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Rate of clinically significant prostate cancer on repeated biopsy after a diagnosis of atypical small acinar proliferation

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Abstract

Introduction: Current guidelines recommend repeat biopsy within 3-6 months for the diagnosis of atypical small acinar proliferation (ASAP) on prostate biopsy.
Objectives: We aimed to evaluate the rate of progression of ASAP to clinically significant prostate cancer on repeat biopsy specimens and determine prognostic factors associated with progression.
Patients and Methods: In a retrospective study we reviewed data of patients who had a prostate biopsy in our institution from March 2014 to March 2018. Gleason grade group (GGG) was conducted for pathology reporting. Logistic regression analysis was conducted for statistical analysis.
Results: A total of 981 patients were identified of which 117 (12%) of them had a diagnosis of ASAP on their index biopsy. Out of these 16 (14%) patients underwent re-biopsy. Baseline clinicopathologic factors included a median age of 61 years, median pre-biopsy prostate-specific antigen (PSA) of 6.75 ng/mL and a mode of 1 core with ASAP. Median time interval between index and repeat biopsy was 10.5 months. The results of repeat biopsies were distributed across GGG system as follows; 12(75%) benign, 2 (12.5%) GG1, 1 (6.25%) GG2, and 1 (6.25%). We found no association between age, pre-biopsy PSA, and number of cores with ASAP, and progression of ASAP to clinically significant prostate cancer.
Conclusion: Our study showed that patients with a diagnosis of ASAP are more likely to have a benign pathology on repeat biopsy. This finding supports previous studies regarding rethinking current guidelines for utility of repeat biopsy in patients with the diagnosis of ASAP.

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Introduction

Cancers are among the most common causes of death worldwide, and prostate cancer is one of the most common types of cancer and the second leading cause of cancer related mortality (1). Prostate cancer also imposes a significant public health burden and is a major cause of morbidity and mortality among men worldwide (2). Recently the clinical course of prostate cancer has shifted toward a more indolent nature (3).

Atypical small acinar proliferation (ASAP) is a focus of glandular proliferation with atypia but it not sufficient enough for diagnosing prostate adenocarcinoma (4). ASAP has a diagnosis rate of 5% on prostate biopsy and previous studies showed a 30%-50% progression rate to prostate cancer on repeat biopsy (5,6). Prior studies have categorized re-biopsy outcomes after diagnosis of ASAP, into clinically significant versus indolent disease (7,8). Existing data on clinical significance of ASAP with regard to re-biopsy outcomes is conflicting, some studies show a prevalence of clinically significant prostate cancer as high as 51% while others reported a predominance of low-grade cancer (9).

Current guidelines of National Comprehensive Cancer Network (NCCN) and European Association of Urology (EAU) recommend that patients diagnosed with ASAP on initial biopsy undergo repeat prostate biopsy with extended pattern within 3-6 months (10,11). Recent studies regarding

Key point

In a retrospective study, we found patients with a diagnosis of atypical small acinar proliferation are more likely to have a benign pathology on repeat biopsy. This finding supports previous studies regarding rethinking current guidelines for utility of repeat biopsy in patients with the diagnosis of atypical small acinar proliferation.

epidemiological aspects of prostate cancer in Iran suggest differences with respect to disease nature compared to other parts of the world (2).

Prostate biopsy is with some disadvantages, including risk of infection in an era of increasing resistance to fluoroquinolone antibiotics, physical morbidity, emotional concern of diagnosis of indolent cancer and costs to patients and health care system (12,13), all of which necessitate conducting efficient approaches regarding patient selection for prostate biopsy.

Objectives

We aimed to evaluate the rate of progression of ASAP to clinically significant prostate cancer, defined as Gleason grade groups (GGG) ≥2 on re-biopsy specimens (14). We also sought to evaluate the prognostic value of initial prostate specific antigen (PSA) level, age, and number of biopsy cores with ASAP, for predicting clinically significant prostate cancer on repeat biopsy with the aim of finding factors for selecting higher risk patients who would benefit more from repeat biopsy than others.

Patients and Methods

Study design

We conducted a retrospective chart review of patients who underwent standard 12 core trans-rectal ultrasound-guided prostate biopsy at our institution from March 2014, to March 2018. We identified a total of 981 patients who underwent prostate biopsy under the indication of elevated PSA levels or abnormal digital rectal examination. Those with a prior diagnosis of prostate cancer were excluded. A total of 117 cases remained who had ASAP on their index biopsies. Out of these 117 patients, 16 underwent repeat biopsy, and the remaining 111 patients were excluded because of lack of follow up. All pathological diagnoses were established by a single pathologist.

