10-cm line where 0 corresponds to 'no bladder sensation' and 10 to 'strong desire to void') were used for evaluating the grade of bladder sensation. Compression maneuver for 5 s was carried out to maintain a state of '7'on the VAS scale. By way of experiment, we tried the 5-s pushing task to confirm the state of VAS '7'. During the 5-s pushing task, the subject's lower abdomen was swiftly pushed for 5 s. In the empty phase, which is the state of VAS '0', we pushed the subject's lower abdomen in the same pressure as the pressure before micturition. Change of the hemoglobin concentration was measured during provoking desire to void using a 52-channel NIRS machine. Objects laid down on the bed in a dim room with their eyes open throughout the measurements. Each measurement consisted of: (i) 10-s pre-task baseline; (ii) 5-s pushing task; and (iii) 10-s post-task baseline. After the pushing maneuver, all subjects urinated and the voided volume was measured. Afterwards, the pushing maneuver for the state of 'empty' was done. We did not take any urodynamic measurements. We just asked the subjects about bladder sensations during study.

Recording

A multi-channel NIRS topography system (ETG-4000: Hitachi Medical Corporation, Tokyo, Japan) was used in this study.[10-12] The number of monitoring channels of ETG-4000 was 52. In our study, oxyhemoglobin, deoxyhemoglobin and total hemoglobin (sum of oxyhemoglobin and deoxyhemoglobin) were measured with NIRS. This system irradiates light at 780- and 830-nm wavelengths through an optical fiber to the same measurement point simultaneously. Then the infrared light is guided to the scalp surface through an optical fiber bundle. The reflection of infrared light is received by the sensor which is placed on the scalp, 3 cm away from the emitting probe. The 33 probes placed on the subjects' frontal area could measure the relative concentration of hemoglobin. The measurement regions were set in the 6 × 30 cm frontal area (Fig. 1). The lowest probes in the frontal shell were positioned along the Fp1-Fp2 line based on the international 10 to 20 system used for recording an electroencephalography. The pretask zero baseline was determined as the mean at the start of the measurement period and the posttask baseline was determined as the mean across 10–50 s. In addition, linear fitting was carried out on the data between two baselines. The waveforms of oxyhemoglobin, deoxyhemoglobin and total hemoglobin changes were acquired from all subjects during compression maneuver from 52 channels. The rate of data sampling was 0.1 s at multiple sampling channels. We tried to exclude motion artifacts by asking the subjects to avoid moving and to look blankly at one point on the ceiling during the measurements. Moreover, data with some 'motion artifacts' were excluded from further analyses. Oxyhemoglobin changes were analyzed using the first-order correction to exclude task-unrelated changes during the task. The pre-task baseline was determined as the mean across the last 10 s of the pre-task period and the post-task baseline was determined as the mean across the last 10 s of the post-task period, and a linear fitting was carried out based on the data between the two baselines. Moving average methods were applied to remove short-term motion artifacts in the analyzed data.

Data analysis

The obtained data were statistically analyzed with the integral mode. We repeated a series of task performances three times. Because the data with artifacts such as body movement are not a target signal, they were excluded for analyses. We calculated our data to analyze brain activity without some motion artifacts. Oxyhemoglobin, deoxyhemoglobin and total hemoglobin data were compared. These obtained data, which were averaged from the stimulation beginning, were compared between the sensation of artificially induced desire to void and the sensation of the state of empty bladder with paired Student's *t*-tests in each recording site (Fig. 2). Some reactions observed in these areas have already been pointed out by some other investigators.[13] In this analysis, we focused the change of 'oxyhemoglobin' concentration during the task procedure in detail to understand the frontal lobe responses to bladder sensation of induced desire to void.

Results

The mean voided volume was 233 ± 67 mL.

Figure 3 shows the average whole time series for levels of oxyhemoglobin, deoxyhemoglobin and total hemoglobin when subjects perceived a desire to void that was induced by pressing the lower abdomen for three repetitions recorded from every channel covering the frontal lobe. The time-course patterns of the changes differed depending on the measuring channels.

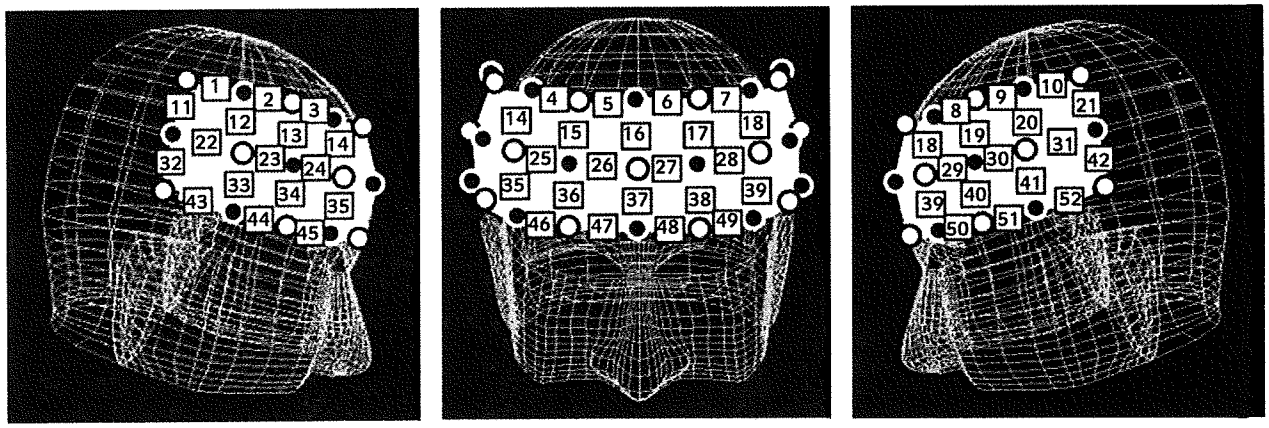

Fig. 1 The measurement area on the frontal region. The measurement points were set in the 6 × 30 cm frontal area. (a) Location of incident optical fibers, detection optical fibers and measurement positions (channels). Channels 1–52 are depicted as white squares and located between incident optical fibers and detection optical fibers. Incident optical fibers and detection optical fibers are shown as white and black circles, respectively. ○, incident optical fibers; ●, detection optical fibers; □, measurement positions.

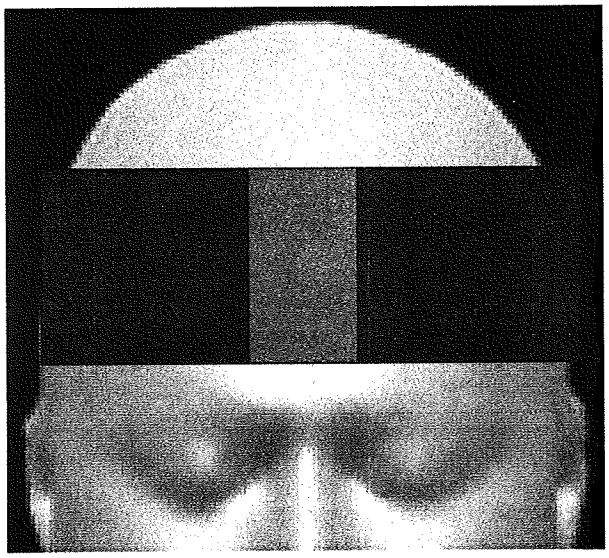

Fig. 2 Recording sites were lateral frontal and medial frontal sites. ■, lateral frontal; ■, medial frontal.

