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Final Results of a Safety and Efficacy Trial of Preoperative Sequential Chemoradiation Therapy for the Nonsurgical Treatment of Early Breast Cancer: Japan Clinical Oncology Group Study JCOG0306

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Key Words
Clinical trial · Doxorubicin · Early stage breast cancer · Paclitaxel · Preoperative chemotherapy · Radiation therapy

Abstract
Objective: To explore the possibility of nonsurgical treatment of primary breast cancers by a sequential treatment of chemotherapy and radiotherapy. ***Methods:*** We conducted a safety and efficacy trial of chemotherapy and radiation therapy sequentially as primary therapy in patients with stage I–IIIA breast cancer. All patients underwent mastectomy or lumpectomy 12–16 weeks after the completion of radiation therapy to maximize the effect of radiation therapy. The primary endpoint was the pathological complete response (pCR) rate. ***Results:*** Between June 2004 and April 2005, one hundred eight patients were enrolled. Thirty six percent of the entire population achieved a pCR, which could not reject the null hypothesis. The pCR rate was 57% in patients with hormone receptor (HR)-negative/HER-2-positive tumors and 52% in patients with triple-negative tumors. While 7% of the HR-negative/HER2-positive patients recurred, a higher incidence of recurrence (24%) was observed in triple-negative tumors in a follow-up of 4.5 years. The rate of breast-conserving surgery was 88.9% (96/108). ***Conclusion:*** The pCR rate was not high enough, even though preoperative sequential chemoradiation therapy did not increase the risk of operative complications and could achieve a high rate of breast-conserving surgery.

Introduction

Radical mastectomy, which was brought to completion by William S. Halsted [1] in the latter half of the 19th century, was regarded as the standard therapy for primary breast cancer for around a century thereafter. In the 1970s and later, limited operations such as modified radical mastectomy and breast-conserving surgery spread [2, 3]. In the 1980s, inoperable locally advanced breast cancer cases were first treated with anticancer agents, followed by surgical extirpation of reduced tumors. Namely, preoperative or neoadjuvant chemotherapy was performed in order to ren-

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der inoperable cases operable [4]. In the latter half of the 1990s, this therapeutic strategy was extended to operable breast cancer cases in an attempt to improve the breast conservation rate. A number of randomized trials comparing preoperative and postoperative chemotherapies demonstrated that preoperative chemotherapy was comparable to postoperative chemotherapy in terms of survival, and that it was superior in terms of the breast conservation rate [5–8]. Preoperative chemotherapy has thus been ranked among the standard therapies for primary breast cancer.

Preoperative radiotherapy has also been performed since the 1980s, aimed at improving the breast conservation rate and local control. The breast conservation rate had so far improved up to 10–20% with a radiation dose of 45–50 Gy plus a boost of 10 Gy, but the pathological complete response (pCR) rate was still unsatisfying at 5% or so [9]. Limited operation has been supported by the progression of medical as well as radiation therapy before and after surgery. In clear view of this trend, it is considered a future task of clinical oncology of breast cancer to investigate whether 'nonsurgical therapy' such as medical or radiation therapy can be substituted for surgery in appropriate cases. Therefore, we investigate in this study whether preoperative chemoradiation therapy can achieve a high pCR rate. If the pCR rate is proven to be high enough, we can consider introducing nonsurgical treatment as a test regimen in future studies.

Patients and Methods

Patient Population

This multicenter, open-label, single-arm, phase II clinical trial was conducted at 29 institutions throughout Japan. The protocol was reviewed and approved by the JCOG Clinical Trial Review Committee and the institutional review board of each participating institution.

Patients were included in this trial if they met all of the following criteria: (1) core needle biopsy-proven invasive breast cancer (female only); (2) clinical stage I–IIIA (UICC/TNM system 1997); (3) tumor diameter of 2–5 cm confirmed by breast ultrasound sonography; (4) existence of all tumors within the planning target volume of the boost radiation, if multifocal lesions exist in the same breast; (5) patients without bilateral breast cancer (metachronous contralateral breast cancer was allowed); (6) age between 20 and 70 years; (7) ECOG performance status of 0 or 1; (8) no previous treatment with chemotherapy or radiotherapy; (9) adequate organ function [absolute neutrophil count (ANC) ≥1,500/mm^3, platelet count ≥100,000/mm^3, serum creatinine ≤1.5 mg/100 ml, GPT (ALT) ≤60 IU/l, and total bilirubin ≤1.5 mg/100 ml], and (10) written informed consent.

Patients were excluded if they met any of the following criteria: (1) current history of malignant neoplasms except for curative carcinoma in situ or mucosal carcinoma, (2) pregnant or lactating women or women with an intention to bear children, (3) active infectious disease, (4) past history of an allergic reaction to cremophor EL (polyoxethylated castor oil) or polysorbate, (5) interstitial pneumonia or fibroid lung revealed by chest X-ray, (6) poorly controlled or insulin dependent diabetes mellitus, and (7) psychological disease or psychological symptoms that interfered with entering this trial.

Endpoints

The primary endpoint was the pCR rate. The secondary endpoints were adverse events, clinical response rate, rate of breast-conserving surgery, relapse-free survival (RFS), and overall survival (OS).

The pCR is designated to include patients with complete disappearance of tumor cells or noninvasive tumor residues in the breast after protocol treatment, regardless of axillary lymph node metastasis. The pCR was assessed by the central review board, consisting of three pathologists, on a representative slice of surgical specimen which is determined by local site pathologists. Hematoxylin and eosin (H&E)-stained slides were prepared from the primary tumor for evaluation. A blinded central review board evaluated the pathological response independently of the local pathologists.

The rate of breast-conserving surgery was defined by the proportion of patients who underwent conserving surgery in relation to the eligible patients. RFS was defined as the time from randomization to the diagnosis of relapse, progressive disease, or death from any cause, and was censored at the date on which relapse-free status was verified. Secondary tumor was not treated as an event of RFS. OS was defined as the time from randomization to death from any cause, and was censored at the final follow-up date.

Toxicity was evaluated according to National Cancer Institute Common Toxicity Criteria (version 2).

Study Treatment

Chemotherapy

Four courses of doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2 (AC) administered intravenously on day 1 every 3 weeks were followed by 12 courses of weekly paclitaxel 80 mg/m^2, prior to radiation therapy and surgery. Although the method of premedication was left to the judgment of each investigator, administration of 5-HT3 antagonist and dexamethasone was strongly recommended on the AC regimen. Dexamethasone was given before weekly paclitaxel.

Dose Modification. AC could be postponed for a maximum of 16 days if the ANC was <1,500/mm^3 or the platelet count was <75,000/mm^3. If any nonhematological toxicity except for alopecia did not recover to grade 1 during this period, the protocol treatment had to be discontinued.

Paclitaxel could be postponed for a maximum of 16 days if the ANC was <1,000/mm^3 or the platelet count was <75,000/mm^3. If any nonhematological toxicity except for alopecia, neuropathy (motor, sensory), edema, arthralgia, and myalgia did not recover to grade 1, and if alopecia, neuropathy (motor, sensory), edema, arthralgia, and myalgia did not recover to within grade 2 during this period, the protocol treatment had to be discontinued.

Radiation Therapy

Patients received radiation therapy after the completion of chemotherapy. Radiation therapy with a dose of 45 Gy in 25 fractions over 5 weeks using tangential fields to the whole breast followed by a 10-Gy boost in 5 fractions over 1 week to the original tumor region was delivered.

Surgery

Twelve to 16 weeks after the completion of sequential chemoradiation therapy, patients underwent appropriate surgery according to the size and position of the primary tumor. The surgical margin in lumpectomy specimens had to be free of invasive or noninvasive breast cancer; otherwise a repeat excision had to be performed. Sentinel lymph node biopsy was allowed for clinical N(–) patients before chemoradiation therapy.

Hormone Receptor and HER2 Overexpression

Estrogen receptor (ER) status and progesterone receptor (PgR) status were determined by immunohistochemistry at each institute. Tumors with >10% positively stained tumor cells were classified as positive for ER and PgR. HER2 status was also determined at each institute by immunohistochemistry or by fluorescence in situ hybridization (FISH) analysis. HER2-positive tumors were defined as 3+ on immunohistochemistry staining or as positive by FISH.

Study Design and Statistical Methods

This trial was designed to evaluate safety and efficacy in terms of the pCR rate of preoperative sequential chemoradiation therapy. In this study, the sample size was determined to be 104 patients, considering: (1) providing at least 90% power with a one-sided alpha of 0.05 based on an expected pCR rate of 50% and a threshold of 35%, and (2) having the 95% CI of the estimated pCR rate within ±10% around 50% for sufficient precision of pCR in order to support decision-making for a next phase trial.

If the null hypothesis of the primary endpoint is rejected, a preoperative sequential chemoradiation therapy will be considered as a promising investigational new regimen in a proceeding phase III trial which compares nonsurgery to surgery after preoperative chemoradiation therapy.

Statistical analyses were performed with SAS release 9.1 (SAS Institute, Cary, N.C., USA). This trial was registered UMIN-CTR (www.umin.ac.jp/ctr/) as No. C000000114.

Interim Analysis for Futility and Monitoring

In this phase II trial, an interim analysis was planned once for futility when the 7th eligible patient's pathological response was evaluated. If there was at least one pCR case, registration was continued. If the true pCR rate were as expected (50%), the probability of no pCR case among the first 7 eligible patients would be less than 1%; thus, the registration was to be discontinued for futility. The JCOG Data and Safety Monitoring Committee (DSMC) independently reviews the interim analysis report and recommends that the trial either be continued or terminated early. Central monitoring is performed every 6 months by the JCOG Data Center to evaluate and improve study progress and quality.

