

Early change in prostate-specific antigen levels as a predictive marker for overall survival during vintage hormonal therapy for metastatic hormone-sensitive prostate cancer

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Abstract

Background

The effect of early changes in prostate-specific antigen (PSA) levels after androgen deprivation therapy (ADT) in metastatic hormone-sensitive prostate cancer (mHSPC) patients has not been well investigated. Here, we evaluated the effect of factors that lead to castration-resistant prostate cancer (CRPC) progression and overall survival (OS) in mHSPC.

Methods

Medical records of 71 consecutive primary mHSPC patients treated with ADT were analyzed. Factors predicting the time to CRPC and OS in these patients were evaluated at 3 months after ADT induction.

Results

The median times to CRPC and OS were 15 months and 92 months, respectively. In multivariate analysis using Cox proportional hazards regression, a Gleason score of 8 or more ($p = 0.004$), extent of disease value (EOD) of 2 or more ($p = 0.004$), and a PSA level of 1% or more of the pretreatment levels after 3 months of ADT ($p = 0.017$) were independent predictors of shorter time to CRPC. For OS, a PSA level of 1% or more after 3 months of ADT was the independent predictor ($p = 0.004$).

Conclusion

% PSA was an important factor that correlated with poor prognosis at 3 months after ADT induction.

Background

Androgen deprivation therapy (ADT) had been the standard of care for metastatic hormone-sensitivity prostate cancer (mHSPC). However, the effects of ADT on mHSPC substantially varies, and some patients show early resistance (1, 2). The mechanisms have been extensively investigated so far. Not only clinical data such as metastatic burden, but also molecular mechanisms such as androgen receptor have been investigated, suggesting a relationship with clinical results in several studies (3–5). However, to date, no prognostic classification is universally accepted for use in clinical practice or in clinical trials.

Between 2014 and 2017, docetaxel and abiraterone acetate were shown to increase the survival rate of men commencing ADT for mHSPC (6–9). As a result, abiraterone acetate has been administered in Japan for high-risk cases of mHSPC since 2018. However, problems or adverse events associated with long-term use of docetaxel or abiraterone acetate for mHSPC have not been solved. In addition, some prostate cancer patients who received chemotherapy experienced severe toxicities, particularly the Asian

patients (10, 11). Therefore, it is important to determine the marker that shows a poor response to ADT to screen appropriate candidates for the administration of early docetaxel and abiraterone acetate combined with ADT.

Several biomarker candidates have been found that are associated with the prognosis of ADT treated mHSPC patients (12), and a risk stratification models for mHSPC using these risk factors have been proposed (4, 12). Furthermore, recent studies showed that dynamic changes in prostate-specific antigen (PSA) at the early stages of prostate cancer had a higher effect on clinical outcome in patients with mHSPC and/or CRPC than that of pretreatment variables (13). However, there is less evidence about the effect of early changes in PSA after ADT in patients with mHSPC.

In this study, we aimed to assess whether early PSA change after ADT administration is predictive marker for mHSPC patients treated with ADT.

Methods

We retrospectively reviewed the medical records of 71 consecutive primary mHSPC patients (mean age 69 years) treated with ADT at the University of the Ryukyus Hospital and Naha City Hospital between January 2005 and June 2018. All patients were included in this study. Our institutional ethics review board approved this study.

The local evaluation was performed by rectal examination, transrectal ultrasound, or magnetic resonance imaging (MRI). Evaluation of the regional lymph nodes was performed with computed tomography (CT) or MRI. Evaluation of distant metastasis was performed with CT, bone scintigraphy, or ¹⁸F-fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-PET/CT).

Patients were considered to be on ADT if they were on any luteinizing hormone-releasing hormone (LHRH) agonists or LHRH antagonists, or had undergone surgical castration or combined androgen blockade (CAB). CAB included a combination of LHRH agonists or LHRH antagonists and flutamide or bicalutamide, or surgical castration and flutamide or bicalutamide. For the drug treatments, we administered 11.25 mg leuprorelin acetate once every 3 months or 10.8 mg goserelin acetate once every 3 months as an LHRH agonist, and we administered degarelix acetate initially at 240 mg and then once a month at 80 mg as an LHRH antagonist. We administered 125 mg flutamide three times daily or 80 mg bicalutamide once daily as an antiandrogen.

CRPC was defined as 1) an increase in prostate-specific antigen (PSA) levels based on the definition of prostate cancer working group 2 (PCWG2) (14), 2) exacerbation on image evaluation, or 3) the judgment of the attending physician (including a change of drug).

