The Prostate 66:439 – 444 (2006)

Time Course of Serum Testosterone and Luteinizing Hormone Levels After Cessation of Long-Term Luteinizing Hormone-Releasing Hormone Agonist Treatment in Patients With Prostate Cancer

Haruki Kaku, Takashi Saika,* Tomoyasu Tsushima, Shin Ebara, Takashi Senoh, Toyoko Yamato, Yasutomo Nasu, and Hiromi Kumon

Department of Urology, Okayama University, Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Okayama, Japan

INTRODUCTION. In order to elucidate the influence of hormone-releasing hormone (LH-RH) agonist therapy cessation on pituitary/testicular function and its clinical implications, we investigated prospectively hormonal (luteinizing hormone: LH; testosterone: T) responses in patients with prostate cancer who received long-term LH-RH 10 agonist therapy.
PATIENTS AND METHODS. A consecutive 32 patients who had received LH-RH agonist therapy over 24 months were enrolled. As a baseline, T and LH were measured at the time of LH-RH agonist therapy cessation, monthly for 3 months, and subsequently, every 3 months.
RESULTS. The median duration of LH-RH agonist therapy was 30 months (24–87 months) with median follow-up duration of 24 months following cessation. All patients had castrated T levels and suppressed LH levels at baseline. Median duration of castrated T levels following cessation was 6 months. Median time to normalization of T levels was 24 months. LH levels returned to normal within 3 months in all cases. Patients who received androgen deprivation therapy for 30 months or longer required a longer time for recovery of T levels. Patients over 65 years of age showed a statistically significant longer time for recovery of T levels ($P = 0.0167$).
CONCLUSIONS. Long-term LH-RH agonist therapy has remarkable effects on serum T level that last for a significant time after cessation, a fact that should be applied to the interpretation of both PSA and serum T levels after cessation of androgen deprivation therapy. *Prostate 66: 439–444, 2006.*

KEY WORDS: **prostate cancer; cessation of LH-RH; testosterone; luteinizing hormone**

INTRODUCTION

Luteinizing hormone-releasing hormone (LH-RH) agonist therapy is widely used as a medical, reversible alternative to orchiectomy in patients with prostate cancer. Reversibility and recovery of a normally functioning hypothalamic-pituitary-testicular axis after cessation of LH-RH agonist therapy should be considered in cases using it as neoadjuvant and/or adjuvant therapy in conjunction with radiation therapy [1] or radical surgery [2]. It also should be considered for patients with clinically localized or locally advanced disease. Meanwhile, in cases of advanced prostate cancer, intermittent endocrine therapy has been used in an attempt to delay the onset of the endocrine refractory period or to reduce the adverse reactions to continuous endocrine therapy [3,4]. In addition, since serum prostate specific antigen (PSA)

*Correspondence to: Takashi Saika, MD, PhD, Department of Urology, Okayama University, Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, 2-5-1 Shikata-cho, Okayama 700-8558, Japan. E-mail: saika@cc.okayama-u.ac.jp
Received 16 June 2005; Accepted 26 July 2005
DOI 10.1002/pros.20341
Published online 2 December 2005 in Wiley InterScience (www.interscience.wiley.com).

expression is strongly androgen dependent, the therapeutic and prognostic significance of PSA values measured before serum testosterone has normalized after androgen deprivation therapy cessation is questionable.

In several studies, the serum luteinizing hormone (LH) or testosterone (T) levels rose gradually after extending the administration interval of a 1-month depot of LH-RH agonist from 4 to 6 weeks [5,6]. The authors of these studies have therefore insisted that the administration period needs to be strictly complied with to keep the T levels within the castrated level. By contrast, some reports have stated that patients showed continuous suppressed T levels for more than 6 months after cessation of LH-RH agonist treatment [7,8]. The time course of serum testosterone levels after LH-RH agonist therapy cessation seems to provide important information for determining the schedule of both intermittent endocrine therapy and LH-RH agonist therapy as adjuvant therapies for radical prostatectomy or radical radiotherapy.

However, to our knowledge, the time course of recovery of LH or testosterone T levels after LH-RH agonist therapy cessation has been the focus of only a few small or short-term studies [5–11]. We undertook the present study to examine the recovery in serum LH and T levels following LH-RH agonist therapy cessation in patients with prostate cancer who received LH-RH agonist therapy for a minimum of 2 years as an adjuvant therapy for radical prostatectomy or external beam radiotherapy. This information will allow clinicians to better interpret PSA levels obtained after the termination of androgen deprivation therapy.

