DOI: *10.4081/aiua.2026.14731*

ORIGINAL PAPER

Prognostic value of Ki67 and PSA-immunostaining in De Novo metastatic hormone-sensitive prostate cancer

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Summary ***Introduction: Prostate cancer comprises biologically distinct subtypes. Ki67 reflects tumour proliferation, while prostate-specific antigen immunostaining (PSA-IHC) indicates differentiation, with low PSA-IHC suggesting dedifferentiation. The prognostic role of these markers in de novo metastatic hormone-sensitive prostate cancer (mHSPC) remains unclear.***

Aim: To evaluate the prognostic value of Ki67 and PSA-IHC, individually and combined, in de novo mHSPC, and explore their relevance across treatment modalities.

Methods: We retrospectively analysed patients diagnosed with de novo mHSPC (2015-2020) who ultimately died from prostate cancer. Clinical data included age, ISUP grade, baseline and 7-month PSA, metastatic sites, and first-line treatment. Ki67 (MIB-1) and PSA-IHC were quantified as the percentage of positive nuclei and cytoplasmic staining, respectively. The 75th percentile defined high vs. low expression. Endpoints were biochemical (bPFS), radiological (rPFS), castration-resistant progression free survival (CRPC-FS), and overall survival (OS). Exploratory analyses were performed by treatment type: androgen receptor pathway inhibitors (ARPIs) or taxanes.

Results: Sixty-seven patients were included (median age 77 years). Most had high-grade tumours (ISUP ≥ 3, 83.6%). High Ki67 (> P75) correlated with shorter OS (10 vs. 21 months, p = 0.013). PSA-IHC > P75 predicted longer bPFS (13 vs. 9 months, p = 0.027). Combined stratification identified distinct prognostic groups (p = 0.034): PSA-IHC low/Ki67 high defined a high-risk phenotype with poor outcomes, particularly among taxane-treated patients (p = 0.006).

Conclusions: Combined Ki67 and PSA-IHC assessment refines risk stratification in de novo mHSPC, identifying a high-risk PSA-IHC low/Ki67 high subgroup with markedly worse prognosis. These findings warrant prospective validation.

Key words: *Prostate cancer; Metastatic hormone-sensitive prostate cancer; Ki67; Prostate-specific antigen (PSA); Immunohistochemistry.*

Submitted 14 December 2025; Accepted 23 December 2025

Introduction

Prostate cancer (PCa) remains the most frequently diagnosed malignancy and one of the leading causes of cancer-related death among men worldwide (1). Although most patients are initially diagnosed with localized disease, approximately 10-15% present with de novo metastatic prostate cancer, and many others will eventually progress after local treatment (2, 3).

Over the past decade, the treatment landscape for *metastatic hormone-sensitive prostate cancer* (mHSPC) has changed dramatically. Large phase III trials demonstrated that treatment intensification with docetaxel (CHAARTED, STAMPEDE) or novel hormonal *agents androgen receptor pathway inhibitors* (ARPIs) such as abiraterone acetate (LATITUDE, STAMPEDE), enzalutamide (ENZAMET, ARCHES), apalutamide (TITAN), and darolutamide (ARASENS) significantly improves overall survival compared with *androgen deprivation therapy* (ADT) alone (4-9). These trials led to the regulatory approval and incorporation of these ARPIs into international guidelines as standard options for the treatment of metastatic hormone-sensitive prostate cancer. Specifically, abiraterone, enzalutamide, apalutamide, and darolutamide are now approved for men with de novo or recurrent mHSPC. However, despite these therapeutic advances, substantial heterogeneity in treatment response persists. Some patients experience rapid progression and early mortality despite optimal therapy, whereas others maintain long-term disease control even with ADT alone (10, 11). This variability underscores the need for biological markers that can inform treatment personalization, helping clinicians to identify which patients may benefit more from ARPIs-based versus taxane-based strategies (12).

