

The Association Between Hot Flashes and Renal Dysfunction After Androgen Deprivation Therapy With Radiotherapy in Japanese Patients With High-risk Prostate Cancer

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Abstract. *Background/Aim:* We investigated the changes in and characteristics of renal function in Japanese patients with high-risk prostate cancer (PCa) who underwent radiotherapy and long-term androgen deprivation therapy (ADT), including those seen after the ADT was discontinued. *Patients and Methods:* Among 60 patients who were pathologically diagnosed with PCa and received ADT for 24 months and radiotherapy, 36 patients who underwent treatment for stage B or C PCa were eligible. We assessed renal function using the estimated glomerular filtration rate (eGFR) and investigated the rate of change in the eGFR (Δ eGFR) during and after ADT. Univariate and multivariate logistic analyses were carried out to identify clinical factors that were significantly associated with renal dysfunction at 36 months. *Results:* The incidence of renal dysfunction at 36 months was 75% (27/36). Multivariate analysis showed that the presence/absence of HF was an independent predictor of renal dysfunction at 36 months. *Conclusion:* Renal function tended to recover after ADT was received for 24 months and subsequently discontinued. The presence/absence of HF represents new and meaningful information for patients receiving ADT, and high-risk PCa patients prior to ADT.

Androgen deprivation therapy (ADT) is the major treatment for progressive prostate cancer (PCa). Although ADT has been shown to improve oncological outcomes (1), it is associated with a non-negligible risk of important side

effects (1-3). There are numerous well recognized adverse effects of ADT, which include hot flashes (HF), loss of libido, fatigue, gynecomastia, anemia, and osteoporosis. In addition, obesity, insulin resistance, and dyslipidemia were recently suggested to be potential metabolic complications of ADT (4). The long-term use of ADT also has deleterious effects on cardiovascular health (5).

Although it has been reported that the use of ADT is significantly associated with an increased risk of acute kidney injury (AKI) in patients with newly diagnosed non-metastatic PCa (mPCa) (6), there have been few studies about the outcomes of renal function after the discontinuation of ADT. We reported that renal dysfunction occurred relatively early during ADT and that hypertensive PCa patients that receive ADT are at high risk of developing renal dysfunction (7). Furthermore, we reported that the discontinuation of ADT tended to result in improvements in renal function and that the renal dysfunction caused by 6 months' ADT is transient (8). However, to the best of our knowledge, no studies have been performed to assess renal function after 2 years of ADT. It would be very interesting to examine whether renal function improves after prolonged ADT.

Therefore, we investigated the trends and characteristics of renal function in Japanese patients with high-risk PCa who underwent radiotherapy and long-term ADT.

Patients and Methods

Study subjects. This was a retrospective study based on data extracted from electronic records. Patients that underwent prostate biopsy examinations (PBx) at the Department of Urology, Teikyo University Chiba Medical Center (Ichihara, Japan), between April 2009 and August 2015 were included in this study. The PBx were performed transrectally under ultrasonography and local anesthesia. They were conducted routinely using the 14-region template in all patients. The biopsy specimens were examined by a dedicated histopathologist at our hospital. All of the patients who participated in this study had been pathologically diagnosed with PCa and had undergone ADT for 24 months and radiotherapy for stage B or C

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Key Words: High-risk prostate cancer, renal dysfunction, estimated glomerular filtration rate, ADT, hot flashes.

Table I. Patient characteristics.

No. of patients	n=36
Age (years, mean±SE)	70±0.8
PSA (ng/ml, mean±SE)	16.3±2.9
Testosterone (ng/ml, mean±SE)	4.3±0.3
Hemoglobin (g/dl, mean±SE)	14.9±0.1
Stage (N)	
B/C	18/18
BMI (kg/m ² , mean±SE)	24.8±0.4
Gleason score	
7/8/9	12/15/9
Hot Flashes	
Positive/Negative	17/19
Hypertension (N)	
Positive/Negative	23/13
Diabetes Mellitus (N)	
Positive/Negative	29/7
Dyslipidemia (N)	
Positive/Negative	29/7

PSA: Prostate-specific antigen; BMI: body mass index.

disease. Risk classification was performed using the National Comprehensive Cancer Network (NCCN) system (9). High-risk PCa was defined as a prostate-specific antigen (PSA) level of >20 ng/ml, a Gleason score of ≥8, or stage T3a disease. The standard treatment for high-risk PCa at our institution involves ADT for 6 months, followed by radiotherapy, and then ADT for a further 18 months. Regarding the ADT, all of the patients received 24 months of treatment with a luteinizing hormone-releasing hormone (LH-RH) agonist (10.8 mg goserelin acetate or 11.25 mg leuprolide acetate). An oral non-steroidal antiandrogen (80 mg bicalutamide daily) was administered at the initiation of ADT, and combined androgen blockade (CAB) was also performed.

