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Quantitative evaluation of lower urinary tract symptoms using a visual analog scale in men undergoing permanent brachytherapy

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ABSTRACT

PURPOSE: A previous study showed that a visual analog scale (VAS) that measures quality of life (QOL) in relation to each of the seven items on the International Prostate Symptom Score (IPSS) was found to be significantly more able to identify a patient's chief complaint. The aim of this study was to assess the two questionnaires with special reference to the symptom that the patient most wants treated via the concomitant use of the IPSS and VAS after permanent brachytherapy (PBT).

METHODS AND MATERIALS: A total of 156 men undergoing PBT were enrolled. The IPSS and VAS were evaluated at the preimplantation stage and at 1–3 months, 6–9 months, and 1 year after PBT. The correlations between the IPSS-QOL score and the total for the 14 symptoms questions included in the IPSS and VAS were statistically calculated. Multivariate analysis was used to investigate which factors could be used to predict the IPSS-QOL after PBT.

RESULTS: The correlation coefficients between the IPSS-QOL score and the seven questions on the VAS were higher than those between the IPSS-QOL and the seven questions on the IPSS. Multivariate analysis showed that the strongest factor for determining IPSS-QOL at each time point was nocturia on the VAS.

CONCLUSIONS: The VAS scale reflected the change in the patients' QOL more precisely than the IPSS, which examines the frequency of lower urinary tract symptoms. Nocturia plays a key role in determining QOL. VAS could be a promising tool for assessing satisfaction in patients with lower urinary tract symptoms after PBT.

Keywords: Prostate cancer; Permanent brachytherapy; Lower urinary tract symptom; International prostate symptom score; Visual analog scale

Introduction

After receiving approval in 2003 in Japan, permanent brachytherapy (PBT) has been increasingly selected for low-risk prostate cancer patients, and it now occupies an important position as a main curative treatment in addition to radical prostatectomy. Currently, about 20,000 patients have undergone this treatment in Japan. Urologists mainly manage oncological outcomes and morbidity during the followup period. In morbidity management, investigation and improvement of urination symptoms are the major concerns after PBT. The severity of urination symptoms is usually assessed with the International Prostate Symptom Score (IPSS) worldwide. The time course of the changes in the IPSS after PBT in Japanese have been reported by many researchers (1–3), and it is well known that the IPSS rises immediately after PBT and then rapidly improves, generally after about 6 months, as reported in Western countries (4–7). However, the IPSS is a numerical representation of the frequency of urine retention and urination symptoms, and it is uncertain whether it highlights the most significant symptoms for patients with various background urination symptoms, that is, symptoms requiring treatment. In 2006, Ushijima *et al.* (8) assessed the quality of life (QOL), and identified the chief complaints, of patients with lower urinary tract symptoms (LUTS) using the visual

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analog scale (VAS) questionnaire, a possible replacement for the IPSS, and observed that it had significant benefits.

The objective of this study was to analyze the factors in determining urination-related QOL after PBT using the VAS questionnaire and IPSS.

Methods and materials

The subjects were 159 patients with localized prostate cancer who had undergone PBT in April 2005 or thereafter (2 or more years ago). Retention requiring transient urethral catheter placement after PBT occurred in 3 patients, and these patients were excluded. The remaining 156 patients were included in the analysis. Of the 156 patients, 141 were treated with seed implantation alone and 15 were treated with combined external beam radiotherapy.

The patients who were referred from other institutions and had been receiving hormonal therapy discontinued their hormonal therapy before the PBT.

The characteristics of the 156 patients are shown in Table 1. The prostate-specific antigen level before treatment was lower than 10 mg/mL in all patients, and the prostate volume at the time of the interactive planning stage was lower than 20 cc in 111 patients (71%).

For the seed, ^{125}I was used in all patients using the hybrid interactive Mick technique reported by Grado *et al.* (9), Grado (10) , and Shanahan *et al.* (11, 12). A preplanning volume study was performed 3–4 weeks before the seed implantation.

At the time of the preplanning volume study and interactive planning stage, we determined the clinical target volume as the prostate plus a 3-mm margin. The prescribed dose delivered to the clinical target volume, which was equivalent to the planning target volume, was 145 Gy. The loading pattern was modified peripheral loading. The prostate V_{150} limitation ranged from 20% to 60% of the prostate volume.

Table 1
Patient characteristics

Factor	*n*
Age (median), yr	45–80 (69)
i-PSA (median), ng/mL	2.9–9.3 (6.96)
Gleason score	
6	131
3+4	25
Prostate volume (mL)	
<20	111
20< x <30	29
>30	16
Risk classification	
Low	129
Intermediate	27

i-PSA = initial (before definite diagnosis) prostate-specific antigen.

The VAS questionnaire used in the study was initially developed by Ushijima *et al.* (8) in 2006. The VAS questionnaire (Fig. 1) was printed on the back of the IPSS, and the patients were instructed to reply to both questionnaires. Briefly, the topics of the eight QOL-related questions in the VAS questionnaire were the same as those of the questions in the IPSS. Individual patients marked the severity of their symptoms with an "X" on a 10-cm line (the left and right ends represented "delighted" and "terrible," respectively).

Alpha-blocker (tamsulosin hydrochloride or naftopidil) treatment was initiated immediately after the PBT in all patients and was then discontinued when their LUTS had been alleviated after consultation with the patients. The patients replied to the IPSS and VAS questionnaires before and immediately after the PBT, as well as 1, 3, 6, and 9 months and 1 year after the PBT. After 1 year, only the patients who complained of urination symptoms were asked to reply to the questionnaires. The subjects were also asked about their chief complaint in interviews immediately after the PBT and at 1 and 3 months after the PBT, and the correlations between their chief complaint and the maximum IPSS and VAS scores were analyzed. The correlations between the IPSS-QOL score and the answers to individual IPSS and VAS symptom questions were investigated at each time point, and predictors of the IPSS-QOL score were sought from among the IPSS and VAS items using multiple regression analysis.

The time courses of the changes in the replies to the IPSS and VAS were compared using the Mann-Whitney test. For correlation analysis, Pearson correlation coefficient was used. Data analysis was performed using SPSS/Win version 8.0 (SPSS Japan Inc., Tokyo, Japan) and Statistica/Win statistical programs (StatSoft Japan Inc., Tokyo, Japan). A p level of 5% or lower was regarded as significant.

Results

In the 156 men, CT examination was performed 30 days after treatment (Day 30 CT) to analyze dosimetric parameters. The evaluable parameters were as follows: pD_{90}: 170 (130–190) Gy, pV_{100}: 98.3% (88.5%–100%), pV_{150}: 55.6% (29.5–81.4), uD_{90}: 160 (130–213) Gy, and uD_5: 210(149–258) Gy.

IPSS-VAS sheets were collected from all 156 patients (100%) before treatment and from 154 (99%), 152 (97%), 155 (99%), and 149 (96%) patients immediately and 1, 3, 6, and 9 months after treatment, respectively. The collection rate at 1 year after the PBT was 93% (145/156). Excluding incomplete IPSS and VAS forms, the total number of replies collected at 1–3 months, 6–9 months, and 1 year after the PBT was 298, 290, and 137 (effective reply rate: 97%, 95%, and 95%), respectively, and these responses were analyzed.

The IPSS-QOL score was 4 or higher (slightly unsatisfactory or worse) at 1–3 months after the PBT in 182

Visual Analog Scale for QOL Questionnaire for Bother about a Symptom

Example	 Delighted Pleased Mostly satisfied Mixed about equally satisfied and dissatisfied Mostly dissatisfied Unhappy Terrible Delighted Terrible If you have an urinary symptom, how would you rate your bother? Please mark on the linear scale above in accordance with the satisfaction with each urinary symptom. For example: Unhappy (as shown above)
1. Incomplete emptying :A sensation of not emptying your bladder completely after you finished urinating.	Delighted Terrible
2. Frequency :To urinate again less than two hours after you finished urinating.	Delighted Terrible
3. Intermittency :To stop and start again several times when you urinate.	Delighted Terrible
4. Urgency :Difficulty to postpone urination.	Delighted Terrible
5. Weak stream :A weak urinary stream.	Delighted Terrible
6. Hesitancy :Strain to begin urination.	Delighted Terrible
7. Nocturia :Frequent voiding at night.	Delighted Terrible

Visual Analog Scale for QOL due to Total Urinary Symptoms

If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that? Please mark on the linear scale below.

