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ORIGINAL ARTICLE

Transcriptomic and clinical heterogeneity of metastatic disease timing within metastatic castration-sensitive prostate cancer

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Background: Metastatic castration-sensitive prostate cancer (mCSPC) is commonly classified into high- and low-volume subgroups which have demonstrated differential biology, prognosis, and response to therapy. Timing of metastasis has similarly demonstrated differences in clinical outcomes; however, less is known about any underlying biologic differences between these disease states. Herein, we aim to compare transcriptomic differences between synchronous and metachronous mCSPC and identify any differential responses to therapy.

Patients and methods: We performed an international multi-institutional retrospective review of men with mCSPC who completed RNA expression profiling evaluation of their primary tumor. Patients were stratified according to disease timing (synchronous versus metachronous). The primary endpoint was to identify differences in transcriptomic profiles between disease timing. The median transcriptomic scores between groups were compared with the Mann–Whitney *U* test. Secondary analyses included determining clinical and transcriptomic variables associated with overall survival (OS) from the time of metastasis. Survival analysis was carried out with the Kaplan–Meier method and multivariable Cox regression.

Results: A total of 252 patients were included with a median follow-up of 39.6 months. Patients with synchronous disease experienced worse 5-year OS (39% versus 79%; $P < 0.01$) and demonstrated lower median androgen receptor (AR) activity (11.78 versus 12.64; $P < 0.01$) and hallmark androgen response (HAR; 3.15 versus 3.32; $P < 0.01$). Multivariable Cox regression identified only high-volume disease [hazard ratio (HR) = 4.97, 95% confidence interval (CI) 2.71-9.10; $P < 0.01$] and HAR score (HR = 0.51, 95% CI 0.28-0.88; $P = 0.02$) significantly associated with OS. Finally, patients with synchronous (HR = 0.47, 95% CI 0.30-0.72; $P < 0.01$) but not metachronous (HR = 1.37, 95% CI 0.50-3.92; $P = 0.56$) disease were found to have better OS with AR and non-AR combination therapy as compared with monotherapy (P value for interaction = 0.05).

Conclusions: We have demonstrated a potential biologic difference between metastatic timing of mCSPC. Specifically, for patients with low-volume disease, those with metachronous low-volume disease have a more hormone-dependent transcriptional profile and exhibit a better prognosis than synchronous low-volume disease.

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Key words: metastatic castration-sensitive prostate cancer, transcriptomic biomarkers, precision medicine, synchronous, metachronous

INTRODUCTION

Prostate cancer represents the most common solid organ malignancy among men accounting for ∼270 000 new cases and >30 000 deaths in the United States in 2022.[1] Some patients with prostate cancer experience an indolent disease course while others have a more aggressive clinical course and biology resulting in metastatic disease and castration resistance which drives prostate cancer mortality.[2] Among men with metastatic castration-sensitive prostate cancer (mCSPC), efforts have aimed to identify those at the highest risk of disease progression and benefit from early treatment intensification.

The volume of metastatic disease has previously demonstrated valuable prognostic information and holds promise in guiding treatment recommendations.[3-5] Specifically, combined systemic therapy with androgen-deprivation therapy (ADT) and docetaxel has demonstrated a significant overall survival (OS) benefit within high-volume but not for metachronous low-volume disease.[6,7] Conversely, prostate radiation has demonstrated benefit in men with synchronous low-volume mCSPC, which however has not been observed in in high-volume/polymetastatic disease.[8,9] Similar to disease volume, timing (*de novo/*synchronous versus metachronous) of metastatic disease has also been implicated in prognosis, with synchronous disease demonstrating worse clinical outcomes.[10,11] Although synchronous disease has been shown to be associated with worse outcomes, the mechanisms underlying respective responsiveness to standard-of-care therapies by timing of disease are poorly understood. Further, the interplay between disease timing and volume remains incompletely understood, with some clinical observations demonstrating a spectrum of disease from more aggressive synchronous high-volume to indolent metachronous low-volume disease.[11] Tumor transcriptomics may provide critical information to better understand this more aggressive phenotype and allow for greater therapeutic precision. Currently, several transcriptomic signatures based on gene expression profiles of the primary tumor have been developed and associated with clinical outcomes.[12-14] More importantly, transcriptomic profiling has demonstrated predictive utility in determining benefit to combined systemic therapy within mCSPC.[15] Herein, we aim to evaluate for differences in transcriptomic profiles relative to timing and volume of metastatic disease and associate them with clinical outcomes and response to therapy.

MATERIALS AND METHODS

We performed an international multi-institutional retrospective review of men with mCSPC who, following informed consent, underwent RNA expression profiling evaluation of their primary tumor via either RNA sequencing (RNA-Seq) or microarray. RNA-Seq was performed via the Tempus xT tissue assay (648-gene mutational DNA panel and full RNA-Seq transcriptome) platform. Microarray was performed via the Veracyte Decipher platform (San Diego, CA) as previously described.[15] Microarray data were normalized using the Single Channel Array Normalization (SCAN) algorithm.[16] Gene expression signatures including androgen receptor activity (AR-A)[13]; PAM50[17]; Post-Operative Radiation Therapy Outcomes Score (PORTOS)[18]; homologous recombination deficiency (HRD)[19]; small cell/neuroendocrine (SC/NE)[20]; and hallmarks of cancer,[21] including androgen response, DNA repair, and epithelial-to-mesenchymal transition (EMT). WNT was calculated for all patients using the GRID software for both RNA-Seq and microarray (Veracyte, Inc). The quality of samples was assessed for the proportion of reads aligning to the reference genome. Read alignments were also assessed for percentage of reads aligning to exonic, intronic, and intergenic regions of the human reference genome (build GRCh38) and corresponding reference annotation. Total genic counts, mitochondrial gene expression, and sample clustering were used to identify any potential outliers. One sample failed quality check and was excluded from analysis. Batch correction between microarray and RNA-Seq was carried out using ComBat to allow for combined analysis.[22]