From a biological standpoint, the proliferation-differentiation axis of prostate tumours may underlie these differences in clinical behaviour and therapeutic response. The proliferation marker Ki67 is a nuclear protein expressed during all active phases of the cell cycle but absent in quiescent (G0) cells (13). High Ki67 expression has been consistently associated with adverse pathological features, biochemical recurrence, and reduced prostate cancer-specific survival (14-16). Despite its well-established prognostic value in multiple solid tumours, Ki67 has not yet been integrated into routine clinical decision-making for prostate cancer, mainly due to methodological variability and lack of standardized thresholds (17).

Prostate-specific antigen (PSA), beyond its established role as a serum biomarker, can also be evaluated by *immuno-*

histochemistry (IHC) to assess tumour differentiation. Strong PSA-IHC expression reflects luminal differentiation and androgen sensitivity, whereas low or absent expression is typically observed in poorly differentiated or neuroendocrine-like variants (18, 19). Reduced PSA-IHC expression has been linked to aggressive disease biology, poor therapeutic response, and shorter survival (20, 21).
Emerging evidence suggests that combining proliferative and differentiation markers may refine biological subtyping and predict treatment response. Tumours with high Ki67 and low PSA-IHC expression may represent a less differentiated, highly proliferative phenotype, potentially associated with lower dependence on androgen signalling and poorer outcomes with ARPI-based therapy, but possibly greater sensitivity to taxane chemotherapy (22-24). Conversely, tumours with low Ki67 and preserved PSA expression may exhibit a more indolent, androgen-driven phenotype, likely to achieve durable control under ARPIs treatment.
Therefore, the present study aimed to evaluate the prognostic and potential predictive value of Ki67 and PSA-IHC, separately and in combination, in patients with de novo mHSPC treated with ADT ± intensification (docetaxel or ARPIs). Specifically, we sought to determine whether these biomarkers can identify subgroups with differential survival outcomes according to the type of systemic therapy received, contributing to the broader goal of biomarker-guided personalization of therapy in advanced prostate cancer.

Materials and methods

We conducted a retrospective cohort study of patients diagnosed with de novo *metastatic hormone-sensitive prostate cancer* (mHSPC) at our institution between January 2015 and December 2020. Eligible patients were those with histologically confirmed adenocarcinoma of the prostate and evidence of metastatic disease at initial presentation, who subsequently died from prostate cancer, ensuring complete survival follow-up. Clinical and pathological information was retrieved from electronic medical records, including age at diagnosis, PSA level at baseline and at 7 months after the start of *androgen deprivation therapy* (ADT), ISUP grade group, baseline *prostate-specific antigen* (PSA) level, and metastatic sites (nodal, bone, and/or visceral). Data regarding systemic therapies administered during the disease course, including *androgen receptor pathway inhibitors* (ARPIs) and taxane-based chemotherapy, were also collected.
Formalin-fixed paraffin-embedded tumour tissue from diagnostic biopsies or transurethral resection specimens was analysed by *immunohistochemistry* (IHC). Ki67 was stained using the MIB-1 monoclonal antibody, and the labelling index was defined as the percentage of positively stained tumour nuclei among all evaluable tumour cells. PSA-IHC was assessed as the percentage of cytoplasmic positivity within tumour cells. For both markers, the 75th percentile (P75) of their respective distributions was used as the cut-off to define high (> P75) and low (≤ P75) expression. Based on these thresholds, patients were stratified into four biomarker-defined subgroups: PSA-IHC high/Ki67 low, PSA-IHC high/Ki67 high, PSA-IHC low/Ki67 low, and PSA-IHC low/Ki67 high.
The primary endpoints were *biochemical progression-free survival* (bPFS), *radiological progression-free survival* (rPFS), *castration-resistant prostate cancer-free survival* (CRPC-FS), and *overall survival* (OS). bPFS was defined as the time from initiation of abiraterone or enzalutamide to biochemical progression, according to the *Prostate Cancer Working Group 3* (PCWG3) criteria — that is, a confirmed increase in PSA of ≥ 25% and ≥ 2 ng/mL above the nadir, verified by a second consecutive measurement at least 3 weeks later. rPFS was defined as the time from treatment initiation to radiologic progression or death (whichever occurred first), with radiologic progression assessed according to RECIST version 1.1 criteria, as the appearance of new lesions or unequivocal enlargement of existing measurable disease. CRPC-FS was defined as the time from treatment initiation to the development of castration-resistant disease, in accordance with the *European Association of Urology* (EAU) criteria. OS was defined as the time from treatment initiation to death from any cause.
Descriptive statistics were used to summarize baseline characteristics. Associations between biomarker levels and clinical or pathological features were evaluated using the chi-square test for categorical variables, and the Mann-Whitney U or Spearman's rank correlation tests for continuous variables, as appropriate. Survival probabilities were estimated using the Kaplan-Meier method, and differences between groups were assessed with the log-rank test. Multivariable Cox proportional hazards regression analyses were performed to identify independent prognostic factors, including PSA-IHC (high vs low, using the P75 cut-off), Ki67 (high *vs* low), and metastatic pattern (bone-only, nodal, or visceral involvement). Additional models were constructed for the four biomarker-defined subgroups.
Exploratory subgroup analyses were conducted according to systemic treatment exposure. Patients were classified as having received ARPIs (abiraterone or enzalutamide) or taxane-based chemotherapy (docetaxel or cabazitaxel) at any line of therapy ("*ever ARPI*" or "*ever taxane*"). Separate Cox regression analyses were performed within each treatment subgroup to assess the prognostic impact of the combined PSA-IHC/Ki67 classification.
All statistical analyses were conducted using IBM SPSS Statistics, version 27.0 (*IBM Corp., Armonk, NY, USA*). A two-sided p-value < 0.05 was considered statistically significant.
The study was approved by the institutional ethics committee.

