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Original Article

Validation of an artificial intelligence-based prognostic biomarker in patients with oligometastatic Castration-Sensitive prostate cancer

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A B S T R A C T

Background: There is a need for clinically actionable prognostic and predictive tools to guide the management of oligometastatic castration-sensitive prostate cancer (omCSPC).

Methods: This is a multicenter retrospective study to assess the prognostic and predictive performance of a multimodal artificial intelligence biomarker (MMAI; the ArteraAI Prostate Test) in men with omCSPC (n = 222). The cohort also included 51 patients from the STOMP and ORIOLE phase 2 clinical trials which randomized patients to observation versus metastasis-directed therapy (MDT). MMAI scores were computed from digitized histopathology slides and clinical variables. Overall survival (OS) and time to castration-resistant prostate cancer (TTCRPC) were assessed for the entire cohort from time of diagnosis. Metastasis free survival (MFS) was assessed for the trial cohort from time of randomization.

Results: In the overall cohort, patients with a high MMAI score had significantly worse OS (HR = 6.46, 95 % CI = 1.44–28.9; p = 0.01) and shorter TTCRPC (HR = 2.07, 95 % CI = 1.15–3.72; p = 0.015). In a multivariable Cox model, MMAI score remained the only variable significantly associated with OS (HR = 6.51, 95 % CI = 1.32–32.2; p = 0.02). In the subset of patients randomized in the STOMP and ORIOLE trials, high MMAI score corresponded to improved MFS with MDT (p = 0.039) compared to patients with a low score, with $p_{interaction} = 0.04$.

Conclusion: The ArteraAI MMAI biomarker is prognostic for OS and TTCRPC among patients with omCSPC and may predict for response to MDT. Further work is needed to validate the MMAI biomarker in a broader mCSPC cohort.

Introduction

Prostate cancer is the leading cause of non-cutaneous cancer in men in the United States and Europe [1]. The incidence of metastatic prostate cancer has been increasing since 2010, with most deaths occurring within 5 years of diagnosis [2]. This underscores the need for clinically

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actionable prognostic and predictive tools for patients with metastatic castration-sensitive prostate cancer (mCSPC) [3,4]. Randomized clinical trials (RCTs) have highlighted a state of limited metastatic disease within mCSPC termed oligometastatic castration-sensitive prostate cancer (omCSPC) that derives a progression-free survival (PFS) benefit from metastasis-directed therapy (MDT) [5–8]. However, the clinical trajectory of omCSPC and responses to MDT are variable and depend on underlying disease biology [9,10].

Emerging evidence supports the use of multimodal artificial intelligence (MMAI) biomarkers that leverage hematoxylin and eosin (H&E) stained histopathology images and clinical data to guide risk-stratification and treatment in patients with cancer [11,12]. The ArteraAI Prostate Test is an AI-derived biomarker with prognostic and predictive outputs to inform the management of patients with localized prostate cancer. It is now supported by NCCN Guidelines (4.2024) as a risk stratification and predictive tool for localized prostate cancer, and is recommended with Simon level IB data based on validation in prospective RCTs [11–13]. Here, we aim to evaluate the multimodal artificial intelligence (MMAI) prognostic biomarker within the setting of omCSPC, including men treated in two omCSPC prospective RCTs (STOMP and ORIOLE).

Materials and methods

We performed a multi-institutional retrospective study of men (n = 222) with omCSPC, defined as ≤ 5 lesions on either conventional (CT or nuclear medicine bone scan) or molecular (PSMA or choline PET) imaging. H&E-stained slides of prostate biopsy or prostatectomy specimen were digitized at 40x magnification. MMAI prognostic score was generated as previously described incorporating AI-detected digital pathology features and select clinical data including age, PSA, and T stage (Prostate Prognostic Model Version 1.2) [11,12]. Patients included those treated at Johns Hopkins Hospital and Ghent Hospital who were treated with standard of care (SOC; n = 171) or enrolled as part of the STOMP (n = 39) and ORIOLE (n = 12) RCTs [5,6], which randomized patients to observation versus MDT. Of these patients, 123 in the SOC group received MDT; 20 in STOMP and 7 in ORIOLE were assigned to the MDT arm. SOC treatments included MDT, ADT (intermittent or continuous), and ADT plus ARSI or docetaxel.

