Post-hoc analysis of changes in renal function of prostate cancer patients: Focus on androgen deprivation therapy

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Abstract

Background To investigate the association between androgen deprivation therapy (ADT) and changes in the estimated glomerular filtration rate (eGFR) in male Japanese prostate cancer patients, based on post-hoc analysis of data from a previous prospective study.

Methods From among 103 prostate cancer patients in whom renal function changes were tracked over 5 years, 88 were divided into a group who completed ADT within 3 years (short ADT group; n = 47) and a group who continued with ADT for more than 5 years (continuous ADT group; n = 41). We compared the groups in terms of the eGFR, calculated based on age and serum creatinine (mg/dL), before ADT initiation and every other year over the next 5 years. This study was approved by the Ethics Committee for Clinical Studies of Gunma University Hospital (Approval No: 8 – 5).

Results The eGFR decreased by 4.91 and 2.89 ml/min in the short and continuous ATD groups, respectively, over the 5-year period following ADT initiation. The respective decreases in the eGFR were 0.98 and 0.58 ml/min/year. No significant difference in the eGFR was observed between the two groups at any measurement point.

Conclusions ADT patients showed a decrease in the eGFR of 0.58–0.98 ml/min/y over a 5-year period, which is about twice as high as that of normal Japanese males. No significant difference in the eGFR by ADT duration was observed.

Background

Prostate cancer has become one of the most prevalent diseases among men in Western countries, and its incidence has also increased in Japan [1]. Androgen deprivation therapy (ADT) is the mainstay treatment for localized, locally advanced, and metastatic prostate cancer [2]. However, even short-term use of ADT can lead to side effects, such as osteoporosis, obesity, sarcopenia, changes in lipid levels, and insulin resistance; the risk of diabetes and cardiovascular morbidities is also increased by ADT [3]. In addition to these widely recognized side effects, ADT increases the incidence of acute kidney injury (AKI). Lapi et al. reported that the use of ADT in newly diagnosed non-metastatic prostate cancer patients was associated with a significantly increased risk of AKI, according to their case-control analysis of medical data extracted from the UK Clinical Practice Research Datalink (linked to the Hospital Episodes Statistics database) [4]. They also reported that antiandrogen or estrogen therapy used in combination with ADT significantly increased the incidence of AKI compared to ADT alone. Androgen blockade by gonadotropin-releasing hormone (GnRH) agonists in combination with oral antiandrogens (odds ratio [OR], 4.50), estrogens (OR, 4.00), other therapeutics (OR, 4.04), and GnRH agonists (OR, 1.93) all increased the incidence of AKI. No reports have examined changes in renal function in prostate cancer patients treated by ADT. Therefore, we conducted a post-hoc study to investigate changes in the renal function of prostate cancer patients who underwent ADT over 5 years, using data from a prospective study conducted at our institute.

Methods

We conducted a prospective single-arm study of 103 prostate cancer patients who started ADT between April 2010 and March 2012 at Gunma University Hospital. The primary endpoint was changes in bone mineral density. Changes in blood chemistry data (including the serum creatinine level) and side effects were the secondary endpoints. The present post-hoc study used the data from the prospective study. We enrolled 88 patients in whom changes in renal function from the start of ADT until March 2017 (5 years) were observed. Of the 15 patients in the prospective study excluded from the present investigation, 2 died from prostate cancer, 2 died from other cancers, 5 were transferred, and 6 were lost to follow-up. We also considered the effect of ADT duration on the estimated glomerular filtration rate (eGFR). The 88 patients were divided into a group that completed ADT treatment within 3 years (short ADT group; n = 47) and a > 5-year ADT treatment group (continuous ADT group). We retrospectively compared the groups in terms of the eGFR, calculated based on age and serum creatinine (mg/dL), before the start of ADT and every other year over the next 5 years (Fig. 1). The eGFR was calculated in the prospective study using the Modification of Diet in Renal Disease (MDRD) formula, which has been widely used in other countries [5]. In this study, we calculated the eGFR using Matsuo's formula, which is a modified version of the MDRD formula that is more accurate for Japanese populations [6]. The formula is as follows:

$$\text{eGFR (mL/min/1.73 m}^2\text{)} = 194 \times \text{Serum creatinine}^{(-1.094)} \times \text{Age}^{(-0.287)}$$

