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ORIGINAL RESEARCH

Validation of a Combined Prognostic Score Using Plasma Tumor DNA and Clinical Features in Metastatic Castration-Resistant Prostate Cancer Patients Treated with Taxanes

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Purpose: There is an urgent need of biomarkers to personalize metastatic castration-resistant prostate cancer (mCRPC) treatment. A new prognostic model described by our group combines molecular characteristics (ptDNA levels), metabolic features from PET-scans (metabolic tumor volume), clinical parameters (visceral metastases), and lab tests (lactate-dehydrogenase levels) in abiraterone or enzalutamide-treated patients. This study aims to validate the score on mCRPC patients undergoing taxane treatment.

Patients and Methods: Twenty-eight patients affected by mCRPC, pre-treated with abiraterone or enzalutamide, candidate for taxane-based treatments, have been prospectively evaluated. All patients underwent a basal PET/CT scan with F-choline and blood samples. The prognostic model previously described was applied to this population; based on the partial results of the parameters, we assigned the patients into three risk groups.

Results: In the 28 patients evaluated, we observed a different median OS among the three risk groups (risk group I, 18.1 months [95% CI: 15.2–33.1 months]; risk group II, 12.7 months [4.9–18.6 months]; and risk group III, 10.1 months [3.4–15.4 months]; p = 0.012). Statistically significant differences were also observed for PFS.

Conclusion: The prognostic score has confirmed to be a good prognostic tool also in a more advanced cohort of patients treated with taxanes. This tool may represent a valid method to refine prognostication and treatment selection in a cohort of patients where biomarkers are scarce.

Keywords: metastatic castration-resistant prostate cancer, cabazitaxel, prognostic score, ptDNA, taxanes

Introduction

Prostate cancer (PCa) is the most frequent neoplasm among men in the majority of countries worldwide.[1] Pca is a heterogeneous disease, characterized by high variability in clinical outcomes. To date, several studies are evaluating the role of prognostic tools, such as Androgen Receptor splice Variants (AR-Vs), AR-gain, BReast CAncer gene (BRCA) status, Cyclin-Dependent Kinase (CDK)-12; however, the high costs and the lack of prospective validation in clinical trials represent the main limitations to their use in the daily clinical practice.[2] Due to several limitations of molecular profiling on metastatic lesions (poorly accessible metastases, intrapatient and tumor heterogeneity, etc), there has been an increasing interest in the use of blood-based biomarkers, through the so-called liquid biopsies, to better characterize tumor molecular drivers and response to treatments. Nucleic acids, proteins, cells and vesicles, circulate in human blood and can be isolated using various molecular techniques.[3,4] The portion of circulating cell-free DNA (cfDNA) derived by

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tumor is named circulating tumor DNA (ctDNA) or plasma tumor DNA (ptDNA).[5] The ptDNA fraction depends on disease setting and tumor spread and can range from 1% or below at the initial stages of the disease, to 90% in patients with high-volume progressing castration-resistant prostate cancer (CRPC) metastases.[6–8] The analysis of ptDNA in mCRPC patients allows to identify genomic features of the tumor. When ptDNA is sufficiently high, there is a strong concordance with tissue findings for the detection of genomic alterations present in concurrently collected metastases biopsies.[9] The presence of a low tumor fraction could be a technical limitation for plasma DNA analyses. However, the introduction of new genomic technologies with high sensitivity and specificity, including next-generation sequencing (NGS), has positively contributed to the study of ptDNA.[10] In prostate cancer, ptDNA itself has been studied as a biomarker. Detection of ptDNA is prognostic, and a change in ptDNA levels during anticancer treatments is associated with differential outcomes with anticancer treatments. An association between pre-treatment ptDNA fraction, assessed by NGS, and clinical outcome was shown in PCa.[7,8,11–13] A randomised Phase 2 study evaluating 202 mCRPC patients treated with first-line abiraterone or enzalutamide showed that low pre-treatment ptDNA fraction was correlated with a good prognosis.[14]

