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INVITED RESEARCH HIGHLIGHT

Prostate Cancer

Relapse of prostate cancer from the viewpoint of total gland volume kinetics theory

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In many cases of prostate cancer, changes of prostate volume were measured very frequently after castration by means of transrectal ultrasound. For short-term observations, a factor called as “reduction time (τ),” which means the time required for the volume of “effective portion” (volume responded to castration) to be reduced to one-tenth of its original value, correlated very well with patients’ prognosis. For long-term observations for relapse, changes of prostate volume could be divided clearly into two types, namely, “metastatic progressive type” with metastasis without volume increase and “local progressive type” with remarkable volume increase without metastasis. “ τ ” in the “local progressive type” was far shorter than that in the “metastatic progressive type.” Much longer survival was obtained when the patient belonged to the “local progressive type,” than to the “metastatic progressive type.” Thus, “ τ ” was the most important and the most reliable factor to predict the prognosis. Based upon these observations, a schematic analysis of prostate cancer relapse was shown.

Transrectal ultrasound (TRS) came into practice near 50 years ago¹ and its excellent function for size measurement² has contributed much to the pathophysiology of the prostate.³ For this purpose, the chair-type scanner⁴ is particularly suitable because the prostate is fixed stably in sitting position, and

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the insertion of the probe can be controlled precisely. Although prostate-specific antigen (PSA) kinetics has been a point of emphasis in modern clinical evaluation, gland volume has been feasible for a longer period. In this article, we present the narrative of total gland volume changes for men initiating androgen deprivation therapy as correlated to clinical outcomes.

KINETICS OF HORMONE THERAPY⁵

The volume of the prostate in patients with prostate cancer is reduced after castration without exception. Very frequent measurement of the volume revealed that the reduction curve had an exponential function as shown in **Figure 1**. Usually, measurement was taken once every day for the first postoperative week, once every 2 days for the second week, then once every week for 3 months. Since rapid volume reduction occurred immediately after castration, such frequent measurement was very important. To analyze the finding, a modeling of reduction curves was made. It was assumed that the total volume consisted of the “effective portion,” which was reduced after castration and the “ineffective portion,” which did not change (**Supplementary Figure 1**).

The reduction curve was simulated in logarithmic formula shown in **Figure 2**. The kinetic change of prostatic volume was thus indicated by three factors: the effective portion (a), the ineffective portion (b) and the reduction time (τ). The value of “ a ” reduced with the time elapsed (t), approaching the value of “ b ”. The reduction time (τ) means the time required for the value of “ a ” to be reduced to one-tenth of its original value. This “ τ ” shows how rapidly the prostate shrinks after castration and its value is represented in “days.” The τ is the only and most important factor to control the total course of prostate cancer.

The factor, “ τ ”, corresponded well to each clinical parameter. Among three factors in the formula, only τ increased remarkably with the advancement of grading and staging, in a survey of 82 patients with prostate cancer (**Table 1**).

In all cases of Stage D cancer, with a τ <30 days, patients survived for >5 years after castration, while all cases with a τ of >30 days died of cancer within 5 years of castration. As for Stage C patients, a similar difference in survival between cases with a τ greater or less than 30 days was observed at 7 years after castration (**Figure 3**).

Kaplan–Meyer survival time curves were compared between τ and Gleason score in 24 prostate cancer patients in Stage D (**Supplementary Figure 2**).⁶ The subjects were divided into two groups, namely, more or less than 30 days of the reduction time, τ , while >8 or <7 of Gleason score. Difference among two groups was statistically significant by τ but was insignificant by Gleason score.

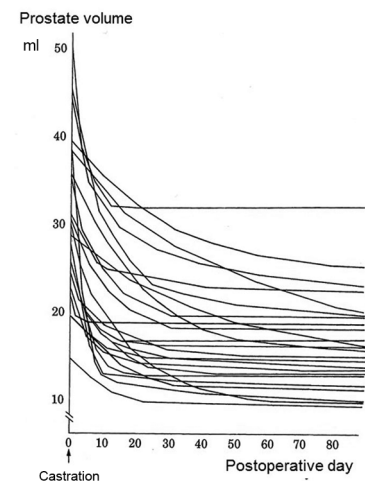


Figure 1: Reduction curve of prostate volume after castration in patients with prostate cancer ($n = 82$).

