

**ORIGINAL****Changes in levels of prostate-specific antigen and testosterone following discontinuation of long-term hormone therapy for non-metastatic prostate cancer**

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**Abstract : Introduction :** We evaluated changes in levels of prostate-specific antigen (PSA) and testosterone following discontinuation of long-term hormone therapy for non-metastatic prostate cancer. **Patients and Methods :** Treatment was discontinued in 31 patients with non-metastatic prostate cancer (clinical stage B-C) after  $\geq 5$  years of hormone therapy, during which time PSA level had been maintained less than 0.5 ng/ml. PSA and testosterone levels were measured after discontinuation of therapy. PSA  $>4.0$  ng/ml was defined as PSA relapse in this study. **Results :** Mean age at discontinuation of hormone therapy was 78.7 years (range, 66-90). Mean duration of follow-up after discontinuation of therapy was 25.5 months. PSA non-relapse rate was quite high (87.1%). 4 of the 31 patients showed PSA relapse, after 12-24 months. Testosterone level exceeded castration level ( $<1.0$  ng/ml) in 3 patients, each of whom developed PSA relapse. **Conclusions :** During follow-up, the PSA relapse rate was relatively low. These results suggest that treatment may be safely discontinued in many prostate cancer patients. In addition, rate of testosterone recovery after treatment discontinuation may be associated with PSA relapse. When considered the adaptation of discontinued, or intermittent hormone therapy for aged people, these findings may be useful. *J. Med. Invest.* 61 : 35-40, February, 2014

**Keywords :** hormone therapy, discontinuation, PSA value, testosterone level, PSA relapse

**INTRODUCTION**

Hormone therapy for prostate cancer is not generally considered to achieve the complete cure seen with surgical treatment or radiotherapy, with

tumor-depression effects supposedly disappearing following discontinuation of hormone therapy.

Hormone therapy for prostate cancer is thus positioned as a standard treatment for metastatic prostate cancer at present, but as shown in the CaPSURE database, the proportion of hormone therapy for localized prostate cancer has tended to increase rapidly in recent years (1). Particularly in Japan, hormone therapy has been used rather than surgical treatment for early-stage localized prostate cancer in many cases, unlike the situation in Europe and

Received for publication July 31, 2013 ; accepted September 5, 2013.

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America. This difference is probably closely related to the health insurance system in Japan.

A recent study reported that discontinuation of medical treatment after long-term hormone therapy for localized prostate cancer causes no relapse of cancer (2). That report has attracted a great deal of attention. If prostate cancer can be controlled by long-term hormone therapy, subsequently enabling discontinuation of medical treatment, this finding will have great significance.

Accordingly, to confirm the effects of long-term hormone therapy for prostate cancer, a multi-center investigation was undertaken to determine whether discontinuation of medical treatment results in relapse among clinically controlled cases that have received long-term hormone therapy for non-metastatic prostate cancer.

## PATIENTS AND METHODS

Between 2005 and 2010, hormone therapy was discontinued in our institutions for 31 patients with non-metastatic prostate cancer (clinical stage B-C) after receiving  $\geq 5$  years of hormone therapy with PSA levels maintained less than 0.5 ng/ml. In contents of hormone therapy, luteinizing hormone-releasing hormone (LH-RH) agonist monotherapy and maximal androgen blockade (MAB) therapy were included. LH-RH agonist (Goserelin acetate 10.8 mg or leuprorelin acetate 11.25 mg) was administered subcutaneously every three months. In the case of MAB therapy, flutamide (375 mg/day) or bicalutamide (80 mg/day) was administered orally in addition to LH-RH agonist. However, patients who had also received surgery or radiotherapy were excluded. All participants in this study agreed to discontinue treatment and the study protocols were approved by the ethics review board at our hospital. PSA and testosterone levels were measured within 1 month before the discontinuation of hormone therapy. After confirming the absence of metastatic lesions on bone scintigraphy and computed tomography of the chest, abdomen and pelvis, hormone therapy was discontinued. PSA and testosterone levels were then measured every 1-3 months after discontinuation of therapy. Imaging examinations were performed as needed. For the purposes of this study, PSA relapse was defined as PSA level  $> 4.0$  ng/ml. When PSA relapse or a recurrent lesion was confirmed, hormone therapy was resumed. However, when patients wished the resumption of

hormone therapy, their wishes were approved in any cases. And we treated these cases as censored data. Testosterone level  $< 1.0$  ng/ml was defined as the castration level, so a level  $\geq 1.0$  ng/ml indicated significant recovery from castration level in this study.

