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 ($\leq$ 0.5)	3	2		1	11	8
	T1b ($>$ 0.5 to $\leq$ 1.0)	16	12		2	1	1
	T1c ($>$ 1.0 to $\leq$ 2.0)	61	44		Unknown	5	4
	T2 ($>$ 2.0 to $\leq$ 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
					$\geq$ 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).

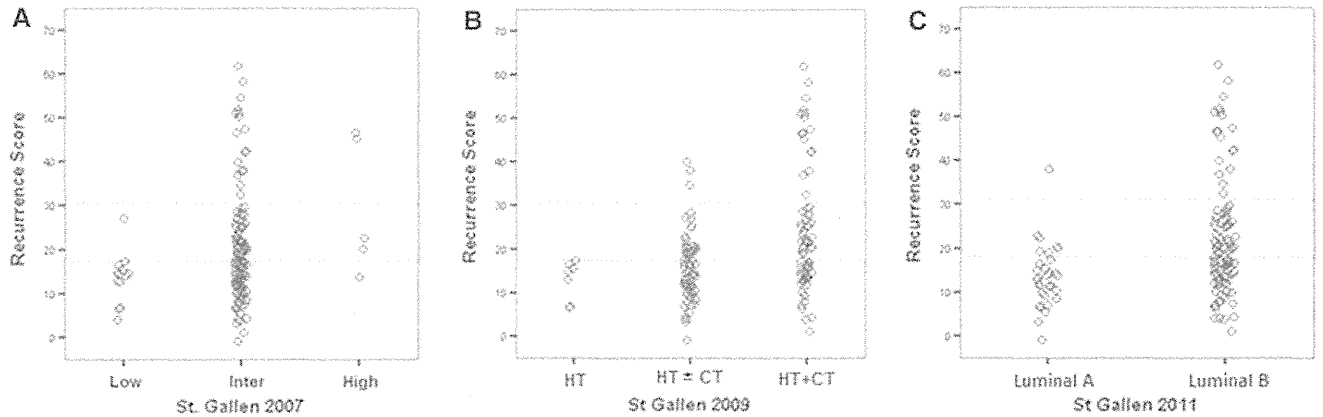

Fig. 1 **a** Comparison between St. Gallen 2007 and RS. Nearly all of the cases in the intermediate risk group were incorrectly classified under the St. Gallen criteria. **b** Comparison between St. Gallen 2009 and RS. We used the practical nuclear grading for the evaluation of tumor proliferation, but 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

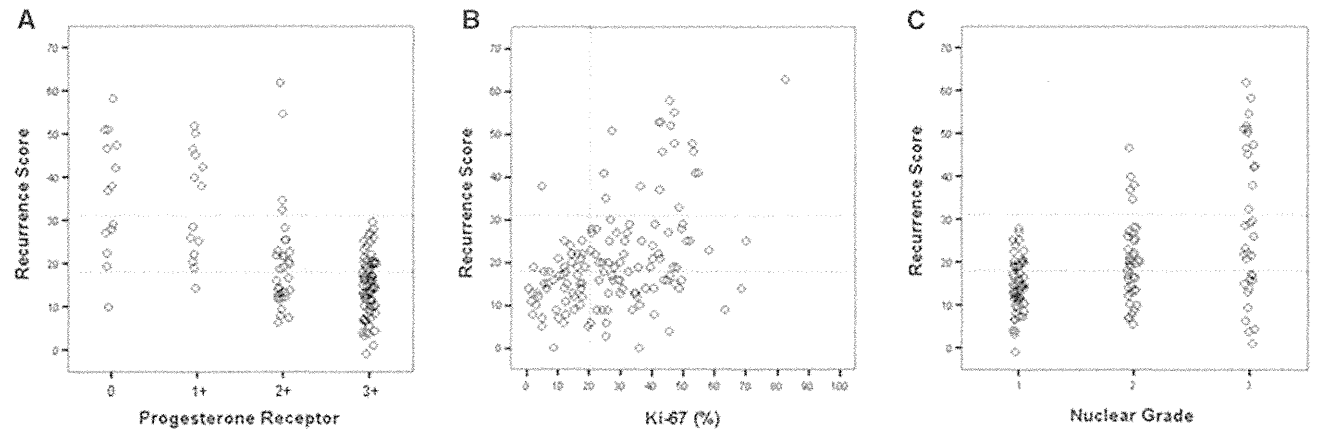

Fig. 2 **a** Correlation between PR and RS was negatively correlated with RS (r 0.53). No patients had high RS with PR(3+). **b** A correlation between Ki 67 and RS was observed (r 0.42). Only one patient (2 %) had high RS with Ki 67 (<20 %). **c** Correlation between NG and RS was observed (r 0.41).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