Results

Sixty-seven patients were included, with a median age of 77 years at diagnosis (IQR 68-85). Most tumours were high grade (83.6% ISUP ≥ 3). Bone metastases were present in 86.4% of patients, nodal in 37.9%, and visceral in 13.6%. Median Ki67 expression was 13.8% (IQR 2-35) and median PSA-IHC 90% (IQR 80-95). Baseline clinicopathological characteristics are summarised in Table 1.
High Ki67 was significantly associated with higher ISUP grade (p = 0.023), whereas low PSA-IHC expression correlated with the presence of nodal metastases (p = 0.006). No significant associations were found between either

Table 1.
Baseline clinicopathological characteristics of the cohort.

Variable	N (%) or median (IQR)
AGE (YEARS)	77 (68-85)
ISUP ≥ 3	56 (83.6%)
NODAL METASTASES	25 (37.9%)
BONE METASTASES	58 (86.4%)
VISCERAL METASTASES	9 (13.6%)
KI67 (%)	13.8 (2-35)
PSA-IHC (%)	90 (80-95)

Table 2.
Association between Ki67 and PSA-IHC expression and clinicopathological variables – p-values from Mann-Whitney or Kruskal-Wallis tests.

Variable	Ki67 p-value	PSA-IHC p-value
ISUP grade	0.023	0.200
Nodal metastases	0.275	0.006
Bone metastases	0.927	0.372
Visceral metastases	0.827	0.491
Age	0.977	0.080
Baseline PSA	0.933	0.388
ΔPSA	0.843	0.816

