

**Table 2** continued

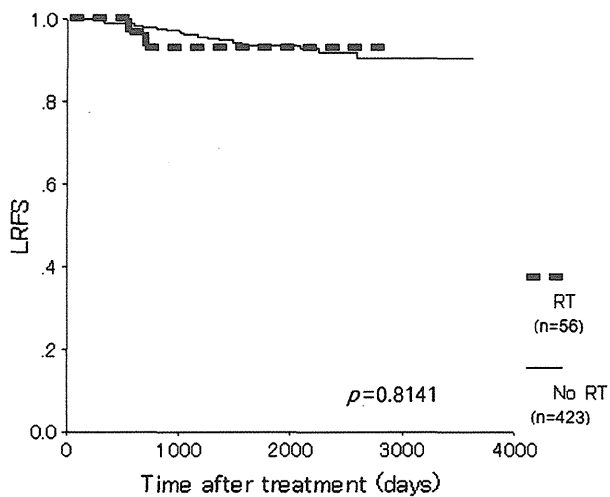
	≥4 positive nodes					
	Chemotherapy (n = 268)			No chemotherapy (n = 42)		
	HR	95% CI	p	HR	95% CI	p
Nuclear grade			0.366			0.598
G1/2	1			1		
G3	1.457	0.646–3.291		1.635	0.263–10.175	
Lymphatic invasion			<0.001			0.716
Absent/1+	1			1		
2+/3+	5.076	2.065–12.480		0.664	0.073–6.013	
Vascular invasion			0.025			0.609
Absent	1			1		
Present	2.122	1.101–4.092		0.041	0.001–854.7	
Estrogen receptor			0.003			0.056
Negative	1			1		
Positive	0.314	0.147–0.671		0.136	0.018–1.051	
Progesterone receptor			0.006			0.574
Negative	1			1		
Positive	0.345	0.162–0.735		0.516	0.051–5.179	
HER2			0.115			0.590
Negative	1			1		
Positive	1.862	0.859–4.035		0.039	0.001–544.67	

HR hazard ratio, CI confidence interval, IDC invasive ductal carcinoma, ILC invasive lobular carcinoma, G grade, HER2 human epidermal growth factor receptor 2

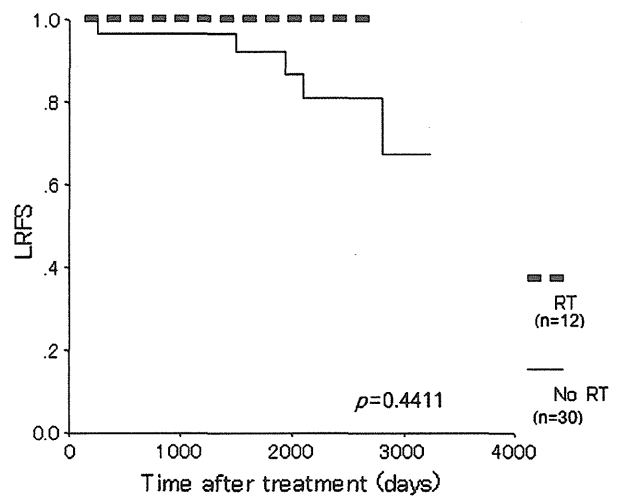
**Table 3** Hazard ratio of locoregional recurrence-free survival by tumor characteristics at presentation in patients with 1–3 or ≥4 metastatic nodes treated with chemotherapy (multivariate analysis)

	1–3 positive nodes (n = 370)			≥4 positive nodes (n = 268)		
	HR	95% CI	p	HR	95% CI	p
Tumor size (mm)						0.300
≤50				1		
>50				1.519	0.689–3.351	
Lymphatic invasion			0.017			0.001
Absent/1+	1			1		
2+/3+	3.938	1.275–12.163		4.861	1.896–12.462	
Nuclear grade			0.049			
G1/2	1					
G3	3.118	1.001–9.730				
Vascular invasion			0.012			0.498
Absent	1			1		
Present	4.433	1.384–14.202		1.317	0.594–2.919	
Estrogen receptor			0.365			0.049
Negative	1			1		
Positive	0.588	0.186–1.855		0.402	0.161–0.998	
Progesterone receptor			0.002			0.087
Negative	1			1		
Positive	0.177	0.060–0.521		0.455	0.184–1.123	

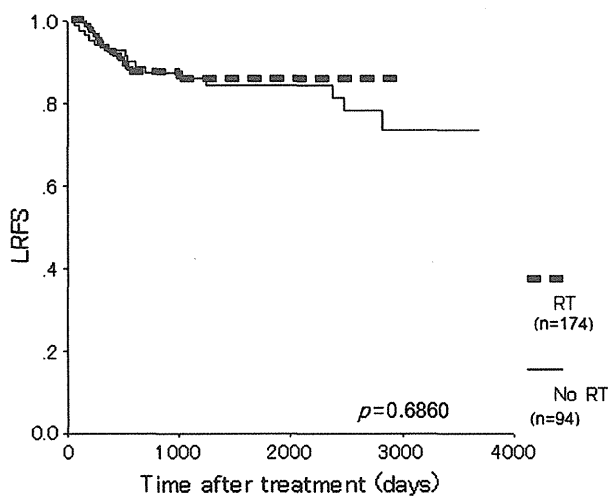
LRFs locoregional recurrence-free survival, HR hazard ratio, CI confidence interval



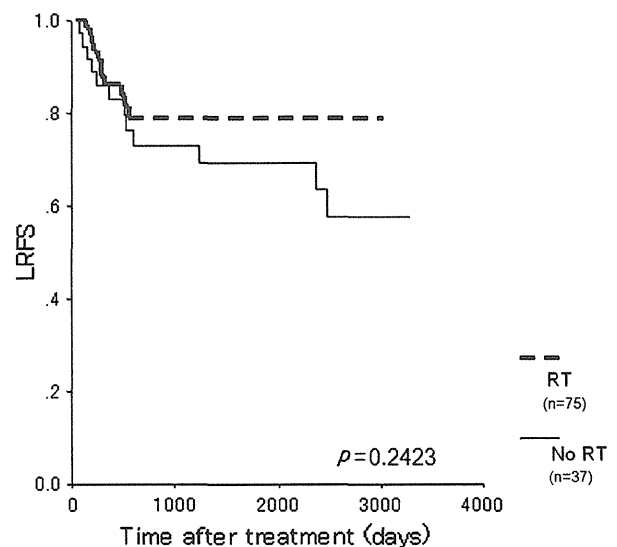
**Fig. 1** Locoregional recurrence-free survival (LRFS) in patients with 1–3 positive nodes who received chemotherapy. RT radiation therapy



**Fig. 3** Locoregional recurrence-free survival (LRFS) in patients with  $\geq 4$  positive nodes who did not receive chemotherapy. RT radiation therapy



**Fig. 2** Locoregional recurrence-free survival (LRFS) in patients with  $\geq 4$  positive nodes who received chemotherapy. RT radiation therapy



**Fig. 4** Locoregional recurrence-free survival (LRFS) in the high-risk group of patients with  $\geq 4$  positive nodes who received chemotherapy. RT radiation therapy

in such cases, because almost all the patients with LRR had metastatic lymph nodes, and metastatic lymph nodes were similar to systemic metastasis.