Patient data including age, pre-biopsy PSA, number of cores with ASAP, presence of prostate cancer and Gleason score on repeat biopsy were extracted. The primary outcome was the rate of progression of ASAP to clinically significant prostate cancer on repeat biopsy. Secondary outcome was evaluating the prognostic value of clinicopathologic factors including age, pre-biopsy PSA and number of cores with ASAP, for predicting clinically significant prostate cancer on repeat biopsy.

Statistical analysis

We conducted regression analysis using pathology from repeat biopsies for evaluating clinicopathologic predictors related to progression. Outcome variable was Gleason group defined by GGG system. Linear regression was used for analysis of continuous outcome variables. Logistic regression was used for the analysis of categorical outcome variables. *P* values below 0.05 were considered statistically significant. SPSS version 21.0 was used for the data analysis.

Results

A total of 981 patients were identified of which 117 (12%) of them had a diagnosis of ASAP on their index biopsy. Out of these, 16 (14%) patients underwent re-biopsy. Baseline clinicopathologic factors included a median age of 61 years, median pre-biopsy PSA 6.75 ng/mL and a mode of 1 core with ASAP (Table 1). Median time interval between index and repeat biopsy was 10.5 months. The results of repeat biopsies were distributed across GGG system as follows: 12 (75%) benign, 2 (12.5%) GG1, 1 (6.25%) GG2, and 1 (6.25%) GG3 (Figure 1).

The association of clinicopathologic factors with clinically significant prostate cancer in the context of GGG on repeat biopsy was examined using logistic regression analysis (Table 2). According to our logistic regression analysis, there was no association between age, pre-biopsy PSA and number of cores with ASAP, and a diagnosis of clinically significant prostate cancer on repeat biopsy.

Discussion

In our study on men with a clinical suspicion of prostate cancer who underwent prostate biopsy and had an index biopsy result of ASAP, we found that the majority of those who were managed based on recent guidelines and underwent repeat biopsy, were diagnosed with benign disease. In our study out of 16 re-biopsies only 2 (12.5%) were diagnosed with clinically significant prostate cancer. This finding suggests that current management strategies may reflect an aggressive approach which is not in line

Table 1. Patient demographic and clinical characteristics

Characteristic	No. (%)
Age, years, median (IQR)	61 (55-64)
PSA (ng/mL), median (IQR)	6.75 (5.52-8.19)
Number of ASAP cores, mode (range)	1 (1-4)
Time to repeat biopsy, months, median (IQR)	10.5 (6-20.5)

IQR interquartile range, PSA prostate-specific antigen, ASAP atypical small acinar proliferation.

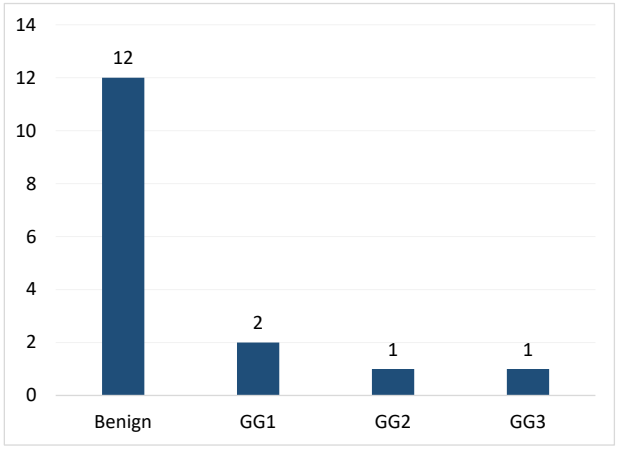

Figure 1. Distribution of re-biopsy pathology according to Gleason grade grouping.

Table 2. Association of clinicopathologic features with subsequent diagnosis of clinically significant prostate cancer using logistic regression

Factor	OR	95% CI	*P* value
Age	1.10	0.94-1.29	0.252
Pre-biopsy PSA	0.97	0.84-1.11	0.659
Number of ASAP cores	2.71	0.23-32.01	0.427

ASAP, atypical small acinar proliferation; CI, confidence interval; OR, odds ratio; PSA, prostate-specific antigen.

with active surveillance for low-risk prostate cancer.

