osteosarcoma involving the left occipital bone. Ten years earlier, she was diagnosed with cancer of the uterine body and underwent resection surgery. Two years after that surgery, she underwent chemotherapy and whole-brain radiation therapy (WBRT, total 30 Gy with 10 fractions) including the cerebellum for brain metastasis. Six years after the WBRT, she was diagnosed with a radiation-induced osteosarcoma involving the left occipital bone, and she underwent resection surgery and successive chemotherapy using methotrexate. One year after that surgery and chemotherapy, the subcutaneous tumor appeared again in the left occipital region and rapidly enlarged over a period of only 3 months (Figure 1A). Magnetic resonance images (MRI) showed the epidural tumor invasion (Figure 2A and A'). Eventually, the patient could not walk because of acutely developing cerebellar ataxia. This tumor was diagnosed as a recurrence of the radiation-induced osteosarcoma in accord with the above Cahan's criteria [3].

We performed BNCT for the radiation-induced osteosarcoma because the lesion/normal brain (L/N) ratio of fluoride-labeled boronophenylalanine positron emission tomography (FBPA-PET) was enough high, as shown in Figure 3A and B (L/N ratio: 3.8) [12]. For the BNCT, neutron irradiation was applied at Kyoto University Reactor.

The patient was administered 500 mg/kg of BPA intravenously for 3.2 hours (200 mg/kg for initial 2 hours, prior to neutron irradiation, 100 mg/kg for 1.2 hours during neutron irradiation). The boron concentration in the blood was monitored by sampling every 1 hour after boron compound administration until neutron irradiation was completed. The boron concentrations from BPA in the tumor and normal brain were estimated from the L/N ratio of 18 F-BPA on PET. The neutron fluence rate was simulated by the dose-planning system, SERA (Idaho National Engineering and Environmental Laboratory, Idaho Falls, ID) and the total doses to the tumor and normal brain were simulated. The neutron irradiation time was determined not to exceed 13 Gy-Eq to the normal brain in accordance with our recent protocol of BNCT for high-grade meningiomas [10]. For this case, irradiation time was 70 minutes and B10 concentration of the venous blood was judged as 37.2 ppm during the neutron irradiation. Here, Gy-Eq (Gy: Gray) means an X-ray dose that can give biologically equivalent effects to total BNCT radiation. The scalp just above the tumor was covered with the bolus composed of sodium polyacrylate with 1 cm-thickness to gain the superficial neutron flux. After the treatment, the doses given were re-estimated precisely and are shown in Table 1. We hypothesized the boron concentrations of the blood, brain, and skin were equal, as we did in the previous BNCT. RBE and CBE values employed here were listed in Table 2.

Absorbed physical dose and X-ray-equivalent dose (Gy-Eq) are calculated with the following formula;

$$E_{Total} = E_{B10} + E_{Thermal} + E_{Fast} + E_{\gamma}$$

$$E_{B10} = (C_{BSH} \times CBE_{BSH} + C_{BPA} \times CBE_{BPA}) \times 7.43 \times 10^{-14} \times \Phi_{Thermal}$$

$$E_{Thermal} = N \times RBE_{Thermal} \times 6.78 \times 10^{-14} \times \Phi_{Thermal}$$

$$E_{Fast} = RBE_{Fast} \times D_{Fast}$$

$$E_{\gamma} = RBE_{\gamma} \times D_{\gamma}$$

D: physical absorbed dose (Gy),
ΦThermal: fluence of theraml neutron (cm-2),
N: nitrogen concentration (2%, here)
C: B10 concentration (ppm).

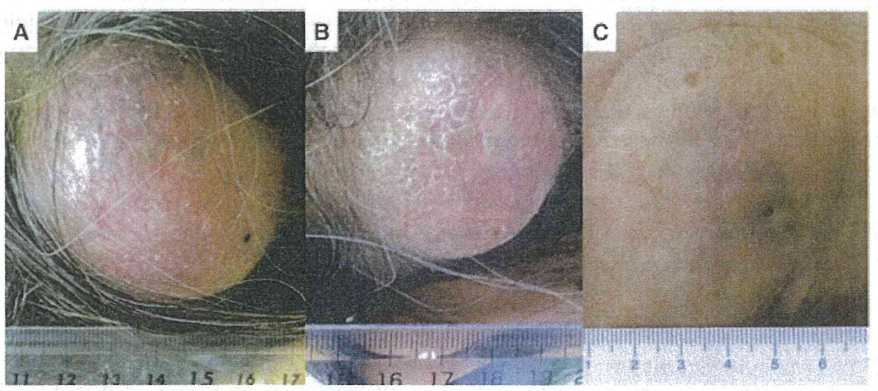

Figure 1 Marked improvement of the subcutaneous tumor at 3 weeks after the application of BNCT. A: Just prior to the BNCT; the tumor is elastic hard, and painful. **B**: Seven days after the BNCT; the tumor is soft and no longer painful. **C**: At 2 months after the BNCT, the tumor had shrunk drastically without radiation damage to the skin.

