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ORIGINAL ARTICLE

Optimal sequencing strategy using docetaxel and androgen receptor axis-targeted agents in patients with castration-resistant prostate cancer: utilization of neutrophil-to-lymphocyte ratio

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Abstract

Purpose To investigate the prognostic value of neutrophil-to-lymphocyte ratio (NLR) for the selection of the optimal sequencing strategy using docetaxel and androgen receptor axis-targeted (ARAT) agents in patients with M0 or M1 castration-resistant prostate cancer (CRPC). Currently, there is a need to identify biomarkers to guide optimal sequential treatment in CRPC.

Methods This multicenter, retrospective analysis included 303 consecutive patients initially diagnosed with M0 or M1 CRPC between September 2009 and March 2017. Of these, 52 (17.2%) patients received pre-docetaxel ARAT agents and 189 (62.4%) patients received post-docetaxel ARAT agents. The prognostic ability of NLR at CRPC diagnosis regarding radiographic progression-free survival (rPFS) and cancer-specific survival (CSS) were investigated. For the analysis, the NLR level was dichotomized at 2.5, and evaluated according to sequencing strategy.

Results Multivariate analysis revealed NLR ≥ 2.5 as an independent predictor of a lower risk for CSS. During the median follow-up of 18.5 months, patients with NLR ≥ 2.5 exhibited significantly lower 1-year rPFS ($p = 0.011$) and 2-year CSS rates ($p = 0.005$) compared to patients with NLR < 2.5. Among patients with NLR < 2.5, the post-docetaxel ARAT agent sequencing group exhibited higher 1-year rPFS ($p = 0.031$) and 2-year CSS ($p = 0.026$) rates compared to the pre-docetaxel ARAT agent sequencing group. Among patients with NLR ≥ 2.5, rPFS and CSS rates were comparable regardless of ARAT agent sequencing.

Conclusion NLR ≥ 2.5 at CRPC diagnosis is associated with a lower risk for CSS. Patients with NLR < 2.5 should primarily be offered docetaxel considering the survival benefit of docetaxel-to-ARAT agent sequencing.

Keywords Docetaxel · Lymphocytes · Neutrophils · Prostatic neoplasms · Castration resistant · Survival

Introduction

A decade ago, docetaxel was the only agent demonstrating improved overall survival for metastatic castration-resistant prostate cancer (CRPC) [1]. However, advances in clinical research have resulted in notable changes in the treatment of metastatic CRPC with the approval of five novel drugs in the last 8 years. These approved agents include hormonal, chemotherapeutic, radiopharmaceutical, and immunotherapeutic drugs [2]. In the current era of multidisciplinary treatment options for metastatic CRPC, clinicians seek to achieve cumulative survival benefit. At the same time, reaching a consensus on the optimal sequencing of these agents to maximize patient survival poses a new challenge.

The ideal sequencing strategy is to identify an approach specific to patient subgroups. However, these agents were developed concurrently within a short period of time, and there is no robust data on the optimal sequential strategy in relation to the use of docetaxel. Androgen receptor axis-targeted (ARAT) agents, namely, abiraterone and enzalutamide, have shown survival benefits in both pre-docetaxel

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and post-docetaxel settings [3–6]. However, intrinsic and acquired resistances to abiraterone and enzalutamide have been reported, in which 19.6% and 21% of patients, respectively, did not exhibit a prostate-specific antigen (PSA) response [6, 7]. Moreover, cross-resistances have been observed between abiraterone and enzalutamide, and docetaxel, with reduced activity when agents are used in sequence, and it is unclear whether docetaxel treatment is affected by the prior use of ARAT agents [8, 9].

Seeking clinically validated biomarkers which may facilitate decision for sequencing, molecular studies have proposed biomarkers based on potential resistance mechanisms, including androgen receptor (AR) amplification, mutation, and AR splice variants [10]. Among these, AR-V7 seems a promising molecular biomarker for predicting response to ARAT agents and aid treatment sequencing [2]. However, the detection of circulating tumor cells and assessment messenger RNAs for AR-V7 is costly and not all institutions have appropriately equipped laboratories. Hence, there is an unmet clinical need for a cost-effective and widely available biomarker which may aid the selection of sequencing priority between docetaxel and ARAT agents.

Neutrophil-to-lymphocyte ratio (NLR), a marker of host inflammation, has been shown to be prognostic across several solid tumors, including CRPC [11, 12]. The objective of this retrospective study was to validate the prognostic impact of NLR on radiographic progression-free survival (rPFS) and cancer-specific survival (CSS) in patients with CRPC treated with docetaxel and ARAT agents. In addition, we investigated whether NLR may be utilized to facilitate the judicious application of sequential treatment to maximize survival benefit.