The second reason was that our median follow-up duration of 59.6 months was shorter than in other RCT studies. Taghian et al. [22] reported that the median time to develop isolated LRR was 2.0 years and the majority of LRR occurred within the first 4 years. Our study duration was more than 4 years and covered the time period when the majority of LRR was thought to occur. However, because LRFS was getting worse after 2000 days in this study, the incidence time of LRR may differ in Japanese patients and longer follow-up is needed.

RT brought better prognosis for  $n \geq 4$  patients, as in other studies, and especially for the patients who had all

independent risk factors. Although there was no significantly difference, these results showed that PMRT also had an effect in Japanese patients. This study was a retrospective analysis and the small number of patients compared with RCT studies was the reason why there was no significant difference. In  $n \geq 4$  patients, those with lymphatic invasion and hormone receptor-negative status were a LRR high-risk group and PMRT was an essential treatment.

The role and efficacy of RT for patients with 1–3 positive nodes has been discussed but a consensus has not

been reached. To determine the high-risk factors for LRR in patients with 1–3 positive nodes, we analyzed the relationship between clinicopathological characteristics and LRR. The severity of lymphatic invasion, the presence of vascular invasion, NG 3 and PgR-negative status were independent risk factors for LRR. Kyndi et al. [23] reported that patients with hormone receptor-negative status had significantly smaller improvements in LRR control after PMRT. In other analyses, large tumor size, extranodal extension and inadequate dissection were additional risk factors [5, 18, 19]. In this study, patients with 1–3 positive nodes had good outcomes. In addition, since there were only two patients with all high-risk factors, the role of RT for this subgroup was not proven. The presence of high-risk factors for LRR might define an indication for RT in patients with 1–3 positive nodes.

In conclusion, the role and efficacy of PMRT in patients who received adequate axillary lymph node dissection were limited. The role of PMRT in patients with 1–3 positive nodes was unclear, and the detection of a high-risk subgroup based on clinical trials is necessary to determine whether such patients would benefit from PMRT.

**Conflict of interest** None.

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## Prognostic factors for stage IV hormone receptor-positive primary metastatic breast cancer

Akiko Kawano · Chikako Shimizu ·  
Kenji Hashimoto · Takayuki Kinoshita ·  
Hitoshi Tsuda · Hirofumi Fujii · Yasuhiro Fujiwara

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### Abstract

**Background** The purpose of this work was identify potential prognostic factors for survival in patients with primary metastatic hormone receptor-positive breast cancer undergoing endocrine therapy (ET) as first-line treatment.

**Methods** We investigated the clinical and pathological characteristics of 69 newly diagnosed stage IV hormone receptor-positive breast cancer patients undergoing ET between 1999 and 2009, and correlated these factors with disease progression and overall survival.

**Results** Multivariate regression analysis revealed that progesterone receptor (PgR) positivity (hazard ratio (HR) 0.248;  $p = 0.001$ ) and clinical benefits of first-line ET (HR 0.386;  $p = 0.008$ ) were significant prognostic factors for survival. When first-line ET was not effective, patients for whom second-line ET was effective survived significantly longer than those for whom second-line ET was not effective (median survival time, 45.3 vs. 25.8 months;  $p = 0.0411$ ).

**Conclusions** PgR positivity and clinical benefits of first-line ET were independent prognostic factors for patients with hormone receptor-positive stage IV breast cancer. Moreover, the benefits of second-line ET in patients with a tumor resistant to first-line ET suggests the existence of drug-specific resistance to ET.

**Keywords** Stage IV breast cancer · Second-line endocrine therapy · Prognostic factor · PgR · Clinical benefit

### Introduction

In Japan approximately 10% of breast cancer patients present with distant metastasis at the time of diagnosis. In the 1980s, median survival time (MST) was approximately 18–24 months with or without anticancer treatment [1, 2]. Recently, however, survival of these patients has been significantly improving because of the development of novel drugs and application of alternative modes of administration of previously developed drugs [3].

In patients with metastatic or recurrent breast disease, visceral disease and shorter disease-free interval have been associated with poor survival outcome [4]. With regard to the phenotype of the primary tumors, estrogen receptor (ER) and progesterone receptor (PgR) negativity, HER2 overexpression, larger initial tumor size, and number of involved lymph nodes are associated with worse survival [5, 6]. In addition, the period of endocrine therapy (ET) treatment and hormone receptor-positivity are significant prognostic factors for survival [3, 4, 6], supporting the claim that the therapeutic decision has been appropriately directed toward ER, PgR, and HER2 [6], and that more drugs should be developed in this direction.

A. Kawano · C. Shimizu (✉) · K. Hashimoto · Y. Fujiwara  
Breast and Medical Oncology Division, National Cancer Center  
Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan  
e-mail: cshimizu@ncc.go.jp

A. Kawano · H. Fujii  
Medical Oncology Division, Jichi Medical University Hospital,  
3311-1 Yakushiji, Shimotsuke, Tochigi 329-0498, Japan

T. Kinoshita  
Breast Surgery Division, National Cancer Center Hospital,  
Tokyo, Japan

H. Tsuda  
Pathology Division, National Cancer Center Hospital, Tokyo,  
Japan

Recently, tumor subtypes defined by their gene expression have been widely reported to be determinants of the prognosis of primary breast cancer [7–9]. Each tumor subtype has its own clinical features and clinical outcomes, and it requires a different treatment strategy. Therefore, there is also a need to recognize prognostic factors specifically associated with each tumor subtype.

Treatment guidelines described by Hortobagyi et al. [10], the National Comprehensive Cancer Network (NCCN), the European Society for Medical Oncology (ESMO), and the Japanese Breast Cancer Society (JBCS) recommend endocrine therapy (ET) as the optimum initial treatment for hormone receptor-positive metastatic breast cancer patients. However, not all patients with hormone receptor-positive breast tumors benefit from ET. Therefore, we conducted this retrospective exploratory study to identify potential prognostic factors for patients with stage IV hormone receptor-positive primary metastatic breast cancer undergoing ET.

## Patients and methods

### Patients

We identified 69 female patients newly diagnosed with stage IV hormone receptor-positive breast cancer who were prescribed ET as first-line systemic therapy at the National Cancer Center Hospital in Tokyo between 1999 and 2009. The follow-up period was completed in September 2010. This study protocol had been approved by the institutional review board at the National Cancer Center Hospital in Tokyo.

### Methods

All patients had invasive carcinoma histologically confirmed by core needle biopsy of the primary site. In 2000–2002, ER and PgR were detected by use of the specific antibodies 1D5 (Dako, Glostrup, Denmark) and 1A6 (Ventana Medical Systems, Tucson, AZ, USA) respectively; in 2003–2004, clones ER88 and PgR88 (Kyowa Medex, Tokyo, Japan); and in 2005–2009, clones 1D5 and PgR636 (Dako) were used. Levels of hormone receptor positivity were defined as positive staining in more than 1% or more than 10% of the tumor cell nuclei. HER2 expression was measured by use of HercepTest™ (Dako) in 2000–2002 and 2005–2009, and by use of Nichirei (Tokyo, Japan) anti-HER2/neu polyclonal antibodies in 2003–2004. HER2 positivity was defined as an immunohistochemistry (IHC) score of 3+ (intense staining of the cell membrane in more than 10% of the cancer cells) or positive fluorescence in situ hybridization (FISH) HER2

amplification signals (HER2/CEP17 signal ratio of 2 with IHC score of 2+).

