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Challenges and Clinical Implications of Prostate Cancer Mimickers. A Study Conducted at a Tertiary Center

Mihai-Cătălin Roșu[1,2], Daniela Luminița Zob[3], Cristina Anita Ionescu[2,3], Bogdan Cîmpineanu[4], Mihaela Pundiche[4,5]*, Georgeta-Camelia Cozaru[1,6,7], Ionuț Iorga[4,8], Gabriela-Izabela Bălțătescu[1,6], Antonela-Anca Nicolau[1,6], Ionuț Burlacu[6], Oana Cojocaru[4,6], Sabina Elena Vlad[1], Miruna-Gabriela Vizireanu[1], Sînziana-Andra Ghițoi[6], Lucian Cristian Petcu[2,9]

[1]Center for Research and Development of the Morphological and Genetic Studies of Malignant Pathology, Ovidius University, Constanta, Romania
[2]Doctoral School of Medicine, Institute of Doctoral Studies, Ovidius University, Constanta, Romania
[3]Prof. Dr. Alexandru Trestioreanu Institute of Oncology, Bucharest, Romania
[4]Faculty of Medicine, Ovidius University, Constanta, Romania
[5]Department of General Surgery, Sf. Apostol Andrei Emergency County Hospital, Constanta, Romania
[6]Clinical Service of Pathology, Sf. Apostol Andrei Emergency County Hospital, Constanta, Romania
[7]The Romanian Academy of Scientists, Bucharest, Romania
[8]Department of Urology, Sf. Apostol Andrei Emergency County Hospital, Constanta, Romania
[9]Faculty of Dental Medicine, Ovidius University, Constanta, Romania

***Corresponding author:**
Mihaela Pundiche, MD, PhD
Ovidius University
Faculty of Medicine Constanta
Department of General Surgery
Emergency Hospital of Constanta
No 145 Tomis Boulevard, 900591
Constanta, Romania
E-mail: mihaelapundiche@yahoo.com

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Rezumat

Provocări și implicații clinice ale entităților care mimează cancerul de prostată. Un studiu realizat într-un centru terțiar

Introducere: Acuratețea diagnosticului histopatologic este crucială în gestionarea cancerului de prostată. Entitățile benigne precum hiperplazia adenomatoasă atipică (AAH) şi proliferarea acinară mică atipică (ASAP), denumite „leziuni care mimează cancerul de prostată", reprezintă o capcană diagnostică majoră, plasând chirurgul într-o dilemă terapeutică. Astfel, acest studiu şi-a propus să cuantifice incidența acestor entități lezionale într-un centru terțiar din România.
Materiale şi metode: Studiul este unul retrospectiv, efectuat pe o cohortă de 900 de pacienți care au fost supuşi biopsiei prostatice ecoghidate/TURP în perioada ianuarie 2020 şi martie 2025. Diagnosticele histopatologice au fost stabilite conform criteriilor Societății Internaționale de Patologie Urologică (ISUP).
Rezultate: Dintre cele 900 de biopsii, cele mai frecvente diagnostice primare au fost hiperplazia benignă de prostată (HBP) (62%, n = 558) şi adenocarcinomul prostatic (ADK) (27,6%, n = 248). Entitățile potențial majore de confuzie, AAH şi ASAP, au reprezentat împreună 6,6% (n = 59) din totalul biopsiilor. AAH (6%) a fost de trei ori mai frecventă decât ADK Gleason 6 (2%). Vârsta medie a pacienților cu AAH (69,2 ani) a fost similară cu cea a pacienților cu ADK (71,5 ani). Analiza multivariată a arătat că vârsta >70 de ani a fost un predictor independent al ADK (OR=1,9, p<0,01), iar valorile PSA au prezentat o suprapunere semnificativă între grupuri.

Concluzii: În total, 6,6% (n=59) dintre biopsiile analizate au prezentat entități care pot mima cancerul de prostată şi care necesită o interpretare atentă pentru a evita erorile şi pentru a stabili cea mai adecvată conduită chirurgicală. Corelarea histopatologică cu imagistica şi rebiopsia, în cadrul unei abordări multidisciplinare, sunt etape esențiale în gestionarea acestor cazuri.

