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Original article

Feasibility of breast conserving surgery for Paget's disease

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ABSTRACT

Introduction: The standard treatment for Paget's disease of the breast is mastectomy. Since it is frequently associated with underlying carcinoma, many surgeons are reluctant to choose breast conserving surgery for Paget's disease.
Patients and methods: We retrospectively analyzed a series of 59 patients with Paget's disease who had undergone mastectomy at the National Cancer Center Hospital between 1963 and 2009.
Results: In 55 of 59 cases (93%) there was underlying carcinoma in the ipsilateral breast. Clinically, 27 (46%) patients had no evidence of other tumors, but 23 (85%) had underlying histopathologically confirmed carcinoma. Based on the data from this subset, cone excision with a 3-cm radius and a 4-cm radius could completely resect any underlying malignancy in 74% and 85% of patients, respectively.
Conclusion: As Paget's disease is frequently accompanied by underlying intraductal and/or invasive carcinoma, patients should be carefully selected for breast conserving surgery.

Introduction

Paget's disease of the breast is a relatively uncommon tumor which is estimated to represent 1–2% of all breast cancers.[1–4] For patients with Paget's disease of the breast, mastectomy is generally considered the standard treatment. It is recommended as the standard therapy by the National Comprehensive Cancer Network guideline.[5] Since underlying intraductal spread or invasive carcinoma is frequently detected by histopathological examination of mastectomy specimens from patients with Paget's disease, surgeons have been reluctant to employ breast conserving procedures for Paget's disease.[6] On the other hand, breast conserving surgery combined with radiotherapy to the remaining breast parenchyma has been shown to be equally efficacious in achieving local control and similar survival rates in patients with early Paget's disease.[7] Recently, selected patients with Paget's disease of the breast were treated with breast conserving surgery with survival rates similar to those achieved with mastectomy.[7]

However, Paget's disease is a heterogeneous disease which presents with varying levels of underlying ductal carcinoma in situ (DCIS) and/or invasive carcinoma components in the breast parenchyma.[7] It may present with a palpable mass or abnormalities on the mammogram, but either finding may be absent.[7] In one study, mammography failed to reveal any abnormalities in 43% of patients with Paget's disease.[2] Early reports suggest that cases of Paget's disease without any underlying DCIS or invasive carcinoma components are rare, representing at most 8% of patients with Paget's disease.[8–10]

The aim of this study is to assess the feasibility of breast conserving surgery for Paget's disease of the breast, especially for patients with disease that is limited to nipple–areolar complex. We retrospectively reviewed data on the histological extension of the disease from 59 patients, and simulated how much breast parenchyma should be resected if the conserving surgery were to be performed.

Patients and methods

We reviewed the case records of all patients with clinically apparent and histopathologically confirmed Paget's disease who had undergone surgery at the National Cancer Center Hospital in Tokyo, Japan, between 1963 and 2009. All eligible cases had a preoperative biopsy or cytology. Cases were excluded from analysis when Paget's disease was an incidental histological finding where mastectomy was performed for invasive carcinoma. In 11,335 breast cancer patients who had undergone surgery during that period, 63 (0.6%) were diagnosed with Paget's disease clinically. Four patients were excluded because they received chemo-radiotherapy,

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chemotherapy alone, or radiotherapy alone. The case records of the remaining 59 patients with Paget's disease of the breast were included in the retrospective analysis.

Mastectomy was performed on all patients. Axillary lymph node dissection was performed at the discretion of the surgeon. Sentinel lymph node biopsy was performed in cases after 2002.

For all patients, mastectomy specimens of Paget's disease were cut at intervals of 1–1.5 cm. Confirming the spread of intraductal component macroscopically, we cut around the nipple and made tissue blocks as many as possible. We made 15 to 20 blocks for each patient. Histopathological diagnosis was done by more than two pathologists who were specialized in breast cancer.

Statistical analysis

The Kaplan–Meier method was used to estimate disease-specific overall survival from the date of the initial surgery to death from extension of Paget's disease or underlying invasive carcinoma. Data were right-censored at the time of the last follow-up or death from other causes.

Results

All 59 cases with clinically apparent and histopathologically confirmed Paget's disease are summarized in Table 1. The median age was 55 years, ranging from 25 to 82 years. The patients constituted 58 women and 1 man. Clinically, all patients had eczema or erythema of the nipple. Nipple discharge was reported in 34 patients (58%). There was a palpable mass in the ipsilateral breast of 13 patients (22%).

Preoperative mammography was performed in 57 patients (97%), with no abnormality detected in 31 patients (53%). In 26 (44%) patients, there were mammographic findings suggesting a calcification or mass in the ipsilateral breast. Preoperative ultrasonography (US) was performed in 39 patients (68%), computed tomography (CT) in 3 patients (5%) and magnetic resonance imaging (MRI) in 8 patients (14%). When all these investigations were considered, 27 (46%) of the 59 patients had only clinical manifestations of Paget's disease without evidence of any other tumors.

In accordance with our departmental practices, mastectomy was performed in all cases. Radical mastectomy was performed in 16 cases (27%), and modified radical mastectomy in 30 cases (51%). These two procedures included Level III axillary lymph node dissection. In 11 cases, simple mastectomy with sentinel lymph node biopsy was performed. In the remaining 2 cases, simple mastectomy was performed: one patient had a history of breast conserving surgery with axillary lymph node dissection for ipsilateral breast cancer, and the other patient received a synchronous contralateral mastectomy with axillary lymph node dissection for advanced breast carcinoma. In the latter patient, preservation of ipsilateral axially lymph nodes was intended to improve the patient's quality of life.

Histopathological findings included typical intraepidermal Paget's cells in the nipple or areolar region in all 59 patients (Table 2). In 55 of 59 cases (93%) there were underlying

Table 1
Characteristics of 59 cases with clinically apparent and histopathologically confirmed Paget's disease.

		No. of patients ($n = 59$)
Sex	Male	1 (2%)
	Female	58 (98%)
Age (years), median 55 (ranger 25–82)	<50	20 (34%)
	≥50	39 (66%)
Presenting symptoms	Nipple eczema or erythema	59 (100%)
	Nipple discharge	34 (58%)
	Palpable mass	13 (22%)
Mammography findings	No abnormality	31 (53%)
	Abnormality (calcification or mass)	26 (44%)
	Unknown	2 (3%)
Operative procedure	Radical mastectomy	16 (27%)
	Modified radical mastectomy	30 (51%)
	Simple mastectomy with SLNB[a]	11 (19%)
	Simple mastectomy only	2 (3%)
Adjuvant therapy	None	49 (83%)
	Chemotherapy	5 (9%)
	Hormonal therapy	3 (5%)
	Unknown	2 (3%)

[a] Sentinel lymph node biopsy (including lymph node sampling).