Clinical and laboratory assessments. The rate of change in the estimated glomerular filtration rate (Δ eGFR) was used to evaluate renal function in each period. Δ eGFR was calculated using the following formula: (eGFR at 1/3/6/12/18/24/36 months-pretreatment eGFR)/pretreatment eGFR×100). We investigated the following factors as potential risk factors for renal dysfunction after 24 months' ADT and at 12 months after the discontinuation of ADT (at 36 months): age, the levels of PSA, the levels of testosterone, the levels of hemoglobin, clinical stage, body mass index, the Gleason score, the presence/absence of HF, the presence/absence of hypertension, the presence/absence of diabetes mellitus, and the presence/absence of dyslipidemia. Also, to assess the presence/absence of renal dysfunction at 36 months, the mean rate of decline in the eGFR seen over 6 months in healthy Japanese aged ≥40 years was calculated based on data from a previous study (10). Then, this value was compared with the mean eGFR value seen at 36 months. If the mean Δ eGFR value for the healthy individuals was lower than the mean Δ eGFR value seen at 36 months, we considered the patient to have renal dysfunction. A previous study found that HF occurred in 93% of males, and first arose at a median 4.0 months after the first injection of an LH-RH analogue (11). Therefore, in the present study

Table II. Renal assessment after 36 months.

Variable	Dysfunction (n=27)	Normal function (n=9)	p-Value
Age (years, mean±SE)	71±0.9	68±1.6	0.3586
PSA (ng/ml, mean±SE)	18±3.7	11±2.1	0.2978
Testosterone (ng/ml, mean±SE)	4.2±0.3	4.5±0.8	0.5804
Hemoglobin (g/dl, mean±SE)	14.9±0.2	15±0.1	0.558
Stage (N)			
B/C	11/16	7/2	0.0543
BMI (kg/m ² , mean±SE)	25.1±0.5	23.9±0.7	0.3708
Gleason score			
7/8/9	10/10/7	2/5/2	0.5932
Hot Flashes			
Positive/Negative	9/18	8/1	0.0038*
Hypertension (N)			0.3035
Positive/Negative	16/11	7/2	
Diabetes Mellitus (N)			0.81
Positive/Negative	22/5	7/2	
Dyslipidemia (N)			0.4446
Positive/Negative	21/6	8/1	

PSA: Prostate-specific antigen; BMI: body mass index. * $p<0.05$.

we investigated the presence/absence of HF within 12 months after the administration of an LH-RH analogue. However, we did not assess the frequency or severity of HF.

Ethical approval. The institutional review board of Teikyo University approved this study (TUIC-COI 19-1407).

Statistical analysis. The results are shown as the mean±standard error (SE). The Wilcoxon rank-sum test and Chi-squared test were used for the statistical analyses. All analyses were performed with JMP version 10 (SAS Institute Inc., Cary, NC, USA). Probability values of <0.05 were considered statistically significant.

Results

Thirty-six patients who underwent ADT for 24 months and radiotherapy were evaluated in this study (Table I). CAB was employed in all cases. Regarding the presence/absence of renal dysfunction at 36 months, renal dysfunction was observed in 27 of the 36 cases (75%) (Table II). During the ADT, the patients' eGFR tended to decrease until 24 months, but increased during the period from 24 to 36 months (Figure 1). Univariate analyses showed that the incidence of renal dysfunction at 36 months was significantly associated with the presence/absence of HF (Table III). Multivariate analysis showed that the presence/absence of HF (odds ratio=7.77, 95% confidence interval=1.4-76.1, $p=0.0172$) was an independent predictor of renal dysfunction at 36 months (Table III). In a comparison of the estimated Δ eGFR with the measured Δ eGFR, at 12 months after the discontinuation of ADT the measured Δ eGFR was insignificantly lower than the estimated Δ eGFR, but tended to have increased (Table IV, Figure 2).