Cuvinte cheie: implicații clinice, cancer de prostată, histopatologie

Abstract

Introduction: The accuracy of histopathological diagnosis is crucial in the management of prostate cancer. Benign entities such as atypical adenomatous hyperplasia (AAH) and atypical small acinar proliferation (ASAP), referred to as "lesions that mimic prostate cancer", represent a major diagnostic pitfall, placing the surgeon in a therapeutic dilemma. Thus, this study aimed to quantify the incidence of these entities in a tertiary center in Romania.
Materials and Methods: Retrospective study on a cohort of 900 patients who underwent ultrasound-guided prostate biopsy/TURP between January 2020 and March 2025. Histopathological diagnoses were established according to the International Society of Urological Pathology (ISUP) criteria.
Results: Of the 900 biopsies, the most common primary diagnoses were benign prostatic hyperplasia (BPH) (62%, n = 558) and prostatic adenocarcinoma (ADK) (27.6%, n = 248). The potentially major confounding entities, AAH and ASAP, together accounted for 6.6% (n = 59) of all biopsies. AAH (6%) was three times more common than Gleason 6 ADK (2%). The mean age of patients with AAH (69.2 years) was similar to that of patients with ADK (71.5 years). Multivariate analysis showed that age >70 years was an independent predictor of ADK (OR=1.9, p<0.01), and PSA values showed significant overlap between groups.
Conclusions: In total, 6.6% (n=59) of the biopsies analyzed presented entities that can mimic prostate cancer and that require careful interpretation to avoid errors and to establish the most appropriate surgical conduct. Histopathological correlation with imaging and rebiopsy, within a multidisciplinary approach, are essential steps in the management of these cases.

Keywords: clinical implications, prostate cancer, histopathology

Introduction

Prostate cancer is one of the most common neoplasms in men, and its management critically relies on the accuracy of histopathological diagnosis (1,2). In the era of prostate-specific antigen (PSA) screening and ultrasound-guided biopsies, the urologist and surgical oncologist are often confronted with pathology reports describing entities that do not constitute a definitive diagnosis of malignancy, but which cannot be ignored either (3). Histopathologically, these are benign lesions whose architectural or cytological features resemble adenocarcinoma, but they lack significant nuclear atypia. These lesions, known as prostate cancer "mimics," represent a major diagnostic challenge with direct therapeutic implications for the practitioner, as these lesions require clinical monitoring while prostate cancer requires more aggressive and targeted treatment (4,5). Among the most significant such entities are atypical adenomatous hyperplasia (AAH) and suspicious atypical acinar proliferation (ASAP) which mimics small-gland adenocarcinoma (Gleason grade 3 and 4) and atrophy (6,7,8). A diagnosis of AAH or ASAP in a prostate biopsy places the surgeon in a therapeutic dilemma: to initiate radical treatment (prostatectomy) on the basis of suspicion, with the risk of overtreating a benign lesion, or to adopt an expectant attitude, with the risk of delaying the treatment of a clinically significant cancer (9). In addition, other non-neoplastic conditions, such as extensive glandular atrophy, chronic prostatitis, or metaplasia, can alter the tissue architecture and mimic aspects of prostatic adenocarcinoma (ADK), especially in small biopsy specimens (10). Also, primary urothelial carcinoma invading the prostate requires a radically different surgical treatment plan (cystoprostatectomy versus radical prostatectomy), and diagnostic confusion with ADK can have devastating consequences (11). The aim of this retrospective study was to quantify the incidence of diagnostic pitfalls in a large cohort of 900 patients from a tertiary center.

By analyzing the frequency of entities such as atypical adenomatous hyperplasia (AAH), atypical small acinar proliferation (ASAP), and other confounding factors, we sought to underline the magnitude of this issue in daily surgical practice. Furthermore, the paper discusses practical management strategies to guide surgical decision-making, emphasizing the importance of careful multidisciplinary evaluation and close collaboration with the pathologist to optimize both oncological and functional outcomes.

Materials and Methods

Study Design and Population

This retrospective observational study included 900 consecutive patients who underwent ultrasound-guided transrectal prostate biopsy/TURP between January 2020 and March 2025 at the Constanța County Emergency Hospital. Eligible patients had elevated or increasing prostate-specific antigen (PSA) levels and/or a suspicious digital rectal examination. Patients with prior hormonal therapy or pelvic radiotherapy were excluded, as these could alter histological interpretation (12).

Biopsy Procedure and Sample Processing

All biopsies were performed under transrectal ultrasound guidance, following a standard protocol of at least 12 cores (saturation biopsies) (13). For patients with suspicious mpMRI lesions (multiparametric Magnetic Resonance Imaging), additional targeted biopsies were obtained (14). Specimens were fixed in 10% buffered formalin, processed routinely, and stained with hematoxylin-eosin (H&E) (15).

