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.

Conflict of interest

None declared.

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RESEARCH ARTICLE

Risk Factors for Clinical Metastasis in Men Undergoing Radical Prostatectomy and Immediate Adjuvant Androgen Deprivation Therapy

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Abstract

Background: Adjuvant androgen deprivation therapy (ADT) is a treatment option for prostate cancer (PC) patients after radical prostatectomy (RP). Although it can achieve a good progression-free survival rate, some patients still develop clinical metastasis. We here investigated risk factors of clinical metastasis in post-prostatectomy patients who received immediate adjuvant ADT. Materials and Methods: We identified 197 patients with non-metastatic PC who underwent RP at our institution between 2000 and 2012, followed by adjuvant ADT. The associations of various clinicopathologic factors with clinical metastasis (primary endpoint) and cancer-specific survival (secondary endpoint) were assessed. Multivariate analysis was conducted using a Cox proportional hazards model. Median follow-up was 87 months after RP. Results: Nine (4.6%) patients developed clinical metastasis and six (3.0%) died from PC. Eight of nine metastatic patients had a pathologic Gleason score (GS) 9 and developed bone metastasis, while the remaining one had pathologic GS 7 and developed metastasis only to para-aortic lymph nodes. On multivariate analyses, pathologic GS ≥9 and regional lymph node metastasis (pN1) were independent predictors of clinical metastasis and pathologic GS ≥9 was an independent predictor of cancer-specific death. Conclusions: Pathologic GS ≥9 and pN1 were independent predictors of clinical metastasis in post-prostatectomy patients who received immediate adjuvant ADT. Furthermore, pathologic GS ≥9 was an indispensable condition for bone metastasis, which may imply that patients with GS ≤8 on adjuvant ADT are unlikely to develop bone metastasis.

Keywords: Adjuvant - androgen deprivation therapy - clinical metastasis - prostate cancer - radical prostatectomy

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Introduction

More than 1,112,000 patients worldwide were estimated to be diagnosed with prostate cancer (PC) in 2012, resulting in more than 307,000 deaths (Ferlay et al., 2013). In Japan, PC is the fourth, most commonly diagnosed cancer in men, with an estimated incidence of 51,534 cases (11.8% among 437,787 cancer patients of all primary sites) in 2008, and accounts for about 9,800 deaths annually in the latest data as of May 2014 (Matsuda et al., 2014). Most men diagnosed in the prostate-specific antigen (PSA) era have favorable disease characteristics that are curable by surgery or radiation therapy. However, the subset of men with high-grade (Gleason score [GS] ≥8) or extraprostatic disease (T3/T4 or lymph node involvement) have a risk of treatment failure as high as 70% when treated with surgery alone (Petrovich et al., 2002; Roehl et al., 2004; Carver et al., 2006; Nguyen et al., 2009; Dorff et al., 2011). Adjuvant androgen deprivation therapy (ADT), as well as adjuvant radiotherapy, has been a common treatment option for these patients with high risk PC for a long time in Asia (Akaza et al., 2013), but its efficacy has not been well studied.

Recently, we have reported favorable long-term results of immediate ADT after radical prostatectomy (RP) in Japanese patients with pT3N0 PC, including a 10-year biochemical progression-free survival rate of 88.3% and cancer-specific survival rate of 96.3% after a median follow-up period of 8.2 years (Sato et al., 2014). However, despite such excellent outcomes, some patients still develop clinical metastasis.

Here we investigated risk factors of clinical metastasis in post-prostatectomy patients who received adjuvant ADT.