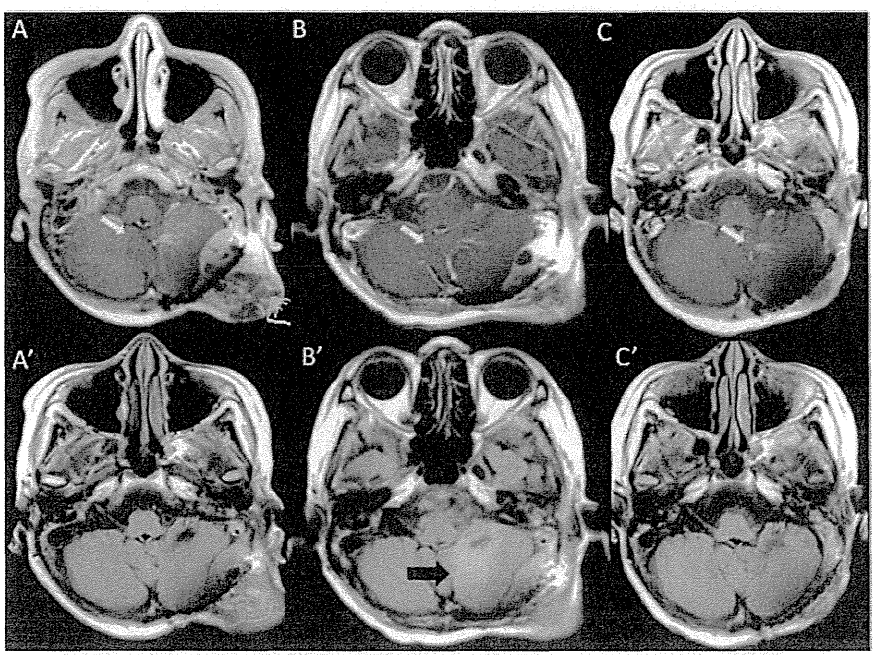

Figure 2 MRI of the patient's brain before and after the BNCT. White arrows indicate a venous angioma, which was recognized incidentally and judged as a sectional standard of MRI. **A**: Gd-enhanced T1-weighted MRI of the brain 1 month before the BNCT. There was a subcutaneous and epidural tumor mass. **B**: Gd-enhanced T1-weighted MRI at 4 days after BNCT. The tumor mass was reduced. **C**: Gd-enhanced T1-weighted MRI of the brain 3 months after BNCT. The tumor mass was further reduced. **A'**: Fluid-attenuated inversion recovery (FLAIR) MRI of the brain 1 month before BNCT. **B'**: FLAIR MRI of the brain 4 days after BNCT. The tumor mass was reduced, but the edema had worsened. A black arrow indicates the cerebellar edema. **C'**: FLAIR MRI of the brain 3 months after BNCT. The tumor mass was further reduced, and the edema had disappeared.

For this patient, we estimated that the minimum tumor and maximum normal brain and skin doses were 67.7, 12.7 and 12.4 Gy-Eq, respectively in the BNCT, simulated from F-BPA-PET imaging and the blood BPA concentration (Table 1).

At one day after the BNCT, the patient's gait disturbance was aggravated. Computed tomography at that time showed aggravation of peri-lesional edema (data not shown). Remarkably, the MRI taken 4 days after the BNCT demonstrated the definitive shrinkage of the mass, but the left cerebellar edema was still there (Figure 2B and B'). We then treated the edema with dehydrators and steroids. The symptoms gradually improved.

At only 3 weeks after the BNCT, the patient was able to walk again stably without aid. The subcutaneous tumor was reduced dramatically without radiation injury of the scalp, with time after BNCT, as shown in Figure 1B and C. The only adverse effect was hair loss in neutron-irradiation field, as shown in Figure 1C. MRI showed the further reduction of tumor and the disappearance of the cerebellar edema (Figure 2C and C'), 3 months after BNCT. Also F-BPA-PET taken 2 months after BNCT showed faint tracer uptake, indicating some metabolic change at least by this treatment (Figure 3A' and B', L/N ratio as 1.2).

Discussion

Radiation-induced osteosarcoma is not common. It has an aggressive nature, high recurrence rate, and poor prognosis. A standard therapy protocol has not yet been established for non-resectable tumors, but it was reported that particle radiotherapy (treatment with proton and carbon beams) had a therapeutic effect on these tumors [7,13].

In the present case, the tumor was chemo-resistant and difficult to totally resect because it invaded the left transverse and sigmoid venous sinuses. In addition, the subcutaneously extended tumor invaded the surface of the skin, and we thus suspected that a skin deficit due to surgery was inevitable and that particle radiotherapy for this tumor was likely to cause severe radiation-induced adverse effects on the scalp. The tumor was radiation-induced, and the cerebellum and overlying scalp had a history of X-ray treatment. Moreover, osteosarcomas have the characteristic of being radioresistant, i.e., X-ray-resistant. In light of these medical circumstances, we chose BNCT as the treatment modality for this patient. In the present case, the patient was successfully treated by BNCT without skin damage even though her tumor invaded the superficial scalp.