The role of ptDNA changes in response to treatment, also termed plasma DNA dynamics, has also been evaluated as an early assessment of therapy efficacy for mCRPC. Patients with an increase in ptDNA fraction had a significantly increased risk of progression at 3-month radiographic assessment, conversely, patients with a decrease in ptDNA fraction had a significantly higher chance of having a response to anticancer treatments.[15]

PtDNA has been used to identify biomarkers of resistance to cabazitaxel in metastatic castration-resistant prostate cancer patients. In a recent work, ptDNA changes from baseline to cycle 3 were strongly associated with outcomes, both for overall survival (OS) and progression-free survival (PFS).[16] These results highlighted the potential of adding ptDNA assessment to routine monitoring of mCRPC patients. Studies about prognostic biomarkers in mCRPC patients are not limited to molecular features but also include numerous clinical, laboratory and metabolic imaging-related elements that have been correlated with outcomes. The role of F^{18}Choline-PET (FCH)-derived parameters to predict the clinical outcome of mCRPC patients treated with abiraterone or enzalutamide has been studied, and whole-body tumor burden parameters based on metabolic tumor volume (MTV) and total lesion activity (TLA) measured by FCH-PET were found to be prognostic.[17] In addition, the presence of visceral metastases appears to be an important predictor of clinical outcome in mCRPC patients treated with both hormonal agents and taxanes but also with radiometabolic therapies such as Lutetium-labelled prostate-specific membrane antigen (Lu-PSMA).[18–21] Lactate dehydrogenase (LDH) is a key enzyme in the last step of the glycolysis pathway and is related to the glycolysis level of the tumor. It has been demonstrated that there is a linear correlation between LDH levels and the progression of PCa; higher LDH levels are associated with higher risk of tumor progression.[22]

In a previous work, the prognostic role of the combination among molecular, clinical, and radiological features of 102 patients with mCRPC receiving abiraterone or enzalutamide was assessed showing that ptDNA, MTV and serum lactate dehydrogenase together with visceral metastasis were independent predictors of both OS and PFS.[23] In the present study, we sought to interrogate the novel prognostic model in a more advanced cohort of patients treated with taxanes and to further validate the prognostic score.

Materials and Methods

Patient Population and Data Collection

Patients included in the analysis were all treated at the Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", in Meldola, Italy. In this work, we analyzed the data of 28 mCRPC patients pretreated with at least one of abiraterone or enzalutamide and eligible for a taxane-based treatment (docetaxel or cabazitaxel). Ten patients received cabazitaxel and 18 patients were treated with docetaxel. All patients treated with cabazitaxel have been previously treated with docetaxel, according to prescriptive rules in Italy. Docetaxel has been administered at the initial dosage of 75 mg/mq and cabazitaxel has been administered at 25 mg/mq. Both treatments were conducted every 3 weeks. Dose reductions have been performed according to clinical or toxicity criteria. Taxane treatment was continued up to a maximum of 10 cycles or until disease progression.

Relevant data from all consenting patients after registration were electronically collected. The collected data included demographic details, primary treatments for prostate cancer, tumor characteristics, treatment timelines, hormonal regimens, administered chemotherapies, and outcome data as disease progression or follow-up status. Progressive disease has been defined according to Prostate Cancer Working Group 2 (PCWG2) progression criteria.[24]

PtDNA Analysis

Blood samples collection has been conducted within a previously established prospective biological study (IRST-B073, approval nr. L3P1380), in our Institution.

Patients underwent baseline blood sampling prior to treatment start, after 3 months, and at disease progression. Blood samples have been stored in the Bioscience laboratory of the Institute. Peripheral blood of patients was collected and stored at −80°C for the subsequent molecular analyses. Genomic DNA was extracted with QIAamp DNA mini kit (Qiagen) and quantified using Qubit dsDNA BR Assay kit (Thermo Fisher Scientific).