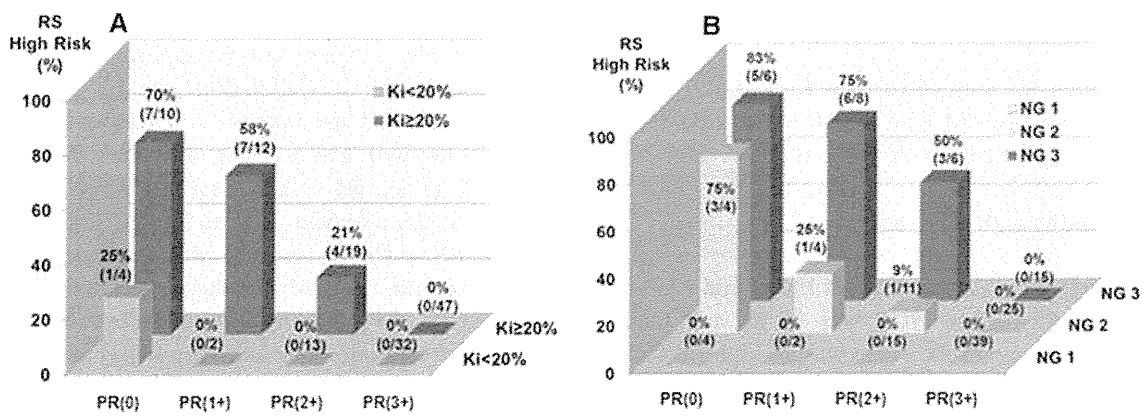

Fig. 3 **a** PR and Ki 67 in the high RS cases. The rate of high RS with PR(0) and Ki 67 (≥20 %) was 70 %, that of PR(1+) and Ki 67 (≥20 %) was 58 %, and that of PR(2+) and Ki 67 (≥20 %) was 21 %. **b** PR and NG in the high RS cases. Among the high RS cases, the rate of PR(0) and NG3 was 83 %, that 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

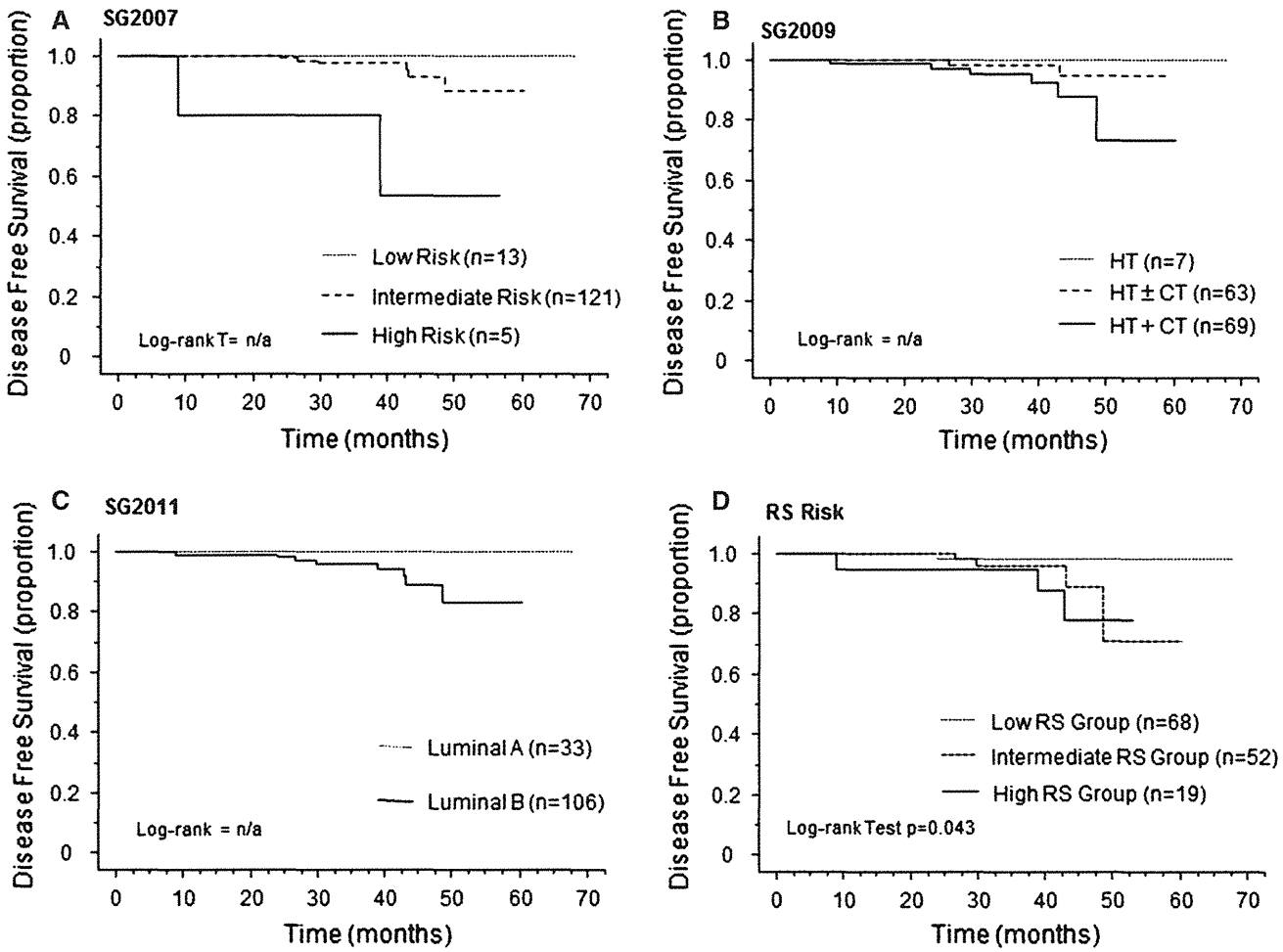

Fig. 4 Kaplan Meier curves for disease free survival. St. Gallen **a** 2007, **b** 2009, **c** 2011, **d** RS group. There was no recurrence case in the low risk group of St. Gallen 2007, the HT group of St. Gallen 2009 and the luminal A group of St. Gallen 2011 (a log rank test was not available)