Oxyhemoglobin concentration change at each site is shown in Figure 4. Recording sites were the lateral and median frontal regions. Significant difference was observed between the artificially induced bladder sensation of 'desire to void' and 'empty' at each site. Oxyhemoglobin increases during the states of artificial desire to void were significantly larger than those during the states of empty bladder in the bilateral and medial frontal areas ($P < 0.05$). Furthermore, the figures suggest that the medial part may not be as activate as the bilateral parts. Oxyhemoglobin concentrations continued to increase during the task period, peaked at the end of the task period, and decreased gradually in the post task period. Oxyhemoglobin concentrations that were increased by the compression maneuver were observed in the bilateral and medial frontal sites.

Discussion

Changes in regional cerebral blood flow and hemoglobin oxygen saturation, which reflect the areas of neuronal activity, occur in the cerebral cortex. These changes could be measured using f-MRI or PET according to experimental studies by several investigators in the urological field.[13 17] Carrying out such examinations is not suitable for subjects who are feeling the desire to void. Brain imaging by these techniques requires a large apparatus and subjects are not free to move around. On the other hand, NIRS has a few advantages such as a compact construction,

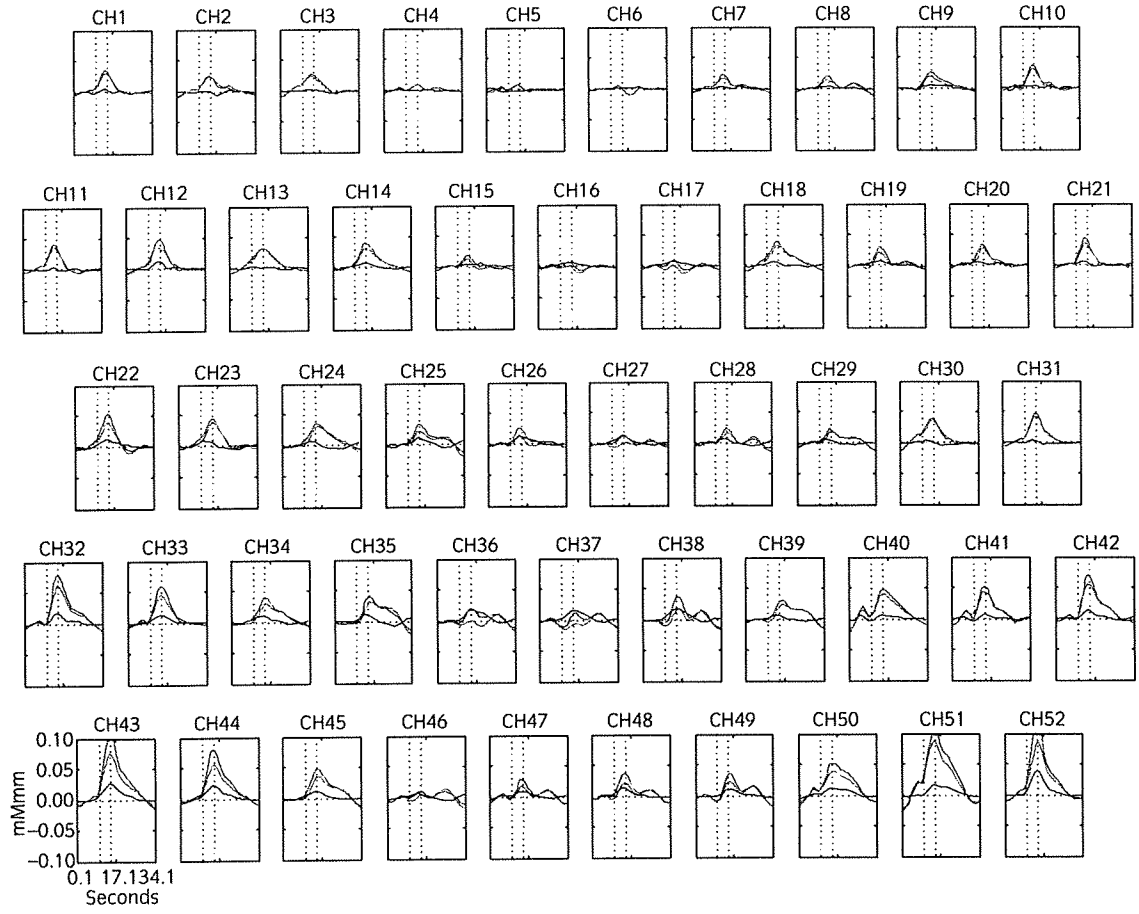

Fig. 3 Grand average waveforms of hemoglobin concentration changes during 'before-voiding' in healthy men. Grand average waveforms of oxyhemoglobin (red line), deoxyhemoglobin (blue line), and total hemoglobin (green line) changes during cognitive activation (between two vertical light blue lines).