Thus, τ may be a better prognostic predictor than Gleason score.

KINETICS OF RELAPSE

The volume of the prostate was measured again very accurately in patients with advanced prostate cancer treated by castration and showed relapse after temporary recovery. Changes of prostate volume could be divided clearly into two types, namely, “metastatic progressive type” without volume increase and “local progressive type” with remarkable volume increase (Supplementary Figure 3).

In a case of the “local progressive type,” the prostate volume decreased for 6 months, then increased day by day. The patient died of cancer 39 months after castration. Throughout the course, no progression was observed on bone metastasis (Figure 4).

Another case of the “metastatic progressive type,” the prostate volume kept stable at the lowest level after castration, in spite of progression on bone metastasis. The patient died of cancer 98 months after castration (Supplementary Figure 4).

On a schema for prostate volume change after castration and relapse (Supplementary Figure 5), velocity of prostate volume reduction after castration is indicated by reduction time, τ , while that of prostate volume increasing after relapse is expressed by doubling time, which is time needed for the volume to be doubled.

Survival time and doubling time after relapse in a total of 23 cases are shown in Table 2. Doubling time in the “local progressive type” ranged from 150 to 740 days, separating into two groups with that of approximately 200 days and of 700 days. Notice that the progression of metastasis never occurred in the “local progressive type.”

Between τ and the survival duration in each case, a weak reverse correlation (Shorter the τ , longer the survival) was found (Supplementary Figure 6).

τ in the “local progressive type” was far shorter than that in the “metastatic progressive type” (Table 3 and Supplementary Figure 7).

In the “local progressive type,” a weak reverse correlation was again observed between τ and doubling time (Supplementary Figure 8). τ in the group of 700 days doubling time was clearly shorter than that in the group of 200 days doubling time (Supplementary Figure 9).

Based on these findings, a law is proposed for prostate cancer relapse. First, relapse is either of local progression or of metastatic progression. The both types never occur simultaneously in a patient. Second, when

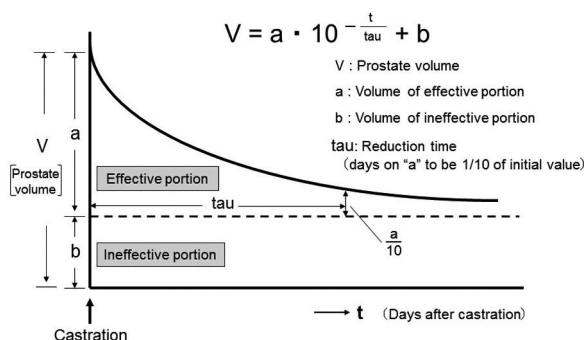


Figure 2: Schema of prostate volume reduction.

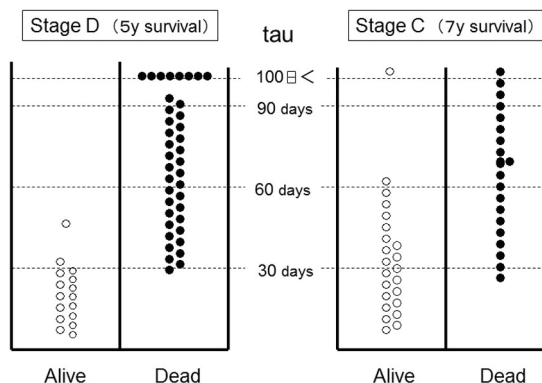


Figure 3: Tau and survivals of prostate cancer patients after castration.