PtDNA analysis has been performed in Biosciences Laboratory of IRST. Cell-free DNA was extracted from 1 to 2 mL of plasma with the QIAamp Circulating Nucleic Acid Kit (Qiagen, Santa Clarita, CA, USA) and quantified by spectrophotometric evaluation (NanoDrop_ ND-1000; Celbio, Milan, Italy) or Quant-iT High Sensitivity Pico-Green Double-Stranded DNA Assay Kit (Invitrogen, Carlsbad, CA, USA). In plasma and patient-matched germline DNA, targeted NGS was assessed by the PGM Ion Torrent using a 316 or 318 Chip aiming to reach 10009 coverage per target. The ptDNA fraction for each plasma sample has been estimated using an ad-hoc customized computational tool (CLONET). CLONET is a computational tool used to estimate the clonality of somatic genomic aberrations in tumors. It is designed to compute the clonality of somatic copy number changes, point mutations, and rearrangements in a coherent mathematical model enabling the estimation of the clonal composition of a tumor sample, and allow to estimate the fraction of tumor DNA within total cfDNA.[25] This computational tool is able to detect the presence of ptDNA in samples with >0.05 ptDNA.

Positron Emission Tomography/Computed Tomography (PET/CT) Scans

Before starting the new treatment line with taxanes, each patient underwent a PET/CT scan with F-choline for baseline tumor staging. PET scans have been performed at the Department of Nuclear Medicine at IRST, Meldola (Italy).

FCH-PET/CT scans were carried out on an integrated PET/CT system (Discovery LS camera; General Electric Medical Systems, Waukesha, WI, USA) in 2D acquisition mode for 3 min per bed position. The PET/CT scan takes 45 min after intravenous injection of 18F-methylcholine (3.7 MBq_kg _1 of body weight, AAA-Advanced Accelerator Applications, Meldola, Italy). The field of view included the skull to midfemurs. Low dose CT (120 kV, 80 mA) without contrast agents was made for attenuation correction and as an anatomical map. The emission data were adjusted for scatter, random coincidence events, and system dead time.

Semiquantitative criteria based on the maximum standardized uptake value (SUVmax) and the target-to-background ratio were utilized to aid the visual analysis. The metabolic tumor volume (MTV) parameter was obtained by adding each three-dimensional volume of interest, and for each lesion volume and SUV mean was multiplied and then summed to have the total lesion activity (TLA).

Metabolic features, such as SUVmax, TLA and MTV were evaluated analyzing images of F^{18}CH PET/CT with the involvement of nuclear medicine specialists.

Statistical Analysis

Progression-free survival was considered as the time between the first day of taxane-based therapy and the date of progression disease or death (whichever came first). Overall survival was considered as the time between the first day of taxanes treatment and the date of death from any cause or the date of the last follow-up visit.

In the original work by Conteduca et al,[23] the prognostic score was obtained considering the presence or absence of visceral metastases and the presence of values (MTV value on choline PET scans, ptDNA levels, serum LDH levels) higher or lower than a statistically defined median. A risk score was so obtained to allocate each patient in pre-defined risk classes (I–III). Prognostic scores were generated, with the identification of three groups of patients with significantly

Table 1 Multivariable Analysis of Overall Survival (OS) After Backward Stepwise Procedure in the Training Cohort

	Factor Estimate (Standard Error)	Standard Error	P	HR (95% CI)	Partial Score
MTV	0.599	0.268	0.026	1.82 (1.08–3.08)	1.00
ptDNA	0.848	0.289	0.003	2.34 (1.32–4.12)	1.40
Visceral metastasis	1.033	0.383	0.007	2.81 (1.33–5.95)	1.70
Serum LDH, U L^{-1}	1.239	0.331	0.0002	3.45 (1.81–6.60	2.10
Risk groups	**No pts (%)**				**Total score**
I	22 (33.9)				< 1.4
II	24 (36.9)				1.4–2.8
III	19 (29.2)				> 2.8

Abbreviations: MTV, metabolic tumor volume; ptDNA, plasma tumor DNA; LDH, lactate dehydrogenase; HR, hazard ratio; U-L, upper-limit.

different median OS and PFS. From a statistical point of view, categorical variables were summarized using frequency whereas continuous variables were described using median value and interquartile range. In the reference work, median fraction of ptDNA before starting treatment was 0.188 (0.014–0.96). The association between categorical variables was determined using the chi-squared or Fisher's exact test, as appropriate. Spearman correlation was used to assess the association between continuous variables. Univariable and multivariable Cox regression models were used to explore potential factors able to predict PFS and OS and to estimate hazard ratios (HR) and their 95% confidence interval (CI).

