSA values, prostate cancer can be seen on low PSA values as well. Thus, it is not the only symptom of prostate cancer, and it is evaluated with nomograms. For patients with high PSA values or patients that have a significant finding on DRE, a transrectal ultrasonography-guided prostate biopsy is

applied. Routinely second biopsy is recommended for the patients with ASAP detected as a result of the biopsy. In this study, we aimed to discuss the necessity of the second biopsy routinely for the patients with ASAP, and which patient group must be applied the second biopsy absolutely.

MATERIALS AND METHODS

2295 cases applied prostate biopsy due to high PSA or significant DRE findings in our clinic between January 2008 and January 2016 were evaluated retrospectively. On 228 of 2295 prostate biopsy patients ASAP was determined, and 217 cases whose data were reached taken into the study. 10 or 12 biopsy specimens were taken from the patients, from apex to floor and far lateral and lateral areas. For the patients ASAP detected on the biopsy specimens, a second prostate biopsy is recommended after 3 months from the first biopsy. 12, 16 or 18 samples were taken from the cases second prostate biopsy was applied. Before the first and the second biopsy, total PSA, free PSA, free/total PSA rate, PSA density were calculated, and data analysed with histopathologic results. Because data disagree with a normal distribution, they are summarized by the median, minimum, and maximum values. To compare first and second biopsies, Wilcoxon signed rank test is used. The significance level is taken as 0,05 for all tests.

RESULTS

The median age of 120 patients ASAP detected was 63,06 (40-78). Prostate volume is mean 54, 04 mL (10-140). Median total PSA value 8,63 ng/ml (0,9-32,5), free PSA value 1,59 ng/ml (0,0017-8,9), free/total PSA rate 19,77% (0,0014-0,79), PSA density 0,1959 ng/mL/cc (0,01-0,98) were detected. Average in 1,3 (1-5) of the biopsy specimens, ASAP was determined. As a result of the second biopsy of 120 patients with ASAP, second biopsy result was reported as benign for 73 patients (60,8%), ASAP was reported for 24 patients (20%) and prostatic adenocarcinoma was reported for 23 patients(19,2%). Although statistically significant decrease($p<0,001$) was determined on total PSA, free PSA and PSA density tests of the patients whose second biopsy is reported as benign, no difference on free/total PSA rates was available ($p=0,077$). For the group whose second biopsy was ASAP again, there was no difference on any variable. While total PSA values of the patients whose second biopsy showed increased PCa ($p=0,009$), there was no difference in free PSA values ($p=0,297$). Also, in PCa group, free/total PSA value decreased ($p<0,001$) and PSA density values increased ($p=0,010$). (Table1).

Table 1 Total PSA, free PSA, f / t PSA and PSA Density measurements before the first and second biopsy and statistical comparative analysis of the patients who were followed with high PSA levels.

The second Biopsy results	Variable	The first biopsy Median (Min.-Max.)	The second biopsy Median (Min.-Max.)	p
Asap (n=24)	Total PSA	6,33 (2,29-32,50)	5,79 (2,08-32,00)	0,113
	Free PSA	1,25 (0,38-8,90)	1,26 (0,40-4,20)	0,305
	F/T PSA	0,18 (0,06-0,62)	0,18 (0,09-0,46)	0,782
	PSA Dan	0,16 (0,04-0,65)	0,17 (0,04-0,48)	0,297
Benign (n=73)	Total PSA	6,30 (2,50-31,00)	5,00 (0,30-30,60)	<0,001
	Free PSA	1,30 (0,40-6,50)	1,03 (0,05-4,50)	<0,001
	F/T PSA	0,20 (0,03-0,50)	0,21 (0,04-0,65)	0,077
	PSA Dan	0,14 (0,04-0,98)	0,10 (0,01-0,70)	<0,001
CA (n=23)	Total PSA	6,21 (0,90-19,00)	6,51(1,20-19,20)	0,009
	Free PSA	0,77 (0,002-4,47)	0,65 (0,20-3,35)	0,297
	F/T PSA	0,13 (0,001-0,79)	0,10 (0,01-0,26)	<0,001
	PSA Dan	0,16 (0,01-0,77)	0,18 (0,02-0,80)	0,010

72 (60%) of the 120 patients ASAP detected, a decrease in total PSA value was seen before the second biopsy. For 59 (81,94%) of 72 patients, second biopsy result was benign. Although ASAP occurred in 11 (15,27%) of 13 patients whose total PSA value decreased, prostate cancer was determined in 2 patients (2,77%) only (Table 2). On 48 (40%) of 120 patients ASAP was detected, it was seen that total PSA value increased before the second biopsy. 15 (31,25%) of 48 patients were benign, 13 (27,08%) of them ASAP again and 20 patients (41,66%) were diagnosed as prostate cancer (Table 3).