The primary objective was to evaluate overall survival (OS) between patients with high- and low-MMAI scores. The secondary objective in the entire cohort was to evaluate time to castration-resistant prostate cancer (TTCRPC). Both OS and TTCRPC were assessed from time of diagnosis and visualized using the Kaplan-Meier method and log-rank test. A univariable Cox regression model was used to evaluate the association between clinical variables and outcomes. A multivariable Cox model for OS was built using *a priori*-selected covariates (due to small number of OS events): MDT and enhanced systemic therapy with androgen deprivation therapy (ADT) plus androgen receptor signaling inhibition (ARSI) or docetaxel as important treatment variables, and timing (synchronous versus metachronous oligometastatic disease presentation) due to its known prognostic importance [14]. Significance for Cox regression models was calculated using the Wald test.

An additional secondary objective was to evaluate the MMAI score as a biomarker to predict response to MDT within a subset of patients enrolled on the STOMP and ORIOLE RCTs. Given too few OS and castration-resistance events for this subset, we evaluated MMAI for metastasis-free survival (MFS). MFS was defined from time of randomization to development of a new metastasis (by conventional or molecular imaging) or death from any cause. Molecular imaging detected metastasis were required to have a correlate lesion on the CT portion of PET-CT. For the STOMP/ORIOLE subset of patients, an interaction test was performed between MDT treatment and MMAI score.

Results

MMAI scores were calculated for 222 men with omCSPC. Median follow-up was 41.4 months. Patient characteristics are detailed in Table 1. Patients with high MMAI scores (>0.527) had higher PSA at metastasis (median 5.35 vs 3.00, p = 0.008), higher Gleason score (69.4 % vs 39.6 % Grade Group ≥ 4, p < 0.001), greater percentage of synchronous metastatic disease (28.2 % vs 8.1 %, p < 0.001), and were more likely to have bone metastases (55.5 % vs 39.6 %, p = 0.019).

Patients with a high MMAI score had significantly worse overall survival (OS) on univariable Cox regression (HR = 6.46, 95 % CI = 1.44–28.9; p = 0.01) (Table 2). MMAI score outperformed all other clinical variables assessed. In the multivariable Cox regression using prespecified variables, MMAI score was the only variable significantly associated with OS (HR = 6.51, 95 % CI = 1.32–32.2; p = 0.02) (**Table S1**). The median OS was 108.4 months for the MMAI-high group versus "not reached" for the MMAI-low group (Fig. 1, p = 0.005). Given most patients had metachronous disease treated with MDT, we also evaluated the prognostic impact of MMAI score in this more clinically

Table 1
Patient Characteristics.

	MMAI Low (n = 111)	MMAI High (n = 111)	P value
PSA at diagnosis (ng/mL)	5.95 (2.26–10.05)	9.61 (5.00–35.40)	<0.001
Gleason Grade Group			< 0.001
< 4	67 (60.4 %)	34 (30.6 %)	
≥ 4	44 (39.6 %)	77 (69.4 %)	
PSA at metastasis	3.00 (1.09–8.63)	5.35 (1.44–26.28)	0.008
Age at metastasis (years)	68.0 (63.02–72.2)	67.0 (62.0–72.0)	0.274
Number of Metastasis			0.195
1	59 (53.2 %)	43 (38.7 %)	
2	22 (19.8 %)	43 (38.7 %)	
3	25 (22.5 %) (25)	16 (14.4 %)	
4	2 (1.8 %)	8 (7.2 %)	
5	3 (2.7 %)	1 (0.9 %)	
Disease Timing			< 0.001
Metachronous	102 (91.9 %)	79 (71.2 %)	
Synchronous	9 (8.1 %)	32 (28.8 %)	
Pelvic LN	55 (49.5 %)	48 (43.6 %)	0.38
Distant LN	23 (20.7 %)	24 (21.8 %)	0.84
Bone	44 (39.6 %)	61 (55.5 %)	0.019
Visceral	4 (3.6 %)	1 (0.91 %)	0.18
ADT	44 (39.6 %)	53 (47.7 %)	0.18
MDT	84 (75.7 %)	66 (59.4 %)	0.009
Enhanced Systemic Therapy*	15 (13.5 %)	5 (4.5 %)	0.019

*ADT + ARSI/Docetaxel.
ADT: Androgen Deprivation Therapy; ARSI: Androgen Receptor Signaling Inhibitor; LN, lymph node; MDT: Metastasis Directed Therapy; PSA: prostate specific antigen. Continuous variables reported as Median (IQR).

Table 2
Univariable Cox regression for OS.