Table 2
Clinicopathological features of 59 patients with clinically apparent and histopathologically confirmed Paget's disease.

	Paget's disease ($n = 59$)	Clinically Paget's disease alone[a] ($n = 27$)
Paget's disease alone	4 (7%)	4 (15%)
Paget's disease with underlying carcinoma	55 (93%)	23 (85%)
Noninvasive carcinoma		
DCIS	23 (39%)	15 (55%)
Invasive carcinoma		
IDC with a predominant intradactal component	12 (20%)	7 (26%)
Papillotubular carcinoma	2 (3%)	0 (0%)
Solid tubular carcinoma	7 (12%)	1 (4%)
Scirrhous carcinoma	7 (12%)	0 (0%)
Mucinous carcinoma	1 (2%)	0 (0%)
Unkown	3 (5%)	0 (0%)
ER status		
Negative	17 (74%)	11 (79%)
Positive	6 (26%)	4 (27%)
Unknown	36	12
PgR status		
Negative	17 (77%)	11 (79%)
Positive	5 (23%)	3 (21%)
Unknown	37	13
HER2 status		
Negative	4 (21%)	3 (21%)
Positive	15 (79%)	11 (79%)
Unknown	40	13
Tumor size		
≤2 cm	17 (29%)	11 (40%)
>2–5 cm	26 (43%)	10 (37%)
>5 cm	11 (19%)	5 (19%)
Unknown	5 (9%)	1 (4%)
Tumor status		
pTis	27 (48%)	19 (70%)
pT1	17 (29%)	8 (30%)
pT2	8 (14%)	0 (0%)
pT3	4 (6.8%)	0 (0%)
Unknown	3 (5.1%)	0 (0%)
Nodal status		
Negative	48 (81%)	26 (96%)
Positive	11 (19%)	1 (4%)
Histological grade		
G1	1 (4%)	1 (6%)
G2	16 (57%)	10 (59%)
G3	11 (39%)	6 (35%)
Unknown	31	10

DCIS ductul carcinoma in situ, *IDC* invasive ductal carcinoma, *ER* estrogen receptor, *PgR* progesterone receptor.
[a] No clinical evidence of other breast tumors in addition to Paget's disease.

components of DCIS and/or invasive carcinoma; only 4 cases had Paget's disease alone limited to nipple–areolar complex. Although 27 (46%) of the 59 patients had only clinical manifestations of Paget's disease without evidence of any other tumors, 23 (85%) had underlying DCIS and/or invasive carcinoma components (Table 2).

In the 55 patients with underlying carcinomas, 23 (42%) had DCIS and 32 (58%) had invasive carcinoma. The most common histological subtype was invasive ductal carcinoma (IDC) with a predominant intraductal component, followed by solid tubular carcinoma and scirrhous carcinoma, which are both subtypes of IDC. Among the 27 cases which were clinically diagnosed as Paget's disease alone, DCIS was the most frequent underlying component (Table 2).

Immunohistochemical data on estrogen receptor (ER), progesterone receptor (PgR), and HER2 were available for the most recent 23, 22, and 19 cases, respectively. ER was positive in 6 (26%), PgR was positive in 5 (23%), and HER2 was positive in 15 (79%) (Table 2). We retested HER2 status for these 19 cases, and confirmed that 10 were score 3+, and 5 were score 2+ by two pathologists. These 5 score 2+ cases were confirmed as HER2 positive by using fluorescence in situ hybridization method. Similar percentages were found in the subsets of patients with the clinical diagnosis of Paget's disease alone and Paget's disease with underlying carcinoma (Table 2).

In patients with Paget's disease and underlying carcinoma, the combined tumor size was 5.0 cm or smaller in 43 cases (73%). In these patients, most tumors were pTis or pT1 (44 of 59, 77%). Adjuvant therapy was administered to only 8 patients.

The median length of follow-up was 6.98 years (range, 0.11–30.70 years). We could follow-up 39 patients (66%) for more than 5 years and 19 patients (32%) for more than 10 years. The disease-specific overall survival curve for all patients in the study is shown in Fig. 1. Five-year and 10-year survival rates were 87.6% and 84.8%, respectively. In the 27 patients with clinical Paget's disease alone, both the 5-year and 10-year survival rates were 100%. At present, 44 of the 59 patients are alive without recurrence and 1 patient is alive with recurrence. Among the 14 patients who died, 8 died due to recurrence, 1 died due to another cause but had recurrence, 5 died of other diseases without recurrence. One of the breast conserving surgeries of choice for patients with clinical manifestations of Paget's disease alone is cone excision of the nipple–areolar complex. If this procedure were performed in the 27 patients with the clinical diagnosis of Paget's disease alone, the rate of successful complete resection is estimated to be 52% with a 2 cm excision radius, 74% with a 3 cm radius, and 85% with a 4 cm radius.

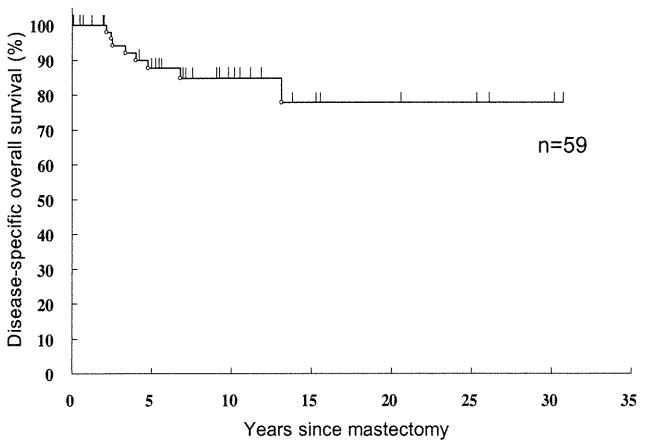

Fig. 1. Kaplan–Meier estimates of disease-specific overall survival in 59 patients with clinically apparent and histopathologically confirmed Paget's disease who had undergone mastectomy at the National Cancer Center Hospital between 1963 and 2009. The 5-year and 10-year disease-specific survival rates were 87.6% and 84.8%, respectively.

Discussion

Paget's disease represents 0.6% of all breast cancer cases in the surgical series from the National Cancer Center in Tokyo, Japan when cases of Paget's disease detected incidentally during histological examination were excluded.

Mastectomy has historically been the standard procedure for Paget's disease because of the high frequency of occult breast malignancy identified in surgically resected specimens.[5,7] Recently some reports recommend the use of breast conserving surgery, but its use in patients with Paget's disease is still controversial.[7,11–13] Although Dalberg K et al. report no significant difference in survival rates between patients who received mastectomy and those who received breast conserving surgery,[7] we should take into consideration the potential selection bias because patients offered breast conserving surgery tend to have less advanced malignancies than the patients who receive mastectomies. In their study, the survival rate of patients who underwent breast conserving surgery was similar to that of patients who underwent mastectomy, but the survival rate might have been much higher if mastectomy had been performed to the former patients, because these patients might have had residual cancer.