QOL due to your total urinary condition	 Delighted Terrible

Fig. 1. Visual analog scale questionnaire used to evaluate the patients' satisfaction with thir QOL in relation to each of the seven International Prostate Symptom Score items. QOL = quality of life.

patients (61%). In these 182 cases, we analyzed the correlations between the chief complaint and the highest score among the seven IPSS parameters or among the seven VAS parameters. The chief complaint matched the item with the highest score on the IPSS in 94 of the 182 cases (52%). In contrast, the item with the highest score on the VAS questionnaire matched the chief complaint in 135 of the 182 cases (74%). When we limited our analysis to cases in which the patient was dissatisfied immediately after the PBT based on their IPSS-QOL score, the correlation

between the chief complaint and the highest VAS score was significantly higher than that between the chief complaint and the highest IPSS (2×2 chi-square test: $p < 0.01$).

The time course of the changes in the scores for the eight IPSS domains (including QOL) and eight VAS domains before and after PBT are shown in Fig. 2. The scores for all 16 items had significantly increased at 1–3 months ($p < 0.05$).

The correlations between the scores for each IPSS or VAS item and the IPSS-QOL score before treatment and immediately, 1–3 and 6–9 months, and 1 year after PBT are shown in Table 2 (a-d). The correlation coefficients of the VAS domains in the three posttreatment periods were significantly higher than the corresponding values for the IPSS.

The predictors of IPSS-QOL identified from among the 14 symptom parameters of the VAS and IPSS by multivariate analysis are shown in Table 3. In all three periods, the most significant predictor of IPSS-QOL was VAS-nocturia (p value: 1–3 months, 0.002; 6–9 months, 0.0092; 1 year or later, 0.0038).

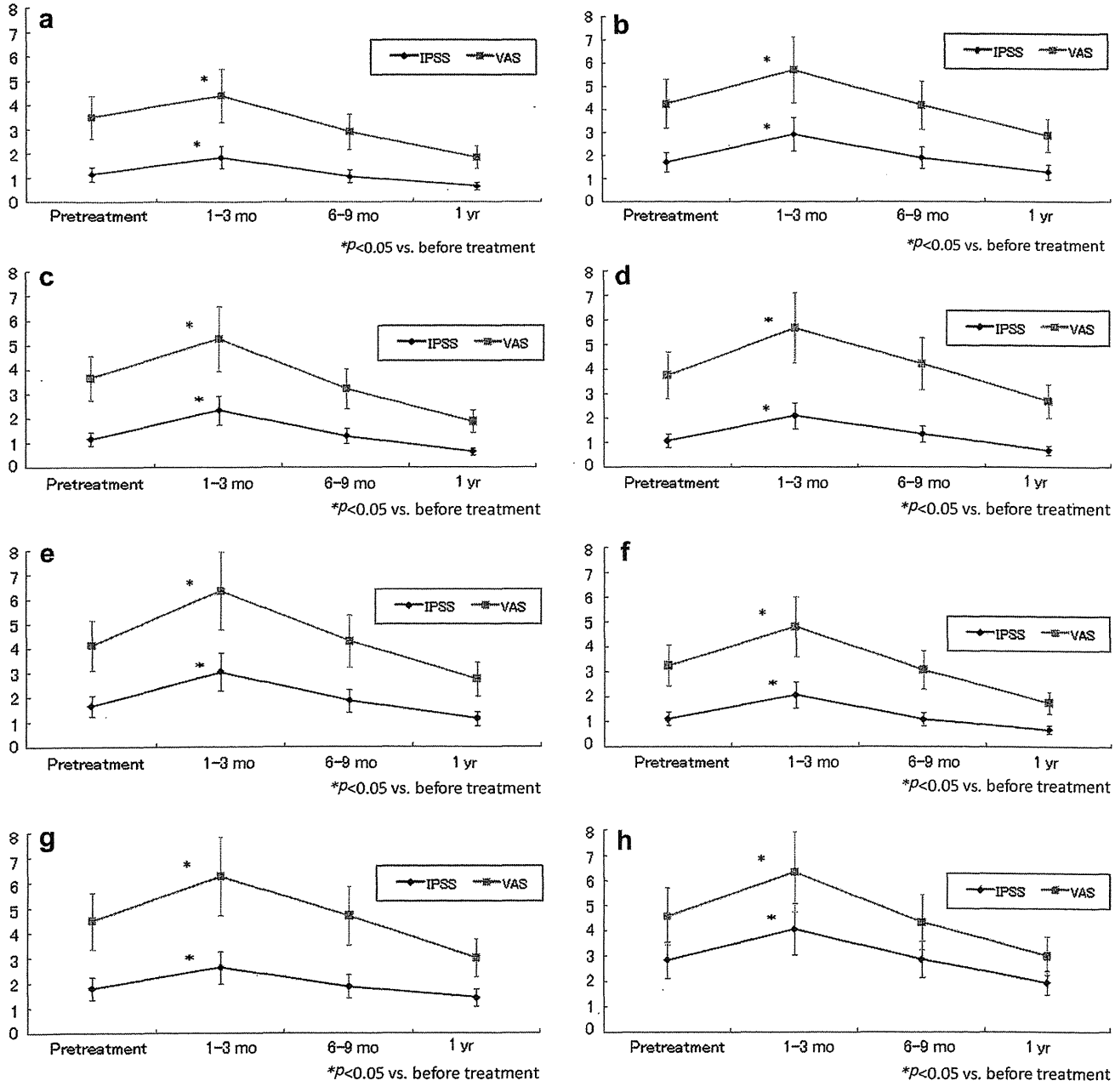

Fig. 2. Time course of the scores for the eight IPSS domains (including QOL) and VAS domains before and after PBT. (a) Incomplete emptying, (b) frequency, (c) intermittency, (d) urgency, (e) weak stream, (f) hesitancy, (g) nocturia, (h) total QOL. IPSS = International Prostate Symptom Score; QOL = quality of life; VAS = visual analog scale; PBT = permanent brachytherapy; M = month; y = year.

Table 2
Correlation of IPSS and VAS domains with IPSS-QOL in the four periods before and after treatment

	IPSS				VAS			
Coefficient	*p*-1	*p*-2	*p*-3	*p*-4	*p*-1	*p*-2	*p*-3	*p*-4
Incomplete emptying	0.633	0.472*	0.523*	0.613*	0.633	0.522*	0.633*	0.719*
Frequency	0.732*	0.615*	0.781*	0.815*	0.777*	0.685*	0.862*	0.888*
Intermittency	0.659*	0.578*	0.644*	0.684*	0.667*	0.605*	0.666*	0.735*
Urgency	0.724*	0.618*	0.712*	0.785*	0.683*	0.682*	0.818*	0.853*
Weak stream	0.610*	0.544*	0.564*	0.622*	0.605*	0.629*	0.667*	0.724*
Hesitancy	0.621*	0.530*	0.390*	0.592*	0.685*	0.661*	0.618*	0.733*
Nocturia	0.619*	0.458*	0.592*	0.688*	0.734*	0.522*	0.804*	0.834*

IPSS = International Prostate Symptom Score; QOL = quality of life; VAS = visual analog scale.
p-1 = before treatment; *p*-2 = 1–3 months after treatment; *p*-3 = 6–9 months after treatment; *p*-4 = after 1 year.
* $p < 0.01$ (IPSS vs. VAS at the same period).