Results

Patient Characteristics

Between June 2004 and April 2005, one hundred eight patients were prospectively enrolled from 29 institutions. As no patient was ineligible, 108 patients were assessed for safety and efficacy. First 7 successive eligible patients were analyzed to evaluate interim pathological efficacy according to the protocol. None of them showed a pathologically complete response, which made the DSMC recommend discontinuation of the trial. At the time of the recommendation of the DSMC, patient accrual was completed because the patient enrollment rose rapidly beyond our expectations. For the patient who had not undergone preoperative radiation therapy, the preoperative treatment was changed to the standard therapy (preoperative AC-weekly paclitaxel followed by surgery ± postoperative radiation therapy) after the recommendation of the DSMC. Thus, 82 patients completed the protocol treatment and 9 discontinued the treatment due to aggravation of the primary tumor,

Table 1. Patient characteristics

	Patients (n)	%
Total	108	
Age, years		
Median (range)	50 (23–69)	
Tumor size		
T1c	1	1
T2	104	96
T3	3	3
Axillary nodal status		
N0	54	50
N1	52	48
N2	2	2
Stage		
I	1	1
IIA	52	48
IIB	51	47
IIIA	4	4
IIIB	0	0
ER and PR		
Both negative	39	36
Either one positive	67	62
Unknown	2	2
HER2		
Overexpression	34	31
Negative	71	66
Unknown	3	3
Histological type		
Invasive	107	99
DCIS	1	1
Histological grade		
1	19	18
2	34	31
3	27	25
Not assessed (not IDC)	6	6
Unknown	22	20
Sentinel LN biopsy		
Performed	12	11
Not performed	96	89

DCIS = Ductal carcinoma in situ; IDC = invasive ductal carcinoma; LN = lymph node.

while 7 and 5 terminated the treatment due to adverse events and patient refusal related to adverse events, respectively. Five patients discontinued due to a recommendation to change treatment modalities at the trial termination.

The median age of the eligible 108 patients was 50 years, and 54% of patients were premenopausal. One hundred four patients had T2 tumors (96%), with 3 patients having T3 tumors and 1 having T1 tumors (table 1). Thirteen patients had papillotubular tumors, with 19 patients having solid tubular tumors and 46 having schiras tumors. The remaining patients had other histological types.

The toxic effects in chemotherapy and radiation therapy are shown in tables 2 and 3.

Surgery

Of all of the eligible cases, 106 underwent surgery and 2 did not because of disease progression (breast conservation surgery in 96 and mastectomy in 10 including 1 patient who underwent mastectomy after breast conservation surgery because of a positive margin). The breast conservation rate was 88.9% (96/108). The breast conservation rate was 94.0% (78/83) if the analyzed patients were limited to those who completed the protocol therapy. Eight patients underwent reoperation 0–49 days after the initial surgery for reasons of positive surgical margins in 4, surgical wound dehiscence in 2, and other events in 2 patients.

Evaluation of Pathological Efficacy

Of all 106 surgical cases, 27 had pCR (complete) including 1 patient with residual tumor in the nodes, while 12 had pCR with ductal carcinoma in situ including 1 patient whose status of residual tumor in the nodes was unknown. The intention-to-treat analysis revealed that the pCR rate was 36.1% (39/108), which was lower than expected and could not reject the null hypothesis ($p = 0.44$). The pCR rate was 41.6% (37/89) if analysis was limited to patients who completed the protocol therapy. Recurrence status and the relationship between the pCR rate and hormone receptor (HR)/HER2 subtype are shown in table 4. Triple-negative breast cancer and HER2 one had a pCR rate of 52 and 57%, respectively, whereas luminal type cancer showed a pCR rate of 24%. Recurrence status including local and distant metastases differed very much from one subtype to another.

Clinical Efficacy Evaluation

Forty-six patients went into CR while 37 went into PR. The clinical complete response rate was 42.6% (46/108).

The RFS and OS are depicted in figures 1 and 2, respectively. The 4-year RFS and OS were 84.1% (95% CI 75.6–89.8) and 93.5% (95% CI 86.8–96.8), respectively.

Table 2. Treatment-related toxicities – chemotherapy

	AC (n = 108)		Weekly paclitaxel (n = 106)	
	all grades	grades 3 and 4	all grades	grades 3 and 4
Nonhematologic toxicities, n (%)				
Fatigue	55 (51)	2 (2)	52 (49)	1 (1)
Anorexia	52 (48)	3 (3)	23 (22)	1 (1)
Nausea	78 (72)	1 (1)	21 (20)	0
Mucositis/stomatitis	40 (37)	0	19 (18)	0
Vomiting	44 (41)	4 (4)	4 (4)	0
Febrile neutropenia	3 (3)	3 (3)	1 (1)	1 (1)
Neuropathy: motor	2 (2)	0	20 (19)	4 (4)
Neuropathy: sensory	3 (3)	0	83 (78)	4 (4)
Hematologic toxicities, n (%)				
Leukocytes	85 (79)	23 (21)	92 (87)	16 (15)
Hemoglobin	23 (21)	0	62 (58)	1 (1)
Platelets	1 (1)	0	0	0
Neutrophils	74 (69)	27 (25)	70 (66)	11 (11)
GPT	44 (41)	1 (1)	61 (58)	0

Table 3. Treatment-related toxicities – radiation therapy

	All grades	Grades 3 and 4
Early-phase toxicities, n (%)		
Radiation dermatitis	74 (83)	0
Radiation pneumonitis	0	0
Late-phase toxicities, n (%)		
Radiation dermatitis	54 (61)	0
Radiation pneumonitis	1 (1)	0

Eighty-nine patients who received radiation therapy as the protocol treatment were evaluated.

Table 4. Recurrence status and relationship between pCR rate and HR/HER2 subtype in all eligible 108 patients

Subtype	n	pCR, n (%)	Recurrence status		
			local, n	distant, n	total, n (%)
HR+/HER2–	46	11 (24)	2	8	10 (22)
HR+/HER2+	20	8 (40)	0	3	3 (15)
HR–/HER2–	25	13 (52)	2	4	6 (24)
HR–/HER2+	14	8 (57)	0	1	1 (7)
Unknown	2	0 (0)	0	0	0 (0)

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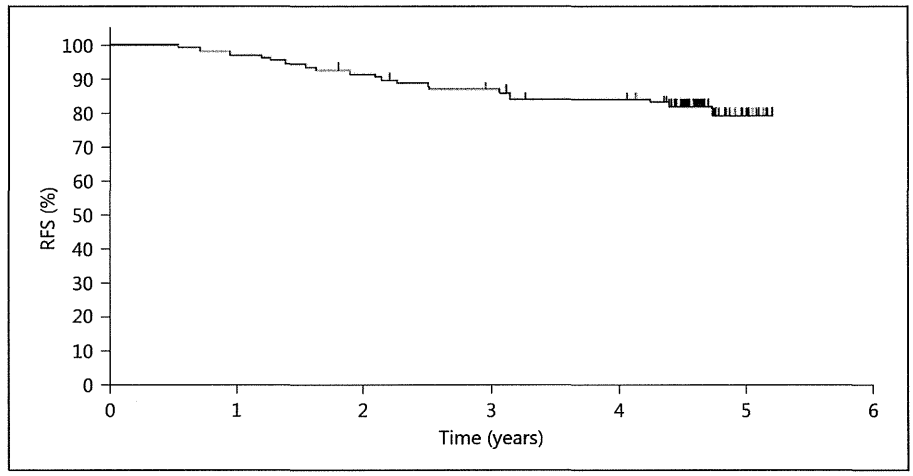

Fig. 1. RFS of the study patients.

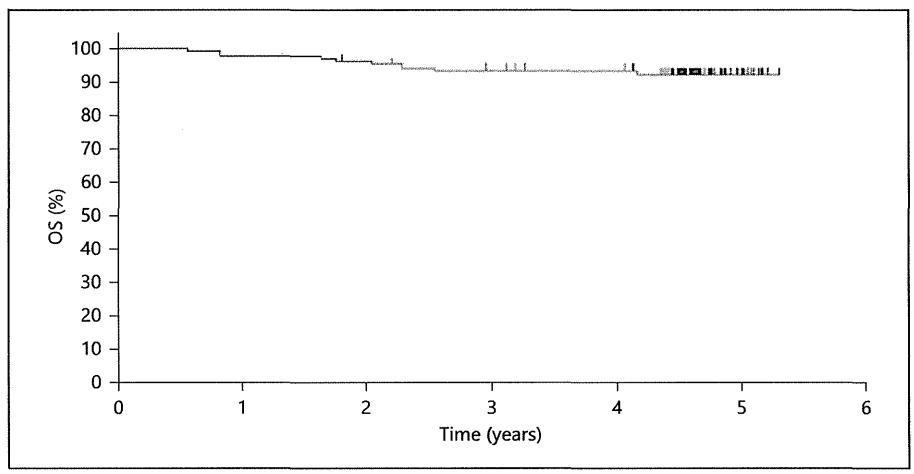

Fig. 2. OS of the study patients.

Discussion

This study was performed to evaluate the effect of chemotherapeutic regimens, which were expected to be most efficacious at the time of the start of this study, combined with radiation therapy using an index of a pCR rate. This study is significant in exploring effective systemic or local therapy.

This study showed that preoperative sequential chemoradiation therapy was effective and tolerable. Green et al. [10] reported a pCR rate of 30% in their study, where their chemotherapeutic regimen as well as their definition of a pCR rate was comparable to ours. Our pCR rate of 36.1% exceeded theirs by 10% or less in the local irradiated sites, which seem to explain our results.

On the other hand, pCR rates differed greatly between breast cancer subtypes. The triple-negative subtype as well as the HER2 subtype had a pCR rate higher than 50%, whereas the luminal subtype showed a pCR rate of 24%. More interestingly, recurrence rates differed very much from one subtype to another. These results revealed that the accuracy of prognosis estimation based on the pCR rate differed among subtypes although the pCR rate was assumed to be a surrogate marker of long-term survival. This is consistent with the results of a retrospective German study [11].