There were some other reports which recommended breast conserving surgery or conserving surgery plus radiotherapy.[14–16] We have to accept their thinking to some extent. In the simulation by the present study, the rate of successful complete resection was estimated to be 52% with a 2 cm excision radius, 74% with a 3 cm radius, and 85% with a 4 cm radius. Especially, in four patients, tumor extension was limited within nipple–areola complex. Therefore, breast conservation surgery might be able to resect tumors completely for some of patients with Paget's disease.

Another issue that may be raised is that the extent of parenchyma to be resected around nipple–areolar complex is unclear even if breast conserving surgery is considered for patients with clinical manifestations of Paget's disease alone. We could acknowledge the importance of appropriate marking of the margins and assessment of clearance microscopically as some patients may choose to attempt breast conservation by excision of the nipple areola complex with underlying tissue and proceed to radiotherapy if the margins are clear, or with options of tumor bed excision or mastectomy if the margins are not clear.

In the present series, all 59 patients had a histopathological diagnosis of Paget's disease before surgery. Of the 27 patients (46%) with Paget's disease with no evidence of other breast tumors on clinical examination, 85% had underlying DCIS and/or invasive carcinoma in the breast tissue by histopathological examination of the surgical specimen. Previous reports on breast conserving surgery have provided no precise recommendations on how to treat these patients.[7] Hence, we have continued to choose mastectomy rather than resection of the nipple–areolar complex or cone excision for these patients. Cone excision with a 3-cm radius could have completely resected the underlying DCIS and/or invasive carcinoma components in 74% of the patients in this series. With a 4 cm excision radius, the rate of incomplete resection is estimated to be 15%. However, such wide excision may no longer be properly called breast conserving surgery. Therefore, we would continue to choose mastectomy. We argue that more extensive investigation is necessary for patients with Paget's disease of the nipple, possibly including both breast ultrasound and breast MRI. If we could identify preoperatively the patients with the disease

limited within nipple areola complex by these modalities, these patients would be candidates for breast conservation therapy.

In some patients, breast conserving surgery would be of potential utility if appropriate marking of the margins by imaging modalities and clearance of margins by histological examination are guaranteed. In conclusion, since Paget's disease frequently harbors underlying breast cancer, the option of breast conserving surgery should be considered carefully.

Conflict of interest statement

The authors have no conflict of interest.

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Image of the Month

A Case of Metaplastic Carcinoma of the Breast

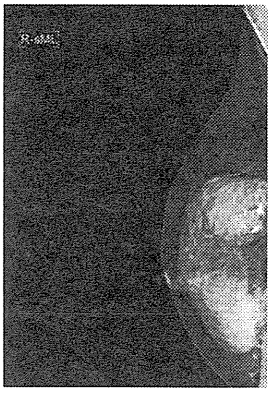

Figure 1.

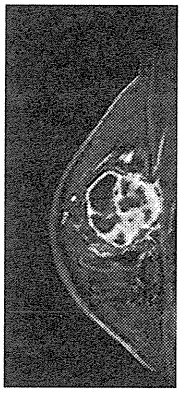

Figure 2.

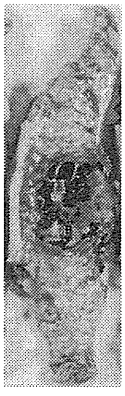

Figure 3.

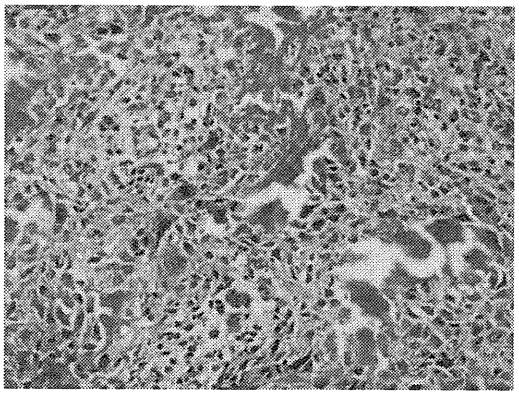

Figure 4.

A 53-year-old female noticing a firm mass in the upper outer quadrant of the right breast was referred to our hospital. Mammography revealed a well-demarcated tumor accompanied with large calcifications at its edge (Fig. 1).The tumor was 2.8 cm in diameter with heterogeneous enhancement on magnetic resonance imaging. A needle biopsy of the tumor showed spindle type metaplastic carcinoma with epithelial cells and osteoclast, which was negative for hormonal receptor (HR) but positive for HER2. Neoadjuvant chemotherapy using trastuzumab was administered, but the tumor increased in size and invaded the pectoralis major muscle (Fig. 2).Thus, chemotherapy was discontinued and total mastectomy with axillary lymph nodes dissection was performed.

The pathological diagnosis was metaplastic carcinoma with cartilaginous and osseous metaplasia with no lymph node metastasis (Figs 3 and 4). Most of the tumor cells were viable and negative for both HR and HER2. The patient is doing well 1 year after surgery with no adjuvant therapy.

A metaplastic carcinoma of the breast is a rare cancer that includes ductal carcinoma and sarcoma components with apparent transition between them. The reported 5-year overall survival rates range from 28 to 68%, which is poorer than ordinary invasive ductal carcinoma of the breast.

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Original contribution

Prognostic significance of mitotic figures in metastatic mammary ductal carcinoma to the lymph nodes☆,☆☆

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Summary We previously reported that the number of mitotic figures in metastatic mammary carcinoma to the lymph nodes accurately predicted the outcome of patients with invasive ductal carcinoma with nodal metastasis. To confirm these previous findings, the present study investigated the number of mitotic figures and other histologic characteristics in metastatic mammary carcinoma to the lymph nodes and their associations with patient outcome according to nodal status and the histologic grade of primary invasive ductal carcinomas in a different series of 1039 patients with invasive ductal carcinoma. Multivariate analyses examining well-known clinicopathologic factors, the number of mitotic figures in the primary invasive ductal carcinomas, the grading system for lymph vessel tumor emboli, the p53 Allred score risk classes of tumor-stromal fibroblasts forming and not forming a fibrotic focus, and 9 histologic features of metastatic mammary carcinoma to the lymph nodes were performed. The presence of 6 or more mitotic figures in metastatic mammary carcinoma to the lymph nodes significantly increased the hazard ratios for tumor recurrence and tumor-related death among patients with invasive ductal carcinoma as a whole, those with nodal metastasis, and those with a histologic grade of 2 or 3. The presence of 6 or more mitotic figures in metastatic mammary carcinoma to the lymph nodes also significantly increased the hazard ratio for tumor recurrence among patients with histologic grade 1 invasive ductal carcinoma. In conclusion, this study clearly confirmed the excellent outcome predictive power of the number of mitotic figures in metastatic mammary carcinoma to the lymph nodes.