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

Nao Tamai [a], Motoko Horii [b], Kimie Takehara [a], Shizuko Kato [c], Yuko Yamamoto [a], Ayumi Naito [d], Mikiko Tayama [e], Yoko Tamahashi [e], Seigo Nakamura [f], Takafumi Kadono [g], Makoto Oe [a], Takashi Nagase [a], Hiromi Sanada [a,*]

[a] Department of Gerontological Nursing/Wound Care Management, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan
[b] Faculty of Nursing, Josai International University, 1 Gumyo, Togane-shi, Chiba, Japan
[c] Department of Nursing, Shukutoku University, 673 Nitonacho, Chuo-ku, Chiba-shi, Chiba, Japan
[d] Fujisawa City Hospital, 2-6-1 Fujisawa, Fujisawa-shi, Kanagawa, Japan
[e] St. Luke's International Hospital, 9-1 Akashi-cho, Chuo-ku, Tokyo, Japan
[f] Department of Breast Surgical Oncology, Showa University School of Medicine, 1-5-8 Hatanodai, Shinagawa-ku, Tokyo, Japan
[g] Department of Dermatology, Faculty of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo, Japan

Keywords:
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

* Corresponding author. Tel.: +81 3 5841 3419; fax: +81 3 5841 3442.
E-mail addresses: ntamai-tky@umin.ac.jp (N. Tamai), hsanada-tky@umin.ac.jp (H. Sanada).

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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.

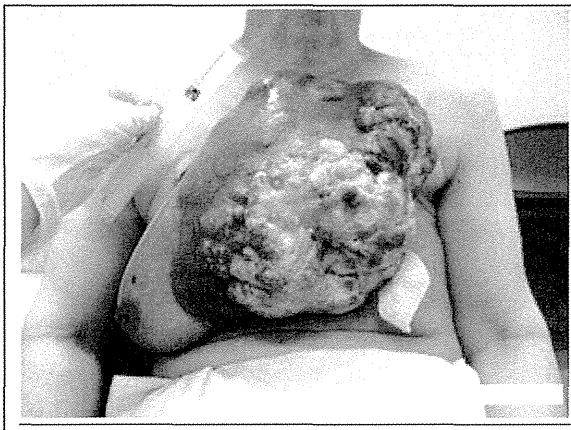
The patients' wounds and the condition of the surrounding skin were examined by visual inspection and by palpation (pressing down with a finger and pinching of tissues) (Bates Jensen et al., 1992; Sussman and Bates Jensen, 2007).

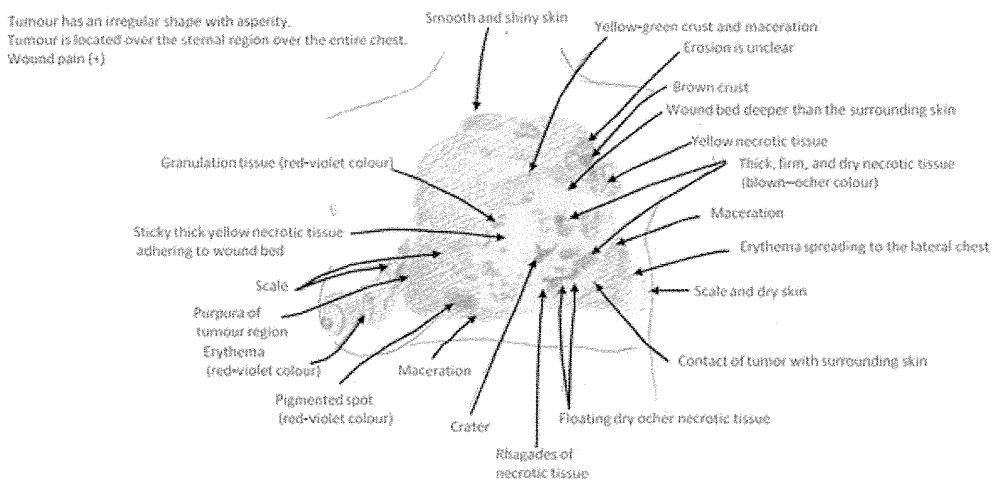
Morphoqualitative analysis of MAD

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)

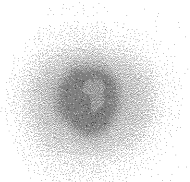
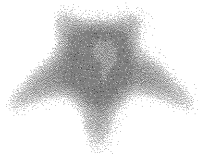
Median (range), n (%).
HER-2: human epidermal growth factor receptor type 2.
[a] Multiple answers.

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.

Kinoshita et al., 2009; Nanjo et al., 2011), thereby providing clues to effective nursing interventions. We identified 'half fusiform shape over the dressing' as a key morphological characteristic of MAD. This shape was observed at the edge of the breast, possibly sug gesting exudate leakage along this edge. We also consider 'radial shape matching the dressing' to be a morphological characteristic of MAD and suggest that this is caused by the skin coming in contact with excess wound exudates absorbed by the dressing. Other non MAD types of morphological characteristics were also identified in the peri wound skin. Dermatitis with 'line shape matching the tape' may be caused by repeated tape stripping (Mohammed et al., 2011), contact dermatitis related to the adhesive tape (Russell and Thorne, 1955) or sweat or wound exudates pre sent at the taping site. The 'erythema' of the dermatitis that appeared in 'shape matching the subcutaneous tumour' in 'elevated portion of the subcutaneous tumour' or 'irregular shape spreading over the trunk' in 'body trunk' may be considered as a morpho logical characteristic of cancer (Manning, 1998; Thiers, 1986). These findings may make it possible to distinguish between MAD and other skin changes. This distinction is clinically very important because nurses have many options for wound care in cases of MAD (leakage check, selection of dressing, method for attaching the dressing or assessment of daily self care activities). In this context, our morphoqualitative analyses of MAD are quite important for evaluating the possible causes of MAD as well as for selecting effective interventions.