Discussion

Currently, the IPSS is generally used for the assessment of LUTS after permanent seed prostate brachytherapy (PBT). A direct association between the severity of LUTS early after PBT and QOL has been reported (13). To interpret the time course of the changes in IPSS score after PBT, the aggravation of IPSS-QOL is investigated before the selection of an appropriate drug therapy based on the scores for the seven domains concerning the frequency of urine retention and urination symptoms. In routine clinical practice, the type and dose of alpha-blockers are selected, and when the score for urine retention is high, anticholinergic drug administration is considered based on the residual urine volume detected by the Overactive Bladder Score (OABSS) questionnaire, which is used to assess overactive bladder symptoms.

The time course of the scores for IPSS-QOL and seven IPSS domains after PBT showed similar changes to those detected for VAS-QOL and the corresponding VAS domains, respectively. However, in the acute phase, that is, 1–3 months after PBT, when the patients were limited to those with a slightly unsatisfactory IPSS-QOL (4 points or higher), the correlation between the chief complaint, the problem for which the individual patient most wanted treatment, and the item with the highest score on the VAS scale was significantly stronger than the correlation between the chief complaint and the item with the highest IPSS, indicating that although the changes in the two scales were similar in large populations, when investigating the problem for which individual patients most want treatment based on objective numerical values, it is better to measure their responses on a continuous VAS scale rather than use the frequency scale used in the IPSS.

Table 3
Multiple stepwise linear regression analysis of the best predictor of patient IPSS-QOL among the seven VAS items

Significant parameters	F-value	Coefficient	*p*-Value
1–3 mo after treatment			
VAS-nocturia	**5.71**	**0.3615**	**0.0219**
VAS-incomplete emptying	1.99		0.1670
6–9 mo after treatment			
VAS-nocturia	**7.50**	**0.4015**	**0.0092**
VAS-urgency	**4.47**	**0.3206**	**0.0410**
After 1 yr			
VAS-nocturia	**8.84**	**0.2961**	**0.0038**
IPSS-abdominal straining during micturition	3.84		0.0532

IPSS = International Prostate Symptom Score; QOL = quality of life; VAS = visual analog scale.

To assess LUTS immediately after PBT, investigating the problems related to urination symptoms in individual patients by comparing the frequency scales of the seven domains is not necessarily accurate. The correlation coefficients between IPSS-QOL and each item on the IPSS and VAS after PBT were calculated and demonstrated the superiority of the continuous scale used in the VAS. In all periods, the correlation coefficients for the VAS findings were higher than those of the IPSS in all seven domains, suggesting that the continuous VAS scale more accurately reflects IPSS-QOL than the IPSS frequency scale.

Blaivas *et al.* (14) reported that the pathophysiology and severity of protracted LUTS after PBT were different from those in the general population. Interestingly, in a comparison of the correlations between the IPSS-QOL score and IPSS or VAS domain scores in prostatic hypertrophy, the correlation coefficients of the domains ranged from 0.35 to 0.531 and 0.409 to 0.659, respectively (8). In contrast, in the acute phase at 1–3 months after PBT, the coefficients ranged from 0.458 to 0.618 and 0.522 to 0.685, respectively, showing that the correlations between IPSS-QOL and the various IPSS and VAS domains were generally higher in the acute phase after PBT than in LUTS patients. The development of acute LUTS because of seed placement might cause numerical increases in all domains of both the IPSS and VAS within a short time.

To maintain QOL after PBT, which is directly connected to daily living activities, it is important to identify the LUTS symptoms that require treatment. Bittner *et al.* (15) reported that the aggravation of the total IPSS and dysuria frequency, a urination symptom domain, was significantly protracted in 175 patients who developed acute urinary morbidity of

1029 PBT-treated patients. Ohashi *et al.* (3) performed multivariate analysis involving Japanese PBT-treated patients and found that the maximum IPSS increase was best predicted by a lower preimplantation IPSS in both the monotherapy and combined therapy groups. As described above, the persistence of a high IPSS and/or a significant increase in an IPSS cannot be directly connected to problematic LUTS symptoms. The factor most significantly correlated with the IPSS-QOL score in all three analytical periods after treatment was nocturia on the VAS. Blaivas *et al.* (14) performed a urodynamic study involving 33 patients with protracted LUTS after PBT (median time after treatment: 1.5 years). In comparison with randomly extracted general LUTS patients, although no significant difference was noted in the frequency of urethral obstruction between the two groups, the frequency of detrusor overactivity was significantly higher (28/33 vs. 252/541, $p < 0.001$). Although the time points after the treatment were different, our study, including our 1-year analysis, suggested that nocturia, a urine retention symptom domain, is an important QOL-determining factor. To the best of our knowledge, there have been no reports on PBT with regard to detrusor overactivity, excluding one report in which trospium was found to be useful (16). It is necessary to analyze the safety and usefulness of detrusor overactivity-reducing drugs with regard to their effects on nocturia.

The main limitation of this study was the small number of cases. In addition, it is insufficient to discuss differences in the difficulties suffered by patients before PBT according to severity alone. Regarding patient factors, subanalysis of the influence of nocturia-associated factors via a stratified analysis of the prostate volume before treatment and the dose used is necessary. Because the prostate volume of Japanese subjects is relatively small compared with that of Western patients, analyses limited to patients with prostatic enlargement and similar analyses at doses higher than 145 Gy are necessary.

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Health Related Quality of Life for Monosymptomatic Enuretic Children and Their Mothers

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Abbreviations and Acronyms

DDAVP = desmopressin therapy

HRQOL = health related quality of life

QOL = quality of life

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Study received institutional review board approval.

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Purpose: There have been few reports addressing how nocturnal enuresis affects the health related quality of life of patients and their mothers. Thus, we evaluated the health related quality of life of enuretic children and their mothers.

Materials and Methods: The health related quality of life of 139 patients with nocturnal enuresis and that of their mothers were evaluated before and after treatment. The children's health related quality of life was evaluated with the Kid-KINDL® protocol. The mothers' health related quality of life was evaluated using the SF-36®, the SDS (Self-Rating Depression Scale) for rating depression and the STAI (State-Trait Anxiety Inventory) for assessing anxiety.

Results: In the health related quality of life of enuretic children, the family domain score was significantly lower than that of controls ($p = 0.02$). In the health related quality of life of the mothers as shown by SF-36, the vitality domain score was significantly lower compared to controls ($p = 0.01$). The evaluation of the STAI score demonstrated a higher state anxiety score ($p = 0.003$), which represents current suffering from anxiety, and a similar trait anxiety score ($p = 0.22$), which represents a similar level of underlying tendency to anxiety. There was no significant difference between the mothers of enuretic children and the controls in the SDS evaluation. After treatment for enuresis the health related quality of life score was improved not only for the enuretic children as assessed by the Kid-KINDL protocol, but also for the mothers of enuretic children as assessed by the SF-36 and STAI.

Conclusions: Similar to other pediatric chronic diseases, nocturnal enuresis is a condition that negatively affects the health related quality of life of children and their mothers. Impaired health related quality of life can be improved after the successful treatment of nocturnal enuresis.

Key Words: quality of life, enuresis

PRIMARY nocturnal enuresis is a common disorder. Although the spontaneous resolution rate was reported to be 15% to 16% per year,[1] this disorder causes psychological and social distress in children and their families.[2] In the clinic it is common to see enuretic children and their mothers frustrated about the disease. Therefore, treatment of enuresis should be intended not only to cure the disease but also to eliminate the suffering related to the condition.