We did not achieve a pCR rate as expected in this study. To realize nonsurgical treatment in the future, it may be necessary to limit patients to those of a subgroup that is efficaciously treated with preoperative sequential chemoradiation therapy at least. The results of this study suggest that patients with HER2 subtype breast cancer may be candidates for such subgroups. Since this study was done before data of trastuzumab use in the adjuvant setting was published, the agent was not prescribed to patients with HER2-positive tumors in this trial. Many papers demonstrating the efficacy of preoperative use of an-

ti-HER2 agents, including trastuzumab, have been published [12, 13]. We are interested in a future study in which an anti-HER2 agent is added to preoperative sequential chemoradiation therapy in HER2-positive breast cancer. Especially, pCR of dual HER2 blockade therapy performed in the trial of Neosphere and NeoALLTO reached 50–60% [14, 15]; therefore, a dual HER2 blockade strategy will develop the possibility of nonsurgical treatment in the near future.

In conclusion, the expected percentage of pCR was not achieved even though preoperative sequential chemoradiation therapy did not increase the risk of operative complications and could achieve a high success rate of breast-conserving surgery.

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Disclosure Statement

The authors declare that they have no competing interests.

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ORIGINAL ARTICLE

The value of progesterone receptor expression in predicting the Recurrence Score for hormone-receptor positive invasive breast cancer patients

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Abstract
Background Oncotype DX® (ODX) is a well-validated assay for breast cancer treatment planning. We explored whether the conventional pathological factors could pick up high risk patients without the help of the ODX.
Methods The ODX was performed on 139 hormone receptor-positive invasive breast cancers in a single Japanese institution. The recurrence risk was compared between the ODX and the St. Gallen Consensuses. The correlations were analyzed between the Recurrence Score (RS) measured by ODX and the pathological factors. In addition, we performed a follow-up survey and examined the association of the RS with the confirmed recurrence or death.
Results The ODX classified 68 (49 %) as low RS, 52 (37 %) as intermediate RS, and 19 (14 %) as high RS cases. Correlations were noted between RS and progesterone receptor (PR) ($r = -0.53$), Ki-67 ($r = 0.42$), and nuclear grade (NG) ($r = 0.41$). None had a high RS with PR(3+) or NG1. Only one high RS patient had a Ki-67 (<20 %). The combinations of high RS with PR(0)/Ki-67 (≥20 %) and PR(1+)/Ki-67 (≥20 %) were 70 and 58 %, respectively. The combinations with high RS and PR(0)/NG3, PR(0)/NG2, and PR(1+)/NG3 were 83, 75, and 75 %, respectively. The median follow-up was 39.1 months (range 24.0 67.8). There were one low RS (1 %), four intermediate RS (8 %), and three high RS patients (16 %) who developed local or distant recurrence.
Conclusion Hormone receptor-positive invasive breast cancers are stratified with the combinations of PR/Ki-67 or PR/NG. Some of the high recurrence risk cases might be identified without the ODX.

Keywords Breast cancer · Oncotype DX · Progesterone receptor · Nuclear grade · Ki-67

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Introduction

Hormone receptor status is one of several clinicopathological tumor characteristics used for treatment planning and for assessing prognosis of early breast cancer. Hormone receptor-positive breast cancers generally do not benefit from chemotherapy. Only 15 % of patients with hormone receptor positive early breast cancers treated with tamoxifen alone recur over a 10-year period. Therefore, an estimated 85 % of these patients would be overtreated if adjuvant cytotoxic chemotherapy were universally administered [1]. The utilization of molecular genomic profiling has increased in recent years. Perou et al. [2] suggested that each breast cancer subtype might reflect intrinsic molecular differences in mammary epithelial biology. Sørlie et al. [3]

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suggested that the luminal epithelial estrogen receptor-positive group could be classified into at least two subgroups as defined by both hormone receptor and HER2 expression into luminal subtype A and luminal subtype B. Luminal A breast cancers have a low risk of relapse and luminal B breast cancers show a worse prognosis [4]. In addition, the clinical and pathologic response to chemotherapy is higher in the luminal B subtype than in the luminal A subtype [5]. For these reasons the distinction between luminal type breast cancers is of great clinical interest for treatment planning.

The Onco*type*DX® (ODX) is a clinically validated, 21-gene assay that predicts both the likelihood of distant recurrence and the magnitude of adjuvant chemotherapy benefit for patients with hormone receptor-positive breast cancer [1, 6]. The St. Gallen Expert Consensus, the National Comprehensive Cancer Network, and the American Society of Clinical Oncology guidelines have all described the application of both pathological markers and genomic profiling for breast cancer management [7–9].

In this study, we compared the results of the ODX with those of the St. Gallen Conferences. We also investigated the relationship between the Recurrence Score (RS) measured by the ODX and commonly used pathological factors to assess whether high recurrence risk cases could be identified without the ODX. In addition we performed a follow-up survey in this cohort.

Patients and methods

From October 2007 to October 2010, the ODX assay was performed on 139 hormone receptor-positive invasive breast cancer patients in our institution. To confirm the prognostic value of the ODX results, the risk categories were compared with the well-known St. Gallen 2007, 2009, and 2011 Consensuses [7, 10, 11]. In the St. Gallen 2007 Consensus, the use of nuclear grade was allowed [10]. The pathological evaluation with nuclear grading has clinically been widespread in Japanese institutions and mentioned in "General Rules for Clinical and Pathological Recording of Breast Cancer". We used the practical nuclear grading for the St. Gallen 2009 instead of histological grading. Second, the correlations between the RS and the conventional pathological factors were analyzed. The pathological factors consisted of tumor size (T), lymph node metastasis (N), nuclear grade (NG), lymphatic and vascular invasion (LI, VI), estrogen receptor (ER), progesterone receptor (PR), HER2, and Ki-67. The expression of ER and PR was measured with the Allred score. In brief, an Allred score 0 or 2 equated to 0, score 3 or 4 to 1+, score 5 or 6 to 2+, and score 7 or 8 to 3+. HER2 expression was evaluated by the HercepTest (Dako, Glostrup, Denmark). Ki-67 was identified with the MIB-1 antibody (Dako, Glostrup, Denmark) and was automatically scored with an Ariol-SL50 instrument (Applied Imaging) at Genetic Laboratory Co., Hokkaido, Japan. In brief, Ariol-SL50 was set up to remove stromal cells, inflammation cells by the nuclear shape and size. The intraductal lesion was excluded from the counting area. Ki-67 was calculated as the ratio of Ki-67-positive cancer cells to total cancer cells. The measurement counted more than 1,000 cancer cells/spot and was performed at 5 hot spots. The Ki-67 labeling index was calculated by the average of 5 hot spots. In addition we used the same tissue sections to examine Ki-67 and ODX. The cutoff value of Ki-67 was 14 % according to the St. Gallen 2011 Conference [11]. However, the Ki-67 staining and counting methods are different in each institution. A Ki-67 cutoff value of 20 % was the most approved of the St. Gallen 2013 expert panels for defining luminal B subtype [12]. In this study we adopted the practical and simple cutoff value of 20 %. The pathological diagnosis was performed under the supervision of one experienced pathologist (K.S.).

The patient characteristics are summarized in Table 1. The ages ranged from 25 to 73 years with a mean of 50 years. The numbers of premenopausal and postmenopausal patients were 82 (59 %) and 57 (41 %), respectively. Mastectomy specimens were available for 134 patients (96 %), and core biopsy samples were used for the others. Eighty patients (58 %) had tumors less than 2 cm in diameter. Eighty-three patients (60 %) had negative axillary nodes, 12 patients (9 %) had isolated tumor cells (ITC), five patients (4 %) had micrometastasis (pN1mi), and 34 patients (24 %) were pN1. Five patients (4 %) had more than four positive nodes. Sixty patients (43 %) were NG1, 44 patients (32 %) were NG2, and 35 patients (25 %) were NG3. Seventy-three patients were LI0 (53 %), and 122 patients were VI0 (88 %). In terms of the biological markers, 120 (86 %) women were ER(3+) and 79 (57 %) were PR(3+). Only one patient (1 %) had HER2 overexpression. Fifty-one patients (37 %) had low Ki-67 expression (<20 %) and 88 patients (63 %) had high Ki-67 expression (≥20 %).

In 68 low RS cases, 67 patients were treated with adjuvant hormonal therapy alone and one patient received no treatment. In 52 intermediate RS cases, 15 patients were treated with adjuvant chemotherapy followed by hormonal therapy and the others received hormonal therapy alone. In 19 high RS cases, all patients were treated with adjuvant chemotherapy followed by hormonal therapy.

Spearman rank correlation coefficients were calculated. When the r was >0.4 or <-0.4 for two factors, they were considered correlated. Kaplan Meier analysis was used to calculate and visually display disease free survival curves; a log-rank test was used to compare curves. These analyses were performed with StatView for Windows version 5 and IBM SPSS Statistics version 20.