Materials and methods

Study population

This multicenter retrospective analysis included 353 consecutive patients who progressed to M0 or M1 CRPC between September 2009 and January 2017. Patients were excluded from the analysis if they had incomplete clinical data ($n=23$), were lost to follow-up ($n=12$), or had an unknown cause of death ($n=15$). As a result, 303 patients were included in the final analysis. Prostate cancer staging was determined according to the 7th American Joint Committee on Cancer TNM system, with the definition of bone metastasis based on either demonstrable metastatic deposits upon imaging studies (bone scan, computed tomography, magnetic resonance imaging, or ^{18}F-FDG-positron emission tomography/computed tomography) or by pathologic confirmation.

The sequencing of docetaxel chemotherapy and ARAT agents was based on physician discretion and patient preference. Each agent was administered as: docetaxel 75 mg/m^2 intravenously once every 3 weeks with prednisone 10 mg daily; enzalutamide 160 mg daily; and abiraterone 1000 mg daily with prednisolone 5 mg or 10 mg daily. Each regimen was continued until radiographic disease progression, intolerable side effects, or patient refusal.

Prostate-specific antigen measurements were performed every 1–3 months, and computed tomography and bone scans were performed every 2–4 months. This study was approved by the institutional ethics committee after a review of the study protocol (3-2014-0112).

Data collection and definitions

The clinical and pathological characteristics of the patients at M0 or M1 CRPC diagnosis were retrieved from the institutional electronic medical record database. The data obtained at CRPC diagnosis comprised patient age, body mass index (BMI), stage, Charlson Comorbidity Index (CCI), Eastern Cooperative Oncology Group performance score (ECOG PS), previous local treatments, site of metastasis, PSA kinetics pertaining to luteinizing hormone-releasing hormone agonists, androgen-deprivation therapy initiation to CRPC onset period, and laboratory values including PSA, peripheral blood hemoglobin, albumin, alkaline phosphatase, neutrophil, and lymphocyte levels. The duration of docetaxel, abiraterone, and enzalutamide administration and radiographic assessments were obtained during CRPC treatment. NLR was calculated from absolute counts of neutrophils divided by lymphocytes.

Castration-resistant prostate cancer was defined using the Prostate Cancer Working Group 2 criteria as the progression of disease or elevation of serum PSA levels and serum testosterone levels of <50 ng/dL or <1.7 nmol/L [13]. rPFS and CSS intervals were defined as the intervals from the first date of CRPC diagnosis to the date of radiographic progression on first-line treatment and death from PCa, respectively. Radiographic progression was assessed according to the Response Evaluation Criteria in Solid Tumors version 1.1. Patient survival and causes of death were investigated based on the National Cancer Registry Database or institutional electronic medical records.

Statistical analysis

Demographic data of patients and tumors were compared between groups using descriptive statistics. The Mann–Whitney *U* test and the Fisher exact test were used to compare continuous and categorical variables, respectively. The optimal cutoff value of NLR was calculated based on a sensitivity analysis using the Youden's Index. Kaplan–Meier

curves were used to estimate rPFS and CSS between the NLR groups and the ARAT sequencing groups according to NLR subgroups. Multivariate analysis was performed using Cox proportional hazards regression models to adjust for potential confounders in predicting survival. Variables considered potential predictors for multivariate modeling were selected by univariate analysis. All statistical analyses were performed using SPSS version 18 (SPSS Inc., Chicago, IL, USA). All tests were two sided, with statistical significance set at $p < 0.05$.

Study aims

The primary aim of the study was to identify prognostic factors associated with rPFS and CSS in patients diagnosed with M0 or M1 CRPC. The secondary aim was to investigate the prognostic value of NLR for setting an optimal sequencing strategy using docetaxel and ARAT agents.

Results

Baseline characteristics

The clinicopathologic features of each group are presented in Table 1. The NLR level was dichotomized at 2.5 based on the Youden's Index. Patients with NLR ≥ 2.5 had higher PSA and lower albumin levels at CRPC diagnosis than patients with NLR < 2.5. The two groups were comparable in the distributions of potential survival prognosticators of CRPC. There were no differences in baseline features between the ARAT sequencing groups.

Because of the National Health Insurance policy of the Republic of Korea, the use of abiraterone was restricted for chemo-naïve CRPC patients, and therefore the predominance of enzalutamide use was observed in the post-docetaxel setting.

Predictors of survival

In the Cox regression analyses, patient age, BMI, Gleason score ≥ 8, T stage ≥ 3, and NLR ≥ 2.5 were associated with an increased risk of radiographic progression (Table 2). PSA level at CRPC diagnosis, albumin, and alkaline phosphatase levels, Gleason score ≥ 8, number of docetaxel cycles administered, and NLR ≥ 2.5 were associated with an increased risk of cancer-specific mortality (Table 3). Of note, the docetaxel-to-ARAT agent sequencing was an independent predictor of rPFS and CSS. There were no differences in rPFS and CSS according to the type of ARAT agents in both pre-docetaxel and post-docetaxel settings (data not shown).

