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Prostate Specific Antigen (PSA) and Time to PSA Nadir as a Prognostic Value for Castration-Resistant Prostate Cancer

FirmantyaHadi Pranata[1], Wahjoe Djatisoesanto[1], Doddy Moesbadianto Soebadi[1]
Department of Urology, Faculty of Medicine, Universitas Airlangga,
Dr. Soetomo General-Academic Hospital[1]

Abstract— Prostate cancer patients often suffer castration-resistant prostate cancer (CRPC), resulting in high mortality rates. Few is still known regarding the factors affecting survival in CRPC patients. We aimed to evaluate PSA level and time to PSA nadir as a prognostic marker for survival in CRPC patients. This is an analytical retrospective study evaluating castration-resistant prostate cancer patients' survival. Evaluated data included sex, age, initial PSA level, final PSA level, time to PSA nadir (TTN), time to CRPC progression (TTC), and survival status. There were 24 patients with CRPC included in this study. There is a significant difference($p<0.05$)of initial PSA level between surviving patients (445,7 $\pm$ 165,6 ng/mL) and patients who died (200.7 $\pm$ 144.9 ng/mL). The association between TTN and TTC was also significant ($R=0.737$, $p<0.05$). The differences of PSA nadir level, TTN, and TTC between the groups were insignificant ($p>0.05$). There is a significant difference of initial PSA between surviving and non-surviving patients, whereas no notable differences are apparent in PSA nadir level, time to PSA nadir, and time to CRPC progression. However, there is an association between the time to PSA nadir and CRPC progression.

Keywords— Prostate specific antigen, PSA nadir, Prostate cancer, castration-resistant prostate cancer

1. Introduction

Prostate cancer is the second most common malignancy in men, comprising almost 15% of all male cancers worldwide [1]. It is believed that one in 25 men is likely to be diagnosed with prostate cancer in his lifetime [2]. Primary androgen deprivation therapy (ADT) is the gold standard of therapy for metastatic prostate cancer. However, in some casesdisease progression may occur at various intervals after ADT[3].This progression is defined as castration-resistant prostate cancer (CRPC)[4]. Little is currently known about the factors affecting the survival of patients with CRPC.One of the most commonly evaluated prognostic parameters is prostate specific antigen (PSA) level, even though using PSA as a single predictor for prognosis in prostate cancer patients may be unreliable[5]. Recent studies proposed the utilization of initial PSA level, time to PSA nadir (TTN), PSA nadir level, and time to CRPC (TTC) among other parameters for predicting the prognosis of CRPC patients[6].This study aimed to evaluate PSA level and time to PSA nadir as a prognostic marker for survival in CRPC patients.

2. Materials and Methods

This is an analytical retrospective study evaluating the prostate cancer patients based on the medical record date of Dr. Soetomo General-Academic hospital from January 2013 to December 2020. All prostate cancer patients receiving treatment with castration-resistant progression were included. Evaluated data included sex, age, initial PSA level, final PSA level, time to PSA nadir (TTN), time to CRPC progression (TTC), and survival status. The progression of CRPC is defined as a rising PSA level and or radiographic progression evidence despite medical or surgical castration [7]. Initial PSA level of the patients is defined as the PSA level when the patient was admitted, whereas final PSA nadir level is defined as the lowest level after castration. Time to PSA nadir is defined as the time from castration until the lowest level of PSA is reached. Time to CRPC is defined as the time from PSA nadir level to castration-resistant development. All variables are presented descriptively in graphs.A Shapiro-Wilk test was performed to evaluate the normality of distribution. An Independent T-test was used to evaluate the differences of both times between

the surviving and non-surviving groups of patients if the data was normally distributed, otherwisea Mann-Whitney U test would be used. The association between time to PSA nadir and time to castration-resistant progression was analyzed using a correlation analysis. This study has been approved by the ethical committee of Dr. Soetomo General Academic Hospital with the ethical number: 0392/129/XI/2020.