The primary end-point was the non-relapse period for PSA level after discontinuation of hormone therapy. The secondary end-point was the duration required to recover from castration level of testosterone after discontinuation of hormone therapy.

## RESULTS

Mean PSA level for the 31 patients at the diagnosis of prostate cancer was 26.0 ng/ml (range, 2.2-186.0), and clinical stage was B in 22 patients, and C in 9 patients. Gleason score was  $\leq 6$  in 16 patients, 3+4 in 5 patients, 4+3 in 3 patients, and  $\geq 8$  in 7 patients. Mean age at discontinuation of hormone therapy was 78.7 years (range, 66-90), and mean duration of hormone treatment was 64.5 months (range, 60-96). Hormone therapy comprised LH-RH agonist alone in 4 patients, MAB in 19 patients, and alteration from MAB therapy to LH-RH agonist alone in 8 patients (Table 1).

Overall mean duration of follow-up was 25.5

Table 1 Patient and tumor characteristics (n=31)

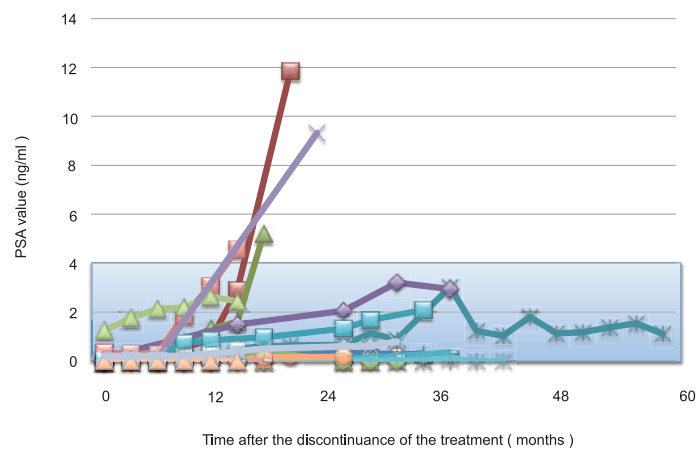
	Value
Age at end of endocrine therapy (years)	
Mean	78.7
Range	66-90
PSA value at diagnosis of prostate cancer (ng/ml)	
Mean	26.0
Range	2.2-186.0
Duration of endocrine therapy (months)	
Mean	64.5
Range	60-96
Contents of endocrine therapy (n)	
LH-RH agonist alone	4
MAB therapy	19
MAB→LH-RH agonist alone	8
Clinical stage (n)	
Stage B	22
Stage C	9
Gleason score (n)	
$\leq 6$	16
3+4	5
4+3	3
$\geq 8$	7

months (range, 14-57). Two of the 31 patients requested resumption of hormone therapy during this study. PSA relapse was identified in 4 patients (12.9%), with non-relapse in 27 (87.1%). Mean duration of follow-up was 18.3 months (range, 15-20) for PSA relapse cases, compared to 25.6 months (range, 13-57) for PSA non-relapse cases. No prostate cancer-specific deaths were identified during this study (non-specific death, 4 patients).

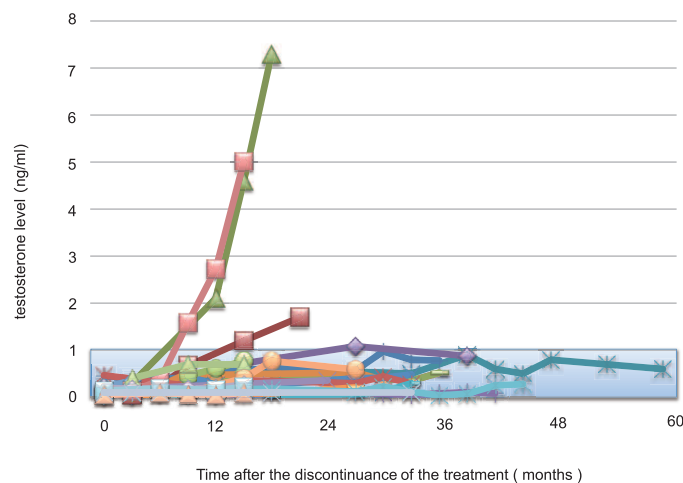
Viewing the transition of PSA levels after discontinuation of hormone therapy, the 4 patients who developed PSA relapse showed increases in the early stage after discontinuation, and PSA relapse was confirmed in all 4 patients within 12-24 months

