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Atypical Small Acinar Proliferation at Index Prostate Biopsy: Rethinking the Re-Biopsy Paradigm

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Abstract

Purpose—Guidelines for atypical small acinar proliferation (ASAP) diagnosed on prostate biopsy recommend repeat biopsy within 3–6 months after diagnosis. We sought to discern the rate of detecting clinically significant prostate cancer on repeat biopsy and predictors associated with progression.

Materials and Methods—We performed a retrospective chart review of patients who underwent prostate biopsy at our institution from January 1, 2008 to December 31, 2015. Gleason grade group (GGG) system and D'Amico stratification were used to report pathology and risk stratification, respectively. Logistic and linear regression analyses were performed.

Results—A total of 593 patients underwent transrectal ultrasound-guided prostate biopsy, of which 27 (4.6%) had the diagnosis of ASAP. Of these, 11 (41%) had a repeat biopsy. Median time from diagnosis to repeat biopsy was 147 days (IQR: 83.5–247.0). Distribution across the GGG system on repeat biopsy was as follows: 7 (63.6%) benign, 3 (27.3%) GG1, and 1 (9.1%) GG2. ASAP was not associated with subsequent diagnosis of clinically significant prostate cancer (OR=0.46, 95% CI: 0.064 to 3.247, p=0.432). There was no association between ASAP and high cancer risk (ASAP: $\beta = -0.12$; p=0.204).

Conclusions—Patients diagnosed with ASAP managed according to guideline recommendations are more likely diagnosed with benign pathology and indolent prostate cancer on repeat biopsy. These findings support prior studies suggesting refinement of guidelines in regards to the appropriateness and timeliness of repeat biopsy among patients diagnosed with ASAP.

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Keywords

ASAP; Atypical small acinar proliferation; Prostate biopsy; prostate cancer

INTRODUCTION

Prostate cancer remains the most commonly diagnosed solid organ tumor among U.S. men with an estimated 161,360 new cases and 26,730 deaths in 2016¹. With recent stage migration², the natural history of prostate cancer has shifted toward a more indolent course in a majority of newly diagnosed cases³. There are concerted efforts to limit the overdiagnosis and potential overtreatment of indolent disease⁴.

Atypical small acinar proliferation (ASAP) represents a focus of suspicious prostate glands without adequate atypia to establish a diagnosis of cancer⁵. ASAP occurs at a rate of up to 5% on prostate biopsies, and it is known from prior studies that 30–50% of patients with an initial diagnosis of ASAP have progression to prostate cancer on repeat biopsy^{6,7}. Previous studies have risk-stratified prostate cancer into clinically significant versus indolent disease on repeat biopsy following the diagnosis of ASAP^{8,9}. However, existing data on its implication with regard to disease risk are conflicting. While some studies have reported a predominance of low-grade cancer on repeat biopsy after ASAP diagnosis, other studies have observed a relatively high incidence of clinically significant disease, up to 51%¹⁰. However, these reports are likely misleading given their definition of clinically significant prostate cancer using a modified Epstein criteria. Thus, the incidence of clinically significant disease may not be as predominant as these studies report. We sought to compare the rate of progression of ASAP into clinically significant prostate cancer using a contemporary series of patients who underwent 12-core prostate biopsy.

Current National Comprehensive Cancer Network (NCCN) and European Association of Urology (EAU) guidelines recommend extended pattern repeat biopsy with focus at the initially positive site to be performed within 3–6 months of initial ASAP diagnosis^{11,12}. We sought to discern the rate of detecting all prostate cancer as well as clinically significant prostate cancer, defined as Gleason grade groups (GGG) 2, on repeat biopsy¹³. Secondary outcomes included all clinicopathologic features associated with clinically significant prostate cancer on repeat biopsy. We hypothesized that patients diagnosed with ASAP managed according to NCCN recommendations are more likely diagnosed with benign pathology and/or indolent disease than clinically significant prostate cancer on repeat biopsy.

