Prostate cancer detection following diagnosis of atypical small acinar proliferation

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ERICSON KJ, WENGER HC, ROSEN AM, KIRILUK KJ, GERBER GS, PANER GP, EGGENER SE. Prostate cancer detection following diagnosis of atypical small acinar proliferation. *Can J Urol* 2017;24(2):8714-8720.

Introduction: *To report the incidence and characteristics of cancer following a diagnosis of atypical small acinar proliferation (ASAP) and comment on current clinical practice recommendations.*

Materials and methods: *We reviewed patients that underwent prostate biopsy between 2008 and 2013 at a single institution. Men with ASAP without previous cancer were included. Clinicopathologic features including prostate-specific antigen (PSA), presence of ASAP or cancer, tumor volume, number of involved cores, and Gleason score were analyzed in men that received a repeat prostate biopsy.*

Results: *Of 1450 men, ASAP was found in 75 (5%) patients. Repeat biopsy was performed in 49 (65%) patients. Fifteen (31%) were diagnosed with cancer, 10 (20%) with ASAP, and 24 (49%) were benign. PSA, age, and number of cores with ASAP were not associated with cancer. Gleason 6 disease was diagnosed in 12 (80%) patients. Gleason ≥ 7 cancer was found in 3 patients, or 6% of all patients with a repeat biopsy. The average linear amount of tumor was 3.2 mm, and the average tumor volume was 14.2%.*

Conclusion: *In a contemporary prostate biopsy series, the incidence of ASAP was 5%. Among men with ASAP, incidence of cancer at repeat biopsy was 31%, with the overwhelming majority being low grade and low volume. Patients with ASAP may not require repeat biopsy within 6 months in the appropriate clinical context.*

Key Words: male, prostate, follow up studies, biopsy, prostatic neoplasms

Introduction

Atypical small acinar proliferation (ASAP) is reported when a few small atypical glands are present in a needle core biopsy that do not meet the threshold for diagnosis or exclusion of cancer because of too few glands and/or insufficient qualitative features, despite the use of ancillary immunostains. ASAP on prostate biopsy is associated with an increased likelihood of prostate cancer on subsequent biopsy[1-10] and has been identified in 0.9%-7.8% of all patients undergoing prostate biopsy.[1-4,11,12] Cancer detection rates in these patients during subsequent biopsies vary from 27%-59%.[1-9] Based on the elevated risk of cancer, the National Comprehensive Cancer Network (NCCN) prostate

Accepted for publication December 2016

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cancer screening guidelines suggest repeat 12-core biopsy with increased sampling from the original ASAP site and adjacent areas within 6 months of the original biopsy.[13] The focus of our study is to report the incidence and characteristics of prostate cancer after diagnosis of ASAP.

Materials and methods

We reviewed the clinical and pathological records of 1450 consecutive men who underwent trans-rectal ultrasound-guided prostate biopsy at the University of Chicago Medical Center between July 2008 and December 2013. The indication for biopsy was either an elevated prostate-specific antigen (PSA) or abnormal digital rectal exam (DRE). A single urologist performed all of the biopsies using 12-core template sampling from the medial and lateral sextants in an outpatient clinic setting. Patients who had a biopsy revealing ASAP without evidence of cancer and subsequently underwent repeat biopsy at our institution were included in the study. A diagnosis of ASAP was rendered by pathologists if there was a small focus of atypical glands that was insufficient to reach the confidence threshold for a diagnosis of cancer. While the threshold in diagnosing limited cancer among the institutional pathologists may vary, the reasons for ASAP diagnosis were quantitative (generally if < 3 glands) or qualitative (e.g. equivocal nuclear features, atypical glands adjacent to prostatic intraepithelial neoplasia (PIN), indefinite immunostaining pattern, resemblance to benign mimics, obscuring inflammation, etc.). The decision for a second review was at the discretion of the primary pathologist. The decision to perform a repeat prostate biopsy was left to the discretion of the referring urologist. Patients with a previous diagnosis of prostate cancer on earlier prostate biopsy (e.g. active surveillance patients) prior to ASAP were excluded. On subsequent biopsies for ASAP, core sampling included two additional cores taken from the areas with ASAP on initial biopsy.