Patients included those treated on the CHAARTED,[4] STOMP,[23] and ORIOLE[24] clinical trials as well as those who underwent transcriptomic evaluation off-trial at Ghent University and Johns Hopkins Hospital. Details of the transcriptomic subsets of the CHAARTED[15] and STOMP/ORIOLE[25] clinical trials have previously been described. Synchronous disease was defined as presence of metastatic disease at first diagnosis of prostate cancer. Metachronous disease was defined as metastatic recurrence following definitive prostate treatment. RNA expression profiling for patients with metachronous disease was performed on the initial localized prostate cancer specimen. Patients were stratified by volume of disease according to a modified version of the CHAARTED criteria.[4] Modified high-volume disease was defined as the presence of either visceral metastases or four or more bone metastasis with at least one outside the spine or pelvis visible on either conventional or enhanced (choline C-11 positron emission tomography) imaging. Modified low-volume disease was defined as metastatic disease visible on either conventional or enhanced imaging not meeting high-volume criteria. All lesions on enhanced imaging had a correlate lesion on conventional imaging, but were not required to meet RECIST criteria.[26] This modified definition was used as patients on the STOMP trial were staged by choline C-11 positron emission tomography/computed tomography. Initial management was classified as monotherapy (ADT

alone for synchronous; ADT alone or metastasis-directed therapy alone for metachronous) or AR + non-AR combination therapy (ADT + docetaxel or ADT + prostate/metastasis-directed radiotherapy). Follow-up data and clinical endpoints were collected through serial physical examination, conventional imaging, and prostate-specific antigen measurements.

The primary endpoint of interest was to identify differences in transcriptomic profiles between timing of disease. Median transcriptomic scores were reported for both metachronous and synchronous cohorts and compared with Mann–Whitney *U* test within the RNA-Seq, microarray, and combined batch-corrected cohorts. The proportion of patients with low androgen signaling was also compared between synchronous and metachronous patients with chi-square test. Low AR-A was defined as $\leq$11 as previously described.[13] Low hallmark androgen response (HAR) was defined as less than the median. Secondary analyses included determining clinical and transcriptomic variables associated with time to castration-resistant prostate cancer (ttCRPC) and OS from the time of metastasis diagnosis. Castration resistance was defined according to Prostate Cancer Working Group 3 criteria.[27] Subset analyses evaluated response to therapy and clinical and transcriptomic differences accounting for both timing and volume of disease. Survival analysis was performed with the Kaplan–Meier Method and compared with log-rank test. Multivariable Cox regression were conducted for ttCRPC and OS including variables with $P < 0.1$ on univariable Cox regression. For all analyses, a P value ≤ 0.05 was considered statistically significant. All statistical analyses were conducted using SPSS v26 (IBM, Inc, New York, NY).

RESULTS

A total of 252 patients were included in this analysis with a median follow-up of 39.6 (interquartile range 23.5-59.6) months. A detailed list of demographic and disease characteristics is presented in Table 1. Patients with synchronous disease accounted for 60.0% of the cohort. Treatment modalities included ADT with or without docetaxel (63.5%; microarray cohort), ablative radiation therapy with or without systemic therapy (33.0%; RNA-Seq cohort), or observation (3.6%; RNA-Seq cohort). Transcriptomic evaluation was performed with either microarray (63.5%) or RNA-Seq (36.5%). Patients with synchronous disease had a significantly higher prostate-specific antigen and Gleason Grade Group and were much more likely to have high-volume disease (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2023.04.515).

Within the entire cohort, patients with synchronous metastatic disease experienced significantly worse outcomes (Figure 1). The median and 5-year ttCRPC rates were 15.4 versus 91.0 months and 24% versus 78% for synchronous and metachronous disease, respectively ($P < 0.01$). The median and 5-year OS were 48.8 months versus not reached and 39% versus 79% for synchronous and metachronous disease, respectively ($P < 0.01$).

Using the total cohort and comparing among batch-corrected transcriptomic signatures, synchronous metastatic disease was found to have a significantly lower median AR-A (11.78 versus 12.64; $P < 0.01$) and HAR (3.15 versus 3.32; $P < 0.01$) (Figure 2) compared with metachronous disease. In addition, patients with synchronous disease were significantly more likely to have low AR-A (37.7% versus 19.8%; $P < 0.01$) and low HAR (58.3% versus 37.6%; $P < 0.01$; Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2023.04.515). No other differences between the timing of metastatic disease were identified when comparing using PAM50, PORTOS, HRD, SC/NE, hallmark p53, hallmark DNA repair, hallmark EMT, or hallmark WNT gene signatures (Supplementary Table S2, available at https://doi.org/10.1016/j.annonc.2023.04.515). Given the difference in patient populations between those who underwent microarray and RNA-Seq, differences in androgen response signatures, AR-A and HAR, were also compared within each cohort. HAR was significantly lower among patients with synchronous disease in both RNA-Seq ($P < 0.01$) and microarray ($P = 0.03$) cohorts when examined individually. The AR-A scores were only noted to be significantly lower within the RNA-Seq ($P < 0.01$) and trended toward but did not reach statistical significance in the microarray ($P = 0.09$) cohort.