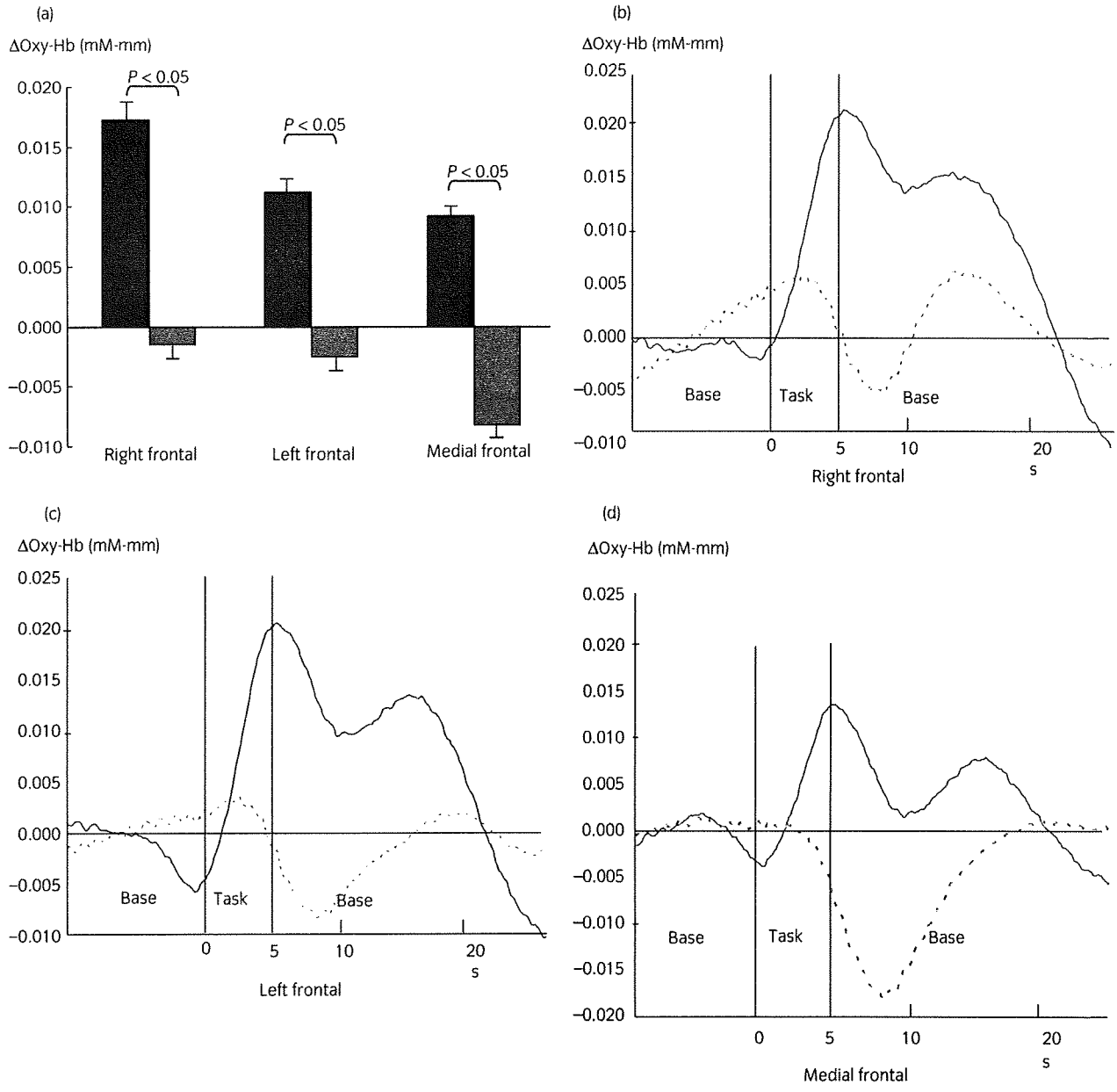

Fig. 4 Oxyhemoglobin concentration change from beginning of stimulation. Recording sites were lateral and medial frontal sites. Bar graphs indicate the results of statistical analysis. Waveforms represent averaged oxyhemoglobin concentration during procedure. ■, before; ■, after. ——, before; - - -, after.

temporal resolution, non-invasiveness and no restriction. It has been used to evaluate brain activity in response to visual, cognitive, auditory, and motor stimuli in adult, infant and even neonate subjects.[7,8,18,19]

For the first time in a urological report, we used a 52-channel NIRS machine in the analysis of the differences between waveforms pre and post micturition. It might demonstrate that the expected activations of frontal cerebral lobe were measured in resting subjects during the artificial sensation of desire to void. The authors have examined within-subject reproducibility and intra-individual variability by repeated measurements to calculate test-retest repeatability and consistency of effect. The signal amplitudes vary between sessions. However, the distance between the activation centers in each session is considerably small. The statistically significant increases of oxy-hemoglobin were detected on several channels on the frontal area. Our results coincide with previously obtained facts by fMRI and PET. Some studies using PET or functional MRI revealed that the lateral part of the frontal lobe was often activated during the storage phase.[20] According to our study, the frontal regions were specifically activated during the artificial sensation of desire to void. In addition, our data revealed that activation in the frontal area could be asymmetric with some individual variations. This might reflect brain laterality in dominance. Significant difference was not observed between the bilateral activation of frontal lobe by artificially induced bladder sensation ($P = 0.19$). Since our task represented more socially demanding procedures, the more pronounced ipsi-lateral activation could be reasonably explained by the need of more self-control. While activation of lateral cortices was not evident in

our study, further studies are essential to investigate whether the change of cerebral activation patterns are due to individual characteristics or different features to feel the desire to void.

We consider some of the limitations of NIRS as follows: (i) the NIRS machine could measure only 'relative' concentration of hemoglobin. Since the estimation of hemoglobin concentration would depend on the assumed near infrared path length, the difference among individuals might influence the results; and (ii) the NIRS probes used in our present study could cover only a part of the cerebral area. We could not measure regional cerebral blood volume over gap regions. For these reasons, the impact of the NIRS study should be carefully analyzed.

Near infrared spectroscopy has limits that we should take into consideration, but it also has a lot of advantages and availabilities. NIRS may be most useful in mapping human brain activity during both dynamic and static tasks, for which f-MRI and PET techniques are hardly suited because the situations in which the subjects experience the procedure are not natural and are restricted by many apparatuses surrounding the subjects. The subjects are not invaded by the NIRS machine using the near infrared ray throughout the procedure. Functional MRI is totally noninvasive and based on physiology-dependent intrinsic signal changes to provide well-resolved functional brain maps. These intrinsic signal changes are consistent with the idea that neural activation increases regional cerebral blood flow and concomitantly increases venous-blood oxygenation.[21] Changes of cerebral blood flow and arterial oxygenation by means of a NIRS machine reflect the brain activities more exactly. Furthermore, results obtained from NIRS will largely benefit from these methodological studies and the role of NIRS would be admitted as a remarkable and accurate tool particularly for cognitive examination. The advantage of NIRS is that it could demonstrate the central nervous activity of both dynamic and static phases in more natural situations, because it could measure relative concentrations of hemoglobin every 0.1 s without fixation of the body of each examinee.

There is a bias in this measurement. Because young Japanese volunteers had not agreed to undergo the study of cystometry, we used 'artificial sensation' for desire to void. Although it was an artificial micturition desire in this study, brain response was observed by NIRS. NIRS was suggested to be a useful tool for measuring the brain response to LUTS (lower urinary tract symptoms). Further studies are needed to investigate the influence of other dysuria, such as enuresis, urinary urgency, residual sensation, incontinence, urinary frequency, nocturia, and micturion pain. Moreover, since we postulated that the frontal cortex plays a crucial role in controlling desire to void, further studies should also investigate the means by which cerebral cortex controls adaptive mind, behavior, and action to the social surrounding environment. The role of the frontal cortex may be the sense of desire to void, enduring urgency or decision to void, but it is important to continue to try to replicate observations in various ways and in larger numbers of subjects. Data from NIRS could provide new perspectives and for the first time offer the paradigms for the understanding of voiding control. NIRS may be applied to the evaluation of cortical activation patterns due to a lot of various symptoms at storage phase and voiding phase, such as overactive bladder, and may enable us to study how these patterns are modified during the treatment period.

Conclusions

Our present study could demonstrate that the expected activations of frontal cerebral lobe were measured in resting subjects before micturition. Furthermore, this examination suggested that NIRS was useful to evaluate the central nervous response during urination. Now we are applying this device to study the response pattern of some patients with urination disorder such as overactive bladder, interstitial cystitis or neurogenic bladders.

