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Real world analysis of metastatic prostate cancer demonstrates increased frequency of PSA-imaging discordance with visceral metastases and up front ARAT/docetaxel therapy

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Author contributions

Takuto Hara: Conceptualization; data curation; formal analysis; investigation; methodology; writing – original draft and review and editing. Tomoaki Terakawa: Conceptualization; data curation; formal analysis; investigation; methodology; writing – review and editing. Yasuyoshi Okamura: data curation; review and editing. Yukari Bando: data curation; review and editing. Junya Furukawa: data curation; review and editing. Kenichi Harada: review and editing. Yuzo Nakano: writing – review and editing. Masato Fujisawa: supervision.

Abstract

Background: The objective of this study was to evaluate the background and treatment course of patients with metastatic prostate cancer, with a particular focus on radiographic progression in the absence of prostate-specific antigen (PSA) progression.
Methods: The study population consisted of 229 patients with metastatic hormone-sensitive prostate cancer (HSPC) who received prostate biopsy and androgen deprivation therapy at Kobe University Hospital between January 2008 and June 2022. Clinical characteristics were retrospectively evaluated using medical records. PSA progression-free status was defined as ≤1.05 times greater than that from 3 months before. Multivariate analyses were performed using the Cox proportional hazards regression model to identify parameters associated with time to progression on imaging without PSA elevation.
Results: A total of 227 patients with metastatic HSPC without neuroendocrine prostate cancer were identified. The median follow-up period was 38.0 months, with a median overall survival of 94.9 months. Six patients exhibited disease progression on imaging without PSA elevation during HSPC treatment, three during first-line castration-resistant prostate cancer (CRPC) treatment, and two during late-line CRPC treatment. The rate of disease progression without PSA elevation at 3 years after treatment initiation was 7.4%. Multivariate analysis revealed that organ metastases and upfront treatment with docetaxel or androgen receptor axis-targeted therapy were independent prognostic factors for imaging progression without PSA elevation.
Conclusions: Disease progression on imaging without PSA elevation occurred not only during HSPC treatment and first-line CRPC treatment, but also during late-line CRPC treatment. Patients with visceral metastases or those treated with upfront androgen receptor axis-targeted or docetaxel may be more prone to such progression.

Abbreviations
ARAT, androgen receptor axis-targeted
CRPC, castration-resistant prostate cancer
CT, computed tomography
HSPC, hormone-sensitive prostate cancer
NEPC, neuroendocrine prostate cancer
OS, overall survival
PC, prostate cancer

PCWG, prostate cancer clinical trials working group
PSA, prostate-specific antigen

Introduction

Recent years have seen numerous clinical trials aimed at understanding the biology and treatment of metastatic castration-resistant prostate cancer (CRPC). The Prostate Cancer Clinical Trials Working Group (PCWG)[1,2] has developed criteria for the evaluation of treatment efficacy in these trials.

The PCWG2 and PCWG3 criteria incorporate not only prostate-specific antigen (PSA) trends, but also imaging findings in the evaluation of disease progression. Recent clinical trials in prostate cancer have used radiographic progression-free survival (PFS) in addition to PSA PFS as endpoints[3,4]. Various guidelines[5,6] stress the importance of routine imaging examinations in the management of metastatic CRPC.

Previous clinical trials in metastatic CRPC[7] have reported instances of imaging progression without PSA elevation during treatment, and this phenomenon has also been observed in real-world clinical practice[8]. In the metastatic hormone-sensitive prostate cancer (HSPC) clinical trials, the sub-analysis of the CHAARTED[9] and ARCHES[10] trials reported imaging progression without PSA elevation, which has been a cause of concern among clinicians who often rely on PSA alone to assess disease status. However, there is a lack of real-world data regarding such progression patterns in metastatic HSPC and a lack of understanding of the rate of this progression throughout prostate cancer treatment, regardless of treatment line or individual therapeutic agent.

The current study aimed to examine the background and treatment course of patients with metastatic prostate cancer who had been followed consecutively since their initial diagnosis, with a particular focus on radiographic progression in the absence of PSA progression.

Materials and Methods

This retrospective study analyzed clinicopathological data from 229 patients with metastatic HSPC who underwent prostate biopsy and systemic androgen deprivation therapy between January 2008 and June 2022, and who subsequently received consecutive medical care in routine clinical settings at our institution.

The study design was approved by the Research Ethics Committee of Kobe University Hospital (No. 220211) and informed consent was obtained in the form of opt-out on the website.