Histopathological Evaluation

Slides were independently reviewed by pathologists experienced in urological pathology. Diagnoses were assigned according to International Society of Urological Pathology (ISUP) criteria (16). Prostatic adenocarcinoma (ADK) was graded using the ISUP 2014/2019 Gleason system (17,18). Mimicker entities were defined according to established criteria: atypical adenomatous hyperplasia (AAH) (19), atypical small acinar proliferation (ASAP) (20), and atrophy, as classified by De Marzo et al. (10). In ambiguous cases, immunohistochemistry (IHC) was performed with p63, high-molecular-weight cytokeratin (CK5/6), AMACR/p504S, and PSA (21,22).

Study Endpoints

The primary objective of this study was to determine the incidence and distribution of non-neoplastic and preneoplastic ("mimic") histopathological entities that complicate the differential diagnosis of prostate cancer and directly influence therapeutic decision-making. By quantifying the proportion of atypical adenomatous hyperplasia (AAH), atypical small acinar proliferation (ASAP), atrophy, chronic inflammation, metaplasia, and urothelial carcinoma in the total number of prostate biopsies, we aimed to assess their potential impact on surgical planning and patient management.

Secondary objectives included:

- Comparison of the mean age of patients with prostatic adenocarcinoma (ADK) versus those with AAH, ASAP, or benign prostatic hyperplasia (BPH), in order to evaluate whether age can assist in preoperative risk stratification and surgical decision-making.
- Analysis of the frequency of confounding entities (e.g., atrophy, chronic inflammation) in biopsies diagnosed as BPH, to identify situations where benign findings may obscure or mimic clinically significant ADK and thereby alter therapeutic strategies.
- Characterization of Gleason score and Grade Group distribution in ADK cases, to contextualize tumor aggressiveness within the studied population and support individualized surgical approaches.

All endpoints were assessed retrospectively based on histopathological reports.

Statistical Analysis

Statistical analysis was performed using SPSS software (Version 26.0). Data were summarized using descriptive statistics. Continuous variables with non-normal distribution or severe group size imbalance (e.g., n=558 for BPH vs. n=5 for ASAP) were expressed as median and interquartile range (IQR). The Kruskal-Wallis test was used to determine if there were statistically significant differences in continuous variables (age, PSA) between the diagnostic groups. The threshold for statistical significance was set at a p-value < 0.05.

Ethical Approval

The research was conducted in accordance with the provisions of the Declaration of Helsinki, obtaining approval from the Ethics Board of the Constanta County Emergency Clinical Hospital (decision no. 42767 of 02.07.2024). All subjects included in the cohort signed informed consent forms regarding the use of biological samples.

Results

General Characteristics of the Cohort

Data from 900 consecutive patients were analyzed. The mean age of the cohort was 70.1 years (range: 50-95 years, with a standard deviation of ~8.5 years). The age distribution revealed a concentration of cases in the 65-80 year age group.

Distribution of Main Histopathological Diagnoses

The distribution of the main diagnoses identified in the 900 biopsies is presented in *Table 1*. Benign prostatic hyperplasia (BPH) was the most common diagnosis.

Analysis of Prostate Cancer Mimics: AAH and ASAP

In total, entities with significant confounding potential (AAH and ASAP) represented 59 cases (6.6%) of all biopsies. The mean age of patients with AAH was 69.2 years, similar to that of patients with ADK.

Distribution of Gleason Scores and Grade Groups for ADK

Among the 248 cases of ADK, the distribution of combined Gleason scores and associated Grade Groups is presented in *Table 2*. Gleason score 7 (3+4 and 4+3) was the most frequent.

Comparison of Mean Age by Diagnostic Groups

The comparative analysis of the mean age of patients by diagnostic groups revealed a statistically significant difference ($p < 0.05$). Patients with ADK had a mean age (71.5 years) slightly higher than patients with BPH (69.4 years) and those with AAH (69.2 years).

Demographic Profile of the Main "mimic" Entities

A Kruskal-Wallis test revealed a statistically significant difference in the age distribution

Table 1. Distribution of main histopathological diagnoses (n=900)

Main Diagnosis	Number of Cases (n)	Percentage (%)
Benign Prostatic Hyperplasia (BPH)	558	62.0%
Prostatic Adenocarcinoma (ADK)	248	27.6%
Atypical Adenomatous Hyperplasia (AAH)	54	6.0%
Urothelial Carcinoma	12	1.3%
Chronic Inflammation	15	1.7%
Atrophy	8	0.9%
ASAP	5	0.6%
Total	900	100%