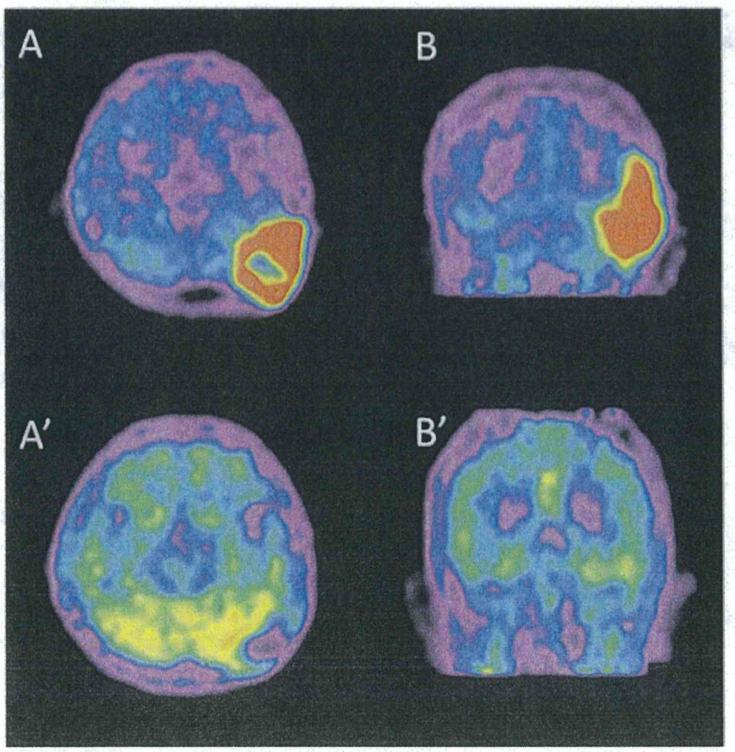

Figure 3 Fluoride-labeled boronophenylalanine-PET imaging of the brain before and after BNCT. Fluoride-labeled boronophenylalanine-PET imaging taken 1 month prior to BNCT (**A** and **B**) and 2 months after BNCT (**A'** and **B'**). **A** and **A'**: axial imaging, **B** and **B'**: coronal imaging. In **A** and **B**, L/N ratio was calculated as 5.0. This is theoretical proof of tumor selective destruction using BPA in BNCT. Also absorbed doses were simulated with this L/N ratio. 2 months after BNCT, **A'** and **B'** show the decreased L/N ratio as 1.2, indicating the marked effectiveness.

We recently reported the effectiveness of BNCT for radiation-refractory high-grade meningiomas [10]. In that report, we speculated that the difference in tumor shrinkage between the alpha and lithium particles provided by BNCT and other particles such as carbon and protons may be ascribed to the difference in LET noted above and their fraction size [10].

Other types of particle radiotherapy and some stereotactic radiotherapies which have been tried recently for tumors were applied as multi-fraction. The reduction of

Table 1 Estimated dose distribution at the central axis of neutron-irradiation field

Depth (cm)	Total dose (tumor) (Gy-eq)	Total dose (skin) (Gy-eq)	Total dose (mucosa) (Gy-eq)	Total dose (brain) (Gy-eq)	Thermal neutron (Gy-eq)	Fast neutron (Gy-eq)	γ-ray (Gy-eq)	Boron dose (tumor) (Gy-eq)
0.00	5.28E + 01	1.24E + 01	2.08E + 01	8.37E + 00	5.05E-01	2.13E + 00	1.00E + 00	4.92E + 01
0.50	6.79E + 01	----------	2.61E + 01	9.90E + 00	6.56E-01	1.87E + 00	1.22E + 00	6.41E + 01
1.00	8.06E + 01	----------	3.06E + 01	1.12E + 01	7.83E-01	1.64E + 00	1.43E + 00	7.67E + 01
1.50	8.47E + 01	----------	3.20E + 01	1.16E + 01	8.24E-01	1.35E + 00	1.63E + 00	8.09E + 01
2.00	9.00E + 01	----------	3.39E + 01	1.21E + 01	8.77E-01	1.17E + 00	1.80E + 00	8.62E + 01
2.50	9.38E + 01	----------	3.53E + 01	1.26E + 01	9.13E-01	1.11E + 00	1.92E + 00	8.98E + 01
3.00	9.55E + 01	----------	3.58E + 01	1.27E + 01	9.31E-01	9.77E-01	2.02E + 00	9.16E + 01
3.50	9.53E + 01	----------	3.57E + 01	1.27E + 01	9.30E-01	8.63E-01	2.09E + 00	9.14E + 01
4.00	9.18E + 01	----------	3.44E + 01	1.22E + 01	8.94E-01	7.72E-01	2.11E + 00	8.80E + 01
4.50	8.62E + 01	----------	3.24E + 01	1.16E + 01	8.38E-01	6.91E-01	2.10E + 00	8.26E + 01
5.00	7.97E + 01	----------	3.00E + 01	1.08E + 01	7.74E-01	6.18E-01	2.08E + 00	7.62E + 01
5.50	7.15E + 01	----------	2.70E + 01	9.79E + 00	6.93E-01	5.54E-01	1.99E + 00	6.82E + 01
5.80	6.77E + 01	----------	2.56E + 01	9.31E + 00	6.55E-01	5.12E-01	1.95E + 00	6.45E + 01

Table 2 RBE (relative biological effectiveness) factor

Radiation	Tumor	Brain	Skin
Thermal neuton	3.0	3.0	3.0
Epithermal neutron	3.0	3.0	3.0
^{10}B (n,α)^{7} Li: BPA	3.8	1.35	2.5
γ-ray dose	1.0	1.0	1.0

the tumor mass was thus not very prominent, and it was difficult to improve the patients' symptoms by means other than BNCT. BNCT can deliver high dose particles in a tumor-selective fashion in a single session, and in some cases the resulting reduction of the tumor was fast; this rapid shrinkage might contribute to the prompt elimination of symptoms [10]. Indeed, the present patient, within a very short time, exhibited improvement of her gait disturbance due to cerebellar ataxia.

Only a couple of articles were published with regard to pre-clinical study of BNCT for osteosarcoma in in vitro cell culture and animal experiments [14-17]. Among them, Russian research group reported successful treatment of dog osteosarcoma case by BNCT. Also only one preliminary report was published with regard to a BNCT-treated osteosarcoma case in head and neck region with limited description, so far [18]. We are not sure of the compound biological effectiveness (CBE) of BPA for osteosarcomas, and we were only able to estimate CBE as being the same for glioblastoma (i.e., 3.8) [19] as we did for high-grade meningioma [10]. For the estimation of the prescribed dose for this case, we adopted the reported value of CBE and relative biological effectiveness of neutron itself for tumors and normal tissues [20]. Thereafter the estimated tumor dose was uncertain in this case. However, as a result of the BNCT, the tumor shrank rapidly, the patient's clinical symptoms improved, metabolically scarce uptake of the amino-acid tracer was observed in the follow-up PET imaging and no serious damage was observed in the scalp and brain, so far at 6 months after BNCT, although the observation period was short.

Based on this outcome, we found that BNCT was an effective treatment for our patient. However, careful follow-up or the use of bevacizumab may be necessary in some cases [21], because WBRT that has been already performed may cause brain radiation necrosis.