Studies of children's health related quality of life have been performed for pediatric chronic diseases such as

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atopic dermatitis,[3,4] asthma,[5] psychiatric diseases[6] and cancers.[7] The importance of measuring patient HRQOL in pediatric disease as a tool to evaluate the therapeutic effect is well recognized. However, few reports have addressed how nocturnal enuresis affects the HRQOL of patients and their mothers. We hypothesized that nocturnal enuresis may affect not only the patients' but also their mothers' HRQOL, and that the treatment may improve their quality of life. Therefore, we evaluated the HRQOL of affected children and their mothers before and after treatment.

MATERIALS AND METHODS

A total of 211 children who presented at our institute from 2005 to 2009 with monosymptomatic enuresis were recruited for this study along with their mothers. Patients with concomitant conditions such as asthma or atopic dermatitis, or with mothers undergoing medical treatment were excluded from analysis. The children and their mothers were given a full explanation of the study, and written consent was secured.

A total of 211 families were enrolled in the study, and several families were excluded. There were 5 families that met the exclusion criteria and 10 families with inappropriate documentation of HRQOL questionnaires. With the longest followup being 36 months, 57 families did not achieve cure of enuresis, including those lost to followup.

The HRQOL of 139 enuretic children and their mothers was evaluated before and after treatment. At our outpatient clinic most patients were accompanied only by their mothers, while visits with fathers only or with other caregivers were rare. Although both parents came in some cases, the number was small. On the other hand, QOL or anxiety is thought to be different for both genders and, thus, we focused only on the mother in the study inclusion criteria.

According to International Children's Continence Society guidelines the children were first treated with alarm therapy or DDAVP for nocturnal enuresis.[8] The second line treatment was the alternate of alarm or DDAVP. The combination of alarm and DDAVP was used as the third line treatment. The control group consisted of 109 age and gender matched pairs of volunteer children without nocturnal enuresis, and their mothers, who were confirmed to be free of any medical conditions under treatment.

The Kid-KINDL protocol was used to evaluate the HRQOL of the children.[9,10] This questionnaire consists of the 6 domains of physical well-being, emotional well-being, self-esteem, family, friend and school. Each domain contains 4 items for a total of 24 items. The responders select their responses for each item from the 5 possible answers of never, seldom, sometimes, often or always. A low score indicates poor HRQOL whereas a high score indicates good HRQOL. The maximum total score for each domain is 20 points. Furthermore, a children's version (for the children to describe their own HRQOL) and a parent's version (for the parents to describe their child's HRQOL) were prepared. The children and their parents were specifically instructed to fill out the questionnaires by themselves and not to discuss their responses. We used a standardized Japanese version of the Kid-KINDL protocol which was prepared after evaluation of its validity and reliability.[11]

The HRQOL of the mothers was evaluated using the SF-36, SDS and STAI. All items were addressed in a short answer format and responders completed the questionnaires by themselves. The SF-36 is a scientifically reliable and validated method developed in the United States for the measurement of HRQOL. The HRQOL is a widely used international measure, and has been translated into more than 50 languages after full evaluation at the level of its conceptual framework and as a psychometric test. The SDS is a self-evaluating measurement of depression developed by Zung.[12,13] This scale consists of 20 items with the 4 possible responses for each item of a little of the time, some of the time, a good part of the time or most of the time. A high score indicates a higher degree of depression. The STAI, developed by Spielberger, is a self-reported measure of anxiety.[14] It consists of 20 items with 4 possible responses for each item of not at all, somewhat, moderately so or very much so. A high score indicates a greater degree of anxiety. The SDS and STAI have been widely used in the field of psychosomatic medicine.

Statistical analysis of each set of data was conducted using the Student and paired t tests. Values were expressed as means ± SD. The unpaired t test was used to compare mean values of QOL scores as well as clinical parameters of controls vs patients. The paired t test was used to compare mean values of QOL scores before vs after treatment. The significance level was less than 0.05. This study was conducted in accordance with the study guidelines approved by the institutional review board.

RESULTS

Of the 139 patients 110 were male (79.1%), mean age was 9.7 ± 2.6 years and mean number of enuresis episodes was 12.6 per 2 weeks. In the control group 81 of 109 (74.3%) were male and mean age was 9.9 ± 2.5 years. There were no significant differences between enuretic patients and healthy volunteers in terms of age and gender ($p = 0.64$, $p = 0.54$). Mean age of the 139 mothers of patients was 39.8 ± 4.3 years compared to the control group at 38.5 ± 4.6 years. The age of mothers with enuretic children was comparable to that of the healthy volunteers ($p = 0.48$).

During the observation period from 3 to 18 months all 139 patients were cured, with 62 by alarm therapy as first line therapy, 56 by DDAVP as first line therapy, 8 by alternating alarm and DDAVP as second line therapy, and 13 by the combination of alarm and DDAVP as third line therapy.

The total score of the family domain subscale of the Kid-KINDL protocol in enuretic children was

Table 1. *HRQOL evaluated with SF-36 of mothers of enuretic children*

	Mean ± SD HRQOL Score				
	Mothers of Pts Before Treatment	Mothers of Pts After Treatment	Healthy Volunteers	p Value Mothers of Pts Before vs After Treatment*	p Value Mothers of Pts Before Treatment vs Mothers of Healthy Volunteers†
Physical functioning	91.7 ± 10.5	92.5 ± 8.8	91.9 ± 9.1	0.58	0.89
Role physical	88.9 ± 17.3	91.2 ± 15.5	90.7 ± 13.5	0.35	0.44
Body pain	73.1 ± 17.0	72.8 ± 19.8	71.9 ± 22.2	0.91	0.68
General health	66.2 ± 17.1	67.2 ± 16.2	65.3 ± 16.0	0.69	0.71
Vitality	60.1 ± 10.1	64.8 ± 17.9	66.1 ± 16.6	0.03	0.01
Social functioning	89.5 ± 16.3	89.1 ± 15.8	88.4 ± 17.2	0.86	0.66
Role emotional	89.9 ± 17.1	88.6 ± 17.7	90.4 ± 16.3	0.62	0.84
Mental health	70.8 ± 17.2	72.4 ± 17.6	72.6 ± 16.8	0.54	0.48

* Paired t test.
† T test.

significantly lower than that in the healthy volunteers (14.7 ± 3.4 vs 15.7 ± 2.9 points, p = 0.02), and improved after successful treatment to a level comparable to that before treatment (14.7 ± 3.4 vs 15.7 ± 2.8 points, p = 0.04). In contrast, the total subscale score of the family domain in enuretic children evaluated by the mothers was not impaired compared to that of healthy volunteers (15.0 ± 2.4 vs 15.3 ± 2.6, p = 0.23).

The results of the mothers' HRQOL as evaluated by SF-36 are shown in table 1. The HRQOL scores of the mothers with children with nocturnal enuresis were significantly lower than those of the healthy volunteers in the vitality domain (60.1 ± 10.1 vs 66.1 ± 16.6 points, p = 0.01). The SF-36 score in the vitality domain for the mothers of enuretic children improved from 60.1 ± 10.1 to 64.8 ± 17.9 after treatment.

The state anxiety scores of the mothers of children with nocturnal enuresis were significantly higher than those of the control group (42.0 ± 7.8 vs 37.3 ± 12.8 points, p = 0.003). Their state anxiety score decreased from 42.0 ± 7.8 to 38.7 ± 11.2 points after treatment. There were no significant differences in trait anxiety score or SDS scores between the mothers of enuretic children and the healthy volunteers (table 2).

DISCUSSION

We often observe that the mothers visiting our clinic with their enuretic children tend to worry more about the disease than do the children. Thus, we paid attention not only to the enuretic children but also to their mothers, and we assessed how the condition of nocturnal enuresis and its treatment affected the HRQOL of the children and their mothers.