Survival outcome and implications for sequencing according to NLR

Survival results as of September 2017 were used in this analysis and are presented in Table 4 and Figs. 1, 2, and 3. During the median follow-up period of 18.5 months, the median rPFS and CSS following the diagnosis of CRPC were 5.7 and 17.0 months, respectively. Among 303 patients, 191 (63.0%) cancer-specific deaths were noted, which translated to a 2-year CSS rate of 46.8%.

The median follow-up period of the censored patients was 22.0 months; therefore, survival analyses were performed for events that occurred within 24 months. Patients with NLR ≥ 2.5 exhibited significantly lower 1-year rPFS ($p = 0.011$) and 2-year CSS rates ($p = 0.005$) compared to patients with NLR < 2.5 (Fig. 1). There were no differences in rPFS and CSS rates between the ARAT agent sequencing categories (data not shown). With NLR ≥ 2.5 revealed as a prognostic factor of rPFS and CSS in the multivariable analyses, rPFS and CSS outcomes were compared between ARAT sequencing groups according to NLR category. Among patients with NLR < 2.5, men who received ARAT agents in the post-docetaxel setting exhibited significantly higher rPFS and CSS rates compared to men who received ARAT agents in the pre-docetaxel setting. However, survival outcomes were comparable regardless of sequencing strategy among patients with NLR ≥ 2.5 (Figs. 2, 3).

Discussion

Systemic treatment for metastatic CRPC has rapidly evolved, and various new agents have been approved based on randomized phase III trials. With these multidisciplinary treatment options, drug selection and sequencing for the individual patient have become unclear, and there is limited data on the optimal sequencing of these treatments. Our goal was to estimate the survival of patients with CRPC treated with docetaxel and ARAT agents to facilitate the judicious application of sequential treatment and set targets for therapy. Our data indicate that docetaxel may be offered as first-line treatment for patients with pretreatment NLR < 2.5, if not otherwise contraindicated for chemotherapy.

We observed that high pretreatment NLR was associated with worse rPFS and CSS. Our results are consistent with several studies for various cancers, including CRPC [12, 14]. High NLR was associated with poorer progression-free survival in patients with metastatic CRPC across different treatments including abiraterone, docetaxel, and ketoconazole [11, 15, 16]. The biological basis underlying this phenomenon is unclear. However, it is presumed that the increased NLR may arise from altered tumor-inflammatory cell reactions, an indicator of progressive malignancy [17].

Table 1 Clinicopathological characteristics of castration-resistant prostate cancer patients, stratified by neutrophil-to-lymphocyte ratio and androgen receptor axis-targeted agent sequencing

	Overall ($n=303$)	NLR		p	ARAT agent sequencing		p
		<2.5 ($n=146$)	≥ 2.5 ($n=157$)		Pre-docetaxel ($n=52$)	Post-docetaxel ($n=176$)	
Age	66.5 (61.0–71.8)	66.0 (61.0–71.0)	67.0 (59.5–73.0)	0.865	67.0 (61.0–73.0)	65.5 (60.7–70.3)	0.629
Body mass index	23.5 (21.5–25.2)	23.8 (21.5–25.2)	23.1 (21.1–25.3)	0.339	24.2 (22.2–24.1)	24.2 (21.9–25.9)	0.866
PSA at CRPC	69.2 (15.0–182.0)	43.2 (13.3–123.4)	89.1 (18.7–265.5)	0.012	38.6 (13.2–88.0)	59.3 (14.9–160.6)	0.194
Hemoglobin	12.0 (10.7–13.0)	12.5 (11.5–13.4)	11.6 (10.1–12.7)	0.202	12.3 (11.3–13.6)	12.3 (10.9–13.2)	0.638
Albumin	4.0 (3.7–4.4)	4.2 (3.9–4.5)	3.9 (3.5–4.3)	<0.001	4.1 (3.9–4.5)	4.1 (3.7–4.4)	0.071
ALP	109.0 (70.0–209.0)	102.5 (65.7–195.2)	128.0 (76.5–225.5)	0.694	108.0 (74.0–209.2)	114.0 (73.5-221.0)	0.174
T stage				0.204			0.917
$\leq$T2	35 (11.6%)	24 (16.4%)	11 (6.7%)		32 (61.5%)	108 (61.4%)	
$\geq$T3	268 (88.4%)	122 (83.6%)	146 (93.3%)		20 (38.5%)	68 (38.6%)	
N stage				0.394			0.432
N0	141 (46.5%)	65 (44.5%)	76 (48.4%)		27 (51.9%)	75 (42.6%)	
N1	162 (53.5%)	81 (55.5%)	81 (51.6%)		25 (48.1%)	101 (57.4%)	
M stage				0.366			0.063
M0	65 (21.5%)	25 (17.1%)	40 (25.5%)		19 (36.5%)	34 (19.3%)	
M1	238 (78.5%)	121 (82.9%)	117 (74.5%)		33 (63.5%)	142 (80.7%)	
Metastatic site							
Bone	162 (53.4%)	79 (54.1%)	83 (52.9%)		25 (48.1%)	110 (62.5%)	0.309
Visceral	12 (3.9%)	4 (2.7%)	8 (5.1%)		3 (5.8%)	4 (2.3%)	0.144
Lymph node	138 (45.5%)	64 (43.8%)	74 (47.1%)		20 (38.5%)	79 (44.9%)	0.547
Gleason score				0.353			0.168
$\leq$7	87 (28.7%)	40 (27.4%)	47 (29.9%)		21 (40.4%)	97 (55.1%)	
$\geq$8	216 (71.3%)	106 (72.6%)	110 (70.1%)		31 (59.6%)	79 (44.9%)	
CCI				0.352			0.876
$\leq$1	219 (72.3%)	112 (76.7%)	107 (68.2%)		27 (51.9%)	88 (50.0%)	
$\geq$2	84 (27.7%)	34 (23.3%)	50 (31.8%)		25 (48.1%)	88 (50.0%)	
ECOG PS				0.113			0.881
$\leq$1	213 (70.3%)	111 (76.3%)	102 (64.8%)		45 (86.5%)	156 (88.6%)	
$\geq$2	90 (29.7%)	35 (23.7%)	55 (35.2%)		7 (13.5%)	20 (11.4%)	
Primary treatment							
Prostatectomy	97 (32.0%)	52 (35.8%)	45 (28.7%)	0.561	30 (57.7%)	84 (47.7%)	0.312
Radiation therapy	30 (68.0%)	11 (7.5%)	19 (12.1%)	0.181	11 (21.1%)	20 (11.3%)	0.127
Docetaxel cycles	4.0 (2.0–9.0)	3.0 (3.0–10.0)	4.0 (2.0–9.0)	0.255	5.0 (3.0–9.0)	6.0 (3.0–12.0)	0.396
ARAT agents							0.453
Enzalutamide	167 (73.2%)				37 (71.1%)	130 (73.9%)	
Abiraterone	61 (26.8%)				15 (28.9%)	46 (26.1%)	

