Timing of Radiographic Progression Relative to Prostate-Specific Antigen Kinetics in Patients with Metastatic Castration-Sensitive Prostate Cancer Receiving Upfront Androgen Receptor Signaling Inhibitor Therapy

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Purpose: Prostate-specific antigen (PSA) progression does not always coincide with radiographic progression in patients with metastatic castration-sensitive prostate cancer (mCSPC) receiving upfront androgen receptor signaling inhibitor (ARSI) therapy. We evaluated the timing of radiographic progression according to predefined PSA kinetic periods.

Materials and Methods: We retrospectively reviewed 82 consecutive patients with synchronous mCSPC treated with upfront ARSI therapy between April 2018 and May 2024. The median follow-up duration was 23 months (interquartile range [IQR], 14–38). PSA kinetics were categorized into three predefined periods: pre-PSA nadir (treatment initiation to PSA nadir), post-PSA nadir/before PSA progression (PSA nadir to PSA progression), and post-PSA progression. Radiographic progression events were classified according to these PSA kinetic periods.

Results: During follow-up, 33 patients (40%) experienced PSA progression and 26 (31.7%) developed radiographic progression. Among the 26 radiographic progression events, 1 (3.8%) occurred during the pre-PSA nadir period, 7 (26.9%) during the post-PSA nadir/before PSA progression period, and 18 (69.2%) during the post-PSA progression period. Overall, 25 of 26 radiographic progression events (96.2%; 95% confidence interval [CI]: 81.1%–99.3%) occurred after PSA nadir. The only patient who developed radiographic progression before PSA nadir was subsequently diagnosed with small-cell carcinoma of the prostate. PSA nadir levels and time to PSA nadir were comparable between patients who developed radiographic progression before and after PSA progression.

Conclusion: Radiographic progression before PSA nadir was uncommon in this cohort, whereas a substantial proportion of progression events occurred after PSA nadir but before PSA progression. These findings suggest that PSA nadir may serve as a useful temporal reference point for radiographic surveillance during upfront ARSI therapy. However, these observations should be considered hypothesis-generating and require validation in larger prospective multicenter studies.

Keywords: androgen deprivation therapy; androgen receptor antagonists; metastatic castration-sensitive prostate cancer; prostate-specific antigen; disease progression

INTRODUCTION

Upfront therapy combining androgen receptor signaling inhibitors (ARSI) with androgen deprivation therapy (ADT) has demonstrated significant survival benefits for patients with metastatic castration-sensitive prostate cancer (mCSPC) in large phase III trials such as ARCHES and TITAN.[1,2] Prostate-specific antigen (PSA) has traditionally been used as a biomarker to monitor treatment efficacy in prostate cancer. However, recent evidence indicates that some patients with mCSPC receiving upfront ARSI therapy experience radiographic progression before PSA progression, a phenomenon termed "discordant progression."[3] In the post hoc analysis of ARCHES, 67.1% of patients and, in the TITAN trial, 52.2% experienced discordant progression despite ongoing PSA response and the absence of PSA progression.[3,4] In the current ARSI era, discordant progression appears to be increasingly common, raising concerns regarding the reliability of PSA alone as a disease-monitoring tool. Strong androgen receptor blockade markedly suppresses PSA transcription due to the presence of androgen response elements in the PSA promoter.[5]

The optimal timing and frequency of radiographic evaluation during upfront ARSI therapy remain controversial, as highlighted by the 2022 Advanced Prostate Cancer Consensus Conference.[6] Because delayed detection of radiographic progression may adversely affect treatment decisions and subsequent clinical outcomes, determining the appropriate timing of imaging assessments is of considerable clinical importance. This study aimed to examine the timing of radiographic progression in relation to PSA kinetics—specifically before PSA nadir, between PSA nadir and PSA progression, and after PSA progression—in patients with mCSPC receiving upfront ARSI therapy.