References

1 Elbadawi A, Yalla SV, Resnik NM. Structural basis of geriatric voiding dysfunction. Detrusor overactivity. *J. Urol.* 1993; **150**: 1668–80.
2 Blok BF, De Weerd H, Holstege G. Ultrastructural evidence for a paucity of projections from the lumbosacral cord to the pontine micturition center or M-region in the cat: a new concept for the organization of the micturition reflex with the periaqueductal gray as central relay. *J. Comp. Neurol.* 1995; **359**: 300–9.
3 Blok BF, Holstege G. The central nervous system control of micturition in cats and humans. *Behav. Brain Res.* 1998; **92**: 119–25.
4 Wray S, Cope M, Delpy DT, Wyatt JS, Reynolds EO. Characterization of the near infrared absorption spectra of cytochrome aa3 and haemoglobin for the non-invasive monitoring of cerebral oxygenation. *Biochim. Biolphys. Acta* 1988; **933**: 184–92.
5 Jobsis-vander Vliet FF, Piantadosi CA, Sylvia AL, Lucus SK, Keizer HH. Near-infrared monitoring of cerebral oxygen sufficiency. Spectra of cytochrome c oxidase. *Neurol. Res.* 1988; **10**: 7–17.
6 Villringer A, Planck J, Hock C, Schleinkofer L, Dirnagl U. Near infrared spectroscopy (NIRS): a new tool to study hemodynamic changes during activation of brain function in human adults. *Neurosci. Lett.* 1993; **154**: 1–2.
7 Isobe K, Kusaka T, Nagano K *et al.* Functional imaging of the brain in sedated newborn infants using near infrared topography during passive knee movement. *Neurosci. Lett.* 2001; **299**: 221–4.
8 Taga G, Asakawa K, Maki A, Konishi Y, Koizumi H. Brain imaging in awake infants by near-infrared optical topography. *Proc. Natl Acad. Sci. USA* 2003; **100**: 10722–7.
9 Homma Y, Yoshida M, Seki N *et al.* Symptom tool for overactive bladder syndrome-overactive bladder symptom score. *Urology* 2006; **68**: 318–23.
10 Yamashita Y, Maki A, Koizumi H. Measurement system for noninvasive dynamic optical topography. *J. Biomed. Opt.* 1999; **4**: 414–17.
11 Sato H, Fuchino Y, Kiguchi M *et al.* Intersubject variability of near-infrared spectroscopy signals during sensorimotor cortex activation. *J. Biomed. Opt.* 2005; **10**: 44001.
12 Sato H, Kiguchi M, Maki A *et al.* Within-subject reproducibility of near-infrared spectroscopy signals in sensorimotor activation after 6 months. *J. Biomed. Opt.* 2006; **11**: 014021.
13 Griffiths D, Derbyshire S, Stenger A, Resnik N. Brain control of normal and overactive bladder. *J. Urol.* 2005; **174**: 1862–7.
14 Blok BF, Willemsen AT, Holstege GA. PET study on brain control of micturition in humans. *Brain* 1997; **120**: 111–21.
15 Athwal BS, Berkley KJ, Hussain I *et al.* Brain responses to changes in bladder volume and urge to void in healthy men. *Brain* 2001; **124**: 369–77.
16 Matsuura S, Kakizaki H, Mitsui T, Shiga T, Tamaki N, Koyanagi T. Human brain region response to distention or cold stimulation of the bladder: a positron emission tomography study. *J. Urol.* 2002; **168**: 2035–9.
17 Takao T, Tsujimura A, Miyagawa Y *et al.* Brain responses during the first desire to void: a positron emission tomography study. *Int. J. Urol.* 2008; **15**: 724–8.
18 Miyai I, Tanabe H, Sase I *et al.* Cortical mapping of gait in humans: a near-infrared spectroscopic topography study. *NeuroImage* 2001; **14**: 1186–92.
19 Otsuka Y, Nakato E, Kanazawa S, Yamaguchi MK, Watanabe S, Kakigi R. Neural activation to upright and inverted faces in infants measured by near infrared spectroscopy. *NeuroImage* 2007; **34**: 399–406.
20 Griffiths D, Tadic SD. Bladder control, urgency, and urge incontinence: evidence from functional brain imaging. *Neurourol. Urodyn.* 2008; **27**: 466–74.
21 Ogawa S, Tank DW, Menon R *et al.* Intrinsic signal changes accompanying sensory stimulation: functional brain mapping with magnetic resonance imaging. *Proc. Natl Acad. Sci. USA* 1992; **89**: 5951–5.

International Journal of Urology (2009) 16, 522–525 doi: 10.1111/j.1442-2042.2009.02291.x

Short Communication

Cancer-related pain and quality of life in prostate cancer patients: Assessment using the Functional Assessment of Prostate Cancer Therapy

Tetsuya Fujimura,[1] Satoru Takahashi,[2] Haruki Kume,[1] Takumi Takeuchi,[1] Clinical Study Group of Tokyo University Affiliated Hospitals,[3] Tadaichi Kitamura[4] and Yukio Homma[1]

[1]Department of Urology, Faculty of Medicine, The University of Tokyo, Tokyo, [2]Department of Urology, Faculty of Medicine, The Nihon University, Tokyo, [3]Clinical Study Group of Tokyo University Affiliated Hospitals, Tokyo, and [4]Asoka Hospital, Tokyo, Japan

Abstract: The objective of this study was to assess disease-associated pain and quality of life (QOL) in patients with prostate cancer (PC). A total of 102 PC patients (clinical stage B, C: 20, D2: 82) patients were enrolled. QOL was assessed using the Functional Assessment of Cancer Therapy, General and Prostate (FACT-G/P). Disease-specific pain response was assessed using the visual analog scale and the face rating scale. In patients with stage D2 PC, mean age, serum prostate-specific antigen level, and performance status were 72.5 ± 7.1 years (range, 55–88), 217 ± 467 ng/mL (range, 0.1–2600), and 1.4 (0–4), respectively. The score of physical well-being and FACT-P was significantly lower in stage D2 patients, compared with those of stage B/C ($P = 0.02$, 0.0088, respectively). Performance status, extent of disease, and the visual analog scale were related with a poor QOL score ($P = 0.0054$, 0.01, <0.0001, respectively). Thirty-two patients (39%) had disease-specific pain, and 25 patients received a related treatment. Ten patients under morphine analgesics maintained better QOL in almost all domains, compared with the seven patients without any painkillers. Combined use of FACT and pain scales enhances the objective assessment of QOL and pain status in PC patients. Control of disease-associated pain is crucial to improving QOL in stage D2 PC patients.

Key words: FACT, prostate cancer, QOL.

Introduction

In patients with stage D2 prostate cancer (PC), an improvement of quality of life (QOL) is one of the most important matters for judging the end-point of treatment. Now, the Functional Assessment of Cancer Therapy (FACT), the Medical Outcomes Study short-form 36-item health survey (SF-36), and the University of California Los Angeles (UCLA) index are available for high-quality evaluation,[1–3] but there are few reports on the validation of the Japanese translations.[4,5] Most published studies concern patients with early PC.[6–9] However, there has been little attention paid to formal evaluation of QOL as a primary end-point in stage D2 cases.[10–13] We used the FACT-prostate (P) questionnaire and the visual analog scale (VAS) at Tokyo University and five affiliated hospitals, and evaluated the QOL in stage D2 PC cases cross-sectionally.

Methods

Patient characteristics

A total of 102 patients, including 20 cases of stage B/C, and 82 cases of stage D2 PC, at Tokyo University Hospital or an affiliated hospital between 1999 and 2005 were involved in the study. The stage D2 patients' characteristics are described in Table 1. The age of the patients ranged from 55 to 88 years (mean 72.5 ± 7.1), and serum prostate-specific antigen (PSA) level ranged from 0.1 to 2600 ng/mL (mean 217 ± 467). The mean performance status (PS) was 1.4 (0–4), including 0 ($n = 32$), 1 ($n = 36$), 2 ($n = 7$), 3 ($n = 6$), and 4 ($n = 1$). The extent of bone disease was evaluated according to the scoring system described previously. Extent of disease included 0 ($n = 5$), 1 ($n = 31$), 2 ($n = 21$), 3 ($n = 19$), and 4 ($n = 6$). All patients were treated with surgical castration or medical castration. Seventy-one patients received anti-androgen therapy. Seventeen patients were treated with irradiation to the metastatic bone site. Mean patient follow-up period was 33.2 ± 33.5 months (range 1 to 144). The data of twenty patients with clinically localized PC were used as control.