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1. Introduction

Many studies have reported the prognostic significance of nodal metastasis and have emphasized that the number of nodal metastases is the most significant prognostic parameter in predicting the outcome of patients with invasive ductal carcinoma with nodal metastasis [1-5]. Among other parameters associated with nodal metastasis, the presence of extranodal invasion or the dimensions of the nodal metastases have been reported to be important prognostic parameters [1-10]. We previously examine which factors of metastatic mammary carcinoma to the lymph nodes were significantly associated with the outcome of patients with invasive ductal carcinoma and clearly demonstrated that the number of mitotic figures in metastatic mammary carcinoma to the lymph nodes was the most important factor for accurately predicting the outcome of patients with invasive ductal carcinoma with nodal metastasis [11].

To confirm these previous findings, the present study investigated the number of mitotic figures in metastatic mammary carcinoma to the lymph nodes and other histologic characteristics of metastatic mammary carcinoma to the lymph nodes known to be significantly associated with patient outcome according to nodal status in a different patient series of patients with invasive ductal carcinoma of the breast. We confirmed that the number of mitotic figures in metastatic mammary carcinoma to the lymph nodes was a very important outcome predictive factor for patients with invasive ductal carcinoma independent of the nodal status and the histologic grade of the primary invasive ductal carcinoma.

2. Materials and methods

2.1. Cases

The subjects of this study were 1039 consecutive patients with invasive ductal carcinoma of the breast who did not receive neoadjuvant therapy and were surgically treated at the National Cancer Center Hospital between January 2000 and December 2005. The invasive ductal carcinomas were diagnosed preoperatively using a needle biopsy, aspiration cytology, mammography, or ultrasonography. All the patients were Japanese women, ranging in age from 23 to 72 years (median, 55 years). All the patients had a solitary lesion; 495 patients were premenopausal, and 544 were postmenopausal. A partial mastectomy had been performed in 456 patients, and a modified radical mastectomy had been performed in 583 patients. A level I and a level II axillary lymph node dissection had been performed in all the patients, and a level III axillary lymph node dissection had been performed in some of the patients.

Of the 1039 patients, 870 received adjuvant therapy, consisting of chemotherapy in 217 patients, endocrine therapy in 280 patients, and chemoendocrine therapy in 373 patients. The chemotherapy regimens were either anthracycline based with or without taxane or non–anthracycline based. The endocrine therapy regimens consisted of tamoxifen with or without a gonadotropin-releasing hormone agonist, tamoxifen with or without an aromatase inhibitor, an aromatase inhibitor alone, or a gonadotropin-releasing hormone agonist alone. No cases of inflammatory breast cancer were included in this series. All the tumors were classified according to the present Union Internationale Contre le Cancer pTNM classification [12]. The protocol for this study (20-112) was reviewed by the Institutional Review Board of the National Cancer Center.

For the pathologic examination, the surgically resected specimens were fixed in 10% formalin; and the size and gross appearance of the tumors were recorded. The tumor size was confirmed by comparison with the tumor size on the histologic slides.

2.2. Histologic examination

Serial sections of each primary tumor area were cut from paraffin blocks. One section from each tumor was stained with hematoxylin and eosin and was examined histologically to confirm the diagnosis; the other sections were used for immunohistochemistry. The following 10 histologic factors of the primary invasive ductal carcinomas were evaluated: (1) invasive tumor size (≤20 mm, >20 to ≤50 mm, >50 mm), (2) histologic grade (1, 2, and 3) [13], (3) number of mitotic figures in the primary invasive ductal carcinoma (≤5 and >5), (4) tumor necrosis (absent or present) [14], (5) fibrotic focus (absent, fibrotic focus diameter ≤8 mm, fibrotic focus diameter >8 mm) [15,16], (6) grading system for lymph vessel tumor emboli [17,18], (7) blood vessel invasion (absent or present), (8) adipose tissue invasion (absent or present), (9) skin invasion (absent or present), and (10) muscle invasion (absent or present).

The nodal metastases were evaluated using single sections of each node or half of each node stained with hematoxylin and eosin. The nodal metastases were not examined immunohistochemically in this study. The 9 histologic parameters of metastatic mammary carcinoma to the lymph nodes listed in Table 1 were examined [11]. We randomly searched for mitotic figures in metastatic mammary carcinoma to the lymph nodes using midpower magnification fields (×10 or ×20) of the tumor area and selected 1 high-power magnification field (×40) of the tumor area with the highest number of mitotic figures in metastatic mammary carcinoma to the lymph nodes to determine the largest number of metastatic mammary carcinoma to the lymph nodes exhibiting mitotic figures (Fig. 1) [11]. In the primary invasive ductal carcinoma, the presence of 6 or more mitotic figures in 1 high-power magnification field

Table 1 Histologic factors of metastatic mammary carcinoma to the lymph nodes

Factors
No. of nodal metastases
No nodal metastasis
1-3 nodal metastases
4-9 nodal metastases
≥10 nodal metastases
Maximum dimension of metastatic mammary carcinoma to the lymph nodes (mm)
No nodal metastasis
≤20
>20
Histologic grade
No nodal metastasis
Grade 1
Grade 2
Grade 3
No. of mitotic figures in metastatic mammary carcinoma cells visible in 1 high-power magnification field
No nodal metastasis
≤5
>5
Fibrotic focus
No nodal metastasis
Absent
Present
Tumor necrosis
No nodal metastasis
Absent
Present
Grade of stromal fibrosis in metastatic mammary carcinoma to the lymph nodes
No nodal metastasis
None
Mild
Moderate
Severe
No. of lymph nodes with extranodal invasion
No nodal metastasis
≤5
>5
No. of extranodal blood vessel tumor emboli
No nodal metastasis
≤9
>9

was assessed in the same manner as for metastatic mammary carcinoma to the lymph nodes to enable a direct comparison. The histologic grade and presence of tumor necrosis in metastatic mammary carcinoma to the lymph nodes were evaluated in the same manner as for the primary invasive ductal carcinomas.