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Received August 2025 & Accepted August 2026

Table 1. Baseline characteristics of patients with mCSPC receiving upfront ARSI therapy (N = 82)

Variables	Category	Patients (n = 82)[a]
Age (years), median (IQR)		73 (70–79)
ECOG PS, n (%)	0–1	63 (77)
	2	19 (23)
Hemoglobin (g/dL), median (IQR)		13.3 (11.8–14.4)
LDH (IU/L), median (IQR)		210 (175–524)
ALP (IU/L), median (IQR)		277 (104–702)
Albumin (g/dL), median (IQR)		4.1 (3.6–4.4)
PSA (ng/mL), median (IQR)		361 (87–1591)
Gleason grade group, n (%)	1–4	41 (50)
	5	41 (50)
Visceral metastasis, n (%)	Presence	18 (22)
	Absence	64 (78)
Extent of disease, n (%)	0–2	52 (63)
	3–4	30 (37)
CHAARTED high volume, n (%)		59 (72)
LATITUDE high risk, n (%)		71 (87)
ARSI, n (%)	Abiraterone acetate	41 (50)
	Apalutamide	23 (28)
	Enzalutamide 18 (22)	
PSA progression cases, n (%)		33 (40)
Radiographic progression cases, n (%)		26 (32)
Follow-up period (months), median (IQR)		23 (14–38)

Abbreviations: ALP, alkaline phosphatase; ARSI, androgen receptor signaling inhibitor; ECOG PS, Eastern Cooperative Oncology Group performance status; IQR, interquartile range; LDH, lactate dehydrogenase; mCSPC, metastatic castration-sensitive prostate cancer; PSA, prostate-specific antigen.
[a] Data are presented as median (interquartile range) or number (percentage).

MATERIALS AND METHODS

Study Population

We retrospectively reviewed the medical records of 91 consecutive patients with synchronous mCSPC treated at our institution between April 2018 and May 2024. Eligible patients received upfront ARSI therapy in combination with ADT and had available serial PSA measurements and radiographic follow-up data. Patients with missing clinical data (n = 6) or enrollment in concurrent clinical trials (n = 3) were excluded. Consequently, 82 patients were included in the final analysis. All patients presented with synchronous metastases confirmed by computed tomography (CT), bone scintigraphy, and/or whole-body magnetic resonance imaging (MRI).

No patients had received prior systemic therapy for metastatic disease, including docetaxel, before initiation of upfront ARSI therapy. ARSI therapy was initiated within 3 months of ADT initiation, with a median interval of 0 months (range, 0–3 months). No patients underwent prostate radiotherapy, metastasis-directed therapy, cytoreductive prostatectomy, or other local therapy to the primary tumor or metastatic lesions during the study period. In addition, no patients had neuroendocrine or small-cell carcinoma histology at baseline.

Given the retrospective exploratory design of this study, no formal sample size calculation was performed prior to data collection. Instead, all consecutive eligible patients treated during the study period were enrolled.

Treatment and Follow-up

Serum PSA was measured monthly, and radiographic evaluations were performed every 6 to 12 months or earlier if clinically indicated. CT and bone scintigraphy were the primary imaging modalities used for routine surveillance, whereas whole-body MRI was used selectively as an adjunctive modality when clinically indicated. Earlier imaging assessments were performed at the discretion of the treating physician in cases of PSA elevation, new symptoms, worsening clinical status, or suspected disease progression.

Subsequent treatments after radiographic or PSA progression were administered at the discretion of the treating physician and were not included in the present analysis, which focused on the timing of radiographic progression relative to PSA kinetics.

Definitions of PSA and Radiographic Progression

The follow-up duration was divided into three periods according to PSA kinetics: (1) pre-PSA nadir: from treatment initiation to PSA nadir; (2) post-PSA nadir/before PSA progression: from PSA nadir to PSA progression; and (3) post-PSA progression: after PSA progression. PSA nadir was defined as the lowest PSA level recorded after initiation of upfront ARSI therapy. PSA progression was defined according to the Prostate Cancer Clinical Trials Working Group 3 (PCWG3) criteria as a $\geq$ 25% and $\geq$ 2 ng/mL increase above the nadir, confirmed by a second measurement.[7] Radiographic progression was defined as new lesions or unequivocal growth of existing lesions on CT, MRI, or bone scintigraphy according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 or PCWG3 criteria.[7,8]

Outcomes

Baseline clinical characteristics, including Eastern Cooperative Oncology Group performance status (ECOG PS), Gleason grade group, metastatic sites, and disease risk classification (CHAARTED and LATITUDE criteria), were extracted from medical records. Radiographic progression events were recorded for each PSA kinetic period. The primary analysis evaluated the distribution of radiographic progression events across the three predefined PSA kinetic periods.

Statistical Analysis

This study was designed as an exploratory descriptive analysis to characterize the timing of radiographic progression relative to predefined PSA kinetic periods rather than to test a prespecified hypothesis. Therefore,

Table 2. Distribution of radiographic progression events according to PSA kinetic period (N = 26).