Correspondence: Tetsuya Fujimura MD PhD, Department of Urology, Faculty of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan. Email: fujimurat-uro@h.u-tokyo.ac.jp

Received 21 December 2008; accepted 19 February 2009.
Online publication 6 April 2009

Questionnaire

We used the Japanese versions of FACT-G/P questionnaires to evaluate QOL. The questionnaire was handed to the patients for self-administration by the support staff of the clinic before contact with the urologist. The questionnaire consists of five domains including physical well-being (PWB), social/family well-being (S/FWB), emotional well-being (EWB), functional well-being (FWB), and a PC subscale.[4] Patients were asked a five-point response scale ranging from 'not at all' to 'very much'. The total QOL score is 164 points. We used the VAS and the face rating scale (FRS) to assess pain status. VAS is measured according to the length from the left side to where the patient makes a mark on a 10-cm line ranging from 'no pain' to 'strong pain'. We evaluated the correlation between the QOL score and the clinical characteristics.

Statistical analysis

Correlations between the QOL score and clinical characteristics (age, serum PSA level, extent of disease [EOD], VAS, and FRS) were evaluated using the t-test, χ^2-test, or Mann–Whitney U-test. P-values less than 0.05 were regarded as statistically significant.

Results

The scores obtained in the questionnaire are summarized in Table 2. The mean score of each domain was: PWB, 19.8 ± 6.9; SWB,

23.6 ± 8.4; EWB, 16.6 ± 5.7; FWB, 17.3 ± 7.1; FACT-P, 27.2 ± 9.8; and total score, 103.9 ± 28.3. Compared with control patients, the score of PWB and FACT-P was significantly lower in stage D2 PC patients ($P = 0.02$, 0.0088, respectively). These patients complained of general fatigue, cancer pain, restriction of daily life, and urinary disturbance.

The QOL scores of patients with PS ≥ 2 including PWB, FWB, FACT-P, and total score were significantly lower than that of patients with PS < 2 ($P = 0.017$, 0.04, 0.0007, and 0.0054, respectively) (Fig. 1a). The QOL scores of patients with EOD ≥ 2, such as PWB, SWB, and total score were significantly lower than that of patients with EOD < 2 ($P = 0.02$, 0.03, and 0.01, respectively) (Fig. 1b). The patients with VAS ≥ 30 have significantly reduced QOL, such as PWB, FWB, FACT-P, and total score ($P < 0.0001$, 0.0007, <0.0001, and <0.0001, respectively) (Fig. 1c).

Table 1 Patient characteristics in stage D2 prostate cancer ($n = 82$)

Age		55–88 (72.5 ± 7.1)
Serum PSA (ng/mL)		0.1–2600 (217 ± 467)
Performance status	0	32
	1	36
	2	7
	3	6
	4	1
Histopathological class (degree of differentiation)	well	1
	moderate	27
	poor	54
Extent of disease	0	5
	1	31
	2	21
	3	19
	4	
Treatment	TAB	71
	LHRH/Castration	82
	Irradiation	17
	Others	3
Painkillers	None	57
	NSAIDs	15
	Morphine	10

LHRH, luteinizing hormone-releasing hormone; NSAIDs, non-steroidal anti-inflammatory drugs; PSA, prostate-specific antigen; TAB, total androgen blockade.

Thirty-two patients had cancer pain, and 25 patients were treated with painkillers (non-steroidal anti-inflammatory drugs [NSAIDs] in 15 patients, and morphine analogs in 10 patients). Seven patients were not treated with any pain-relief product, although their VAS was larger than 30 mm. Figure 1d demonstrated the analyses of VAS, PWB, SWB, EWB, FWB, FACT-P and FACT-G/P in patients with no painkillers ($n = 7$), NSAIDs ($n = 15$), and morphine analgesia ($n = 10$). There were significant differences between the VAS scores in the three groups (no painkiller vs morphine; $P = 0.0094$, and no painkiller vs NSAIDs; $P = 0.007$). Although the data did not reach statistical significance because of the small sample size, the QOL scores, such as FACT-P and FACT-G/P in patients with morphine tended to be better than those with no painkillers ($P = 0.08$, 0.10, respectively).

Discussion

It is well known that the FACT, the SF-36 and the UCLA index are high-quality questionnaires for evaluating the QOL of patients with urological cancer.[5 9] However, most published studies using the Japanese translation have concerned patients with early PC.[7–9] We demonstrated a vertical section of QOL scores in stage D2 PC patients and related this to a pain treatment. Because the FACT questionnaire is well designed to be cancer-specific, multi-dimensional in structure, and appropriate for self-administration, we consider FACT-G/P as a suitable questionnaire to assess advanced PC patients. This study showed that metastatic PC patients have reduced QOL particularly in PWB and FACT-P compared with localized PC patients. These patients suffered from a feeling of worthlessness, cancer pain, limitations in physical activity, and voiding dysfunction. Interestingly, the scores for SWB and EWB in stage D2 patients were equivalent to that of control patients. The result attributed to support and encouragement from the patient's family. These findings suggest that FACT-G/P and VAS have an important role to play in gaining an understanding of metastatic PC patients.

A recent study described health-related QOL in 341 patients with early and advanced PC. Caucasian ($n = 292$), African-American ($n = 33$) and other ethnic ($n = 16$) participants enrolled in this study.[14] The data revealed that FACT scores of patients with metastatic disease were significantly lower than those of patients with localized disease in functioning, physical, social and prostatic aspects. Interestingly, this study also pointed out that the emotional domains of the QOL questionnaire were somewhat less vulnerable to the influence of disease progression relative to the physical and functional domains. In addition, the absolute figures of each domain were equivalent to those of the present study. Therefore, there are no significant differences between Caucasian/ African-American and Japanese QOL scores in PC patients.

Table 2 Relationship of FACT scores between control and stage D2 prostate cancer patients

QOL domain (full score)	Control ($n = 20$)	Stage D2 ($n = 82$)	P-value
PWB (28)	24.8 ± 3.3	19.8 ± 6.9	0.02
SWB (36)	22.7 ± 6.4	23.6 ± 8.4	0.72
EWB (24)	17.3 ± 3.6	16.6 ± 5.7	0.67
FWB (28)	20.4 ± 4.4	17.3 ± 7.1	0.16
FACT-P (48)	35.5 ± 7.4	27.2 ± 9.8	0.0088
Total score (164)	120.8 ± 12.8	103.9 ± 28.3	0.06

EWB, emotional well-being; FACT-P, Functional Assessment of Prostate Cancer Therapy; FWB, functional well-being; PWB, physical well-being; QOL, quality of life; SWB, social well-being.