A Weibull multiple-regression model to assess the matched impact of molecular, laboratory and imaging characteristics on outcome was used. From a full model including these factors, a final parsimonious model by using a backward selection procedure was achieved. The prognostic score was built on the final model consisting of the four previously cited factors. Partial scores were procured by splitting the value of each regression coefficient by the smallest regression coefficient. The total score for each patient resulted from a sum of appropriate partial scores, and three patient groups with different median survival probabilities were recognized. For OS, if the total score was below 1.4, between 1.4 and 2.8, and >2.8, patients were classified as group I, group II and group III, respectively. For PFS, if the total score was 1 or below, between 1.0 and 2.1, and >2.1, patients were classified as group I, group II and group III (Tables 1 and 2, respectively[23]). The numerical value of each partial score and its relative weight is directly proportional to the prognostic power of each single parameter.

This model was adopted for the population considered in this study. For each patient, we obtained and recorded in a specific spreadsheet the values relating to the 4 factors considered within the prognostic score described previously.

Table 2 Multivariable Analysis of Progression-Free Survival (PFS) After Backward Stepwise Procedure in the Training Cohort

	Factor Estimate (Standard Error)	Standard Error	P	HR (95% CI)	Partial Score
MTV	0.586	0.271	0.031	1.80 (1.06–3.06)	1.00
ptDNA	0.645	0.266	0.015	1.91 (1.13–3.21)	1.10
Visceral metastasis	0.997	0.424	0.019	2.71 (1.18–6.22)	1.70
Serum LDH, U L^{-1}	1.204	0.323	0.0002	3.33 (1.77–6.27)	2.05
Risk groups	**No pts (%)**				**Total score**
I	15 (23.1)				< 1.0
II	34 (52.3)				1.0–2.1
III	16 (24.6)				> 2.1

Abbreviations: MTV, metabolic tumor volume; ptDNA, plasma tumor DNA; LDH, lactate dehydrogenase; HR, hazard ratio; U-L, upper-limit.

Depending on the individual scores obtained in the 4 elements considered, the patients were distributed into the three risk classes (I–III).

Survival curves for each risk class were estimated by the Kaplan–Meier method, and comparisons were made using the logrank test. All P-values were two-sided, and a $P < 0.05$ was defined as statistically significant. Statistical analyses were done with SAS 9.4 software (SAS Institute, Cary, NC, USA).

Ethics Statement

The study was performed in accordance with the Good Clinical Practice and the Declaration of Helsinki. Each patient provided informed consent. The study protocol was approved by the ethics committee active at the Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", in Meldola, Italy, since 2017. All the patients enrolled in the study have been followed up within a pre-existing prospective biological study (IRST-B073, approval nr. L3P1380), previously approved by the same local ethics committee.

Results

The clinical characteristics of the study population are presented in Table 3. For each patient, the status of the 4 features considered in the prognostic model was assessed and partial scores were assigned generating a total score. Based on the results of Table 4, each patient was associated with a different risk class. During the observation period, all events in terms of PFS and OS occurred, making the data mature and definitive for analysis. All patients were considered suitable to start treatment with taxanes and the death events occurred in all cases due to progression of oncological disease, minimizing the potential confounding role of any comorbidities.

Table 3 Patients' Characteristics

		Taxane Patients (n=28) n. (%)
Age	≤ 74 yrs	16 (57.1)
	> 74 yrs	12 (42.9)
AR CN	Normal	21 (75)
	Gain	7 (25)
Visceral metastases	No	27 (96.4)
	Yes	1 (3.6)
Gleason score	6–7	12 (46.2)
	8–10	14 (53.8)
Nr. previous line	1–2	18 (64.3)
	> 2	10 (35.7)
ECOG PS	0–1	25 (89.3)
	≥ 2	3 (10.7)
ALP	< 129	21 (75)
	≥ 129	7 (25)
LDH	< 225	18 (64.3)
	≥ 225	10 (35.7)

(*Continued*)

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Table 3 (Continued).