The multivariable cox regression model was built with clinical and transcriptomic variables associated with outcomes on univariable regression (Supplementary Table S3, available at https://doi.org/10.1016/j.annonc.2023.04.515). On multivariable analysis, ttCRPC was significantly shorter

Table 1. Demographic characteristics ($N = 252$)

Age, median (interquartile range), years	64 (56.3-70.0)
PSA at metastasis, median (interquartile range)	20.5 (3.2-152.9)
Gleason Grade Group, *n* (%)	
1	11 (4.4)
2	39 (15.5)
3	27 (10.7)
4	42 (16.7)
5	125 (49.6)
Unavailable	7 (2.8)
Timing, *n* (%)	
Synchronous	151 (60.0)
Metachronous	101 (40.0)
Disease burden, *n* (%)	
Low volume	126 (50.0)
Conventional detection	54 (42.9)
Enhanced detection	72 (57.1)
High volume	126 (50.0)
Conventional detection	125 (99.2)
Enhanced detection	1 (0.8)
Treatment, *n* (%)	
ADT monotherapy	76 (30.2)
ADT + docetaxel	84 (33.3)
MDT monotherapy	39 (15.5)
MDT + systemic therapy	44 (17.5)
Observation	9 (3.6)
Transcriptomic evaluation	
Microarray	160 (63.5)
RNA-Seq	92 (36.5)

ADT, androgen-deprivation therapy; MDT, multidrug therapy; PSA, prostate-specific antigen; RNA-Seq, RNA sequencing.

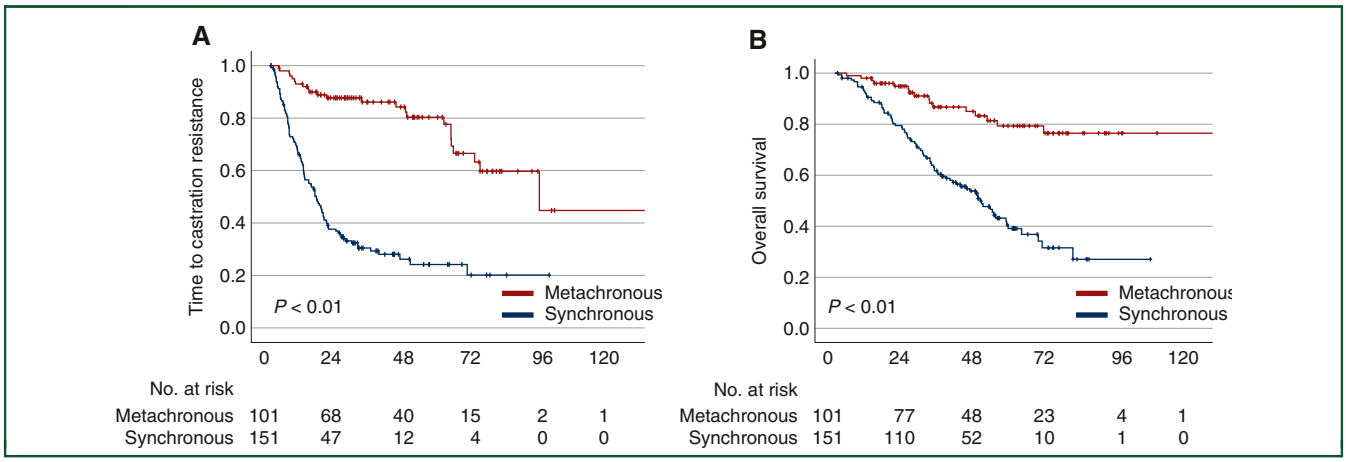

Figure 1. **Kaplan–Meier survival curves of (A) time to castration-resistant prostate cancer and (B) overall survival stratified by timing of disease.**

with high-volume disease [hazard ratio (HR) = 5.22, 95% confidence interval (CI) 3.11-8.77; $P < 0.01$] and longer with increasing HAR score (HR = 0.56, 95% CI 0.35-0.88; $P = 0.02$). Similarly, OS was significantly shorter with high-volume disease (HR = 4.97, 95% CI 2.71-9.10; $P < 0.01$) and longer with increasing HAR score (HR = 0.51, 95% CI 0.28-0.88; $P = 0.02$; Table 2). Notably, when accounting for volume of disease and transcriptomic differences, timing of disease was not associated with a difference in either ttCRPC (HR = 1.67, 95% CI 0.94-2.96; $P = 0.08$) or OS (HR = 1.18, 95% CI 0.61-2.31; $P = 0.62$). Given the primary biologic difference between timing of disease appeared to be related to androgen response, we hypothesized that patients with synchronous disease would derive a greater benefit from AR and non-AR combination therapy (defined as either ADT plus docetaxel or ADT plus ablative radiation). Figure 3 demonstrates that patients with synchronous (HR = 0.47, 95% CI 0.30-0.72; $P < 0.01$) but not metachronous (HR = 1.37, 95% CI 0.50-3.92; $P = 0.56$) disease have an improvement in OS with multimodal therapy as compared with monotherapy (P value for interaction = 0.05). Supplementary Figures S2 and S3, available at https://doi.org/10.1016/j.annonc.2023.04.515 demonstrate ttCRPC and OS for the microarray cohort (monotherapy versus ADT plus docetaxel) and the RNA-Seq cohort (monotherapy versus ADT plus ablative radiation).