MATERIALS AND METHODS

We performed a retrospective chart review of patients who underwent standard 12-core transrectal ultrasound-guided prostate needle biopsy at our institution from January 1, 2008 to December 31, 2015. A total of 593 consecutive patients who underwent prostate biopsy were identified. Indications for transrectal ultrasound-guided prostate biopsy included elevated PSA and/or abnormal digital rectal exam. Patients with prior diagnosis of prostate cancer were excluded from the study. Out of 27 patients diagnosed with ASAP, 11 patients underwent repeat biopsy. The remaining 16 patients with initial ASAP diagnosis were

excluded either due to incomplete medical records and/or lack of follow-up. All pathologic diagnoses were established by a single expert genitourinary pathologist. Patients were counseled by urologists to undergo repeat prostate biopsy within 3–6 months after initial prostate biopsy. This study was approved by the Institutional Review Board at our organization.

Patient demographics and biopsy characteristics, including age, race/ethnicity, Charlson Comorbidity Index (CCI), pre-biopsy PSA, presence of prostate cancer, and Gleason score on repeat biopsy were extracted. The primary outcome was the rate of progression to clinically significant prostate cancer (GGG ≥ 2) on repeat biopsy^{14–16}. Secondary outcomes were associations of clinicopathologic features with clinically significant prostate cancer.

We performed regression analysis using histologic diagnoses from repeat biopsies to discern clinicopathologic predictors associated with progression. Outcome variables were D'Amico risk classification and Gleason group defined by GGG system. Linear regression was used in analysis of continuous outcome variables. Logistic regression was used in the analysis of categorical outcome variables. We also examined patient characteristics and ASAP by comparing covariates (age, PSA, CCI) and comorbidities (diabetes mellitus type II, hypertension, myocardial infarction, congestive heart failure, and surgical histories of coronary artery bypass graft and cardiac stent placement).

RESULTS

A total of 593 patients were identified, of which 27 (4.6%) had a diagnosis of ASAP. Of those diagnosed with ASAP on initial biopsy, 11 (41%) underwent repeat biopsy. Baseline clinical and pathologic features included a median age of 60 years, median pre-biopsy PSA 6.59, and a median CCI of 3 (Table 1). One (9%) patient had an abnormal DRE with cT2a disease. Median time from initial ASAP diagnosis to repeat prostate needle biopsy was 4.9 months (IQR: 2.8–8.3). The distribution across GGG on repeat biopsy was the following: 7 (64%) benign, 3 (27%) GG1, and 1 (9%) GG2 (Figure 2).

We examined the associations of clinical and pathologic factors with clinically significant prostate cancer in the context of GGG (Table 2) and D'Amico risk classifications on subsequent biopsy using logistic regression analysis and linear regression analysis, respectively (Table 3). In a logistic regression analysis, ASAP was not associated with subsequent diagnosis of prostate cancer (odds ratio [OR], 0.46; 95% confidence interval [CI], 0.06–3.25, $P=0.432$). In a linear regression analysis, there was no association between ASAP and classification of cancer risk (ASAP: $\beta=-0.12$; $P=0.204$).

To identify features associated with subsequent diagnosis of clinically significant prostate cancer on repeat biopsy, we examined associations of clinical and pathologic characteristics among men with and without subsequent cancer diagnosis. Among comorbidities, only myocardial infarction was statistically significant, with lower incidence in patients with ASAP ($t=2.99$; $P<0.01$). Lower age and higher CCI were significantly associated with higher GGG (Age: OR, 0.85; CI, 0.75–0.96) (CCI: OR, 5.23; CI, 2.51–10.90) and higher D'Amico risk (Age: $\beta=-0.33$; $P=0.006$) (CCI: $\beta=0.68$; $P<0.001$).

In addition, we conducted a subgroup analysis comparing the age and CCI score of patients diagnosed with ASAP who underwent a repeat biopsy ($n_{\text{Rbx}}=11$) and patients with ASAP who did not have a repeat biopsy ($n_{\text{noRbx}}=16$). Patients who underwent repeat biopsy had significantly higher CCI score than patients who did not have a repeat biopsy (mean $\text{CCI}_{\text{Rbx}}=4.18$, mean $\text{CCI}_{\text{noRbx}}=2.25$, $P=0.003$). The patient groups did not differ in mean age ($n_{\text{Rbx}}=59.8$ years, $n_{\text{noRbx}}=61.5$ years, $P=0.252$).