SUBJECTS AND METHODS

The subjects of this study were 32 patients with prostate cancer (Table I). The serum testosterone level before the start of LH-RH agonist therapy was 3.91–9.4 ng/ml (median, 5.2; mean, 5.37 ng/ml). The LH-RH agonist dosing period was 24–87 months (median, 30 months; mean, 33.4 months). The follow-up period after LH-RH agonist therapy cessation was 6–84 months (median, 24 months; mean, 25.1 months). Fourteen patients received LH-RH agonist monotherapy while 18 patients received concomitant antiandrogen therapy. The concomitant drugs used were chlormadinone acetate in eight cases (100 mg/day for 3–38 months; median, 6 months; mean, 10.8 months), flutamide in six cases (375 mg/day for 2–24 months; median, 5.5 months; mean, 10 months), chlormadinone acetate followed by flutamide in two cases and other drugs in two cases.

T, LH, and PSA levels were prospectively measured before the start of LH-RH agonist therapy (using 3.75 mg of leuprorelin or 3.6 mg of goserelin), at the conclusion of this therapy (baseline levels), and subsequently at 1, 3, and 6 months after cessation and every 6 months thereafter. PSA levels were measured primarily using a Tandem-R kit, which was later replaced with a high sensitivity PSA kit. The measurement of testosterone and LH was discontinued for patients in whom the disease recurred during the study period.

Stat-View 5.0 (SAS Institute, Cary, NC) was used for statistical analysis.

RESULTS

Serum LH levels ranged from 0.04 to 1.09 mIU/ml (mean, 0.25 mIU/ml; normal range, 1.8–5.2 mIU/ml) after LH-RH therapy cessation and were suppressed in all cases. Three months after LH-RH agonist therapy cessation, serum LH levels ranged from 0.23 to 12.65 mIU/ml (mean, 3.39 mIU/ml). Recovery of LH level to the normal range had a median duration of 4.5 months. After 6 months, all cases were within the normal range. Serum LH levels remained high in all cases (Fig. 1a,b).

Serum T levels at LH-RH agonist therapy cessation ranged from 0.1 to 0.8 ng/ml (mean, 0.23 ng/ml;

TABLE I. Clinical and Pathological Characteristics

No of Pts	32	Reteropubic radical prostatectomy		23
		Radiation therapy		7
		Others		2
Age	53–83	(Median/mean 71/68 years old)		
Stage			Grade	
A2		1	Well	7
B		9	Moderate	20
C		20	Poor	4
D1		2	Unknown	1
Duration of LH-RH agonist (mos.)		24–87(median/mean 30/33)		
Follow-up duration (months) after LH-RH agonist		6–84(median/mean 24/25)		