We evaluated the HRQOL of children with nocturnal enuresis using the Kid-KINDL protocol as a way to measure the states of health and adaptability of the subjects in their daily life. The unique feature of this questionnaire is that it can be used to evaluate the children's HRQOL in the views of affected children as well as their parents. Although the use of the same questionnaires for enuretic children and their mothers is optimal to evaluate HRQOL, fully validated questionnaires for adults and children are not yet available. The mothers frequently complain of anxiety about enuresis in their children. Thus, not only the SF-36 but also the SDS and STAI were used to evaluate the mothers' anxiety and depressive state in addition to HRQOL.

Previous literature has shown that enuresis causes distress and low self-esteem for children.[2,15] Enuresis also has major social and economic implications

Table 2. *HRQOL evaluated with SDS and STAI in mothers of enuretic children*

	Mothers of Pts Before Treatment	Mothers of Pts After Treatment	Healthy Volunteers	p Value Mothers of Pts Before vs After Treatment*	p Value Mothers of Pts Before Treatment vs Mothers of Healthy Volunteers†
Mean ± SD STAI:					
State	42.0 ± 7.8	38.7 ± 11.2	37.3 ± 12.8	0.02	0.003
Trait	39.9 ± 9.1	37.9 ± 11.5	37.7 ± 14.2	0.20	0.22
Mean ± SD SDS	38.7 ± 8.2	38.4 ± 8.5	38.0 ± 7.3	0.49	0.40

* Paired t test.
† T test.

for the family, with increasing intolerance as the child grows. We demonstrated that the disease affected patient HRQOL in terms of social relationships in families and not self-esteem. Social relationships with friends or school were not impaired by the disease, which may be because the enuresis occurs at home at night and, therefore, does not affect daily activities at school or after school.

This study showed a discrepancy in HRQOL between the children and their mothers in the family domain. It has been recognized that parents tend to report higher children's QOL than their children do in the general population sample. Parent-proxy scores on QOL are not equivalent to child-self scores, and evaluating the perspectives of children and parents is important.[16]

We found impairment of the mothers' vitality scores in the SF-36, which may be the result of their burden of additional time and effort as well as the financial impact of washing bed linen, changing bedclothes and replacing mattresses etc.[15,17] In contrast, a previous report demonstrated that the mothers of enuretic children recorded more bodily pain and worse role emotional subscales on the SF-36.[18] The authors speculated that the mother's bodily pain and other somatic complaints might be explained by so-called masked depression.

Chronic diseases in children such as epilepsy or cancer are reported to affect their mothers' psychiatric condition as evaluated by the SF-36 or SDS.[19,20] Chronic stress is thought to be a risk factor for psychosomatic psychiatric illnesses such as anxiety and depression disorders.[21] In this study the mothers with enuretic children demonstrated more anxiety compared with normal controls by STAI, but no differences were seen in depression scores on the SDS.

In terms of the mothers' HRQOL, our findings suggest that the mothers of children with nocturnal enuresis are likely to have less vitality and to be more anxious. The 2 possible assumptions for these comments are that 1) they experienced decreased vitality and increased anxiety due to the nocturnal enuresis of their children, and 2) they previously had anxieties and less vital character and so they brought their children to the clinic. The mothers of enuretic children had a lower state anxiety score than the mothers of healthy volunteers, which represents current suffering from anxiety. The trait anxiety scores were similar for mothers of enuretic children and mothers of healthy volunteers, which represent a low level of underlying tendency to anxiety. These results suggest that the disease itself causes the anxiety for the mothers of enuretic children.

The major limitation of this study is the lack of evaluation of the HRQOL of families who did not achieve cure of enuresis. Although most of the cases that did not achieve cure were lost to followup or were noncooperative for HRQOL assessment, we must follow patients and their parents' HRQOL until cure is achieved. Nevertheless, our findings indicate that anxiety levels and low vitality in mothers, as well as decreased concern over the relationships with the family in enuretic children, can be resolved after the successful treatment of nocturnal enuresis, which may contribute to improvement in overall HRQOL.

In conclusion, similar to other pediatric chronic diseases, nocturnal enuresis is a condition that negatively affects the HRQOL of children as well as their mothers. Their impaired HRQOL can improve after the successful treatment of nocturnal enuresis.

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EDITORIAL COMMENT

The authors of this article are to be commended for their efforts to document and quantify the far-reaching effects of enuresis on children and their mothers. Although these effects on HRQOL have generally been assumed to exist, they have not been scientifically documented in enuresis so effectively. One of the significant aspects of this study is that it draws attention to the fact that enuresis must no longer be considered a developmental disorder of little significance that only carries low morbidity. Thus, it should not be left to resolve untreated on its own. This article clearly demonstrates that mothers who bring their children to medical attention do so not only to seek a cure for their child's problem, but also to alleviate their own often unexpressed anxiety and mental suffering. It is interesting that the authors compare the HRQOL in enuresis to that in chronic diseases such as epilepsy and cancer for the subjects and their mothers and, thus, for their families. Of even greater interest is the reversal of these noxious effects after the enuresis is cured. This article emphasizes the importance of enuresis management by expert practitioners who are trained in devoting the necessary time and effort to bring a cure to enuretic patients and their families.

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Image of the Month

A Case of Multidisciplinary Treatment for a Massive Locoregional Recurrence of Breast Cancer

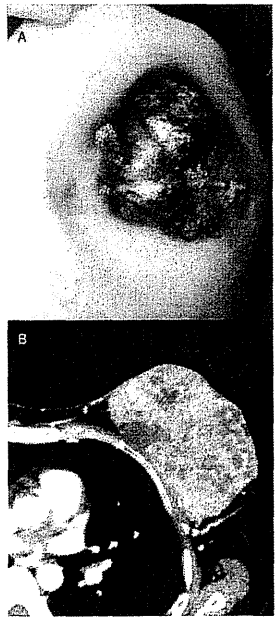

Figure 1.

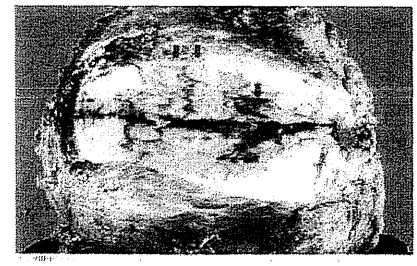

Figure 2.

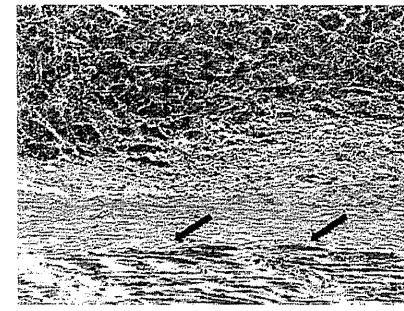

Figure 3.

A 36-year-old woman presented to our hospital with a huge tumor, measuring 11 cm in diameter, in her left breast. She had a past history of preoperative systemic chemotherapy and breast-conserving surgery for her left breast cancer 6 months before in another hospital. The tumor fixed stiffly on the chest wall, and invasion to the pectoral muscle was suspected. Because computed tomography showed a small metastatic nodule in the left lung, she initially received systemic chemotherapy. After six cycles of anthracycline treatment, the lung nodule disappeared, while the locoregional tumor remained unchanged (Fig. 1A and B, red arrows). Surgery to reduce the tumor burden and improve her quality of life was proposed, and the patient underwent tumorectomy with autologous latissimus dorsi musculocutaneous flap reconstruction.

Macroscopic examination of the resected specimen revealed a large, expanding solid mass (Fig. 2, green arrows) with cystic change indicating tumor necrosis (Fig. 2, blue arrow). Pathologically, the tumor consisted of high-grade invasive ductal carcinoma with massive lymphatic invasion. Because these findings were consistent with those of the primary tumor resected in the previous hospital, the diagnosis of recurrent breast cancer was confirmed. Pathological examination also showed that the tumor was very close to, but not invading, the major pectoral muscle (Fig. 3, black arrows), and most of the tumor cells were viable (chemotherapeutic effect; Grade 0).