(Figure 1). In terms of testosterone level after discontinuation of hormone therapy, recovery to above castration level was found in 3 patients from an early stage, with levels maintained below castration level during follow-up in all other cases (Figure 2). All 3 patients with testosterone recovery to above castration level developed PSA relapse.

Comparison of parameters between PSA non-relapse and relapse cases showed that median PSA level in relapse cases at the time of prostate cancer diagnosis tended to be higher (19.5 ng/ml ; range, 11.1-186.0) than in non-relapse cases (9.8 ng/ml ; range, 2.2-70.5). In addition, median age at discontinuation of hormone therapy tended to be lower in



**Figure 1 :** Changes in PSA level after discontinuation of hormone therapy. PSA level > 4.0 ng/ml was defined as PSA relapse in this study (outside the blue area in Figure 1). The color lines showed the change of PSA level of each cases. Four patients experienced PSA relapse from 12 months to 24 months after discontinuation of treatment.



**Figure 2 :** Changes in testosterone level after discontinuation of hormone therapy. Testosterone level  $\geq 1.0$  ng/ml indicated significant recovery from castration level in this study (outside the blue area in Figure 2). The color lines showed the change of testosterone level of each cases. Recovery to above castration level was found in 3 patients and all 3 patients developed PSA relapse.

relapse cases (74 years ; range, 66-76) than in non-relapse cases (80 years ; range, 67-90). Conversely, no specific tendencies in clinical stage or Gleason score at diagnosis were observed, and non-relapse cases included patients with stage C or Gleason score 4+3 or  $\geq 8$ . Also, contents of long-term hormone therapy and duration of hormone therapy showed no specific tendencies between groups. Final testosterone level and median rate of testosterone increase were 0.29 ng/ml (range, 0.10-1.27) and 0.005 ng/ml/month in non-relapse cases, and 3.35 ng/ml (range, 0.36-7.29) and 0.246 ng/ml/month in relapse cases. Both the final level and rate of increase were higher in relapse cases than in non-relapse cases (Table 2).

Table 2 Comparison between each parameter in PSA non-relapse and relapse cases

	PSA non-relapse (n=27)	PSA relapse (n=4)
PSA value at diagnosis of prostate cancer (ng/ml)		
Median	9.8	19.5
Range	2.2-70.5	11.1-186.0
Clinical stage (n)		
Stage B	19	3
Stage C	8	1
Gleason score (n)		
$\leq 6$	14	2
3+4	5	0
4+3	3	0
$\geq 8$	5	2
Contents of endocrine therapy (n)		
LH-RH agonist alone	4	0
MAB therapy	17	2
MAB→LH-RH agonist alone	6	2
Duration of endocrine therapy (months)		
Median	61.0	68.0
Range	60-62	60-96
Age at end of endocrine therapy (years)		
Median	80	74
Range	67-90	66-76
Final testosterone level (ng/ml)		
Median	0.29	3.35
Range	0.10-1.27	0.36-7.29
Rate of testosterone increase (ng/ml/month)		
Median	0.005	0.246
Range	-0.006-0.052	0.011-0.436

## DISCUSSION

Hormone therapy has held a place as one of the key treatment strategies for prostate cancer since Huggins *et al.* reported its efficacy in 1941 (3). Hormone therapy is chosen for treatment of localized prostate cancer more often in Japan than in Europe and America. In a study of cancer-specific survival rates for prostate cancer treated using hormone therapy as the initial therapy, Akaza *et al.* reported good results of 91% at 5 years and 78% at 10 years (4). Similarly, Ueno *et al.* reported an 8-year survival rate of 89.1% (5). However, the likelihood of radical cure of prostate cancer by hormone therapy, and the subsequent clinical results at discontinuation of hormone therapy, have remained unclear until now, leaving room for argument.