Immunohistochemical staining for estrogen receptors, progesterone receptors, p53, and HER2 products in the primary invasive ductal carcinoma was performed using an autoimmunostainer (Optimax Plus; BioGenex, San Ramon, CA). The antigen retrieval device for the Optimax Plus was an autoclave, and each specimen was immersed in citrate buffer and incubated at 121°C for 10 minutes. Immunoperoxidase staining was performed using a labeled streptavidin-biotin staining kit (BioGenex) according to the manufacturer's instructions. The antibodies that were used were antiestrogen receptor mouse monoclonal antibody ER88 (BioGenex), antiprogesterone receptor mouse monoclonal antibody PR88 (BioGenex), anti-HER2 mouse monoclonal antibody CB11 (BioGnex), and p53 mouse monoclonal antibody DO7 (Dako, Glostrup, Denmark). ER88, PR88, and CB11 were previously diluted, and DO7 was applied at a dilution of 1:100. After immunostaining, the sections were counterstained with hematoxylin. Sections of the invasive ductal carcinomas that were positive for estrogen receptor, progesterone receptor, HER2, and p53 were used each time as a positive control. As a negative control, the primary antibody was replaced with normal mouse immunoglobulin.

Slides of primary invasive ductal carcinomas immunostained for estrogen receptor, progesterone receptor, and p53 were scored using the Allred scoring system, as described previously [19-21]. Briefly, each entire slide was evaluated using light microscopy. First, the proportion of positively stained tumor cells was estimated (0, none; 1, <1/100; 2, 1/100 to <1/10; 3, 1/10 to <1/3; 4, 1/3 to 2/3; and 5, >2/3). Next, the average intensity of positively stained tumor cells was estimated (0, none; 1, weak; 2, intermediate; and 3, strong). The proportion and intensity scores were then added to obtain the total score, which ranged from 0 or 2 to 8. The Allred scores for estrogen receptor, progesterone receptor, and p53 expression in the primary invasive ductal carcinomas were then classified into the following 3 categories [22]: (1) Allred score for estrogen receptor (0 or 2, 3-6, and 7 or 8); (2) Allred score for progesterone receptor (0 or 2, 3-6, and 7 or 8); and (3) Allred score for p53 (0 or 2 or 3, 4-6, and 7 or 8). The Allred score risk classification for p53 in primary

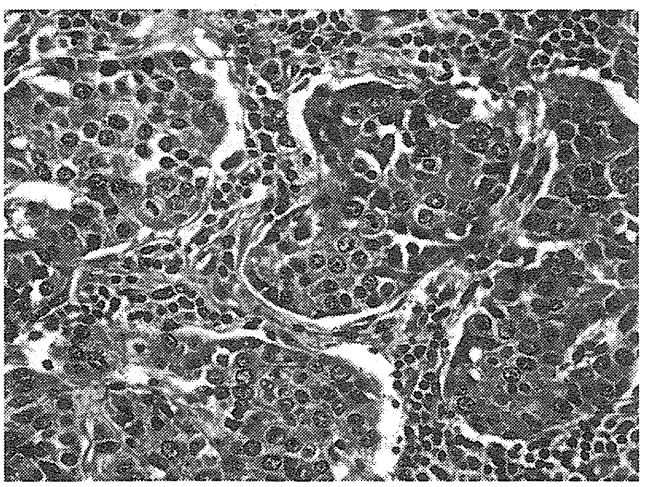

Fig. 1 Histologic features of metastatic mammary carcinoma to the lymph nodes. Six mitotic figures are visible in the tumor cells (arrows).

tumor-stromal fibroblasts forming and not forming fibrotic foci has been described in our previous study [23]. As the distribution of tumor-stromal fibroblasts expressing p53 is scattered, even in primary invasive ductal carcinomas with tumor-stromal fibroblasts with Allred scores of 4 to 8, we modified the Allred scoring system to assess the expression of p53 in tumor-stromal fibroblasts as follows. First, we scanned the entire tumor section stained for p53 at medium power (objective ×10 and ocular ×10) to identify the region with the highest proportion and intensity scores for p53 expression (ie, a "hot spot"), then the highest intensity score (0, none; 1, weak; 2, intermediate; 3, strong), not the average intensity score as in the original methodology, and the highest proportion score (0-5) for the expression of p53 were evaluated using 1 high-power field (hot spot, objective ×40 and ocular ×10). The proportion and intensity scores for the tumor-stromal fibroblasts were then added to obtain the total score, which ranged from 0 or 2 to 8. Finally, we devised an Allred score risk classification for p53 in tumor-stromal fibroblasts in invasive ductal carcinomas based on the combined Allred scores for p53 in tumor-stromal fibroblasts forming and not forming fibrotic foci (Table 2). The HER2 status of the primary invasive ductal carcinomas was semiquantitatively scored using a scale of 0 to 3 according to the level of HER2 protein expression [24] and was classified into 3 categories: 0 or 1, 2, or 3.

Table 2 Overall Allred score classification of p53 in tumor-stromal fibroblasts forming and not forming a fibrotic focus in primary invasive ductal carcinomas

Primary invasive ductal carcinoma with a fibrotic focus	Score class
Allred scores of p53 in tumor-stromal fibroblasts forming a fibrotic focus	
0, 2, or 3	0
4-8	2
Allred scores of p53 in tumor-stromal fibroblasts not forming a fibrotic focus	
0 or 2	0
3	1
4-8	2
Total (A + B)	0-4
Primary invasive ductal carcinoma without a fibrotic focus	**Score class**
Allred scores of p53 in tumor-stromal fibroblasts not forming a fibrotic focus	
0 or 2	0
3	1
4-8	2
Total	0-2
Allred score risk classes for p53 in tumor-stromal fibroblasts forming and not forming fibrotic foci in primary invasive ductal carcinomas	
Low-risk class	0 and 1
Intermediate-risk class	2 and 3
High-risk class	4

Data from Hasebe et al [23].

2.3. Patient outcome and statistical analysis

Survival was evaluated using a median follow-up period of 78 months (range, 32-116 months) until April 2010. Of the 1039 patients with invasive ductal carcinoma, 865 patients were alive and well, 174 had developed tumor recurrences, and 81 had died of their disease at the end of the study period. The tumor recurrence-free survival and overall survival periods were calculated using the time of surgery as the starting point. Tumor relapse was considered to have