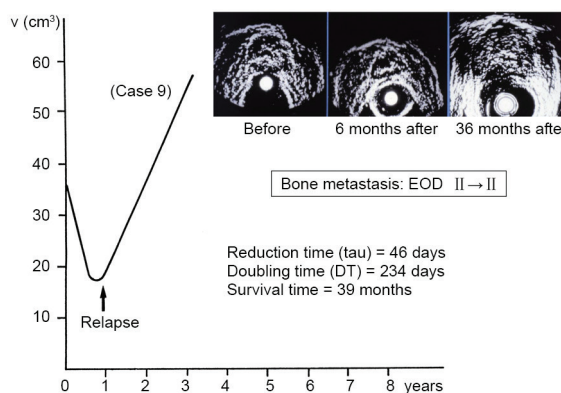


Figure 4: A case of “local progressive type.”

Table 1: Grading and staging of PCa and three factors (n=82)

	n	Tau	a	b
Grading				
Well	30	32.9±25.0	13.2±8.1	17.2±6.2
Moderate	32	64.4±114.2	15.2±7.7	19.9±13.1
Poor	19	105.8±228.4	14.8±10.7	21.1±9.0
Undifferentiated	1	43.5	16.5	23.0
Staging				
Stage B	16	35.0±26.9	11.0±5.1	17.5±6.4
Stage C	24	38.6±23.4	15.8±7.4	19.6±14.6
Stage D	42	86.6±177.9	14.8±9.9	19.7±7.9

PCa: prostate cancer

Table 2: Survival duration and DT after relapse in two types (n=23)

Case	Bone metastasis (EOD*)	Survival duration (months)	Cause of death	Tau after castration (days)	DT after recurrence (days)
Local progressive type					
1	I	36	Other than carcinoma	57	150
2	I	10	Carcinoma death	50	180
3	I	140	Carcinoma death	51	200
4	I	67	Carcinoma death	73	208
5	I	74	Other than carcinoma	28	210
6	I	37	Carcinoma death	57	228
7	II	39	Other than carcinoma	46	234
8	I	44	Carcinoma death	62	235
9	I	15	Other than carcinoma	38	300
10	I	63	Other than carcinoma	19	630
11	I	93	Carcinoma death	8	706
12	0	30	Carcinoma death	30	720
13	I	34	Other than carcinoma	17	740
Metastatic progressive type					
14	III	63	Carcinoma death	27	∞
15	III	68	Carcinoma death	34	∞
16	III	18	Carcinoma death	67	∞
17	III	30	Carcinoma death	85	∞
18	III	23	Carcinoma death	93	∞
19	III	26	Carcinoma death	>100	∞
20	III	19	Carcinoma death	>100	∞
21	III	52	Carcinoma death	>100	∞
22	IV	24	Carcinoma death	>100	∞
23	III	29	Carcinoma death	>100	∞

*EOD: extent of disease. DT: doubling time.

relapse occurs, longer survival will be obtained if it belongs to the “local progressive type,” than to the “metastatic progressive type.”

Such a prognostic inclination is provided by proper τ in each patient. In cases with shorter τ , basically relapse may be fewer. Even if it relapses, much chance will be available to be the “local progressive type.” In cases having τ shorter than 30 days, the relapse type must be the local progression. Moreover, the doubling time of local progression will be longer in cases with shorter τ . In summary, shorter the τ , longer the survival is obtained. τ of 30 days (that means 1 month) is a turning point at all times.

THE REASON WHY “TAU” IS SO IMPORTANT TO DEFINE PROGNOSIS

The fundamental characteristic of prostate cancer cell might be simulated to “Shionogi carcinoma,” which is an androgen-dependent experimental breast cancer cell line in rat (Supplementary Figure 10). In this cell line, the initiation starts from a single androgen-dependent cancer cell. However, in the course of proliferation, loss of androgen-dependency appears in some portion of cell groups as one of the malignant transformations. After that, androgen-independent cells live together

Table 3: Tau in “local progressive type” and “metastatic progressive type”

Type	Mean tau (days)
Local progressive (n=13)	41.2±19.6*
Metastatic progressive (n=10)	80.6±28.6*

* $P<0.005$

with original dependent cells at the definite proportion. Though dependency is different each other but both types of cells originated from a single clone.⁸

If these evidences in “Shionogi carcinoma” could be deduced to prostate cancer cells, the following suppositions will be tenable:

1. Cancer tissue consists of a mixture of androgen-dependent cells and androgen-independent cells. The ratio of both types of cells is fixed in each case
2. Both types of cells are originally generated from a single clone so that their doubling time is identical.
3. Androgen-dependent cells survive only under the existence of androgen while androgen-independent cells can survive without androgen.