SPSS software (ver. 25.0; IBM Corp., Armonk, NY, USA) was used for the statistical analysis. A p-value < 0.05 was considered significant. This study was approved by the Ethics Committee for Clinical Studies of Gunma University Hospital (Approval No: 8 − 5), who also approved the inclusion of patients from other facilities.

Results

The patient characteristics are shown in Table 1. All cases analyzed in this study had an eGFR ≥ 45 ml/min. The mean age of the short ADT group was 67.9 ± 4.7 years and that of the continuous ADT group patients was 71.3 ± 5.4 years. The continuous ADT group was significantly older at the start of treatment than the short ADT group (p = 0.002, Student's *t*-test). All patients in the short ADT group received curative intensity-modulated radiation therapy (75 Gy) and an average of 25.4 ± 8.2 months of ADT treatment. The median prostate-specific antigen (PSA) level in the short ADT group was 8.34 ± 10.7 ng/ml, and that in the continuous ADT group was 13.4 ± 73.67 ng/ml (p = 0.024, Student's *t*-test). The prostate cancer stage distribution was not significantly different between the short and continuous ADT groups. Significantly more metastatic cases were observed in the continuous ADT group, whereas all cases were localized cancer cases in the short ADT group (p = 0.024, Mann–Whitney *U* test). No significant difference in total Gleason score was observed between the groups (p = 0.398, Mann–Whitney *U* test). No significant group differences were observed in height, weight, or body mass index. Significantly more patients in the short ADT group had a history of hypertension (p = 0.015, χ^2-test). No

significant group differences were observed in history of diabetes, heart disease, use of anticoagulants, hyperlipidemia, or the presence of other carcinomas.

The median eGFR before treatment was 68 ml/min (range: 54–75 ml/min) in the short ADT group and 72 ml/min (range: 55–81 ml/min) in the continuous ADT group. In both groups, the eGFR values at each measurement point before treatment, and at 6 months and 1, 2, 3, 4, and 5 years after treatment, are shown in Fig. 2. The eGFR decreased by 4.91 ml/min (6.40%) in the short ADT group and by 2.89 ml/min (4.19%) in the continuous group over the 5-year period after the start of treatment. The eGFR decreased by 0.98 ml/min/year in the short ADT group and by 0.58 ml/min/year in the continuous group. No significant group difference in the eGFR was observed at any measurement point. A retrospective check of the medical records revealed no cases in either group of renal dysfunction due to dysuria, such as urinary retention. Also, there was no case of AKI in either group.