Prostate biopsy specimens were evaluated according to the Gleason Grading System[11]. Cases with treatment-naive neuroendocrine prostate cancer (NEPC) in their biopsy specimens were excluded. Clinicopathological examinations were graded according to the American Joint Committee on Cancer 8th staging system[12]. Prior to initiation of systemic therapy, all patients underwent radiological evaluation with chest to pelvis computed tomography and radionuclide bone scan. The images were interpreted by the treating physician based on the PCWG2 criteria[1].

Treatment details were determined by each treating physician. PSA follow-up for HSPC patients was every 1–3 months and computed tomography（CT）follow-up was generally every 12 months; for CRPC patients, PSA follow-up was monthly, and CT was generally every 6 months. Imaging studies are also performed at the onset of pain or urinary symptoms. According to the analysis of clinical trials[7,9], the absence of PSA progression was defined as ≤1.05 times greater than that from 3 months prior. The time from initiation of androgen deprivation therapy to imaging progression without PSA elevation was examined. Patients who died from other causes were treated as statistically censored.

All statistical analyses were performed using EZR (version 1.55, Saitama Medical Center, Jichi Medical University, Saitama, Japan)[13], and $P<0.05$ was considered significant. Time to imaging progression without PSA elevation and overall survival (OS) rates were calculated by the Kaplan–Meier method, and differences were analyzed by the log-rank test. The prognostic significance of certain parameters was assessed by the Cox proportional hazards regression model.

Results

The patient flow diagram is shown in Figure 1. Two hundred twenty-seven metastatic HSPC patients without NEPC components were identified. With a median follow-up of 38.0 months, the median OS was 94.9 months (95% CI 77.3–111.7). There were 11 cases of imaging progression without PSA elevation. Twenty-seven patients progressed to CRPC before 2014, when ARAT and cabazitaxel became available, and two of these patients had disease progression without PSA elevation. Eighty-one patients progressed to CRPC after 2014, and nine patients had disease progression without PSA elevation. The Sankey

diagram of treatment progression for patients before and after 2014 and the timings of disease progression without PSA elevation are shown in Figure 2. Table 1 shows the backgrounds of patients overall, patients who maintained HSPC status or progressed to CRPC with PSA elevation, and patients who had disease progression without PSA elevation. Patients with disease progression without PSA elevation had a predominantly higher rate of organ metastases at the start of systemic therapy.

Patients with disease progression without PSA elevation are detailed in Table 2. Six patients had disease progression without PSA elevation during HSPC treatment: three patients during first-line CRPC treatment and two patients during late-line CRPC treatment. The lines of treatment in which patients experienced disease progression without PSA elevation varied, with a median time to disease progression without PSA elevation of 28.1 months (range: 3.6–61.3). Eight of the 11 patients had biopsies of progressive lesions, 6 had neuroendocrine transformation, and 2 had high-grade adenocarcinoma without androgen receptor expression. Table 2 also shows two patients with neuroendocrine transformation with PSA elevation.

The Kaplan–Meier curve for time to imaging progression without PSA elevation for the entire patient population is shown in Figure 3. The rate of progression without PSA elevation was 7.4% after 3 years of treatment.

Univariate analysis of the Cox proportional hazards model identified organ metastasis and upfront ARAT or docetaxel as significant prognostic markers for patients at risk of progression without PSA elevation. Multivariate analyses identified organ metastases and upfront ARAT or docetaxel as significant prognosticators. The Kaplan–Meier curve for time to imaging progression in relation to organ metastases and upfront ARAT or docetaxel are illustrated in Figure 4A and 4B, respectively.

Discussion

While PCWG2 and PCWG3 are well-known definitions of elevated PSA, there is no formal definition of non-rising PSA. The criteria for non-rising PSA was defined as an increase of 5% or less from the PSA level of 3 months before, as described in previous studies[7,9]. The incidence of disease progression without PSA elevation during treatment for metastatic HSPC and metastatic CRPC was 3% and 5%, respectively, which is lower than reported in clinical trials[7,9]. In addition, the definition of disease progression in the report by Armstrong et al.[10] differed from the present study in that it was defined as an increase in PSA from nadir, but the incidence in the present study was slightly lower than in this HSPC study.

This discrepancy in incidence may be partly attributed to differences in follow-up periods and methods. In this study, all CRPC patients and all upfront ARAT patients had monthly PSA measurements. In clinical trials, PSA was generally performed every 12 weeks, except around the time of treatment initiation. Additionally, in our series, imaging tests were generally performed 1–2 times per year at the discretion of the treating physician, while in clinical trials they were performed as frequently as every 12 weeks[7,9,14]. This may have strongly influenced the small number of patients with disease progression without PSA elevation in this study.