We next aimed to evaluate timing of disease in relation to disease volume. As noted previously, patients were stratified into low- (50.0%) and high- (50.0%) volume disease. Among patients with high-volume disease, there were no significant differences between timing of disease in either 3-year ttCRPC (42% versus 17%; $P = 0.124$) or OS (46% versus 54%; $P = 0.67$). Conversely, among patients with low-volume disease, metachronous metastasis was associated with significantly better 3-year ttCRPC (92%

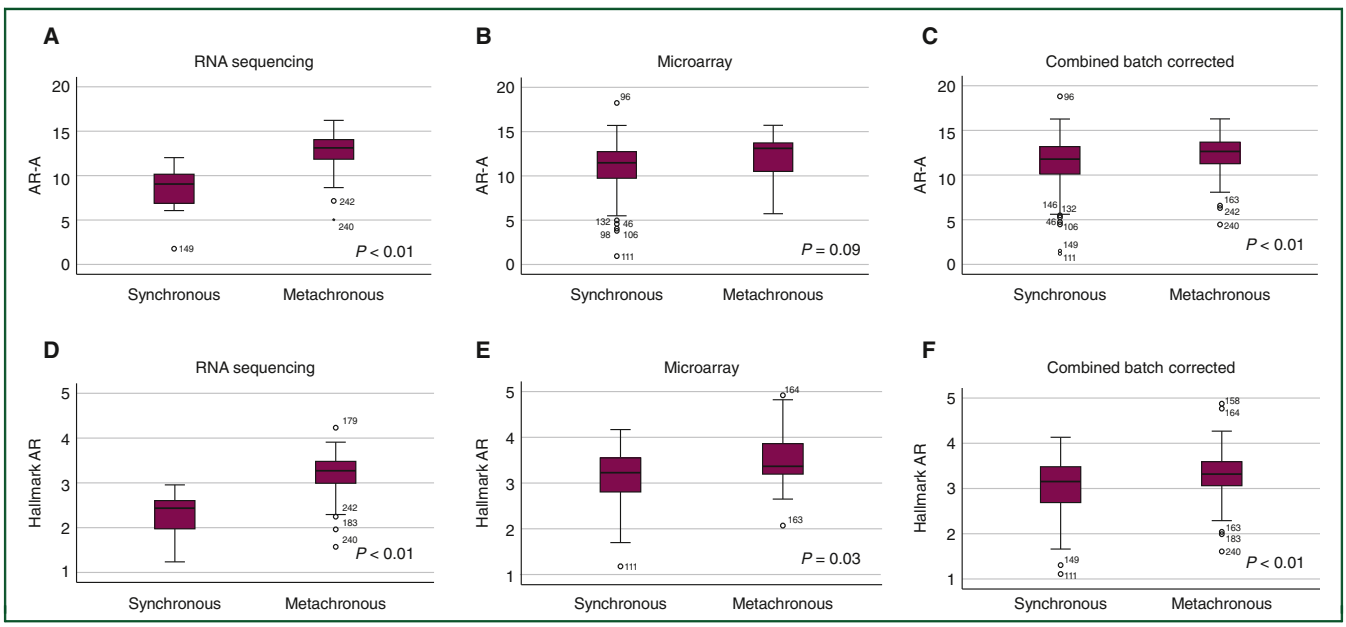

Figure 2. **Boxplots comparing androgen receptor activity (AR-A) and hallmark AR transcriptional scores of metachronous and synchronous disease for (A and D) RNA-sequenced, (B and E) microarray, and (C and F) combined cohorts.**

Table 2. Multivariable Cox regression for ttCRPC and OS

Characteristic	HR (95% CI)	*P* value
ttCRPC		
Synchronous (versus metachronous)	1.69 (0.95-2.99)	0.07
High volume (versus low volume)	**5.22 (3.11-8.77)**	**<0.01**
PSA at metastasis	1.00 (1.00-1.00)	0.65
Gleason Grade Group	1.17 (0.98-1.41)	0.08
AR-A score	1.02 (0.92-1.14)	0.71
Hallmark androgen response	**0.56 (0.35-0.89)**	**0.02**
SC/NE	0.56 (0.03-9.22)	0.69
OS		
Synchronous (versus metachronous)	1.19 (0.61-2.31)	0.62
High volume (versus low volume)	**4.97 (2.71-9.10)**	**<0.01**
PSA at metastasis	1.00 (1.00-1.00)	0.69
Gleason Grade Group	1.20 (0.95-1.51)	0.12
AR-A score	1.02 (0.89-1.18)	0.75
Hallmark androgen response	**0.51 (0.28-0.88)**	**0.02**
Hallmark DNA repair	2.18 (0.83-5.76)	0.12

AR-A, androgen receptor activity; CI, confidence interval; HR, hazard ratio; OS, overall survival; PSA, prostate-specific antigen; SC/NE, small cell/neuroendocrine; ttCRPC, time to castration-resistant prostate cancer.

versus 64%; $P < 0.01$) and OS (94% versus 76%; $P < 0.01$; Figure 4A-D). Comparing transcriptomic differences demonstrated that synchronous disease had a lower HAR in low- ($P = 0.03$) but not high- ($P = 0.35$) volume disease (Figure 4E and F). Finally, within this cohort, evaluating treatment by time and volume of disease demonstrated that upfront multimodal therapy was associated with longer ttCRPC among patients with high-volume ($P < 0.01$), may improve with synchronous low-volume ($P = 0.07$), and does not have significant benefit in metachronous low-volume ($P = 0.18$) disease (Supplementary Figure S4, available at https://doi.org/10.1016/j.annonc.2023.04.515).