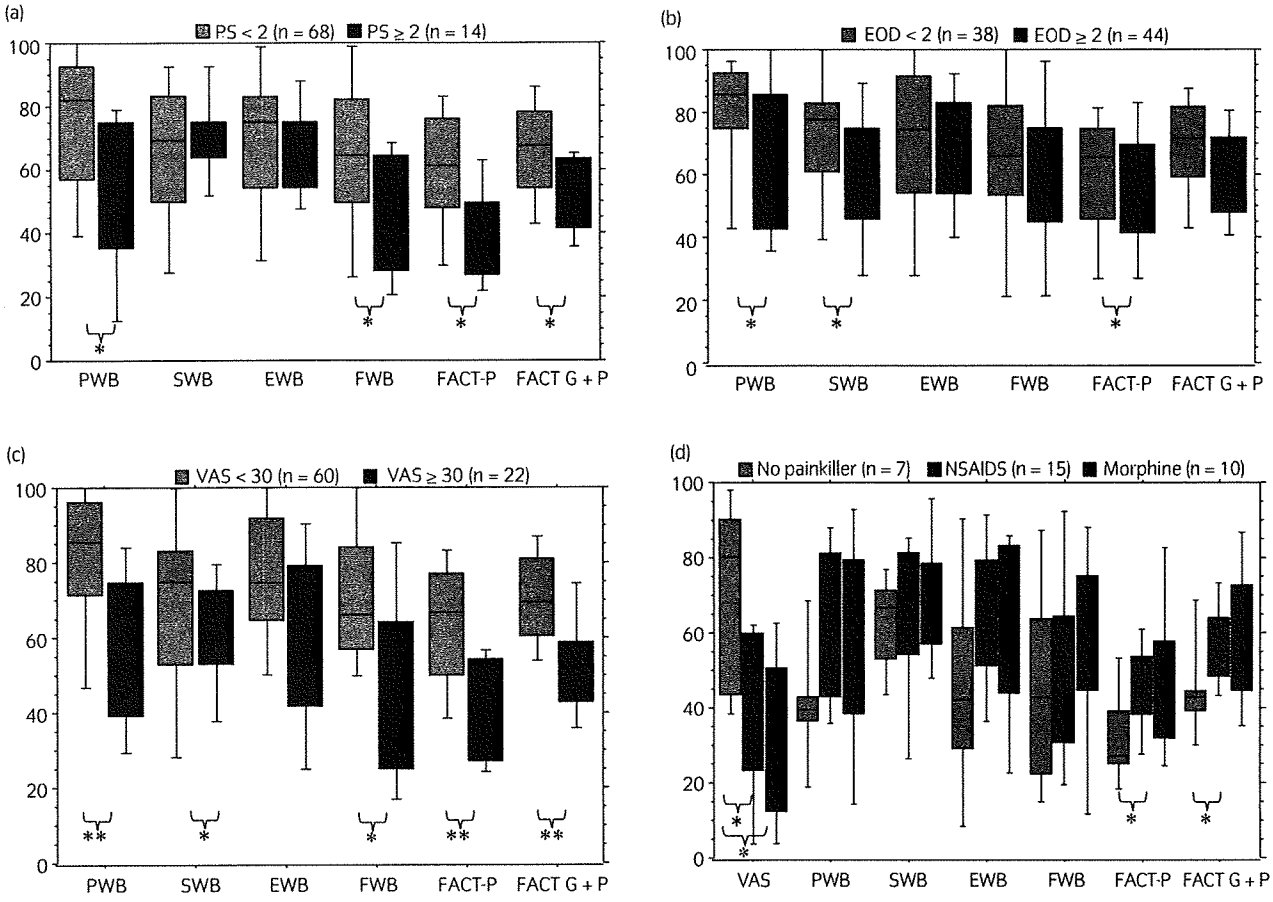

Fig. 1 Correlation of the Functional Assessment of Cancer Therapy, General and Prostate (FACT-G/P) quality of life (QOL) score with clinical parameters, including: (a) performance status (PS); (b) extent of disease (EOD); (c) visual analog scale (VAS); and (d) painkillers in stage D2 prostate cancer patients (n = 82). The QOL scores of patients (PS ≥ 2, EOD ≥ 2, or VAS ≥ 30) were lower than that of patients (PS < 2, EOD < 2, or VAS < 30) in each domain. *P-value (Mann–Whitney U-test) <0.05, **P < 0.0001. EWB, emotional well-being; FWB, functional well-being; PWB, physical well-being; SWB, social well-being.

The present study showed that cancer pain relief is an important factor of QOL in stage D2 patients. Although the patients tended not to complain about cancer pain to their physician, seven patients actually had severe pain (VAS ≥ 30) without any opioid analgesics. They complained that they could not do what they wanted to do because of cancer pain or neuropathic pain in the questionnaire. Surprisingly, although there are many senior urologists concerned with the present study, our results revealed that they tended to be reluctant to treat their patients with morphine painkillers. The reason why these physicians did not treat their patients with morphine analogs might be that endocrine therapy is also effective for pain relief. Actually the current morphine consumption per capita in Japan is still less than one-sixth of the consumption in the USA.[15] Recently, soluble morphine, which is quickly effective for cancer pain, and transdermal fentanyl are commercially available in addition to traditional per os or suppository morphine.[16] The combination therapy of morphine, fentanyl, and mexiletine are needed for cancer and neuropathic pain in advanced cancer patients.[17] On the other hand, the present study also suggests that patients treated with morphine had a better QOL score, compared with the patients without painkillers. These findings suggest that using a self-administration questionnaire and VAS in out-patients helps urologists to gather quantitative data on the physiological and mental condition of their patients and to take immediate action to address complaints regarding pain.

We investigated FACT in stage D2 PC patients with the use of a cross-sectional survey. The information in the questionnaire could help the physician gain an understanding of their patients. Further longitudinal investigations are warranted to evaluate QOL in patients with advanced PC and hormone-refractory PC.

References

1 Esper P, Mo F, Chodak G *et al.* Measuring quality of life in men with prostate cancer using the functional assessment of cancer therapy-prostate instrument. *Urology* 1997; **50**: 920–8.
2 Litwin MS, Hays RD, Fink A *et al.* The UCLA Prostate Cancer Index: Development, reliability, and validity of a health-related quality of life measure. *Med. Care* 1998; **36**: 1002–12.
3 Eton DT, Lepore SJ, Helgeson VS. Early quality of life in patients with localized prostate carcinoma: An examination of treatment-related, demographic, and psychosocial factors. *Cancer* 2001; **92**: 1451–9.
4 Hinotsu A, Niimi M, Akaza H *et al.* Development of Japanese version of QOL questionnaire for bladder and prostate cancer patients using FACT-BI and P: Pilot study. *Gan To Kagaku Ryoho* 1999; **26**: 657–66 (in Japanese).