The interval between imaging studies is an important consideration. Many guidelines recommend imaging for metastatic CRPC approximately every 3–6 months. However, there remains a lack of consensus among experts, such as the Advanced Prostate Cancer Consensus Conference[15], regarding the imaging follow-up policy during metastatic HSPC treatment, particularly with regards to the timing and modality. Nevertheless, some literature suggests that regular imaging studies are imperative[9,10]. In our investigation, we discovered that certain metastatic HSPC patients exhibited progression of their disease without PSA elevation within months of their last CT, suggesting that regular imaging follow-up is important. However, patients with metastatic prostate cancer have a more prolonged prognosis, typically ranging between 4–7 years[15,16], and the median OS in our study was 94.9 months. In this series, the timing of disease progression without PSA elevation varied from HSPC to CRPC in patients who received multiple lines of therapy. Additionally, patients with progression without PSA elevation were observed after 5 years of systemic therapy. The cumulative exposure dose for CT and bone scintigraphy every 3 months for 5 years, as per the clinical trial, exceeds approximately 500 msV[17]. Therefore, it is imperative to develop imaging modalities and protocols that are specifically tailored to the patient's condition in actual clinical practice, rather than for clinical trials. In light of this, it is crucial to consider which patients require more frequent imaging, because we examined the prognostic factors of imaging progression without PSA elevation. Our analysis revealed that patients predisposed to this progression pattern were those with visceral metastases or who had received upfront ARAT or docetaxel therapy.

Disease progression without PSA elevation is a phenomenon that was known before the advent of ARAT[18], but there are no papers discussing the difference between vintage androgen deprivation therapy and ARAT. The incidence of these progressions was significantly higher in patients treated with upfront ARAT and docetaxel in the current study. In the univariate analysis, in addition to patients with visceral metastases, patients with lymph node metastases and T4 patients were more likely to have disease progression

without PSA elevation, but these patients were more likely to have received ARAT or docetaxel (Supplemental Table 1). It is important to note that the current study is not sufficient to conclude any disadvantages associated with upfront ARAT or docetaxel therapy because the observation period of the cases was too short and the number of cases was insufficient. Further studies are required to establish any definitive conclusions.

It has been suggested that many prostate cancers with disease progression without PSA elevation are associated with NEPC[19,20]. In the current study, 75% of patients who underwent lesion biopsy and were found to have disease progression without PSA elevation were diagnosed with NEPC. Although no real-world data have been reported showing a direct increase in NEPC by ARAT, preclinical data suggest that ARAT may induce the neuroendocrine transformation. Luo et al.[21] demonstrated that Enzalutamide-induced upregulation of long non-coding RNA p21 facilitates prostate cancer neuroendocrine transformation. Asberry et al. [22] reported the expression of neuroendocrine-related proteins and mRNA in prostate cancer cells early after ARAT therapy.

Conversely, as demonstrated in Table 2, cases of NEPC with elevated PSA were also observed, indicating the presence of heterogeneity in these pathologies. The remaining 25% of cases with disease progression without PSA elevation did not exhibit neuroendocrine transformation, but rather very undifferentiated adenocarcinoma cells were detected. These cells were negative for cell surface androgen receptors, yet negative for synaptophysin and chromogranin A, which are characteristic of NEPC, and appeared to be "intermediate atypical carcinoma", as proposed by Beltran et al.[23]. A study (NCT02099864) is currently underway to biopsy exacerbations in enzalutamide-treated patients and is expected to provide insights into the pathological background of prostate cancer without PSA elevation.

This study has several limitations. First, it was a retrospective study with a relatively small sample size. Additionally, there was an inconsistency in the treatment policy because of the wide range of time periods. Furthermore, the appropriateness of this method of analysis remains uncertain because the analysis of time to imaging progression without PSA elevation was predicated on the assumption that a consistent castrated state is a risk factor and changes in treatment do not affect the risk of such a progression pattern. It is relatively simple to calculate the incidence rate in metastatic HSPC; however, we contend that examining the rate of imaging progression without PSA elevation for each treatment sequence in prostate cancer, which has many emerging new treatments, may impede our understanding of this uncommon progression pattern.

Conclusions

Our study found that disease progression on imaging without PSA elevation was not only observed during HSPC treatment and first-line CRPC treatment, but also during late-line CRPC treatment. Additionally, patients with visceral metastases or who were treated with upfront ARAT or docetaxel may be at higher risk of this type of progression.

Acknowledgments

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Conflict of interest

None declared.

Approval of the research protocol by an institutional review board

This study was approved by the ethics committee of Kobe University (IRB No. 220211).

Informed consent

Informed consent was obtained in the form of opt-out on the website.

Registry and the registration No. of the study/trial

N/A.

Animal studies

N/A.

Data availability statement

The data generated in this study are available upon request from the corresponding author.