Table 1 Patient characteristics

		Number	%			Number	%
Age (mean, range)	(50.4, 25 73)			Lymphatic invasion			
Menopausal state					0	73	53
	Premenopausal	82	59		1	51	37
	Postmenopausal	57	41		2	8	6
Specimen					3	2	1
	Biopsy	5	4		Unknown	5	4
	Mastectomy	134	96	Vascular invasion			
Tumor size					0	122	88
	T1a (≤ 0.5)	3	2		1	11	8
	T1b (> 0.5 to ≤ 1.0)	16	12		2	1	1
	T1c (> 1.0 to ≤ 2.0)	61	44		Unknown	5	4
	T2 (> 2.0 to ≤ 5.0)	54	39	Estrogen receptor			
	T3 ($5.0 <$)	4	3		0	1	1
	T4b	1	1		1+	3	2
Lymph node status					2+	15	11
	pN0	83	60		3+	120	86
	ITC	12	9	Progesterone receptor			
	pN1mi	5	4		0	14	10
	pN1	34	24		1+	14	10
	pN2	4	3		2+	32	23
	pN3	1	1		3+	79	57
Nuclear grade				HER2			
	1	60	43		0	75	54
	2	44	32		1+	39	28
	3	35	25		2+	24	17
					3+	1	1
				Ki 67			
					< 20 %	51	37
					≥ 20 %	88	63

Results

RS and the St. Gallen Conferences

The ODX assay revealed 68 (49 %) low RS cases, 52 (37 %) intermediate RS cases, and 19 (14 %) high RS cases. The comparison between the St. Gallen 2007 and RS is described in Fig. 1a. Nearly all of the cases in the intermediate risk group were incorrectly classified under the St. Gallen criteria. The comparison between the St. Gallen 2009 and RS is shown in Fig. 1b. We used the practical nuclear grading for the evaluation of tumor proliferation, but histological grading was only mentioned in the St. Gallen 2009 Consensus. HT denotes a relative indication for hormonal therapy alone. CT denotes a relative indication for chemotherapy. The high RS cases were appropriately classified into the HT + CT group; however, some low RS cases were also included in this group. The comparison between the St. Gallen 2011 and RS is shown in Fig. 1c. Most of the high RS cases were included in the luminal B group; however, some low RS cases were also classified into the luminal B group.

RS and pathological factors

PR and RS were negatively correlated ($r = -0.53$). No high RS had PR(3+) (Fig. 2a). Correlations between RS and Ki-67 or NG were also identified ($r = 0.42$ and 0.41, respectively) (Fig. 2b, c). There was no high RS patient with NG1. There was only one high RS patient (2 %) with Ki-67 (<20 %). On the other hand, the correlations with T, N, LI, VI, ER, and HER2 were weaker (r ranging from -0.33 to 0.22) (Table 2).

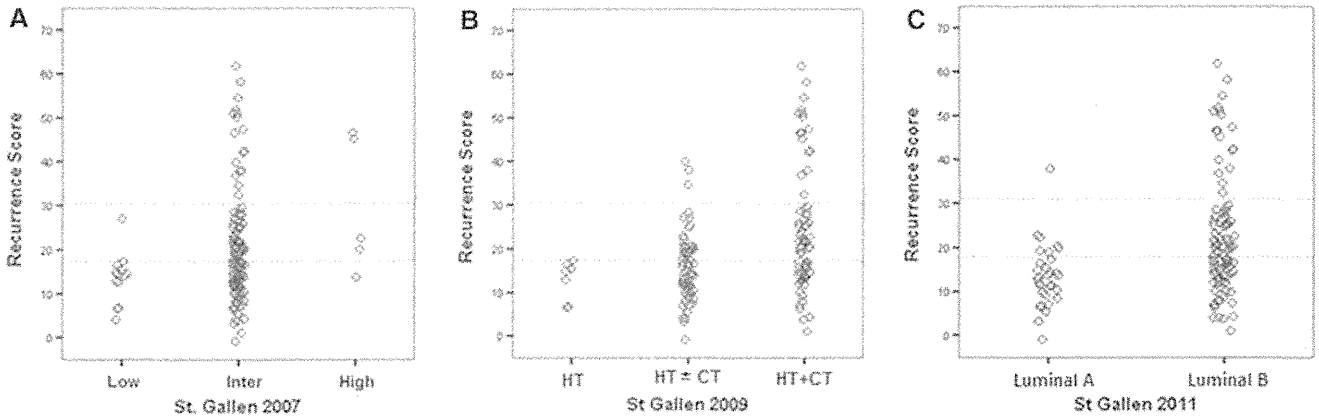

Fig. 1 **a** Comparison between St. Gallen 2007 and RS. Nearly all of the cases in the intermediate risk group were incorrectly classified under the St. Gallen criteria. **b** Comparison between St. Gallen 2009 and RS. We used the practical nuclear grading for the evaluation of tumor proliferation, but histological grading was only mentioned in the St. Gallen 2009 Consensus. HT denotes a relative indication for hormonal therapy alone. CT denotes a relative indication for chemotherapy. The high RS cases were appropriately classified into the HT + CT group. However, some low RS cases were also included in this group. **c** Comparison between St. Gallen 2011 and RS. Most of the high RS cases were included in the luminal B group. However, some low RS cases were also classified into the luminal B group

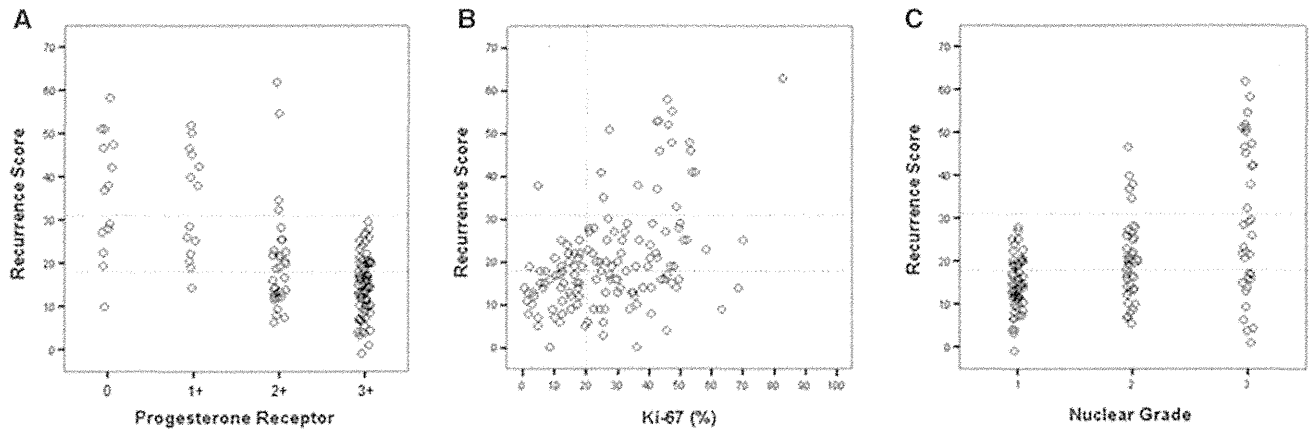

Fig. 2 **a** Correlation between PR and RS was negatively correlated with RS (r 0.53). No patients had high RS with PR(3+). **b** A correlation between Ki 67 and RS was observed (r 0.42). Only one patient (2 %) had high RS with Ki 67 (<20 %). **c** Correlation between NG and RS was observed (r 0.41). There was no high risk patient in the NG1

PR and Ki-67 in the high RS cases

The rate of high RS with PR(0) and Ki-67 (≥20 %) was 70 %, that of PR(1+) and Ki-67 (≥20 %) was 58 %, and that of PR(2+) and Ki-67 (≥20 %) was 21 % (Fig. 3a).

PR and NG in the high RS cases

Among the high RS cases, the rate of PR(0) and NG3 was 83 %, that of PR(0) and NG2 was 75 %, and that of PR(1+) and NG3 was 75 %. There was no high RS patient with PR(3+) or NG1 (Fig. 3b).

Disease free survival

The median follow-up for all patients after the operation was 39.1 months (range 24.0 67.8). Kaplan Meier curves for disease free survival of the St. Gallen Consensuses are shown in Fig. 4. There was no recurrence case in the low risk group of the St. Gallen 2007, the HT group of the St. Gallen 2009 and the luminal A group of the St. Gallen 2011 (a log-rank test was not available). There were one low RS (1 %, RS = 17), four intermediate RS (8 %, RS = 28, 25, 24, and 19), and three high RS patients (16 %, RS = 48, 46, and 33) who developed local or distant recurrence (Fig. 4d). Of these cases only one high RS patient (RS = 46) was dead 9 months following surgery as a result of multiple bone and lung metastases.

Discussion

Cheang et al. [13] reported that breast cancers could, in clinical practice, be classified into subtypes based on the

Table 2 Correlations between pathological factors and RS

Pathological factor	*r*
Progesterone receptor	0.526
Ki 67	0.422
Nuclear grade	0.411
Estrogen receptor	0.332
HER2	0.224
Lymph node status	0.193
Tumor size	0.161
Lymphatic invasion	0.117
Vascular invasion	0.056

Spearman rank correlation coefficients were calculated. When the *r* was >0.4 or < 0.4 for two factors, they were considered correlated

immunohistochemical (IHC) evaluation of ER, PR, HER2, and Ki-67. They also defined the cutoff value of the Ki-67 labeling index at 13.25 % to classify the luminal type breast cancers. Cuzick [14] also reported that these four IHC biomarkers (IHC4 score) provide prognostic information, which could be considered at least equivalent to the RS. By using these IHC biomarkers many physicians risk stratify each patient and plan treatment on the basis of risk and biomarkers.

Molecular genomic profiling is integral to the postoperative treatment planning of breast cancer patients. Eighty-four percent of the Expert Panel of the 12th St. Gallen Consensus Meeting approved the ODX to predict the effectiveness of adjuvant chemotherapy in hormone receptor-positive disease. In this study, we compared the risk classification of the St. Gallen Conferences with the ODX and found that the St. Gallen Consensuses were of limited usefulness for the risk classification of the luminal B subgroup because the treatment strategies were not suitable for all patients. The St. Gallen Consensuses require further refinement in order to prevent over- and under-treatment of luminal B breast cancer patients.