Two months after the second surgery, locoregional recurrence as well as lung metastasis were detected, and the patient underwent oral fluoropyrimidine S-1 monotherapy.

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The Breast Journal

Primary Leiomyosarcoma of the Breast

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A 61-year-old woman was referred to our hospital with a history of a right breast lump for about 2 months' duration.

On physical examination, an elastic firm, mobile lump measuring 3 cm in diameter was palpable in the upper outer quadrant of the right breast. The lump was not adhering to muscle or skin. No lymphadenopathy was apparent.

Mammography showed a dense, well-circumscribed mass. There was no micocalcification (Fig. 1). Ultrasonography showed a well-circumscribed, hypoechoic mass with a heterogeneous internal echo with clear margins. Acoustic shadowing from the mass was also noted (Fig. 2). Doppler flow imaging showed abundant blood flow signal on the margin of the mass. Magnetic resonance imaging (MRI) showed a phyllodes-shaped hypointense mass on T1 imaging and heterogeneous intensity on T2 imaging. A margin of the mass was well contrasted on early phase, but the inner part of the mass was poorly contrasted (Fig. 3). The mammography, ultrasonography, and MRI images were compatible with a fibroadenoma or a phyllodes tumor. Abnormalities were not observed in a blood examination including the tumor marker. There was no family history of breast cancer.

Core needle biopsy was performed that revealed overgrowth of stromal cells with cigar-shaped nuclei and intermediate mitotic activity – up to 9 mitotic figures per 10 high power fields (HPFs). There were no epithelial cells. The patient underwent wide local excision; axillary lymphadenectomy was not performed.

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Macroscopically, the tumor (2.2 cm × 1.5 cm in size) had a firm grayish white surface with sharply demarcated margins surrounded by breast parenchyma. Histologically, the tumor was composed of spindle-shaped cells with cigar-shaped nuclei, and

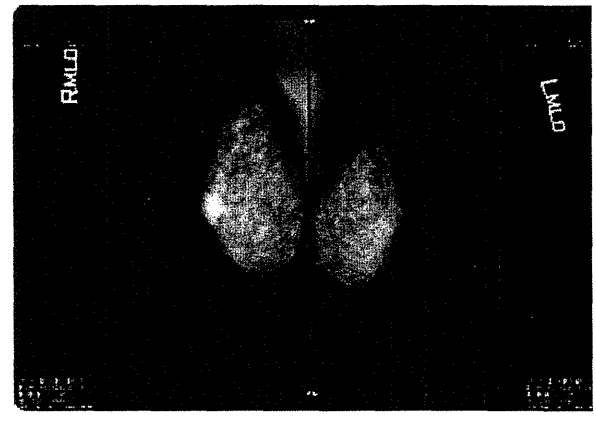

Figure 1. Mammography showing a well-circumscribed mass with no microcalcification.

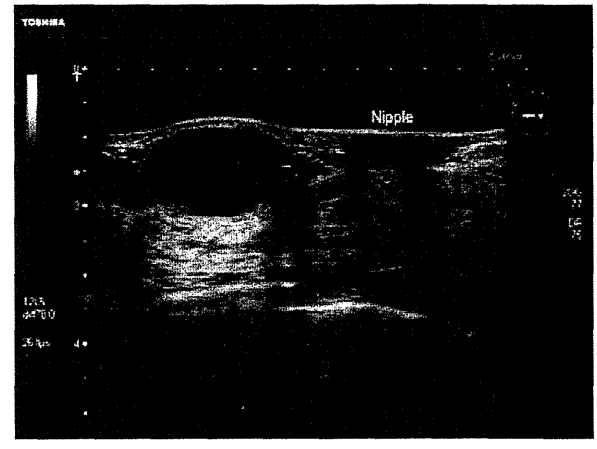

Figure 2. Ultrasonography showing a well-circumscribed, hypoechoic mass with a heterogeneous internal echo.

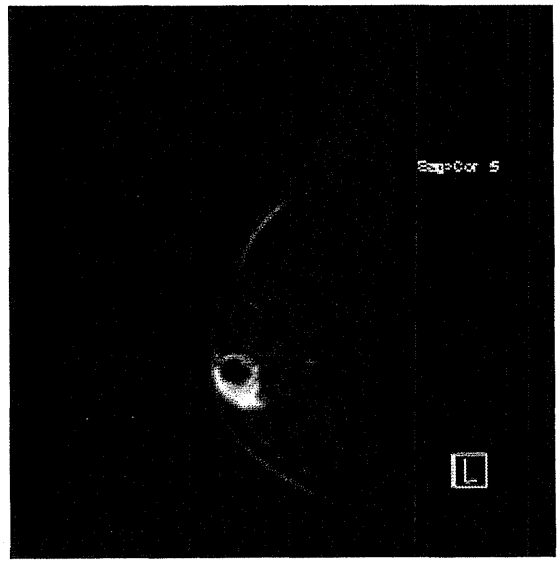

Figure 3. MRI showing a phyllodes-shaped heterogeneous intensity on T2 imaging. A margin of the mass was well contrasted on early phase, but the inner part of the mass was poorly contrasted.

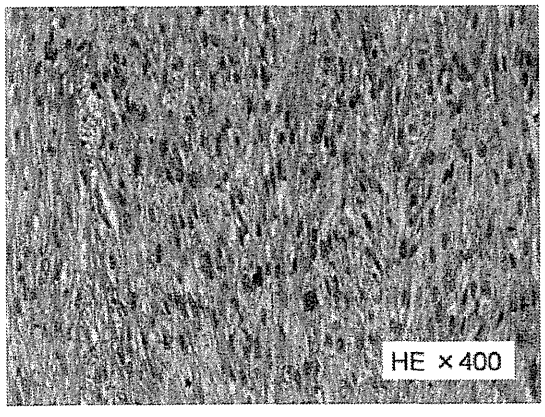

Figure 4. Histopathology of leiomyosarcoma showing bundles of spindle-shaped cells with cigar-shaped nuclei. Leiomyosarcoma showing marked pleomorphism and mitotic activity (Hematoxylin & Eosin, ×400).

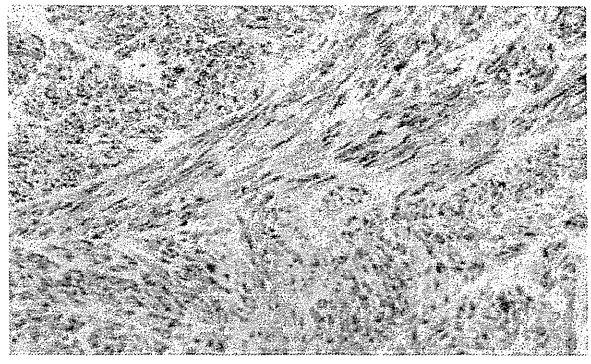

Figure 5. Section of tumor showing immunopositivity for desmin. Similar positivity was also found for muscle-specific actin (×200).

areas showing marked pleomorphism and significant mitotic activity – over 10 mitotic figures per HPFs (Fig. 4). There were no lobules and ducts. There was no necrosis.

Immunohistochemistry showed positive staining with antibodies to desmin, smooth muscle actin (Fig. 5). The tumor did not stain for myogenin, S-100, cytokeratins, p63, CD34, c-kit. About 40% of the tumor showed positive staining with Ki67. In view of the cellular pleomorphism and the level of mitotic activity, this tumor was considered a leiomyosarcoma.

At review, 18 months after surgery, there has been no evidence of local recurrence or metastasis.

Leiomyosarcoma does not metastasize frequently, but some cases reported that local recurrence or distant metastases were found over 10 years after initial surgery. Long-term monitoring of all patients is essential.

CONFLICTS OF INTEREST

None.