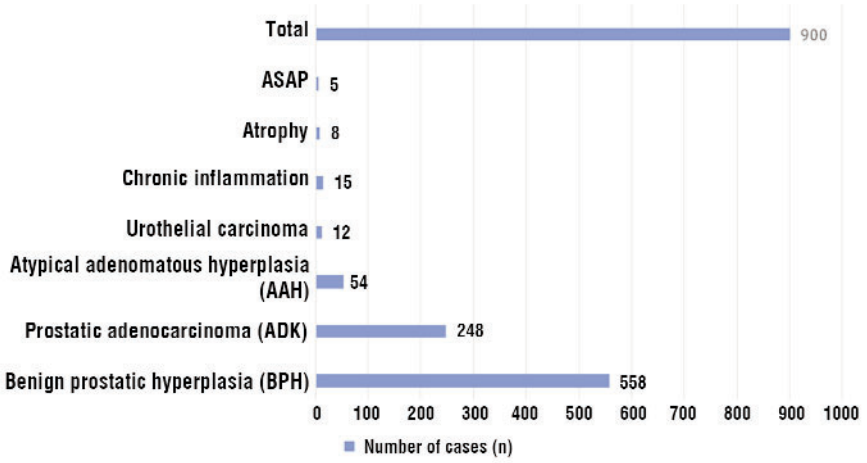
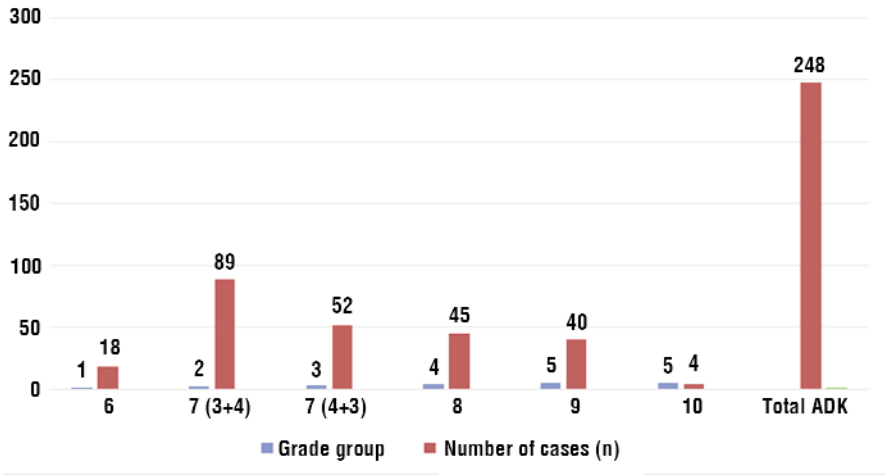


Table 2. Distribution of Gleason scores and Grade Groups in ADK cases (n=248)

Combined Gleason Score	Grade Group	Number of Cases (n)	Percentage of ADK (%)
6	1	18	7.3%
7 (3+4)	2	89	35.9%
7 (4+3)	3	52	21.0%
8	4	45	18.1%
9	5	40	16.1%
10	5	4	1.6%
Total ADK		248	100%



between the main diagnostic groups (p = 0.028), with the median age of ADK patients being higher than that of BPH patients (*Table 3*).

Distinction Between AAH and ADK Gleason Score 6 (Grade Group 1)

One of the most difficult practical distinctions is between AAH and well-differentiated ADK (Gleason 6). The data in *Table 4* illustrate this issue, showing that the number of cases of AAH is comparable to that of cases of ADK Grade Group 1.

As shown in *Table 4*, atypical adenomatous hyperplasia (AAH) was identified in 54 cases (6%), three times more frequent than low-grade prostatic adenocarcinoma (Gleason score 6, Grade Group 1), detected in only 18 cases (2%). This highlights one of the most challenging diagnostic dilemmas in prostate pathology: distinguishing between AAH and well-differentiated adenocarcinoma. Since their histological features overlap significantly, the risk of misclassification is considerable. From a therapeutic perspective, this distinction is crucial, as misinterpreting AAH as carcinoma may lead to unnecessary radical prostatectomy with its functional complications, while under-recognition of carcinoma may delay curative treatment.

Table 3. Comparison of patient age between main diagnostic categories using non-parametric tests.