Necrotic tissue type and wound exudate leakage were identified as factors related to MAD surrounding MBWs. Debridement of necrotic tissues is usually encouraged to prevent bacterial infection or colonisation [European Wound Management Association (EMWA), 2004]. However, debridement is not recommended for MBWs because of bleeding risk. It is thus reasonable to consider that the thick necrotic tissue associated with MBWs may be a focus of infection (Anazawa, 2005). Cameron et al. (Cameron and Powell, 1996) reported that exudates from some types of ulcers may contain a component that irritates the skin, leading to eczema or even loss of epithelium. Notably, they found that exudates from infected wounds may be even more irritating. We consider that MAD in our patients could have been caused by irritant exudates produced by bacteria. Further study is required before this point can be addressed in detail.

Our findings have several implications for nursing care of MBWs. Frequent dressing changes or the use of a more absorbent dressing are strongly recommended for patients with MBW, particularly those with massive exudates or thick necrotic tissues. All patient behaviours in everyday life, such as changing clothes, should be carefully assessed to ensure that the dressing remains attached without exudate leakage. With respect to thick necrotic tissues, antimicrobial drugs or a silver dressing should be used to control the bacterial load. New wound care products should also be developed, such as an ointment or a dressing that will directly inactivate irritant exudates. It should be stressed that the contri bution of nurses is indispensable in this type of study because of the morphoqualitative analysis method used and because meticulous wound care cannot be achieved unless the nurses build an intimate rapport with their patients.

There are some limitations of this study. First, careful consid eration is required before our data related to the prevalence of MAD are extrapolated to the general population because the sample size of this study was small and a possible bias cannot be ruled out. In addition, we could not show a precise causal relationship between MAD and related factors because this was a cross sectional study. Histopathological observation is required for a more precise diag nosis of MAD, although biopsy was practically difficult in cases such as ours.

Conclusion

This study revealed the prevalence and morphoqualitative characteristics of MAD surrounding MBWs.

It is important for nurses to understand the findings of MAD related to wound exudates ('radial shape matching the dressing' or 'half fusiform shape over the dressing') for appropriate skin care of patients with MBWs. Our study is important for evaluating the possible causes of MAD as well as selecting effective nursing in terventions by nurses. In brief, nurses could provide necessary care for patients with necrotic tissue type (thick and yellow or black necrotic tissue) and wound exudate leakage.

Conflict of interest

None declared.

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Axillary lymph node dissection in sentinel node positive breast cancer: is it necessary?

Seigo Nakamura

Purpose of review
Sentinel lymph node biopsy (SLNB) has become a gold standard procedure for axillary lymph node evaluation in clinically node negative patients. In those patients with positive SLNB, completion axillary lymph node dissection (ALND) has been routely performed. Recent clinical trials suggest that ALND is not necessary in some cases, even when the sentinel lymph node (SLN) is positive. The appropriate conditions under which ALND may be eliminated are defined in this review.

Recent findings
The American College of Surgeons Oncology Group (ACOSOG) Z0011 trial studied the impact of SLNB alone versus completion axillary node dissection (AND) on survival in clinically node negative breast cancer patients undergoing partial mastectomy and whole breast irradiation who were found to have a positive SLN on pathological evaluation. Results of this study showed no survival advantage for complete AND in patients with one or two positive SLNs. In other words, those patients appeared to be treated safely without completion AND.

Summary
Despite the small sample size and limited stastical power and the relatively short median follow up for ACOSOG Z0011, many breast cancer teams no longer believe it mandatory to perform axillary dissection for patients with one or two positive SLNs. The results of other prospective randomized trials called After Mapping of the Axilla: Radiotherapy Or Surgery study and International Breast Cancer Study Group trial 23 01 study will be available soon, and may further change the confidence with which ALND is performed or eliminated.

Keywords
After Mapping of the Axilla: Radiotherapy Or Surgery study, American College of Surgeons Oncology Group Z0011, axillary dissection, sentinel lymph node biopsy

INTRODUCTION

Sentinel lymph node biopsy has become a gold standard procedure for women with breast cancer who present with clinically negative axillary lymph nodes [1–4]. Lymphedema and paresthesias occur in approximately 5–8% of patients after sentinel node biopsy (SNB) and 10–20% of patients after axillary lymph node dissection (ALND) [5▪▪,6–9]. SNB is, thus, the optimum approach in terms of morbidity for the assessment of axillary metastasis in clinically node-negative breast cancer.

The results of American College of Surgeons Oncology Group (ACOSOG) Z0010 and National Surgical Adjuvant Breast and Bowel Project (NSABP) B32 trials help estimate the prevalence and prognostic significance of positive sentinel lymph nodes (SLNs) found only by immunohistochemistry [10–12]. Among patients with negative intraoperative frozen section who are found to be SLN positive on final pathologic examination, the risk of non-SLN metastases is low [13–15]. A growing number of patients are electing not to undergo completion ALND; a decision that may in part be due to the adoption of a predictive nomogram based on pathologic variables for the risk of non-SLN metastasis [16,17].

Retrospective studies have indicated that in up to 40–60% of cases with a positive sentinel node the sentinel node is the only positive node [13–15,18].