		Taxane Patients (n=28) n. (%)
NLR	< 3	16 (57.1)
	≥ 3	12 (42.9)
CgA	< 120	16 (57.1)
	≥ 120	12 (42.9)
Hb	> 12.5	15 (53.6)
	≤ 12.5	13 (46.4)
Previous prostatectomy	No	16 (57.1)
	Yes	12 (42.9)
Previous radiotherapy	No	16 (57.1)
	Yes	12 (42.9)
PSA (median value)	< 23.24	10 (35.7)
	≥ 23.24	18 (64.3)
MTV (median value)	< 102.79	14 (50)
	≥ 102.79	14 (50)
SUV (max)	< 83.60	9 (32.1)
	≥ 83.60	19 (67.9)
TLA (median value)	< 391,343	28 (100)
	≥ 391,343	0 (0)
ptDNA (median value)	≤ 0.188	10 (35.7)
	> 0.188	18 (64.3)

Table 4 Distribution of Patients in the 3 Risk Classes

Risk Group	No pts (%)	Total Score
I	8 (28.6)	<1.4
II	10 (35.7)	1.4–2.8
III	10 (35.7)	>2.8

Abbreviations: AR CN, androgen receptor copy number; ECOG, Eastern Cooperative Oncology Group; PS, performance status; ALP, Alkaline phosphatase; LDH, lactate dehydrogenase; NLR, neutrophil-to-lymphocyte ratio; CgA, Chromogranin; Hb, Haemoglobin; PSA, prostatic specific antigen; MTV, metabolic tumor volume; SUV, standardized uptake value; TLA, total lesion activity; ptDNA, plasma tumor DNA.

Table 5 Survival Analysis for OS and PFS According to the Three Risk Groups

Risk Groups	N. pts / N. Events	Median OS (Months) (95% CI)	p	Median PFS (Months) (95% CI)	p
I	8/8	18.1 (15.2–33.1)		11.7 (10.0–13.6)	
II	10/10	12.7 (4.9–18.6)		5.0 (3.0–6.9)	
III	10/10	10.1 (3.4–15.4)	0.012	2.8 (0.7–5.0)	0.0006

The four values evaluated in the prognostic model (with their relative scores) were: ptDNA: partial score of 1.4 if over the median value of 0.188; MTV: partial score of 1 if over the median value of 102.79; visceral metastases: partial score of 1.7 if present; LDH: partial score of 2.1 if above the upper limit value of the laboratory.

The survival probability of the three categories of patients was established by the prognostic score. Survival probabilities were assessed by the exponential model and by the Kaplan–Meier method. For the 28 patients evaluated we observed a different median OS among the three risk groups (risk group I, 18.1 months [95% CI, 15.2–33.1 months]; risk group II, 12.7 months [95% CI, 4.9–18.6 months]; and risk group III, 10.1 months [95% CI, 3.4–15.4 months]; p = 0.012).

The survival analysis results are summarized in Table 5. Overall survival curve is shown in Figure 1. The taxane patients group was also evaluated for PFS. Considering the comparable prognostic weight of the four variables included in the prognostic score, we decided to use the same prognostic partial scores evaluated for OS. We observed a different median PFS among the three risk groups (risk group I, 11.7 months [95% CI, 10.1–13.6 months]; risk group II, 5.0 months [95% CI, 3.0–6.9 months]; and risk group III, 2.8 months [95% CI, 0.7–5.0 months]; p = 0.0006). Results of the PFS according to risk groups are summarized in Table 5. The survival curve for PFS is shown in Figure 2.