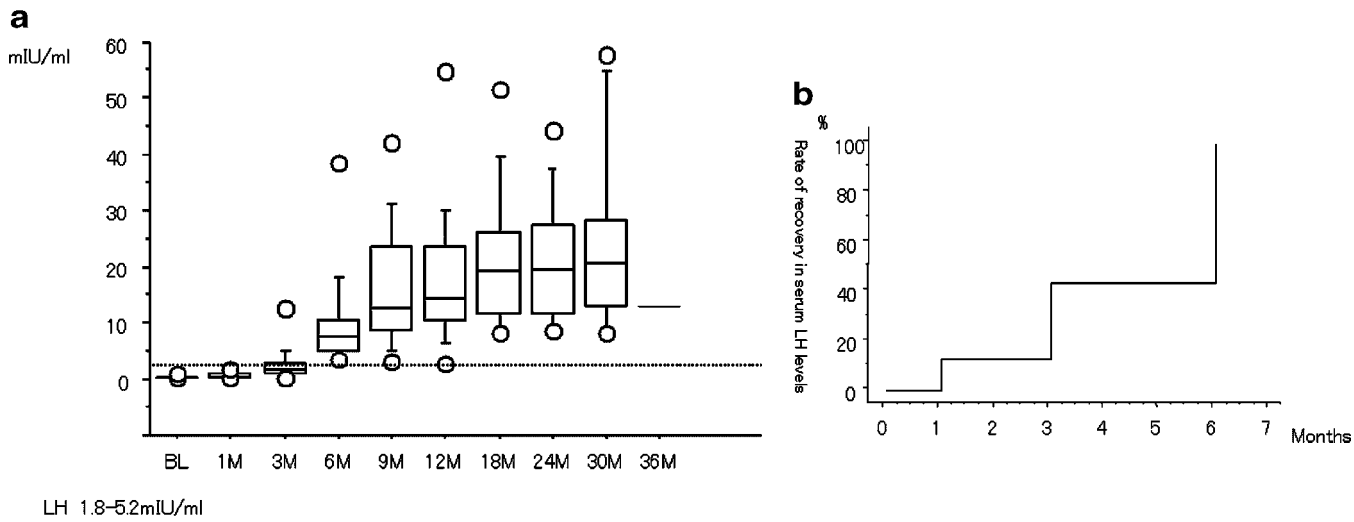

Fig. 1. **a**: Response of LH after cessation of LH-RH agonist therapy. **b**: Response of LH after withdrawal of LH-RH agonist therapy.

normal range 2.9–10.7 ng/ml), and in all patients, were below the castration level (less than 1.0 ng/ml). Serum T levels at 3 months after cessation averaged 0.94 ng/ml (range, 0.1–4.4 ng/ml), significantly higher than those recorded at the time of cessation ($P = 0.0034$). The percentage of patients whose T levels returned to above the castration level at 3 months after cessation was 26.9%. The percentage of patients whose T levels recovered to normal range at 3 months after cessation was 11.6%. At 6 months after cessation, serum T levels had returned to above the castration level in 69.0% of patients, and were within normal range for 20.7% of patients. At 12 months, T levels had returned to above the castration level in 82.6% and were within the normal range for 39.1% of 23 patients. At 24 months, T levels had returned to above the castration level in 89.5% and recovered to within normal range in 52.6% of 19 patients. In 3 of the 32 cases, T levels did not normalize even after 48 months, showing 0.2, 1.4, and 2 ng/ml, respectively, at that time (Fig. 2a,b).

Kaplan–Meier analysis of the events (returning T levels to above the castration level and then back to normal range) revealed that the median duration required for returning the serum T level to above the castration level was 6 months, and that the median duration required for T levels to move within normal range was 30 months (Fig. 3).

A trend was observed: T level recovery in patients receiving LH-RH agonist therapy for more than 30 months was delayed longer than in patients who had received it for less than 30 months ($P = 0.0583$; Fig. 4). T level recovery was significantly more rapid in patients below 65 years of age as compared to patients older than 65 years ($P = 0.0167$). Between the LH-RH agonist monotherapy group (n = 14) and the LH-RH agonist—anti-androgen combined therapy group (n = 16; $P = 0.2169$), T level recovery did not differ, nor did it between patients who underwent total prostatectomy (n = 23) and patients who received radiotherapy (n = 7; $P = 0.2087$).

DISCUSSION

We believe the current study is of the longest term and with the largest groups of patients to have serum T levels measured after LH-RH agonist therapy. In particular, all patients had confirmed T levels in the normal range at the start of therapy and at the castrated level at cessation, and none of the past studies observing T level recovery after discontinuing LH-RH agonist therapy has investigated its relationship to long-term treatment periods (Table II).

There are some reports of T level recovery after relatively short-term (less than 1 year on average) LH-RH agonist therapy [3–9]. Nejat et al. [7] reported that T level recovery did not differ between 24 patients who received therapy for less than 4 months and 44 patients who received it for 4 months or longer. They observed, however, that the small number of patients (7) who received the therapy for 24 months or more required significantly more time for T level recovery as compared to the 61 patients who received therapy for less than 24 months ($P = 0.003$). Oefelein et al. [9] also reported that for patients who received LH-RH agonist therapy for a mean period of 7 months (range, 3–49 months), the time required for T level recovery was significantly prolonged depending on the treatment period ($P = 0.05$). Thus, it appears that T level recovery to normal range in half of all patients after cessation of short-term LH-RH agonist therapy may take about