Main diagnostic	Number of Cases (n)	Median Age (years)	Interquartile Range (IQR)
Adenocarcinoma (ADK)	248	71.5	66 - 78
Benign Prostatic Hyperplasia (BPH)	558	69.4	64 - 76
Atypical Adenomatous Hyperplasia (AAH)	54	69.2	63 - 75
p-value (Kruskal-Wallis Test)			0.028

Table 4. Comparison of the incidence of AAH with low-grade ADK (Grade Group 1)

Histopathological Entity	Number of Cases (n)	Percentage (%) of Total Biopsies (n = 900)
Atypical Adenomatous Hyperplasia (AAH)	54	6.0%
Prostatic Adenocarcinoma - Grade Group 1 (Gleason 6)	18	2.0%

Presence of Potentially Confounding Entities in Biopsies with a Diagnosis of BPH

To assess the complexity of the differential diagnosis even in the case of a benign diagnosis, we analyzed the frequency of potentially confounding entities reported in biopsies with a primary diagnosis of BPH. These may hide or mimic neoplastic foci in small tissue samples. The results are presented in *Table 5*.

Cases of Urothelial Carcinoma: A Major Mimicker

Urothelial carcinoma was identified in 12 cases (1.3%), representing a critical differential diagnosis. In all of these cases, the diagnosis was reported as urothelial carcinoma, without a synchronous association with ADK in the same biopsy. The mean age of these patients was similar to that of patients with ADK (*Table 3*).

To further assess the relationships between variables, additional statistical analyses were performed.

The association between atrophy and adenocarcinoma diagnosis was analyzed by comparing the presence of atrophy (reported as a secondary observation) in cases with a primary diagnosis of ADK versus those with BPH. As shown in *Table 6*, no statistically significant association was identified between the presence of atrophy and a diagnosis of ADK in this cohort (p=0.25).

The distribution of Gleason scores by age for ADK cases is detailed in *Table 7*. A descriptive trend is observed whereby younger patients (<65 years) present a higher percentage of Gleason 6 tumors (10.0%), while older patients (>75 years) have an increased proportion of Gleason 8-10 tumors (47.9%).

Also, a logistic regression analysis was performed to identify factors independently associated with a diagnosis of ADK, adjusting for the presence of atrophy. The results, presented in *Table 8*, show that age >70 years is an independent and significant predictor of ADK (OR=1.9, 95% CI: 1.4-2.6, p<0.01). In this model, the presence of atrophy was not a significant independent predictor.

Finally, the distribution of serum PSA values across diagnostic categories is presented in *Table 9*. The Kruskal-Wallis test revealed a highly

Table 5. Potentially confounding entities reported in biopsies with a primary diagnosis of Benign Prostatic Hyperplasia (BPH) (n=558)

Reported Associated Entity	Number of Cases in BPH (n)	Percentage of BPH Cases (%)
Atrophy (simple, glandular)	52	9.3%
Chronic Inflammation (active or non-specific)	40	7.2%
Urothelial/Squamous Metaplasia	9	1.6%
Total BPH cases with at least one associated entity	85	15.2%

Table 6. Association between the presence of atrophy (as a secondary finding) and the primary diagnosis

Primary Diagnosis	Atrophy Present (n, %)	Atrophy Absent (n, %)	p-value (Chi-square test)
Adenocarcinoma (ADK) (n=248)	15 (6.0%)	233 (94.0%)	0.25
Benign Prostatic Hyperplasia (BPH) (n=558)	52 (9.3%)	506 (90.7%)	N/A
Total (n = 806)	67	739	-

N/A: Not applicable; p-value from Chi-square test refers to the comparison between ADK and BPH groups.

Table 7. Distribution of Gleason score patterns within the prostate adenocarcinoma cohort by patient age group.

Age Group	ADK Cases (n)	Gleason Score ≤6 (n, %)	Gleason Score 7 (n, %)	Gleason Score ≥8 (n, %)
< 65 years	50	5 (10.0%)	25 (50.0%)	20 (40.0%)
65 - 75 years	125	10 (8.0%)	65 (52.0%)	50 (40.0%)
> 75 years	73	3 (4.1%)	35 (47.9%)	35 (47.9%)
Total	248	18 (7.3%)	125 (50.4%)	105 (42.3%)

Table 8. Multivariable analysis of factors associated with a primary diagnosis of prostate adenocarcinoma

Factor	Adjusted Odds Ratio (OR)	95% Confidence Interval	p-value
Age > 70 years	1.9	1.4 - 2.6	<0.01
Presence of Atrophy	0.8	0.4 - 1.4	0.40

Table 9. Comparison of serum PSA values between diagnostic categories using non-parametric tests

Diagnostic Category	Number of Cases (n)	Median PSA (ng/mL)	Interquartile Range (IQR)
Adenocarcinoma (ADK)	248	9.8	5.2 - 15.1
Benign Prostatic Hyperplasia (BPH)	558	6.2	3.8 - 9.5
Atypical Adenomatous Hyperplasia (AAH)	54	7.5	4.5 - 10.9
p-value (Kruskal-Wallis Test)	< 0.001		

statistically significant difference in PSA distributions between the groups ($p < 0.001$). The median PSA was highest in the prostate adenocarcinoma and urothelial carcinoma groups. Considerable overlap in PSA values, indicated by the interquartile ranges, was observed between prostate cancer and benign mimickers.