DISCUSSION

Here, we report on the biologic and clinical differences between two distinct groups of mCSPC based on timing of metastasis. Specifically, we have identified that synchronous mCSPC is associated with a lower androgen response transcriptomic profile. Further, we have demonstrated that while synchronous metastatic disease experiences a more aggressive clinical course on univariable analysis, consistent with prior reports, when accounting for disease volume and androgen response biology, timing of metastatic disease alone no longer appears to be as strong of a prognostic indicator. Further, we have demonstrated that patients with

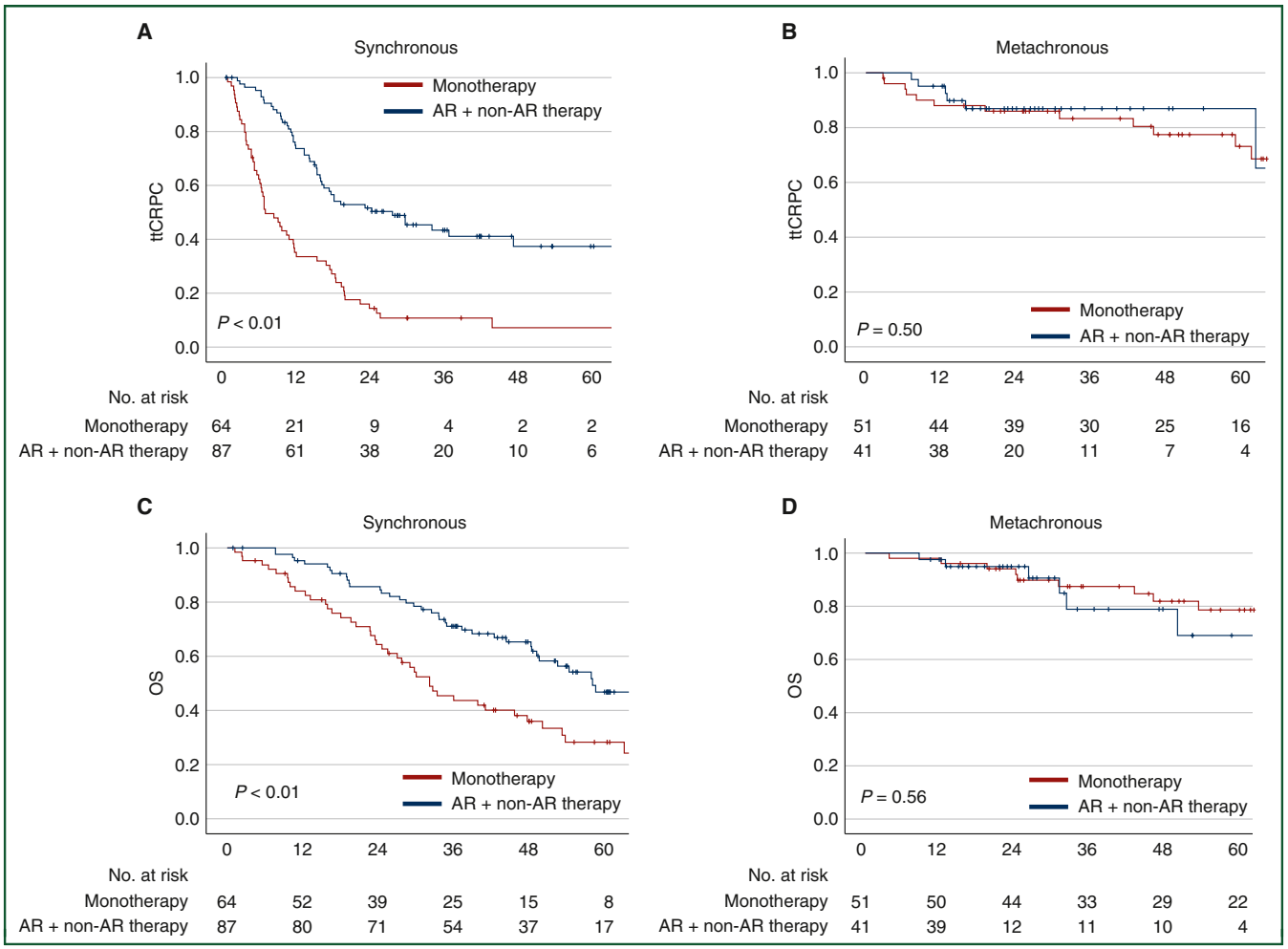

Figure 3. Kaplan–Meier survival curves of time to castration-resistant prostate cancer (ttCRPC) and overall survival (OS) of (A and C) synchronous and (B and D) metachronous metastatic disease stratified by multimodal therapy versus monotherapy.
AR, androgen receptor; AR-A, androgen receptor activity.