Biopsy pathology results including presence of ASAP or cancer, number of involved cores, tumor volume, and Gleason score were analyzed along with PSA values prompting the initial biopsy. Multiple pathologists with a focus on urologic cancers performed pathologic review. When necessary, intra-departmental review of slides was performed to confirm ASAP. After formalin fixation, needle biopsy cores were routinely processed and serially cut at 5 μm thickness in 6 levels. Step levels 1, 3 and 6 were stained with hematoxylin and eosin and the intervening levels (2 and 4) were used for immunohistochemical work up if needed. Immunohistochemical stains included keratin 34βE12, p63 and/or alpha methyl CoA racemase. For patients subsequently diagnosed with cancer, treatment modality and outcomes were evaluated.

TABLE 1. **Pathological findings for initial biopsies with ASAP**

Total biopsies	1450	
No. of ASAP without cancer	75 (5.2%)	
No. of cores ASAP per patient	n	
1	52 (69.3%)	
2	4 (5.3%)	
3	4 (5.3%)	
Unspecified	15 (20%)	
Total	75	
PSA prompting biopsy w/ASAP	PSA (ng/ml)	
Overall average	7.9	
Average for pts w/o cancer	7.1	p = 0.4
Average for pts w/ cancer	8.2	

ASAP = atypical small acinar proliferation
PSA = prostate-specific antigen

Results

Over the 66-month period, 1450 patients underwent prostate biopsy. Seventy-five patients (5.2%) had ASAP without evidence of cancer and were included in the analysis, Table 1. Additional pathologists reviewed ASAP diagnoses in 18 cases (24%). Mean PSA level prompting biopsy in those with ASAP was 7.9 ng/mL. Forty-nine (65%) patients with ASAP underwent repeat biopsy in the same clinic at a mean of 6.7 months (interquartile range 2.0-7.7 months) following the initial diagnosis. Men undergoing a repeat biopsy were similar to those not undergoing repeat biopsy, Table 2. Among those with repeat biopsy, 10 (20%) had ASAP, 24 (49%) were benign, and 15 (31%) were diagnosed with cancer, Table 3. The mean age of men with benign findings at repeat was 67.0, ASAP 65.1, cancer was 68.2 (p = 0.61). Mean length of time to diagnosis of cancer was 5.8 months. One patient with a benign repeat biopsy was subsequently diagnosed with Gleason grade 6 cancer 26 months after initial ASAP diagnosis. Another patient with ASAP at repeat biopsy subsequently had benign findings, followed by Gleason grade 6 cancer 43 months after initial ASAP

TABLE 2. **Baseline characteristics of patients with ASAP**

	Repeat biopsy (%)	No repeat biopsy (%)	p value
ASAP diagnoses	49	26	
Age	67.0 ± 7.5	65.7 ± 9.5	0.5
Race			0.9
White	26 (53.1)	13 (50.0)	
Black	16 (32.7)	10 (38.5)	
Other	7 (14.5)	3 (11.6)	
Mean PSA (ng/dL)	7.5 ± 4.1	8.6 ± 9.2	0.5
Cores ASAP +			0.6
1	34 (69.4)	18 (69.2)	
≥ 2	6 (12.2)	2 (7.7)	
Unknown	9 (18.4)	6 (23.1)	

ASAP = atypical small acinar proliferation; PSA = prostate-specific antigen

diagnosis, Table 4. These two patients were included in the benign and ASAP group, respectively, as the indications for biopsy that revealed cancer were not ASAP.

In patients subsequently diagnosed with prostate cancer (n = 15), mean PSA was 8.28 ng/mL, whereas mean PSA level in patients re-biopsied without cancer was 7.10 ng/mL (p = 0.35). Twelve patients were diagnosed with Gleason 6 (80%) and 1 each with Gleason 3+4 (7%), Gleason 4+3 (7%) and Gleason 8 (7%). In those with cancer, 87% of patients had ≤ 25% cancer in positive cores (mean 14.2%) and 80% had ≤ 5 mm total linear length of cancer (mean 3.2 mm).