Data are median (interquartile range) and number (%)

ALP alkaline phosphatase, *ARAT* androgen receptor axis-targeted, *CCI* Charlson Comorbidity Index, *CRPC* castration-resistant prostate cancer, *ECOG PS* Eastern Cooperative Oncology Group performance score, *NLR* neutrophil-to-lymphocyte ratio, *PSA* prostate-specific antigen

High NLR reflects a relatively high neutrophil count or a relatively low lymphocyte count. The increase in neutrophils is considered a proxy of increased neutrophil-dependent inflammation, which may potentially promote tumorigenesis [12]. The decrease in lymphocytes has been observed to be associated with immunosuppression in several cancer types [18]. Moreover, low lymphocyte count has been suggested to reflect a suboptimal lymphocyte-mediated response to the tumor which contributes to cancer progression [19].

The biology underlying improved survival observed with docetaxel-to-ARAT agent sequencing in patients with low pretreatment NLR is unclear; however, several reasons for this have been proffered. First, there is increasing evidence that disease progression is dependent on interactions

Table 2 Cox-regression models for the association of risk factors with radiographic progression following docetaxel chemotherapy

	Univariate			Multivariate		
	HR	(95% CI)	*p*	HR	(95% CI)	*p*
Age	1.040	(1.017–1.063)	< 0.001	1.029	(1.003–1.055)	0.031
Body mass index	0.899	(0.852–0.949)	< 0.001	0.959	(0.893–1.030)	0.014
Laboratory values[a]						
PSA	1.001	(1.000–1.001)	< 0.001	1.000	(1.000–1.001)	0.244
Hemoglobin	1.001	(1.000–1.002)	0.083			
Albumin	0.449	(0.325–0.619)	< 0.001	0.800	(0.526–1.215)	0.295
Alkaline phosphatase	1.001	(1.000–1.001)	< 0.001	1.001	(1.000–1.001)	0.059
NLR ≥ 2.5	1.503	(1.098–2.057)	0.011	1.535	(1.131–1.898)	0.038
Stage						
≥ T3 vs. ≤ T2	1.505	(1.098–2.064)	0.011	1.463	(1.019–2.101)	0.039
N1 vs. N0	1.136	(0.828–1.561)	0.429			
M1 vs. M0	0.945	(0.661–1.351)	0.756			
Site of metastasis						
Bone	1	(reference)				
Visceral	0.934	(0.652–1.338)	0.710			
Gleason score (≥ 8 vs. ≤ 7)	1.598	(1.172–2.179)	0.003	1.505	(1.028–2.204)	0.035
Charlson comorbidity score	1.081	(0.800–1.461)	0.611			
ECOG	2.319	(1.521–3.535)	< 0.001	1.091	(0.581–2.050)	0.786
ARAT agent sequencing						
Pre-docetaxel	1	(reference)				
Post-docetaxel	0.658	(0.486–0.892)	0.007	0.650	(0.418–0.810)	0.045