Discussion

This is the first study to investigate the association between ADT and changes in eGFR in Japanese prostate cancer patients. The eGFR did not vary by duration of ADT. ADT has been reported to increase the incidence rates of cardiovascular disease and metabolic syndrome, which are widely recognized side effects of this therapy. In a population-based study, Azoulay et al. reported that ADT may increase the risk of stroke/transient ischemic attack (TIA). They reported that current users of GnRH agonists and oral antiandrogens, and patients who underwent bilateral orchiectomy, had a higher risk of stroke/TIA compared to those not undergoing ADT [7]. Keating et al. reported that ADT using a GnRH agonist was associated with an increased risk of diabetes and cardiovascular disease. Treatment with a GnRH agonist is associated with a significantly higher risk of incident diabetes (adjusted hazard ratio [aHR] = 1.28), incident coronary heart disease (aHR = 1.19), myocardial infarction (aHR = 1.28), sudden cardiac death (aHR = 1.35), and stroke (aHR = 1.22) [8]. Braga-Basaria et al. suggested that metabolic syndrome is present in more than 50% of prostate cancer patients undergoing ADT. Additionally, they reported that ADT increases the risk of cardiovascular events, as well as the prevalence of obesity and dyslipidemia [9]. Dyslipidemia and hyperglycemia may adversely affect glomerular function by expanding and thickening the interstitial tubular membranes [10]. Dyslipidemia is a known risk factor for thrombosis, which increases the risk of AKI in patients with hyperlipidemia undergoing post-cardiac surgery by inducing oxidative stress [10]. As mentioned above, many studies have reported on ADT in association with metabolic syndrome and cardiovascular events, but few have determined the relationship between ADT and renal function. In 2013, Lapi et al. conducted the first case-control analysis of ADT based on the medical records of 10,250 patients. They revealed that ADT use was significantly associated with an increased risk of AKI in a cohort of patients with newly diagnosed non-metastatic prostate cancer [4]. In 2014, Gandaglia et al. reported that administration of GnRH agonists, but not bilateral orchiectomy, increased the risk of AKI in patients with prostate cancer [11]. However, in a Letter to the Editor, Smith pointed out several problems with the paper of Lapi et al. He suggested that AKI is not a known complication of hypogonadism in the general population, and has not been reported as an adverse event in any large randomized study. In addition, he suggested that Lapi et al. did not adequately control for the

confounding effects of prostate cancer progression [12]. Although Lapi et al. discussed the incidence of AKI [4], no study has reported a change in the eGFR based on serum creatinine in ADT-treated prostate cancer patients. We agreed with Smith in questioning the development of AKI in patients undergoing ADT, which prompted us to conduct the present study. No significant difference in eGFR was observed between our short (ADT duration < 3-year; median, 25.4 months) and continuous groups during the 5-year period following treatment initiation. Regarding the effects of ADT on eGFR, we found that changes in the eGFR were generally reported in elderly men. Imai et al. reported a decline in the eGFR of a general Japanese population in a 10-year follow-up study conducted in 2007. They calculated rates of eGFR decline over 10 years of 0.35, 0.31, 0.37, and 0.42 mL/min/year in those aged 40–49, 50–59, 60–69, and 70–79 years, respectively. In the overall study population, proteinuria occurred in 2.6% of the males. Overall, males with proteinuria had a two-fold higher mean rate of eGFR decline compared to patients without proteinuria [13]. The change in eGFR in our ADT patients (0.58–0.98 ml/min/year) was closer to that in patients with proteinuria than in normal men in the report of Imai et al. ADT appears to influence the eGFR to some extent regardless of the treatment period.

As well as several strengths, our study also had some limitations. First, it was limited by a post-hoc design and small sample size; we could not exclude the possibility of selection bias. Furthermore, significant group differences were observed in mean age and PSA levels, and significantly more patients had a history of hypertension in the short ADT group. Also, the number of patients who showed early progression was significantly higher in the short ADT group. Moreover, all patients in the short ADT group received radiation therapy for curative purposes, and the absence of this therapy in the continuous ADT group may have affected the results. However, no postrenal failure occurred in any case in this study. Second, we believe that better comparisons could be made if a control group could be a prostate cancer patient who did not receive ADT as a control group, for example, a group of patients who had undergone radical prostatectomy. This study was unsuitable because it divided the patients into two groups based on the results of the single-arm study. Finally, our study was limited by a lack of data on serum testosterone. It is well known that the effects of castration are prolonged after stopping ADT, but testosterone recovery in patients in the short ADT group was not assessed. The median duration of ADT treatment in that group was approximately 2 years (median, 25.4 months), but no test was performed to determine whether testosterone had recovered after ADT had been discontinued. However, testosterone was stopped within 3 months of the start of ADT in all cases.

Conclusions:

The eGFR decreased by 0.58–0.98 ml/min/y in our ADT patients, which are about twice as high as the rate of decrease in normal Japanese males, and approximately the same as in urine protein-positive male patients. Although the decrease in the eGFR may have been slightly higher than that of normal males, we suggest that a large decrease in the eGFR may not play a role in the development of AKI. In addition, no significant difference in the eGFR was observed according to the duration of ADT.