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Figure legends

Figure 1. Patient flow diagram. CRPC, castration-resistant prostate cancer; HSPC, hormone-sensitive prostate cancer; PSA, prostate-specific antigen.

Figure 2. Sankey diagram of treatment course in patients with castration-resistant prostate cancer (CRPC) before December 2013 and in patients with CRPC after January 2014 (B). ARAT, androgen receptor axis-targeted; CBZ, cabazitaxel; Doc, docetaxel; NEPC, neuroendocrine prostate cancer; PSA, prostate-specific antigen.

Figure 3. Kaplan–Meier curve about time to disease progression without prostate-specific antigen elevation in all patients.

Figure 4. Kaplan–Meier curve of time to disease progression without prostate-specific antigen elevation in all patients with visceral metastasis (A) and upfront androgen receptor axis-targeted (ARAT) or docetaxel (DOC) therapy (B). CAB, combined androgen blockade.

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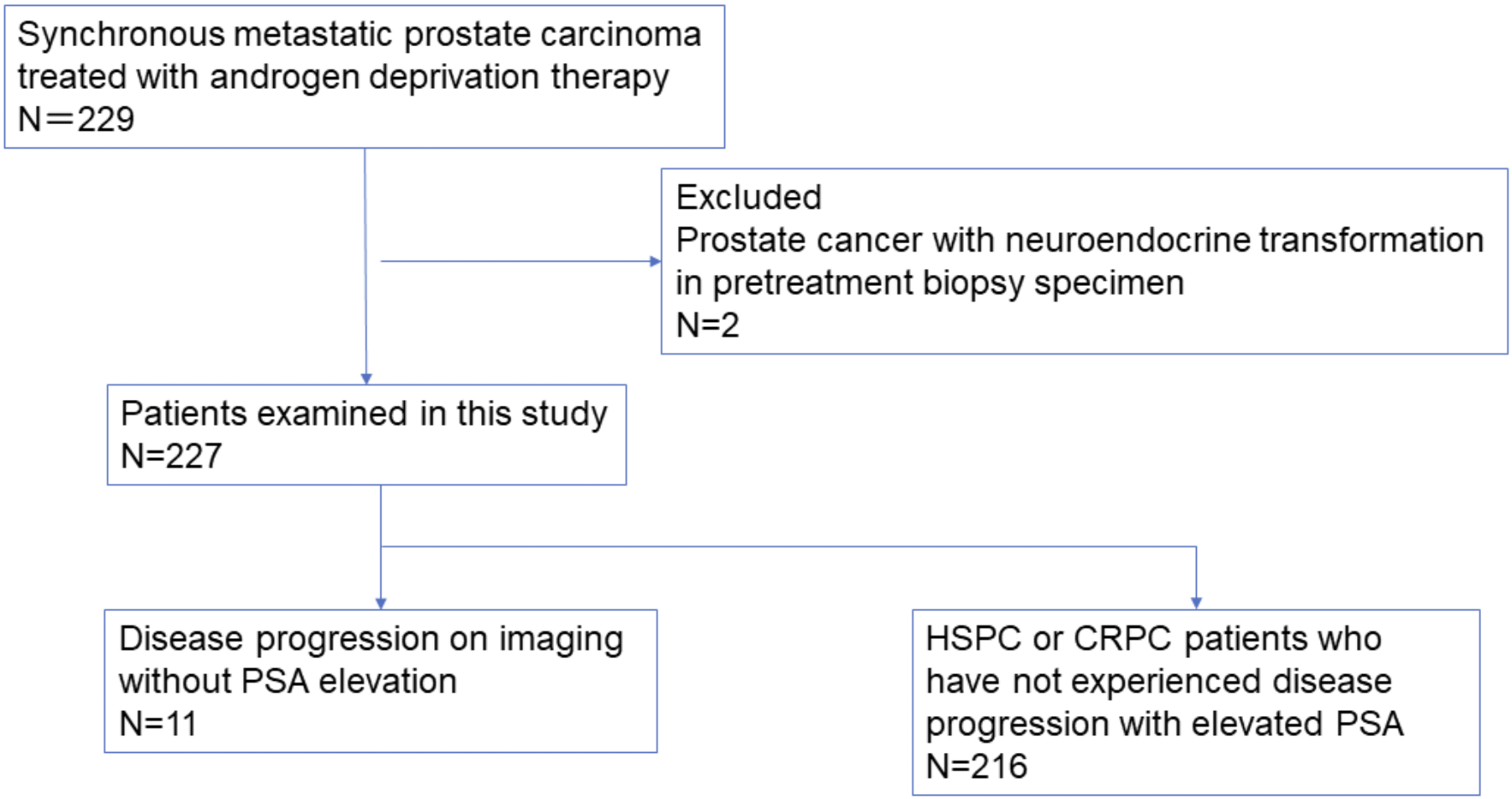
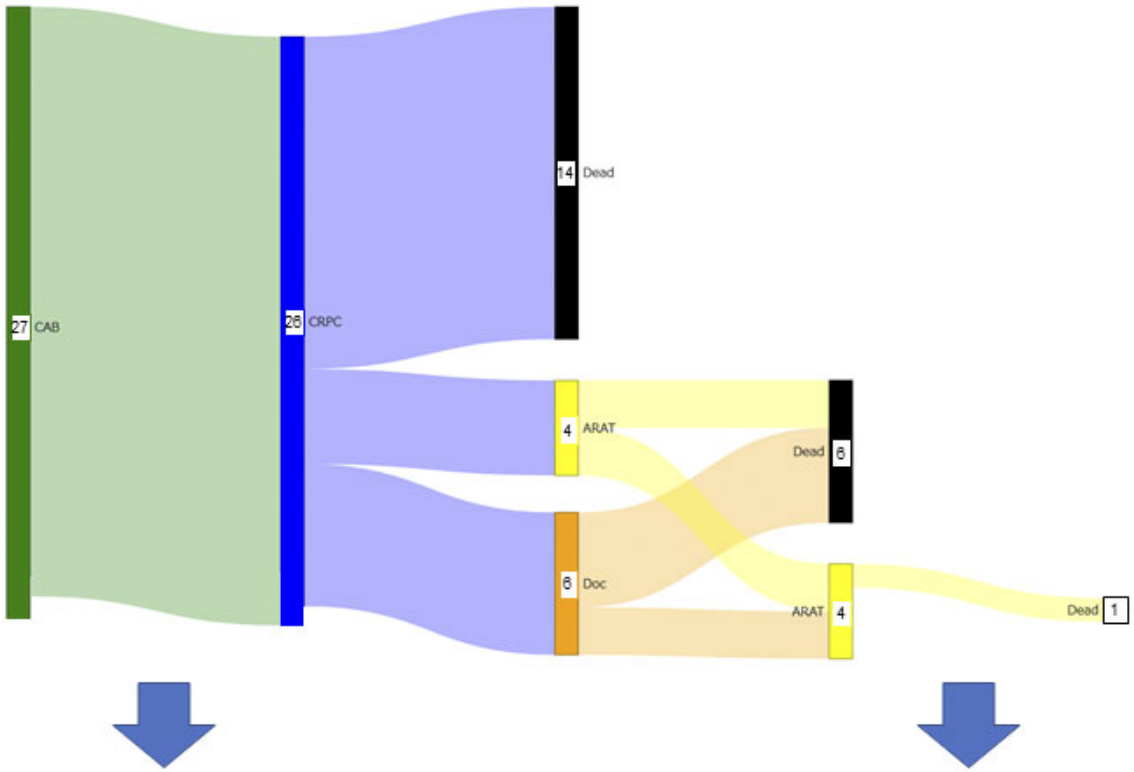
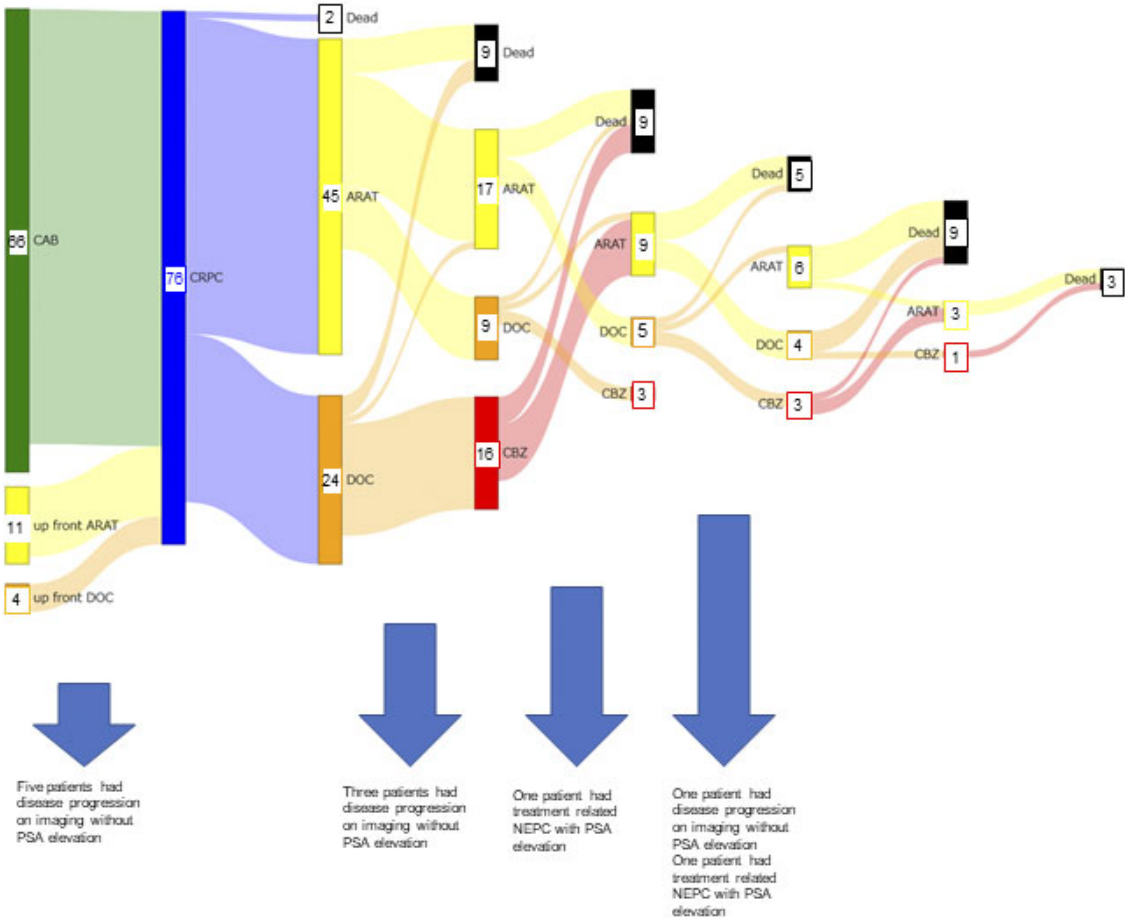
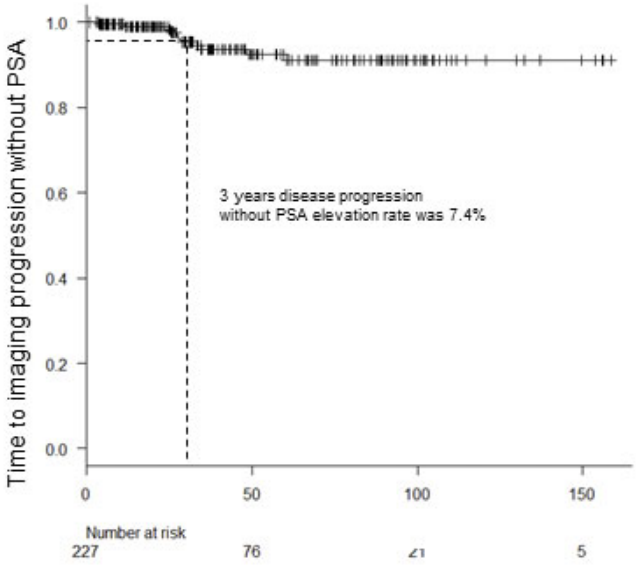