Variable	HR (95 % CI)	p-value
MMAI (high vs low)	6.46 (1.44–28.9)	0.01
Timing (synchronous vs metachronous)	3.83 (1.24–11.9)	0.02
ADT	2.42 (0.86–7.11)	0.11
Enhanced systemic therapy	2.12 (0.46–9.77)	0.33
iPSA	1.00 (0.99–1.01)	0.48
Grade Group ≥ 4	1.25 (0.43–3.61)	0.68
PSA at metastasis	1.00 (0.98–1.02)	0.92
MDT	1.04 (0.34–3.22)	0.94

HR, hazard ratio; MMAI, multimodal artificial intelligence; ADT, androgen deprivation therapy; iPSA, initial prostate-specific antigen; MDT, Metastasis Directed Therapy.

homogenous cohort (Fig. S1), which similarly demonstrated that high MMAI score associated with worse OS (p = 0.029). High MMAI score was also associated with shorter TTCRPC (HR = 2.07, 95 % CI = 1.15–3.72; p = 0.015), with median TTCRPC of 74 months for the MMAI-high group versus 113 months for the MMAI-low group (Fig. 1, p = 0.013).

In the STOMP/ORIOLE subset (N = 51, median follow-up 64 months), MMAI score was not prognostic for MFS (HR = 0.78, 95 % CI = 0.39–1.58; p = 0.50) (Fig. S2). However, MMAI score appeared to predict for MDT benefit. Patients with MMAI-high (p = 0.039) but not MMAI-low (p = 0.69) demonstrated improved MFS with MDT (Fig. 2). The test for interaction between MDT treatment and MMAI score showed p = 0.04.

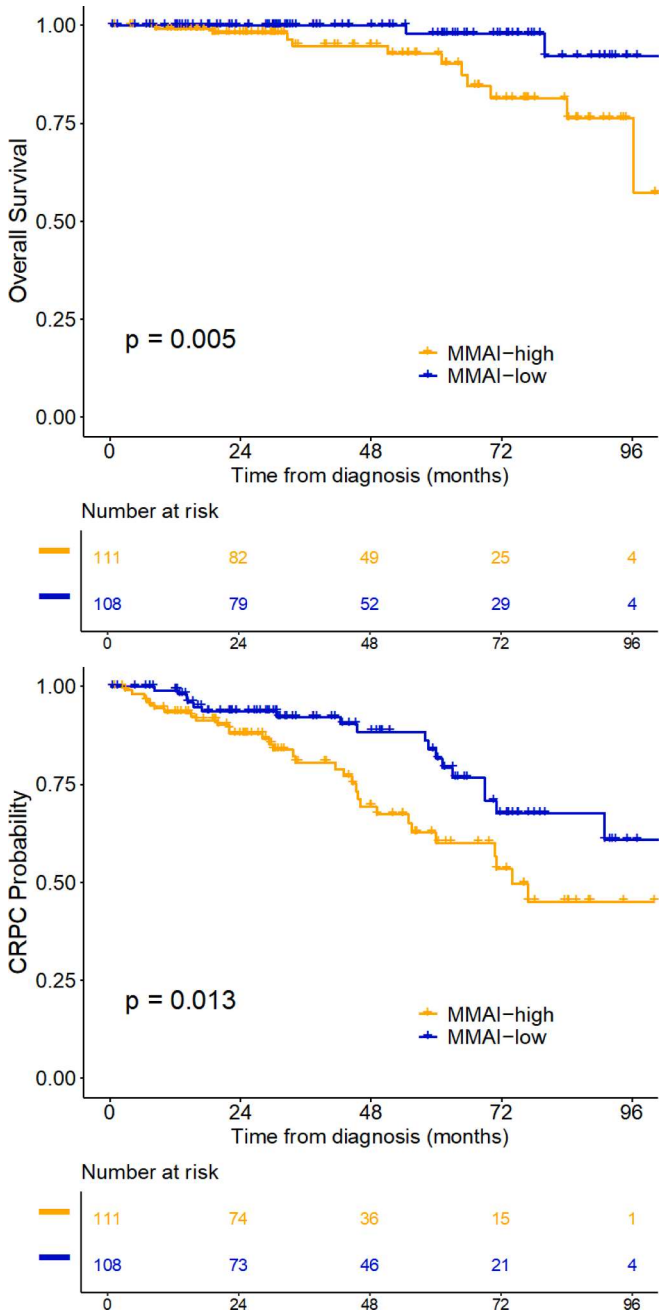

Fig. 1. Kaplan-Meier estimates of overall survival (OS) and time to castration-resistant prostate cancer (TTCRPC) for oligometastatic castration-sensitive prostate cancer (omCSPC) stratified by MMAI score. P-value computed using log-rank test.