3. Results

3.1. Baseline Characteristics

There were 24 patients with CRPC included in this study. The average age of the samples were 65.54±7.5years old. The initial PSA of patients was 388.57 ± 596.7 ng/mL. Medical castration was performed on four patients, whereas surgical castration was performed on 20 patients. It took approximately 308.4 ±293.7 days for the PSA level to reach PSA nadir. The average level of lowest PSA level was 46.4± 112.5 ng/mL. The average time for the patients to develop CRPC was 554.1 ± 437.1 days.

3.2 Initial PSA and Patient Survival

There were seven patients who died and 17 patients who survived until the last period of observation. The average initial PSA level of surviving patients was 445,7 ± 165,6 ng/mL and 200.7 ± 144.9 ng/mL for patients who did not survive. The Shapiro-Wilks test result indicated a normal distribution of data ($p>0.05$), thus, an independent T-test was used for a comparative analysis. There is a significant difference of initial PSA level between the groups ($p<0.05$) as shown in figure 1.

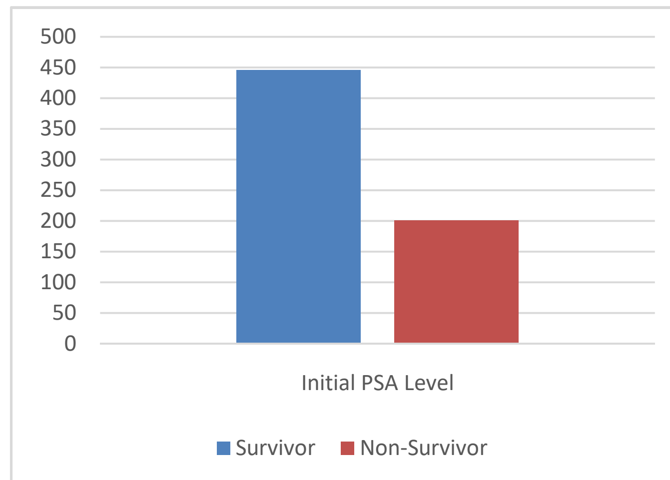

Figure 1. Initial PSA LevelDifferences between Surviving and Non-surviving Patients

3.2 PSA Nadir and Patient Survival

On average, the PSA nadir level among patients who survived was 42,8 ± 131,9 ng/dL, whereas the average PSA nadir level among patients who died was 42,7 ± 48,7 ng/dL. Mann-Whitney test was used to compare both groups due to the abnormal data distribution ($p<0.05$). The difference between both groups in figure 2 was insignificant ($p>0.05$).

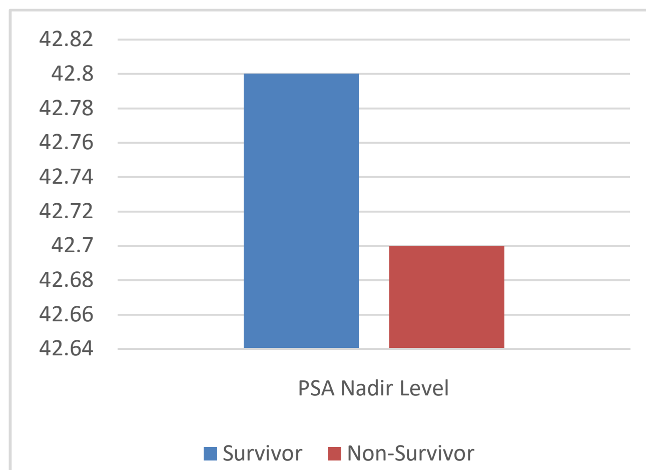

Figure 2. PSA Nadir Level Differences between Surviving and Non-surviving Patients

3.3 TTN and Patient Survival

The average TTN of the surviving patients was 318,5 ± 176,9 day, whereas the TTN of patients who died was 284,1 + 510,5 days. The abnormal distribution of the data led to the use of Mann-Whitney test for comparison ($p<0.05$). The analysis resulted in an insignificant difference between the two groups ($p>0.05$), as shown in figure 3.