Department of Breast Surgical Oncology, Showa University School of Medicine, Tokyo, Japan

Correspondence to Seigo Nakamura, Department of Breast Surgical Oncology, Showa University School of Medicine, 1-5-8 Hatanodai Shinagawa-ku, Tokyo 142-8666, Japan. Tel: +81 3 3784 8000; fax: +81 3 3784 8707; e-mail: seigonak@med.showa-u.ac.jp

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KEY POINTS

- From the result of ACOSOG Z0011, AND may safely be omitted in breast conservation patients whose tumor size is 5 cm or less with clinically node negative and who will have whole breast radiation and appropriate systemic adjuvant therapy.
- Because there are several critiques to ACOSOG Z0011, we should carefully follow up such patients who have not received axillary dissection and pay attention to the result of other similar studies (AMAROS study and International Breast Cancer Study Group 23 01.)

A positive SLN will prompt a recommendation for systemic therapy in the vast majority of women. Whether surgical excision of any positive nonsentinel nodes would improve long-term outcome has been an issue of uncertainty.

ACOSOG Z0011 is a prospective randomized trial to determine the effects of complete axillary node dissection (AND) on survival of patients with SLN metastasis of breast cancer [19,20▪▪]. Women who were eligible for the trial had tumors less than 5 cm, clinically negative axillary lymph nodes, lumpectomy to negative margins, no neoadjuvant chemotherapy, planned whole breast irradiation, and 1 or 2 positive SLNs. Almost all received systemic adjuvant chemotherapy and/or endocrine therapy. The results show that ALND is not associated with 5-year overall survival and 5-year disease-free survival. Cases of lymphedema were significantly higher in the ALND group. Therefore, this study does not support the routine use of ALND in breast cancer with 1–2 involved SLNs and undergoing breast conserving therapy including whole breast irradiation. This requires that the role of ALND be reconsidered [21▪].

THE MANAGEMENT OF ISOLATED TUMOR CELLS OR MICROMETASTASIS IN SENTINEL NODES

It has been a standard practice to perform ALND in breast cancer patients with positive SLN, and this is done in the majority of patients. However, controversy exists over the management of patients found to have positive SLN by immunohistochemical (IHC) staining alone. Tan *et al.* [22] reported worse survival for patients with occult metastasis detected by serial sectioning and immunohistochemistry. The results of the ACOSOG Z0010 and NSABP B32 trials will help estimate the prevalence and prognostic significance of positive SLN found only by immunohistochemistry [23,24]. A systematic review by Bear *et al.* also concluded occult axillary node metastases detected by serial sections and/or IHC staining of SLN are prognostically significant [24]. However, NSABP B-32 showed the magnitude of the difference in outcome at 5 years was quite small (1.2 percentage points) [25]. Therefore, there appears to be little clinical benefit of including IHC analysis of hematoxylin and eosin stained negative sentinel nodes in patients with breast cancer [26].

THE MANAGEMENT OF AXILLARY MACROMETASTASIS: RETROSPECTIVE STUDY

Veronesi *et al.* [26] from the European Institute of Oncology presented 10-year follow up of their single-institution trial designed to compare outcomes in patients who received no axillary dissection if the sentinel node was negative, with patients who received complete axillary dissection. From March 1998 to December 1999, 516 patients with primary breast cancer under 2 cm were randomized either to SNB and complete axillary dissection (axillary dissection arm) or to SNB with axillary dissection only if the sentinel node contained metastases (sentinel node arm). Eight patients in the axillary dissection arm had false-negative sentinel nodes on histologic analysis: a similar number [8, 95% confidence interval (CI) 3–15] of patients with axillary involvement was expected in sentinel node arm patients who did not receive axillary dissection; but only two cases of overt axillary metastasis occurred. There were 23 breast cancer-related events in the sentinel node arm and 26 in the axillary dissection arm (log-rank, $P = 0.52$), whereas overall survival was greater in the sentinel node arm (log-rank, $P = 0.15$). They concluded that preservation of healthy lymph nodes may have beneficial consequences. Even though there might be around 5% false-negative rate in the sentinel node arm, axillary dissection should not be performed in clinically node-negative patients without performing SNB.

Spiguel *et al.* [27▪] retrospectively reviewed their institution's 12-year experience with SNB alone for a tumor-positive sentinel node. Among 3 806 patients who underwent SNB, 2 139 underwent SNB alone, of which 1 997 were tumor negative and 123 were tumor positive. Sentinel nodes were staged node-positive (N1mic or N1) according to American Joint Committee on Cancer criteria.

Mean age was 57 years (range 32–92 years) and mean tumor size was 1.9 cm (range 0.1–9 cm). Eighty-nine (72%) underwent lumpectomy and 34 (28%) underwent mastectomy. Ninety-three percent of patients underwent some form of adjuvant

therapy. Forty-two patients (34%) did not undergo radiation and there were no axillary recurrences in this group. At median follow-up of 95 months, there has been only one axillary recurrence (0.8%) and 13 deaths, four of which were attributed to metastatic breast cancer and the rest to nonbreast-related causes.

They also concluded that axillary recurrence is rare after SNB alone especially in case of favorable patient or tumor characteristics (older age, ER positive and Her2 negative etc.) and standard use of adjuvant therapy.