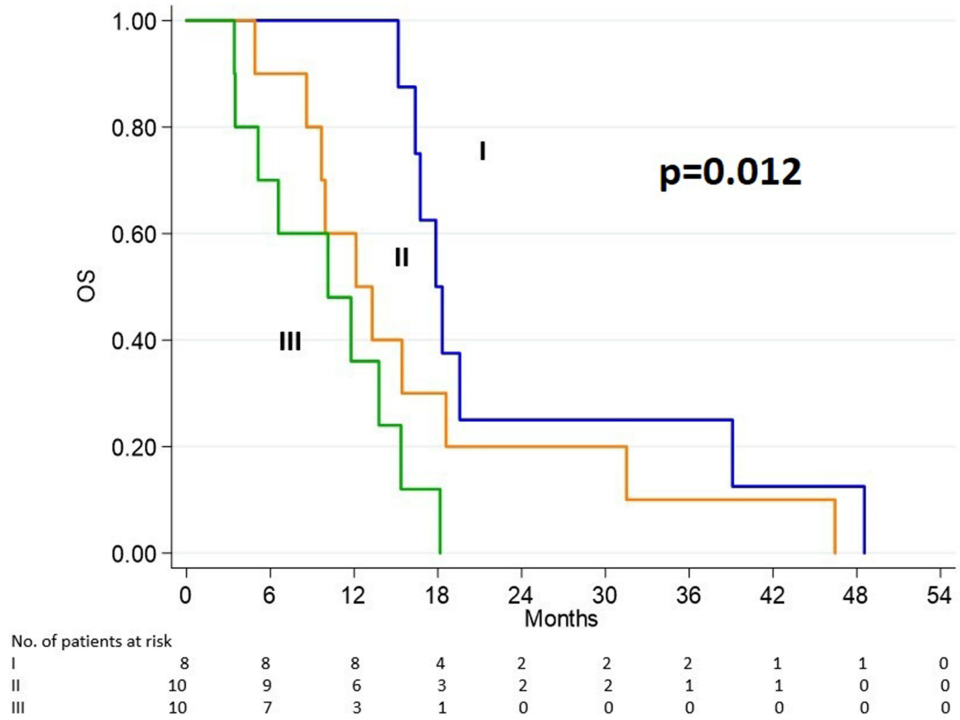

Figure 1 Risk group survival probabilities. Kaplan–Meier curve for overall survival (OS) by OS risk groups.

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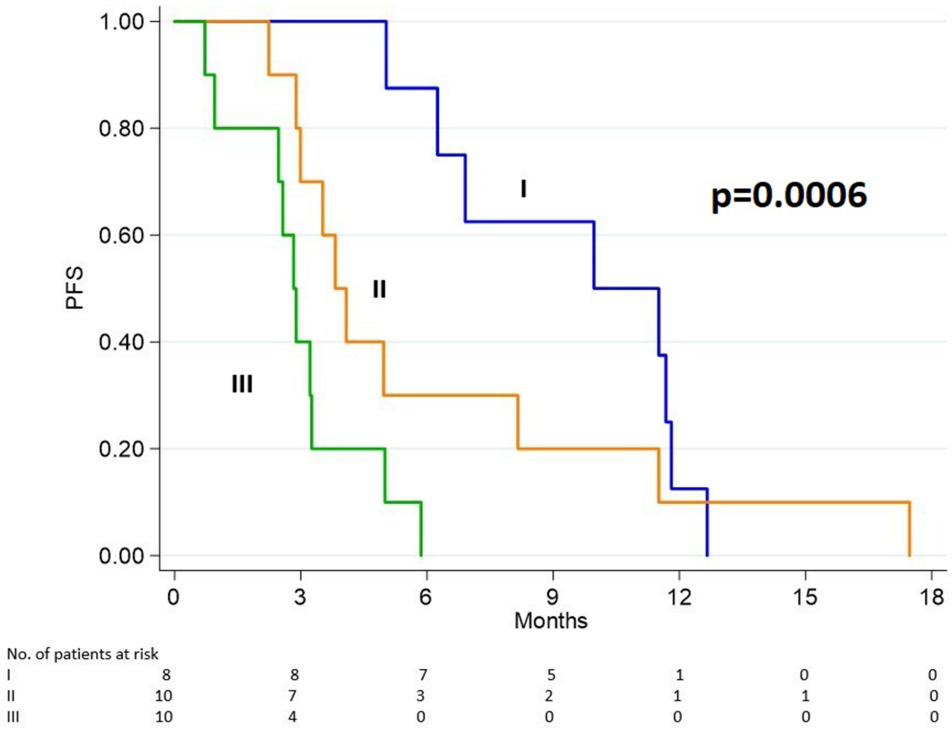

