Kinetic Analysis of Prostatic Volume and Prostate Specific Antigen (PSA) in Patients with Advanced Prostatic Cancer Treated by Castration

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OKIHARA, K., WATANABE, H., SAITOH, M. and KOJIMA, M. Kinetic Analysis of Prostatic Volume and Prostate Specific Antigen (PSA) in Patients with Advanced Prostatic Cancer Treated by Castration. Tohoku J. Exp. Med., 1998, 185 (1), 37-44 — The clinical usefulness of the kinetic analysis of prostate specific antigen (PSA) in patients with advanced prostatic cancer treated by castration has not yet been evaluated. The reduction of both prostatic volume and PSA was monitored in 37 patients with Stage C and Stage D prostatic cancer. The change of prostatic volume was measured frequently by transrectal ultrasonography (TRS) after castration, as was the change of PSA. A kinetic analysis of both prostatic volume and PSA was made by comparing the reduction time $\tau$ (PSA) (speed of the reduction of PSA) and $\tau$ prostatic volume (PV). There was a statistically significant correlation between $\tau$ (PSA) and $\tau$ (PV) in patients with a $\tau$ (PV) of less than 30 days. However, no correlation was observed in patients with a $\tau$ (PV) of more than 30 days, because the $\tau$ (PSA) in this group fell into a relatively low range similar to the group with a $\tau$ (PV) of less than 30 days. It was assumed that the change of PSA after castration reflected mainly the response of the hormone dependent portion of the total cancer volume. However, all data of $\tau$ (PV) with a $\tau$ (PSA) less than 10 days were within 30 days. In conclusion, $\tau$ (PSA) might be promising as a prognostic factor after castration in patient with advanced prostatic cancer, although $\tau$ (PSA) was not a direct substitute for $\tau$ (PV).

Transrectal sonography (TRS) (Watanabe et al. 1975) is currently the most reliable means of measuring prostatic volume (PV) (Watanabe et al. 1974). In 1988, we reported the change of PV after castration in 82 cases of prostatic cancer measured by TRS (Ohe and Watanabe 1988). According to our kinetic study, the total PV in patients with prostatic cancer decreased exponentially after castration without exception, approaching a constant plateau level (the volume of the

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Address for reprints: Koji Okihara, M.D., Department of Urology, Kyoto Prefectural University of Medicine, Kawaramachi-Hirokoji, Kyoto 602-0841, Japan.
ineffective portion). Based on this finding, a formula for the regression curve in treating prostatic cancer was established, and can be expressed as

\[ V = a \cdot 10^{-t/\tau(PV) + b} \]  

where \( V \) is the total PV, \( a \) is the volume of the effective portion, \( b \) is the volume of the ineffective portion, while the reduction time \( \tau(PV) \) is a constant representing the time interval required for the effective portion responding to treatment to be reduced to 1/10 (Fig. 1). \( \tau(PV) \) was important in predicting the prognosis of patients with advanced (Stage C and Stage D) disease, treated by castration (Watanabe et al. 1997). We concluded from the data that the critical point for prognosis may be a \( \tau(PV) \) of 30 days.

Okihara (1995) clarified why the prognosis of patients was so dependent to \( \tau(PV) \). When a prostatic cancer recurred, cases having a \( \tau \) of less than 30 days did not show metastatic progression, only local progression. Prostatic cancer cases having a \( \tau \) greater than 30 days had local or metastatic progression, but the doubling time of the local progression was shorter than that in prostatic cancer cases having a \( \tau \) of less than 30 days. Accordingly, prostatic cancer cases with high \( \tau \) had a strong possibility of developing metastatic progression or rapid local progression on recurrence.

\( \tau(PV) \) is thus an excellent predictor of the prognosis in patients with advanced prostatic cancer. However, careful size assessment by frequent TRS is required. If the kinetics of PSA were an alternative to those of PV, the information could be obtained more easily. In the present study, the usefulness of the kinetic analysis of PSA after castration was evaluated in comparison with that of PV.