The time to CRPC was defined as the period from the day ADT was started to the day CRPC was diagnosed. Overall survival (OS) was defined as the time from the start of ADT to the date of death from any cause. All factors that predicted the time to CRPC and OS were evaluated. These included PSA value

at diagnosis, Gleason score at biopsy, Tumor Node Metastasis (TNM) classification before treatment, extent of disease (EOD) value, presence or absence of visceral metastasis, presence or absence of CAB therapy, presence or absence of bone modifying agents (BMA), and the % PSA at 3 months after ADT induction. The patients were divided into two groups based on PSA levels (≤ 261 ng/mL vs. > 261 ng/mL). The % PSA, at 3 months after ADT, was used to divide patients into two groups: a group with 1% or more of the pretreatment levels ($\text{PSA} \geq 1\%$) and a group with lower PSA levels ($\text{PSA} < 1\%$).

The statistical software used was JMP version 12, and the analyses of time to CRPC and OS were estimated using the Kaplan-Meier method and tested using the log rank test. Prognostic factors were analyzed by Cox proportional hazard regression. For multivariate analysis, we included all factors examined in univariate analysis. All p-values < 0.05 were defined as statistically significant.

Results

The average patient age was 69.3 ± 8.1 years (mean \pm SD), and the median PSA level at diagnosis was 261 ng/mL (interquartile range [IQR]: 92.5–618 ng/mL). A Gleason score of 8 or higher was found in 60 cases (85%). According to the TNM classification, 41 (58%) cases were classified as T3 and above. That is, more than half were locally progressive, and 43 (61%) were classified as N1. Bone metastasis was observed in 65 cases (92%), and visceral metastasis was observed in 17 cases (24%). 38 (58%) cases had an EOD score of 2 or above ($\text{EOD} \geq 2$). CAB therapy was administered to 69 (97%) patients. Approximately half of these cases, 34 cases (48%) used BMA. The median PSA level after 3 months of ADT was 2.6 ng/mL (0.03–1092), and the median % PSA at 3 months after ADT administration was 1.1%. (Table 1).

Table 1
Patient characteristics

(N = 71)		
Age		69.3 ± 8.1
PSA (ng/ml)		261 (IQR: 92.5–618)
Gleason score	8 or higher	60 (85%)
T stage	1	1 (1%)
	2	26 (37%)
	3	24 (34%)
	4	17 (24%)
	unknown	3 (4%)
N stage	0	28 (39%)
	1	43 (61%)
M stage	bone	65 (92%)
	visceral	17 (24%)
mCRPC		57 (80%)
EOD score of 2 or more		38 (57%)
CAB therapy		69 (97%)
used BMA		34 (48%)
Median PSA levels after 3 months of ADT		2.6 (0.03–1092)
Median PSA levels after 3 months of ADT (%)		1.1 (0.01–103.7)
Median observation periods (months)		38 (5-156)

The median observation period was 38 months (5–156), during that period, 57 patients (80%) progressed to CRPC. The median time to CRPC was 15 months (Fig. 1). The median OS was 92 months (Fig. 2).

In patients with an EOD ≥ 2 , the time to CRPC was significantly shorter ($p = 0.033$) than in patients with an EOD 1 and below (EOD ≤ 1). In the group of a PSA $\geq 1\%$ after 3 months of ADT, the time to CRPC was significantly shorter ($p = 0.027$) (Supplementary figure), and OS was also significantly shorter ($p = 0.01$). Lymph node metastasis and visceral metastasis were not significant factors in either the time to CRPC or OS (Table 2).

Table 2

Associations of potential baseline covariates with the time to CRPC and OS				
Covariates	Time to CRPC, HR (95%CI)	P-value	OS, HR (95%CI)	P-value
PSA levels \geq 261 ng/ml	1.17 (0.69–1.98)	0.553	1.08 (0.39–2.99)	0.876
Gleason score, 8 or higher	1.74 (0.81–3.75)	0.158	4.07 (0.53–31.14)	0.177
N stage	1.59 (0.91–2.75)	0.101	2.38 (0.77–7.31)	0.130
visceral metastasis	1.45 (0.80–2.63)	0.218	1.65 (0.46–5.92)	0.446
bone metastasis, EOD 2 or more	1.80 (1.05–3.10)	0.033	0.94 (0.34–2.62)	0.911
Used BMA	0.79 (0.47–1.34)	0.389	0.51 (0.18–1.44)	0.205
PSA levels after 3 months of ADT, 1% or more	1.84 (1.07–3.16)	0.027	7.05 (1.58–31.41)	0.010

In multivariate analysis using Cox proportional hazards regression, a Gleason score of 8 or more ($p = 0.004$), an EOD ≥ 2 ($p = 0.004$), and PSA $\geq 1\%$ after 3 months of ADT ($p = 0.017$) were found to be independent predictors of shortening the time to CRPC (Table 3). On the other hand, in OS, a PSA $\geq 1\%$ after 3 months of ADT was the independent predictor ($p = 0.004$).