Most molecular profiling assays are costly and generally not covered by medical insurance, which poses a barrier to universal adoption. Klein et al. [15] reported that the use of pathology-generated equations could be used to estimate the RS for breast cancer patients. Ingoldsby et al. [16] also suggested that the combinations of traditional pathological parameters and biomarkers corresponding to 10 genes (ER, PR, Ki-67, HER2, BCL2, CD68, aurora A kinase, surviving, cyclin B1, and BAG1) could be used as an alternative to the RT-PCR assay to reduce the number of patients that need further analysis by the ODX. In light of their studies we assessed whether commonly used pathological factors could substitute for the RS. Our results indicated that the RS was moderately correlated with PR, Ki-67, and NG. Cancello et al. [17] reported that the ER(+)/PR(−)/HER2(−) subgroup was associated with a reduced breast cancer-related survival and overall survival when compared with the ER(+)/PR(+)/HER2(−) subgroup. They concluded that the loss of PR identified luminal B breast cancer subgroups at higher risk of relapse and death, both with HER2-positive and HER2-negative disease. Kurebayashi et al. [18] indicated that hormonal therapy alone could not prevent distant metastasis with PR-negative breast cancers and/or with cancers showing marked lymphovascular invasion or high Ki-67 labeling index in a Japanese multi-institute cohort study. The significance of IHC assessment of PR was also emphasized in the St. Gallen International Breast Cancer Conference 2013 [12]. Prat et al. [19] reported that the new proposed IHC-based definition of luminal A tumors was hormone receptor-positive/HER2-negative/Ki-67 less than 14 % and PR more than 20 %. With respect to hormonal therapy, the ER(+)/PR(+) subgroup shows a better response to selective ER modulator therapy than ER(+)/

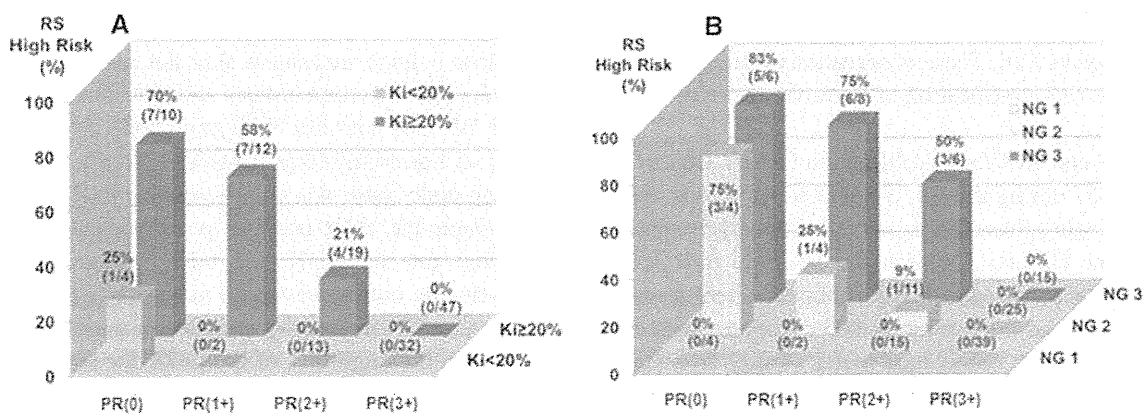

Fig. 3 **a** PR and Ki 67 in the high RS cases. The rate of high RS with PR(0) and Ki 67 (≥20 %) was 70 %, that of PR(1+) and Ki 67 (≥20 %) was 58 %, and that of PR(2+) and Ki 67 (≥20 %) was 21 %. **b** PR and NG in the high RS cases. Among the high RS cases, the rate of PR(0) and NG3 was 83 %, that of PR(0) and NG2 was 75 %, and that of PR(1+) and NG3 was 75 %. There was no high RS patient with PR(3+) or NG1

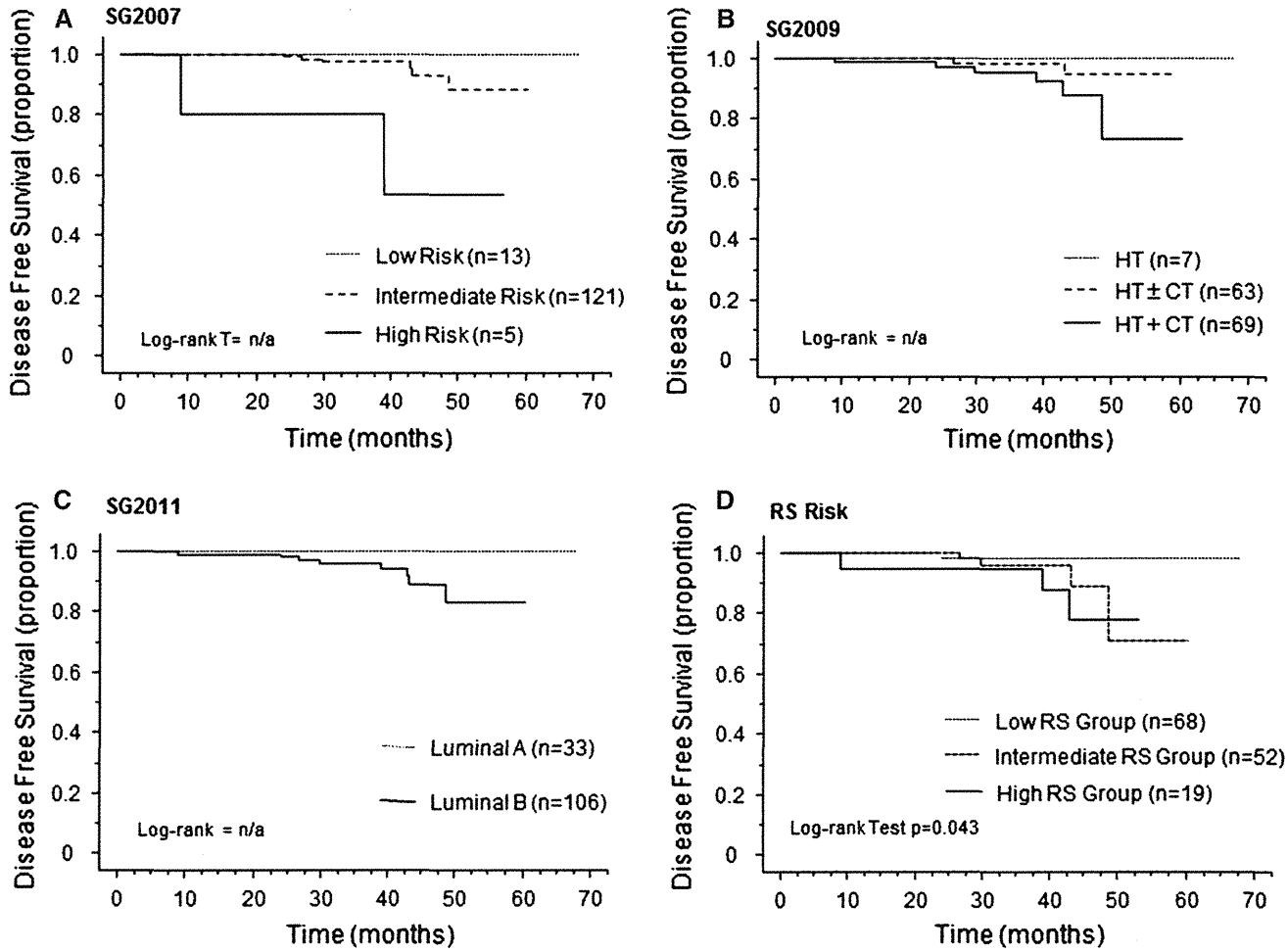

Fig. 4 Kaplan Meier curves for disease free survival. St. Gallen **a** 2007, **b** 2009, **c** 2011, **d** RS group. There was no recurrence case in the low risk group of St. Gallen 2007, the HT group of St. Gallen 2009 and the luminal A group of St. Gallen 2011 (a log rank test was not available)

PR(−) cancers. PR is a marker of a functional ER, and the expression of PR approximates ER activity. In addition, it has been suggested that the absence of PR may reflect hyperactive cross talk between ER and growth factor signaling pathways [20]. These observations increase the value of PR in the risk stratification of hormone receptor-positive breast cancer.

Both NG and Ki-67 are proliferation factors. Cancer cells express Ki-67 during the G1, S, G2, and M phases, but not during the resting phase G0. In particular, the expression level is low in the G1 and S phases and peaks in mitosis [21]. Nuclear grade is defined as the sum of both nuclear atypia and mitotic count. For these reasons, NG correlates with Ki-67 expression. Ki-67 is widely used to risk stratify breast cancer [13]; however, our data failed to show a perfect correlation between Ki-67 and the RS, suggesting that Ki-67 itself is insufficient for risk stratification. We combined PR and Ki-67 or PR and NG and found that this combination of factors resulted in comparable risk stratification as obtained with ODX. In contrast, N, T, LI, and VI, which are also highly prognostic clinical factors in early breast cancers, did not correlate with the RS in this study. With regard to lymph node metastasis, it was reported that the routine use of IHC to look for low volume metastasis was not indicated, because the presence of micrometastasis did not change management [11]. We also consider that lymph node metastasis is not so fatal to hormone receptor-positive breast cancers because lymph node status was poorly relative to RS ($r = -0.193$). Although the node-positive postmenopausal patients are eligible for the ODX, the node-positive premenopausal patients are not; however, 20 node-positive premenopausal cases (24 %) are actually included in this study. We should ascertain the eligibility of the ODX for the premenopausal node-positive breast cancer patients in the RxPONDER trial (SWOG S1007), which is an ongoing clinical trial designed to address this question.

This study was limited in terms of generalizability by the selection of patients from a single institution. All cases,

however, were reviewed and analyzed by a single pathologist, which resulted in consistent scoring.

We propose that the combinations of PR/NG or PR/Ki-67 be used to select patients for further risk stratification via ODX.

Conclusions

Hormone receptor-positive invasive breast cancers are stratified with the combinations of PR/Ki-67 or PR/NG. Some of the high recurrence risk cases might be identified without the ODX.

Conflict of interest The authors declare that they have no conflict of interest.