Figure 2 Kaplan–Meier curve for progression-free survival (PFS) by risk groups.

Discussion

In recent years, several prognostic scores have been evaluated by integrating different clinical characteristics and associating them with prognosis in patients with mCRPC undergoing various anticancer treatments.[26–33] Most of these nomograms have had a limited role in clinical practice. The elements considered in the above-mentioned prognostic models included, among the others, the expression of androgen receptor variant 7 (AR-V7) in circulating tumor cells (CTCs), many genetic aberrations involving androgen receptor (AR), PTEN (phosphatase and TENsin homolog), PI3K (phosphatidylinositol 3-kinases)/AKT pathway and Homologous Recombination Repair (HRR).

A recent prospective study showed the utility of integrating functional imaging using 18F-sodium fluoride PET/CT scan and CTC analysis in mCRPC patients treated with enzalutamide.[34] The Authors demonstrated a different expression of AR and AR-V7 in different metastatic sites and also the presence of neuroendocrine markers that may be responsible for a heterogeneous response to enzalutamide.

More recently, the correlation and the prognostic value of cfDNA concentrations and PSMA-positive tumor volume (PSMA-TV) in men with PCa undergoing Ga-PSMA-11 PET imaging has been evaluated.[35] This work demonstrated that cfDNA might be used as a biomarker of advanced, aggressive mCRPC but that it does not reliably reflect total tumor burden or prognosis. In comparison, Gallium-PSMA PET scans seem to provide a better prognostic assessment of tumor burden across the spectrum of PCa disease progression. These studies, however, did not propose a real prognostic tool.

Furthermore, De Laere et al developed a risk stratification system, using both clinical features and TP53-alteration status in liquid biopsy, to stratify patients treated with androgen receptor signaling inhibitors (ARSI) in good or poor prognostic subgroups.[36] No functional imaging data were used in this model.

The work by Conteduca et al,[23] which has been previously described in detail and which represents the basis of development of the present work, sought to improve outcome prediction in mCRPC patients, through the combination of ptDNA analysis and functional imaging. The novel prognostic score proposed and validated in patient treated with abiraterone and enzalutamide, obtained its prognostic power from the demonstration of the association between ptDNA fraction with metabolic tumor activity and the number of lesions, as similarly shown in previous NGS studies on plasma samples from mCRPC.[37,38] This assumption suggests that ptDNA fraction may provide interesting aspects of tumor

biology and volume that may not be exhaustively described only by common clinical factors. The interesting observation that both ptDNA and metabolic tumor activity were independent predictors of clinical outcomes in multivariate regression models promises to increase the accuracy of tumor response prediction and prognostication in mCRPC patients when these two elements are combined within a prognostic score. Conteduca et al[23] also demonstrated that ptDNA levels in plasma are significantly correlated with the number of metastases, clinical variables, and choline uptake parameters like SUVmax, MTV, and TLA in metastatic patients.

A recent poster presented at ESMO 2023 congress, evaluated ptDNA to identify biomarkers of resistance to cabazitaxel in mCRPC patients demonstrating that ptDNA changes from baseline to cycle 3, were strongly associated with outcomes (OS e PFS). These results highlighted the potential of adding ptDNA assessment to routine monitoring of mCRPC patients.[16]

This prognostic score evaluated patients at baseline of treatment with abiraterone and enzalutamide both in pre- and post-docetaxel settings.