ARAT androgen receptor axis-targeted, *CI* confidence interval, *CCI* Charlson comorbidity score, *ECOG* Eastern Cooperative Oncology Group, *HR* hazards ratio, *NLR* neutrophil-to-lymphocyte ratio

[a]Values obtained at the diagnosis of castration-resistant prostate cancer

between tumor and host factors [20]. The host systemic inflammation has been suggested to be linked to functional decline and poor performance and nutritional status [21]. Patients devoid of pro-inflammatory response, reflected by low NLR, may have better tolerated first-line cytotoxic chemotherapy. For patients who received ARAT agents as first-line therapy, the long-term use of ARAT agents and related side effects may have exerted suboptimal efficacy to docetaxel. Second, systemic inflammation may have exerted different influences on intrinsic or acquired resistances to docetaxel and ARAT agents. The individual survival benefits of abiraterone and enzalutamide before and after docetaxel have been observed [3, 6]. However, response rates to ARAT agents among men who received previous treatment with docetaxel have been reported to be modest, suggesting the existence of cross-resistance [8, 9]. Several mechanisms of drug resistance in patients with highly pre-treated metastatic CRPC have been proposed, namely, expression modifications of the androgen receptor and variants, and increased steroidogenesis [22, 23]. The situation is further complicated by accumulating evidence that inflammatory response plays key roles in the resistance mechanisms via regulating AR signaling and its modulated inflammatory cytokines and chemokines [24, 25]. At the same time, androgen/AR signaling has been shown to affect pro-inflammatory signaling and induce immune inflammation, lending support to the notion that intermittent administration of ARAT agents may potentially reduce alterations in inflammatory responses [24, 26]. In all, systemic inflammation, as partly reflected by the NLR, may have caused multiple levels of alterations to CRPC treatment efficacy and contributed to different responses to docetaxel and ARAT agent sequencing as observed in our study.

The identification of clinical biomarkers to stratify patients for optimal sequencing strategy is imperative in the current era of multidisciplinary treatment options for metastatic CRPC. However, none of the proposed biomarkers have been prospectively validated and are limited by cost-effectiveness concerns. Therefore, the decision between docetaxel and ARAT agents is based on practical considerations pertaining to drug availability and reimbursement in most institutions. Moreover, physicians might prefer to consider abiraterone or enzalutamide prior to docetaxel, especially for patients with poor performance status who are unfit for docetaxel. As the first study to utilize NLR to stratify patients for optimal sequencing, our observation implies that cross-resistance between docetaxel and ARAT agents may be linked to

Table 3 Cox-regression model for the association of risk factors with cancer-specific mortality

	Univariate			Multivariate		
	HR	(95% CI)	*p*	HR	(95% CI)	*p*
Age	1.038	(1.016–1.061)	0.001	1.528	(1.103–2.117)	0.068
Body mass index	0.968	(0.901–1.041)	0.382			
Laboratory values[a]						
PSA	1.001	(1.000–1.001)	< 0.001	1.001	(1.000–1.001)	0.011
Hemoglobin	1.001	(0.999–1.002)	0.306			
Albumin	0.408	(0.301–0.553)	< 0.001	0.469	(0.327–0.675)	< 0.001
Alkaline phosphatase	1.001	(1.000–1.001)	< 0.001	1.001	(1.000–1.001)	< 0.001
NLR ≥ 2.5	1.559	(1.152–2.109)	0.004	1.446	(1.048–1.994)	0.038
Stage						
≥ T3 vs. ≤ T2	0.865	(0.524–1.430)	0.271			
N1 vs. N0	1.251	(0.922–1.697)	0.152			
M1 vs. M0	1.528	(0.983–2.376)	0.062			
Site of metastasis						
Bone	1	(reference)				
Visceral	1.221	(0.517–2.882)	0.649			
Gleason score (≥ 8 vs. ≤ 7)	1.957	(1.441–2.658)	< 0.001	2.045	(1.483–2.818)	< 0.001
Charlson comorbidity score	1.201	(0.896–1.609)	0.221			
ECOG	1.802	(1.216–2.670)	0.003	0.946	(0.675–1.326)	0.747
Docetaxel cycles	0.926	(0.900–0.953)	< 0.001	0.891	(0.869–0.921)	< 0.001
ARAT agent sequencing						
Pre-docetaxel	1	(reference)				
Post-docetaxel	0.621	(0.461–0.835)	0.002	0.761	(0.624–0.956)	0.032

ARAT androgen receptor axis-targeted, *CI* confidence interval, *CCI* Charlson comorbidity score, *ECOG* Eastern Cooperative Oncology Group, *HR* hazards ratio, *NLR* neutrophil-to-lymphocyte ratio