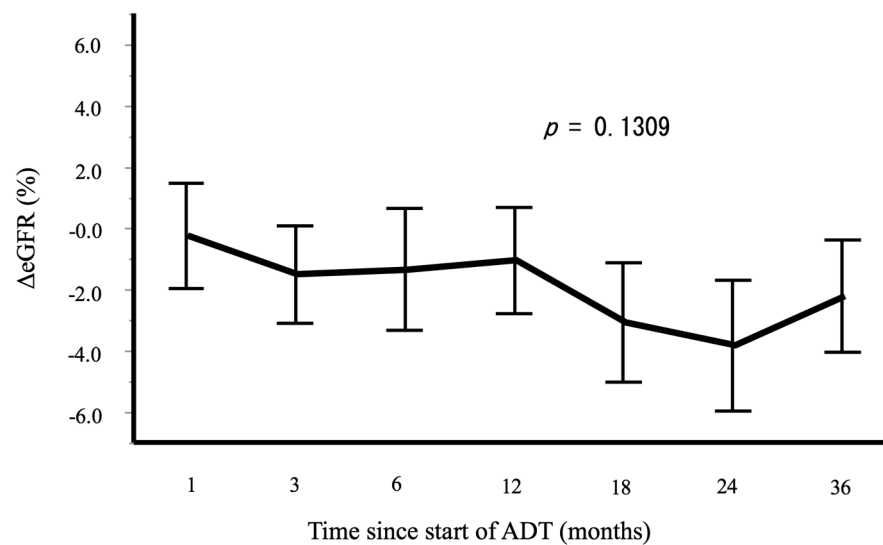


Figure 1. The rate of change in renal function during 24 months of androgen deprivation therapy (ADT) and after the discontinuation ADT (24-36 months) in patients with high-risk prostate cancer. There was no statistically significant change in the Δ eGFR during the ADT.

Table III. Univariate and multivariate analyses to identify predictors of renal dysfunction after 36 months.

	Univariate analysis			Multivariate analysis		
	OR	95%CI	p-Value	OR	95%CI	p-Value
Hot Flashes	0.0625	0.0067-0.580	0.0038	7.77	1.4-76.1	0.0172

OR: Odds ratio; CI: confidence interval.

Discussion

This was the first study to investigate the changes in renal function that occur after the discontinuation of ADT in Japanese patients with high-risk PCa. Moreover, it was confirmed that 75% of the patients treated with ADT for 24 months exhibited reduced renal function at 12 months after the discontinuation of ADT; *i.e.*, at 36 months. We previously reported that renal dysfunction due to ADT for PCa occurs early in the course of treatment (7). Moreover, we reported that the renal dysfunction caused by 6 months' ADT is transient (8). However, in the present study renal function tended to decrease after ADT, and it was suggested that renal function may improve after the discontinuation of ADT in Japanese high-risk PCa patients. Specifically, our findings indicated that the renal dysfunction induced by 24 months' ADT is temporary.

Although ADT has been shown to have beneficial effects against PCa progression, serious adverse events can occur during such treatment (12). In particular, ADT results in reduced testosterone levels, leading to a hypogonadal

Table IV. Longitudinal changes in measured and estimated Δ eGFR.

Period	Measured Δ eGFR	Estimated Δ eGFR	p-Value
12 months	-1.02±1.73	-0.59±0.03	0.4303
24 months	-3.81±2.12	-1.13±0.04	0.5656
36 months	-2.20±1.83	-1.70±0.06	0.2281

Data are shown as the mean±SE. eGFR: Estimated glomerular filtration rate.

condition marked by metabolic changes, such as dyslipidemia (13), hyperglycemia (14), and an increase in fat mass (15). Recently, it was reported that ADT has harmful effects on renal dysfunction. Specifically, it was found that ADT for newly diagnosed non-mPCa significantly increased the risk of AKI (6). Also, the latter study showed that when the ADT treatment period was split into tertiles, the highest risk of AKI occurred within the first tertile (<386 days) (6).

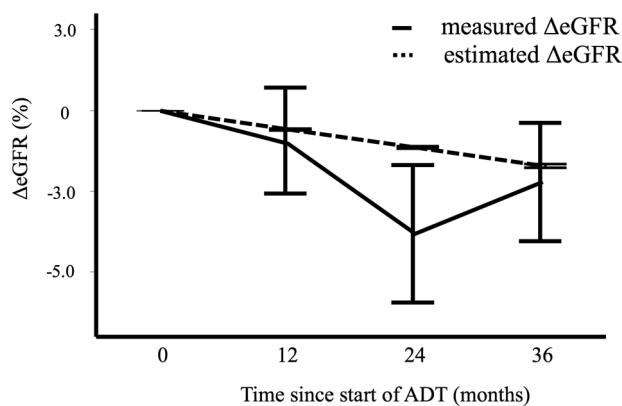


Figure 2. Comparison between the measured $\Delta eGFR$ and estimated $\Delta eGFR$. The measured $\Delta eGFR$ tended to increase from 24 to 36 months.