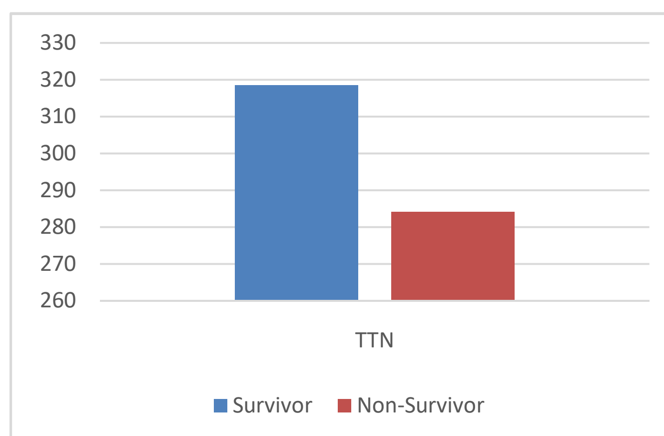

Figure 3. Time to PSA Nadir Level Difference between Surviving and Non-surviving Patients

3.4 TTC and Patient Survival

Patients who survived had an average TTC of 598,9 ± 431,1 days, whereas the TTC of patients who did not survive was 445.2 ± 499,2 days. Mann-Whitney test showed an insignificant difference between the two groups shown in figure 4 ($p<0.05$).

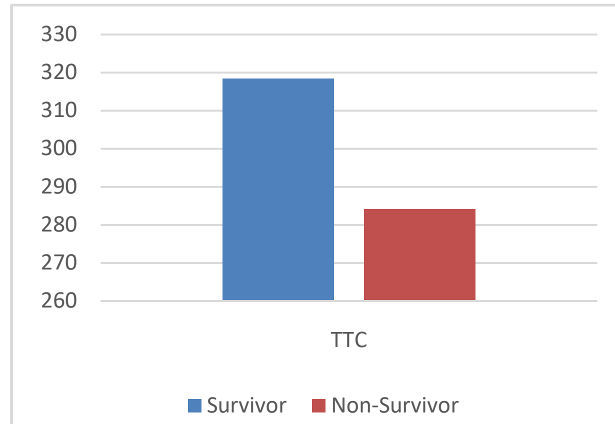

Figure 4. Time to Castration-Resistant Progression between Surviving and Non-surviving Patients

3.5 Correlation Between TTN and TTC

A Pearson correlation analysis was performed between the TTN and TTC variables, resulting in a significantly positive association with an association strength of 0.737 ($p<0.05$), as shown in figure 5.

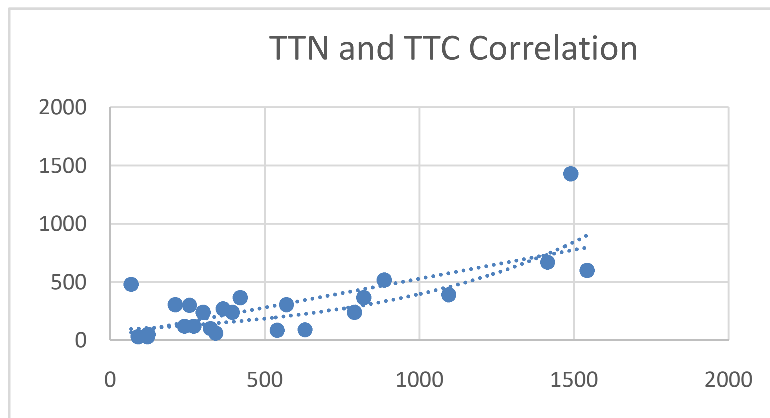

Figure 5. Correlation Analysis of TTN and TTC

4. Discussion

PSA tests are utilized daily for both prostate cancer screening and progression monitoring[8]. During androgen deprivation therapy (ADT), PSA monitoring is useful to evaluate response to treatment. Most patients displayed areduction in PSA levels in the first month following ADT treatment [9].In this study, there were 24 evaluated patients with CRPC. The majority of patients