Fig. 1. Reduction curves of prostatic volume.

\[ V = a \cdot 10^{-t/\tau} + b \]

\( V_0 \), total value; \( a \), effective portion; \( b \), ineffective portion; \( \tau \), reduction time.
**Materials and Methods**

Thirty seven patients (age range 58-80 years, mean 74 years) who suffered from advanced prostatic cancer confirmed by biopsy with no previous treatments were chosen for the study. They were initially treated by castration between January 1994 and April 1997 at the Kyoto Prefectural University of Medicine. Histopathology revealed adenocarcinoma in all cases, classified into well ($n=5$), moderately ($n=27$) and poorly ($n=5$) differentiated cancer, respectively. Clinical stages were determined by digital rectal examination and various image modalities. Twenty one patients were in Stage D$_2$ with bone metastases including one lung metastasis, and 16 were in Stage C.

PV was measured by the planimetry method (Watanabe et al. 1974). Horizontal sections of the whole prostate were taken from the base to the apex at 0.5 cm intervals by ultrasonic equipment with the patient seated (Aloka, SSD-520, Tokyo) using a 5 MHz transducer. The volume of the whole prostate was calculated from the sum of the areas of each step section multiplied by 0.5. Serum PSA levels were determined by Delfia PSA immunoradiometric assay (Pharmacia Fine Chemicals Inc., Uppsala, Sweden).

Both PV and serum PSA value were measured before castration, as well as on the 1st, 3rd, 5th, 7th, 10th and 14th days after castration. After the third post-therapeutic week, these values were taken once every month. When the PSA level reached a nadir level after castration, this became the definition of the lowest PSA level in the kinetic study.

Putting the clinical data of each PV into the formula according to the least-squares method, $\tau(PV)$ was calculated for each patient. Statistical analysis between the 2 groups was performed using the Student's $t$-test. $p$-Values of 0.05 were taken as the limit of statistical significance.

**Results**

In all patients, PV decreased exponentially after castration and $\tau(PV)$ could be calculated. This ranged between 7 and 100 days. There was no significant difference of $\tau(PV)$ between Stage C ($41.6 \pm 23.4$ days) and Stage D ($44.3 \pm 22.6$ days, $p > 0.05$) patients.

The pretreatment PSA levels were elevated abnormally in all patients with a median level of 66 ng/ml (range: 15.8 to 5510). There was no statistical correlation between pretreatment PSA and $\tau(PV)$ (Fig. 2).

The mean time for the PSA to reach its lowest level was 5.8 months (s.d.: 3.1 months). The lowest PSA level (PSA nadir) ranged between 0.1 and 65 ng/ml, and had a median level of 2.4 ng/ml.

The measured PSA also decreased exponentially after castration without exception (Fig. 3). Accordingly, equation (1) could also be adopted in the kinetic analysis of PSA. The PSA regression was analysed in the same way as $\tau(PV)$,
Fig. 2. Relation between $\tau$(PV) and pretreatment PSA.
Patients were classified into 4 subgroups according to PSA level (-50, 51-99, 100-599, 600-). There were no significant differences in each subgroup.
(PSA: -50; 37.6±28.4, 51-99; 37.8±36.2, 100-599, 48.1±23.9, 600-; 30.9±19.2)

dividing the total PV into two portions:

Effective portion(a) = Pretreatment PSA - PSA nadir
Ineffective portion(b) = PSA nadir

From this definition, the regression curve for PSA could also be expressed by an exponential function:

\[
\text{Pretreatment PSA} = a \cdot 10 - t/\tau(\text{PSA}) + b
\]

where $\tau(\text{PSA})$ is a constant which represents the time interval required for (a) to be reduced in numerical value of PSA to one-tenth. $\tau(\text{PSA})$ ranged between 4 and 44 days. There was no significant difference between $\tau(\text{PSA})$ in cases with Stage C (21.6±9.5 days) and those Stage D (22.8±10.3 days, $p > 0.05$).