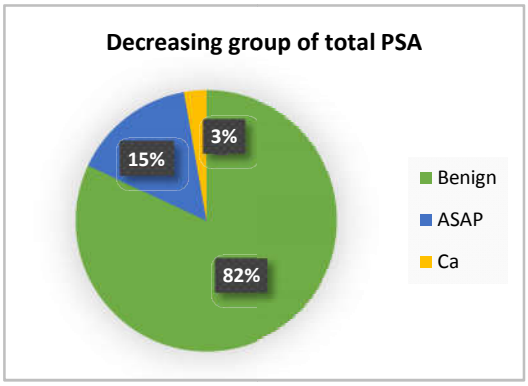

Table 2 Decreasing group of total PSA.

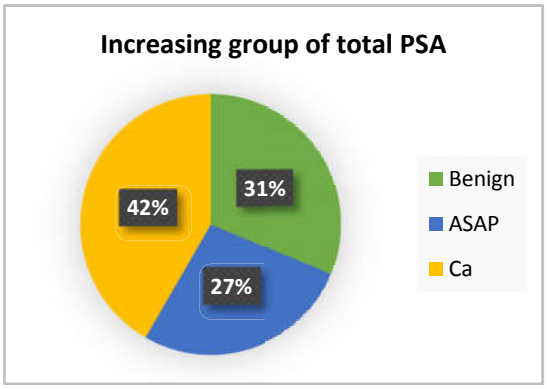

Table 3 Increasing group of total PSA

DISCUSSION

Although prostate cancer is still up-to-date in recent years, with developing technology and with opportunities of early diagnosis, it is seen more commonly in daily urology practice. One of the most important indicators at the beginning of diagnosis is serum PSA level. Besides high PSA, findings such as nodule existence in prostate tissue during DRE, asymmetry, and palpable induration affect biopsy decision. While cut-off values of PSA level are contradictive, they are the leading factors of prostate biopsy decision. Histopathologic results such as BPH, prostatitis, atrophy, adenosis, PIN or ASAP can be seen on the patients that transrectal ultrasonography-guided prostate biopsy was applied due to high PSA. For the first time, ASAP was defined as focal focuses comprise of little acinar structures that are constituted by epithelial cells by Bostwick and his friends in 1995 (4). ASAP, identifying a situation that pathologists cannot make clear decisions, is stated in situations which include lesional area's smallness (<0,4mm) is contradictive and indefinite, the existence of morphologic and/orimmunohistochemical features. ASAP is seen in 5% of the patients applied prostate biopsy due to high PSA or abnormal finding during DRE (5,6,7). In our study, this rate was 9,93%. ASAP patients can be classified as low and high suspicious. In a study Scattoni and his friends made

by benefiting from this classification, they showed there is no difference of getting cancer between these two groups after repeated biopsies (8). Second biopsy timing can change according to the low and high-risk group. However in the literature, the second biopsy is recommended for the patients ASAP detected after 3-6 months. (9)