JJCO Japanese Journal of Clinical Oncology

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Clinical Trial Note

A Randomized Controlled Trial Comparing Primary Tumour Resection Plus Systemic Therapy With Systemic Therapy Alone in Metastatic Breast Cancer (PRIM-BC): Japan Clinical Oncology Group Study JCOG1017

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This trial is being conducted to confirm the superiority, in terms of overall survival, of primary tumour resection plus systemic therapy to systemic therapy alone in patients with Stage IV breast cancer who are not refractory to primary systemic therapy. The inclusion criteria for the study are as follows: untreated patients with histologically confirmed invasive breast cancer with one or more measurable metastatic lesions diagnosed by radiological examination. All patients receive primary systemic therapy according to the estrogen receptor and human epidermal growth factor receptor type-2 status of the primary breast cancer after the first registration. After 3 months, the patients without disease progression are randomized to the primary tumour resection plus systemic therapy arm or the systemic therapy alone arm. The primary endpoint is the overall survival, and the secondary endpoints are proportion of patients without tumour progression at the metastatic sites, yearly local recurrence-free survival, proportion of local ulcer/local bleeding, yearly primary tumour resection-free survival, adverse events of chemotherapy, operative morbidity and serious adverse events. The patient recruitment was commenced in May 2011. Enrolment of 410 patients for randomization is planned over a 5 year recruitment period. We hereby report the details of the study.

Key words: breast medicine – metastasis – breast-basic – surgery

INTRODUCTION

The incidence of metastatic breast cancer (Stage IV), defined as a primary breast tumour with distant metastasis, is increasing, accounting for ~3% of all newly diagnosed patients with breast cancer in Japan, not significantly different from the 6% reported from the USA according to the Surveillance, Epidemiology and End Results data. The treatment of Stage IV breast cancer has traditionally been palliative care with chemotherapy, hormonal therapy and/or radiation therapy (1,2). According to the Hortobagyi algorithm (3), hormonal therapy is chosen as the first therapy for hormone receptor-positive Stage IV breast cancer without life-threatening metastases. If the tumour is hormone receptor-negative or resistant to hormone therapy, chemotherapy is used, although it might severely impair the quality of the patient's life. Current anti-tumour drugs, such as

anthracyclines and taxanes, are quite effective, as are molecular-target drugs, such as trastuzumab. Resection of the primary tumour is not considered a curative treatment; it is used solely as local therapy to prevent uncontrolled chest wall disease. Therefore, the local surgery is performed relatively late in the treatment course, and only if the primary tumour and metastases have been reduced and controlled with the systemic therapy.

The possibility of surgical procedures improving the survival of these patients has been reported by several retrospective studies (4–8); however, these studies essentially suffer from biases such as arbitrary patient selection, diverse timing of surgery or various regimens of systemic therapy. Therefore, this subject still remains a hotly debated topic at major breast conferences. Improvements in primary systemic therapies have increased the numbers of Stage IV patients with resectable small primary tumours and metastatic lesions controllable by treatment. With all of these new developments, we need definitive guidelines for the treatment of these patients. It will be necessary to perform prospective studies for evaluation of the efficacy of primary tumour resection for Stage IV breast cancer. This trial is being conducted to investigate the efficacy of primary tumour resection plus systemic therapy and that of systemic therapy alone for patients with Stage IV breast cancer. Breast cancers with resistance to primary systemic therapy (PST) increase during the primary resection and need to take next regimen immediately. So we randomize only Stage IV breast cancer which is still sensitive to systemic therapy in this study.

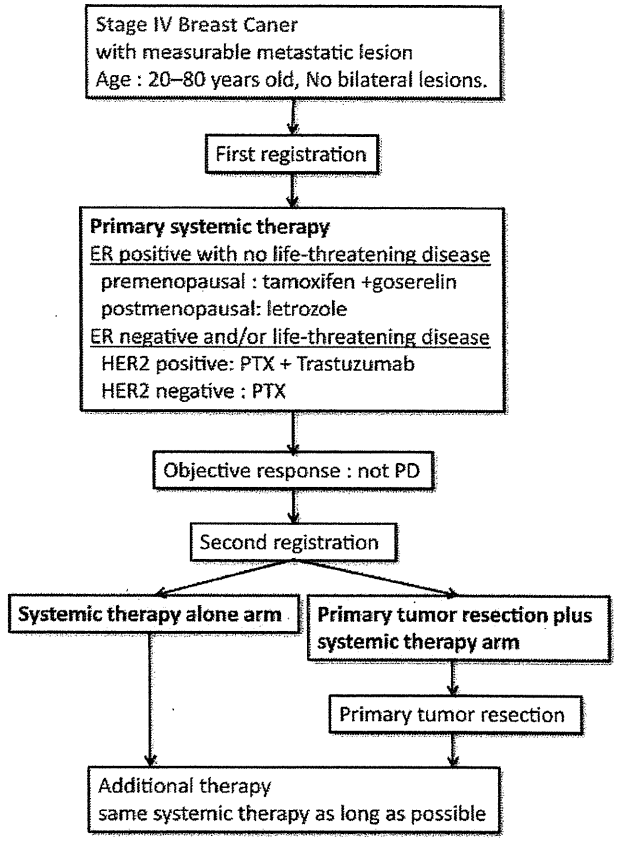

Figure 1. Study Schema. A randomized controlled trial comparing primary tumour resection plus systemic therapy with systemic therapy alone in metastatic breast cancer (PRIM-BC): Japan Clinical Oncology Group Study JCOG1017. ER, estrogen receptor; HER2, human epidermal growth factor receptor type-2; PTX, paclitaxel; PD, progressive disease.

STUDY PROTOCOL

Purpose

This study is being conducted to confirm the superiority, in terms of overall survival, of primary tumour resection plus systemic therapy to systemic therapy alone in untreated breast cancer patients with metastatic lesions (Stage IV) who are not refractory to conventional PST according to the estrogen receptor (ER) and human epidermal growth factor receptor type-2 (HER2) status of the primary lesions (Fig. 1).

Study Setting

This study is a multi-institutional prospective randomized controlled trial being conducted with the participation of 30 hospitals belonging to the JCOG Breast Cancer Study Group.

Endpoints

The primary endpoint is overall survival (OS), which is defined as the number of days from randomization (second registration) to death from any cause, and it is censored at the last follow-up date when the patient is alive. The secondary endpoints are the proportion of patients without tumour progression at the metastatic sites, yearly local recurrence-free survival, proportion of local ulcer/local bleeding, yearly primary tumour resection-free survival, adverse events of chemotherapy, operative morbidity and serious adverse events.

Eligibility Criteria

Inclusion criteria

First registration

(1) Histologically confirmed invasive breast cancer in biopsy specimens obtained from the tumour.
(2) The presence/absence of overexpression of ER and HER2 in the tumour examined.
(3) Neither bilateral breast cancer nor invasion to the contralateral breast.
(4) At least one measurable metastatic lesion other than the breast tumour and axillary lymph nodes detected by computed tomography or magnetic resonance imaging before primary registration.
(5) No brain metastasis.
(6) Women aged 20–80 years old.

(7) Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 or 1. PS 2 caused by the symptoms of bone metastasis is also eligible.
(8) No surgery, chemotherapy or radiotherapy for any other malignancies within the previous 5 years.
(9) No history of invasive breast cancer. Non-invasive breast cancer resected completely by partial mastectomy is also eligible.
(10) Neither prior chemotherapy for breast cancer nor prior radiotherapy for the ipsilateral breast (radiotherapy for bone metastasis within 30 Gy and up to 10 times before the registration is allowed).
(11) Adequate organ functions.
(12) Availability of written informed consent.

Second registration (after primary therapy)

(1) Primary therapy was administered after the first registration and the protocol treatment has not been discontinued.
(2) Objective response to primary chemotherapy was not progressive disease or not evaluable (NE).
(3) Within 28 days from the date of response evaluation.
(4) Adequate organ functions.
(5) Complete resection expected to be possible by total or partial mastectomy without resection of adjacent organs and/or wide skin transplantation.
(6) No active bleeding from the breast tumour necessitating blood transfusion within 28 days prior to the second registration.