Medical records were retrospectively reviewed for date of first diagnosis, date of birth, sex, histology, site of metastases, date of treatment start, treatment used, response to treatment, and date of disease progression for each of those treatments. All patients included in this study had the primary tumor as a measurable lesion. Before treatment started, all the primary tumors were measured by use of calipers. Measurement of tumor markers (CEA, CA15-3, and ST439), thoracoabdominal CT scan, and bone scintigraphy were done in all cases before treatment to screen metastatic lesions. The primary tumor was evaluated at every visit at 2–4 month intervals. Tumor markers were measured at every visit if they were elevated before treatment. Other imaging tests were done using the same modality as used before treatment when tumor growth was suspected by physical examination, symptoms, or tumor marker. Tumor response was evaluated according to WHO criteria by the investigators. Patients were classified as having a clinical benefit if they had complete response (CR), partial response (PR), or stable disease (SD) for 6 months or longer. Overall survival (OS) was calculated from the date of first diagnosis of breast cancer, with death from any cause regarded as an event. Patients who were alive at last follow-up were censored at the last follow-up date.

### Statistical analysis

Statistical analysis was performed using the Statistical Package for Social Sciences (SPSS) 11.0 software (SPSS, Chicago, IL, USA). All categorical data were compared by use of chi-squared tests or Fisher's exact tests. Survival curves were derived from Kaplan–Meier estimates, and the curves were compared by use of log-rank tests. Multivariate analysis with Cox proportional hazards regression models was used to identify independent prognostic factors in all patients. All tests were two-sided. Statistical significance was set at 0.05.

## Results

### Characteristics of the patients

Sixty-nine patients with primary metastatic breast cancer were included in this study. The median follow-up period was 30.3 months (range: 2.0–102.4). The clinical characteristics of all 69 patients are shown in Table 1. Median age at diagnosis was 53 years (range 27–86). More than two-thirds were postmenopausal at diagnosis. Over half were categorized as clinical factor T4, approximately

**Table 1** Patients' characteristics

Characteristic	Number of patients	%
All patients	69	100
Age at diagnosis		
Median (range)	53 (27–86)	–
<50 years	22	32
≥50 years	47	68
Menopausal status		
Premenopause	22	32
Postmenopause	47	68
Clinical T factor (UICC sixth edition)		
T0	1	1
T1	2	3
T2	11	16
T3	16	23
T4	39	57
Clinical N factor (UICC sixth edition)		
N0	16	23
N1	31	45
N2	12	17
N3	6	9
Site of metastasis		
Liver	16	23
Lung	26	38
Bone	48	70
Brain	1	1
Skin	3	4
Lymph node	13	19
Bone and soft tissue only	31	45
Histology		
Invasive ductal carcinoma	65	94
Invasive lobular carcinoma	3	4
Others	1	1
Histological grade		
1 (well differentiated)	2	3
2 (moderately well or partially differentiated)	39	57
3 (poorly differentiated)	22	32
Unknown	5	7
ER status		
≥10% of positively stained nuclei	63	91
<10% but ≥1% of positively stained nuclei	1	1
<1% of positively stained nuclei (negative)	2	3
Uninterpretable/missing	3	4
PgR status		
≥10% of positively stained nuclei	44	64
<10% but ≥1% of positively stained nuclei	12	17

**Table 1** continued

Characteristic	Number of patients	%
<1% of positively stained nuclei (negative)	12	17
Uninterpretable/missing	1	1
HER2 status		
Positive	8	12
Negative	60	87
Uninterpretable/missing	1	1
First-line ET		
TAM + LHRH analog	23	33
AI	40	58
TAM	6	9

*UICC* Union Internationale Contre le Cancer, *ER* estrogen receptor, *PgR* progesterone receptor, *HER2* human epidermal growth factor receptor 2, *TH* endocrine therapy, *TAM* tamoxifen, *LHRH* luteinizing hormone-releasing hormone, *AI* aromatase inhibitor

three-fourths were node-positive, and above 90% had invasive ductal carcinoma. All of the premenopausal women received tamoxifen (TAM) plus luteinizing hormone-releasing hormone (LHRH) analog therapy, and all of the postmenopausal women received TAM alone (until year 2000) and anastrozole (from 2001 onward) as first-line ET. The clinical benefit rate (CBR) of the first-line ET was 67% (0% CR, 29% (20/69) PR, and 38% (26/69) SD longer than 6 months).

#### OS and associated prognostic factors

MST was 44.5 months (95% confidence interval (CI) 34.3–54.7). The results of the univariate analysis for OS are shown in Table 2. PgR positivity was defined by staining of more than 1% of the tumor cell nuclei (MST 48.4 vs. 28.5 months;  $p = 0.0036$ ) and clinical benefits of first-line ET (MST 49.0 vs. 29.6 months;  $p = 0.0170$ ) were identified as significant prognostic factors (Figs. 1, 2). PgR status and CBR of first-line ET remained significant after performing multivariate analysis (Table 3).

#### Relationship between responsiveness to ET and survival

Among the 46 responders to first-line ET, 4 patients continued to receive first-line ET, 7 received chemotherapy, 5 received palliative care, and 34 patients received second-line ET after failure of first-line ET. Of the 34 patients receiving second-line ET, 18 patients responded, 14 did not, and the disease was not evaluated for 2. Among the 23 non-responders to first-line ET, 11 received chemotherapy, 3 received palliative care, and 9 received

**Table 2** Univariate analysis of prognostic factors

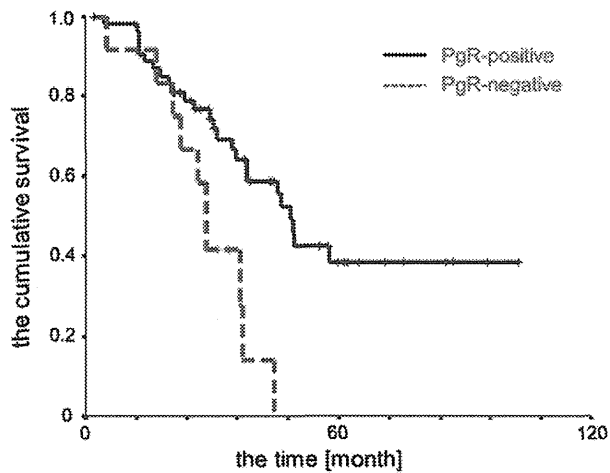
	Number of patients	MST (m)	95% CI	<i>p</i> value
Age at diagnosis				
<50 years	22	45.3	39.7–50.9	
≥50 years	47	36.5	20.2–52.8	0.6363
Menopausal status				
Premenopause	22	45.3	NA	
Postmenopause	47	38.3	28.0–48.6	0.3057
Clinical T factor (UICC sixth edition)				
T0–T3	30	45.3	27.9–62.7	
T4	39	38.3	22.0–54.6	0.4818
Clinical N factor (UICC sixth edition)				
N0	16	38.3	28.3–48.3	
N1–N3	53	46.1	31.9–60.3	0.9641
Site of metastasis				
Liver				
+	16	34.8	23.3–46.3	
–	53	46.1	33.0–59.2	0.0871
Lung				
+	26	37.1	23.6–50.6	
–	43	45.3	30.9–59.7	0.2552
Bone				
+	48	38.3	23.8–52.8	
–	21	44.5	31.0–58.0	0.9119
Bone and soft tissue only				
+	31	49.0	NA	
–	38	38.2	26.6–49.8	0.1614
Estrogen receptor status				
Positive (≥10% of stained nuclei)	63	38.3	27.6–49.0	
Negative (<10% of stained nuclei)	3	NA	–	0.2511
Positive (≥1% of stained nuclei)	64	38.3	29.0–47.6	
Negative (<1% of stained nuclei)	2	NA	–	0.1142
Progesterone receptor status				
Positive (≥10% of stained nuclei)	44	46.1	31.3–60.9	
Negative (<10% of stained nuclei)	24	37.1	33.5–40.7	0.4113
Positive (≥1% of stained nuclei)	56	48.4	43.3–53.5	
Negative (<1% of stained nuclei)	12	28.5	25.3–31.7	0.0036*
HER2/neu receptor status				
Positive	8	NA	–	
Negative	60	44.5	35.1–53.9	0.2813
Clinical benefit rate (first-line ET)				
Positive (CR + PR + ≥6 m SD)	46	49.0	26.9–71.1	
Negative (PD + <6 m SD)	23	29.6	26.3–32.9	0.017*