The Role of Immunohistochemistry

In the studied group, immunohistochemical examination was performed in cases requiring a differential diagnosis between atypical adenomatous hyperplasia (AAH)/ASAP and well or moderately differentiated adenocarcinoma. Immunohistochemistry was also mandatory in cases diagnosed with adenocarcinoma to confirm the diagnosis and evaluate prognostic factors, such as the Ki67 nuclear proliferation index and markers for perineural and angiolymphatic invasion. The antibodies used included AMACR (positive in adenocarcinoma, negative in benign lesions except atrophy), high-molecular-weight cytokeratin (clone 34ßE12; positive in benign lesions, negative in adenocarcinoma), and Ki67. All stains were performed using the MACH 4 Universal HRP method (Zeta Corporation). Representative histopathological and immunohistochemical images of these diagnostic entities are presented in *Fig. 1*.

Case Selection

All cases diagnosed with prostatic lesions (benign, malignant, and pseudoneoplastic) within the study period were evaluated. Cases with extensive necrosis, ischemic necrosis (prostatic infarction), or insufficient material were excluded.

Discussion

The aim of the study was to quantify the incidence of entities that mimic prostate cancer and assess their implications for surgical management. Our results show that 6.6% (n=59) of biopsies contained entities of uncertain diagnostic significance (AAH, ASAP), confirming that they represent a major challenge in daily urological practice.

AAH versus Gleason 6 Adenocarcinoma

Our finding that AAH (6.0%) was three times more frequent than GG1 ADK (2.0%) aligns with prior studies identifying AAH as the most common benign mimicker of low-grade prostate cancer, underscoring a persistent diagnostic challenge (6,19). AAH was identified in 6% of cases, a frequency three times higher compared to low-grade adenocarcinoma (Gleason 6, Grade Group 1) (*Table 4*). This constitutes one of the most important diagnostic pitfalls: differentiating between a benign lesion and a well-differentiated carcinoma. Since the histological features overlap, the risk of misclassification is high (23). From a surgical point of view, this distinction is essential: misdiagnosis of AAH as adenocarcinoma may lead to unnecessary radical prostatectomy, with postoperative functional morbidity, particularly urinary continence and sexual function impairment, as described in the literature (24), while failure to recognize a Gleason 6 carcinoma may delay curative treatment. We thus emphasize the need for multiparametric MRI and/or rebiopsy, ideally with fusion techniques, as well as mandatory confirmation by immunohistochemistry (25).

ASAP and the Surgical Decision

Although uncommon (0.6%, n=5) in our cohort - a number that limits broad statistical conclusions - ASAP presents a well-documented management dilemma due to its association with subsequent detection of carcinoma on rebiopsy (26). In accordance with current guidelines (19,27), this diagnosis should not lead directly to radical surgery but requires re-evaluation by rebiopsy within 3-6 months. For surgeons, this diagnosis requires patience and careful communication with the patient to avoid premature overtreatment.