It is reasonable that these patients be managed according to active surveillance guidelines therefore overutilization of biopsy of prostate would be minimized (8,10). These patients could undergo a less morbid repeat prostate biopsy with template (15) or they could be further evaluated with newer imaging modalities including multi-parametric magnetic resonance imaging (16,17).

This study reached a constellation of important findings. First it confirms the progression rate of ASAP to clinically significant prostate cancer to be low. Ynalvez et al reported a 9.1% of progression rate of ASAP to clinically significant cancer on re-biopsy (18). A multi-institutional study also showed the rate of clinically significant cancer diagnosis on repeat biopsy to be 8% (8). Furthermore, another study found a one-year progression of ASAP to prostate cancer of 38%, however only 11% had clinically significant disease (7). In another study there was a 51% cancer progression rate on repeat biopsy, however this result is misleading due to their use of modified Epstein criteria for defining clinically significant prostate cancer. Due to incomplete documentation, they were only capable of using this criterion only on half of their prostate cancer patients (9). Taking the results of these studies into account, their rate of progression to clinically significant prostate cancer in those with ASAP on index biopsy is comparable to our low-progression rates.

Second, our study showed that age, pre-biopsy PSA, and number of cores diagnosed with ASAP on index biopsy, were not associated with progression to clinically significant prostate cancer and they cannot be used as prognostic factors for defining high risk subgroups. Previous studies have found evidence in favor of our findings. Ynalvez et al found no relation between pre-biopsy PSA and progression to prostate cancer on repeat biopsy (18). Ericson et al showed that age, pre-biopsy PSA and number of ASAP cores had no prognostic value for prostate cancer progression from ASAP (19). Previous studies suggested other factors, such as PSA density as predictors of progression to prostate cancer on repeat biopsy (7).

Third our study showed a higher rate of ASAP diagnosis (12%) on prostate biopsies compared to previous studies. Previous studies showed an approximate rate of ASAP diagnosis of 5% on index prostate biopsies (4,20-22). This along with a lower incidence of prostate cancer in Iran (2), could imply a difference in the natural course of prostate neoplasia natural course in the Iranian population, necessitating further epidemiological studies regarding the natural course of prostate cancer in this population. Moreover, the re-biopsy rates in our study are dramatically lower than other studies (14% versus 41%-76%) (7,18,19). This finding could be because of inefficient patient follow-up or urologist's conservative approach to performing repeat biopsy in these patients.

Our study showed higher rates of ASAP diagnosis on index biopsies compared to other multi-institutional and retrospective studies (12% versus 3.8-5.3%) (4, 20-22). About 12.5% rate of ASAP progression to clinically significant prostate cancer in our study was comparable to other similar series (9, 16, 18, 20).

Conclusion

Those patients with ASAP on index biopsy are more likely to be diagnosed with benign pathology or clinically insignificant prostate cancer on repeat biopsy, if managed according to current EAU and NCCN guidelines. These recommendations are thus too aggressive for repeat biopsy with regard to current concepts of active surveillance for low-risk prostate cancer. Further studies are required for externally validating these findings and evaluating the benefit and the interval of repeat biopsy in patients diagnosed with ASAP.

Limitations of the study

A contextual perspective should be kept in mind when interpreting the results of our study. First, limitations due to retrospective study design and the small sample size of patients with repeat biopsy. Second, our sample may be limited with regard to generalizability to other populations. Third, because the diagnosis of ASAP is under reconsideration, our results may not be compatible with recent pathological descriptions. Lastly, none of our patients underwent any additional diagnostic studies such as magnetic resonance imagining as use of magnetic resonance imaging for patients with negative index biopsy and those undergoing active surveillance is on the rise.

Authors' contribution

Conceptualization: MY and PRS.
Methodology: MY and PRS.
Validation: MY, PRS and HM.
Formal analysis: PRS.
Investigation: MY, PRS, HM and AY.
Resources: HM & MY.
Data curation: MY & HM.
Writing—original draft preparation: AY and PRS.
Writing—review and editing: MY.
Visualization: MY.
Supervision: MY.
Project administration: MY.
Funding acquisition: MY.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

The research followed the tenets of the Declaration of Helsinki. Informed consents were obtained from all patients. The study was approved by the ethical committee of Isfahan University of Medical Sciences (ethical code; IR.AJUMS.REC. 295144). This study was extracted from the M.D thesis of Payam Riahi Samani (Thesis #295144) at Isfahan University of Medical Sciences. Besides, ethical issues (including plagiarism, data fabrication and double publication) have been completely observed by the authors.

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