\* *p* < 0.05

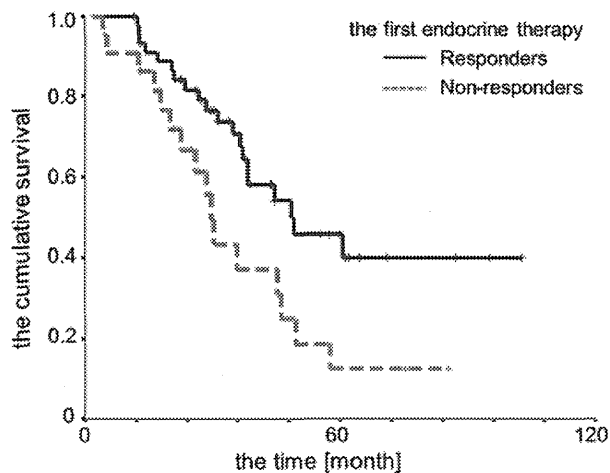
MST median survival time, NA not available, UICC Union Internationale Contre le Cancer, HER2 human epidermal growth factor receptor 2, ET endocrine therapy, CR complete response, PR partial response, SD stable disease, PD progressive disease

immediate second-line ET because of the absence of visceral metastases and the patient's own desire to receive ET. Four of the 9 patients who had initial resistance to first-line ET experienced clinical benefits with second-line ET; 2 had received anastrozole and 1 had received letrozole as first-line ET and TAM as second-line ET,

whereas another had received TAM plus LHRH analog as first-line ET and medroxyprogesterone (MPA) as second-line ET (Table 4). In this population, patients who benefited from second-line ET had significantly longer OS than those who did not (MST 45.3 vs. 19.9 months; *p* = 0.0002).



**Fig. 1** Overall survival as a function of the progesterone receptor status. *Solid line*: progesterone receptor-positive patients, median 48.4 months (43.3–53.5). *Dashed line* progesterone receptor-negative patients, median 28.5 months (25.3–31.7).  $p = 0.0036$



**Fig. 2** Overall survival as a function of the clinical benefit rate of the first endocrine therapy. *Solid line*: responders to the first endocrine therapy, median 49.0 months (26.9–71.1). *Dashed line* non-responders to the first endocrine therapy, median 29.6 months (26.3–32.9).  $p = 0.0170$

**Table 3** Multivariate analysis of prognostic factors

Characteristic	HR	95% CI	$p$ value
Progesterone receptor status			
Negative (<1% of stained nuclei)	3.75	1.67–8.42	0.001
Clinical benefit rate (first-line ET)			
Negative	2.63	1.32–5.24	0.006

HR hazard ratio, CI confidential interval, ET endocrine therapy

## Discussion

Previous studies have shown that hormone receptor positivity is a strong prognostic marker in non-selected patients with metastatic or recurrent breast cancer [3, 5, 6, 11]. In this study, PgR positivity and clinical benefits of first-line ET were identified as independent prognostic factors for stage IV hormone receptor-positive breast cancer patients undergoing ET as the initial treatment.

Several predictors of response to second-line or subsequent ET for breast cancer—including tumor grade, ER positivity, PgR positivity, and previous ET responsiveness—have been suggested in previous studies [12–15]. Some authors have reported that 20–30% of patients with resistance to first-line ET benefit from sequential second-line ET [12, 13]. Wilson suggested that the biological characteristics of the patients and the acquired tumor changes may explain the responsiveness of some patients [12]. However, the ET options mainly used at the time of those studies (oophorectomy, hypophysectomy, androgen, estrogen, progestin, and aminoglutethimide, among others) are no longer used. Hence, those results may not be directly applicable to the current situation, in which ET consists mainly of anti-estrogens and selective aromatase inhibitors.

In this study, 4 of the 9 first-line ET-resistant patients benefitted from second-line ET, suggesting the existence of drug-specific endocrine resistance. It is important clinically to be aware of drug-specific resistance to avoid proceeding to chemotherapy rather than to second-line ET.

Several studies have suggested PgR is a strong predictor of responsiveness to TAM, indicating that ER-positive/PgR-positive tumors are strongly associated with survival benefit of patients receiving TAM treatment, in contrast with ER-positive/PgR-negative tumors [16, 17]. On the other hand, for patients undergoing letrozole treatment, PgR expression and responsiveness to treatment have a non-linear (inverted U-shape) relationship [18]. Treatment with anastrozole more effectively prevented recurrence of ER-positive/PgR-negative tumors than that of ER-positive/PgR-positive tumors [19].

Most studies have supported a role of HER2 in TAM resistance [20]. Indeed, crosstalk between ER and growth factor receptor signaling pathways has been suggested. For example, estrogen and TAM phosphorylate and activate the ER, ultimately activating growth factor-mediated signals [21, 22]. In contrast, Ellis et al. [18] reported that letrozole was more effective than TAM against ErbB-1- and/or ErbB-2-positive and ER-positive tumors. In our study, HER2 did not emerge as a prognostic marker for patients treated with first-line ET. We believe the reason is that 40 (50%) of the patients had received anastrozole as first-line ET.



**Table 4** Characteristics of second-line ET responders who had initial resistance to first-line ET

N	Menopause status	First line ET			Second line ET		
		Drug	Best response	Duration (month)	Drug	Best response	Duration (month)
1	Post	LTZ	PD	4.6	TAM	PR	15.8
2	Post	ANZ	PD	4.5	TAM	LSD	7.3
3	Pre	TAM/ LHRHa	PD	3.9	MPA	PR	6.6
4	Post	ANZ	PD	1.8	TAM	LSD	14.8

ET endocrine therapy, LTZ letrozole, ANZ anastrozole, TAM tamoxifen, LHRHa luteinizing hormone-releasing hormone analog, PD progressive disease, PR partial response, LSD stable disease more than 6 months

We have initially investigated known prognostic factors by use of multivariate Cox regression analysis. PgR and other potential biomarkers predictors of endocrine resistance will be examined in validation studies. Notably, stage IV breast cancer provides an optimum setting for such translational research because serial tissue sampling of the primary tumor may be readily achieved.

This study had some limitations inherent in retrospective analyses. First, we used three kinds of antibody to detect PgR expression of the tumor and two kinds of systems to detect HER2 expression. Results from every antibody or system were indicative of significant differences in our analysis, however. Second, we did not perform imaging studies every fixed period because this study was performed in a clinical practice setting. Therefore, we may have not estimated the CBR exactly.