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Table 1. Clinicopathologic Features of 197 Prostate Cancer Patients Who Received Adjuvant Androgen Deprivation Therapy Following Radical Prostatectomy

Parameter	Value
Median age, yr (IQR)	67 (62-70)
Median preoperative PSA, ng/mL (IQR)	14.2 (7.95-30.5)
Clinical tumor stage, no. (%)	
T1	58 (29.4)
T2	65 (33.0)
T3/4	74 (37.6)
Pathologic tumor stage, no. (%)	
T2	40 (20.3)
T3a	74 (37.6)
T3b	53 (26.9)
T4	30 (15.2)
Pathologic GS, no. (%)	
5	14 (7.1)
6	20 (10.2)
7	82 (41.6)
8	19 (9.6)
9	61 (31.0)
10	1 (0.5)
Regional lymph node metastasis, no. (%)	27 (13.7)
- Status of positive lymph nodes	
Median no. of positive lymph nodes (IQR)	1 (1-3)
Average no. of positive lymph nodes	2.5
Median no. of removed lymph nodes (IQR)	8 (6-13)
Average no. of removed lymph nodes	10.3
Extraprostatic extension, no. (%)	135 (68.5)
Lymphovascular invasion, no. (%)	119 (60.4)
Positive surgical margin, no. (%)	158 (80.2)
Seminal vesicle invasion, no. (%)	71 (36.0)
Perineural invasion, no. (%)	159 (80.7)
Neoadjuvant hormonal therapy, no. (%)	24 (12.2)
Combined adjuvant radiotherapy, no. (%)	19 (9.6)
Median follow-up, mo (IQR)	87 (44-108)

*IQR, interquartile range; PSA, prostate-specific antigen; GS, Gleason score

Materials and Methods

Reviewing 855 patients who underwent RP at our institution between 2000 and 2012, we identified 197 with non-metastatic (pT2-4N0-1M0) PC who received continuous immediate adjuvant ADT after surgery. This cohort includes 105 patients with pT3N0M0 PC who underwent RP plus immediate adjuvant ADT (Sato et al., 2014). Surgical procedure included bilateral obturator lymph node dissection in all cases. Regional lymph node metastases (pN1) were found in 27 (13.7%) with a median number of positive nodes of one (interquartile range [IQR]: 1-3) out of 8 removed (IQR: 6-13) (Table 1). We assessed the associations of various clinicopathologic factors with the occurrence of clinical metastasis (the primary endpoint) and cancer-specific survival (the secondary endpoint). Univariate and multivariate analyses were carried out using log-rank tests and Cox proportional hazards model, respectively. Patients who discontinued ADT were counted as censored at the point of discontinuation. The median follow-up was 87 months (IQR: 44-108 months) after RP (Table 1). All statistical analyses were carried out using JMP version 9.0.2 (SAS Institute, Cary, NC, USA). A value of $p<0.05$ was considered significant.

This study was approved by the Ethics Committee of the Graduate School of Medicine and Faculty of Medicine, The University of Tokyo.

Results

Nine (4.6%) patients developed clinical metastasis and six (3.0%) died from PC during the follow-up period. Eight of nine metastatic patients had pathologic GS 9 and developed bone metastasis, while the remaining one had pathologic GS 7 and developed metastasis only to para-aortic lymph nodes. In other words, pathologic GS ≥9 was an indispensable condition for bone metastasis in our cohort (Table 2). For reference, the exceptional case with pathologic GS 7 and para-aortic lymph node metastasis was the one which we previously reported to achieve three-year progression-free survival by zoledronic acid administration even after developing aggressive castration-resistant PC (Taguchi et al., 2012). Univariate analysis showed that clinical tumor stage ≥T3, pathologic GS ≥9, pN1, lymphovascular invasion, and seminal vesicle invasion were significantly associated with clinical metastasis and cancer-specific survival (Table 3). Multivariate analysis identified pathologic GS ≥9 and pN1 as independent predictors of clinical metastasis. Pathologic GS ≥9 was also an independent predictor of cancer-specific death (Table 4).