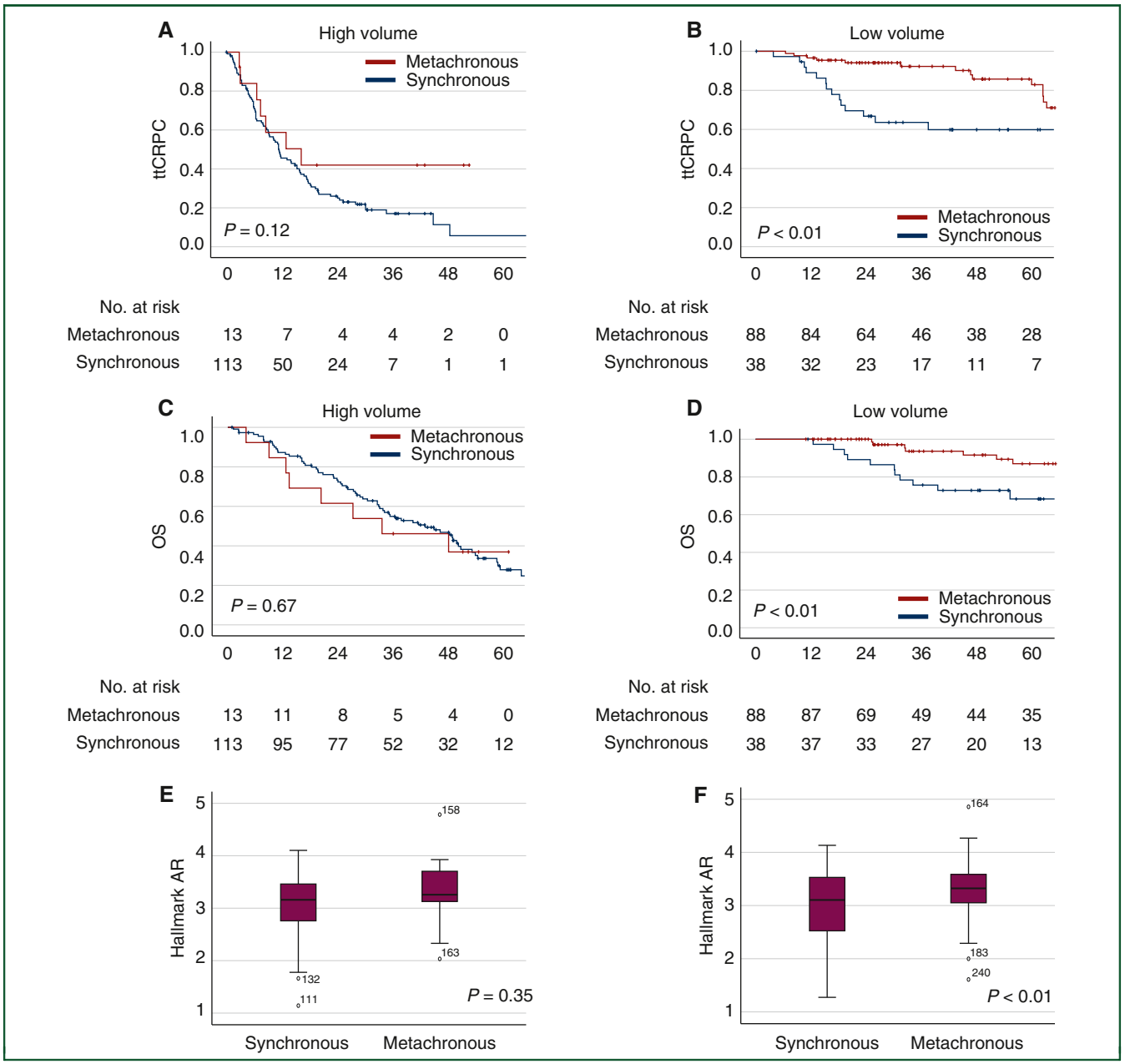

Figure 4. Kaplan–Meier survival curves of time to castration-resistant prostate cancer (ttCRPC) of (A and C) high-volume and (B and D) low-volume disease stratified by timing of disease. Boxplot of hallmark androgen receptor (AR) transcriptional score of metachronous and synchronous disease for (E) high- and (F) low-volume disease.
OS, overall survival.

synchronous (but not metachronous) disease may experience improved outcomes with AR + non-AR combination therapy, likely as a result of their lower androgen response profile. This aligns with clinical trials showing that ADT plus docetaxel has a clear effect in high-volume (synchronous and metachronous) disease and less—but still some effect—in men with synchronous low-volume disease who also benefit from radiating the primary. Docetaxel has no effect on metachronous low-volume disease.[7] Specifically, we demonstrate that the clinical and biologic difference between disease timing is predominantly driven by patients with metachronous disease within the low-volume subgroup.