In conclusion, we suggest PgR and clinical benefit as prognostic markers for patients with stage IV hormone receptor-positive primary metastatic breast cancer. In addition, we emphasize the evidence that some patients might benefit from second-line ET even after failure of first-line ET.

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## Paclitaxel-induced peripheral neuropathy in patients receiving adjuvant chemotherapy for breast cancer

Yuko Tanabe · Kenji Hashimoto · Chikako Shimizu · Akihiro Hirakawa · Kenichi Harano · Mayu Yunokawa · Kan Yonemori · Noriyuki Katsumata · Kenji Tamura · Masashi Ando · Takayuki Kinoshita · Yasuhiro Fujiwara

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### Abstract

**Background** The long-term outcomes and risk factors of paclitaxel-induced peripheral neuropathy (PIPNe) have not yet been fully elucidated.

**Methods** We identified 219 breast cancer patients who received paclitaxel as adjuvant chemotherapy between 2002 and 2009. We retrospectively analyzed the incidence, time to onset, duration, and risk factors for PIPNe by chart review.

**Results** Of the 219 patients, 212 developed PIPNe (97%) during a median follow-up time of 57 months (range 5.3–95.5). Median time to PIPNe onset was 21 days (range 11–101) for the entire patient population; 35 days (range 14–77) for weekly administration and 21 days (range 11–101) for tri-weekly administration. PIPNe caused termination of paclitaxel treatment in 7 patients (4%). Median duration of PIPNe was 727 days (range 14–2621 days). PIPNe persisted in 64 and 41% of patients at 1 and 3 years after initiating paclitaxel, respectively. Age  $\geq 60$  years and severity of PIPNe were significantly associated with PIPNe duration.

**Conclusions** PIPNe persists longer in older patients and in those who experience severe neuropathy. Further studies to identify the risk factors for PIPNe are warranted.

**Keywords** Breast cancer · Paclitaxel · Peripheral neuropathy

### Introduction

Paclitaxel (PTX) is a key component of many therapeutic regimens in both early-stage and metastatic breast cancer [1–4]. PTX, a microtubule-stabilizing agent, binds to microtubules and abolishes their dynamic behavior, leading to inhibition of cell proliferation [5]. The agent is known to cause peripheral neurotoxicity (PN), which may result in discontinuation of treatment and poor quality of life.

The incidence of PTX-induced PN (PIPNe) is known to depend on several factors, including dosages per cycle, treatment schedule, duration of infusion, cumulative dosage, and co-morbidity such as diabetes [6–11]. Although the clinical response of tumors to PTX is an important factor in selecting a chemotherapy regimen, it is also prudent to evaluate the risk of developing PN associated with each regimen, especially for patients already at high risk for neuropathy. The risk of sensory neuropathy is proportional to the dose of PTX administered. Grade 3 or 4 sensory neurotoxicity occurs in 20–35% of patients receiving 250 mg/m<sup>2</sup> every 3 weeks compared to 5–12% using doses  $\leq 200$  mg/m<sup>2</sup> every 3 weeks [12]. The weekly schedule is associated with higher neurotoxicity than the tri-weekly schedule. In a previous study, grade 3 neuropathy occurred significantly more often with the weekly regimen than with the tri-weekly regimen (24 vs. 12%) [13]. In another study, which compared weekly versus

Y. Tanabe · K. Hashimoto · C. Shimizu (✉) · K. Harano · M. Yunokawa · K. Yonemori · N. Katsumata · K. Tamura · M. Ando · T. Kinoshita · Y. Fujiwara  
Department of Breast Oncology and Medical Oncology,  
National Cancer Center Hospital, 5-1-1 Tsukiji,  
Chuo-ku, Tokyo 104-0045, Japan  
e-mail: cshimizu@ncc.go.jp

A. Hirakawa  
Department of Management Science, Graduate School  
of Engineering, Tokyo University of Science,  
1-3 Kagurazaka, Shinjuku-ku, Tokyo 162-8601, Japan

tri-weekly PTX dosages, it was reported that grade 2, 3, or 4 neuropathy occurred more frequently with weekly than with tri-weekly PTX administration (27 vs. 20%, respectively) [14].

The time to onset of PIPN was previously determined in a phase III trial of patients with metastatic breast cancer treated with PTX (175 mg/m<sup>2</sup>) every 3 weeks; the mean total dose at the onset of grade 2 neurotoxicity was 715 mg/m<sup>2</sup> [15]. However, there are limited data available describing the outcome of PIPN and risk factors of severe PN. We therefore conducted a retrospective study to determine the duration of PIPN and to identify potential factors predicting severe or persistent PN.

## Patients and methods

### Data collection

This study included breast cancer patients treated with PTX as adjuvant chemotherapy at the National Cancer Center Hospital between 2002 and 2009. All patients met the following criteria: female gender; age >18 years; recipients of lumpectomy or mastectomy; and presentation of more than one axillary lymph node metastasis, as determined pathologically. The following patients were excluded from this study: those previously treated with PTX, those who presented with severe neuropathy before initiating PTX treatment, and those who discontinued PTX treatment after only 1 cycle for any reason.

We performed chart reviews for all patients to obtain the following information: age; gender; stage; hormonal status; human epidermal growth factor receptor-2 (HER2) status; previous surgical procedures (lumpectomy or mastectomy); adjuvant chemotherapy; adjuvant radiotherapy; PTX administration schedule; date of the first documentation of PIPN; maximum grade of PIPN; date of disappearance of PIPN symptoms. This study was approved by the local institutional review board.

### Treatment schedule

Chemotherapy consisted of anthracycline followed by PTX regimens as generally recommended for high-risk breast cancer patients, according to the St. Gallen risk criteria at our division [16, 17]. However, therapeutic options could vary based on the physician's discretion. Patients received either 80 mg/m<sup>2</sup> of PTX on days 1, 8, and 15 of each 21-day interval for 4 cycles, following anthracycline plus cyclophosphamide (AC) (weekly administration schedule), or 175 mg/m<sup>2</sup> of PTX on day 1 of each 21-day interval for 4 cycles, following AC (tri-weekly administration schedule).

### Grading of PIPN

Patients were evaluated during and after chemotherapy by medical oncologists. We graded PIPN retrospectively according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0 [18]. Grade 1 PIPN had paresthesias including tingling, but not interfering with function, while grade 2 had sensory alterations or paresthesias interfering with function but not interfering with activities of daily living (ADL). Grade 3 had sensory alterations or paresthesias interfering with ADL. Patients were determined to have PIPN if their score for sensory neuropathy was grade 1 or higher. The severity of pain was not evaluated in this study because of insufficient data.

### Statistical analysis

The time to onset of PIPN was defined as the time from the date of PTX administration to the date of the first documentation of PIPN. The duration of PIPN was defined as the time from the date of first documentation of PIPN to the date of disappearance of the PIPN symptoms described. The time to onset and duration of PIPN were estimated by the Kaplan–Meier method. We used multivariate Cox regression analysis to identify the variables associated with the time to onset and duration of PIPN. Furthermore, to identify the risk factors for PIPN above grade 2, we applied multivariate logistic regression analysis. A 2-sided  $P < 0.05$  was considered statistically significant. All analyses were performed by SAS software, version 9.2 (SAS Institute, Cary, NC, USA).