biomarker and age or baseline PSA. Detailed biomarker-clinicopathological correlations are presented in Table 2.
In univariable analyses, patients with high Ki67 (> P75) had shorter overall survival (median 10 vs. 21 months, p = 0.013). High PSA-IHC expression (> P75) was associated with longer bPFS (median 13 *vs.* 9 months, p = 0.027) but showed no significant association with rPFS, CRPC-FS, or OS. These results are summarised in Table 3. PSA decline at 7 months was not correlated with either marker.
Kaplan-Meier survival curves illustrating these associations are shown in Figure 1 (Ki67 and OS) and Figure 2 (PSA-IHC and bPFS). High Ki67 expression was consistently associated with poorer OS, whereas PSA-IHC positivity correlated with prolonged biochemical control.
Combined stratification according to PSA-IHC and Ki67 identified distinct prognostic groups (p = 0.034), with PSA-IHC-high/Ki67-low tumours showing the most favourable OS (28 months) and PSA-IHC-high/Ki67-high tumours the poorest (6 months).
When combining both biomarkers into four subgroups, patients with PSA-IHC-low/Ki67-high tumours (reference group) had significantly worse bPFS than all other groups

Figure 1.
Kaplan-Meier curves for overall survival according to Ki67 expression (≤ P75 vs > P75).

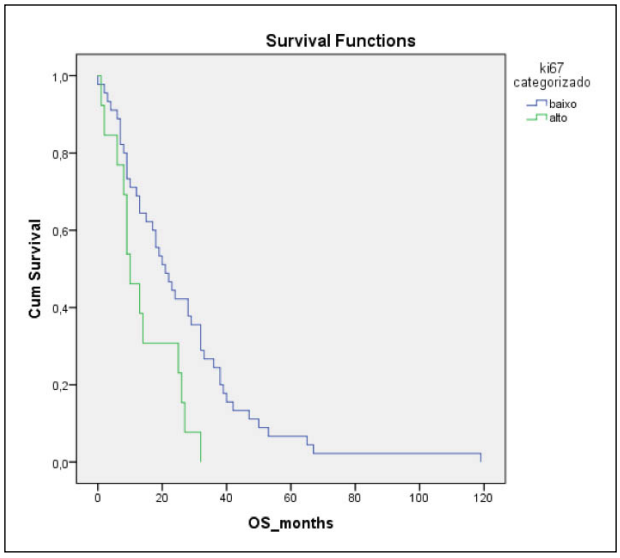
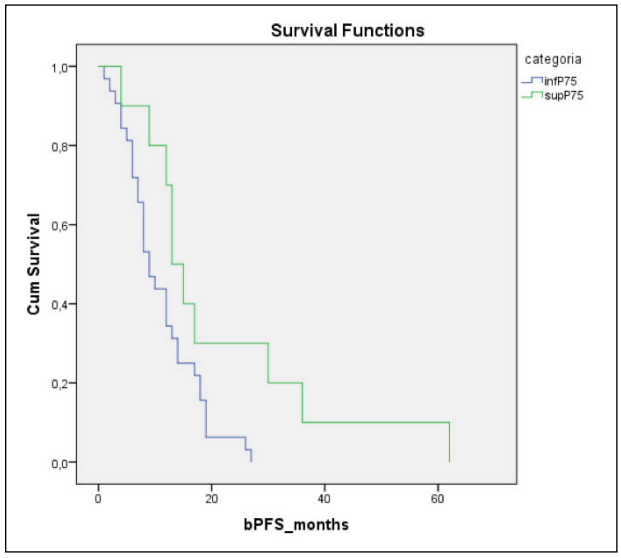


Figure 2.
Kaplan-Meier curves for biochemical progression-free survival according to PSA-IHC expression (≤ P75 vs > P75).



(HR 0.32, 95% CI 0.11-0.94, p = 0.039), with consistent but non-significant trends toward improved OS, rPFS, and CRPC-free survival in the remaining subgroups.
In multivariable Cox regression models including PSA-

Table 3.
Univariable survival analyses according to Ki67 and PSA-IHC expression (simplified) – Only significant associations are presented. No relevant differences were observed for rPFS or CRPC-FS.