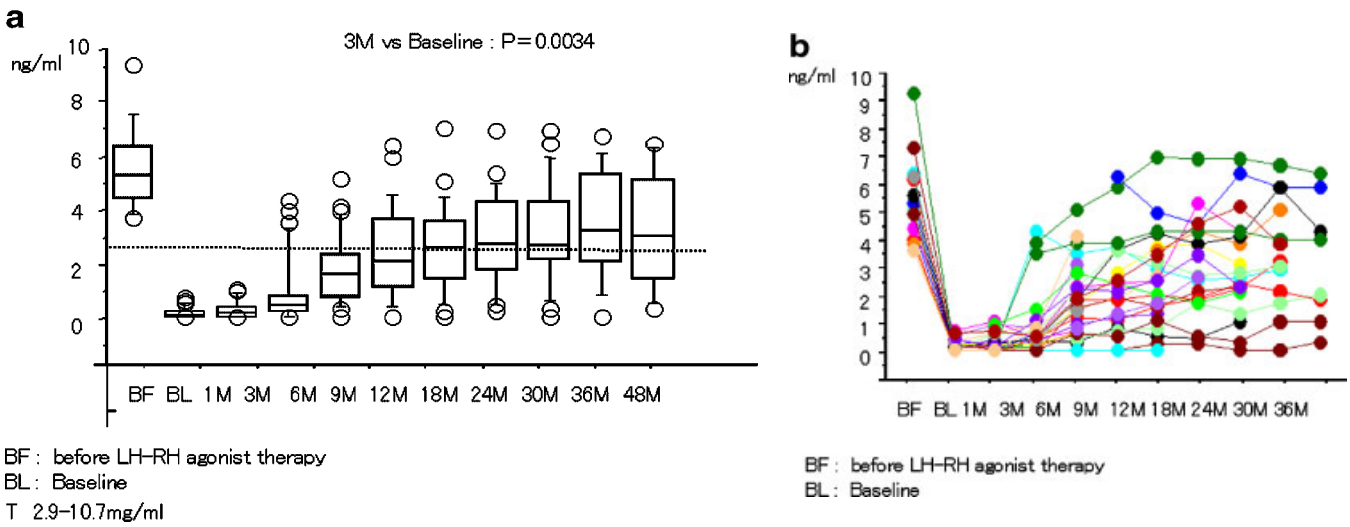

Fig. 2. Response of Tafter cessation of LH-RH agonist therapy (**a**) box plot analysis, (**b**) individual responses. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

6 months. Only a small percentage of these patients continued to have suppressed testosterone levels depending on the treatment period.

By contrast, a couple of studies have reported patients receiving long-term LH-RH agonist therapy lasting for 2 years or more. Kreis et al. [10] reported in 1988 that cancer recurrence was seen in 3 of 40 patients who received long-term LH-RH agonist therapy. These three patients received 3.6 mg/month goserelin therapy for 1.5–3 years and their T levels returned to above the castration level 7–8 weeks after therapy cessation. Their T levels continued to rise gradually but did not return to the pre-treatment level during the 12-month follow-up period following cessation. Hall et al. [11] reported that 9 months were required for T levels in 50% of all patients to return to above the castration level after the cessation of endocrine therapy lasting for 38.6 months on average (range, 25–82 months), and that the T levels at 12 months were still significantly lower than the normal range. The observation period after cessation of treatment in their study was, however, short (12 months). In the current study, all 32 patients received longer-term endocrine therapy (3.75 mg/month of leuprorelin or 3.6 mg/month of goserelin): 33 months on average (range, 24–87 months). Moreover, these patients were followed for longer periods, 6–84 months (median, 24 months; mean, 25 months) after therapy cessation. In our study, T levels returned to normal range in 20.7% of the patients at 6 months, but only 40% at 12 months and 52.4% at 24 months. The median time required for T levels to return to above the castration level was 6.0 months. The median time required for T

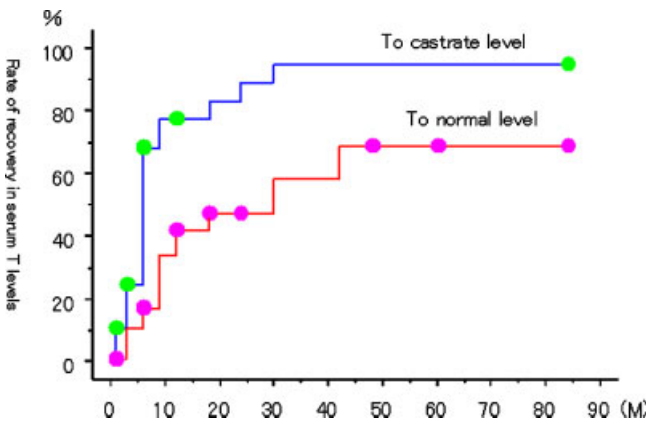

Fig. 3. Recovery of T to castrate and normal level after cessation of LH-RH agonist therapy. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