## Results

### Patient characteristics

Of the 227 patients initially identified, 2 were excluded due to severe neuropathy induced by combination chemotherapy with AC before being treated with PTX. Several patients discontinued systemic therapy before completion of 1 cycle due to the following adverse events: severe liver dysfunction (grade 3) ( $n = 3$ ), acute renal failure (grade 3) ( $n = 1$ ), allergic reaction (grade 3) ( $n = 1$ ), and interstitial pneumonitis (grade 3) ( $n = 1$ ). Finally, a total of 219 patients were included; 212 patients (97%) developed PIPN which was characterized by numbness and tingling, while 7 had no PIPN symptoms. The maximum severity of PIPN reached in each of the 212 patients was as follows: grade 1, 159 patients (75%); grade 2, 45 patients (21%); and grade 3, 9 patients (4%). Two patients needed dose modifications due to PIPN above grade 2. No patients postponed or skipped the scheduled PTX due to PIPN.

Baseline characteristics of the population are listed in Table 1. The median age of patients was 53 years (range 22–70). Eighteen patients had diabetes mellitus without neuropathy complications at baseline. Disease-free survival and overall survival were evaluated with a median follow-up time of 57.1 months (range 5.3–95.5). A total of 25 patients received weekly PTX: 23 following AC and 2 without AC. The remaining 194 patients received tri-weekly PTX: 182 following AC and 12 without AC. The mean dose intensity was 58 mg/week (range 16–80). Treatment cessation was deemed necessary in 9 patients (4%); reasons for cessation were PIPN (8 patients, 3 with

grade 1, 1 with grade 2, and 5 with grade 3) and myelosuppression (1 patient).

#### PIP development time

The median time taken for the total patient group to develop PIPN was 21 days (range 11–101) (Fig. 1). With weekly administration of PTX, the median time taken to develop PIPN was also 21 days (range 11–101); the median time with tri-weekly administration was 35 days (range 14–77).

#### Cumulative dose

The mean cumulative dose at the onset of grade 1 or higher PIPN was 175 mg/m<sup>2</sup> for patients treated with PTX every 3 weeks and 320 mg/m<sup>2</sup> for weekly PTX patients.

#### Diabetes mellitus

Of 18 diabetic patients, all had PIPN and 3 had maximum grade 3 PIPN. Median time to PIPN onset was 21 days (range 20–21), and median duration of PIPN was 287 days (range 70–503). In patients without diabetes, median time to PIPN was 21 days (range 20–21), and median duration of PIPN was 231 days (range 190–271).

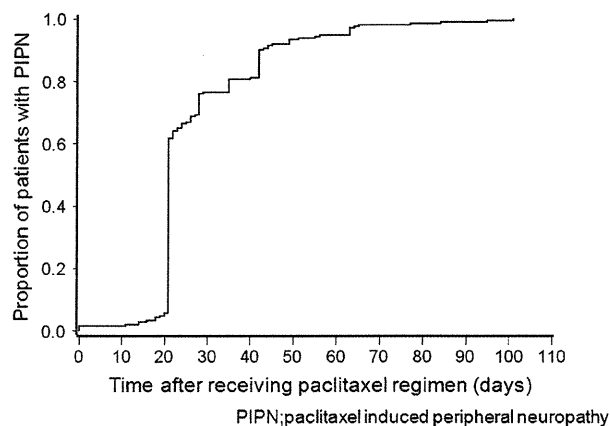
#### Risk factors correlated with PIPN

Multivariate analysis using a logistic regression model after stepwise selection revealed no significant correlations between time to PIPN onset and maximum PIPN severity (Table 2), while there were significant correlations between duration of PIPN and age (>60 years old) ( $P = 0.027$ ) and between duration of PIPN and maximum PIPN severity ( $P = 0.015$ ) (Table 3). Moreover, we could not identify

**Table 1** Patient characteristics

Variables	triPTX ( <i>N</i> = 188)	wPTX ( <i>N</i> = 24)	All ( <i>N</i> = 212)
<b>Age</b>			
Median (range)	53 (22–70)	52 (32–68)	53 (22–70)
<60 (%)	141 (75.0)	17 (70.8)	158 (74.5)
≥60 (%)	47 (25.0)	7 (29.2)	54 (25.5)
<b>Sex (%)</b>			
Female	187 (99.5)	24 (100.0)	211 (99.5)
Male	1 (0.5)	0 (0.0)	1 (0.5)
<b>Lymph (%)</b>			
<4	118 (62.8)	12 (50.0)	130 (61.3)
≥4	70 (37.2)	12 (50.0)	82 (38.7)
<b>Tumor size (%)</b>			
<5 cm	153 (81.4)	18 (75.0)	171 (80.7)
≥5 cm	35 (18.6)	6 (25.0)	41 (19.3)
<b>Surgery (%)</b>			
Mastectomy	114 (60.3)	16 (66.7)	130 (61.3)
Lumpectomy	73 (39.2)	8 (33.3)	81 (38.2)
Excisional biopsy	1 (0.5)	0 (0.0)	1 (0.5)
<b>Systemic therapy (%)</b>			
Chemo	56 (29.8)	8 (33.3)	64 (30.2)
Chemo + endocrine	132 (70.2)	16 (66.7)	148 (69.8)
<b>Radiation (%)</b>			
No	69 (36.7)	8 (33.3)	77 (36.3)
Yes	119 (63.3)	16 (66.7)	135 (63.7)
<b>Hormone (%)</b>			
Negative	48 (25.5)	5 (20.8)	53 (25.0)
Positive	140 (74.5)	19 (79.2)	160 (75.0)
<b>HER2 (%)</b>			
Negative	156 (83.0)	16 (66.7)	172 (81.1)
Positive	32 (17.0)	8 (33.3)	40 (18.9)
<b>Diabetes mellitus (%)</b>			
No	171 (91.0)	23 (95.8)	194 (91.5)
Yes	17 (9.0)	1 (4.2)	18 (8.5)

triPTX tri-weekly paclitaxel, wPTX weekly paclitaxel, chemo chemotherapy



**Fig. 1** Time taken for the total patient group to develop paclitaxel-induced peripheral neuropathy

**Table 2** Multivariate analysis for factors associated with time to PIPN

Variables	HR	95% CI	P value	
<b>Regimen</b>				
triPTX	1			
wPTX	0.66	0.43–1.03	0.070	
<b>Age</b>				
<60				
≥60	0.99	0.72–1.37	0.960	
<b>Lymph</b>				
<4				
≥4	1.20	0.82–1.77	0.341	
<b>Tumor size (cm)</b>				
<5				
≥5	0.98	0.68–1.42	0.917	
<b>Radiation</b>				
No				
Yes	0.78	0.51–1.20	0.259	
<b>Surgery</b>				
Mastectomy				
Lumpectomy	1.08	0.75–1.56	0.666	
<b>Endocrine</b>				
No				
Yes	0.87	0.65–1.18	0.366	
<b>Grade</b>				
1				
2 or 3	1.35	0.97–1.87	0.073	
<b>Diabetes mellitus</b>				
No				
Yes	1.34	0.81–2.21	0.260	

PIPn paclitaxel-induced peripheral neurotoxicity, triPTX tri-weekly paclitaxel, wPTX weekly paclitaxel, HR hazard ratio, CI confidence interval

any correlation with grade 2/3 PIPN (Table 4). Based on the results of multivariate analyses, there were no significant associations between diabetes mellitus and time to PIPN onset ( $P = 0.260$ ) or duration of PIPN ( $P = 0.345$ ) or grade 2/3 PIPN ( $P = 0.229$ ).