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Morphological characteristics of and factors related to moisture-associated dermatitis surrounding malignant wounds in breast cancer patients

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Breast cancer
Malignant fungating wound
Wound care
Palliative
Nursing
Qualitative study

A B S T R A C T

Purpose: Patients with malignant breast wounds (MBWs) have multiple symptoms. In particular, care for exudates or peri wound moisture associated dermatitis (MAD) is difficult. However, MAD has not been distinguished from peri wound dermatitis. Therefore, care for patients with MAD has not been well established. The aim of this study was to describe morphological characteristics of MAD in MBWs and link morphological characteristics of MAD to related factors.
Methods: We conducted a qualitative descriptive study and a cross sectional study. Data were collected by qualitative participant observation and structured interviews. The qualitative descriptive study was conducted using the 'morphoqualitative analysis' method. Data analyses were performed using quali tative research methods. In the cross sectional study, the participants were classified into 2 groups for comparison: with MAD (MAD group) and without MAD (non MAD group).
Results: Characteristics of 24 MBWs were examined. Morphoqualitative analyses of data generated 17 subcategories and 3 categories. We could morphologically define MAD by findings of 'radial shape matching the dressing' and 'half fusiform shape over the dressing'. Regarding factors related to MAD, necrotic tissue type was significantly more severe in the MAD group than in the non MAD group ($p = 0.048$). Wound exudate leakage was significantly more frequent in the MAD group than in the non MAD group ($p = 0.013$).
Conclusion: Our study provides several points for nursing MBWs. Morphoqualitative analyses of MAD are quite important for evaluating possible causes of MAD as well as selecting effective interventions.

Introduction

Breast cancer is the most frequent malignancy in women (Jemal et al., 2011) and is one of the most common neoplasms metasta sizing to the skin (Koga et al., 2010). In particular, any infiltration of the epithelium by tumour cells is defined as a malignant wound (Ashino, 2007). The prevalence rates of malignant wounds in women with breast cancer have been unclear, but previous studies have reported frequencies ranging from 12.1% to 66.3% in patients with metastatic cancer (Koga et al., 2010; Maida et al., 2008).

Malignant breast wounds (MBWs) have multiple symptoms, including exudates, bleeding, pain, odour and problems with the peri wound skin (Maida et al., 2009; Merz et al., 2011; Naylor, 2002; Probst et al., 2009; Schulz et al., 2002). No optimum care protocols for exudates or for the peri wound skin have been established. Everyday control of massive wound exudates over flowing dressings may be very difficult for patients or nurses and

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may result in peri wound moisture associated dermatitis (MAD) (Probst et al., 2009). However, there have been very few studies on MAD in relation to MBWs. Schulz et al. (2002) suggested a number of peri wound problems associated with MBWs, including skin irritation and breakdown, on the basis of caregiver interviews; however, they could not distinguish MAD from peri wound dermatitis caused by other factors (e.g. inflammation associated with cancer, irritated skin by tape or radiodermatitis) (de Haes et al., 2003; Diggelmann et al., 2010; Gray et al., 2011; Murakami et al., 2001; Japanese Nursing Association Wound Care Committee, 2002; Porock and Kristjanson, 1999; Sussman and Bates Jensen, 2007). Their study (Schulz et al., 2002) was also limited by the fact that data were obtained from caregivers and not clinicians.

Many patients with MBWs may not want to be examined by clinicians because of fear, anxiety or stigma related to the appear ance of their MBWs, and this may be the reason why peri wound dermatitis surrounding MBWs remains problematic for clinicians. However, to improve the patient's quality of life, peri wound dermatitis should be intensively investigated in a qualitative manner. We consider that nurses have an advantage when con ducting clinical research related to peri wound dermatitis and MAD in patients with MBWs because compared with doctors, nurses can build a more intimate rapport with their patients. In addition, the distinction between MAD and other forms of dermatitis may be important for nurses because they have more opportunities for direct intervention when treating MAD. We believe that the morphoqualitative analysis method, a nursing research method developed by our group (Nanjo et al., 2011), is a promising approach for further study of MAD surrounding MBWs. This is a form of qualitative research in which the detailed morphological characteristics of skin lesions and wounds on pho tographs are described verbally.

Previous studies have suggested a number of possible risk fac tors for MAD in patients with malignant wounds, including irritant wound exudates (Gray et al., 2011), skin fragility due to cancer therapy (de Haes et al., 2003) and a lack of wound management (Japanese Nursing Association Wound Care Committee, 2002; Sussman and Bates Jensen, 2007). However, the detailed relation ships between MAD and such factors have not been completely elucidated in relation to MBWs. Thus, this study aimed to describe morphological characteristics of peri wound dermatitis and MAD in MBWs using the morphoqualitative method described above and to link morphological characteristics of MAD to related factors, thereby exploring options for preventive nursing.

Materials and methods

Study design

We used a qualitative descriptive study design (morphoquali tative analysis) to identify morphological characteristics specific to MAD of MBWs because this is an appropriate format to determine the facts of the case and to better comprehend the phenomenon (Barker et al., 2002). In addition, in the second part of this study, we used a cross sectional design to identify factors correlated with MAD.

Participants

Patients were recruited between February 2010 and June 2011. The study setting was a breast centre based in a general hospital in Tokyo. The patients were selected on the basis of the following criteria: (i) presence of a malignant wound in an adult woman with breast cancer and (ii) presence of exudates.

We sequentially recruited patients from all 27 patients with MBWs. In total, 24 patients were included in the present study because 3 patients did not provide their consent to participate in the study.

Collection of demographic data

Demographic characteristics were collected from medical re cords by a single researcher and included the following: age, sex, duration of breast cancer, duration of skin infiltration or metastasis, hormone receptors, human epidermal growth factor receptor type 2 (HER 2), operative procedure, metastatic site, wound site, medi cal treatment (within 1 month), radiation therapy (within 90 days) (Cox et al., 1995; World Union Wound Healing Societies (WUWHS), 2007), employment status and comorbidities. A single researcher and attending nurse assessed the scale of performance status (PS) (Ando et al., 2001; Oken et al., 1982), which comprises 5 points (0: good; 4: poor) (Ando et al., 2001; Finkelstein et al., 1988).

Examination of malignant wounds and the surrounding skin

Data were collected by qualitative participant observation and by structured interviews during usual wound care at the outpatient clinic. Initially, the nursing researcher made every effort to estab lish an intimate rapport with the patients. To investigate the rela tionship between the peri wound skin and exposure of wound exudates, the researcher obtained detailed information concerning wound care by interviews and observation. For example, the researcher examined in detail how the dressing was attached to the skin. Moreover, photographs of the malignant wounds and the peri wound skin were taken from various directions by the researcher (N. T.) using a digital camera (RICHO10, RICHO Co., Tokyo, Japan). A commercially available reference colour chart with 9 calibrated colours (Casmatch, BEAR Medic Co., Chiba, Japan) (Iyatomi et al., 2009) was placed on the surrounding skin for ac curate colour description. A flash was not used.

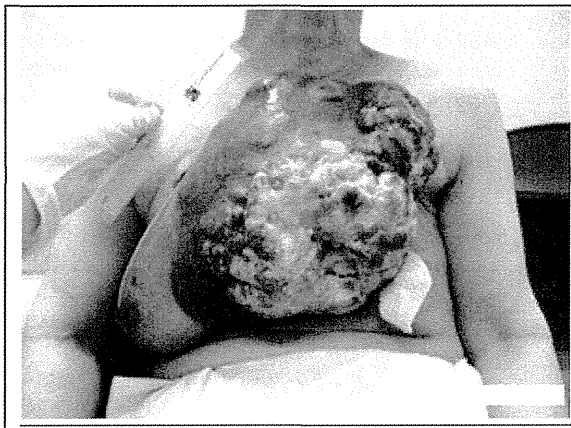
The patients' wounds and the condition of the surrounding skin were examined by visual inspection and by palpation (pressing down with a finger and pinching of tissues) (Bates Jensen et al., 1992; Sussman and Bates Jensen, 2007).

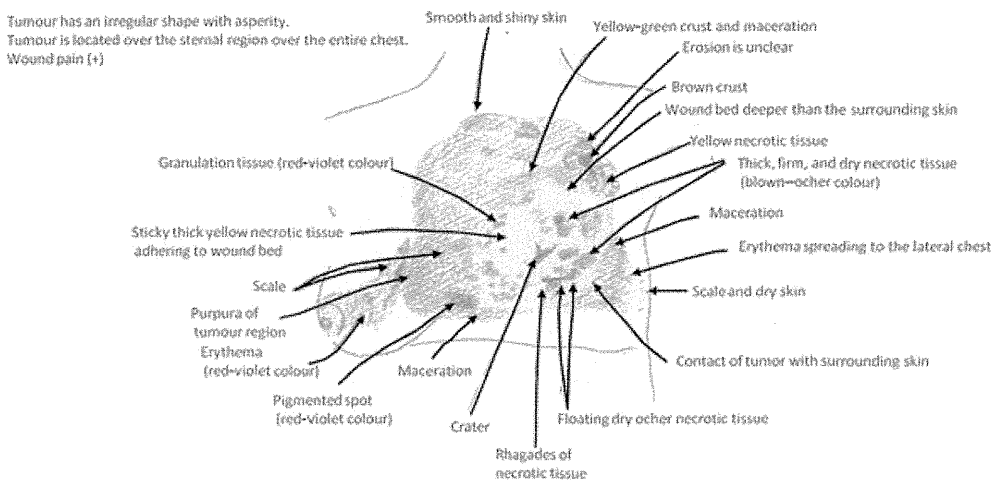
Morphoqualitative analysis of MAD

The qualitative descriptive part of the study was conducted using the morphoqualitative analysis method. This novel method was established by our research group and is a useful approach for qualitatively evaluating details related to wound/skin conditions, their time course and other related factors (Nanjo et al., 2011). De tails related to individual MBWs and the condition of the sur rounding skin were recorded by sketching the photographs and observation by N.T. (Fig. 1). Information from these records was then verbalised in detail to characterise the morphology of the wounds and the surrounding skin for each patient. The following data ana lyses were performed using standard protocols for qualitative nursing research (Gregg, 2008): First, verbal data were divided into multiple simple descriptive codes. Second, subcategories were generated by extracting similar codes for the skin surrounding the malignant wounds. The categories were generated from the same subcategories. The researcher then evaluated the data and derived a conclusion related to morphological characteristics of MAD.