The patient with Gleason 8 disease was African American, had no family history of prostate cancer, and his physical exam was unremarkable. His PSA was 16.4 ng/dL, had 3 of 12 cores with ASAP on initial biopsy and 12 mm of Gleason 8 diagnosed 4 months

TABLE 3. **Pathological findings on subsequent biopsy after initial ASAP diagnosis**

Total patients	75		
No. w/repeat biopsy	49 (65.3%)		
Diagnosis on repeat biopsy	n		
Benign	24 (49.0%)		
ASAP	10 (20.4%)		
Cancer	15* (30.6%)		
Gleason score	n		
6	12 (80.0%)		
3+4	1 (6.7%)		
4+3	1 (6.7%)		
8	1 (6.7%)		
No. cores positive/pt. at initial biopsy	Benign	ASAP	Cancer
1	17	8	9
2	1	1	1
3	1	0	2
Unknown	5	1	3

*one patient with benign findings at repeat biopsy subsequently diagnosed with cancer (patient 20 in Table 4). One patient diagnosed with ASAP at repeat biopsy followed by HGPIN subsequently diagnosed with cancer (patient 26 in Table 4). These patients were included in the benign and ASAP groups, respectively.

ASAP = atypical small acinar proliferation

TABLE 4. **Results for patients with ASAP or cancer on subsequent biopsy**

Patient	Biopsy 1	Biopsy 2	Biopsy 3	Biopsy 4	Biopsy 5	Management	Postop path
1	ASAP 1/12 cores	ASAP 1/12 cores	-	-	-	-	-
2	ASAP 1/12 cores	ASAP 3/12 cores	-	-	-	-	-
3	ASAP 2/12 cores	ASAP 1/12 cores	-	-	-	-	-
4	ASAP 1/12 cores	ASAP (unspecified)	-	-	-	-	-
5	ASAP 1/12 cores	ASAP 1/12 cores	-	-	-	-	-
6	ASAP 1/12 cores	ASAP 1/12 cores	-	-	-	-	-
7	Normal	ASAP 1/12 cores	-	-	-	-	-
8	ASAP 1/12 cores	ASAP 2/12 cores	-	-	-	-	-
9	Normal	ASAP (unspecified)	ASAP (unspecified)	-	-	-	-
10	ASAP (unspecified)	Cancer 3+3=6	-	-	-	AS	-
11	ASAP (unspecified)	Cancer 3+3=6	Cancer 3+3=6	-	-	AS	-
12	ASAP 1/12 cores	Cancer 3+3=6	-	-	-	AS	-
13	ASAP 1/12 cores	Cancer 3+3=6	Normal	-	-	AS	-
14	ASAP (unspecified)	Cancer 3+3=6	Normal	-	-	AS	-
15	Normal	ASAP 1/12 cores	Cancer 3+3=6	Cancer 3+3=6	-	AS	-
16	Normal	Normal	ASAP 1/12 cores	Cancer 3+3=6	-	AS	-
17	ASAP 1/12 cores	Cancer 3+3=6	Normal	Normal	-	AS	-
18	ASAP 1/12 cores	Cancer 3+3=6	-	-	-	Laser ablation	-
19	ASAP 3/12 cores	Cancer 4+4=8	-	-	-	Radiation	-
20*	HG PIN	HG PIN	ASAP (unspecified)	HG PIN	Cancer 3+3=6	Radiation	-
21	ASAP 3/12 cores	Cancer 3+3=6	-	-	-	RALP	3+3=6
22	ASAP 1/12 cores	Cancer 3+3=6	-	-	-	RALP	3+4=7
23	ASAP 1/12 cores	Cancer 4+3=7	-	-	-	RALP	3+4=7
24	ASAP 1/12 cores	Cancer 3+3=6	Cancer 3+3=6	Cancer 3+4=7	-	RALP	3+4=7
25	HG PIN	Normal	ASAP 2/12 cores	Cancer 3+4=7	-	RALP	3+4=7
26*	HG PIN	ASAP 1/12 cores	ASAP 1/12 cores	HG PIN	Cancer 3+3=6	RALP	3+4=7

ASAP = atypical small acinar proliferation; AS = active surveillance; HG PIN = high-grade prostatic intraepithelial neoplasia; RALP = robotic-assisted laparoscopic prostatectomy

after initial biopsy. The original ASAP diagnosis was rendered due to artifactual distortion of the histology as a result of suboptimal biopsy tissue processing. The architecture was suspicious for cancer, but the cytologic detail was not preserved resulting in an indeterminate diagnosis of cancer. One patient had Gleason 4+3 disease. He was African American with no family history of prostate cancer and an unremarkable DRE.

His PSA was 5 ng/dL on dutasteride, had 1 of 12 cores with ASAP on initial biopsy, and was diagnosed 2 months after initial biopsy with 1 mm of Gleason 4+3.