#### Duration of PIPN

The median duration of PIPN was 727 days for the total patient group (range 14–2621) (Fig. 2). With weekly administration, the median duration was not reached (range 14–1089); the median duration for patients with tri-weekly administration was 651 days (range 23–2621). One year after initiating PTX treatment, PIPN (all grades included) persisted in 64% of patients; 3 years after treatment initiation, this number had dropped to 41%.

**Table 3** Multivariate analysis for factors associated with duration of PIPN

Variables	HR	95% CI	P value	
<b>Regimen</b>				
triPTX	1			
wPTX	0.48	0.19–1.21	0.119	
<b>Age</b>				
<60				
≥60	0.55	0.32–0.94	0.027	
<b>Lymph</b>				
<4				
≥4	0.86	0.46–1.59	0.621	
<b>Tumor size (cm)</b>				
<5				
≥5	1.03	0.59–1.77	0.927	
<b>Radiation</b>				
No				
Yes	1.05	0.52–2.12	0.900	
<b>Surgery</b>				
Mastectomy				
Lumpectomy	0.67	0.36–1.26	0.213	
<b>Endocrine</b>				
No				
Yes	1.10	0.70–1.73	0.668	
<b>Grade</b>				
1				
2 or 3	0.53	0.32–0.88	0.015	
<b>Diabetes mellitus</b>				
No				
Yes	0.66	0.28–1.56	0.345	

PIPn paclitaxel-induced peripheral neurotoxicity, triPTX tri-weekly paclitaxel, wPTX weekly paclitaxel, HR hazard ratio, CI confidence interval

#### Discussion

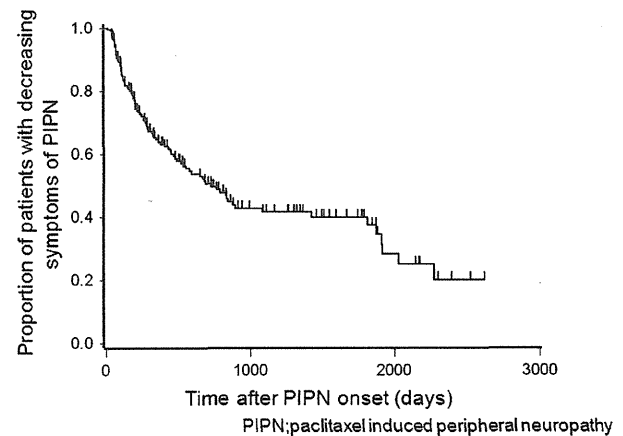
This is the first published report to our knowledge that investigates the time to onset and duration of PIPN among breast cancer patients and explores potential risk factors related to severe and/or persistent PIPN. The data from this study confirm that most patients (97%) developed PIPN with a severity of at least grade 1. Peripheral neuropathy persisted in 64% of patients at 1 year and 41% at 3 years after the first administration of PTX. Approximately half of the patients who received PTX and developed PN experienced recovery from PN within 9 months after cessation of PTX treatment. We found correlations between the maximum PIPN severity and both the time to onset of PIPN and the duration of PIPN. In addition, we observed that PN lasted significantly longer in patients >60 years of age.

**Table 4** Multivariate analysis for factors associated with grade 2 or 3 PIPN

Variables	Odds ratio	95% CI		P value
Regimen				
triPTX	0.57	0.18	1.83	0.345
wPTX				
Age				
<60	1.65	0.81	3.36	0.171
≥60				
Lymph				
<4	0.98	0.40	2.41	0.968
≥4				
Tumor size (cm)				
<5	0.47	0.18	1.24	0.125
≥5				
Radiation				
No	0.98	0.35	2.77	0.975
Yes				
Surgery				
Mastectomy	0.73	0.29	1.82	0.499
Lumpectomy				
Endocrine				
No	0.72	0.36	1.45	0.360
Yes				
Diabetes mellitus				
No	2.05	0.69	6.09	0.197
Yes				
Dose intensity				
<58	1.00	0.50	2.01	1.000
≥58				
Cumulative dose				
<700	0.31	0.08	1.13	0.077
≥700	0.57	0.18	1.83	0.345

PIPn paclitaxel-induced peripheral neurotoxicity, triPTX tri-weekly paclitaxel, wPTX weekly paclitaxel, CI confidence interval

Previous studies have reported that the incidence of PIPN is related to several risk factors, including treatment schedule, doses per course, patient age, diabetes mellitus, and cumulative dose [6–11]. We found no association between the severity of PIPN and the PTX administration schedule including single dose, dose intensity, diabetes mellitus, or interval of administration. In our study, the mean cumulative dose at the onset of grade 1 or higher PN was 175 mg/m<sup>2</sup> for patients treated with PTX every 3 weeks and 320 mg/m<sup>2</sup> for weekly PTX patients. In contrast to an earlier study [14], our clinical outcomes indicated that tri-weekly administration of PTX was associated with more severe PIPN than weekly administration. However, this result may be attributed to frequent hospital

**Fig. 2** Time to resolving PIPN from the time of developing paclitaxel-induced peripheral neuropathy

visits and/or the relatively small number of patients treated by weekly PTX.

Previous reports suggest there are several risk factors for PIPN, including concurrent administration of cisplatin [19] and various genetic predispositions for neuropathy, such as *Wlds* (slow Wallerian degeneration gene) and *CYP3A* genotype [20, 21], but we did not examine any of those risk factors in this study.

Axonal microtubules are composed largely of  $\beta$ -tubulin. Neurotoxicity is caused by disruption of the microtubule structure, impairing axoplasmic transport and leading to dying-back neuropathy [22]. The most widely accepted mechanism of taxane neurotoxicity is a dying-back process that starts from distal nerve endings and progresses to affect Schwann cells, neuron bodies, or axons, resulting in transport changes that disturb cytoplasmic flow in the affected neurons [23]. Another possible cause of PIPN is that sensory nerves may be particularly vulnerable to the inhibition of tubulin assembly, as sensory nerves have long axons. However, motor neurons and C-neurons are not as sensitive to taxanes as are sensory nerves, despite the fact that these neurons are as long as sensory nerves. Some reports suggest that induction of *Ca $\alpha$ 2 $\delta$ -1* expression by PTX in the spinal root may be important, but further investigation is necessary to understand the mechanisms of PIPN [24].

There are no medications that prevent or relieve PIPN. Likewise, there are no laboratory tests that can predict the severity of PN. Management of PIPN is now based on early detection during chemotherapy to prevent its progression to grade 3 or 4. Clinical assessment, including a physical examination, is currently the most reliable method of assessing PIPN because we lack more reliable objective methods, and the symptoms of PIPN, such as numbness, sensory pain, fatigue, and weakness, are complicated [12, 25]. If grade 2 PN is diagnosed, it may be prudent to

withhold PTX until PN improves to at least grade 1; PTX administration can then be resumed at a reduced dose.

There were several limitations to our study. We used physician-based assessments, which relies on patients' report and examiners' interpretation and could have resulted in underestimation and under-reporting of the frequency and severity of PN [26]. In addition, physicians were more prone to quit following symptoms periodically once patients recovered from maximum PIPN. In fact, there were many censored cases in this study (Fig. 2). Therefore, features of PIPN such as location, presence of accompanying symptoms, and triggers for increase or decrease in severity were unclear. This study was retrospective, with censored data; the neurotoxicity corresponding to each grade of PIPN was unclear. In fact, time to onset of PIPN was faster for grades 2 and 3 than grade 1. In order to properly evaluate the correlation between severity and duration of PIPN, we will need further studies to determine whether or not the duration of PIPN is longer when the maximum severity increases from grade 1 to grade 2.