Table 3

Multivariate analysis adjusted for potentially significant covariates in subset of N = 71				
Covariates	Time to CRPC, HR (95%CI)	P-value	OS, HR (95%CI)	P-value
PSA levels \geq 261 ng/ml	1.16 (0.61–2.22)	0.656	2.71 (0.55–13.26)	0.219
Gleason score, 8 or higher	3.55 (1.46–9.89)	0.004	7.58 (0.75–76.94)	0.087
N stage	1.58 (0.87–2.96)	0.138	3.93 (0.98–15.73)	0.053
visceral metastasis	1.98 (0.93–4.03)	0.074	2.91 (0.51–16.71)	0.231
bone metastasis, EOD 2 or more	2.49 (1.34–4.78)	0.004	0.68 (0.18–2.65)	0.583
Used BMA	1.04 (0.57–1.88)	0.900	1.17 (0.33–4.16)	0.802
PSA levels after 3 months of ADT, 1% or more	2.07 (1.14–3.82)	0.017	13.18 (2.34–74.38)	0.004

The time to CRPC was significantly shorter when compared to the group that satisfied all three of the Gleason score of 8 or more, EOD \geq 2 and the PSA \geq 1% after 3 months of ADT, and the other groups, ($p = 0.0171$) (Fig. 3).

Discussion

In this study, we assessed the usefulness of early PSA change after ADT administration as a predictive marker for mHSPC patients treated with ADT. We found that a PSA \geq 1% after 3 months of ADT was a strong predictive factor of OS. In addition, a Gleason score of 8 or more, an EOD \geq 2, and a PSA \geq 1% after 3 months of ADT were significantly associated with shorter time to CRPC.

In previous studies, serum bone markers (15), circulating tumor cells (CTC), (16) and single nucleotide polymorphisms (17) were identified as potential prognostic markers for patients with mHSPC who were administered ADT treatments. Goodman et al. assessed the prognostic factors in 33 mHSPC patients treated with ADT and found that initial CTC values predict the duration and magnitude of response to hormonal therapy. CTC enumeration may identify patients at risk of progression to CRPC before initiation of androgen deprivation therapy (16).

Conversely, other reports focus on the PSA value. PSA-related variables, including initial PSA levels and PSA kinetics, have been the most frequently assessed biomarkers in mHSPC (18). Among the PSA kinetic variables, PSA nadir and time to PSA nadir are promising biomarkers for mHSPC (19, 20). However,

previous studies reported that the median time to PSA nadir was 6–10 months (19, 20), which means that the prognosis was predictable more than half a year after the initiation of ADT. Guangiie et al. reported that a PSA velocity's decline of > 11 ng/mL per month was significantly associated with an increased risk of progression to CRPC after initial ADT (21). Although further studies are needed to identify the best marker among PSA-related variables to predict the outcome of mHSPC patients, PSA change at 3 months is a simple and convenient indicator for the prediction of clinical outcomes. Sato et al. (22) also reported that in the study of ADT for mHSPC, the group with a PSA decreased by 98.5% at 12 weeks after the initiation of treatment had significantly increased PSA progression-free survival and OS. In our study, a PSA $\geq 1\%$ after 3 months of ADT was an independent predictive marker. In their report, patients with visceral metastases were relatively low at 3.3%. On the other hand, in our report, 24% of patients had visceral metastases, which have relatively poor prognoses. It is very interesting to note that, even in such patients, an early PSA decline contributed to significant prolongation of OS. It is suggested that the group with a significant decrease in PSA in the early stage of treatment may have a better prognosis.