A high initial PSA level reflects the severity of tumor characteristics or an asymptomatic tumor for a long period of time, indicating the possibility that the patient is neglectful of his condition[10]. A high PSA level also indicates a high androgen receptor activity of prostate cancer cells[11]. Previous studies also highlighted the mortality risk of a high PSA level [12]. On the contrary, the patients with lower PSA levels in this study have a significantly higher mortality rate compared to patients with relatively higher PSA levels ($p<0.05$). The difference in findings is possibly due to the bias of PSA measurement and age variation among patients. The evaluation of age difference is often not assessed in measuring initial PSA [13].The sensitivity and specificity of PSA measurement is low due to several factors affecting PSA level, such as catheterization, post-coitus, benign prostatic enlargement (BPE), and prostate infection [14].

In this study, there is no correlation between TTN and survival ($p>0.05$). A previous large scale retrospective study evaluating 89 patients from 2000 to 2009 reported a significant association between TN and survival. The study reported a significantly higher overall survival in patients with TTN less than 9 months compared to patients with more than 9 months TTN. They discovered a PSA nadir level of less than 0.2 ng/mL was associated with a better prognosis [15]. A number of studies suggested that TTN and survival rate may be due to nature of some prostate cancer cells which can adapt to castration by utilizing intracrine androgens. During castration, androgen-sensitive cells would perish, while cells which can produce intracrine androgen[9].

The TTC in this study was not associated with the patients' survival rate. These findings are different compared to a previous retrospective study evaluating 287 patients from 1996 to 2009, which reported that TTC is an independent factor to predict overall survival and progression-free survival. The study claimed that TTC less than two years is associated with a worse prognosis [16]. Another retrospective study evaluating 289 patients from 2008 to 2015 reported a positive association between TTC and survival. Interestingly, the study also reported a positive association between hormone sensitive prostate cancer (HSPC) and patient survival [17]. The differences of the findings in this study compared to previous studies may be due to the small number of samples in this study. Several studies suggested that a low TTC is due to PSA volume and PSA doubling time difference [11].

The significant correlation between TTN and TTC in this study highlighted fascinating implications. Previous studies also reported that castration-resistant is faster to occur in patient with short TTB[6]. During castration level, there is a decrease in oncogene retinoblastoma protein (pRB), causing a decrease in cyclin dependent kinase (CDK). This decrease caused an arrest prostatic cancer cell replication. In a terminal proliferation phase, there are two possibilities for prostatic cancer cells, apoptosis or continually producing intracrine testosterone at a certain level of castration [9]. The mechanism of dependent androgen receptors has a role in castration-resistant progression. In some cases, androgen is still available at a low concentration even though the ADT has been given. This condition could lead to an adaptation of prostate cancer cells by amplification and an increase of AR expression via a mutation. The amplification and mutation of AR involve several co-activators and co-repressors. Several studies reported the increase oof FKBP51 co-activator in castrated rats. Co-repressor proteins are lower in CRPC patients. Based on the mechanism, several studies concluded that castration which leads to a short TTN would increase the activity of co-activators, while decreasing the activity of co-repressors, inducing the amplification and mutation of AR[18].

This study is limited due to its retrospective design and small number of samples. The follow-up period of the patients can also be extended to evaluate other factors that may affect survival. The diagnostic modality in this study to evaluate metastasis was also limited.

5. Conclusion

There is a significant difference of initial PSA between surviving and non-surviving patients, whereas no notable differences are apparent in PSA nadir level, time to PSA nadir, and time to CRPC progression. However, there is an association between the time to PSA nadir and CRPC progression.

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