Synchronous metastatic prostate carcinoma treated with androgen deprivation therapy
N＝229
Excluded
Prostate cancer with neuroendocrine transformation in pretreatment biopsy specimen
N=2
Patients examined in this study
N=227
Disease progression on imaging without PSA elevation
N=11
HSPC or CRPC patients who have not experienced disease progression with elevated PSA
N=216

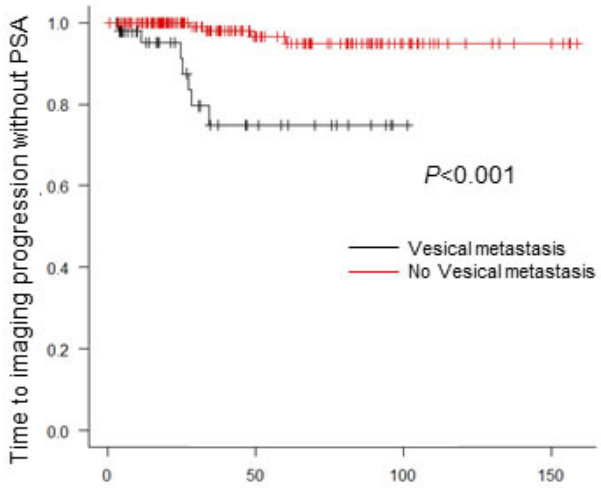


One patient had disease progression on imaging without PSA elevation

One patient had disease progression on imaging without PSA elevation


2 Dead
9 Dead
Dead 9
Dead 5
Dead 9
Dead 3
66 CAB
76 CRPC
45 ARAT
17 ARAT
ARAT 9
ARAT 6
ARAT 3
9 DOC
DOC 5
DOC 4
CBZ 1
CBZ 3
CBZ 3
16 CBZ
24 DOC
11 up front ARAT
4 up front DOC
Five patients had disease progression on imaging without PSA elevation
Three patients had disease progression on imaging without PSA elevation
One patient had treatment related NEPC with PSA elevation
One patient had disease progression on imaging without PSA elevation
One patient had treatment related NEPC with PSA elevation