The independent factors affecting the time to CRPC in our study were: I) a Gleason score of 8 or more, II) an EOD ≥ 2 , and III) PSA $\geq 1\%$ after 3 months of ADT. In the LATITUDE trial (6), visceral metastasis was listed as an item of high risk, but in our study, visceral metastasis was not an independent predictor of poor prognosis. Distant metastasis, particularly visceral metastasis, represents an important negative prognostic factor in prostate cancers (3, 23–26). Peng-Fei et al. investigated the OS of 1358 prostate cancer patients with visceral metastasis and reported that lung metastasis had a better prognosis than brain or liver metastasis (27). In our study, 11 out of 17 patients (65%) with visceral metastasis only had lung metastasis. This might be one of the reasons that visceral metastasis was not shown to be a high-risk factor in our study.

The present study reported that the group with PSA $\geq 1\%$ after 3 months of ADT had a poor prognosis. Based on this result, PSA $\geq 1\%$ after 3 months of ADT may become one of the high-risk factors in mHSPC. However, there are no prospective reports observing a decline in PSA levels in the early stage. Nevertheless, more cases and prospective studies are required in the future for conclusive evidence.

A limitation of the present study is that it is a retrospective analysis performed at two hospitals. As such, the number of cases is small, and there is a possibility that patient and treatment selections might have been biased. In addition, the judgment of the attending physician is adopted as one of the definitions of CRPC, and there is a possibility of the data being affected by the difference in judgments of the attending physicians. However, this study points out the possibility that PSA $\geq 1\%$ after 3 months of ADT correlates with a poor prognosis, which has significant importance.

Conclusion

The median time to CRPC in patients who underwent ADT for mHSPC was 15 months, and the median OS was 92 months. % PSA at 3 months after ADT induction was correlated with a poor prognosis.

Abbreviations

PSA: prostate-specific antigen; ADT:androgen deprivation therapy; mHSPC:metastatic hormone-sensitive prostate cancer; CRPC:castration-resistant prostate cancer; OS:overall survival; EOD:extent of disease value; MRI:magnetic resonance imaging; CT:computed tomography; FDG-PET/CT:¹⁸F-fluorodeoxyglucose-positron emission tomography/computed tomography; LHRH:luteinizing hormone-releasing hormone; CAB:combined androgen blockade; PCWG2:prostate cancer working group 2; TNM:Tumor Node Metastasis; BMA:bone modifying agents

Declarations

Ethics approval and consent to participate

The present study was approved by the internal institutional review board of the University of the Ryukyus (approval number: 1341). This was a retrospective study, and additional informed consent was not required by the board.

Consent for publication

The data do not contain any information that could identify the patient, therefore consent for publication was waived.

Availability of data and material

The data supporting the conclusions used and/or analyzed in this study are available from the corresponding author by request.

Competing interests

The authors declare that they have no competing interests.

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None.

Authors' contributions

SN, MG, and SS: conception or design of the work; acquisition, analysis, or interpretation of data; and drafting or revising the work. MT and TO: acquisition of data and interpretation of data. All authors have read and approved the manuscript.