[a]Values obtained at the diagnosis of castration-resistant prostate cancer

Table 4 Survival outcome of patients with castration-resistant prostate cancer, stratified according to neutrophil-to-lymphocyte ratio and ARAT agent sequencing groups

	Overall	ARAT agent sequencing		
		Pre-docetaxel	Post-docetaxel	*p*
N	303	52	176	NS
CSS, 2-year (%)				
Overall	46.8%	36.4%	49.9%	0.295
NLR < 2.5	51.7%	31.4%	59.2%	0.026
NLR ≥ 2.5	32.6%	41.6%	31.7%	0.766
RFS, 1 year (%)				
Overall	20.7%	19.1%	22.2%	0.359
NLR < 2.5	23.5%	18.1%	28.9%	0.031
NLR ≥ 2.5	14.5%	17.5%	12.0%	0.934
No. cancer-specific deaths (%)	191 (63.0%)	32 (61.5%)	115 (65.3%)	0.145
Median RFS (months)	3.7 (2.3–8.3)	3.0 (2.3–3.8)	4.5 (2.3–9.0)	0.073
Median CSS (months)	15.0 (9.0–25.0)	14.0 (8.0–23.0)	15.5 (9.3–26.0)	0.149
Follow-up period (months)	18.5 (7.3–26.0)	17.0 (9.5–28.5)	20.5 (11.0–29.0)	0.243

Data are number (%) and median (IQR)

ARAT androgen receptor axis-targeted, *CRPC* castration-resistant prostate cancer, *CSS* cancer-specific survival, *NLR* neutrophil-to-lymphocyte ratio, *RFS* radiographic progression-free survival

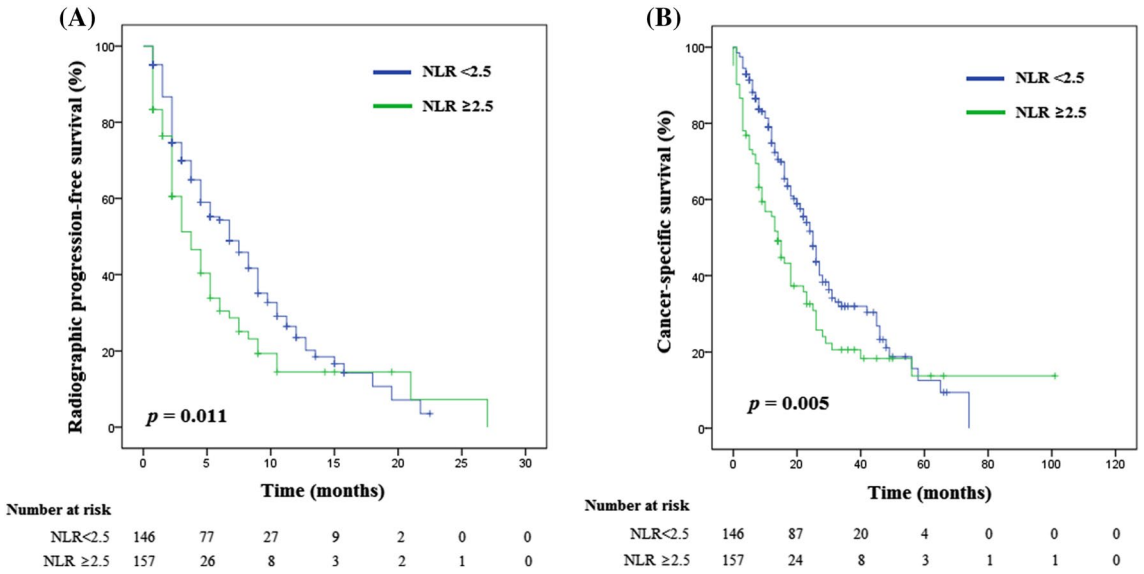

Fig. 1 **a** Radiographic progression-free survival and **b** cancer-specific survival, according to NLR category. *NLR* neutrophil-to-lymphocyte ratio

inflammatory response, and may serve as a cornerstone for the development of therapeutics targeted at neutrophils and lymphocytes.

The strength of the current study includes the incorporation of comprehensive prognosticators of the survival of metastatic CRPC, including patient and tumor characteristics, comorbidities, performance status, laboratory values, and treatment information that were available for all patients. At the same time, several limitations are worth mentioning. First, a selection bias may have existed due to the retrospective nature of the study. There was a lack of a standard therapeutic approach in which physician and patient preferences existed regarding the implementation of a specific treatment. Second, our database did not include information on concurrent inflammatory diseases, infections, hematological disorders, or additional drugs, which may have affected neutrophil and lymphocyte counts. Third, the survival analysis was not stratified according to each ARAT agent type, considering their common mechanisms of AR signaling inhibition. However, results may have differed regarding their different mechanisms of action. Fourth, we did not account for exposures to clinical trials and third-line administrations of radium-223 or cabazitaxel, which may have influenced survival outcome. Fifth, we did not evaluate overall survival which serves as a proxy for drug efficacy in real-life cancer care. Finally, the median follow-up period of the censored patients was 22.0 months and, therefore, a longer-term follow-up is warranted to ensure a stronger conclusion.