Marker	Endpoint	Median (months)	95% CI	Log-rank p	HR (95% CI, continuous)
Ki67 ≤ P75	OS	21.0	14.4-27.6	0.013	1.017 (1.006-1.028)
Ki67 > P75	OS	10.0	5.6-14.4		
PSA-IHC ≤ P75	bPFS	9.0	6.6-11.4	0.027	1.004 (0.992-1.015)
PSA-IHC > P75	bPFS	13.0	9.9-16.1		

IHC (P75), Ki67 (P75), and metastatic pattern, neither biomarker retained independent prognostic significance for any survival endpoint. Trends were generally consistent with the univariable analyses, although estimates were unstable due to sample size limitations and covariate intercorrelations.

Exploratory subgroup analyses were performed to explore potential differences according to treatment class. Among patients treated with ARPIs (abiraterone or enzalutamide), no prognostic effect of the Ki67/PSA-IHC classification was observed (global p = 0.14-0.67 across endpoints). In contrast, in patients treated with taxanes (docetaxel), the biomarker classification was significantly associated with overall survival (global p = 0.006).

Using the PSA-IHC low/Ki67 high subgroup as the reference, patients with PSA-IHC high/Ki67 low and PSA-IHC low/Ki67 low tumours showed markedly improved survival (HRs ≈ 0.03, p = 0.005-0.009), whereas the PSA-IHC high/Ki67 high subgroup yielded unstable estimates due to the small sample size. These findings suggest that the PSA-IHC-low/Ki67-high phenotype may identify a biologically aggressive subset with inferior outcomes under taxane-based therapy, whereas its prognostic impact appears attenuated in patients receiving ARPIs.

Discussion

In this retrospective study, we evaluated the prognostic significance of Ki67 and PSA-IHC expression in patients with de novo *metastatic hormone-sensitive prostate cancer* (mHSPC). Both biomarkers, reflecting tumour proliferation and luminal differentiation respectively, were readily quantifiable by immunohistochemistry on diagnostic tissue samples. We found that high Ki67 and low PSA-IHC expression were associated with more aggressive disease features, and that their combined assessment provided additional prognostic information beyond standard clinical parameters. Notably, the prognostic impact of the combined PSA-IHC/Ki67 profile appeared to differ according to treatment type, being more evident among patients treated with taxanes.

Our findings align with previous evidence supporting Ki67 as a reliable marker of tumour proliferation and poor prognosis in advanced prostate cancer. High Ki67 expression has consistently been associated with shorter progression-free and overall survival, both in hormone-sensitive and castration-resistant settings, particularly among patients treated with *androgen receptor pathway inhibitors* (ARPIs) (25-27). In contrast, PSA or *prostatic acid phosphatase* (PAP) immunostaining typically declines in poorly differentiated or *androgen receptor* (AR)-independent tumours (28, 29). Low PSA-IHC expression likely reflects a loss of luminal differentiation and partial lineage plasticity, biological features commonly linked to castration resistance and neuroendocrine transdifferentiation (30-32).

The combined "*PSA-IHC low/Ki67 high*" phenotype observed in our cohort may therefore identify a subgroup of tumours characterized by high proliferative activity, reduced AR signalling dependence, and aggressive clinical behaviour. Importantly, to our knowledge, this is the first study to integrate PSA-IHC and Ki67 expression into a single classification framework in de novo mHSPC. By capturing both proliferative and differentiation states, this dual-marker approach provides a simple histopathological surrogate for underlying tumour biology that may be overlooked when each marker is assessed independently. Such integration could improve biological stratification beyond conventional clinical parameters and help refine risk assessment at diagnosis. This pattern has been previously associated with early progression under androgen

Declarations

Ethical approval and consent for participate: *This study was conducted in accordance with the principles of the Declaration of Helsinki. Ethical approval was obtained from the CES – Comissão de Ética para a Saúde do Centro Hospitalar e Universitário de Coimbra (Ethics Committee for Health of the Coimbra University Hospital Centre), under protocol number N.º 258/CES, Proc. No. OBS.SF.054-2023. Given the retrospective and observational nature of the study, the requirement for informed consent was waived by the Ethics Committee.*