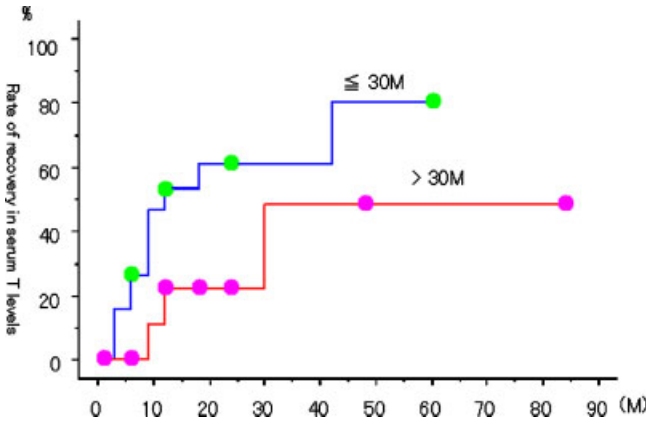

Fig. 4. Response of T according to periods of LH-RH agonist therapy. [Color figure can be viewed in the online issue, which is available at www.interscience.wiley.com.]

TABLE II. The Serum Testosterone Level after Withdrawal of LH-RH Agonist Therapy

Reporters	Year of report	No. of cases	Ages	Duration of LH-RH agonist		Results
Goldenber [3]	1995	47	67	(50–80)	43w	Recover to normal range within 8 weeks
Oefelein [9]	1999	32	71	(54–86)	7.5M	50% cases recover to castrate level at 6 months
Crook [4]	1999	40	—		8M	73% cases recover to normal level at 18 weeks
Nejat [7]	2000	68	71	(46–88)	9M	50% cases recover to castrate level at 7 months
Shahidi [8]	2001	419	68	(50–83)	4M	88% had normal levels in the follow up period
Kreis [10]	1988	3	—		1.5-3Y	Recover to castrate range within 7–8 weeks
Hall [11]	1999	14	70.3	(56–84)	38.6M	50% cases recover to castrate level at 9 months 50% cases recover to normal level over 12 months
Present study	2005	32	68	(53–83)	33M	50% cases recover to castrate level at 6 months 50% cases recover to normal level at 24 months

levels to normalize was 24.0 months. The 20 patients who received therapy for 30 months or more tended to show delayed T level recovery, as compared to the 12 patients who received it for less than 30 months ($P = 0.0583$). Based on these results, 2 years or more are required for T levels to normalize after long-term LH-RH agonist therapy that lasts for about 2 years and the time required for T level recovery increases as the treatment period becomes longer. The fact suggests that PSA rising after cessation of long-term LH-RH agonist therapy should be taken androgen independent cancer regrowth into consideration, especially in case with it within 6 months.

Oefelein et al. [9] reported that the duration for T level recovery increased as the patient's age became higher ($P = 0.03$). In Contrast, Nejat et al. [7] reported that the duration did not differ between 28 patients below 70 years of age and 40 patients older than 70 ($P = 0.10$). In our study, T level recovery was significantly more rapid for the 8 patients below 65 years than for the 24 patients older than 65 ($P = 0.0167$). These results suggest that the effect of LH-RH agonists in suppressing testicular function is more likely to persist in elderly patients.

As for hormonal recovery and modalities of endocrine therapy, Oefelein et al. [9] reported no difference in T level recovery between the LH-RH agonist monotherapy group and the combined androgen blockade (CAB) therapy group ($P = 0.54$). Moreover, in our study, T level recovery did not differ between the LH-RH agonist monotherapy group ($n = 14$) and the CAB therapy group (LH-RH agonist in combination with chlormadinone acetate or flutamide, $n = 16$, $P = 0.2169$).