Declarations

Ethics approval and consent to participate

We explained the study to all participants in this study. All participants agreed in writing to participate. This study was approved by the Institutional Review Board at the Gunma University Hospital (No.8 – 5). There are no administrative permissions or licenses to access the data to formally note. Present studies were conducted according to International Conference on Harmonization/Good clinical Practice (ICH/GCP) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analysed during this study are included in this published article and its supplementary information files. If someone wants to access the data of the study, they can contact the corresponding author (miya.yoshi@gunma-u.ac.jp).

Competing interests

Kazuhiro Suzuki has potential financial conflicts of interest as below, Employment: none, Consultancies: Kazuhiro Suzuki (Takeda Pharmaceutical, Astellas Pharma, Daiichi-Sankyo, Astrazeneca, Sanofi, Janssen, Bayer), Honoraria: Author name (entity name), Stock ownership or options: none, Grants received: Kazuhiro Suzuki (Takeda Pharmaceutical, Astellas Pharma, Daiichi-Sankyo, Ono Pharmaceutical). All other authors have declared that no conflict of interest exists.

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Authors' contributions

All authors have read and approved the manuscript. YM: Conceptualization, data curation, formal analysis, methodology, project administration, writing original draft, and writing review and editing. YS, SA, DO, HN and TS: data curation, formal analysis. MN, HK, HM, YS and KS: review and editing.

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Not applicable.

Abbreviations

ADT; androgen deprivation therapy

AKI; acute kidney injury

eGFR; estimated glomerular filtration rate

GnRH; gonadotropin-releasing hormone

MDRD; Modification of Diet in Renal Disease

OR; odds ratio

PSA; prostate specific antigen

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Table 1

Table 1: Patient characteristics S.D.: Standard Deviation, PSA: prostate-specific antigen, ADT: androgen deprivation therapy, BMI: body mass index, *: Student’s t-test, **: Mann-Whitney U test, †: 2 test

Characteristics	Short ADT	Continuous ADT	P-Value
No. of patients	47	41	
Age (mean ± S.D.)	67.9 ± 4.7	71.3 ± 5.4	p = 0.0019(*)
Initial PSA (ng/ml, median ± S.D.)	8.34 ± 10.74	13.40 ± 73.67	p = 0.0236(*)
Duration of ADT (month ± S.D.)	25.4 ± 8.2	-	-
Stage			
T1-2N0M0	35	21	
T3N0M0	12	12	p = 0.0239(**)
TanyN1 or M1	0	8	
Gleason Score			
GS 6	1	2	
GS 7	23	12	p = 0.398(**)
GS 8–10	23	27	
Patient's body size			
height (cm, mean ± S.D.)	164.3 ± 5.9	163.1 ± 5.2	p = 0.390(*)
weight (kg, mean ± S.D.)	63.5 ± 9.4	62.6 ± 8.9	p = 0.728(*)
BMI (mean ± S.D.)	23.5 ± 3.1	23.5 ± 3.2	p = 0.918(*)
Patient's History			
Diabetes mellitus (n, %)	6 (12.8%)	6 (14.6%)	p = 0.798(†)
Cardiovascular disease (n, %)	9 (19.1%)	13 (31.7%)	p = 0.174(†)
Medication of anticoagulant (n, %)	9 (19.1%)	12 (29.3%)	p = 0.266(†)
Hyperlipidemia (n, %)	6 (12.8%)	3 (7.3%)	p = 0.400(†)
Hypertension (n, %)	22 (46.8%)	9 (22.0%)	p = 0.015(†)
Other carcinoma (n, %)	5 (10.6%)	6 (14.6%)	p = 0.571(†)