Reliability of morphoqualitative data

Reliability of the data collected in this qualitative study, including their credibility, transferability and confirmability, was





Summary

Wound

The subcutaneous mass is located over the sternal region covering the entire chest. The malignant wound is located at the bottom, below the centre of the subcutaneous mass. The diameter of the subcutaneous mass is >10 cm. The malignant wound has an irregular shape and surface. The wound bed is deeper than the surrounding skin. There is another wound with erosion, an irregular surface, and a raised lump in the one o'clock direction. Thick, dry and ocher necrotic tissue is adhered to the wound bed. Floating red-violet granulation tissue with rhagades forms a part of the wound surface. The patient experienced wound pain.

Peri-wound skin

The raised mass is hard with purpura. The skin is smooth and shiny with a pigmented spot. Adhesive exudates and erosion are present at the wound edge between the 12 and 1 o'clock direction. Erosion of the subcutaneous tumour is also present in the 3 to 6 o'clock direction. In particular, the tumour is in contact with the surrounding skin in the 4 to 5 o'clock direction. Pink erythema and scale have spread to the lateral side of the chest. Red-violet erythema with scale has spread toward the nipple along the contralateral edge of the breast.

Fig. 1. Image and detailed description of a malignant breast wound as described in morphoqualitative analyses.

evaluated by Guba's model (Guba and Lincoln, 1989). Regarding credibility, the final subcategories, categories and conclusions regarding MAD were confirmed by consensus between the primary researcher and a wound ostomy continence nurse (WOCN, H. S.). Diagnoses of MAD were checked by a dermatologist (T. K.) and WOCN (H. S.). The intraclass correlation was then calculated. The kappa coefficient was 0.84. To test transferability, conclusions regarding MAD in this study were checked by 2 other nurses who worked in the same breast centre. They verified the documents, including the photographs of MBWs and explanations of morpho logical characteristics. Confirmability refers to the objectivity or neutrality of data interpretation, including the generation of sub categories and categories. In this study, the relevance of the data was reviewed and the interpretation was supervised by 2 wound

care researchers (WOCN, H. S. and M. O.), who reached an agree ment with the principal investigator.

Data collection related to parameters that may be related to MAD

To identify factors correlated with MAD, we also collected the following data: In addition to the demographic and wound/skin morphological data described above, the items on the Bates Jensen wound assessment tool (BWAT) (Bates Jensen et al., 1992) and the malignant wound assessment tool for research (MWAT R) (Schulz et al., 2009) were evaluated as parameters of MBWs. BWAT con sists of 13 items: size, depth, edges, undermining, necrotic tissue type, necrotic tissue amount, exudate type, exudate amount, skin colour of the surrounding wound, peripheral tissue oedema, induration, granulation tissue and epithelialisation. The surface area, height, site (flexure part or flat part) and classification (fun gating or ulcerative) of MBWs were collected from MWAT R. The validity and reliability of BWAT and MWAT R have already been confirmed previously (Bates Jensen et al., 1992; Schulz et al., 2009). The same researcher evaluated the items derived from these assessment tools throughout the study. Inter rater reliability of BWAT was evaluated by calculating the rate of agreement on scores for 24 photographs of MBWs by a plastic surgeon (T. N.), WOCN (H. S.), and the researcher (r 0.72–0.91 for each item). The area of the lesion was measured 3 times from each photograph using Image J software (National Institutes of Health, Maryland, USA), and the median value was used. The tumour height of MBWs was estimated using Schulz's method with a cotton tipped applicator (Schulz et al., 2009).

The following data related to wound management within the preceding month were collected by the participant–observer study (Savage, 2000) and to the structured interview: washing method, number of wound dressing changes, type of dressing, type of ointment, fit of dressing and leakage of wound exudates (Grocott, 1997, 1998; Grocott and Cowley, 2001).

Data related to physical condition and quality of life were collected from medical charts, participant observation or struc tured interview and included laboratory blood investigations, PS (Alexander, 2009; de Haes et al., 2003), pain, upper extremity lymphoedema, mobility of the arm, weakness of the skin, self care, care support and occupation.

Statistical analysis of factors related to MAD

The participants were classified into 2 groups on the basis of the characteristics in the abovementioned morphoqualitative analysis: those with MAD (MAD group) and those without MAD (non MAD group). The data were then compared between the 2 groups. Values were represented with the median (range) unless otherwise indi cated. Differences between the two groups were analysed using Fisher's exact test or the Mann–Whitney U test. A p value <0.05 was considered statistically significant. All analyses were per formed using Statistical Analysis System Ver. 9.2 (SAS Institute Inc., Cary, NC, USA).

The protocol was approved by the Ethical Committee of the Graduate School of Medicine, The University of Tokyo and by St. Luke's International Hospital, Japan. Written informed consent was obtained from all the participants.

Results

Twenty four patients were eligible for participation in the study. Patient characteristics are summarised in Table 1. The median age (range) was 62.0 (36–81) years, and the median duration of experience of malignant wounds was 14.5 (1–87) months. The breast was the most common site of malignant wounds, accounting for 66.6% of all cases. Malignant wounds located on the trunk and upper arms were also included as MBWs if they were derived from breast cancer.

Table 1
Patient characteristics.

			n 24
Age (years)			62.0 (36 81)
Duration of breast cancer (months)			57.5 (3 161)
Duration of malignant wound (months)			14.5 (1 87)
Oestrogen receptor	Positive		13 (54.2)
	Negative		11 (45.8)
Progesterone receptor	Positive		11 (45.8)
	Negative		13 (54.2)
HER-2	Positive		10 (41.7)
	Negative		14 (58.3)
Operation type	Yes	Partial mastectomy	1 (4.2)
		Partial mastectomy + axillary dissection	2 (8.3)
		Total mastectomy	1 (4.2)
		Total mastectomy + axillary dissection	7 (29.1)
	No		13 (54.2)
Metastases[a]	Lung		11 (45.8)
	Liver		5 (20.8)
	Bone		11 (45.8)
	Brain		0 (0.0)
Location of malignant wounds	Breast		16 (66.6)
	Sternal region		3 (12.5)
	Axilla		3 (12.5)
	Thoracoabdominal dorsal region		1 (4.2)
	Brachial region		1 (4.2)
Treatments[a]	Hormone therapy		6 (25.0)
	Chemotherapy		17 (70.8)
	Molecular-targeted therapy		7 (29.2)
	Radiation therapy (local)		0 (0.0)
Performance status	Completely active		3 (12.5)
	Restricted in physically strenuous activity		13 (54.2)
	Ambulatory and capable of self care		6 (25.0)
	Capable of only limited self care		2 (8.3)
	Cannot perform any self care activities		0 (0.0)
Presence of job			3 (12.5)
Comorbidities[a]	Hypertension		4 (16.7)
	Hyperthyroidism		3 (12.5)
	Gynaecological disorder		3 (12.5)
	Diabetes		2 (8.3)
	Hyperlipidaemia		1 (4.2)
	Dermatomyositis		1 (4.2)
	Depression		1 (4.2)

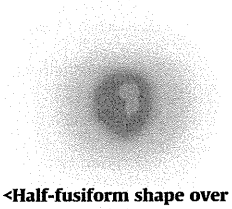
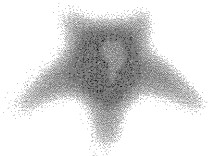
Median (range), n (%).
HER-2: human epidermal growth factor receptor type 2.
[a] Multiple answers.

Morphoqualitative characteristics of MAD

The characteristics of the 24 patients with 24 MBWs were examined by morphoqualitative analyses, which generated 17 subcategories and 3 categories.

Morphological characteristics of peri wound dermatitis associ ated with MBWs were divided into 3 categories: (1) type of skin lesion, (2) shape and (3) location. All the categories and sub categories are shown in Table 2. The type of skin lesion included the following subcategories: 'pigmentation', 'purpura', 'erythema', 'er ythema accompanied by purpura', 'erythema accompanied by wheal', 'erythema accompanied by erosion', and 'erythema accompanied by bulla, pustule, eschar and erosion'. Shape included the following subcategories: 'radial shape matching the dressing',

Table 2
Morphological characteristics of the peri-wound skin around the malignant breast wounds (*n* 24).

[Location]	[Shape]	[Type of skin lesion]
<Location matching the tape away from the malignant wounds (13)>	<Line shape matching the tape (13)>	<Pigmentation (2)> <Erythema (8)> <Erythema accompanied by wheal (2)>
<Periphery of malignant wounds (20)>	<Radial shape matching the dressing (16)>	<Pigmentation (8)> <Erythema (8)>
	 **<Half-fusiform shape over the dressing (4)>**	<Erythema accompanied by purpura (1)> <Erythema accompanied by wheal (1)> <Erythema accompanied by erosion (2)>
<Periphery of the breast (8)>	**<Half-fusiform shape over the dressing (7)>**	<Erythema (3)> <Erythema accompanied by purpura (1)> <Erythema accompanied by wheal (2)> <Erythema accompanied by erosion (1)>
	 <Radial shape matching the dressing (1)>	<Pigmentation (1)>
<*Elevated portion of the subcutaneous tumour* (17)>	<Shape matching the subcutaneous tumour (17)>	<Erythema (3)> <Purpura (14)>
<*Body trunk (carcinoma erysipelatodes or cancer en cuirasse)* (1)>	<Irregular shape spreading over the body trunk (1)>	<Erythema accompanied by bulla, pustule, eschar and erosion (1)>

[ ]: category, < >: subcategory, *Italic font*: cancer site, **Bold font**: newly detected shape, (): number of codes.