We experienced only a case of successful treatment of BNCT for radiation-induced osteosacoma. Hopefully these potential therapeutic effects will be applicable for non-radiation-induced osteosarcomas which are generally refractory for other treatment modalities.

Conclusions

BNCT is an effective treatment for non-resectable radiation-induced skull osteosarcoma. We suggest that BNCT is the only effective therapy for tumors that have invaded the skin. Further applications of BNCT for similar cases are expected.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

S-IM conceived of the study and participated in the follow-up of the patient. GF, SK, NK, MS and KO applied BNCT in the atomic reactor. YS simulated BNCT dose. HS and TK participated in patient care in the hospital. MT and TT referred the patient for S-IM and also participated in the patient care and follow-up at the out-patient clinic. All authors read and approved the final manuscript.

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Original Article

Nocturia in men is a chaotic condition dominated by nocturnal polyuria

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Abbreviations & Acronyms
AIS = Athens Insomnia Scale
AUC = area under the curve
BPH = benign prostatic hyperplasia
BW = body weight
CCI = Charlson Comorbidity Index
CKD = chronic kidney disease
CLSS = Core Lower Urinary Tract Symptom Score
COPD = congestive obstructive pulmonary disease
CVD = cerebral vascular disease
eGFR = estimated glomerular filtration rate
FVC = frequency volume chart
GUD = gastrointestinal ulcer disease
IPSS = International Prostate Symptom Score
LUTS = lower urinary tract symptom
NP = nocturnal polyuria
NPi = nocturnal polyuria index
OAB = overactive bladder
QOL = quality of life

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Objective: To characterize nocturia in men based on frequency volume chart data and symptom profiles assessed using the Core Lower Urinary Tract Symptom Score and Athens Insomnia Scale questionnaires.

Methods: The Core Lower Urinary Tract Symptom Score and Athens Insomnia Scale questionnaires were administered to 299 consecutive treatment naïve men with nocturia (one time per night). Frequency volume chart data were recorded for 2 days. Correlations between nocturia and clinical characteristics including symptom scores, clinical diagnosis, Charlson Comorbidity Index, estimated glomerular filtration rate, uroflowmetry and prostate volume were analyzed.

Results: Patients were divided into five groups: one time ($n = 36$), two times ($n = 65$), three times ($n = 85$), four times ($n = 78$) and five times ($n = 34$) of nocturia. Age, prevalence or severity of chronic kidney disease, hyperlipidemia, low bladder capacity, nocturnal polyuria, urgency, bladder pain and sleep disorders were significantly correlated with the severity of nocturia. The Spearman correlation analysis identified eight possible independent factors for nocturia: age, estimated glomerular filtration rate, urgency, bladder pain, sleep quality, sleepiness during the day, average voided volume and nocturnal volume divided by body weight. Logistic regression analysis showed that nocturnal volume divided by body weight was the strongest factor of nocturia, and 7, 9 and 9.7 mL/kg were practical cut-off values of three, four and five times per night of nocturia, respectively.

Conclusions: Nocturia in men is a chaotic condition dominated by nocturnal polyuria, and related to multiple factors including age, renal function, urgency, bladder pain, insomnia and bladder volume.

Key words: lower urinary tract symptoms, nocturia, nocturnal polyuria, pain and sleep disorder.

Introduction

Nocturia is a complaint that the individual has to wake up at night for one or more times to void.[1] Nocturia is a highly prevalent LUTS that can cause insomnia, impaired mental and somatic health, decreased QOL, and increased mortality.[2–7] Nocturia is a multifactorial condition with several putative etiological factors such as OAB, bladder outlet obstruction, interstitial cystitis, bladder cancer, sleep problems, diabetes mellitus, NP, excessive fluid/caffeine intake and renal or cardiac dysfunction.[3] However, it is difficult to identify the precise etiology of nocturia in individual patients.

Several large cohort studies have shown numerous factors associated with nocturia.[8,9] However, associations among nocturia, other LUTS, sleep disturbance and FVC data have not been fully investigated. In the present study, using the CLSS questionnaire, the AIS and FVC, we attempted to clarify the etiology of nocturia to facilitate appropriate management.[10–12]

Methods

The study was approved by our institutional ethics committee (approval no. 3124). From 2010 to 2012, a cohort of 299 consecutive treatment naïve male patients with a complaint of nocturia (≥1 voiding episode per night) was enrolled in the present study. Treatments such as advice for water intake and prescription of α-blocker, anti-cholinergic or beta-3 adrenergic agent were not given until FVC was recorded.

Questionnaires and FVC

All patients completed the CLSS and AIS. The 10 core symptoms evaluated using the CLSS questionnaire were scored on a scale of 0–3.[10] Voiding frequency was scored as follows: 0 (≤7 times), 1 (8–9 times), 2 (10–14 times) or 3 (≥15 times) during the day and 0 (0 times), 1 (1 time), 2 (2–3 times) and 3 (≥4 times) during the night. Other symptoms were scored according to the frequency of episodes as follows: 0, never; 1, rare; 2, occasionally; and 3, often. Symptom concern was scored from 0 (delighted) to 6 (terrible) according to the IPSS QOL index, and nocturia was also scored using IPSS questionnaire.[13]

The AIS questionnaire comprises eight items.[11,12] The first five pertain to sleep induction, awakening during the night, final awakening, total sleep duration and sleep quality. The remaining three refer to well-being, functioning capacity and sleepiness during the day.[11,12]

In addition to these questionnaires, patients recorded FVC for 2 days. Total 24-h urine volume, nocturnal urine volume and NPi were calculated based on FVC data. Nocturnal urine volume was defined as the sum of voided urine volume during sleeping and at the first voiding in the morning.[1] NPi was defined as the ratio of nocturnal urine volume to total 24-h total urine volume. Single voided volumes were evaluated in the average, minimum and maximum values. Urine volume and single voided volume divided by BW (kg) were also calculated to adjust for interindividual variation in BW.[14]