5 Kakehi Y, Kamoto T, Ogawa O *et al.* Development of Japanese version of UCLA prostate cancer index: A pilot validation study. *Int. J. Clin. Oncol.* 2002; **7**: 306–11.
6 Miller NL, Bissonette EA, Bahnson R *et al.* Impact of a novel neoadjuvant and adjuvant hormone-deprivation approach on quality of life, voiding function, and sexual function after prostate brachytherapy. *Cancer* 2003; **97**: 203–10.
7 Arai Y, Okubo Y, Aoki Y *et al.* Patient-reported quality of life after radical prostatectomy for prostate cancer. *Int. J. Urol.* 1999; **6**: 78–86.
8 Nishiyama T, Kanazawa S, Watanabe R *et al.* Influence of hot flashes on quality of life in patients with prostate cancer treated with androgen deprivation therapy. *Int. J. Urol.* 2004; **11**: 735–41.
9 Namiki S, Tochigi T, Kuwahara M *et al.* Health-related quality of life after radical prostatectomy in Japanese men with localized prostate cancer. *Int. J. Urol.* 2003; **10**: 643–50.
10 Walsh D. Palliative care: Management of the patient with advanced cancer. *Semin. Oncol.* 1994; **21**: 100–6.
11 Jonler M, Nielsen OS, Grenvold M *et al.* Quality of life in patients with skeletal metastases of prostate cancer and states prior to start of endocrine therapy: Results from the Scandinavian Prostate Cancer Group study 5. *Scand. J. Urol. Nephrol.* 2005; **39**: 42–8.
12 Fujimura T, Nishimatsu H, Matsumoto A *et al.* Clinical response to dexamethasone therapy and measuring quality of life in patients with hormone refractory prostate cancer. *Jpn J. Urol. Surg.* 2001; **14**: 1263–9.
13 Turner SL, Gruenewald S, Spry N *et al.* Less pain does equal better quality of life following strontium-89 therapy for metastatic prostate cancer. *Br. J. Cancer* 2001; **84**: 297–302.
14 Rosenfeld B, Roth AJ, Gandhi S, Penson D. Differences in health-related quality of life of prostate cancer patients based on stage of cancer. *Psychooncology* 2004; **13**: 800–7.
15 Takeda F. The development of use of oral morphine within the last 10 years in Japan. *Eur. J. Pain* 2001; **5**: 79–82.
16 Gourlay GK. Treatment of cancer pain with transdermal fentanyl. *Lancet Oncol.* 2001; **2**: 165–72.
17 Guay DR. Adjunctive agents in the management of chronic pain. *Pharmacolotherapy* 2001; **21**: 1070–81.

Int Urol Nephrol (2009) 41:843–846
DOI 10.1007/s11255-009-9570-9

UROLOGY - ORIGINAL PAPER

Metachronous bilateral renal cell carcinoma with an interval of more than 10 years

Haruki Kume · Shinji Teramoto · Tadaichi Kitamura

Received: 8 October 2008 / Accepted: 31 March 2009 / Published online: 21 April 2009

Abstract
Objective Renal cell carcinoma (RCC) is notorious for late recurrence. However, little is known about late recurrence in the contralateral kidney, that is, metachronous bilateral RCC after a long interval. Unlike other recurrent sites, cancer in the contralateral kidney may be a metastatic or a new and independent lesion. The clinical characteristics of such cases formed the basis of this study.
Materials and methods Thirteen well-described cases in the English and Japanese literature were reviewed. Each clinical parameter, such as age, sex, size and number of the tumor(s), and interval, was divided into two groups and compared using the log rank test.
Results The clinical characteristics of these cases were similar to those of sporadic RCC cases, and no specific clinical or pathological features in these cases were found. As to the prognosis, among clinical parameters, cases with multiple second tumors had a favorable outcome compared with cases with a single second tumor.
Conclusions Multiple second tumors may be suggestive of metastasis from the first tumor. The favorable outcome in this group reflects the gentle biological nature of these slow-growing tumors that had taken a long time to become clinically obvious. Because of the limited number of cases in this study, further investigation will be needed.

Keywords Renal cell carcinoma · Bilateral · Late recurrence · Metachronous

H. Kume (✉) · T. Kitamura
Department of Urology, The University of Tokyo Hospital, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan
e-mail: kume@kuc.biglobe.ne.jp

S. Teramoto
Department of Geriatric Medicine, The University of Tokyo Hospital, Tokyo, Japan

Introduction

Renal cell carcinoma (RCC) is notorious for its late recurrence. Various sites of late recurrence have been reported, but late recurrence in the contralateral kidney, or metachronous bilateral RCC after a long interval, is relatively rare and has not been well documented [1].

Renal cell carcinoma has been reported to occur bilaterally in 3–5% of cases. Although about half are metachronous, most of the second tumor(s) occur within 10 years. Only a few cases have been reported in which the interval was more than 10 years.

Importantly, unlike other sites of late recurrence, the contralateral kidney should be carefully analyzed and discussed, because in some cases the new lesion might not be metastasis but a new and independent cancer, that is, de novo RCC. In addition, in cases with a long interval, while it is supposed that

metastasis may be less likely, in contrast, a de novo lesion may become more likely [2, 3].

To our knowledge there is no discussion of this issue in the literature. In this study a list of cases with late recurrence from the English and the Japanese literature was compiled. These cases were re-evaluated, and efforts were made to elucidate the clinical characteristics of cases with late recurrence at the contralateral kidney, that is, metachronous bilateral cases with long intervals.

Materials and methods

In this review, cases were selected in which recurrence was found in the contralateral kidney after more than 10 years from the initial nephrectomy. This interval was chosen because 10 years was proposed by McNichol et al. [4] as a time limit for late recurrence. Cases with multiple metastatic sites, so-called cases in the terminal stage, were excluded, though a few cases with metastatic lesions of one organ were included.

The English medical literature on a web site (PubMed) was searched using the search terms "renal cell carcinoma" and "late recurrence" or "bilateral," "asynchronous" and "renal cell carcinoma" and "English (language)" [5]. The Japanese literature was also searched using Japana Centra Revuo Medicina, which is a frequently used software for searching the Japanese medical literature.

Results

Through a search of the web site, 13 cases were found (5 from the English literature and 8 from the Japanese literature) with detailed clinical information [6–15]. The clinical characteristics of these cases are summarized in Table 1. There were eight males and five females, and the interval between the two tumors ranged from 10 to 24 years (average 15.27 ± 3.93). While in all cases the first tumor was single, five had multiple second tumors, and eight had a solitary second tumor. The size of the first tumor was not described except in one case, and the size of the second tumor ranged from 3.0 to 10 cm (average 5.18 ± 2.19). In all cases the first tumors were treated with nephrectomy. In 11 cases the second tumors were treated with nephrectomy or partial nephrectomy, and in the other two cases the second tumors were treated only symptomatically or with arterial embolization. There were two cases with a single metastatic site: one with a single pulmonary metastatic lesion and one with a single bone metastatic lesion.

In all cases RCC was confirmed histologically.

Although the clinical parameters written in the literatures were limited and in some papers only a little information was available, we made some findings; sex, age at the first tumor, age at the second tumor, the interval between first and second tumors, and size of the second tumor seemed to have little influences on the outcomes. However, patients with multiple second tumors seemed to have a favorable outcome ($p = 0.033$, Fig. 1).

Discussion

That metachronous RCC with a long interval is a rare event was amply confirmed from our search of both the English and Japanese literature, which turned up only 13 cases. The clinical characteristics of these cases appeared to be similar to those of sporadic RCC cases. However, no common clinical or pathological features or characteristics were found in these cases.

Any discussion of bilateral RCC needs to consider the two possibilities involved. Some cases are metastatic from the contralateral RCC, while other cases are of a new and independent origin [2, 3, 15]. However, it is often difficult to differentiate these cases clinically, because these issues have not been well documented in the literature. In early studies some histopathological data were included as to whether such tumors were metastatic or represented bilateral primary disease [2, 3].