It has been reported that the mean rate of decline in the eGFR in healthy Japanese aged ≥ 40 years was 0.36 ml/min/1.73 m²/year (10). In the current study, the mean reduction in the measured eGFR was -1.02% after 12 months of ADT, -3.81% after 24 months of ADT, and -2.2% at 36 months. However, the mean reduction in the estimated eGFR was -0.59% after 12 months of ADT, -1.13% after 24 months of ADT, and -1.7% at 36 months.

HF can occur during ADT in males with PCa as a result of decreased androgen levels (16, 17). It was recently reported that HF occurred in 93% of males during ADT (11). In addition, Nishiyama *et al.* (18) reported that 32 of 55 patients (58.2%) suffered from HF, which adversely affected physical status and quality of life of patients. In the present study, the incidence of HF after 24 months of ADT was 47% (17 cases). Consequently, the incidence of HF may be lower among Japanese patients with high-risk PCa that are treated with ADT and radiotherapy. Dosani *et al.* (11) showed that most males experienced HF when their testosterone levels reached castration-like levels. The current study revealed that renal dysfunction is unlikely to occur in the presence of HF. Therefore, it is suggested that there is a strong association between ADT-related renal dysfunction and testosterone. Japanese patients with PCa are less likely to experience HF after ADT than Western patients; therefore, there may be racial differences in the frequency of HF after ADT.

In the current study, the presence/absence of HF was identified as a predictor of renal dysfunction after ADT. Informing patients prior to the initiation of ADT that HF are a predictor of renal dysfunction would be valuable. In addition, this study suggests that it is important to periodically ask patients about the presence/absence of HF during ADT.

We previously reported that renal dysfunction can occur from 1 month onwards during ADT (8). In the present study, we also found that renal dysfunction occurred early and persisted

throughout the ADT (for 24 months). In the renal system, hyperglycemia and dyslipidemia may disrupt glomerular function by expanding and thickening interstitial tubular membranes (19). Furthermore, by lowering testosterone to levels similar to those seen after castration, ADT may antagonize the vasodilatory effects of testosterone on renal blood vessels (20), while resulting in estrogen deficiency, which may negatively affect renal tubular function (21). Thus, ADT may increase the risk of AKI through these mechanisms. In addition, it has been reported that testosterone levels recovered to nearly 90% of their baseline levels when ADT was discontinued after it had been administered for 12 months (11). In the current study, although we did not measure the subjects' testosterone levels after the discontinuation of ADT, the recovery of testosterone levels may be related to improvements in renal function after the discontinuation of ADT. Investigating the relationship between the levels of testosterone and the eGFR would be of great interest. In the future, we consider that we will be able to clarify the relationship between improvements in renal function and the recovery of testosterone levels after the discontinuation of ADT.

We would like to emphasize several limitations of our study. First, it was a retrospective cohort study, which involved the extraction of electronically stored clinical data, and the sample size was small. Thus, it will be necessary to validate the findings of this retrospective analysis in prospective studies, including randomized studies, with larger populations. Second, the impact of radiotherapy on renal function was not examined. The possibility that bladder function may be adversely affected by radiotherapy could not be excluded. As a result, it is possible that secondary deterioration of renal function occurred in this study. Third, different LH-RH analogues were administered as ADT to the patients. Due to the study's small sample size, multiple LH-RH analogues were grouped under the heading of ADT. Finally, we did not assess the severity or duration of HF. Moreover, serum testosterone levels were not measured after the discontinuation of ADT. In order to verify the association between the recovery of renal function and serum testosterone levels after the discontinuation of ADT, we should have measured serum testosterone levels after the discontinuation of ADT and compared serum testosterone levels with renal function. The examination of serum testosterone levels in real-world clinical practice may be an important issue.

Conclusion

The findings of this study suggested that renal dysfunction occurs early in Japanese patients with high-risk PCa who receive ADT and persists for at least 24 months, but after the discontinuation of ADT renal function tends to improve, and the renal dysfunction caused by 24 months of ADT is transient. The presence/absence of HF after ADT was identified as a predictor of renal dysfunction at 12 months after the discontinuation of ADT. It is very important to

explain to patients that ADT can cause renal dysfunction before ADT is performed and that presence/absence of HF is a predictor of such renal dysfunction.

Conflicts of Interest

The Authors state that they have no conflicts of interest relating to this study.

Authors' Contributions

HM designed the study and acquired the data. HM prepared and edited the article. KM, KO, KH, TS, KA, SK, and YN were involved in patient care and reviewed the electronic records. All of the Authors have read and approved the article.

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