Figures

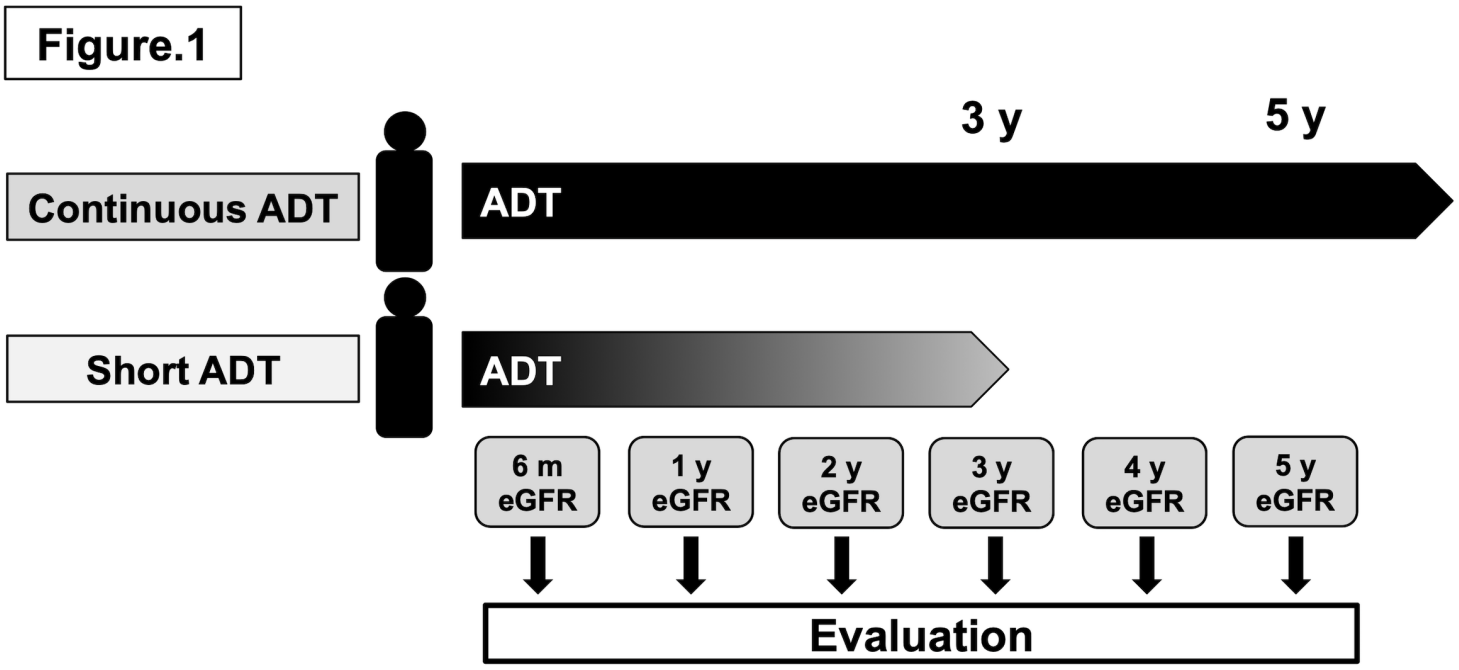
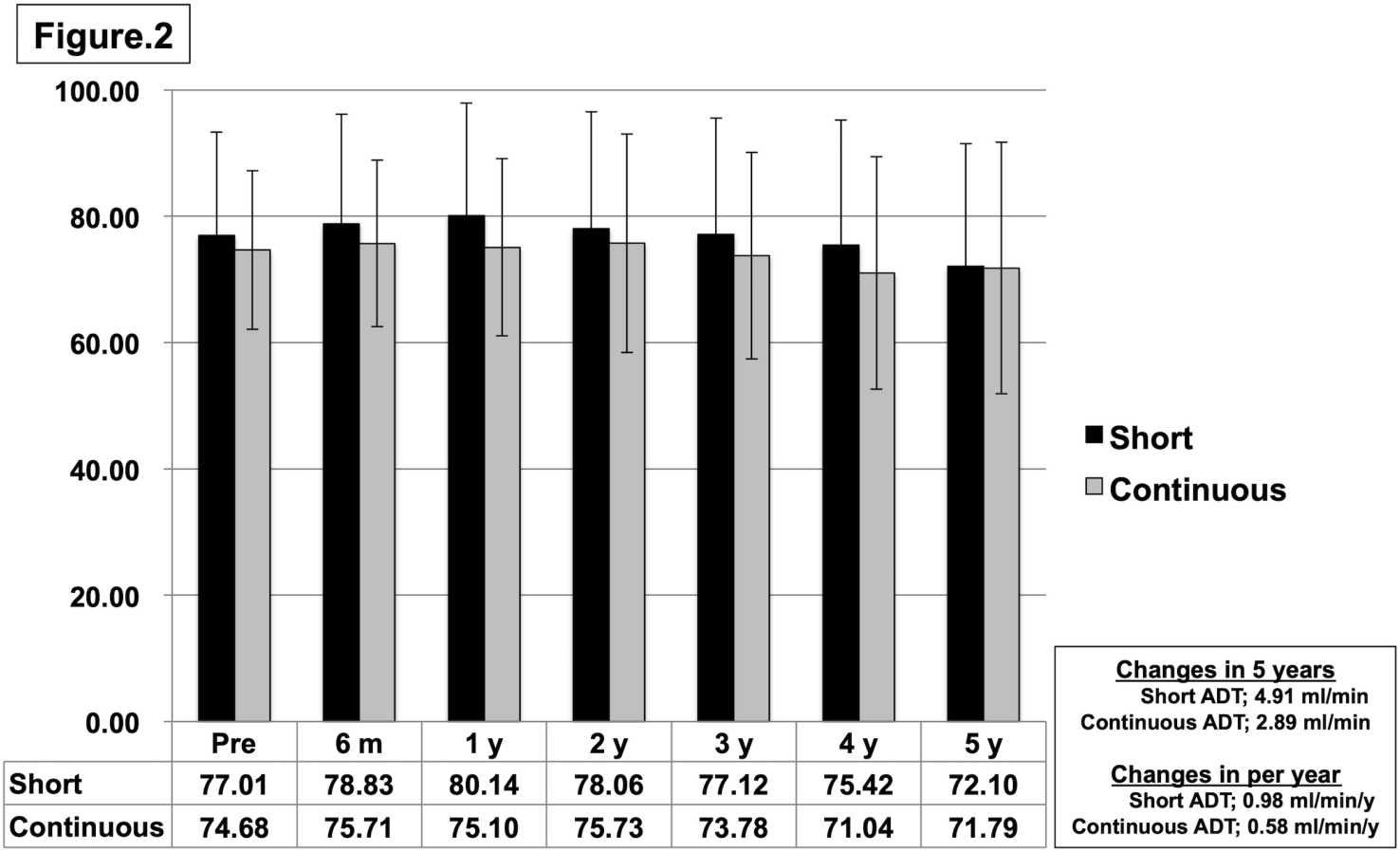


Figure 1

Schematic of the study The 88 patients enrolled in this study were divided into a short androgen deprivation therapy (ADT) group (< 3 years; n = 47) and a continuous ADT group (> 5 years; n = 41). The short ADT group received ADT treatment for an average of 25.4 ± 8.2 months.



	Pre	6 m	1 y	2 y	3 y	4 y	5 y
Short	77.01	78.83	80.14	78.06	77.12	75.42	72.10
Continuous	74.68	75.71	75.10	75.73	73.78	71.04	71.79

Figure 2

Changes in estimated glomerular filtration rate (eGFR)in the two study groups The eGFR values at each measurement point and before treatment. The eGFR decreased by 4.91 ml/min in the short ADT group and by 2.89 ml/min in the continuous group over the 5-years period following treatment initiation. No significant group difference in the eGFR was observed at any measurement point.