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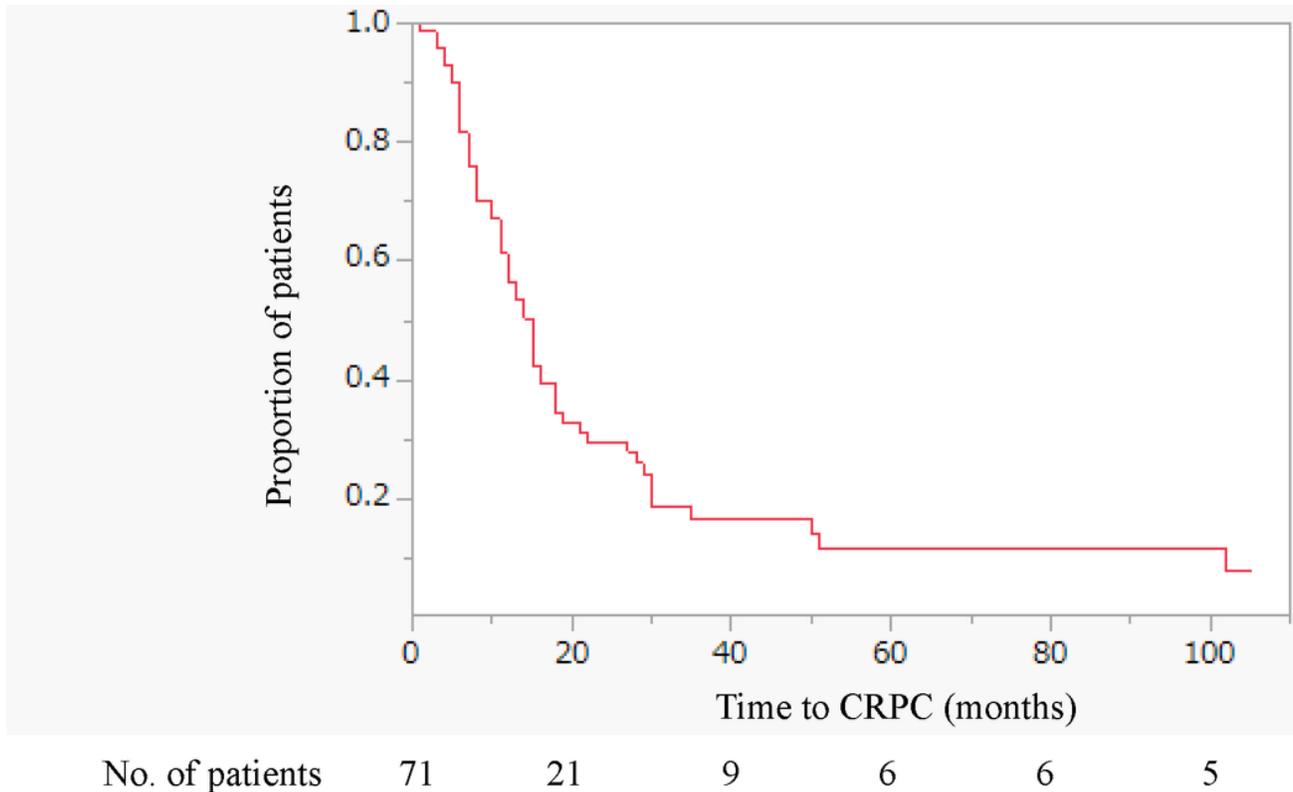
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Figures

Figure 1

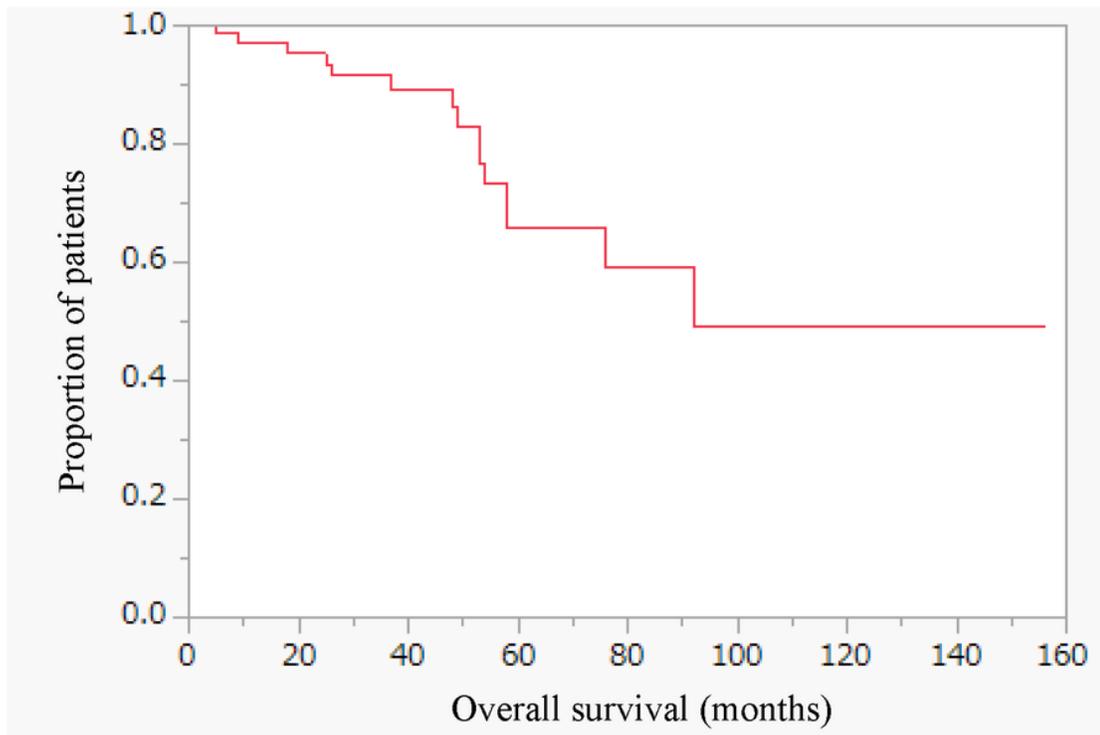


Median time to CRPC: 15 months

Figure 1

This figure is a Kaplan-Meier curve showing the time to CRPC. Median time to CRPC is 15 months.