DISCUSSION

In a cohort of men with a clinical index of suspicion of prostate cancer, we discovered that patients diagnosed with ASAP and managed according to current guidelines are more likely diagnosed with benign pathology and/or indolent prostate cancer on repeat biopsy. Interestingly, out of 11 repeat biopsies only 1 (9%) was diagnosed with clinically significant prostate cancer. Current recommendations may thus represent an aggressive repeat biopsy strategy and fail to reflect the current paradigm of active surveillance for low-risk disease. For example, the recent ProtecT trial provides strong level I evidence regarding the safety and efficacy of active surveillance by demonstrating equivalent overall survival and cancer-specific survival when compared to management with either surgery or radiotherapy^{11,17}. Reasonably, such patients may be best managed in accordance with current active surveillance guidelines to minimize the overutilization of prostate biopsies⁹. Moreover, one can consider further investigation with newer imaging modalities such as multi-parametric magnetic resonance imaging^{18,19} or employ a less morbid transperineal template-guided approach on repeat biopsy²⁰.

Our study has several important findings. First, it reaffirms the rate of progression of clinically significant prostate cancer on repeat biopsy of approximately 10%^{10,16,18,21}. In a multi-institutional review, Leone, et al.⁹ reported that on repeat biopsy 34% were diagnosed with prostate cancer; however, 8% had Gleason 7 disease. Consistent with these findings, Tosoian, et al.¹⁸ demonstrated 5% of patients with ASAP were diagnosed with Gleason 7 disease using magnetic resonance imaging/TRUS fusion-guided for repeat biopsy. Furthermore, another study found 38% of repeat biopsies within 1 year of ASAP diagnosis were upgraded to prostate cancer, but only 11% had clinically significant prostate cancer⁸. Conversely, some studies indicate ASAP has a much higher progression rate to clinically significant prostate cancer. In a retrospective review, Dorin, et al.¹⁰ reported that 51% of patients with prostate cancer on repeat biopsy after initial ASAP diagnosis were determined to have clinically significant tumors, suggesting a strong correlation and need to have aggressive follow-up and re-biopsy regimen. However, this conclusion was misleading given their definition of clinically significant prostate cancer using a modified Epstein criteria. Of the subset of patients with prostate cancer, they were only able to use the Epstein criteria on half of the total prostate cancer samples as documentation was incomplete. Taking this account, their rate of clinically significant prostate cancer among men with ASAP supports our rate at approximately 10%¹⁰.

Second, we found that younger age and increased CCI were associated with progression to clinically significant prostate cancer on repeat biopsy. These are the first reported clinicopathologic factors that are suggested to have a predictive ability in regards to ASAP

progression to clinically significant prostate cancer⁸. This has the potential to identify a subset of patients that would benefit from the current guidelines of repeat biopsy in 3–6 months based on age and comorbidity status. Our study suggests that younger patients who present with ASAP are more likely to have clinically significant prostate cancer on repeat biopsy, while older patients with ASAP are more likely to have benign findings or less aggressive cancer. Prostate biopsy does not come without inherent risks, which include the physical morbidity, emotional uncertainty regarding being diagnosed with indolent cancer and cost to the health care system. Up to 2% of patients undergoing prostate biopsy develop a febrile UTI, bacteremia or acute prostatitis requiring hospitalization, complicated by recent emergence of fluoroquinolone resistance, among other possible biopsy-related complications²². The emotional sequelae of identifying indolent cancer and the decision to undergo treatment or active surveillance, as well as the cost of biopsy (approximately \$347.24/man in the U.S.)²³ – together with the unmeasured cost of cancers missed due to under diagnosis among some men with normal PSA levels - further elevate societal costs of poorly discriminant algorithms to identify candidates for prostate biopsy. Moreover, given our finding that higher CCI is associated with progression to clinically significant prostate cancer, there is the need to consider the risk-benefit ratio of definitive therapy versus active surveillance since these patients would portend a shorter life expectancy and increased risk of complications with more aggressive therapy. Thus, repeat biopsy may not be indicated at such a frequent rate given this data.