'half fusiform shape over the dressing', 'line shape matching the tape', 'shape matching the subcutaneous tumour', and 'irregular shape spreading over the body trunk'. Location included the following subcategories: 'location matching the tape away from the malignant wounds', 'periphery of malignant wounds', 'periphery of the breast', 'elevated portion of the subcutaneous tumour', and 'body trunk (carcinoma erysipelatodes or cancer en cuirasse)'.

We morphologically defined MAD related to wound exudates by participant observation using the characteristic 'radial shape matching the dressing' or 'half fusiform shape over the dressing' because these 2 characteristics were confirmed as evidence of wound exudates causing MAD by the agreement of the researcher, WOCN and a dermatologist. In particular, 'half fusiform shape over the dressing' was a novel morphological characteristic that has never been reported for any other type of wound/dermatitis. The prevalence of MAD due to wound exudates according to our defi nition was 58.3%. In addition, the researcher, WOCN and a derma tologist defined dermatitis caused by the tape as having 'line shape matching the tape'. We defined dermatitis caused by direct inva sion of cancerous cells as having 'shape matching the subcutaneous tumour' or 'irregular shape spreading over the trunk'.

Factors related to MAD

The patients were classed as a part of the MAD group if they had 'radial shape matching the dressing' or 'half fusiform shape over the dressing' and as a part of the non MAD group if they had no peri wound dermatitis, 'line shape matching the tape' or 'shape matching the subcutaneous tumour'. The patient who had dermatitis of 'irregular shape spreading over the trunk' was excluded from subsequent analyses because of the complex path ophysiology (carcinoma erysipelatodes).

The characteristics of the patients in the 2 groups are shown in Table 3. No significant differences in demographic characteristics were observed between the 2 groups.

Table 3
Patient characteristics in each group (*n* 23).

		Moisture-associated dermatitis (MAD) group *n* 14	Non-MAD group *n* 9	*p* value
Age (years)		62.0 (36 81)	61.0 (39 75)	0.950[a]
Duration of breast cancer (months)		70.0 (7 161)	58.0 (3 127)	0.413[a]
Duration of malignant wounds (months)		15.5 (3 87)	14.0 (1 64)	0.776[a]
Oestrogen receptor	Negative	5 (35.7)	5 (55.6)	0.417[b]
	Positive	9 (64.3)	4 (44.4)	
Progesterone receptor	Negative	7 (50.0)	5 (55.6)	1.000[b]
	Positive	7 (50.0)	4 (44.4)	
HER-2	Negative	8 (57.1)	6 (66.7)	1.000[b]
	Positive	6 (42.9)	3 (33.3)	
Operation	Yes	7 (50.0)	3 (33.3)	0.669[b]
	No	7 (50.0)	6 (66.7)	
Lung metastasis	Yes	8 (57.1)	3 (33.3)	0.400[b]
	No	6 (42.9)	6 (66.7)	
Liver metastasis	Yes	3 (21.4)	2 (22.2)	1.000[b]
	No	11 (78.6)	7 (77.8)	
Bone metastasis	Yes	7 (50.0)	4 (44.4)	1.000[b]
	No	7 (50.0)	5 (55.6)	
Location of malignant wounds	Breast	8 (57.2)	8 (88.9)	0.092[b]
	Sternal region	3 (21.4)	0 (0.0)	
	Axilla	3 (21.4)	0 (0.0)	
	Brachial region	0 (0.0)	1 (11.1)	
Hormone therapy	Yes	4 (28.6)	2 (22.2)	1.000[b]
	No	10 (71.4)	7 (77.8)	
Chemotherapy	Yes	9 (64.3)	7 (77.8)	0.657[b]
	No	5 (35.7)	2 (22.2)	
Molecular-targeted therapy	Yes	4 (28.6)	3 (33.3)	1.000[b]
	No	10 (71.4)	6 (66.7)	
Performance status	≤1	8 (57.1)	8 (88.9)	0.176[b]
	≥2	6 (42.9)	1 (11.1)	

Median (range), *n* (%).
HER-2: human epidermal growth factor receptor type 2.
[a] Mann Whitney *U* test.
[b] Fisher's exact test.

Table 4
Factors related to moisture-associated dermatitis (MAD) in breast cancer patients with malignant wounds (wound-related factors) (n 23).

		MAD group n 14	Non-MAD group n 9	p value
BWAT				
Size	≤80 cm^2	10 (71.4)	7 (77.8)	1.000[b]
	>80 cm^2	4 (28.6)	2 (22.2)	
Depth	Shallow crater	2 (14.3)	3 (33.3)	0.343[b]
	Deep crater	12 (85.7)	6 (66.7)	
Edges	Attached	5 (35.7)	3 (33.3)	1.000[b]
	Not attached	9 (64.3)	6 (66.7)	
Undermining	No	12 (85.7)	9 (100.0)	0.502[b]
	Yes	2 (14.3)	0 (0.0)	
Necrotic tissue type	Thin yellow or less	8 (57.1)	9 (100.0)	0.048[b]
	Thick yellow or black	6 (42.9)	0 (0.0)	
Necrotic tissue amount	≤50%	9 (64.3)	6 (66.7)	1.000[b]
	>50%	5 (35.7)	3 (33.3)	
Exudate type	Serous	4 (28.6)	5 (55.6)	0.383[b]
	Purulent	10 (71.4)	4 (44.4)	
Exudate amount	Small	2 (14.3)	5 (55.6)	0.066[b]
	Moderate or large	12 (85.7)	4 (44.4)	
Skin colour surrounding wound	White or grey	2 (14.3)	3 (33.3)	0.343[b]
	Dark red or purple	12 (85.7)	6 (66.7)	
Peripheral tissue oedema	No	3 (21.4)	5 (55.6)	0.179[b]
	Yes	11 (78.6)	4 (44.4)	
Peripheral tissue induration	No	4 (28.6)	4 (44.4)	0.657[b]
	Yes	10 (71.4)	5 (55.6)	
Granulation tissue	Bright, beef red	9 (64.3)	4 (44.4)	0.417[b]
	Pink, dusky-red	5 (35.7)	5 (55.6)	
Epithelialisation	≥50%	0 (0.0)	1 (11.1)	0.391[b]
	<50%	14 (100.0)	8 (88.9)	
MWAT				
Wound surface area (cm^2)		18.8 (4.2 222.5)	7.0 (0.2 113.1)	0.139[a]
Wound height (cm)		2.2 (−1.6 7.0)	0.7 (−2.0 4.5)	0.196[a]
Wound site	Flexure part	10 (71.4)	5 (55.6)	0.657[b]
	Flat part	4 (28.6)	4 (44.4)	
Wound classification	Fungating	7 (50.0)	8 (88.9)	0.086[b]
	Ulcerative	7 (50.0)	1 (11.1)	

Median (range), n (%).
BWAT: Bates-Jensen wound assessment tool, MWAT: malignant wound assessment tool.
[a] Mann Whitney U test.
[b] Fisher's exact test.

Among the variables related to wound status (BWAT and MWAT), necrotic tissue type was significantly more severe (thick, yellow or black necrotic tissue) in the MAD group than in the non MAD group (χ^2 5.22, p 0.048). A higher proportion of patients with a moderate or greater amount of exudate (BWAT score ≥4) tended to be found in the MAD group than in the non MAD group (χ^2 4.41, p 0.066) (Table 4).

Wound exudate leakage was also significantly more frequent in the MAD group than in the non MAD group (χ^2 7.08, p 0.013) (Table 5). There were no differences in variables related to physical condition and quality of life status between the 2 groups (data not shown).

Discussion

To the best of our knowledge, this is the first study to describe detailed morphological characteristics of MAD associated with MBWs. We were able to morphologically define MAD on the basis of findings of dermatitis in 'radial shape matching the dressing' and 'half fusiform shape over the dressing'. Notably, the 'half fusiform shape over the dressing' has not been reported for any other type of wound/dermatitis. According to our definition, MAD accounted for more than half of the cases of peri wound dermatitis examined. Furthermore, necrotic tissue type (thick and yellow or black necrotic tissue) and wound exudate leakage were related to MAD of MBWs.

We also confirmed the usefulness of the morphoqualitative analysis method for describing and defining MAD in this study. This method has been used in previous studies where wound mor phologies such as 'round', 'map', 'rhombic oval', 'line', 'butterfly' and 'leaf' shapes were identified (Fujimoto et al., 2004; Kinoshita et al., 2009; Nanjo et al., 2011). Notably, wound shapes analysed by this method can suggest possible causal factors such as changes in pa tients' positions and uncontrolled pressure (Fujimoto et al., 2004;

Table 5
Factors related to moisture-associated dermatitis (MAD) in breast cancer patients with malignant wounds (factors related to local care) (n 23).

		MAD group n 14	Non-MAD group n 9	p value
Frequency of dressing changes		2 (1 6)	2 (1 4)	0.080[a]
Washing type	Shower	12 (85.7)	9 (100.0)	0.502[b]
	Cleansing with normal saline	2 (14.3)	0 (0.0)	
Dressing type	Gauze only	5 (35.7)	4 (44.4)	1.000[b]
	Absorbent pad	9 (64.3)	5 (55.6)	
Ointment type	Silver sulfadiazine	5 (35.7)	4 (44.4)	1.000[b]
	MTZ	9 (64.3)	5 (55.6)	
Dressing fit	Contact with the wound	5 (35.7)	7 (77.8)	0.089[b]
	Non-contact	9 (64.3)	2 (22.2)	
Exudate leakage	Yes	11 (78.6)	2 (22.2)	0.013[b]
	No	3 (21.4)	7 (77.8)	

Median (range), n (%).
MTZ: Metronidazole.
[a] Mann Whitney U test.
[b] Fisher's exact test.