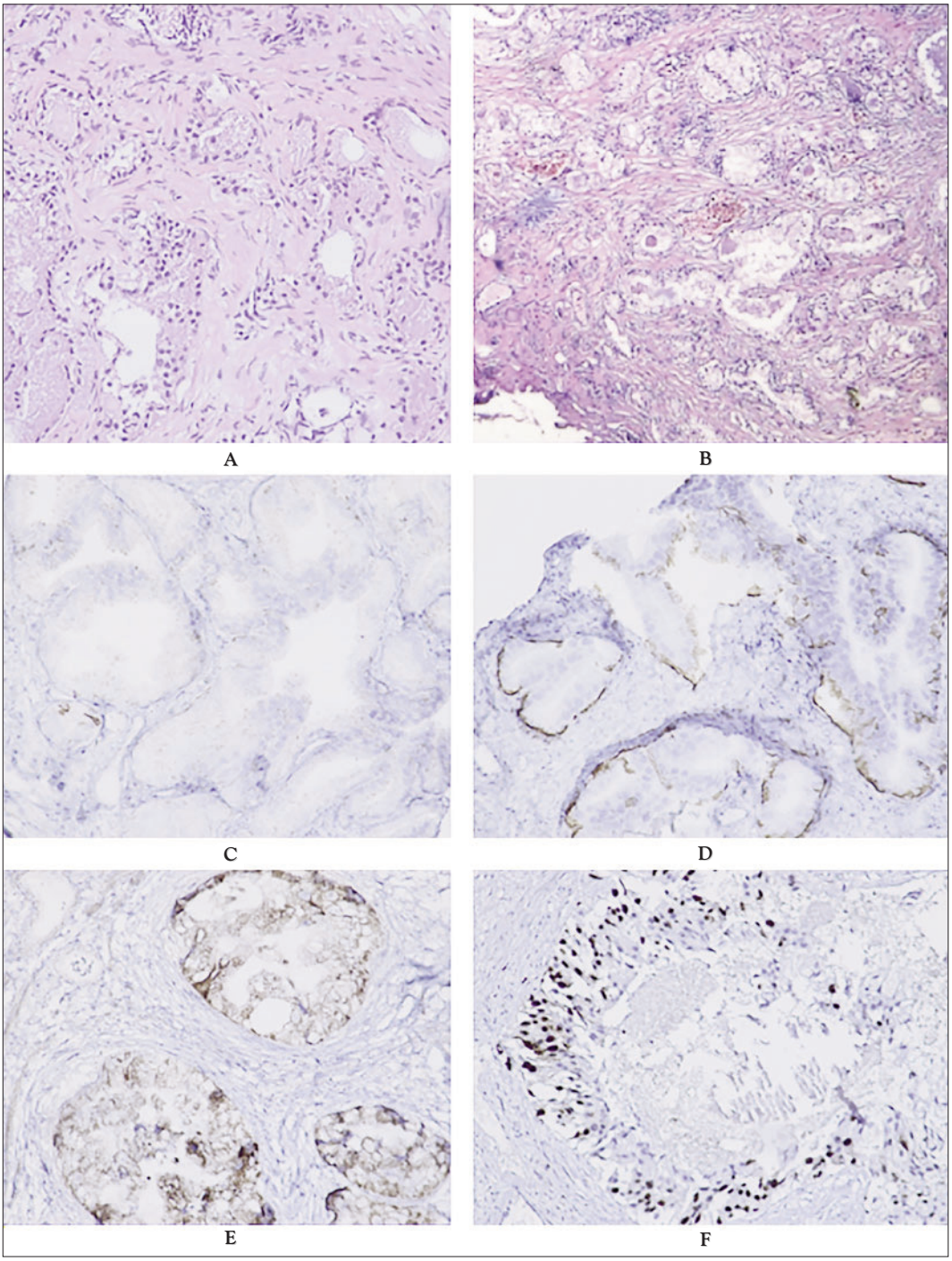


Figure 1. Histopathological and immunohistochemical features of prostate cancer mimics and adenocarcinoma (**A**-1.Small focus of atypical small acinar proliferation suspicious, with stromal infiltrative aspect, H&Ex200; **B -**.HAA focus, body of small acini with stromal infiltrative aspect and indistinct basal cell layer, H&Ex40; **C -** Negative AMACR expression in prostatic epithelial cells - HBP, H&Ex200; **D -** Continuous positive HMWCK and focal discontinuous in the basal cell layer of the acini within a HAA nodule associated with HBP lesions, H&Ex200; **E -** Intensely positive cytoplasmic and granular expression of AMACR in epithelial cells from a Gleason score 4+4 adenocarcinoma, HEx100; **F -** Nuclear Ki 67 positive in more than 10% of tumor cells, poorly differentiated adenocarcinoma, Gleason score 5+4, HEx200)

Other Mimics and Confounding Entities

Chronic atrophy and inflammation were common in BPH biopsies (*Table 5*). Although they may mimic or mask histological adenocarcinoma, our data do not show a significant association between atrophy and adenocarcinoma (p=0.25). This suggests that atrophy reflects a chronically altered prostatic microenvironment rather than a direct precursor of malignancy (30,31). However, persistent clinical suspicion (rising PSA, suspicious lesion on mpIRM) in a patient with a "benign" histopathological report should prompt rebiopsy before ruling out surgical indication.

Urothelial carcinoma, although rare (1.3%), represents the most dangerous pitfall. Confusion with adenocarcinoma can lead to radically different surgical plans (radical prostatectomy vs. cystoprostatectomy), with catastrophic consequences (28). Therefore, in such atypical cases, immunohistochemistry is routinely used in diagnostically equivocal cases.