Third, we found that patients with a diagnosis of ASAP are more likely to have a higher CCI. Previous studies have indicated that diabetes mellitus, benign prostatic hyperplasia, and a history of urinary tract infections increase the risk of infection after prostate biopsy^{24,25}. More recently, studies reveal that while the rate of infection after biopsy has decreased in the past decade, the rate of hospital admission after biopsy has increased in patients with CCI² and diabetes mellitus as the highest risk factors^{26–28}. Our cohort had an average CCI score of 3 with diabetes mellitus being most prevalent noted in 18% of the patients. Subgroup analysis demonstrated that patients who underwent repeat biopsy had significantly higher CCI score than patients who did not have a repeat biopsy however they did not differ in mean age. This shows that even in a patient group with higher CCI scores, a clinicopathologic factor we found to be associated with clinically significant prostate cancer on repeat biopsy, the rate of progression of ASAP into clinically significant disease remains low. Aside from the most common complications of bleeding and infection/sepsis, patients with ASAP are potentially at higher risk for hospital admission after biopsy given their age, CCI score and diabetic disease. In this generation of cost-conscious medicine such risks need to be strongly weighted against necessity and additional cost.

Our findings must be interpreted in the context of the study design. First, our study is limited by its retrospective design and small number of patients with ASAP diagnosis. Although sample size is small and not random, our sample mirrors prior index populations in other series^{8,9}. Our study showed comparable rates of ASAP diagnosis on initial biopsy from larger retrospective studies and multi-institutional databases (4.5% vs 3.8–5.3%)^{5,21,29,30}. Moreover, our progression rate into clinically significant prostate cancer of 9% is similar to that documented in recent risk-stratified focused ASAP studies (10%)^{10,16,18,21}. Second, our sample may not reflected to other patient populations, however, given the relative

heterogeneous race/ethnicity strengthens the generalizability of our findings. Third, interpretation of ASAP is being reconsidered altogether and these results may not be reflective of current pathologic diagnoses and interpretation^{13,31}. Lastly, none of these underwent prostate magnetic imaging or other additional diagnostic tests beyond repeat PSA tests performed and we cannot comment on the applicability of these imaging and markers in this setting. Given the recent recommendations on use of MRI among patients with a prior negative prostate biopsy and/or those considered to be active surveillance candidates, further studies discerning the appropriateness in the context of ASAP diagnosis are needed^{14,19,32}.

CONCLUSIONS

Patients diagnosed with ASAP on index biopsy managed according to EAU and NCCN guideline recommendations are more likely to be diagnosed with benign pathology and indolent prostate cancer on repeat biopsy. Current recommendations may thus represent an overly aggressive repeat biopsy strategy that fails to reflect the current paradigm of active surveillance for low-risk prostate cancer. These findings require external validation in a larger cohort of patients to discern the appropriateness and timeliness of repeat biopsy among patients diagnosed with ASAP.

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Figure 1.
Flowchart of patients diagnosed with ASAP.

Figure 2.
Distribution of Re-Biopsy Pathology According to Gleason Grade Grouping.

Table 1

Patient demographic and clinical characteristics.

Characteristic	N (%)
Age, years, median (IQR)	60 (56–64)
Race/ethnicity	
Caucasian	16 (59.3)
African American	10 (37.0)
Other	1 (3.7)
PSA (ng/mL), median (IQR)	6.59 (4.42–10.55)
Abnormal DRE	1 (3.7)
Family history, positive	4 (14.8)
CCI, median (IQR)	3 (2–4)
Time to repeat biopsy, Months, median (IQR)	4.9 (2.8–8.3)

CCI, Charlson Comorbidity Index; DRE, digital rectal exam; IQR, interquartile range; PSA, Prostate-specific antigen

Table 2

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

Factor	OR	95% CI	p-value
ASAP	0.46	0.06–3.25	0.432
Age	0.85	0.75–0.96	<0.001
CCI	5.23	2.51–10.90	<0.001
PSA	1.02	0.97–1.07	0.383
Constant	123.48	0.97–1.07	0.154

ASAP, Atypical small acinar proliferation; CCI, Charlson Comorbidity Index; CI, Confidence interval; OR, Odds ratio; PSA, Prostate-specific antigen

Table 3

Association of clinicopathologic features with subsequent diagnosis of intermediate and high-risk prostate cancer using linear regression.

Predictors	Unstandardized Coefficients		Standardized Coefficients		t-computed	p-value
	B	Std. Error	β		t	p
Constant	3.43	1.15			2.98	0.004
ASAP	-0.41	0.32	-0.12		-1.28	0.204
Age	-0.06	0.02	-0.33		-2.82	0.006
CCI	0.35	0.06	0.68		5.86	<0.001

ASAP, Atypical small acinar proliferation; CCI, Charlson Comorbidity Index