Conclusions

This observational study provided novel findings suggesting that a pretreatment NLR of < 2.5, used in combination with other biomarkers, may be utilized as a prognosticator of favorable response to docetaxel-to-ARAT agent sequencing in patients with M0 or M1 CRPC. NLR can be easily derived from differential blood count and, if confirmed by additional studies, has the potential for use in daily clinical practice because of its cost-effectiveness. Further investigation on the concurrent suppression of androgen/AR signaling and anti-inflammation signaling seems necessary for the successful development of therapeutic agents for CRPC and a better understanding of the mechanisms underlying disease progression.

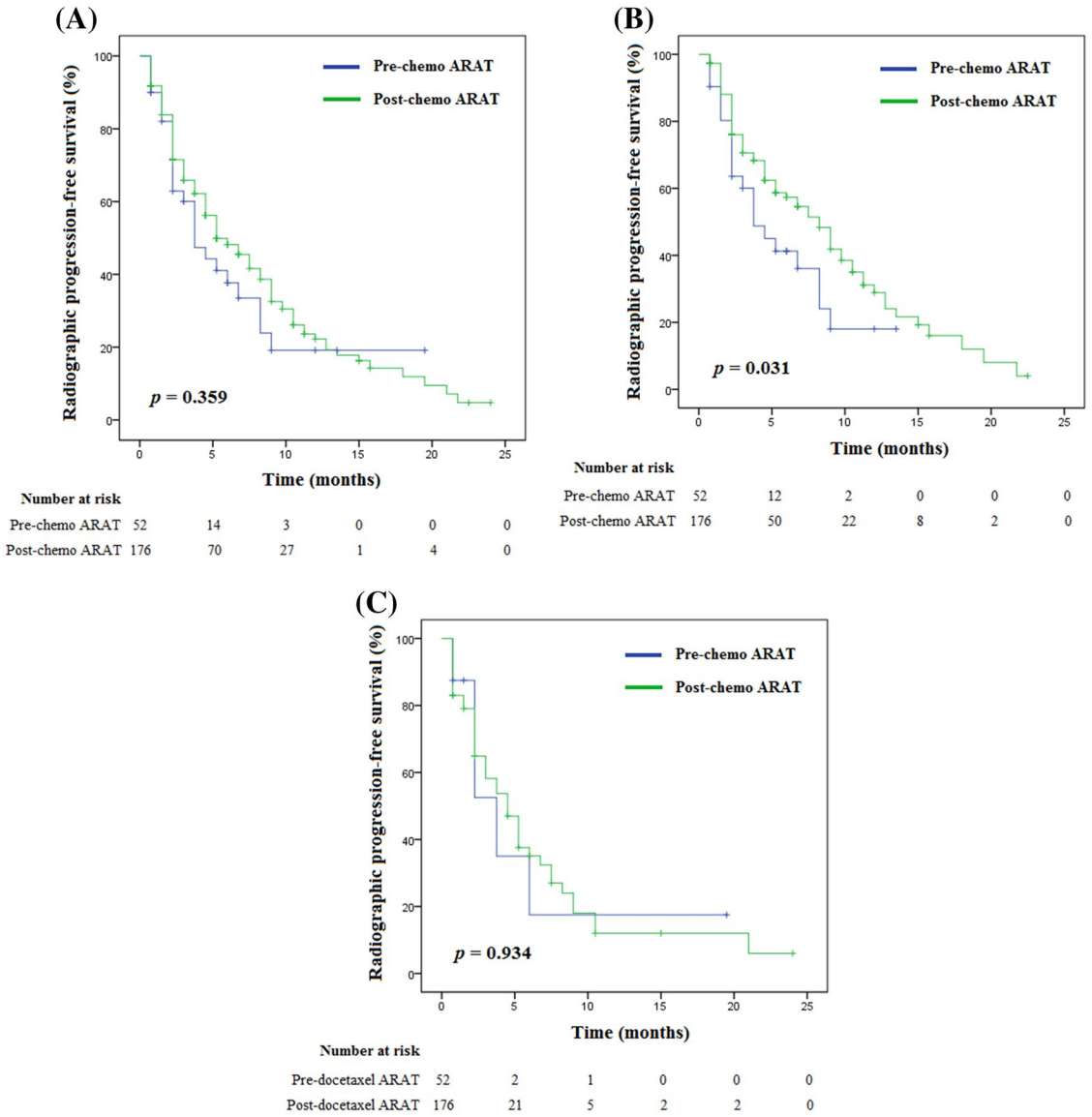

Fig. 2 Radiographic progression-free survival according to ARAT agent sequencing (pre-chemotherapy versus post-chemotherapy) in the **a** overall group, **b** NLR < 2.5 group, and **c** NLR ≥ 2.5 group. *ARAT* androgen receptor axis-targeted, *NLR* neutrophil-to-lymphocyte ratio