High-quality evidence of the prognostic implication of timing of metastatic disease was first reported in secondary analyses of the CHAARTED trail and then in a combined analysis with the GETUG-AFU15 clinical trial.[6,28] Both trials demonstrated significantly improved OS in patients with metachronous metastatic disease (metastatic disease after failure of local treatment) with a median OS nearly two times that of synchronous disease (83.1 versus 46.5 months). Follow-up work by Francini et al.[11] retrospectively reviewed 436 patients with mCSPC and demonstrated OS and ttCRPC could be stratified into three risk groups (low-volume metachronous, low-volume synchronous/high-volume metachronous, and high-volume

synchronous). The results presented here are generally concordant with these findings, demonstrating significantly worse outcomes with synchronous disease. Notably, the results here demonstrate a much larger difference in outcomes by disease timing, which is likely due to an imbalance of disease burden between groups (higher burden of disease among our synchronous cohort). Our results similarly identify three risk groups stratified by time and volume, but high volume has the worst outcomes regardless of disease timing.

To our knowledge, this report is the first to demonstrate a biologic difference between timing of metastatic disease. As we have shown, patients with synchronous disease have lower AR-A and HAR gene signature scores and that within the low-volume cohort, those with metachronous low volume have the higher AR-A score. Spratt et al.[13] have previously demonstrated low AR-A to be associated with less sensitivity to ADT among patients with treatment-naïve prostate cancer. Together, these findings suggest that the difference in AR pathway gene expression is likely contributing to the observed difference in outcomes due to synchronous disease being more resistant to conventional ADT. This hypothesis is also supported by our finding of similar outcomes in high-volume disease regardless of disease timing coupled with no significant difference in androgen transcription score between timing of disease in this cohort. Our observation that timing of metastatic disease becomes a less significant prognostic factor when disease volume and transcriptional profiles are accounted for further supports this hypothesis.

Although understanding the prognostic implications of disease timing is of great interest, understanding the biologic underpinnings is paramount to guide therapeutic decision making as well as identify drivers and potential targets of aggressive disease. Several studies have aimed at understanding which patients may derive the greatest benefit from treatment intensification. Volume of disease has already demonstrated ability to predict response to treatment. Specifically, as first reported by the CHAARTED long-term follow-up study, there is a gradient of prognosis with synchronous high-volume experiencing the worst outcomes followed by metachronous high-volume and synchronous low-volume experiencing intermediate outcomes. The CHAARTED team also documented a gradient of benefit from docetaxel, with most in synchronous high volume to none in metachronous low-volume and intermediate in the other two groups.[4] Pooled data from the CHAARTED and GETUF-AFU15 trials and confirmed in STOPCaP IPD in 2022, which included patients from the STAMPEDE trial, demonstrated that docetaxel confers the greatest OS benefit to those with high-volume disease (high-volume HR = 0.68, 95% CI 0.56-0.82; low-volume HR = 1.03, 95% CI 0.77-1.38).[6,7] Conversely, the ENZAMET trial demonstrated that patients with metachronous low volume may have a greater treatment effect in metachronous low-volume HR (OS): 0.47 (95% CI 0.28-0.79) than synchronous high-volume HR (OS = 0.70, 95% CI 0.47-1.04) with synchronous low volume possibly having an intermediate effect HR (OS = 0.58, 95% CI 0.32-1.04).[29]

Our results and phase III trials presented here demonstrated that patients with synchronous disease experience significantly improved outcomes with AR plus non-AR combination therapy as compared with hormonal therapy alone. Notably, patients with metachronous low-volume disease do not derive the same benefit from ADT plus docetaxel, but they do benefit from ADT plus enzalutamide[30,31] or apalutamide.[32] This improvement in multimodal therapy involving hormonal therapy plus non-AR-targeted (docetaxel or ablative radiation) therapy may be a result of overcoming intrinsic ADT resistance (lower androgen response transcriptional profile) within synchronous disease. Further, when stratifying by volume and timing of disease, both high volume (regardless of timing) and synchronous low volume appear to have improved ttCRPC with AR plus non-AR combination therapy. Low-volume metachronous disease, however, appears to derive no benefit from AR plus non-AR combination therapy likely due to its more indolent biology. Importantly, however, no patients within this cohort received second-generation hormone therapy (i.e. abiraterone, enzalutamide, apalutamide) for mCSPC and future work is needed to determine relationship of transcriptomic profiles and combined AR targeted therapy (e.g. testosterone suppression plus potent AR inhibitor). However, clinical trial data do document a benefit with ADT and enzalutamide plus apalutamide in all subgroups of high and low volume with synchronous and metachronous mCSPC.

This study has several limitations that must be considered when interpreting the results. First, patients with metastasis detected on enhanced imaging were included in analysis and entirely within the metachronous cohort. Many of these patients did not meet RECIST criteria on conventional imaging and were identified primarily via biochemical relapse; a large subset of these metachronous patients would be conventionally classified as nonmetastatic. This earlier stage of disease within our metachronous cohort may have contributed to some of the differences we observed. However, as we already know that docetaxel has little to no OS benefit in conventional M0 disease,[33,34] the data in this 'gray' area are consistent with the M0 literature. Second, a significant batch effect was observed between the RNA-sequenced and microarray patients. Transcriptomic profiles for the RNA-seq cohort were scaled to match those from the microarray cohort to adjust for the difference in dynamic range between RNA-seq and microarray profiles. AR-A scores were further batch corrected prior to combining these data that were influenced by the difference in number of patients with synchronous and metachronous disease in each cohort. This scaling and subsequent batch correction could have diminished the magnitude and significance of the true effect size between synchronous and metachronous disease in our differential expression and Cox regression combined analyses. Another limitation is that the study is likely underpowered to detect a difference in timing of disease within high-volume disease as only 13 metachronous high-volume patients were included in analysis. Therefore the lack of clinical and