In the process of progression (Figure 5 and Supplementary Figure 11), both types of cells proliferate collaboratively at the same doubling time. Castration suddenly cuts

off the androgen supply, so the volume of androgen-dependent cells reduces rapidly while that of androgen-independent cells does not change. Thus, the velocity of volume reduction after castration relates to the proportion of androgen-dependent and – independent cells, that is, the more dominant the androgen-dependent cells, the more rapid a volume reduction occurs. τ means this velocity of reduction.

When a certain period passes after castration, prostate volume reaches a plateau level. At this stage, only androgen-independent cells remain, which begin progression again. The proportion of androgen-dependent and – independent cells is still maintained in the newly generated cancer cells in progression but the volume of androgen-dependent cells does not expand, because they can no longer survive in the new state without androgen. Androgen-independent cells survive, and their volume expands but they occupy only a certain portion of the cancer focus. For that

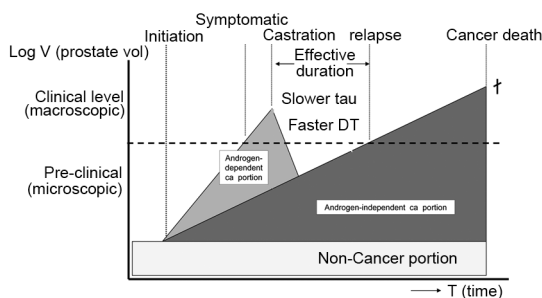


Figure 5: Schema of progression, castration, and relapse of prostate cancer. (In a case with androgen-dependent carcinoma portion of 50%).

reason, the doubling time of cancer in the new state appears to be longer than in the original.

In the first period of progression after the plateau level, the expansion of volume is so small that it cannot be recognized by macroscopic dimension. However, months and years later, the expansion finally reaches a level that can be observed by macroscopic dimension. At the very this point, the relapse of the cancer is diagnosed clinically (Figure 5).

However, in cases having a sufficient androgen-dependent cancer portion, τ is much faster and doubling time of remaining androgen-independent cancer portion is much slower. If the patient dies of other causes than cancer before that the remaining portion reaches the macroscopic level, the disease is judged as cured clinically (Supplementary Figure 11).

CONCLUSION

Complicated phenomenon of prostate cancer relapse was analyzed and was

reconstructed in a simple law. As Charles Huggins pointed out in 1941, prostate cancer is androgen-dependent. Prognosis of prostate cancer may be determined primarily by the proportion of androgen-dependent cells in total cancer cell distribution. The proportion of androgen-dependent cells could be proved by the “kinetics” observation, although retrospectively.

EDITORIAL COMMENT—(BY DR JOHN W DAVIS, DEPARTMENT OF UROLOGY, THE UNIVERSITY OF TEXAS, MD ANDERSON CANCER CENTER, HOUSTON, TEXAS, USA)

One of the most unpredictable aspects of relapsed/metastatic prostate cancer is the prediction of the androgen-dependent phase of the disease. Prior to the approval of multiple drugs in the castrate resistant phase, this time space was a more predictable 20–24 months depending upon performance status. In this article, Professor Watanabe addresses the relapsing phase of the disease

from the viewpoint of gland volume. As a pioneer in TRS who practiced for a substantial period before the PSA era, he brings a unique perspective in documenting outcomes by the speed of gland size reduction. For you history buffs, note the historical articles cited. Moving forward, perhaps gland size can be included in the analyses, even though PSA kinetics has been the modern emphasis.

Supplementary information is linked to the online version of the paper on the Asian Journal of Andrology website.

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