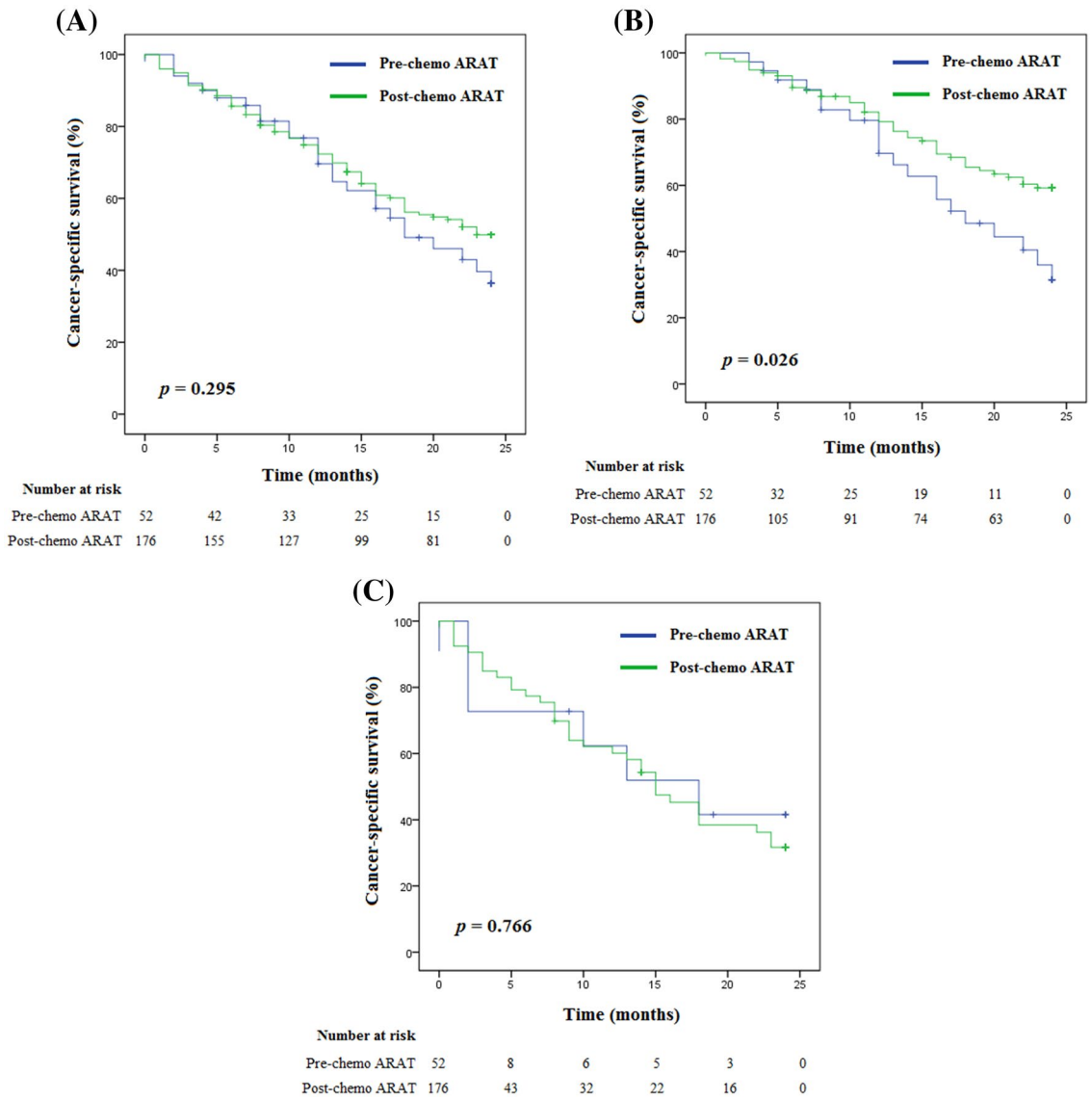

Fig. 3 Cancer-specific survival according to ARAT agent sequencing (pre-chemotherapy versus post-chemotherapy) in the **a** overall group, **b** NLR < 2.5 group, and **c** NLR ≥ 2.5 group. *ARAT* androgen receptor axis-targeted, *NLR* neutrophil-to-lymphocyte ratio

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Compliance with ethical standards

Conflict of interest All of the authors declare that they have no conflicts of interest to declare.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was not required for the purposes of this study as it was based upon retrospective anonymous patient data and did not involve patient intervention or the use of human tissue samples.

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