Figure 2



No. of patients

71

54

34

16

10

5

2

2

Median OS: 92 months

Figure 2

This figure is a Kaplan-Meier curve showing the overall survival. Median overall survival is 92 months.

Figure 3

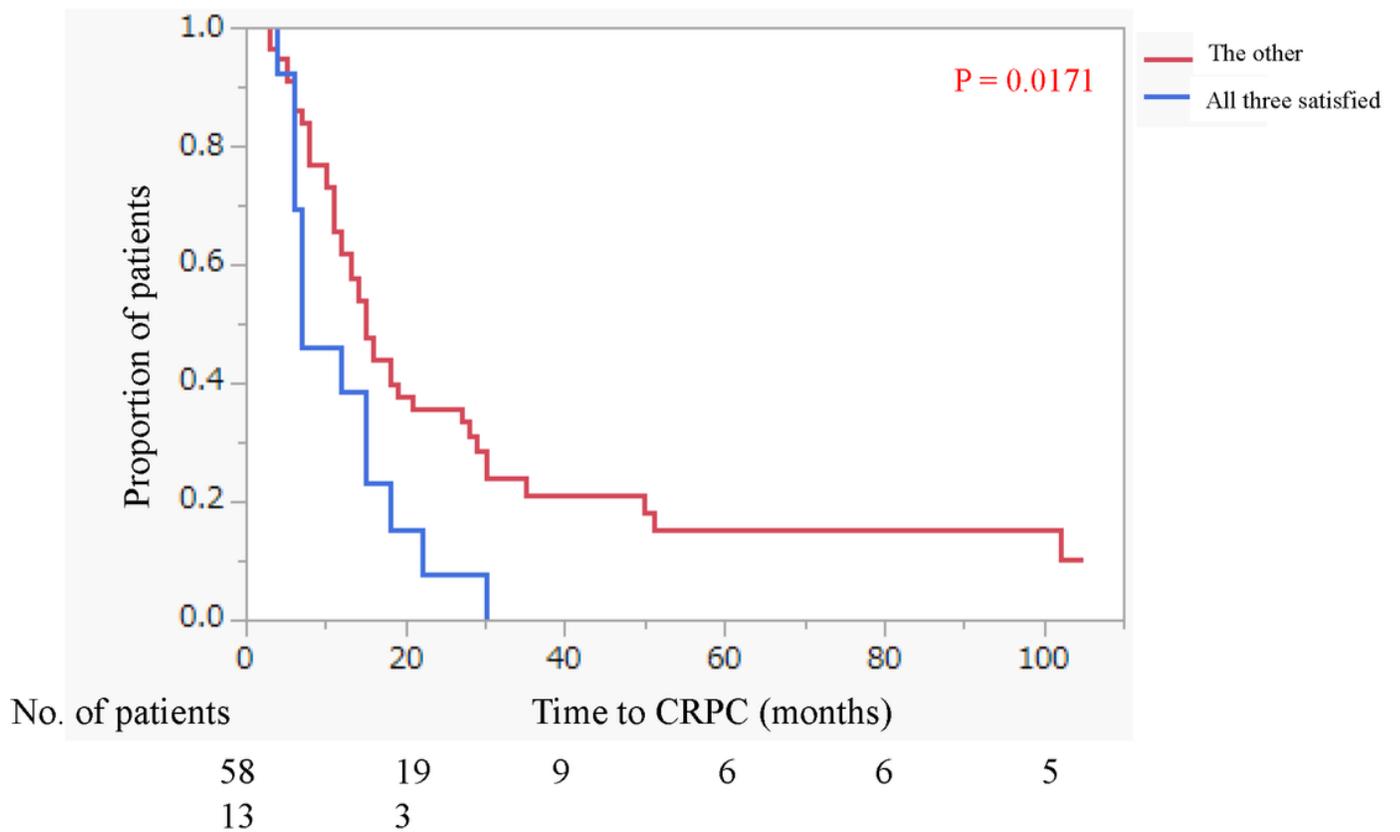


Figure 3

This figure compares Kaplan-Meier curves between the group that satisfied all three and the other group. In time to CRPC, the all-three-satisfied group is significantly shorter than the other group ($p = 0.0171$).

Supplementary Files

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- [revisedversionsupplementaryfigure2020.08.26..png](#)