Discussion

ADT is a well-established treatment modality for patients with advanced PC (Ryan et al., 2005) and is also widely used for older patients with local PC (Situmorang et al., 2012). For surgical patients, a survival advantage with adjuvant ADT was also demonstrated in a small (n=98) trial of lymph node-positive patients (Messing

Table 2. Clinicopathologic Features of Nine Prostate Cancer Patients Who Developed Clinical Metastasis

Patient	Pathologic Tumor Stage	Pathologic GS	Regional Lymph Node Metastasis	Metastatic Site	Outcome (follow-up Period, mo)
1	T3a	7	+	Para-aortic lymph nodes	Alive (121)
2	T3b	9	+	Bone	DOD (40)
3	T3a	9	+	Bone	DOD (22)
4	T4	9	+	Bone	DOD (127)
5	T4	9	+	Bone	Alive (103)
6	T3b	9	-	Bone	DOD (12)
7	T3b	9	-	Bone	Alive (34)
8	T4	9	-	Bone	DOD (33)
9	T3b	9	-	Bone	DOD (103)

*PSA, prostate-specific antigen; GS, Gleason score; DOD, died of disease

Table 3. Univariate Analysis Evaluating the Impact of Various Clinicopathologic Factors on the Risks of Clinical Metastasis and Cancer-specific Death in Patients with Prostate Cancer

Variable		No. of patients	Clinical Metastasis, p-value	Cancer-specific Death, p-value
Age, years	<67†	97	0.82	0.47
	≥67†	100		
Preoperative PSA, ng/mL	≤20‡	127	0.83	0.83
	>20‡	70		
Clinical tumor stage	≤T2	123	0.02*	0.04*
	≥T3	74		
Pathologic tumor stage	≤T2	38	0.12	0.17
	≥T3	159		
Pathologic GS	≤8	136	0.0001*	0.0001*
	≥9	61		
Regional lymph node metastasis	0	166	<0.0001*	0.004*
	1	31		
Extraprostatic extension	0	62	0.17	0.36
	1	135		
Lymphovascular invasion	0	78	0.01*	0.03*
	1	119		
Positive surgical margin	0	39	0.84	0.78
	1	158		
Seminal vesicle invasion	0	126	0.005*	0.009*
	1	71		
Perineural invasion	0	38	0.12	0.21
	1	159		
Neoadjuvant hormonal therapy	0	173	0.24	0.08
	1	24		
Combined adjuvant radiotherapy	0	178	0.39	0.54
	1	19		

†median; ‡criterion for high risk according to NCCN stratification; *statistically significant; PSA, prostate-specific antigen; GS, Gleason score

Table 4. Multivariate Cox Proportional Hazards Regression Analysis Evaluating the Impact of Various Clinicopathologic Factors on the Risks of Clinical Metastasis and Cancer-specific Death in Patients with Prostate Cancer

Variable	Clinical Metastasis HR (95% CI)	p-value	Cancer-specific Death HR (95% CI)	p-value
Clinical tumor stage		0.15		0.34
≤T2	Reference		Reference	
≥T3	2.98 (0.70-20.4)		2.68 (0.39-52.8)	
Pathologic GS		0.02*		0.008*
≤8	Reference		Reference	
≥9	7.82 (1.40-146.2)		N/C (2.20-)	
Regional lymph node metastasis		0.04*		0.28
0	Reference		Reference	
1	4.20 (1.10-17.1)		2.46 (0.45-13.4)	
Lymphovascular invasion		0.07		0.24
0	Reference		Reference	
1	N/C (0.84-87.5)		N/C (0.31-)	
Seminal vesicle invasion		0.19		0.21
0	Reference		Reference	
1	2.69 (0.64-18.3)		3.40 (0.54-65.7)	

*Statistically significant; GS, Gleason score; N/C, not converged (because no patient existed in the reference cohort)

et al., 1999; Messing et al., 2006). While adjuvant radiotherapy is most commonly used for high risk but lymph node-negative patients after RP in Europe and the United States, adjuvant ADT still has an important position in Asia: The Asia Consensus Statement 2013 in the NCCN Clinical Practice Guidelines in Prostate Cancer states that adjuvant ADT is a candidate treatment option as well as radiotherapy and observation for post-prostatectomy patients with adverse features other than lymph node metastasis (Akaza et al., 2013).