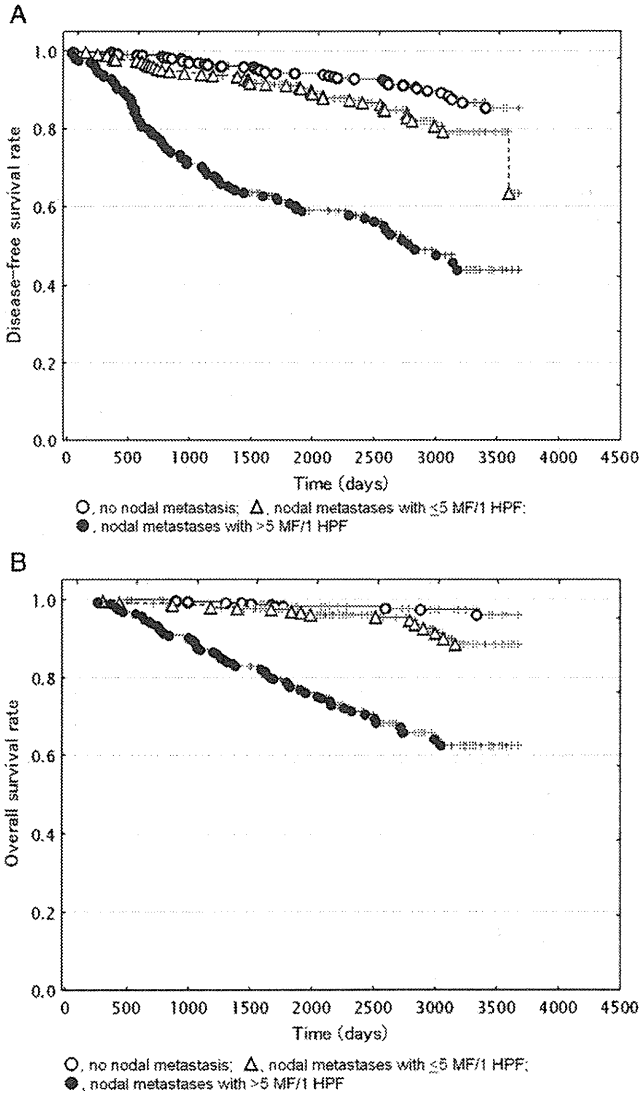

Fig. 2 A and B, Disease-free survival curves and overall survival curves of invasive ductal carcinoma patients according to the number of mitotic figures in metastatic mammary carcinoma to the lymph nodes. Both survival curves decreased significantly according to the number of mitotic figures in metastatic mammary carcinoma to the lymph nodes.

occurred whenever evidence of distant organ metastasis or local recurrence was found.

We analyzed the outcome predictive power of the histologic factors of the primary invasive ductal carcinomas and metastatic mammary carcinoma to the lymph nodes, the immunohistochemical findings, the use of adjuvant therapy (yes or no), and the patient age (≤39 and >39 years) according to the nodal status or the histologic grade of the

Table 3 Multivariate analyses for tumor recurrence and tumor-related death in patients with invasive ductal carcinoma patients overall

	Cases	Tumor recurrence			Tumor-related death		
		Cases (%)	HR, 95% CI	*P*	Cases (%)	HR, 95% CI	*P*
No. of mitotic figures in metastatic mammary carcinoma to the lymph nodes							
No	591	52 (9)	1		13 (2)	1	
<5	283	43 (15)	1		17 (6)	1	
>5	165	79 (48)	2.3 1.5-3.7	<.001	51 (31)	2.3 1.2-4.3	.012
Allred scores for progesterone receptors in primary invasive ductal carcinoma cells							
0 or 2	183	45 (25)	1		23 (13)	1	
3-6	302	59 (20)	0.7 0.5-1.1	.164	35 (12)	0.9 0.5-1.7	.776
7 or 8	554	70 (13)	0.6 0.4-0.9	.020	23 (4)	0.4 0.2-0.7	<.001
Blood vessel invasion							
Absent	890	131 (15)	1		55 (6)	1	
Present	149	43 (29)	1.6 1.1-2.4	.021	26 (18)	1.8 1.1-3.0	.023
Fibrotic focus, diameter (mm), in primary invasive ductal carcinomas							
Absent	664	85 (13)	1		35 (5)	1	
<8	221	37 (17)	1.4 0.8-2.4	.157	14 (6)	1.7 0.8-3.6	.209
>8	154	52 (34)	2.2 1.4-3.5	.001	32 (40)	2.1 1.3-3.6	.004
Grading system for lymph vessel tumor emboli							
Grade 0	664	71 (11)	1		28 (4)	1	
Grade 1	249	39 (16)	1.3 0.8-1.9	.282	15 (6)	1.3 0.7-2.6	.389
Grade 2	97	43 (44)	2.4 1.5-3.8	<.001	22 (23)	2.1 1.2-3.6	.011
Grade 3	29	21 (72)	3.8 2.0-7.2	<.001	16 (55)	2.3 1.2-4.5	.014
Histologic grade of metastatic mammary carcinoma to the lymph nodes							
No	591	52 (9)	1		13 (2)	1	
Grade 1	98	7 (7)	1		1 (1)	1	
Grade 2	172	46 (27)	1.2 0.7-2.0	.638	20 (12)	3.6 1.6-8.0	.002
Grade 3	177	69 (39)	2.0 1.2-3.1	.004	47 (27)	3.9 1.6-9.2	.002
Histologic grade of primary invasive ductal carcinomas							
Grade 1	260	14 (5)	1		1 (0.4)	1	
Grade 2	438	57 (13)	1.6 0.9-3.0	.107	24 (6)	6.4 0.8-48.6	.075
Grade 3	341	103 (30)	2.0 1.0-3.8	.034	56 (16)	8.5 1.1-63.6	.039
p53 Allred score risk classes of tumor-stromal fibroblasts forming and not forming a fibrotic focus in primary invasive ductal carcinomas							
Low	714	69 (10)	1		19 (3)	1	
Inter	263	76 (30)	2.3 1.6-3.3	<.001	42 (16)	3.7 2.1-6.5	<.001
High	46	25 (54)	3.0 1.7-5.3	<.001	17 (37)	4.3 2.1-9.1	<.001

Abbreviations: HR indicates hazard ratio; CI, confidence interval; Low, low risk; Inter, intermediate risk; High, high risk.

primary invasive ductal carcinomas for tumor recurrence and tumor-related death using univariate analyses with the Cox proportional hazards regression model. The factors significantly associated with outcome in the univariate analyses were then used in a multivariate analysis using the Cox proportional hazards regression model. The case-wise and step-down method was applied until all the remaining factors were significant at a P value of less than .05. All the analyses were performed using Statistica/Windows software (StatSoft, Tulsa, OK).

3. Results

3.1. Factors significantly associated with patient outcome

Overall, the presence of 6 or more mitotic figures in metastatic mammary carcinoma to the lymph nodes (Fig. 2A and B), blood vessel invasion, a fibrotic foci with a diameter greater than 8 mm in the primary invasive ductal carcinoma, grade 2 or 3 lymph vessel tumor emboli, histologic grade 3 metastatic mammary carcinoma to the lymph nodes, histologic grade 3 primary invasive ductal carcinoma, and intermediate- and high-risk classes for p53 in tumor-stromal fibroblasts forming and not forming a fibrotic focus in the primary invasive ductal carcinomas significantly increased the hazard ratios for tumor recurrence and tumor-related death in the multivariate analyses (Table 3). An Allred score of 7 or 8 for progesterone receptors in the primary invasive ductal carcinoma significantly decreased the hazard ratios for tumor recurrence and tumor-related death in the multivariate analyses (Table 3). Histologic grade 2 metastatic mammary carcinoma to the lymph nodes significantly increased the hazard ratio for tumor-related death in the multivariate analyses (Table 3).