Time to imaging progression without PSA
1.0
0.8
0.6
0.4
0.2
0.0
3 years disease progression
without PSA elevation rate was 7.4%
0
50
100
150
Number at risk
227
76
5



Number at risk				
Vesical metastasis	49	12	1	0
No Vesical metastasis	178	64	20	5

Figure 4B

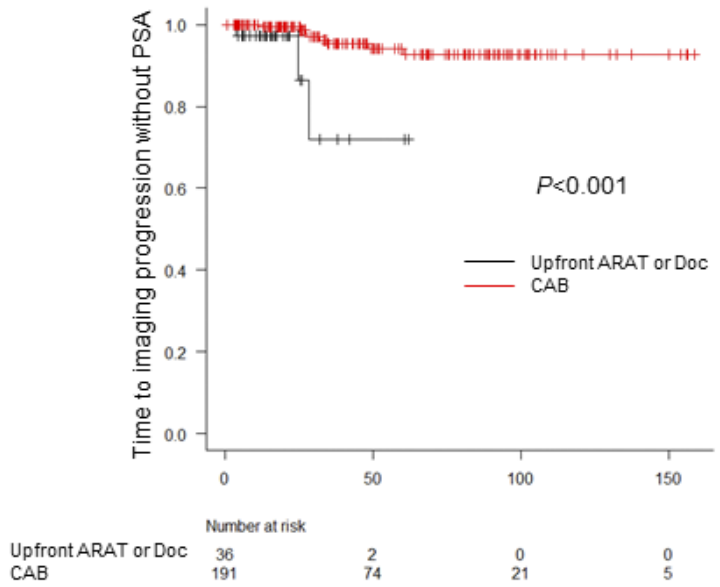

Time to imaging progression without PSA
1.0
0.8
0.6
0.4
0.2
0.0
0
50
100
150
P<0.001
Upfront ARAT or Doc
CAB
Number at risk
Upfront ARAT or Doc 36 2 0 0
CAB 191 74 21 5

Table 1. Patients' characteristics

Characteristics		Overall patients N=227	Patients who have not experienced diseaseprofression on imaging without PSA elevation N=216	Disease progression on imaging without PSA elevation N=11	*P*-value
Age, years (range)		73 (49-92)	73 (49-92)	68 (55-82)	0.053
Initial PSA, ng/ml (range)		219 (0.17-22412)	199 (0.17-22412)	320 (4.5-1663)	0.710
Gleason grade group, n (%)	1, 2	7 (3.1)	6 (2.8)	1 (9.1)	0.091
	3	17 (7.5)	17 (7.9)	0	
	4	102 (44.9)	100 (46.3)	2 (18.2)	
	5	101 (44.5)	93 (43.1)	8 (72.7)	
Clinical T stage, n (%)	1-2	26 (11.5)	26 (12.0)	0	0.552
	3	123 (54.2)	117 (54.2)	6 (54.5)	
	4	78 (34.4)	73 (33.8)	5 (45.5)	
Clinical N stage, n (%)	0	94 (41.4)	92 (42.2)	2 (18.2)	0.129
	1	133 (58.6)	124 (57.4)	9 (81.8)	
Clinical M stage, n (%)	Bone metastasis	196 (86.3)	188 (87.0)	8 (27.3)	0.177
	Visceral metastasis	49 (21.6)	42 (19.4)	7 (63.3)	0.002
	Lung metastasis	47 (20.7)	40 (18.5)	7 (63.3)	
	Liver metastasis	5 (2.2)	3 (1.4)	2 (18.2)	
CHAARTED high volume, n (%)		139 (61.2)	131 (60.6)	8 (72.7)	0.536
LHRH, n (%)	Agonist	1490 (65.6)	74 (34.3)	7 (63.6)	1
	Antagonist	78 (34.4)	142 (65.7)	4 (36.4)	
PSA nadir, ng/ml (range)		0.14 (0.009-399)	0.14 (0.009-399)	0.08 (0.009-34.82)	0.801
Upfront ARAT or Doc, n (%)		36 (15.9)	33 (15.3)	3 (27.3)	0.387
	Upfront ARAT	32 (14.1)	30 (13.9)	2 (18.2)	0.657
	Upfront Doc	4 (1.8)	3 (1.4)	1 (9.1)	0.181