Several studies have shown that RP plus adjuvant ADT provides a good progression-free survival rate. The Southwest Oncology Group (SWOG) S9921 study demonstrated that its ADT-alone control arm of 481 men undergoing adjuvant ADT after RP resulted in a 5-year biochemical progression-free survival rate of 92.5% and a 5-year overall survival rate of 95.9% with a median follow-up of 4.4 years (Dorff et al., 2011). Although being a retrospective study, we also reported a 10-year biochemical progression-free survival rate of 88.3% and

cancer-specific survival rate of 96.3% with a median follow-up of 8.2 years in Japanese patients with pT3N0 PC undergoing adjuvant ADT after RP (Sato et al., 2014). Nevertheless, some patients still develop clinical metastasis and studies evaluating risk factors of clinical metastasis are lacking.

Our study identified pathologic GS ≥9 and pN1 as independent predictors of clinical metastasis in patients with non-metastatic PC who received adjuvant ADT following RP. Furthermore, pathologic GS ≥9 was an indispensable condition for bone metastasis. This may imply that patients with GS ≤8 on adjuvant ADT are unlikely to develop bone metastasis. The results of other studies support these findings. Sundi et al. (2014) reviewed 753 men with National Comprehensive Cancer Network (NCCN), high-risk, localized PC (GS sum 8-10, PSA>20 ng/ml, or clinical stage ≥T3a). They defined very-high-risk localized PC as primary Gleason pattern 5 present on biopsy, five or more cores with GS 8-10, or multiple NCCN high-risk features, and indicated that patients meeting these criteria were at significantly increased risks of metastasis and cancer-specific mortality. Although the treatment modality and time of administration differed, Jackson et al. (2013) demonstrated that Gleason pattern 5 was the strongest pathologic predictor of biochemical recurrence, metastasis, and cancer-specific death in patients receiving salvage radiation therapy following RP. The both studies noted the impact of Gleason pattern 5 on clinical metastasis and cancer-specific death, which may be consistent with our results given that patients with GS ≥9 necessarily demonstrate Gleason pattern 5.

With respect to pN1, a randomized prospective trial demonstrated a survival benefit of adjuvant ADT after RP in the setting of positive lymph nodes, as stated above (Messing et al., 1999; Messing et al., 2006). According to a recent retrospective investigation by Abdollah et al. (2014), which reviewed 1,107 patients with pN1 PC, pathologic GS ≥8, positive surgical margin, number of positive lymph nodes, and combined adjuvant radiotherapy were significant predictors of cancer-specific mortality. In contrast, the current study found no effect of combined adjuvant radiotherapy on cancer-specific survival (Table 3), possibly because the follow-up period was too short.

As in other similar studies, preoperative PSA >20ng/ml (the criterion for high risk according to both the NCCN (Mohler et al., 2010) and D'Amico's risk stratifications (D'Amico et al., 1998) was not associated with clinical metastasis or cancer-specific mortality. The value of 20ng/ml was established to stratify patients at risk of biochemical recurrence (D'Amico et al., 1998), and a higher threshold value may need to be considered for clinical metastasis and cancer-specific mortality. Indeed, we confirmed that preoperative PSA became a significant predictor of clinical metastasis using a cutoff value of >50ng/ml, and of cancer-specific death at a cutoff value of 100ng/ml (data not shown).

Our study was limited by being a retrospective analysis of a limited number of cases at a single institution. Further studies with larger populations are needed to confirm these results. In addition, ADT is associated with some real risks related to metabolic syndrome, which should be taken into account along with the antitumor efficacy (McGrowder et al., 2012).

In conclusion, adjuvant ADT provides compelling survival benefits in high-risk PC patients after RP, but patients with high GS (≥9) still carry a risk of bone metastasis and cancer-specific death. These patients therefore require special attention and might deserve consideration of additional treatment such as combined radiotherapy.

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