Statistical analysis

Differences in symptom scores based on clinical characteristics were analyzed using the Wilcoxon rank sum or χ^2-tests. Correlations between nocturia and clinical parameters were evaluated by Spearman's rank correlation coefficients. A correlation matrix was constructed among the variables, and if a pair of variables had moderate to strong correlation (Spearman's rank correlation coefficient $\rho \geq 0.4$), one variable of the pair that was less correlated with nocturia severity was removed to avoid a multicollinearity problem.[15] Logistic regression analysis was carried out to analyze the correlation between clinical parameters and the nocturia severity. The AUC of receiver operating characteristics was calculated to determine the cut-offs discriminating nocturnal severity. JMP software version 11.0.0 (SAS Institute, Cary, NC, USA) was used for statistical analysis, and $P < 0.05$ was considered statistically significant. Multiple comparisons were allowed as a result of the exploratory nature of the study.

Results

Table 1 shows patient demographics and uroflowmetry results. The mean age was 71 ± 8.6 years. Their urological conditions were BPH ($n = 140$), BPH with OAB wet ($n = 72$), prostate cancer ($n = 12$), prostatitis ($n = 17$; type I: 0, type II: 0, type III: 11, type IV: 6), underactive bladder ($n = 6$) and others ($n = 52$; nocturnal polyuria: 31, insomnia: 14, psychosomatic disorder: 5, adrenal tumor: 2). We diagnosed patients as BPH when there was lower urinary tract dysfunction associated with benign prostatic enlargement. BPH patients with urgency incontinence were regarded as BPH with OAB wet. Patients with incomplete emptying of the bladder presumably as a result of impaired contractility were diagnosed as underactive bladder. Men with high serum PSA levels underwent prostate biopsy to exclude cancer, and questionnaire data obtained before the biopsy were used for analysis.

Comorbidities consisted of myocardial infarction ($n = 51$), heart failure ($n = 9$), cerebral vascular disease ($n = 35$), dementia ($n = 3$), chronic obstructive pulmonary disease ($n = 19$), gastrointestinal ulcer disease ($n = 12$), mild liver disease ($n = 11$), diabetes mellitus ($n = 70$), hemiplegia ($n = 4$), CKD ($n = 93$), any tumor ($n = 40$), hypertension ($n = 123$), and hyperlipidemia ($n = 84$). The CCI was calculated based on the comorbidity data.[16]

The average episodes of nocturnal voiding were 3.0 ± 1.2. Patients were divided into cases with nocturia of one time ($n = 36$), two times ($n = 65$), three times ($n = 85$), four times ($n = 78$) and five times ($n = 34$). Individuals with increased nocturia were significantly older and were more likely to have comorbidities, such as CKD and hyperlipidemia. The CCI and eGFR were significantly worse in men with nocturia of four times compared with those with one time or two times. Meanwhile, no significant differences were observed in serum PSA levels, prostate volume, uroflowmetry and residual urine.

Table 2 shows the responses to the CLSS and AIS questionnaires. As expected, individuals with severe nocturia recorded significantly higher scores of daytime frequency, nocturia and urgency of CLSS. Interestingly, bladder pain had clinical significance between patients with nocturia of three times and one time ($P = 0.02$). IPSS QOL Index was also significantly worse for men with four and five times of nocturia. Individuals with nocturia of four or five times also reported higher scores for awakening during the night, final awakening, total sleep duration, sleep quality and sleepiness during the day of AIS.

For FVC variables, the total urine volume was not significantly different among the five groups (Table 3). The average and maximum voided volumes were decreased significantly, whereas nocturnal urine volume and NPi were increased significantly in men with nocturia of three, four and five times.

Table 4 show Spearman's correlation coefficient (σ) between nocturia and clinical parameters, and the practical cut-off value of each parameter for three, four and five times. For correlation analysis with nocturia, eight clinical parameters (age, eGFR, urgency, bladder pain, sleep quality, sleepiness during the day, average voided volume and nocturnal volume divided by BW) were refined after removing nine potential variables (CCI, voided times per day, maximum voided volume, maximum voided volume divided by BW, nocturnal urine volume, NPi, sleep induction, awakening during the night and final awakening) because of lower correlation coefficients for the latter. In particular, nocturnal volume divided by BW was selected as the representative variable related to nocturnal polyuria, as it was better correlated with nocturia ($r = 0.26$) than nocturnal urine volume ($r = 0.24$) or NPi ($r = 0.24$).

Among the clinical parameters, nocturnal urine volume/BW showed the highest correlation with nocturia ($\sigma = 0.26$), followed by average voided volume, age, urgency, sleep quality, eGFR and sleepiness during the day ($\sigma = -0.21$, 0.20, 0.20, 0.20, –0.17 and