In conclusion, we analyzed the incidence and duration of PIPN and identified correlations between these and several risk factors. We found that the median time to onset of PIPN was 21 days, and the median duration of PIPN was 727 days. Patient age and PIPN severity were the independent risk factors significantly associated with longer PIPN duration. Urgent needs currently include identification of specific risk factors for PIPN, establishment of subjective methods for evaluating PIPN, and development of effective strategies for prevention and treatment of PIPN. To meet these ends, further investigation of the biological mechanisms leading to PIPN is warranted.

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**Conflict of interest** The authors have declared no conflicts of interest.

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## Primary Leiomyosarcoma of the Breast

Tomoya Nagao, MD,\* Takashi Hojo, MD,\* Sadako Tanaka-Akashi, MD,\* Hitoshi Tsuda, MD,<sup>†</sup> and Takayuki Kinoshita, MD\*

\*Department of Breast Oncology, National Cancer Center Hospital, Tokyo, Japan; and <sup>†</sup>Department of Pathology, National Cancer Center Hospital, Tokyo, Japan

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 microcalcification (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.

Address correspondence and reprint requests to: Takashi Hojo, MD, Department of Breast Oncology, National Cancer Center Hospital, 5-1-1, Tsukiji, Chuo-ku, Tokyo, 104-0045, Japan, or e-mail: tahojo@ncc.go.jp

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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

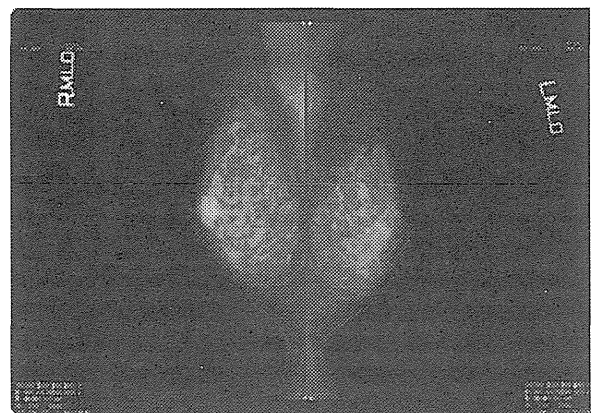


Figure 1. Mammography showing a well-circumscribed mass with no microcalcification.

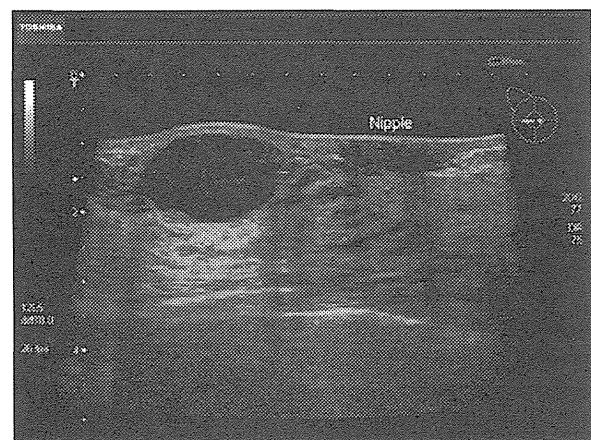
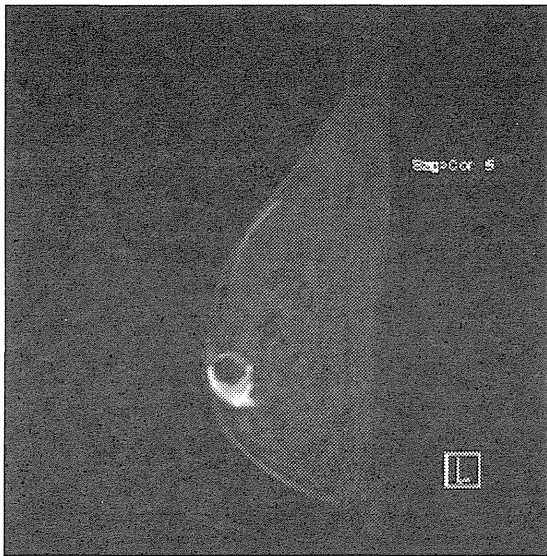
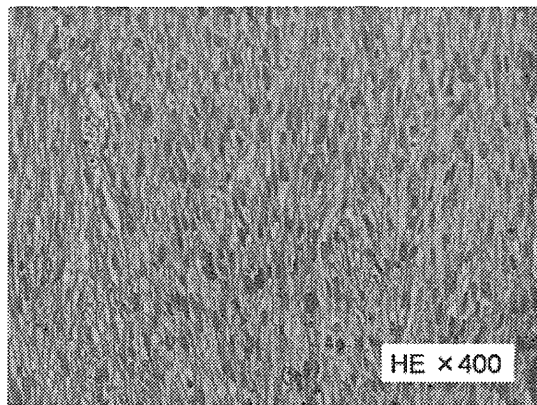


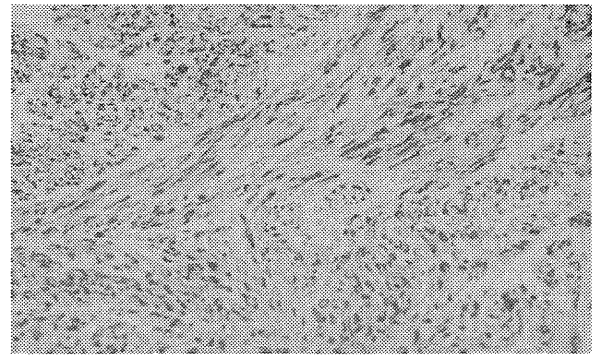
Figure 2. Ultrasonography showing a well-circumscribed, hypoechoic mass with a heterogeneous internal echo.



**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,  $\times 400$ ).



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

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.

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

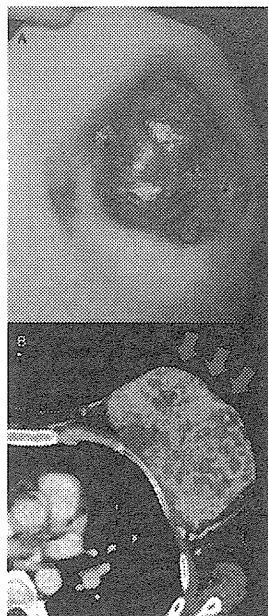


Figure 1.

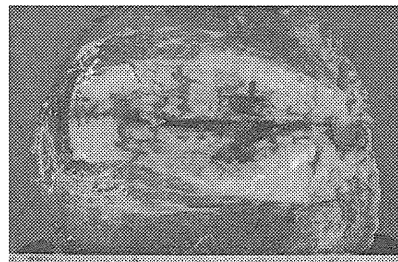


Figure 2.

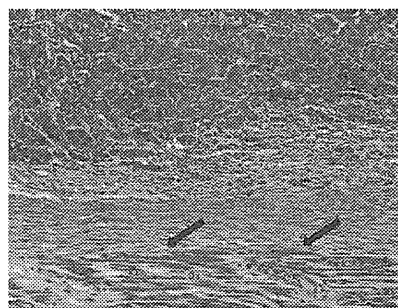


Figure 3.

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.

Sota Asaga and Takayuki Kinoshita  
Breast Surgery Division  
National Cancer Center Hospital  
Tokyo, Japan  
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