In the present work, this prognostic model has been evaluated on further 28 patients. These patients have been treated with docetaxel or cabazitaxel (18 and 10 patients respectively) in a more advanced setting of the disease, considering that in Italy cabazitaxel is approved only after a previous treatment with docetaxel.

We aimed to interrogate the novel prognostic model in a more advanced cohort of patients to further confirm its actual prognostic power. The distribution of patients among the three risk classes is consistent with that reported in the initial work, with the difference of an increased percentage of patients in the highest risk class (36% versus 29%), compatible with the more advanced oncological setting of these patients. This prognostic power was confirmed by positive results and clearly distinct survival curves in OS and PFS, according to risk categories.

We acknowledge some limitations in this study. First, the cohort is quite small, and the monoinstitutional nature of our results could determine regional of institutional biases. On the other hand, however, even with a limited number of patients, the prognostic power of the score was absolutely clear. However, the number of events in terms of OS and PFS in each group make the data stronger.

A further limitation may be the inclusion in the same cohort of both patients treated with cabazitaxel and docetaxel, which are two different drugs. However, the mechanism of action of the two drugs is quite similar, and the setting post-ARSI was the same for all patients, making it possible to consider all patients as a single prognostic group. The availability of validated prognostic scores has a potentially very useful impact in clinical practice. Oncologists have always faced the challenge of defining patients' prognosis with certainty, often causing issues among clinicians in the communications with patients and their families. The prognostic evaluation further validated by this work may allow clinicians to have a better knowledge of the survival probability for different categories of patients, offering more precise data to consider when communicating patients' prognosis. More precise prognostic data may also lead to more informed therapeutic choices. The identification of patients with a particularly negative prognosis, for instance, might allow clinicians to anticipate the discontinuation of potentially useless systemic treatments, avoiding unnecessary side effects and therapeutic obstinacy, and anticipating recourse to palliative and supportive care treatments. Moreover, this could also have implications for the patient's life, both in terms of end-of-life care and personal and family choices.

The use of this novel prognostic score in daily routine may not be easy to apply. PtDNA, among the four elements evaluated in the score, is certainly the most complex to obtain; furthermore, costs may impact its clinical applicability. On the other hand, the development of the technique and the increasingly frequent use of liquid biopsy also in PCa (eg for the evaluation of HRR) could make this technique routinely available, potentially creating standardized diagnostic paths which also may include the evaluation of ptDNA.

Conclusion

Research endeavors on prognostic and predictive biomarkers in mCRPC are intense. The present work has provided further validation of the prognostic power of a novel prognostic score proposed by our group. We have demonstrated that the association between molecular, clinical, laboratory and metabolic features can contribute to define the prognosis of mCRPC patients treated with taxanes and to improve implications in end-of-life care decisions. The increasing use of PET scans with new tracers suggests expanding the research by first confirming the prognostic power of metabolic values

(MTV, TLA, SUV),[37,38] and then incorporating them into the prognostic model here reported. It would be of extreme clinical and scientific interest to expand the analysis also to patients with mHSPC, a setting characterized by patients with better prognosis and tumors with very different biological features. We also aim to conduct a multicenter trial to confirm our data on diverse patient populations.

Ethics

The study was performed in accordance with the Good Clinical Practice and the Declaration of Helsinki. Each patient provided informed consent. The study protocol was approved by the ethics committee active at the Istituto Romagnolo per lo Studio dei Tumori (IRST) "Dino Amadori", in Meldola, Italy, since 2017. All the patients enrolled in the study have been followed up within a pre-existing prospective biological study (IRST-B073, approval nr. L3P1380), previously approved by the same local ethics committee.

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Disclosure

Prof. Dr. Vincenza Conteduca is an advisory/board member in Johnson&Johnson, Astellas, Bayer, Novartis, BMS, AstraZeneca, IPSEN, EISAI, Recordati, GSK, Merck, during the conduct of the study; and consultant/advisory board member Johnson&Johnson, Astellas, Merck, AstraZeneca, Amgen, EISAI, Recordati, Novartis, Ipsen and Bayer, outside the submitted work. The author(s) report no other conflicts of interest in this work.

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