Table 1 Patients' demographics

	Total	Nocturia					*P*-value
		1 (*n* = 36)	2 (*n* = 65)	3 (*n* = 86)	4 (*n* = 78)	5 (*n* = 34)	
Nocturia (times)	3.0 ± 1.2	1.0	2.0	3.0	4.0	5.0	All; <0.0001
Age (years)	71 ± 8.6	68 ± 8.8	68 ± 9.5	71 ± 7.9	73 ± 7.8	72 ± 9.5	1 *vs* 4; 0.007, 2 *vs* 3; 0.03, 2 *vs* 4; 0.001
BW (kg)	63.3 ± 9.7	66 ± 10	64 ± 9.2	63 ± 10	63 ± 9.0	63 ± 11	Not significant
Body mass index (kg/m^2)	23 ± 3.4	24 ± 3.7	23 ± 3.2	23 ± 3.4	24 ± 3.2	24 ± 3.7	Not significant
Clinical diagnosis (*n*)							
BPH	140	13	29	45	38	15	-
OAB wet	72	9	22	14	19	8	
Prostate cancer	12	5	0	3	4		
Prostatitis	17	1	2	9	3	2	
Underactive bladder	6	1	3	1	1	0	
Others	52	7	9	14	13	9	
Comorbidity (*n*)							
Myocardial infarction	51	3	9	14	18	7	0.31
Heart failure	9	2	2	2	1	2	0.58
CVD	35	4	6	12	9	4	0.93
Dementia	3	1	2	0	0	0	0.19
COPD	19	3	5	8	1	2	0.27
GUD	12	1	5	2	2	2	0.45
Mild liver disease	11	2	0	4	4	1	0.44
Diabetes mellitus	70	7	8	27	19	9	0.09
Hemiplegia	4	0	1	1	2	0	0.77
CKD	93	5	15	29	33	12	0.02
Any tumor	40	6	8	10	11	5	0.92
Hypertension	123	10	21	40	35	17	0.12
Hyperlipidemia	84	6	12	35	22	9	0.017
CCI	1.6 ± 1.5	1.3 ± 1.6	1.3 ± 1.4	1.7 ± 1.5	1.9 ± 1.5	1.8 ± 1.7	1 *vs* 4; 0.02, 2 *vs* 4; 0.01
eGFR (mL/min/1.73 m^2) (*n* = 274)	66 ± 16	69 ± 12	71 ± 16	66 ± 16	62 ± 17	64 ± 15	1 *vs* 4; 0.03, 2 *vs* 4; 0.007
Serum PSA (ng/mL) (*n* = 274)	4.5 ± 17	6.7 ± 29	2.6 ± 3.5	2.6 ± 3.3	7.4 ± 26	4.0 ± 11	Not significant
Prostate volume (cm^3) (*n* = 244)	32 ± 18	35 ± 19	33 ± 17	30 ± 17	31 ± 20	33 ± 22	Not significant
Uroflowmetry (*n* = 246)							
Voiding volume (mL)	166 ± 97	186 ± 111	167 ± 99	173 ± 101	161 ± 96	135 ± 77	Not significant
Peak flow rate (mL/s)	11 ± 6.0	12 ± 5.3	12 ± 6.8	12 ± 6.4	10 ± 5.1	11 ± 6.3	Not significant
Residual volume (mL)	50 ± 53	57 ± 69	58 ± 63	49 ± 48	49 ± 47	35 ± 32	Not significant

Data presented as mean ± standard deviation (*n* = 299).

0.12, respectively). The cut-off values for nocturnal urine volume/BW and average voided volume were 7–9.7 mL/kg and 170–204 mL depending on the threshold of nocturia severity.

Discussion

Nocturia is an important health issue, and is commonly encountered during regular clinical practice by urologists and general physicians. Nocturia leads to decreased health-related QOL, increased risks of bone fractures and/or mortality.[17,18] Multiple factors contribute to this condition including LUTS, polyuria and sleep disorders, although studies investigating correlations among these multiple parameters are rare.[19,20] In the current study, we evaluated correlations among LUTS, sleep disturbance and FVC variables in treatment-naïve male patients with nocturia.

The CLSS questionnaire was used to evaluate LUTS, because it is a comprehensive disease non-specific questionnaire thus applicable to a variety of patients. It evaluates 10 LUTS including stress urinary incontinence, urgency incontinence, bladder pain and urethral pain, which are the four symptoms missing in the IPSS, another well-known questionnaire.[10,13] Several validated questionnaires are available for sleep disorders, including AIS, Sleep Problems Scale, Pittsburg Sleep Quality Index and Karolinska Sleep Index. In the present study, the AIS was used, because it is practical and easy to use.[10,11,21]

The present study showed that nocturia is a chaotic condition related to multiple factors including age, comorbidities, average voided volume, nocturnal urine volume, urgency, bladder pain and sleep disorders.

Comorbidities, such as CKD and hyperlipidemia, were highly common in individuals with three of more times per night of nocturia. These systemic diseases might cause NP by increasing urine production during the night. Furthermore, the patients are apt to excessive fluid intake to prevent cerebral or coronary infarction, although it is not recommended by current guidelines.[21] Previous studies showed a high prevalence of increased nocturnal urine volume and NPi (74–88%), which is consistent with current result (70%).[12,20,22] Measuring fluid intake is crucial in diagnosis and management of patients with nocturia; randomized controlled trials have shown that fluid