Of 49 patients who underwent subsequent biopsy after ASAP diagnosis, 34 (69%) had 1 involved ASAP biopsy core, 3 (6%) had 2 involved cores, 3 (6%) had 3 involved cores, and 9 (18%) had ASAP without mention of the number of cores involved, Table 3. There was no association between number of cores with ASAP and Gleason score on subsequent biopsy ($p = 0.3$, Table 3).

Treatment modalities for the 15 patients diagnosed with cancer included active surveillance in 8 (53%), robotic-assisted laparoscopic prostatectomy in 5 (33%), external beam radiation therapy in 1 (7%), and a focal therapy clinical trial in 1 (7%). Of the 5 patients who underwent prostatectomy, pathology revealed 1 patient with Gleason 3+3, and 4 with Gleason 3+4 (2 upgraded from Gleason 6, 1 downgraded from Gleason 4+3). All 5 patients had organ-confined cancers (≤ T2cMxN0/X).

Discussion

ASAP is not a specific diagnosis and incorporates a spectrum of pathologic entities with uncertainty regarding a diagnosis of carcinoma. In many instances ASAP represents an undersampled carcinoma, but in some cases it may represent a benign mimicker of cancer. The incidence of ASAP in our population (5%) was similar to previous reports.[1-4,11,12] Epstein et al in 2006 noted a decreasing incidence of ASAP over time, which they suspected was a result of pathologists' improved ability to diagnose small foci of prostate cancer on needle biopsy.[14] Another potential explanation was the increase in extended core biopsies over time. Herawi et al demonstrated cancer detection rates on subsequent biopsies decreased as the number of initial biopsy sampling cores increased.[15] With the increased accuracy of sampling templates, the likelihood of missing a cancer decreases. Thus, patients with both ASAP and cancer are more likely to be diagnosed with cancer on an initial 12-core biopsy rather than on subsequent biopsies.

Following the diagnosis of ASAP, we observed a subsequent cancer incidence of 31%, similar to previously reported rates of 27%-59%.[1-9] Aside from a study in 1997 showing a 60% risk of cancer, most reports place the subsequent risk between 40%-50%.[10] Epstein et al reported the average risk of cancer for studies through 2006 was 40.2%.[14] Current NCCN practice recommendations are to repeat biopsy within 3-6 months based on these data showing an increased risk of cancer following a diagnosis of ASAP.

The large majority of cancers diagnosed after ASAP are low volume, low grade, and organ confined. In our study, 80% of patients subsequently diagnosed with cancer had Gleason 6 disease, similar to other studies (70%-80%).[16-19] Of all men who received a repeat biopsy in our cohort, Gleason ≥ 7 disease was found in 6% (3/49) of patients. In a recent report, Warlick et al observed Gleason ≥ 7 disease in 28% (26/94) of patients diagnosed with cancer within 1 year of their ASAP diagnosis.[19] Brausi et al performed immediate radical prostatectomy in 25 patients diagnosed with ASAP on prostate needle biopsy without follow up repeat biopsy.[20] All 25 patients were subsequently diagnosed with prostate cancer in their final pathology specimens. Of the 25 patients, 21 (84%) patients had Gleason score ≤ 6. Of the remaining 4 patients, 2 (8%) patients had Gleason 7 disease and 2 (8%) had Gleason 8 disease. Additionally, there was no indication why 25 patients among a total study population of 71 underwent radical prostatectomy while remaining patients were followed and re-biopsied. Performing radical prostatectomy on patients with ASAP is not supported by current data or guidelines.

To our knowledge, no contemporary study has reported tumor volume at repeat biopsy following an ASAP diagnosis. In our cohort, tumor volume was almost uniformly low with 87% having ≤ 25% cancer in positive cores (mean 14.2%) and 80% with ≤ 5 mm in linear length (mean 3.2 mm).