In the study Leone and her friends made on 264 cases, the age range of the cases ASAP monitored is 57 and 69; themedian age is 63 (10). In our study, the median age of 120 patients ASAP detected is 63,06(40-78), and it complies with literature. Trustfully used in daily practice, the main parameter for deciding prostate biopsy is total PSA. With 4 ng/ml cut-off value, PSA has an admissible sensitivity for prostate cancer (11). In a study made by Catalona *et al*., it was stated that PSA cut-off value must be 2,5ng/ml, especially for young patients (12). In a study made by Arcangeli and friends, they showed tumours can be missed approximately at the rate of 20-30% when PSA cut-off value 4 ng/ml was used(13). In our study, the cut-off value was determined as 4 ng/ml due to median age of the patients is 63,06. Only 17 (14,16%) of the 120 ASAP cases had a total PSA value under 4 ng/ml. On 4 of the 17 ASAP cases, prostate adenocarcinoma was detected during the second biopsy. This is parallel to discussions on cut-off values issue, and it shows prostate cancer diagnosis can be missed on low PSA values. Being between 4-10 ng/ml of PSA value is called grey zone. Because high level of negative results gained on biopsies on the patients with greyzone PSA values, in the course of time new parameters such as free/total PSA rate apart from total PSA level, PSA density and PSA doubling time are started to be evaluated. Braver and friends reported that patients in the greyzone can be diagnosed prostate cancer with 95% rate when the free/total PSA threshold value is considered 25%. Thus, 20% of the patients can be saved from the unnecessary biopsy (14). Seamen and friends reported if PSA density threshold value is taken as 0,15ng/mL/cc, there can be an improvement in detecting prostate cancer (15). In our study, by considering ASAP detected 120 patients' average PSA value as 8,63 ng/ml (0,9-32,5), and by thinking it complies with grey zone, and thinking total PSA is not enough for ASAP alone, parameters such as free PSA, free/total PSA rate and PSA density were examined. Detecting free/total PSA rate as 19,77% (0,0014-0,79), considering Braver and friends study, it supports our results' accuracy and reliability. Also in our study, PSA density is 0,1959 ng/mL/cc (0,01-0,98), and when threshold value was considered as 0,15 ng/mL/cc, 68 patients were under the thresholdvalue, and 52 patients were above this threshold value. While prostate cancer was determined on 11 (16,17%) of these 68 patients during the second biopsy, on 12 (23,07%) of 52 patients, prostate cancer was determined. This result does not comply with Seaman and his friends study regarding PSA density. Moreover, when we look at the literature, there are studies showing PSA density has no contribute to diagnosing prostate cancer (16). Because parameters such as total PSA, free PSA, free/total PSA rate and PSA density do not have enough contribution to the biopsy results on ASAP patients, in our study, we re-evaluated these parameters before the second biopsy. 72 (60%) of the 120 patients ASAP detected, a decrease in total PSA value was seen before the second biopsy. For 59 (81,94%) of 72 patients, second biopsy result was reported benign. On 48 (40%) of 120 patients ASAP determined, it was seen that total PSA value increased before the second biopsy and prostate cancer was detectedin 20 (41,66%) of these patients. In the light of these results, we think parameters such as total PSA, free/total PSA rate, PSA density should be reviewed before the second biopsy. In our study, we precipitate that when we evaluate the PSA changes before the second biopsy on the patients with benign result, total PSA, free PSA and PSA density measurements statistically decreased significantly, no changes on the patients came up with ASAP, and it is seen that on patients with prostate adenocarcinoma total PSA values increase while free/total PSA values decrease. This shows how good it is to repeat these parameters before the second biopsy.

ASAP is a powerful risk factor for prostate cancer (17). In our study, after ASAP, second biopsy result was reported as benign for 73 patients (60,8%), ASAP was reported for 24 patients (20%) and prostatic adenocarcinoma was detected in 23 patients(19,2%). When you look at the literature, there is a second biopsy result at higher rates (39-42%) regarding prostate adenocarcinoma (10,18,19). Having higher ASAP rate than the literature, and having the rate getting prostate cancer is lower than the literature can be derived from the existence of different pathologists in histopathologic evaluation, and drawbacks on diagnosing PCa. Maybe if there is no second biopsy implementation made routinely on patients ASAP determined, pathologists could decrease the rate of ASAP diagnosis, and truer histopathologic evaluations can be in question. Although ASAP is a powerful risk factor for prostate cancer, by considering PSA changes, the second biopsy that is going to be applied between 3 and 6 months should not be routine for each patient; itshould be applied for suitable patients only. For this point, another question that should be answered is the reasons why the patients avoid from the second biopsy. In the literature, there are second biopsy rates varying between 47-63%. In our study, the second biopsy could be made for 120 (55,29%) of 217 patients (20). Thus, the other factor as valuable as diagnosing ASAP is to convince the patients that need the second biopsy absolutely.

Although ASAP is a histopathologic stimulant result regarding prostate cancer, routine re-biopsy should not be recommended for each patient. Especially, PSA related parameter changes should be reviewed before the second biopsy, for the group whose PSA value decreasing the second biopsy should not be quick. Considering that prostate cancer possibility of the group whose PSA value is increasing, the second biopsy should be recommended in the early period.

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