Discussion

This study demonstrates for the first time that the ArteraAI MMAI biomarker is prognostic for OS and TTCRPC in patients with omCSPC. Previously, the MMAI biomarker has been shown to be prognostic in localized prostate cancer and predictive for treatment benefit with androgen deprivation therapy [11–13], and was included in the 2024 NCCN guidelines based on a significant improvement in performance over standard risk stratification groups. An advantage of the MMAI model is the ability to use digitized information from routine histology slides at diagnosis (H&E-stained slides created from biopsies during routine care). This has the potential for wide availability and rapid turnaround time as compared to other types of molecular tissue or serum-based markers being investigated for prognostic value [15].

This study also showed that high MMAI score appears to predict benefit of MDT for patients randomized to MDT versus observation in the STOMP and ORIOLE RCTs. Previous work describing a prognostic high-risk genomic signature (based on mutations in *TP53*, *BRCA1/2*, *RB1*, or *ATM*) for omCSPC showed a trend towards prediction of response to MDT [9]. In contrast, the prognostic MMAI score was able to stratify patients into those that benefit most from MDT, which is an unmet need in the omCSPC setting. Importantly however, these findings are limited to benefit of MDT over observation and may not translate in the setting of ADT ± ARSI/docetaxel.

There are other limitations to this study including its retrospective nature. Therefore, the results can be construed as largely hypothesis generating. Furthermore, the MMAI algorithm applied in this cohort was initially trained on data from RCTs of localized prostate cancer rather than metastatic disease. Additionally, most of the cohort presented with metachronous omCSPC (91.9 % for MMAI-low and 71.8 % for MMAI-high cohorts), limiting interpretation of this study for synchronous omCSPC. While the MMAI score was prognostic for OS in the overall cohort (N = 222), it was not prognostic for MFS in the STOMP and ORIOLE subgroup (N = 51), which may be due to small sample size.

In conclusion, we show for the first time in this retrospective study that the ArteraAI MMAI biomarker is prognostic for overall survival and

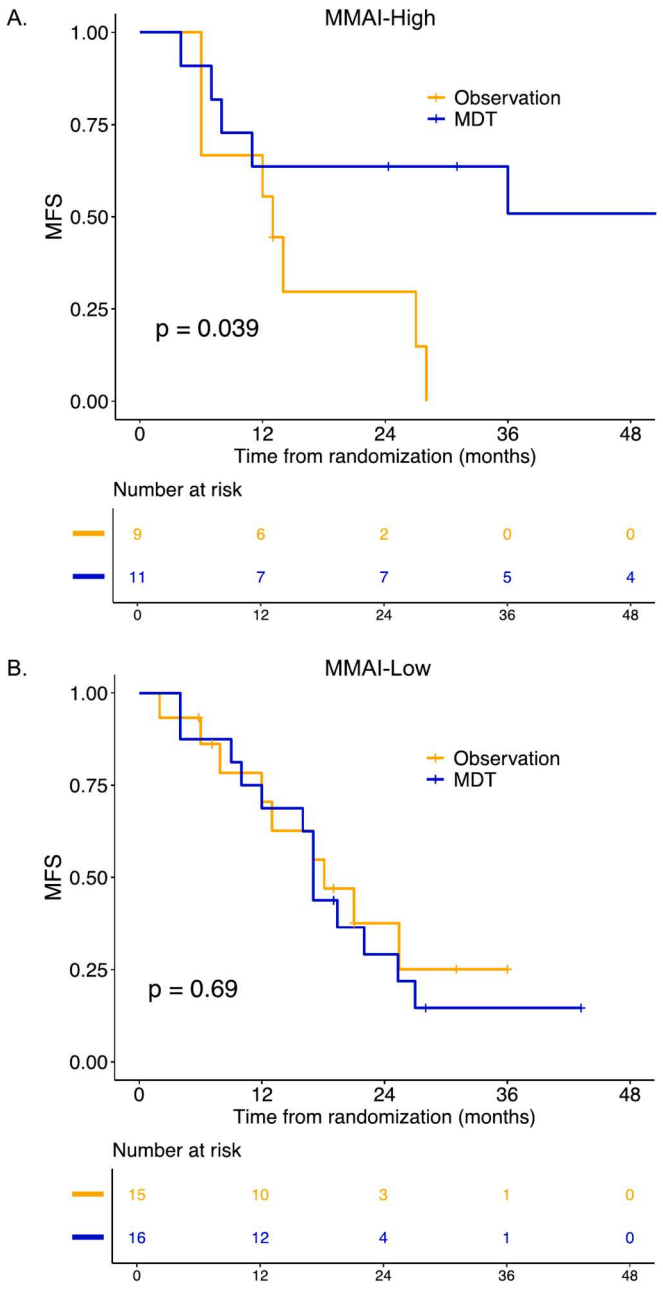

Fig. 2. Kaplan-Meier estimates of metastasis free survival (MFS) for patients in the STOMP and ORIOLE clinical trials randomized to MDT versus observation stratified by high (A) versus low (B) MMAI-score. P-value computed using log-rank test.