Recently, a mutation of the *VHL* gene, which is known to be causative for RCC [16], was analyzed in bilateral RCC cases [15]. In that study it was demonstrated that multiplicity might be suggestive of metastatic RCC in cases with bilateral disease. That is, if the second tumors are multiple, it is likely that these tumors are metastatic from the first tumor [15].

In this study cases with long intervals of more than 10 years were analyzed. Consequently, it is expected

Table 1 Summary of clinical information of bilateral cases with an interval of more than 10 years

Case/sex	First tumor		Interval (years)	Second tumor(s)					Outcome (months)
	Age	Histology		Age	Number of tumors	Diameter[a] (cm)	Histology	Metastasis	
Single second tumors									
1-M [6]	56	Clear cell[b]	16	72	1	3.0	Clear cell[c]	Bone	1.5 Dead[d]
2-M [7]	58	Clear cell, G1, pT1	24	71	1	>10	Clear cell, G2, pT2[b]	None	1.5 Dead[d]
3-M [8]	53	RCC	19	72	1	4.0	RCC, G2	None	5 Dead
4-M [9]	40	Clear cell[b]	15	55	1	5.5	Clear cell, G1, pT1	None	11 Alive
5-M [10]	50	Clear cell, G1, pT1	13	63	1	3.0	Clear cell, G1, pT1	None	12 Alive
6-M [11]	66	Clear cell, G3, pT3a	11	77	1		Clear cell, G3, pT3b[c]	None	12 Dead
7-M [8]	51	RCC	17	68	1	7.0	RCC, G2	None	13 Dead
8-M [12]	50	Clear cell, G1	10	60	1	4.9	Clear cell, G1, pT1	None	20 Alive
Multiple second tumors									
9-M [13]	54	Clear cell, pT1	15	69	3		RCC, pT1	None	12 Alive
10-M [12]	51	Clear cell, G2	11	62	3	6.0, 2.3, 1.5	Clear cell, G2, pT1	None	13 Alive
11-M [8]	44	RCC	21	65	3	8.0, 6.0, 4.0	RCC, G3	None	30 Alive
12-M [14]	28	RCC, G2, pT3b	13	41	2	7.0, 3.5	RCC, G2, pT3a	Lung	32 Alive[e]
13-M [15]	46	Clear cell, G2, pT3b	14.5	60	3	4.1, 1.7, 1.1	Clear cell, G2, pT1	None	66 Alive

[a] Maximum length

[b] With granular cell component

[c] Histology was confirmed by autopsy or biopsy

[d] Treatment-related death

[e] Complete remission of lung metastasis by interferon therapy

that metastatic cases will decrease and bilateral primary cases will increase.

Our study showed a favorable outcome in cases with multiple second tumors. This may appear paradoxical. However, considering that multiple second tumors would indicate metastasis [15], the favorable outcome reflects the gentle biological nature of these slow-growing tumors that took more than 10 years to become clinically obvious. In contrast, in cases with a single second tumor in which a poorer outcome was observed, the biological nature of the second tumor may have presented a greater threat to the patient's life than that of the "cured" first tumor.

Treatment and determination of prognosis in such cases will, of course, remain controversial. Although the number of subjects studied was limited because of the rarity of these cases, we submit that our conclusions will be supported by studies of a larger number of subjects.

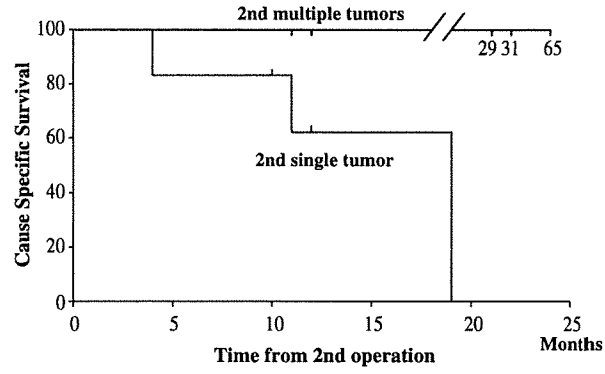

Fig. 1 Survival rate among cases with late recurrence (more than 10 years)

References

1. Petersen RO (1992) Kidney; in urologic pathology, 2nd edn. JB Lippincott, Philadelphia, pp 1–169
2. Small MP, Anderson EE, Atwill WH (1968) Simultaneous bilateral renal cell carcinoa: case report and review of the literature. J Urol 100:8–14

3. Novick AC, Stewart BH, Straffon RA, Banowsky LH (1977) Partial nephrectomy in the treatment of renal adenocarcinoma. J Urol 118:932–936
4. McNichols DW, Segura JW, DeWeerd JH (1981) Renal cell carcinoma: long-term survival and late recurrence. J Urol 126:17–23
5. PubMed [searched 2008 September 20th]. Available from: http://www4.ncbi.nlm.nih.gov/PubMed/
6. Yoshiyuki K, Morisue K, Nakamura I, Sawada K (1998) Asynchronous bilateral renal cell carcinoma: report of a case. Acta Urol Jpn 44:135
7. Kobayashi M, Imai K, Yamanaka H (1986) Bilateral renal cell carcinoma: report of a case. Acta Urol Jpn 32:721–728
8. Henriksson C, Geterud K, Aldenborg F, Geterud K, Zachrisson BF, Pettersson S (1992) Bilateral asynchronous renal cell carcinoma: computed tomography of the contralateral kidney 10–43 years after nephrectomy. Eur Urol 22:209–212
9. Tajika E, Nakamura T (1994) Asynchronous bilateral renal cell carcinoma: report of a case. Urol Surg 7:983–985
10. Gohji K, Kamidono S, Yamanaka N (1990) Renal carcinoma in a solitary kidney. Br J Urol 66:248–253. doi: 10.1111/j.1464-410X.1990.tb14921.x
11. Nakatsu H, Tahara E, Nihira H (1987) Bilateral renal cell carcinoma and its treatment. Hiroshima J Med Sci 36:179–182
12. Shimizu H, Miki M, Koshiba K (1990) Treatment of asynchronous bilateral renal cell carcinoma on our experience of enucleation for two cases. Jpn J Urol 81:1087–1090
13. Bokinsky GB, Goldman M (1980) Multiple renal cell carcinoma in solitary kidney. Urology 15:391–393. doi: 10.1016/0090-4295(80)90476-8
14. Masuda F, Yamazaki H, Makino H (1993) Conservative surgery for advanced renal cell carcinoma in a solitary kidney. KARKINOS 6:1203–1206
15. Kume H, Oda H, Nakatsuru Y, Shimizu Y, Takahashi Y, Matsumoto T, Inoue T, Kameyama S, Kitamura T, Ishikawa T (2000) Genetic identification of bilateral primary or metastatic nonpapillary renal cell carcinoma. BJU Int 86:208–212. doi:10.1046/j.1464-410x.2000.00770.x
16. Gnarra JR, Tory K, Weng Y, Schmidt L, Wei MH, Li H, Latif F, Liu S, Chen F, Duh FM, Lubensky I, Duan DR, Florence C, Pozzatti R, Walther MM, Bander NH, Grossman HB, Brauch H, Pomer S, Brooks JD, Isaacs WB, Lerman MI, Zbar B, Linehan WM (1994) Mutations of the VHL tumor suppressor gene in renal carcinoma. Nat Genet 7:85–90. doi:10.1038/ng0594-85