Approximately 60% of patients with ASAP will not be diagnosed with cancer. Determining clinical or biochemical predictors of cancer amongst patients with ASAP would limit unnecessary prostate biopsies, however finding these predictors remains elusive. Similar to Ploussard et al, we found no statistically significant difference in PSA between those diagnosed with cancer and those with benign findings.[1] Additionally, we found no correlation between the number of biopsy cores with ASAP and subsequent cancer diagnosis. Warlick et al found increasing age and PSA density were predictive of cancer on multivariate analysis, though no cutoffs could be determined.[19] We did not report on PSA density, as prostate volumes are unavailable for all patients. Similarly, Scattoni et al investigated the impact of prostate volume on cancer detection rates. Expectedly, cancer detection rates on repeat biopsy decreased as prostate volume increased.[6] Scattoni et al found ASAP detected along with HGPIN had a subsequent cancer detection rate of 58% versus just 35% for ASAP detected alone.[6] However, this correlation was not supported by Schlesinger et al who reported similar rates in the two groups (33% for HGPIN and ASAP versus 37% ASAP alone).[21]

The subjectivity of diagnosing ASAP leads to inter-observer variability that may complicate clinical decision-making. In large prostate biopsy series, ASAP is diagnosed in 1%-23% of all biopsies with an average of 5%.[14,22] This wide range in incidence reflects the variability of interpretation by pathologists, including among experts. One factor is establishing the quantitative cut off of designating a small atypical focus as cancer with most pathologists requiring at least two glands and supportive immunostains to establish a diagnosis of cancer. In one study, five expert pathologists independently reviewed 20 prostate biopsies with a diagnosis of ASAP. The multirater agreement was $\kappa = 0.39$ (0.29-0.49). All five pathologists came to a 100% agreement for only 7 of 20 biopsies. Most of the variability in this study was seen in smaller lesions (≤ 5 glands) and the most frequent change was an upgrade to adenocarcinoma (49%).[23] In several other studies, biopsies with ASAP were reviewed by expert pathologists and were upgraded to carcinoma in 2.2%-20.3% (median 11.6%) and downgraded to benign in 2%-16.7% (median 5.5%).[3,17,24,25]

Based on our data, it seems reasonable to manage ASAP patients more conservatively than the NCCN currently recommends. While ASAP portends an elevated risk of cancer, the overwhelming majority of patients subsequently diagnosed with cancer have low grade, low volume disease and meet eligibility criteria for active surveillance (AS). Encouragingly, among the 75 men with ASAP, only 3 (6%) were subsequently diagnosed with intermediate or high grade cancers, and the two highest grade cancers had a PSA ≥ 10 ng/mL at the time of ASAP diagnosis. We believe it is preferable to follow up ASAP patients in a manner similar to AS patients with semiannual PSA, DRE, and consideration of repeat biopsy within 1 year.

Conclusion

Our findings and recommendations should be interpreted in the context of our study limitations, which include the retrospective study design, non-standardized follow up regimen, lack of centralized pathology review for each case and relatively few men ultimately undergoing repeat biopsy and prostatectomy. Despite these limitations, our data suggest an isolated finding of ASAP is not necessarily associated with a high risk of intermediate and high grade cancers and may not require repeat biopsy within 6 months in the absence of concerning clinical or biochemical factors.

ASAP at prostate biopsy is uncommonly diagnosed (5%), does not appear to be associated with an elevated risk of intermediate or high grade cancer, and may not require immediate repeat biopsy in appropriate patients. Additional studies involving larger patient numbers are needed to confirm these findings. □