In a recent report, serum T levels rose significantly following total prostatectomy [12]. It seems likely that radiotherapy also affects serum T levels. Of the 32 patients in our study, T level recoveries did not differ between the 23 patients who underwent total prostatectomy and the 7 patients who underwent radiotherapy ($P = 0.2087$). Additionally, it has been reported that treatment with LH-RH agonists reduced testicular Ledydig cell counts and induced thickening of the seminiferous tubule and fibrosis of the surrounding area [13–15]. Shahidi et al. [8] estimated that even short-term LH-RH agonist therapy can suppress Ledydig cells for a long period, based on the fact that LH levels normalized temporarily but later remained high after short-term endocrine therapy cessation. Similarly, we observed that LH levels returned to the normal range temporarily but later remained high for a long period.

Further studies are needed concerning the effects of various factors, including dosing period, patient's age, and concomitant use of antiandrogens on serum testosterone levels. There are many unresolved questions pertaining to, for instance, the effects of total prostatectomy and radiotherapy on testosterone levels and the interpretation of PSA levels after the cessation of LH-RH agonist therapy.

CONCLUSION

Patient age, long-term androgen deprivation and its cessation could have long-term effects on serum T levels. After cessation of LH-RH therapy, both PSA and serum T levels should be evaluated.

REFERENCES

1. Bolla M, Gonzalez D, Warde P, Dubois JB, Mirimanoff RO, Storme G, Bernier J, Kuten A, Sternberg C, Gil T, Collette L, Pierart M. Improved survival in patients with locally advanced prostate cancer treated with radiotherapy and goserelin. N Engl J Med 1997;337:295–300.
2. Soloway MS. Role of induction androgen deprivation before radical prostatectomy. Semin Urol 1995;13:142–147.
3. Goldenberg SL, Bruchovsky N, Gleave ME, Sullivan LD, Akakura K. Intermittent androgen suppression in treatment of prostate cancer: A preliminary report. Urology 1995;45:839–844.
4. Szumacher E, Malone S, Huan S, Segal R. Intermittent androgen suppression in the management of prostate. Urology 1999;53: 530–534.
5. Turkes A, Poeling WB, Grittiths K. The use of a depot LHRH analogue, Zoladex, in the treatment of prostatic cancer: A dose-interval study. Med Sci Res 1987;15:477.
6. Grant JB, Ahmed SR, Shalet SM, Costello CB, Howell A, Blacklock NJ. Testosterone and gonadotrophin profiles in patients on daily or monthly LHRH analogue ICI 118630 (Zoladex) compared with orchiectomy. Br J Urol 1986;58:539–544.
7. Nejat RJ, Rashid HH, Bagiella E, Katz AE, Benson MC. A prospective analysis of time to normalization of serum testosterone after withdrawal of androgen deprivation therapy. J Urol 2000;164:1891–1894.
8. Shahidi M, Norman AR, Gadd J, Huddart RA, Horwich A, Dearnaley DP. Recovery of serum testosterone, LH and FSH levels following neoadjuvant hormone cytoreduction and radical radiotherapy in localized prostate cancer. Clin Oncol 2001;13:291–295.
9. Oefelein MG. Serum testosterone-based luteinizing hormone-releasing hormone agonist redosing schedule for chronic androgen ablation: A phase I assessment. Urology 1999;54:694–699.
10. Kreis W, Budman DR, Delli Bovi P, Vinciguerra V. Rapid rise of serum testosterone following discontinuation of long term treatment of prostate carcinoma with an LHRH-agonist. Onkologie 1988;11:292–293.
11. Hall MC, Fritzsch RJ, Sagalowsky AI, Ahrens A, Petty B, Roehrborn CG. Prospective determination of the hormonal response after cessation of luteinizing hormone-releasing hormone agonist treatment in patients with prostate cancer. Urology 1999;53:898–902.
12. Miller LR, Partin AW, Chan DW, Bruzek DJ, Dobs AS, Epstein JI, Walsh PC. Influence of radical prostatectomy on serum hormone levels. J Urol 1998;160:449–453.
13. Smith JA Jr, UrryRL. Testicular histology after prolonged treatment with gonadotropin-releasing hormone analogue. J Urol 1985;133:612–614.
14. Giberti C, Barreca T, Martorana G, Truini M, Franceschini R, Rolandi E, Giuliani L. Hormonal pattern and testicular histology in patients with prostate cancer after long-time treatment with a gonadotropin-releasing hormone agonist analogue. Eur Urol 1988;15:125–127.
15. Huhtaniemi I, Nikula H, Parvinen M, Rannikko S. Histological and functional changes of the testis tissue during GnRH agonist treatment of prostate cancer. AM J Clin Oncol 1988; 11:S11–S15.