PSA Kinetic Period	Radiographic Progression Events (n = 26), n (%)
Pre-PSA nadir	1 (3.8)
Post-PSA nadir/before PSA progression	7 (26.9)
Post-PSA progression	18 (69.2)

Abbreviations: PSA, prostate-specific antigen.

formal survival analyses, including Kaplan-Meier estimation and hazard ratio analyses, were not performed. Continuous variables were assessed for normality and homogeneity of variance. PSA nadir values and time to PSA nadir were compared between patients who developed radiographic progression during the post-PSA nadir/before PSA progression period and those who developed radiographic progression during the post-PSA progression period. Because several variables did not satisfy the assumptions of normality and/or equal variances required for independent-samples t-tests and the subgroup sample sizes were small, between-group comparisons were performed using the Mann-Whitney U test. Hodges-Lehmann estimates of the median difference with 95% confidence intervals (CIs) were also calculated.

All statistical analyses were performed using JMP version 12.2.0 (SAS Institute Inc, Cary, NC, USA). Statistical significance was set at two-tailed $P < .05$.

Ethics

This study was approved by the Institutional Review Board of Dokkyo Medical University Saitama Medical Center (approval number 22061). The requirement for informed consent was waived owing to the retrospective nature of the study.

RESULTS

Patient Characteristics

The baseline characteristics of the patients are summarized in **Table 1**. The median patient age was 73 years (interquartile range [IQR], 70–79). At baseline, the median PSA level was 361 ng/mL (IQR, 87–1591). Gleason grade group 5 was observed in 41 patients (50%). Visceral metastases were present in 18 patients (22%). High-volume disease was present in 59 patients (72%) according to CHAARTED criteria, and high-risk disease was present in 71 patients (87%) according to LATITUDE criteria. ARSI regimens included abiraterone acetate (n = 41, 50%), apalutamide (n = 23, 28%), and enzalutamide (n = 18, 22%). ECOG PS 0–1 was observed in 63 patients (77%), and PS 2 in 19 patients (23%). The median follow-up duration was 23 months (IQR, 14–38).

PSA and Radiographic Progression

Overall, 33 patients (40%) experienced PSA progression, and 26 patients (32%) developed radiographic progression (**Table 2**). Among the 26 patients who developed radiographic progression, 1 (3.8%; 95% CI: 0.7%–18.9%) experienced progression during the pre-PSA nadir period, 7 (26.9%; 95% CI: 13.7%–46.1%) during the post-PSA nadir/before PSA progression period, and 18 (69.2%; 95% CI: 50.0%–83.5%) during the post-PSA progression period. Overall, 25 of 26 radiographic progression events (96.2%; 95% CI: 81.1%–99.3%) occurred after PSA nadir. The sole pre-nadir radiographic progression event occurred in a patient who initially had Gleason score 4 prostate adenocarcinoma and was subsequently diagnosed with small-cell carcinoma based on histopathological examination of a bladder neck mass resected transurethrally.

Median PSA nadir values were 1.77 ng/mL (IQR, 0.02–7.00) in the post-PSA nadir/before PSA progression group and 2.27 ng/mL (IQR, 0.41–4.46) in the post-PSA progression group, with no evidence of a statistically significant between-group difference (Hodges-Lehmann median difference, 0.17 ng/mL; 95% CI: -4.01 to 3.02 ng/mL; $P = .739$). The median time from treatment initiation to PSA nadir was 4.0 months (IQR, 2.0–7.0) in the post-PSA nadir/before PSA progression group and 5.5 months (IQR, 2.75–14.0) in the post-PSA progression group. The Hodges-Lehmann median difference was 1.0 month (95% CI: -2.0 to 9.0 months; $P = .328$).

DISCUSSION

Our findings highlight that radiographic progression during upfront ARSI therapy for mCSPC most frequently occurs after PSA progression but can also occur before PSA progression, emphasizing the need for strategically timed imaging surveillance. The relatively high proportion of patients with progression in the post-PSA nadir/before PSA progression period underscores the potential clinical utility of using PSA nadir as a reference point for scheduling imaging assessments. Notably, 25 of 26 radiographic progression events (96.2%; 95% CI: 81.1%–99.3%) occurred after PSA nadir, whereas only one event (3.8%) was observed before PSA nadir. The sole pre-nadir progression event occurred in a patient who was subsequently diagnosed with small-cell carcinoma. Although this finding should be interpreted cautiously because it was based on a single case, it further highlights the rarity of radiographic progression before PSA nadir in this cohort. These findings suggest that PSA nadir may represent a clinically meaningful temporal landmark for planning radiographic surveillance during upfront ARSI therapy. Interestingly, PSA nadir levels and time to PSA nadir were comparable between patients who developed radiographic progression during the post-PSA nadir/before PSA progression period and those who developed progression during the post-PSA progression period. Previous studies have demonstrated that a deeper and more rapid PSA response is associated with favorable outcomes in patients with mCSPC receiving intensified hormonal therapy.[9,10] However, our findings suggest that differences in the timing of radiographic progression cannot be explained solely by the depth or speed of PSA response. Radiographic progression may occur despite apparently favorable PSA kinetics, highlighting the limitations of PSA as the sole indicator of disease activity during upfront ARSI therapy.