The German Clinical Interdisciplinary Sentinel study was a large prospective randomized phase III trial performed in 33 German centers [28▪]. One thousand one hundred and eighty two patients with operable, clinically node negative and invasive breast cancer were equally randomized to either a strategy of standard axillary dissection (SAD) independent of the SNB finding (SAD arm, $n = 594$), or to a strategy of performing SAD only in case of a positive SNB finding or failure of sentinel node detection (control arm, $n = 588$), but observation only in patients with negative SNB. The trial was designed to exclude an absolute difference in relapse-free survival (RFS) of 5% after 5 years with sufficient confidence. After a maximum follow-up time of 115 months, a total of 93 RFS events (40/53) and a total of 53 death events (23/30) were observed. Comparisons of RFS yielded a hormone receptor of 1.44 (95% CI 0.95–2.18; $P = 0.084$), and of overall survival yielded a hormone receptor of 1.53 (0.88–2.66; $P = 0.13$). Paresthesia, lymphedema and pain were significantly less common in the SNB-negative group. It means that this trial also showed that the false-negative rate of SNB was negligible in terms of RFS and overall survival.

THE MANAGEMENT OF AXILLARY MACROMETASTASIS: PROSPECTIVE STUDY AND ANOTHER APPROACH

ACOSOG Z0011 is a prospective randomized trial to determine the effects of complete AND on survival of patients with SLN metastasis of breast cancer. Eight hundred and ninety one clinically node-negative patients, T1N0 and T2N0, with one or two H&E positive SLNs (Fig. 1) were randomized to no further axillary surgery or to axillary dissection.

The trial was conducted among 115 centers in the United States between 1999 and 2004. The sample size was not reached to the targeted enrollment (1900 women with final analysis after 500 deaths), but the trial was closed early because mortality rate was lower than expected, and final follow up for data analysis was completed in 2010. [The result was presented at ASCO2010 (Fig. 2) and published in JAMA 2011 [19,20▪▪]].

Type of operation was not associated with outcome in 5-year overall survival (92.5% in the sentinel group, versus 91.8% in the axillary group, Fig. 3) and 5-year disease-free survival (83.9% of the sentinel node group, versus 82.2% of the ALND group (Fig. 4). About 70% of participants in the axillary lymph node group had side effects such as shoulder pain, weakness, infection and tingling, versus 25%

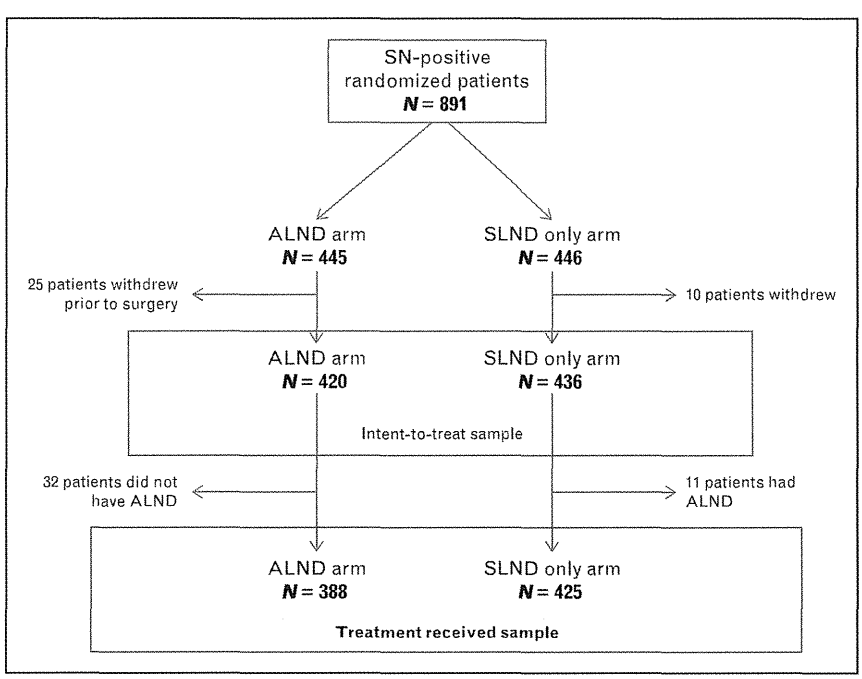

FIGURE 1. ACOSOSG Z0011 patient accrual. Adapted from [20▪▪].

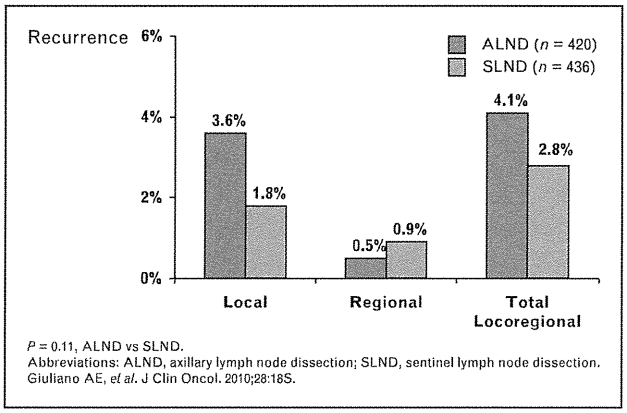

FIGURE 2. ACOSOG Z0011: 5 year recurrence rates. Adapted from [32].

in the sentinel group. Cases of lymphedema were significantly higher in the axillary group. Therefore, this study does not support the routine use of ALND in early nodal metastatic breast cancer in women undergoing breast conservation including whole breast irradiation.