Exclusion criteria (no exclusion criteria at the second registration)

First registration

(1) Simultaneous or metachronous (within 5 years) double cancers.
(2) Infectious disease requiring treatment.
(3) Body temperature of 38°C or higher.
(4) Pregnant or breast-feeding women.
(5) Psychiatric diseases.
(6) Systemic and continuous steroid treatment.
(7) Comorbid unstable angina pectoris or history of myocardial infarction within the previous 6 months.
(8) Uncontrolled hypertension.
(9) Uncontrolled diabetes mellitus or the disease being treated by continuous insulin administration.

Primary Systemic Therapy

All enrolled patients for the first registration receive the PST. PST is decided according to the ER and HER2 status and the disease situation and continued for three cycles.

(i) ER-positive patients with no life-threatening diseases receive the following hormonal therapy.
  (a) Pre-menopausal patients: oral tamoxifen 20 mg/body daily plus goserelin 3.6 mg/body every 4 weeks.
  (b) Post-menopausal patients: oral letrozole 2.5 mg/body daily for 4 weeks.
(ii) ER-negative and/or life-threatening diseases receive the following chemotherapy.
  (a) HER2-positive: paclitaxel (PTX) 80 mg/m^2 (Days 1, 8, 15) plus weekly trastuzumab 2 mg/kg (Days 1, 8, 15, 22) every 4 weeks.
  (b) HER2-negative: PTX 80 mg/m^2 (Days 1, 8, 15) every 4 weeks.

Randomization

After three cycles of PST, the JCOG Data Center confirms the patient eligibility, and randomizes the patients either to the primary tumour resection plus systemic therapy arm or to the systemic therapy alone arm. The randomization is conducted by the minimization method with balancing the arms according to ER status (positive/negative), HER2 status (positive/negative), metastatic site(s) (presence/absence of visceral metastasis) and institution.

Treatments

Primary tumour resection plus systemic therapy arm

The patients undergo the complete resection of the primary lesions after the second registration. Prophylactic axillary lymph node dissection and/or resection of adjacent organs are not allowed. As long as the tumour is resected completely, it does not matter whether the surgical procedure is partial mastectomy or total mastectomy. After the operation, the patients restart to receive the same systemic therapy as before for as long as possible as additional therapy.

Systemic therapy alone arm

After the second registration, the patients continue to receive the same systemic therapy as additional therapy for as long as possible.

All randomized patients are followed for 6 years. Physical, blood and radiological examinations of distant metastases are conducted every 6 months.

Statistical Analysis

Primary analysis and statistical hypothesis

If the overall survival of the patients treated by primary tumour resection plus systemic therapy is significantly longer than that of the patients administered systemic therapy alone, the primary tumour resection will be judged to be the new standard treatment. The estimated median overall survival of patients with Stage IV breast cancer is commonly 24 months (9,10). The duration between the first and the second registration is 4 months. In this study, we shall assume that the median OS in the systemic therapy alone arm after the second registration will be 20 months, and it will be considered a clinically relevant prolongation if

the median OS of primary tumour resection plus systemic therapy is longer by 6.0 months (hazard ratio: 0.77).

Sample size and follow-up period

The primary endpoint will require 359 events in total to be assessed, in order to obtain a statistical power of 80% with a one-sided significance level of 0.05. Thus, the planned sample size is 410 patients for the second registration and 500 patients for the first registration (assuming that 20% of the patients may not proceed to the second registration.) for comparing the two survival curves, assuming an accrual time of 5 years and a follow-up time of 4 years according to the calculation by the method of Schoenfeld and Richeter (11).

Interim analysis and monitoring

An interim analysis is planned to be performed twice, taking into account multiplicity using the Lan and DeMets alpha spending function. The Data and Safety Monitoring Committee (DSMC) of the JCOG independently reviews the interim analysis report, and an early termination of the trial may be considered at that stage. In-house interim monitoring is performed by the Data Center to ensure data submission, patient eligibility, protocol compliance, safety and on-schedule study progress. The monitoring reports are submitted to and reviewed by the DSMC every 6 months.

Registration of the protocol

The protocol was registered at the website of the University Hospital Medical Information Network (UMIN), Japan (protocol ID UMIN000005586), on 11 May 2011. The details are available at the following web address: http://www.umin.ac.jp/ctr/

Participating Institutions (From North to South)

Hokkaido Cancer Center, Tochigi Cancer Center, Jichi Medical University, Gunma Prefectural Cancer Center, Saitama Cancer Center, National Cancer Center Hospital East, Chiba Cancer Center, National Cancer Center Hospital, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo Medical Center, Keio University Hospital, St. Luke's International Hospital, Tokai University School of Medicine, Kanagawa Cancer Center, Kitasato University School of Medicine, Yokohama Rosai Hospital, Niigata Cancer Center Hospital, Shizuoka General Hospital, Aichi Cancer Center Hospital, Nagoya Medical Center, Kinki University School of Medicine, Osaka National Hospital, Okayama University Hospital, Kure Medical Center Chugoku Cancer Center, Fukuyama Medical Center, Hiroshima City Asa Hospital, Shikoku Cancer Center, National Kyushu Cancer Center, Kitakyushu Municipal Medical Center and Nagasaki Medical Center.

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Conflict of interests statement

Hiroji Iwata receives honoraria for speaking events from Chugai Pharmaceutical Co., Ltd.

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CLINICAL TRIAL

Tumor-infiltrating lymphocytes are correlated with response to neoadjuvant chemotherapy in triple-negative breast cancer

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Abstract The purpose of the present study was to identify histological surrogate predictive markers of pathological complete response (pCR) to neoadjuvant chemotherapy (NAC) in triple-negative breast cancer (TNBC). Among 474 patients who received NAC and subsequent surgical therapy for stage II–III invasive breast carcinoma between 1999 and 2007, 102 (22%) had TNBC, and 92 core needle biopsy (CNB) specimens obtained before NAC were available. As controls, CNB specimens from 42 tumors of the hormone receptor-negative and HER2-positive (HR−/HER2+) subtype and 46 tumors of the hormone receptor-positive and HER2-negative (HR+/HER2−) subtype were also included. Histopathological examination including tumor-infiltrating lymphocytes (TIL) and tumor cell apoptosis, and immunohistochemical studies for basal markers were performed, and the correlation of these data with pathological therapeutic effect was analyzed. The rates of pCR at the primary site were higher for TNBC (32%) and the HR−/HER2+ subtype (21%) than for the HR+/HER2− subtype (7%) ($P = 0.006$). Expression of basal markers and p53, histological grade 3, high TIL scores, and apoptosis were more frequent in TNBC and the HR−/HER2+ subtype than in the HR+/HER2− subtype ($P = 0.002$ for TIL and $P < 0.001$ for others). In TNBC, the pCR rates of tumors showing a high TIL score and of those showing a high apoptosis score were 37 and 47%, respectively, and significantly higher or tended to be higher than those of the tumors showing a low TIL score and of the tumors showing a low apoptosis score (16 and 27%, respectively, $P = 0.05$ and 0.10). In a total of 180 breast cancers, the pCR rates of the tumors showing a high TIL score (34%) and of those showing a high apoptosis score (35%) were significantly higher than those of the tumors showing a low TIL score (10%) and those of the tumors showing a low apoptosis score (19%) ($P = 0.0001$ and 0.04, respectively). Histological grade and basal marker expression were not correlated with pCR. Although the whole analysis was exploratory, the degree of TIL correlated with immune response appear to play a substantial role in the response to NAC in TNBC.

Keywords Triple-negative breast cancer · Neoadjuvant chemotherapy · Pathological complete response · Tumor-infiltrating lymphocytes · Tumor cell apoptosis

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