Table 2 Response to CLSS and AIS

	Total	Nocturia					*P* value
		1 (*n* = 36)	2 (*n* = 65)	3 (*n* = 86)	4 (*n* = 78)	5 (*n* = 34)	
CLSS (range 0–3)							
Daytime frequency	1.3 ± 0.9	0.9 ± 0.7	1.5 ± 0.9	1.2 ± 0.9	1.4 ± 0.9	1.4 ± 1.1	1 *vs* 2; 0.0002, 1 *vs* 4; 0.006, 2 *vs* 3; 0.03
Nocturia	2.3 ± 0.7	1.2 ± 0.6	2.0 ± 0.5	2.1 ± 0.5	2.9 ± 0.3	2.9 ± 0.3	1, 2, 3, 4, *vs* 5; <0.0001
Urgency	1.6 ± 0.9	1.2 ± 0.9	1.6 ± 0.8	1.5 ± 1.0	1.7 ± 0.9	2.1 ± 1.0	1 *vs* 4; 0.01, 1 *vs* 5;0.0003, 2 *vs* 5; 0.008, 3 *vs* 5; 0.01, 4 *vs* 5; 0.04
Urgency incontinence	0.7 ± 0.8	0.6 ± 0.8	0.8 ± 0.9	0.5 ± 0.7	0.8 ± 0.9	0.9 ± 1.0	Not significant
Stress urinary incontinence	0.2 ± 0.5	0.2 ± 0.6	0.2 ± 0.4	0.1 ±0.4	0.3 ± 0.6	0.1 ± 0.2	Not significant
Slow stream	1.9 ± 1.1	1.8 ± 1.2	1.7 ± 1.2	1.9 ± 1.1	2.0 ± 1.0	1.8 ± 1.3	Not significant
Straining	1.1 ± 1.1	1.0 ± 1.1	1.0 ± 1.0	1.2 ± 1.1	1.2 ± 1.2	1.2 ± 1.3	Not significant
Incomplete emptying	1.3 ± 1.1	1.1 ± 1.2	1.3 ± 1.1	1.4 ± 1.1	1.4 ± 1.1	1.2 ± 1.2	Not significant
Bladder pain	0.3 ± 0.6	0.08 ± 0.3	0.2 ± 0.6	0.4 ± 0.7	0.3 ± 0.7	0.3 ± 0.7	1 *vs* 3; 0.02
Urethral pain	0.2 ± 0.6	0.2 ± 0.5	0.2 ± 0.5	0.3 ± 0.7	0.2 ± 0.5	0.2 ± 0.6	Not significant
Total scores	11 ± 4.3	8.3 ± 4.0	10 ± 3.8	11 ± 4.0	12 ± 4.4	12 ± 4.3	1 *vs* 2; 0.01, 1 *vs* 3; 0.002, 1 *vs* 4; <0.0001, 2 *vs* 4; 0.03, 2 *vs* 5; 0.04
IPSS QOL index (range 0–6)	4.5 ± 1.2	3.9 ± 1.7	4.3 ± 1.1	4.6 ± 1.2	4.7 ± 0.9	5.1 ± 0.9	1 *vs* 4; 0.04, 1 *vs* 5; 0.001, 2 *vs* 5; 0.0005, 3 *vs* 5; 0.02, 4 *vs* 5; 0.02
AIS (range 0–3)							
Sleep induction	0.7 ± 0.9	0.5 ± 0.9	0.5 ± 0.8	0.7 ± 0.9	0.8 ± 0.9	1.0 ± 1.1	Not significant
Awakening during the night	0.9 ± 0.8	0.6 ± 0.8	0.8 ± 0.7	0.9 ± 0.8	1.0 ± 0.7	1.1 ± 0.9	1 *vs* 4; 0.01, 1 *vs* 5; 0.03
Final awakening	0.9 ± 0.8	0.8 ± 0.9	0.7 ± 0.7	0.7 ± 0.8	0.8 ± 0.7	1.1 ± 0.9	1 *vs* 5; 0.01, 2 *vs* 5; 0.04, 3 *vs* 5; 0.02
Total sleep duration	0.8 ± 0.8	0.6 ± 0.8	0.7 ± 0.7	0.7 ± 0.8	0.8 ± 0.7	1.1 ± 0.9	1 *vs* 5; 0.01, 2 *vs* 5; 0.04, 3 *vs* 5; 0.02
Sleep quality	1.0 ± 0.8	0.7 ± 0.8	0.9 ± 0.7	1.0 ± 0.8	1.1 ± 0.7	1.4 ± 0.8	1 *vs* 2; 0.04, 1 *vs* 3; 0.02, 1 *vs* 4; 0.005, 2 *vs* 5; 0.002
Well-being during the day	0.5 ± 0.7	0.4 ± 0.8	0.4 ± 0.7	0.4 ± 0.6	0.5 ± 0.7	0.6 ± 0.9	Not significant
Functioning capacity during the day	0.6 ± 0.8	0.5 ± 0.7	0.5 ± 0.7	0.6 ± 0.8	0.7 ± 0.8	0.7 ± 0.8	Not significant
Sleepiness during the day	1.1 ± 0.6	0.7 ± 0.6	1.1 ± 0.6	1.1 ± 0.6	1.1 ± 0.6	1.1 ± 0.6	1 *vs* 2; 0.0004, 1 *vs* 3; 0.002, 1 *vs* 4; 0.001, 1 *vs* 5; 0.002
Total scores	6.3 ± 4.4	4.7 ± 4.8	5.6 ± 0.9	6.4 ± 4.2	7.2 ± 4.4		1 *vs* 3; 0.01, 1 *vs* 4; 0.001

Data presented as mean ± standard deviation (*n* = 299).

manipulation improves the symptoms of OAB.[23] Patients with NP are encouraged to decrease nocturnal urine production; exercises, wearing compression stockings and bathing in the evening might decrease nocturnal diuresis.[24]

Scores for bladder pain were significantly higher in cases with three times per night of nocturia. Bladder pain could be attributed to hypersensitivity of the lower urinary tract. Recent investigations showed that the sensory afferent nerves, particularly unmyelinated C fibers, played a critical role in transducing noxious stimuli, such as pain, and that C fibers are activated in patients with BPH and/or OAB, as well as in experimental bladder outlet obstruction models.[25,26] Relieving hypersensitivity might be an important strategy in male patients with nocturia. Technically, CLSS might be more appropriate for screening of LUTS with nocturia, because pain symptom is included in CLSS, but not IPSS.

Data obtained from the AIS questionnaire confirmed impairment of sleep quality by nocturia; awakening during the night (Q2), final awakening (Q3), total sleep duration (Q4), sleep quality (Q5) and sleepiness during the day (Q8) were significantly worse in male patients with nocturia.