biologic differences between timing of disease in this subset should be interpreted cautiously. As mentioned earlier, none of the patients within this study received second-generation hormone therapy, now considered standard of care.[35,36] This represents a major limitation to the interpretability of the clinical outcomes reported herein. Further work validating these findings in the modern era are required to determine whether patients with high-volume and synchronous disease derive a greater benefit with the addition of a non-AR targeting agent to a combination of ADT plus AR signaling inhibitor as compared with those with metachronous low-volume disease. Finally, 17 patients with synchronous disease had exposure to ADT prior to tissue sequencing. Although these samples met stringent quality checks, it is possible that the prior exposure to ADT altered RNA expression of androgen-related genes affecting the androgen transcriptomic signatures.

In this multi-institutional series, we have demonstrated for the first time a biologic difference in the timing of metastatic presentation of CSPC for patients with low-volume disease. Specifically, we have demonstrated that patients with metachronous low-volume metastatic disease have a more ADT-responsive transcriptional profile than those with synchronous low-volume disease, with timing of disease having a greater effect in low-volume disease. Finally, we show that patients with high-volume or synchronous low-volume disease may derive the greatest benefit from multimodal therapy targeting AR and non-AR biologies, potentially a result of this biologic difference.

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DISCLOSURE

PAS reports stocks from Merck and Pfizer. AH reports employment, stock/other ownership interests with Veracyte. YL reports employment with Veracyte. VF reports travel/accommodations/expenses covered by Ipsen. AH reports honoraria, travel/accommodations/expenses covered by UroToday; consulting/advisory role with AstraZeneca and MSD. DYS is a consultant for Isoray; also reports being a consultant and carrying out research for BioProtect. AES reports consulting/advisory role for and receiving honoraria from Astellas Pharma; is on the speaker' bureau and reports receiving honoraria from Tempus; reports receiving honoraria from Bayer, Janssen Biotech, Blue Earth Diagnostics, Decipher Biosciences, Myovant Sciences, and Lantheus Medical Imaging. FF reports carrying out consulting/advisory role for Janssen Biotech, Astellas Pharma, Foundation Medicine, Exact Sciences, Bristol-Myers Squibb, Varian Medical Systems, Novartis, Roivant, Bayer, Myovant Sciences, Tempus, and POINT Biopharma; reports performing consulting/advisory role or has stock/other ownership interests in Serimmune, BlueStar Genomics, and Artera; and receives research funding from Zenith Epigenetics. DS reports consulting/advisory role with AstraZeneca, Bayer, Boston Scientific, Janssen, Novartis, Myovant, Pfizer, GammaTile, Elekta, and Varian. KP reports consulting/advisory role with CUE Biopharma, GloriousMed Technology, and Akrevia Therapeutics; reports leadership, travel/accommodations/expenses, and stock/other ownership interests with CUE Biopharma; stock/other ownership interests with Keystone Biopharma; stock/other ownership interests with Medsyn Biopharma, Oncopia Therapeutics; and research funding from Progenics. SG reports consulting/advisory role with Bayer, MSD Oncology, Amgen, Pfizer, Bristol-Meyers Squibb, Telix Pharmaceuticals, AAA HealthCare, Orion, Novartis, Modra Pharmaceuticals, Myriad Genetics, AstraZeneca, TOLREMO, Silvio Grasso Consulting, WebMD/Medscape, ESMO, Swiss Academy of Multidisciplinary Oncology, Swiss group for Clinical Cancer Research, German-speaking European School of Oncology, Radiotelevisione Svizzera Italiana, and ProteoMediX; also reports travel/accommodations/expenses covered by AstraZeneca. GA reports consulting/advisory role, speakers' bureau, travel/accommodations/expenses, honoraria, research funding from Janssen-Cilag; consulting/advisory role with Veridex, Novartis, Millennium; consulting/advisory role, speakers' bureau, travel/accommodations/expenses covered by Ventana Medical Systems; consulting/advisory role, speakers' bureau, travel/accommodations/expenses, honoraria from Astellas Pharma; consulting/advisory role, travel/accommodations/expenses covered by Medivation, Abbott Laboratories, ESSA, Bayer, and Pfizer; consulting/advisory role and is on the speaker's bureau for AstraZeneca; consulting/advisory role, speakers' bureau, travel/accommodations/expenses covered by Ferring; is on the speakers' bureau for Takeda, Sanofi, Ipsen; has received ICR rewards to inventors of abiraterone acetate (patent/royalty/other intellectual property); and reports research funding from Arno Therapeutics and Innocrin Pharma. NDJ reports honoraria, consulting/advisory role, speakers' bureau, research funding, travel/accommodations/expenses covered by Sanofi and Janssen; honoraria, consulting/advisory role, speakers' bureau, and research funding from Astellas Pharma; honoraria and consulting/advisory role with Bayer; consulting/advisory role with Clovis Oncology and EUSA Pharma; reports consulting/advisory role with and research funding from Pfizer; is on the speakers' bureau for Pierre Fabre, Ferring, and Merck; is on the speakers' bureau and received research funding from AstraZeneca; and research funding from Novartis. TL reports consulting/advisory role with Janssen Oncology; research funding from Ventana Medical Systems, Deep Bio, AIRA Matrix, and Exact Sciences.

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