There was no significant correlation between $\tau$(PV) and $\tau$(PSA) in all the patients (Fig. 4). However, when patients were classified into two groups, as to whether $\tau$(PV) was less or greater than 30 days, a remarkable difference was found between them. $\tau$(PV) (18.2±5.6 days) was almost equivalent to $\tau$(PSA) (17.7±7.1 days) in patients, whose $\tau$(PV) was less than 30 days ($r=0.716$, $p=0.004$). On the other hand, $\tau$(PV) (60.4±18.8 days) was much longer than $\tau$(PSA) (20.6±9.2 days) in patients whose $\tau$(PV) was over 30 days. No statistical correlation
Fig. 3. Changes of both prostatic volume and serum PSA in 2 cases treated by castration. Prostatic volume as well as PSA reduced exponentially, approaching a constant plateau level. In case 1 (■), effective portion (a), ineffective portion (b) of prostatic volume and \( \tau(PV) \) were 30.7 (ml), 34.3 (ml) and 48 days. Pretreatment PSA, PSA nadir (a), PSA nadir (b), and \( \tau(PSA) \) were 137 ng/ml, 2.0 ng/ml and 22 days, respectively. In case 2 (○), (a), (b) of prostatic volume and \( \tau(PV) \) were 11.2 (ml), 33.9 (ml) and 10 days, and (a), (b) of PSA and \( \tau(PSA) \) were 28.3 (ng/ml), 13.5 (ng/ml) and 19 days, respectively.

was found \( (r=0.33, p=0.29) \) (Figs. 5 and 6).

However, all datas of \( \tau(PV) \) with a \( \tau(PSA) \) less than 10 days were within 30 days (Fig. 7).
Fig. 4. Relation between $\tau$(PSA) and $\tau$(PV) in 37 patients. There was no significant correlation between $\tau$(PSA) and $\tau$(PV) ($r=0.28$).

Fig. 5. $\tau$(PV) was almost equivalent to $\tau$(PSA) in patients with $\tau$(PV) less than 30 days.

**Discussion**

PSA usually decreases after androgen deprivation therapy. In particular, the PSA nadir provides important prognostic information (Matzkin et al. 1992; Miller et al. 1992). However, few investigation have been made on the manner of
Fig. 6. $\tau$(PV) was longer than $\tau$(PSA) in all patients with $\tau$(PV) more than 30 days.

Fig. 7. All data of $\tau$(PV) with a $\tau$(PSA) less than 10 days ($n = 7$) were within 30 days, while data of $\tau$(PV) with a $\tau$(PSA) more than 10 days ($n = 30$) ranged between 10 and 100 days.

PSA regression.

Fowler et al. (1994) analysed PSA regression after hormonal therapy by PSA half life. They calculated PSA half life from PSA levels before and 28-days after treatment and concluded that PSA half life had no significance as a prognostic factor.
Both PSA half life and $\tau(\text{PSA})$ represent the regression speed of PSA. However, one important difference between PSA half life and $\tau(\text{PSA})$ was the frequency of PSA measurements. PSA half life was estimated from only 2 data points and a proportionally linear regression of PSA between them was anticipated. The true manner of PSA regression after treatment was not proportionally but logarithmically linear, as shown by the concept of $\tau(\text{PSA})$. From our data, $\tau(\text{PSA})$ was compatible with $\tau(\text{PV})$ as regards the manner of regression. The correlation between $\tau(\text{PV})$ and $\tau(\text{PSA})$ was only found in patients with a $\tau(\text{PV})$ of less than 30 days. $\tau(\text{PSA})$ in cases having a $\tau(\text{PV})$ of more than 30 days fell into the same range as that in cases having a $\tau(\text{PV})$ of less than 30 days, in spite of a considerable distribution of $\tau(\text{PV})$.

The cause of the dissociation between $\tau(\text{PV})$ and $\tau(\text{PSA})$ might be explained that the value of PSA only reflected the trend of the androgen dependent cancer cells. There is a possibility that even in cases in which the majority of the cancer focus was made up of androgen independent cells, resulting in a longer $\tau(\text{PV})$, the trend of PSA change might indicate the trend of the androgen dependent cells, which made up only the minority of the cancer focus, resulting in a shorter $\tau(\text{PSA})$.

However, the evidence that all data of $\tau(\text{PV})$ with a $\tau(\text{PSA})$ less than 10 days were within 30 days might be lead to the conclusion that analysis for the regression of PSA is also promising as a prognostic factor after castration in patients with advanced prostatic cancer, although $\tau(\text{PSA})$ was not a direct substitute for $\tau(\text{PV})$.

References