Concerning the likelihood of radical cure, Labrie *et al.* reported in 2002 that 90% of patients with Stage B or C prostate cancer treated using hormone therapy for > 6.5 years showed no relapse of PSA during 5 years of follow-up (1). As a theory supporting the radical cure of prostate cancer by hormone therapy, Namiki *et al.* stated that "In the progressive cancer stage, hormone therapy-refractory prostate cancer cells increase in 3-4 years, and as a result, hormone therapy-resistance comes to be shown. In contrast, hormone-naive monoclonal cells in the early stage may be susceptible to apoptosis from hormone therapy. Radical cure for prostate cancer may thus be quite possible" (6).

No patients in this study had metastatic prostate cancer, and all patients had PSA < 0.5 ng/ml, representing stable disease status after continuing hormone therapy for  $\geq 5$  years. However, patients with high PSA at diagnosis, high Gleason score, and stage C disease, representing so-called high-risk patients, were included. Even so, only 4 of 31 patients showed PSA relapse after discontinuation of treatment during the mean follow-up period of 25.5 months. Furthermore, the 27 PSA non-relapse cases included 10 of the 12 high-risk patients. Likewise, in this study, the 3 patients in whom testosterone level returned to above castration level after discontinuation of hormone therapy experienced PSA relapse in the same period. Only 1 patient (stage C ; PSA, 184 ng/ml and GS 5+4 at diagnosis) experienced PSA relapse without a recovery in testosterone level. Given these results, not the radical cure of prostate cancer by long-term hormone therapy suggested by Labrie *et al.*, but rather the speed of recovery in blood testosterone level after long-term

hormone therapy was the factor exerting the greatest influence on PSA relapse.

Studies of blood testosterone levels after discontinuation of hormone therapy have reported substantial variations in results. Wilke *et al.* reported that when treatment was discontinued after hormone therapy for  $\geq 24$  months, testosterone level exceeded castration level in 75% of patients within 6 months after treatment discontinuation (7). Conversely, Kaku *et al.* reported that when treatment was discontinued after hormone therapy for a mean of 30 months, testosterone level returned to above castration level within 2 years in 90% of patients (8). According to the reports of Nejat *et al.* and Oefelein *et al.*, patients who have received long-term LHRH agonists require longer to achieve recovery of testosterone levels (9, 10).

In the present study, hormone therapy was continued for longer ( $\geq 60$  months) than in previously reported cases, and very few cases (approximately 10%) showed testosterone levels returning to above castration level during follow-up (mean, 25.5 months). These results suggest the possibility of delaying recovery of testosterone levels with long-term hormone therapy. However, no difference in duration of treatment was apparent between those patients in whom testosterone level returned to above castration level and those in whom no such recovery was recognized. Some reports have stated that the duration of hormone therapy is unrelated to the speed of testosterone recovery after discontinuation of hormone therapy (11). This issue requires clarification in future studies.

In addition, some reports have suggested that recovery is delayed in proportion to the age during the period of testosterone recovery after hormone therapy (10, 12). Mean age at discontinuation of hormone therapy was 73 years (range, 71-76) in patients with testosterone recovery and 80 years (range, 67-90) in patients without testosterone recovery, and many patients without testosterone recovery were of advanced age. However, the small number of cases showing testosterone recovery meant that adequate statistical evaluations could not be performed in this study. When predicting factors of testosterone recovery are specified by further study, appropriateness for the adaptation of discontinued, or intermittent hormone therapy for aged people may be made clear.

In conclusion, among 31 patients with non-metastatic prostate cancer and PSA maintained less than 0.5 ng/ml after  $\geq 5$  years of hormone therapy, we discontinued hormone therapy, then confirmed and

examined the presence of PSA relapse and changes in testosterone level. During follow-up (mean, 25.5 months), the PSA non-relapse rate was quite high (87.1%). These results suggest that many prostate cancer patients receiving treatment may be safely discontinued. In addition, the present findings suggest that a factor exerting major influence on PSA relapse was the speed of testosterone recovery after discontinuation of the treatment, not the radical cure of prostate cancer by long-term hormone therapy. Judgments on when to discontinue hormone therapy may be possible in the future if factors can be identified predicting the rate of testosterone recovery after discontinuation of long-term hormone therapy.

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