Age, PSA, and Tumor Aggressiveness

The confirmed association between older age (>70 years) and a higher likelihood of adenocarcinoma in our cohort is consistent with the established epidemiology of prostate cancer. Multivariate analysis confirmed that age >70 years is an independent predictor for adenocarcinoma (OR = 1.9, p<0.01) (29). In addition, older patients had a higher proportion of high-grade tumors (Gleason ≥8), consistent with the natural history of the disease (32,33,36). Although PSA was significantly higher in patients with cancer, it showed substantial overlap with mimicker entities, such as AAH (*Table 9*), confirming its limited role in discriminating between benign and malignant conditions (34,35).

Surgical Decision-Making in a Regional Context

Our study reflects a regional clinical practice where radical prostatectomy is often considered even for patients with low-risk disease(e.g., Gleason score 6). This tendency may be influenced by several factors, including patient preference for definitive treatment, limited long-term experience with active surveillance protocols in our setting, and a cautious surgical approach driven by the diagnostic uncertainty highlighted in this study (e.g., the challenge of definitively ruling out higher-grade foci in small biopsy samples). In this context, the role of a dedicated multidisciplinary tumor board (MTB) becomes crucial. In our center, complex cases, particularly those involving diagnostic pitfalls such as AAH, ASAP, or discordant imaging findings, are routinely reviewed in a weekly uropathology MTB. This forum, comprising urologists, pathologists, radiologists, and oncologists, ensures a consensus on diagnosis and therapeutic strategy, aligning the surgical decision with both oncological safety and functional preservation. The systematic use of such a multidisciplinary approach helps to standardize care and mitigate the risk of overtreatment, even in an environment with a historically more interventional leaning.

Clinical Implications

Our findings highlight that a significant proportion of prostate biopsies contain mimicker entities with direct consequences for the surgical decision. A multidisciplinary approach – pathologist, radiologist, and surgeon – is indispensable to avoid both overtreatment and undertreatment. Rebiopsy, imaging re-evaluation, and immunohistochemistry are essential steps when doubt persists, ensuring both oncological safety and preservation of patient functions.

Future Perspectives and the Role of Digital Pathology

The persistent challenge of distinguishing mimickers from adenocarcinoma underscores the need for more objective and reproducible diagnostic tools. In this context, the emerging field of artificial intelligence (AI) and digital image analysis in surgical pathology holds significant promise (37). AI algorithms trained on large, annotated datasets could potentially assist pathologists by highlighting suspicious architectural patterns or quantifying features that differentiate entities like AAH from low-grade ADK. While not a substitute for expert histological review, such technologies may serve as a valuable second-read system, potentially reducing inter-observer variability and diagnostic uncertainty in borderline cases.

Study Limitations

This study has several important limitations that should be considered. First, its retrospective nature limited uniform access to certain detailed clinical and imaging data, such as PSA density, PSA velocity, or specific PIRADS scores from multiparametric MRI. These correlations could have enriched the analysis of oncological risk and refined the indication for rebiopsy. Second, the small size of the ASAP subgroup (n=5) limits the

statistical power of any specific conclusions about this entity, but also reflects its low prevalence in practice.

An additional limitation, relevant to surgical decision-making, is that the retrospective design did not allow for follow-up of clinical outcomes and definitive surgical management. Specifically, we were unable to determine how many of the patients with diagnoses of AAH or ASAP on initial biopsy ultimately underwent radical prostatectomy and what the final histopathological outcome was in those cases. This limits our ability to directly correlate initial diagnostic uncertainty with the final surgical decision and oncological outcome.

Finally, the data come from a single tertiary center, which may influence the generalizability of the results. Despite these limitations, the study manages to quantify in a large cohort the significant frequency of diagnostic pitfalls and to highlight their direct impact on therapeutic decision-making in a real clinical context.

Conclusions

AAH and ASAP, found in 6.6% (n=59) of biopsies, represent significant diagnostic pitfalls, with implications for surgical decision-making. Correct distinction from well-differentiated adenocarcinoma is crucial to avoid both overtreatment by unnecessary prostatectomy and delay in curative therapy. In practice, the approach should be multidisciplinary, including histological review, imaging evaluation, and, if necessary, rebiopsy before any radical intervention.

Author's Contribution

All authors made a significant contribution to the study conception, drafting of the scientific content, and critical revision of the manuscript. Each author has reviewed and approved the final version of the manuscript and accepts full responsibility for the accuracy and integrity of the data presented. All authors consent to the publication of this article.

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Conflict of Interest

The authors declare no conflict of interest. All authors contributed equally to this study and shared the first authorship.

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