References

1. Ploussard G, Plennevaux G, Allory Y et al. High-grade prostatic intraepithelial neoplasia and atypical small acinar proliferation on initial 21-core extended biopsy scheme: incidence and implications for patient care and surveillance. *World J Urol* 2009;27(5):587-592.
2. Amin MM, Jeyaganth S, Fahmy N et al. Subsequent prostate cancer detection in patients with prostatic intraepithelial neoplasia or atypical small acinar proliferation. *Can Urol Assoc J* 2007;1(3):245-249.
3. Iczkowski K, Chen H, Yang X, Beach R. Prostate cancer diagnosed after initial biopsy with atypical small acinar proliferation suspicious for malignancy is similar to cancer found on initial biopsy. *Urology* 2002;4295(02):851-854.
4. López JI. Prostate adenocarcinoma detected after high-grade prostatic intraepithelial neoplasia or atypical small acinar proliferation. *BJU Int* 2007;100(6):1272-1276.
5. Yanke B V, Salzhauer EW, Colon I. Is race a positive predictor of cancer on repeat prostate biopsy? *J Urol* 2006;176(3):1114-1117.
6. Scattoni V, Roscigno M, Freschi M et al. Predictors of prostate cancer after initial diagnosis of atypical small acinar proliferation at 10 to 12 core biopsies. *Urology* 2005;66(5):1043-1047.
7. Mancuso PA, Chabert C, Chin P et al. Prostate cancer detection in men with an initial diagnosis of atypical small acinar proliferation. *BJU Int* 2007;99(1):49-52.
8. Mallén E, Gil P, Sancho C et al. Atypical small acinar proliferation Review of a series of 64 patients. *Scand J Urol Nephrol* 2006;40(4):272-275.
9. Ouyang RC, Kenwright DN, Nacey JN, Delahunt B. The presence of atypical small acinar proliferation in prostate needle biopsy is predictive of carcinoma on subsequent biopsy. *BJU Int* 2001;87(1):70-74.
10. Iczkowski KA, Bostwick DG. Atypical small acinar proliferation of the prostate: 16 years' experience. *Pathol Case Rev* 2014;19(3): 147-153.
11. Bostwick DG, Meiers I. Atypical small acinar proliferation in the prostate: clinical significance in 2006. *Arch Pathol Lab Med* 2006;130(7):952-957.
12. Ryu JH, Kim YB, Lee JK, Kim YJ, Jung TY. Predictive factors of prostate cancer at repeat biopsy in patients with an initial diagnosis of atypical small acinar proliferation of the prostate. *Korean J Urol* 2010;51(11):752-756.
13. NCCN Guidelines Panel. Evidence-Based Cancer Guidelines, Oncology Drug Compendium, Oncology Continuing Medical Education. NCCN;2014.
14. Epstein JI, Herawi M. Prostate needle biopsies containing prostatic intraepithelial neoplasia or atypical foci suspicious for carcinoma: implications for patient care. *J Urol* 2006;175(3 Pt 1):820-834.
15. Herawi M, Kahane H, Cavallo C, Epstein JI. Risk of prostate cancer on first re-biopsy within 1 year following a diagnosis of high grade prostatic intraepithelial neoplasia is related to the number of cores sampled. *J Urol* 2006;175(1):121-124.

16. Hoedemaeker RF, Kranse R, Rietbergen JB, Kruger AE, Schröder FH, van der Kwast TH. Evaluation of prostate needle biopsies in a population-based screening study: the impact of borderline lesions. *Cancer* 1999;85(1):145-152.
17. Iczkowski KA, Bassler TJ, Schwob VS et al. Diagnosis of "suspicious for malignancy" in prostate biopsies: predictive value for cancer. *Urology* 1998;51(5):749-757; discussion 757-758.
18. Chan TY, Epstein JI. Follow-up of atypical prostate needle biopsies suspicious for cancer. *Urology* 1999;53(2):351-355.
19. Warlick C, Feia K, Tomasini J, Iwamoto C, Lindgren B, Risk M. Rate of Gleason 7 or higher prostate cancer on repeat biopsy after a diagnosis of atypical small acinar proliferation. *Prostate Cancer Prostatic Dis* 2015;18(3):255-259.
20. Brausi M, Castagnetti G, Dotti A, De Luca G, Olmi R, Cesinaro AM. Immediate radical prostatectomy in patients with atypical small acinar proliferation. Over treatment? *J Urol* 2004;172(3):906-909.
21. Schlesinger C, Bostwick DG, Iczkowski KA. High-grade prostatic intraepithelial neoplasia and atypical small acinar proliferation: predictive value for cancer in current practice. *Am J Surg Pathol* 2005;29(9):1201-1207.
22. Vis AN, Van Der Kwast TH. Prostatic intraepithelial neoplasia and putative precursor lesions of prostate cancer: a clinical perspective. *BJU Int* 2001;88(2):147-157.
23. Van der Kwast TH, Evans A, Lockwood G et al. Variability in diagnostic opinion among pathologists for single small atypical foci in prostate biopsies. *Am J Surg Pathol* 2010;34(2):169-177.
24. Iczkowski KA, MacLennan GT, Bostwick DG. Atypical small acinar proliferation suspicious for malignancy in prostate needle biopsies: clinical significance in 33 cases. *Am J Surg Pathol* 1997;21(12):1489-1495.
25. Renshaw AA, Santis WF, Richie JP. Clinicopathological charecteristics of prostatic adenocarcinoma in men with atypical prostate needle biopsies. *J Urol* 1998;159(6):2018-2022.