Previous analyses from ARCHES and TITAN demon-

strated that more than half of patients with mCSPC experienced discordant progression—radiographic progression without concomitant PSA rise.[3,4] This trend suggests that PSA may be less reliable as a sole monitoring biomarker in the ARSI era, likely due to potent suppression of PSA transcription by androgen receptor blockade.[5]) As a result, reliance solely on PSA kinetics may delay the detection of radiographic progression, potentially missing an opportunity for timely therapeutic intervention.

The early occurrence of radiographic progression before PSA nadir, as observed in one patient in our cohort, may indicate an aggressive histologic subtype such as neuroendocrine prostate cancer (NEPC). In the TITAN trial, some discordant progression cases were associated with NEPC features, including low PSA secretion, rapid progression, and treatment resistance.[3] NEPC remains difficult to diagnose at initial biopsy and typically emerges a median of 20 months after diagnosis.[11] Given its rarity in mCSPC, frequent imaging before PSA nadir may not be necessary unless clinical suspicion for NEPC exists. Our results suggest that PSA nadir could serve as a practical temporal reference for guiding radiographic surveillance intervals. Integrating PSA kinetics with strategically timed imaging assessments may facilitate earlier detection of progression and help optimize surveillance strategies.

Limitations of this study include its retrospective single-institution design, small sample size, and relatively short follow-up period. In addition, residual confounding may have influenced our findings. Differences in disease burden, LATITUDE risk status, visceral metastasis, Gleason grade group, baseline PSA, ECOG performance status, ARSI selection, and timing of ARSI initiation after ADT may have affected the timing of radiographic progression. Because only 26 radiographic progression events occurred in this cohort, adjusted or stratified analyses were not feasible. These findings should be interpreted in light of the potential for residual confounding. Furthermore, imaging was performed every 6 to 12 months according to institutional practice, with earlier assessments performed at the discretion of the treating physician. As a result, the exact timing of radiographic progression may not have been captured precisely. In addition, patients undergoing earlier imaging because of PSA elevation, new symptoms, or clinical suspicion of progression may have had radiographic progression detected sooner than others, potentially introducing detection bias. Prospective multicenter studies are needed to confirm these findings and refine imaging surveillance strategies in the ARSI era.

To our knowledge, this is the first study to explicitly quantify radiographic progression frequencies within three clearly defined PSA kinetic periods in the context of upfront ARSI therapy. While pivotal trials such as ARCHES and TITAN have reported discordant progression, they did not specifically evaluate progression timing relative to PSA nadir. We found that radiographic progression before PSA nadir was rare, with only one event observed, and this patient was subsequently diagnosed with small-cell carcinoma. In contrast, 25 of 26 radiographic progression events (96.2%; 95% CI: 81.1%–99.3%) occurred after PSA nadir. Taken together, our results support the potential utility of PSA nadir as a temporal reference point for radiographic surveillance during upfront ARSI therapy. However, these observations should be considered hypothesis-generating and require validation in larger prospective multicenter studies.

CONCLUSIONS

In patients with mCSPC receiving upfront ARSI therapy, most radiographic progression events occurred after PSA nadir. PSA nadir may therefore represent a useful temporal landmark for radiographic surveillance. Further prospective multicenter studies are needed to validate these findings and determine the clinical utility of PSA-guided imaging strategies.

SUMMARY

In men with advanced prostate cancer receiving hormone therapy, tumor growth on scans rarely occurs before PSA reaches its lowest point. Tracking this PSA low point helps doctors decide the best time for imaging.

ACKNOWLEDGEMENTS

The authors thank the medical and administrative staff of Dokkyo Medical University Saitama Medical Center for their assistance in data retrieval and patient record management.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

DATA AVAILABILITY

The datasets generated and/or analyzed during the current study are not publicly available because of institutional privacy regulations but are available from the corresponding author on reasonable request.

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