Consent for publication: *Not applicable.*

Availability of data and material: *The datasets generated and/or analyzed during the current study are not publicly available due to ethical and legal restrictions imposed by the hospital's data protection policies, but de-identified data may be available from the corresponding author upon reasonable request and with appropriate institutional approvals.*

Competing interests: *The authors declare that they have no competing interests.*

Funding: *This study was supported by the Associação dos Amigos da Urologia e Transplantação Renal. The funding body had no role in the conceptualization or design of the study, data collection, analysis or interpretation of the data, decision to publish, or preparation of the manuscript.*

Authors' contributions: *AMF: Acquisition of clinical data; data curation; data analysis and interpretation; drafting of the original manuscript; critical revision for important intellectual content; RJ: Study conception and design; data curation; data analysis and interpretation; statistical analyses; validation of results; review and editing of the manuscript; AR: Data curation; data analysis and interpretation; statistical analyses; preparation of tables and figures; review and editing of the manuscript; JG: Data curation; data analysis and interpretation; substantial contribution to manuscript writing; critical revision for important intellectual content; language editing; RA: Data curation; data analysis and interpretation; substantial contribution to manuscript writing; critical revision for important intellectual content; language editing; ME: Substantial contribution to manuscript writing; critical revision for important intellectual content; language editing; VQ: Substantial contribution to manuscript writing; critical revision for important intellectual content; language editing; PN: Study concept and design; supervision; contribution to manuscript writing and editing; overall project administration; approval of the final version; VS: Study concept and design; supervision; contribution to manuscript writing and editing; overall project administration; approval of the final version; AF: Funding, study concept and design; supervision; contribution to manuscript writing and editing; overall project administration; approval of the final version. All the authors read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.*

Acknowledgments: *Not applicable.*

deprivation therapy and limited benefit from taxane chemotherapy (33, 34).

Interestingly, the prognostic effect of these biomarkers appeared to vary by treatment class. Among patients who received ARPIs, the PSA-IHC/Ki67 classification had no significant prognostic value across endpoints, suggesting that hormone-targeted therapies may partially mitigate the influence of baseline proliferative or differentiation markers. In contrast, among taxane-treated patients, the biomarker classification was significantly associated with overall survival, with the PSA-IHC-low/Ki67-high subgroup showing particularly poor outcomes. These findings are in line with emerging data indicating that AR-independent, highly proliferative phenotypes may display limited sensitivity even to taxane-based chemotherapy (35, 36). Nonetheless, given the small sample size within treatment-defined subgroups, these results should be interpreted cautiously.

The multivariable analyses should be interpreted with caution given the small sample size and the potential for intercorrelation between clinical and biological variables. Nonetheless, the overall direction of the associations supports the biological plausibility of the combined PSA-IHC/Ki67 classification as a surrogate marker of tumour aggressiveness and reduced androgen receptor dependence.

This study has several limitations. It was a retrospective, single-centre analysis with a relatively small sample size, which limits the strength and generalizability of the conclusions. Because only patients who ultimately died from prostate cancer were included, the cohort was enriched for aggressive, late-stage disease. This approach ensured that all cases represented lethal prostate cancer but may have underestimated survival differences between biomarker-defined subgroups and reduced applicability to the broader mHSPC population. In addition, treatments were heterogeneous, reflecting different therapeutic eras and clinical practices. The biomarker analysis was limited to two immunohistochemical markers, without molecular or genomic validation. Despite these constraints, the consistent trends observed across endpoints support the biological plausibility and potential clinical relevance of the PSA-IHC/Ki67 classification.

From a clinical perspective, both Ki67 and PSA-IHC are inexpensive, reproducible, and easily implemented using routine pathology workflows. Their combined evaluation could enhance biological stratification of patients with metastatic prostate cancer and help identify those with aggressive, androgen-indifferent disease who may benefit from early treatment intensification or alternative strategies. Prospective validation in larger cohorts, ideally incorporating molecular correlates of AR signalling and lineage plasticity, will be essential to confirm their prognostic utility and guide personalized treatment decisions.

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