Table 3 Frequency volume chart variables

	Total	Nocturia					*P* value
		1 ($n = 36$)	2 ($n = 65$)	3 ($n = 86$)	4 ($n = 78$)	5 ($n = 34$)	
Voided time per day	11 ± 3.3	8.9 ± 2.9	11 ± 3.5	11 ± 2.9	12 ± 3.0	13 ± 3.8	1 *vs* 2; 0.002, 1 *vs* 3; 0.001, 1 *vs* 4; <0.0001, 1 *vs* 5; <0.0001, 2 *vs* 5; 0.01, 3 *vs* 4; 0.02, 3 *vs* 5; 0.007
Total urine volume (mL)	1786 ± 621	1723 ± 707	1804 ± 650	1816 ± 540	1767 ± 694	1792 ± 515	Not significant
Total urine volume/BW (mL/kg)	29 ± 11	26 ± 11	29 ± 12	29 ± 9.0	29 ± 14	29 ± 7.7	Not significant
Average voided volume (mL)	171 ± 69	198 ± 68	177 ± 78	181 ± 72	153 ± 59	149 ± 43	1 *vs* 2; 0.03, 1 *vs* 4; 0.003, 1 *vs* 5; 0.001, 3 *vs* 4; 0.007
Average voided volume/BW (mL/kg)	2.7 ± 1.2	3.0 ± 1.1	2.8 ± 1.3	2.9 ± 1.1	2.5 ± 1.2	2.4 ± 0.8	1 *vs* 4; 0.005, 1 *vs* 5; 0.02, 3 *vs* 4; 0.003, 3 *vs* 5; 0.04
Minimum voided volume (mL)	84 ± 47	93 ± 50	90 ± 54	90 ± 52	76 ± 36	66 ± 30	1 *vs* 5; 0.04, 2 *vs* 5; 0.02, 3 *vs* 5; 0.02
Minimum voided volume/BW (mL/kg)	1.3 ± 0.8	1.4 ± 0.9	1.4 ± 0.9	1.4 ± 0.8	1.2 ± 0.6	1.0 ± 0.5	2 *vs* 5; 0.04, 3 *vs* 5; 0.03
Maximum voided volume (mL)	297 ± 119	344 ± 126	313 ± 133	305 ± 119	259 ± 106	284 ± 85	1 *vs* 4; 0.0003, 1 *vs* 5; 0.04, 2 *vs* 4; 0.01, 3 *vs* 4; 0.006
Maximum voided volume/BW (mL/kg)	4.7 ± 2.0	5.3 ± 2.0	5.0 ± 2.3	4.9 ± 1.7	4.2 ± 2.1	4.6 ± 1.3	1 *vs* 4; 0.005, 2 *vs* 4; 0.01, 3 *vs* 4; 0.002, 4 *vs* 5; 0.04
Nocturnal urine volume (mL)	714 ± 348	564 ± 319	623 ± 339	767 ± 340	742 ± 330	871 ± 371	1 *vs* 3; 0.003, 1 *vs* 4; 0.009, 1 *vs* 5; 0.0008, 2 *vs* 3; 0.004, 2 *vs* 4; 0.01, 2 *vs* 5; 0.0006
Nocturnal urine volume/BW (mL/kg)	11 ± 6.0	8.9 ± 5.4	9.6 ± 5.8	12 ± 5.6	12 ± 6.4	14 ± 5.5	1 *vs* 3; 0.002, 1 *vs* 4; 0.01, 1 *vs* 5; 0.0007, 2 *vs* 3; 0.002, 2 *vs* 4; 0.009, 2 *vs* 5; 0.0004
NPi (%)	39 ± 14	33 ± 15	35 ± 14	42 ± 12	42 ± 14	45 ± 16	1 *vs* 3; 0.003, 1 *vs* 4; 0.004, 1 *vs* 5; 0.004, 2 *vs* 3; 0.0008, 2 *vs* 4; 0.0003, 2 *vs* 5; 0.004

Data presented as mean ± standard deviation ($n = 299$).

Table 4 Spearman coefficient (σ) between nocturia and clinical parameters and practical cut-off value of each parameter for nocturia

	ρ	*P*-value	Cut-off for 3	AUC[c]	*P*-value	Cut-off for 4	AUC[c]	*P*-value	Cut-off for 5	AUC[c]	*P*-value
Nocturnal urine volume/BW (mL/kg)	0.26	<0.0001	7	0.66	<0.0001	9	0.60	0.004	9.7	0.65	0.02
Average voided volume (mL)	−0.21	0.0002	204	0.58	0.01	170	0.62	<0.0001	203	0.58	0.03
Age (years)	0.20	0.0005	72	0.63	0.003	75	0.59	0.003	81	0.54	0.03
Urgency	0.20	0.0004	2	0.58	0.03	3	0.58	0.008	3	0.65	0.002
Sleep quality	0.20	0.0005	1	0.58	0.007	1	0.58	0.01	2	0.62	0.006
eGFR (mL/min/1.73 m^2)	−0.17	0.0055	62	0.60	0.004	65	0.58	0.01	56	0.54	0.5
Sleepiness during the day	0.12	0.02	1	0.54	0.11	1	0.53	0.23	1	0.54	0.34
Bladder pain	0.09	0.12	1	0.56	0.02	1	0.51	0.62	0	0.51	0.87

$n = 299$.

Correlation coefficient analysis showed nocturnal urine volume/BW, average voided volume, age, urgency and sleep quality as significant clinical parameters among multiple potential factors. The cut-off values of nocturnal urine volume/BW were calculated as 7, 9 and 9.7 mL/kg, which would be compatible with a previous study.[14] This is also compatible with other previous studies, which reported that nocturnal urine volume and NPi were the strongest factors for nocturia.[8,20] Bladder pain was significant in men with three times per night of nocturia, but not in men with nocturia of four or more times, probably because NP was such a powerful factor in severe nocturia.

A limitation of the present study was a sample characteristic that was 299 Japanese men visiting a university hospital. Obviously, further studies using cohorts of different characteristics or of a larger sample size are warranted. One should be cautious for overestimate of statistical significance incurred by multiple comparisons that were allowed because of the exploratory nature of data analysis.

In conclusion, nocturia in men is a chaotic condition related to multiple factors including low functional bladder capacity, age, urgency, bladder pain and insomnia, but is dominated by nocturnal urine volume. Appropriate assessment and targeted treatment of these factors might improve diagnosis and management of male patients with nocturia.