ARAT, androgen receptor axis-targeted; LHRH, luteinizing hormone-releasing hormone; PSA, prostate-specific antigen

Table 2. Patients with imaging progression without PSA elevation

	Age	Initial PSA, ng/ml	Gleason grade	Clinical stage at initial therapy	Metastatic site at initial therapy	CHAARTED criteria	Course of treatment	PSA 3 months prior to imaging progression, ng/ml	PSA at imaging progression, ng/ml	Site of disease progression on image	Period since last imaging, months	Clinical symptoms	Pathological diagnosis	Time to imaging progression since initial therapy, months
Patients with imaging progression without PSA elevation	75	136	4	T3bNOM1c	Lung	High	CAB-ARAT	0.042	0.04	Primary lesion	12	Present	Poorly differentiated AC	25.8
	68	4.5	5	T4NOM1c	Lung	High	Upfront Doc-ARAT	0.399	0.033	Primary lesion	3	Present	Poorly differentiated AC	25.1
	61	1130	1	T3bN1M1c	Bone, Liver, Lung	High	CAB	0.009	0.009	primary lesion, Subcutaneous, Penis	5	Present	NEPC	27.6
	82	307	5	T4N1M1c	Lung, Bone, Lymph node	High	CAB	0.103	0.085	primary lesion, Lung, Bone	6	Absent	NEPC	11.6
	65	95.8	5	T3bN1M1	Lung, Bone	High	CAB-Doc-ARAT	8.217	6.917	primary lesion Lung, Liver, Lymph node	12	Absent	No examination	35
	72	320	5	T4N1M1c	Lung, Bone, Liver, Lymph node	High	Upfront ARAT	46.912	0.512	Lung, Bone, Lymph node	3	Absent	NEPC	3.6
	56	34.5	5	T3aN1M1b	Bone, Lymph node	Low	CAB	0.009	0.009	Lymph node	4	Present	NEPC	65.7
	74	383	4	T3bN1M1a	Lymph node	Low	CAB	0.071	0.055	Lymph node	6	Absent	NEPC	28.1
	68	394	5	T4N1M1b	Bone, Lymph node	High	CAB	0.009	0.009	Lymph node, Adrenal, Subcutaneous	20	Absent	NEPC	61.3
	54	1663	5	T4N1M1c	Lung, Bone, Lymph node	High	Uofront ARAT- Doc-Cbz- ARAT	312.802	275.134	Bone	3	Absent	No examination	28.7
	55	1108	5	T3bN1M1b	Bone, Lymph node	Low	CAB- Doc	556	563.7	Lymph node	4	Absent	No examination	32.6
Patients with NEPC and PSA elevation	49	110	5	T2NOM1b	Bone	High	Uofront ARAT-ARAT- Doc	2.536	10.17	Lung Bone	3	Present	NEPC	21.7
	66	348	5	T3bN1M1b	Bone, Lymph node	High	CAB- Doc-ARAT-ARAT	17.818	29.788	Bone, Liver	6	Absent	NEPC	46.3

AC, adenocarcinoma; ARAT, androgen receptor axis-targeted; CAB, combined androgen blockade; Cbz, cabazitaxel; Doc, docetaxel; NEPC, neuroendocrine prostate cancer; PSA, prostate-specific antigen

Table 3. Prognostic factors about imaging progression without PSA elevation

Characteristics	Univariate analysis			Multivariate analysis		
	Hazard ratio		*P*-value	Hazard ratio		*P*-value
Age ≤70 years	2.129	0.622-7.286	0.229	-	-	-
iPSA ≥100 ng/ml	1.959	0.519-7.364	0.321	-	-	-
Gleason grade group 1-4	0.294	0.078-1.109	0.071	-	-	-
Clinical T1-3	0.476	0.145-1.561	0.220	-	-	-
Clinical N1	3.990	0.859-18.62	0.077	-	-	-
Bone metastasis	2.214	0.587-8.347	0.241	-	-	-
Visceral metastasis	8.811	2.573-30.166	<0.001	9.025	2.603-31.289	<0.001
CHAARTED high volume	2.750	0.724-10.452	0.138			
LHRH antagonist	1.258	0.368-4.303	0.714	-	-	-
Upfront ARAT or docetaxel	6.281	1.572-25.094	0.009	6.863	1.569-30.211	0.011
PSA nadir ≤0.2	1.253	0.3652-4.302	0.720	-	-	-

ARAT, androgen receptor axis-targeted; LHRH, luteinizing hormone-releasing hormone; PSA, prostate-specific antigen