Among the patients with invasive ductal carcinoma with nodal metastasis, the presence of 6 or more mitotic figures in metastatic mammary carcinoma to the lymph nodes, blood vessel invasion, grade 2 or 3 lymph vessel tumor emboli, and intermediate- and high-risk classes for p53 in tumor-stromal fibroblasts forming and not forming a fibrotic focus in the primary invasive ductal carcinomas significantly increased

Table 4 Multivariate analyses for tumor recurrence and tumor-related death in patients with invasive ductal carcinoma with nodal metastases

	Cases	Tumor recurrence			Tumor-related death		
		Cases (%)	HR, 95% CI	P	Cases (%)	HR, 95% CI	P
No. of mitotic figures in metastatic mammary carcinoma to the lymph nodes							
<5	283	43 (15)	1		17 (6)	1	
>5	165	79 (48)	2.6	<.001	51 (31)	2.8	.004
			1.7-3.8			1.4-5.7	
Allred scores for progesterone receptors in primary invasive ductal carcinoma cells							
0 or 2	79	30 (38)	1		17 (22)	1	
3-6	133	41 (31)	0.7	.151	30 (23)	0.8	.581
			0.4-1.2			0.4-1.7	
7 or 8	236	51 (21)	0.6	.040	21 (9)	0.4	.019
			0.3-0.9			0.2-0.8	
Blood vessel invasion							
Absent	360	86 (24)	1		44 (12)	1	
Present	87	36 (41)	1.8	.007	24 (28)	2.0	.029
			1.2-2.7			1.1-3.8	
Grading system for lymph vessel tumor emboli							
Grade 0	199	34 (17)	1		18 (9)	1	
Grade 1	138	31 (23)	1.3	.306	13 (9)	1.3	.448
			0.8-2.2			0.6-2.9	
Grade 2	83	37 (45)	2.3	<.001	22 (27)	2.2	.030
			1.5-3.4			1.1-4.3	
Grade 3	28	20 (71)	2.8	<.001	15 (53)	2.9	.007
			1.6-4.8			1.3-6.1	
p53 Allred score risk classes of tumor-stromal fibroblasts forming and not forming a fibrotic focus in primary invasive ductal carcinomas							
Low	300	50 (17)	1		18 (6)	1	
Inter	115	51 (44)	2.1	<.001	33 (29)	2.9	.001
			1.4-3.2			1.5-5.7	
High	28	20 (71)	2.8	<.001	16 (57)	4.5	.001
			1.5-5.0			1.8-11.3	

the hazard ratios for tumor recurrence and tumor-related death in the multivariate analyses (Table 4). The Allred score of 7 or 8 for progesterone receptors in the primary invasive tumor cells significantly decreased the hazard ratios for tumor recurrence and tumor-related death in the multivariate analyses (Table 4).

Among the patients with histologic grade 1 primary invasive ductal carcinoma, the presence of 6 or more mitotic figures in metastatic mammary carcinoma to the lymph nodes ($P = .006$), lymph vessel tumor emboli grades 1 ($P = .007$) and 2 ($P = .009$), and a high-risk class for p53 in tumor-stromal fibroblasts forming and not forming a fibrotic focus in the primary invasive ductal carcinoma ($P = .015$) significantly increased the hazard ratios for tumor recurrence in the multivariate analyses. Because only 1 patient died because of her disease in this patient series, a multivariate analysis for tumor-related death could not be performed.

Among the patients with histologic grade 2 primary invasive ductal carcinoma, the presence of 6 or more mitotic figures in metastatic mammary carcinoma to the lymph nodes, a fibrotic foci with a diameter greater than 8 mm in the primary invasive ductal carcinoma, grade 2 or 3 lymph vessel tumor emboli, and intermediate- and high-risk classes for p53 in tumor-stromal fibroblasts forming and not forming a fibrotic focus in the primary invasive ductal carcinoma significantly increased the hazard ratios for tumor recurrence and tumor-related death in the multivariate analyses (Table 5). An Allred score of 3 or more for estrogen receptors in the primary invasive ductal carcinoma significantly decreased the hazard ratio for tumor recurrence and tumor-related death in the multivariate analyses (Table 5).

Among the patients with histologic grade 3 primary invasive ductal carcinoma, the presence of 6 or more mitotic figures in metastatic mammary carcinoma to the lymph nodes, blood vessel invasion, a fibrotic foci with a diameter greater than 8 mm in the primary invasive ductal carcinoma, grade 2 or 3 lymph vessel tumor emboli, and intermediate- and high-risk classes for p53 in tumor-stromal fibroblasts forming and not forming a fibrotic focus in the primary invasive ductal carcinoma significantly increased the hazard ratios for tumor recurrence and tumor-related death in the multivariate analyses (Table 6). The presence of 9 or more extranodal blood vessel tumor emboli significantly

Table 5 Multivariate analyses for tumor recurrence and tumor-related death in patients with histologic grade 2 invasive ductal carcinoma

	Cases	Tumor recurrence			Tumor-related death		
		Cases (%)	HR, 95% CI	*P*	Cases (%)	HR, 95% CI	*P*
No. of mitotic figures in metastatic mammary carcinoma to the lymph nodes							
No	251	19 (8)	1		3 (1)	1	
<5	149	20 (13)	1		9 (6)	1	
>5	38	18 (47)	3.1	<.001	12 (32)	5.4	<.001
			1.6-5.9			2.1-13.5	
Allred scores for estrogen receptors in primary invasive ductal carcinoma cells							
0 or 2	56	15 (27)	1		11 (20)	1	
3-6	57	5 (9)	0.3	.015	2 (4)	0.1	.022
			0.1-0.8			0.02-0.7	
7 or 8	325	37 (11)	0.4	.002	11 (3)	0.2	.001
			0.2-0.7			0.07-0.5	
Fibrotic focus, diameter (mm), in primary invasive ductal carcinomas							
Absent	283	26 (9)	1		10 (3)	1	
<8	99	14 (14)	1.5	.260	5 (5)	1.3	.678
			0.7-2.9			0.4-1.2	
>8	56	17 (30)	3.3	<.001	9 (16)	4.2	.006
			1.7-6.3			1.5-11.8	
Grading system for lymph vessel tumor emboli							
Grade 0	282	26 (9)	1		9 (3)	1	
Grade 1	115	15 (13)	1.5	.260	6 (5)	1.3	.678
			0.8-2.9			0.4-1.2	
Grades 2 or 3	41	16 (39)	3.1	.002	9 (22)	4.2	.006
			1.6-6.4			1.5-11.8	
p53 Allred score risk classes of tumor-stromal fibroblasts forming and not forming a fibrotic focus in primary invasive ductal carcinomas							
Low	336	28 (8)	1		9 (3)	1	
Inter	86	24 (28)	2.4	.003	12 (14)	3.6	.009
			1.4-4.3			1.4-9.3	
High	12	5 (42)	3.7	.014	3 (25)	7.0	.019
			1.3-10.8			1.4-35.8	