Although additional axillary involvement was observed 27% in the ALND group, axillary recurrence rate was extremely low at 0.5% in the SLND group. There are several speculations. One is that systemic adjuvant treatment with hormonal therapy and/or chemotherapy has some effect in preventing locoregional recurrence. And the other is that tangent radiation fields used to the breast also covered the low axillary area and brought a therapeutic effect to the low axillary lymph nodes. Supporting this are the results of NSABP B-04, a trial comparing radical mastectomy (including ALND), total mastectomy without ALND, and total mastectomy with radiation therapy to the regional lymph nodes [27▪]. An update of this study with a median follow-up of 180 months (range 12–221 months) showed that long-term survival did not differ after axillary radiotherapy and axillary dissection. The only difference was better axillary disease control in the group with axillary dissection. In the Z0011 study, all the cases had the radiation to the residual breast, however, the radiation fields were not fully prescribed by the protocol, and the radiotherapy delivered is not fully specified.

There are several critiques for this study. First, the sample size is small because axillary recurrence was observed in two cases in the ALND group and four in the SLND group. Second, median follow up is 6.3 years and too short because most women (83%) had ER-positive cancers and would, thus, be expected to recur late.

From this study, AND may safely be omitted in breast conservation patients whose tumor size is 5 cm or less clinically node negative and who will have whole breast radiation and appropriate systemic adjuvant therapy.

There is another approach for sentinel node positive cases. Kim *et al.* [29] reported the significance of FDG-PET/CT to determine the indication of AND or SNB in breast cancer patients. They performed FDG-PET/CT scans in 137 biopsy-proven breast cancer patients planning to have an SNB to select patients for either AND (PET/CT N+) or SNB (PET/CT N0). In performing SNB, they also

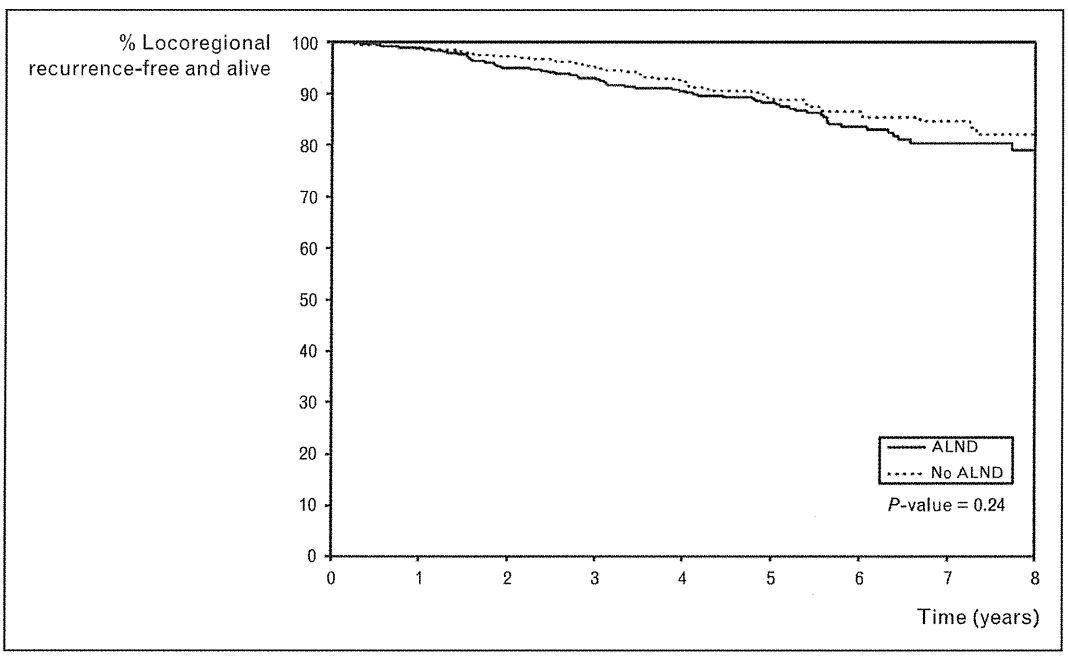

FIGURE 3. ACOSOG Z0011: recurrence free survival. Adapted from [20▪▪].

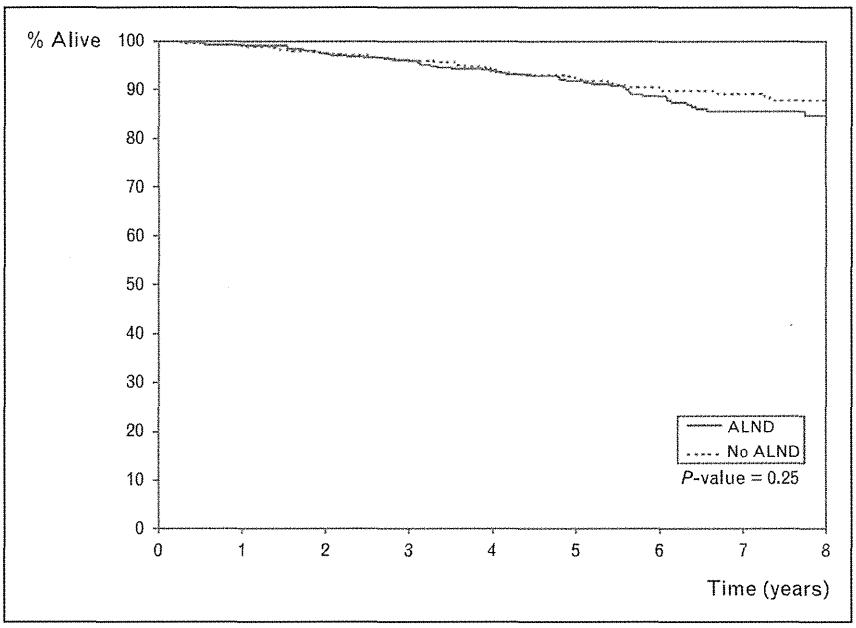

FIGURE 4. ACOSOG Z0011: overall survival. Adapted from [33].

performed additional non-SNB (ADD), which was enlarged at the lower axilla. Twenty-seven patients with positive scans underwent complete AND as a primary procedure, and 110 patients with negative scans underwent SNB and ADD. There were eight cases of false-negative scans, and no case of false-positive scan. Among 110 SNB and ADD cases, there were only eight cases (7.3%) of positive axillary basins in permanent biopsy, including two cases of late positives that had micrometastases in the sentinel node only. On the basis of an FDG-PET/CT, 27 unnecessary SNBs (true positive scans) have been eliminated. They concluded that an FDG-PET/CT reduced both unnecessary SNBs and positive axillary basins, enhancing the identification rates of sentinel node and the accuracy of SNB.