time to castration-resistance among patients with omCSPC and can identify responders to MDT. Further work validating the MMAI biomarker in a broader omCSPC cohort will help to clarify its utility in risk stratification and guidance for use of other standard of care therapies.

CRediT authorship contribution statement

Jarey H. Wang: Writing – review & editing, Writing – original draft, Visualization, Software, Methodology, Investigation, Formal analysis, Data curation. **Matthew P. Deek:** Writing – review & editing, Data curation, Conceptualization. **Adrianna A. Mendes:** Writing – review & editing, Investigation, Data curation. **Yang Song:** Investigation, Formal analysis, Data curation. **Amol Shetty:** Investigation, Formal analysis, Data curation. **Soha Bazyar:** Writing – review & editing, Data curation. **Kim Van der Eecken:** Writing – review & editing, Investigation, Data curation. **Emmalyn Chen:** Writing – review & editing, Methodology, Data curation. **Timothy N. Showalter:** Writing – review & editing, Resources, Methodology, Data curation. **Trevor J. Royce:** Writing – review & editing, Resources, Methodology, Data curation, Resources, Methodology, Data curation. **Tamara Todorovic:** Resources, Methodology, Data curation. **Huei-Chung Huang:** Writing – review & editing, Methodology, Investigation, Data curation. **Scott A. Houck:** Writing – review & editing, Supervision, Methodology, Investigation, Data curation. **Rikiya Yamashita:** Resources, Methodology. **Ana P. Kiess:** Writing – review & editing, Resources, Investigation. **Daniel Y. Song:** Writing – review & editing, Resources, Investigation. **Tamara Lotan:** Resources, Methodology, Data curation. **Theodore DeWeese:** Writing – review & editing, Supervision, Resources. **Luigi Marchionni:** Writing – review & editing, Resources, Investigation. **Lei Ren:** Writing – review & editing, Resources, Investigation. **Amit Sawant:** Writing – review & editing, Resources, Investigation. **Nicole Simone:** Writing – review & editing, Resources, Investigation. **Alejandro Berlin:** Writing – review & editing, Supervision, Resources, Investigation. **Cem Onal:** Writing – review & editing, Resources, Investigation. **Andre Esteva:** Resources, Project administration, Methodology, Conceptualization. **Felix Y. Feng:** Resources, Project administration, Methodology, Conceptualization. **Phuoc T. Tran:** Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Investigation, Funding acquisition, Conceptualization. **Philip Sutera:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Piet Ost:** Writing – review & editing, Supervision, Resources, Project administration, Methodology, Investigation, Data curation, Conceptualization.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: PTT declares a consulting/advisory role and patent with Natsar Pharmaceuticals (Compounds and methods of use in ablative radiotherapy. Patent filed 3/9/2012. PCT/US2012/028475. PCT/WO/2012/122471) licensed with royalties to Natsar Pharmaceuticals. Consulting/advisory role and research funding with Reflexion Medical and Bayer Health. Consulting/advisory role with Regeneron, Dendreon, Noxopharm, Janssen, Myovant Sciences, AstraZeneca, Pfizer, Lantheus. FYF is a consultant for Janssen, Astellas Pharma, Serimmune, Foundation Medicine, Exact Sciences, Bristol-Myers Squibb, and Varian Medical Systems; advisor and stock options at Artera Inc; stock options for serving on the advisory boards from BlueStar Genomics and SerImmune. APK receives research funding from Advanced Accelerator Applications/Novartis (Inst), Merck (Inst), Bayer (Inst), Novartis Pharmaceuticals UK Ltd. PO reports a relationship with Janssen, Advanced Accelerator Applications, Curium, Bayer and MSD that includes: consulting or advisory. Piet Ost reports a relationship with Bayer and Varian that includes: funding grants. EC, TNS, TJR, TT, H-CH, SAH, RY, and AE are employed by Artera Inc. All remaining authors have declared no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2024.110618.

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