Table 6 Multivariate analyses for tumor recurrence and tumor-related death in patients with histologic grade 3 invasive ductal carcinoma

	Cases	Tumor recurrence			Tumor-related death		
		Cases (%)	HR, 95% CI	*P*	Cases (%)	HR, 95% CI	*P*
No. of mitotic figures in metastatic mammary carcinoma to the lymph nodes							
No	167	31 (19)	1		10 (6)	1	
<5	58	16 (28)	1		8 (14)	1	
>5	116	56 (48)	1.9	.007	38 (33)	3.1	.001
			1.2-3.1			1.5-6.1	
Blood vessel invasion							
Absent	280	75 (27)	1		37 (13)	1	
Present	61	28 (46)	2.1	.003	19 (31)	2.0	.017
			1.3-3.3			1.1-3.7	
Fibrotic focus, diameter (mm), in primary invasive ductal carcinomas							
Absent	193	51 (26)	1		24 (12)	1	
<8	69	18 (26)	0.9	.660	9 (13)	1.2	.714
			0.5-1.6			0.5-2.7	
>8	79	34 (43)	1.7	.049	23 (29)	2.0	.037
			1.0-2.9			1.1-3.7	
Grading system for lymph vessel tumor emboli							
Grade 0	205	43 (21)	1		18 (9)	1	
Grade 1	62	15 (24)	0.9	.649	9 (15)	1.0	.945
			0.5-1.6			0.4-2.4	
Grade 2	50	27 (54)	2.2	.005	14 (28)	2.1	.036
			1.3-3.7			1.1-4.0	
Grade 3	24	18 (75)	2.7	.004	15 (63)	3.3	.002
			1.4-5.4			1.6-6.9	
p53 Allred score risk classes of tumor-stromal fibroblasts forming and not forming a fibrotic focus in primary invasive ductal carcinomas							
Low	169	32 (19)	1		9 (5)	1	
Inter	133	49 (37)	2.0	.002	30 (23)	4.0	<.001
			1.9-16.7			1.9-8.6	
High	31	18 (58)	2.3	.014	14 (26)	4.2	.003
			1.2-4.5			1.6-10.7	

increased the hazard ratio for tumor recurrence ($P = .002$), and the presence of a nodal metastasis with a maximum dimension greater than 20 mm significantly increased the hazard ratio for tumor-related death in the multivariate analyses ($P = .032$).

4. Discussion

This study clearly indicated that the number of mitotic figures in metastatic mammary carcinoma to the lymph nodes was a very important histologic predictor of outcome for patients with invasive ductal carcinoma, independent of the nodal status or the histologic grade of the primary invasive ductal carcinoma, confirming the results of our previous study [11]. Furthermore, the number of mitotic figures in metastatic mammary carcinoma to the lymph nodes had a significantly greater outcome predictive power than the number of nodal metastases or the size of the nodal metastases in multivariate analyses performed in this study. These results strongly suggest that the biologic characteristics of metastatic mammary carcinoma to the lymph nodes are more important than the quantity of metastatic mammary carcinoma to the lymph nodes when predicting the outcome of patients with invasive ductal carcinoma.

This study also clearly demonstrated that the number of mitotic figures in metastatic mammary carcinoma to the lymph nodes is superior to the number of mitotic figures in the primary invasive ductal carcinoma for accurately predicting the outcome of patients with invasive ductal carcinoma, independent of the nodal status or the histologic grade of the primary invasive ductal carcinoma. Although the reason for this observation remains unclear, pathologists should evaluate the number of mitotic figures in metastatic mammary carcinoma to the lymph nodes but not necessarily the number of mitotic figures in the primary invasive ductal carcinoma to assess the true malignant potential of invasive ductal carcinomas accurately.

Although the number of mitotic figures is 1 factor that contributes to the histologic grade of the primary invasive ductal carcinoma and metastatic mammary carcinoma to the lymph nodes, the outcome predictive power of the number of mitotic figures in metastatic mammary carcinoma to the

lymph nodes was superior to that of the histologic grade of the primary invasive ductal carcinoma or metastatic mammary carcinoma to the lymph nodes. This finding strongly suggests that pathologists can accurately assess the true malignant potential of invasive ductal carcinomas using only the number of mitotic figures in metastatic mammary carcinoma to the lymph nodes, independent of the structural atypia or nuclear atypia observed in the tumor cells. Furthermore, the multivariate analyses in this study clearly showed the excellent outcome predictive power of the number of mitotic figures in metastatic mammary carcinoma to the lymph nodes among patients with invasive ductal carcinoma regardless of the histologic grade. Thus, the number of mitotic figures in metastatic mammary carcinoma to the lymph nodes may be a very useful histologic factor for the subclassification of patients within each histologic grade of invasive ductal carcinoma into a low- or high-risk category.

This study also clearly showed that the grading system for lymph vessel tumor emboli and the p53 Allred risk classes of tumor-stromal fibroblasts forming and not forming a fibrotic focus are significant predictors of outcome for patients with invasive ductal carcinoma, independent of the nodal status or histologic grade of the primary invasive ductal carcinoma. In addition, the presence of blood vessel invasion was a significant predictor of outcome for patients overall, for patients with nodal metastases, and for patients with histologic grade 2 invasive ductal carcinoma. The fibrotic focus diameter was also a significant predictor of outcome for patients overall and for patients with histologic grade 2 or 3 invasive ductal carcinoma. Thus, in addition to the number of mitotic figures in metastatic mammary carcinoma to the lymph nodes, the grading system for lymph vessel tumor emboli and the p53 Allred risk classes of tumor-stromal fibroblasts forming and not forming a fibrotic focus are likely to be very important predictors of outcome, whereas the presence of blood vessel invasion and the fibrotic focus diameter are likely to be of secondary importance.

In conclusion, this study clearly demonstrated the excellent outcome predictive power of the number of mitotic figures in metastatic mammary carcinoma to the lymph nodes. In the future, investigations of the factors that accelerate the proliferative activity of metastatic mammary carcinoma to the lymph nodes are likely to be very important for devising adjuvant therapies targeting such factors and for improving the prognosis of patients with invasive ductal carcinoma.

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