The After Mapping of the Axilla: Radiotherapy Or Surgery (AMAROS) study has been conducted in The European Organisation for Research and Treatment of Cancer. The main endpoint of this study is axillary recurrence rate (Fig. 5) [30] and secondary endpoints are axillary recurrence free survival, disease-free survival, overall survival, quality of life, shoulder function analysis, and economic evaluation. Four thousand seven hundred and sixty seven patients had already been recruited (Feb 2001~2010). This study is comparing ALND to axillary radiation and will be available in a couple of years.

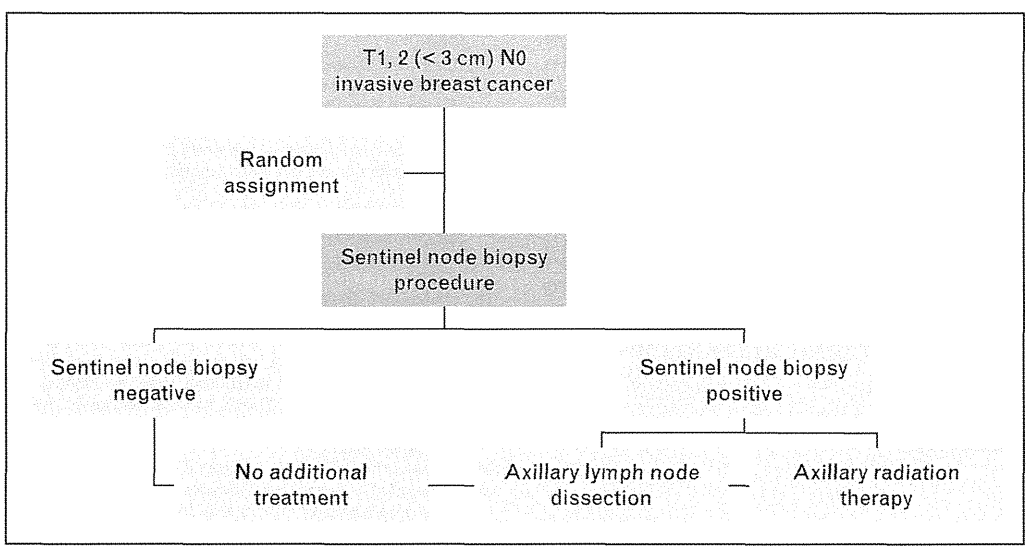

FIGURE 5. AMAROS study design. American Society of Clinical Oncology.

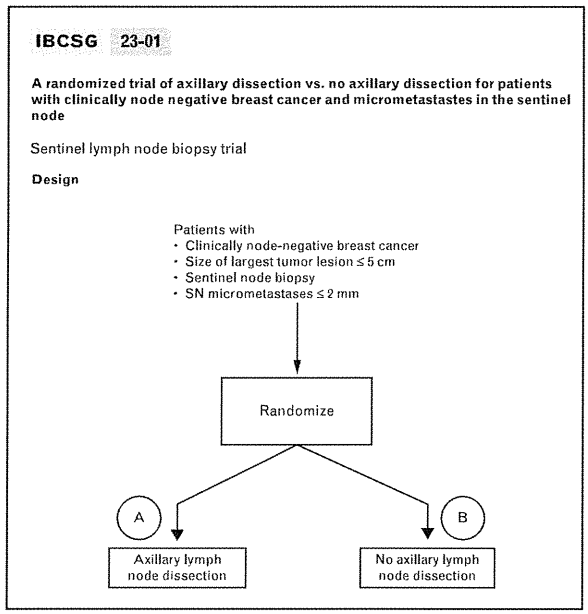

FIGURE 6. IBCSG23 01 study design. http://www.ibcsg.org/Public/Health Professionals/Closed Trials/IBCSG%2023 01/Pages/IBCSG23 01.aspx.

The International Breast Cancer Study Group trial 23–01 study was conducted at the European institute of Oncology in Milan (Fig. 6) [31]. The study included patients with disease limited to a relatively small primary tumor treated with initial SNB. Those who have micrometastasis (≤2 mm) are randomized to axillary dissection or no further treatment. The result of this study is also awaited.

CONCLUSION

This result of ACOSOG Z0011 has profoundly impacted our understanding of axillary management in women with clinically node-negative breast cancer. The results of this study suggest that AND may safely be omitted in breast conservation patients whose tumor size is 5 cm or less with clinically node negative and who will have whole breast radiation and appropriate systemic adjuvant therapy [32,33]. But there are several critiques of the study, and further study is required. In patients for whom axillary dissection is eliminated, careful follow of their axillary is required, and we must also await the results of other similar studies (AMAROS study and International Breast Cancer Study Group 23–01.)

Acknowledgements

None.

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
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Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 000 000).

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