Table 1
Neoadjuvant endocrine trials.

Author or trial name	Number of patients	Design	Duration (month)	Clinical ORR[e]
IMPACT[2]	330	ANA[a] vs TAM[b] vs ANA + TAM	3	37%, 36%, 39%
PROACT[3]	451	ANA vs TAM	3	49.7%, 39.7%
PO24 Trial[4]	337	LET[c] vs TAM	4	55%, 36%
GENARI Trial[5]	29	EXE[d]	4	37.0%
French study[6]	45	EXE	14–27 weeks	70.6%
Gil Gil (Spain)[7]	55	EXE	6	50%
Mustacchi[8]	44	EXE	6	66%

[a] ANA = Anastrozole.
[b] TAM = Tamoxifen.
[c] LET = Letrozole.
[d] EXE = Exemestane.
[e] ORR = objective response rates.

more patients than did tamoxifen. The neoadjuvant drug, exemestane, has been evaluated in several small studies. The results have been promising and warrant further evaluation to determine the optimal therapeutic conditions for hormone receptor-positive patients. Specifically, the optimal treatment duration time and the causal relationship between neoadjuvant endocrine therapy and clinical response are not clear (Table 1). In addition, there are studies that have reviewed the optimal duration time of hormone treatments. Here, we investigated the benefits of 4 and 6 month long neoadjuvant exemestane therapy.

Materials and methods

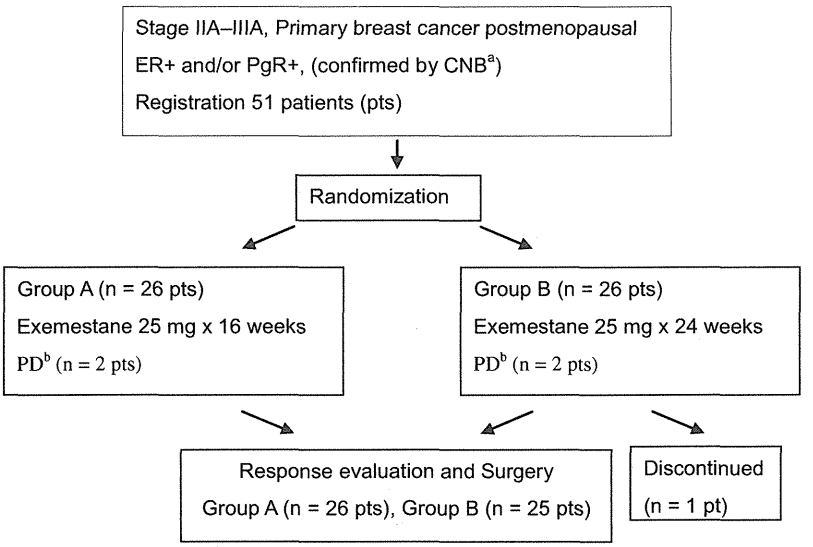
Patients

We enrolled ≥55-year-old post-menopausal women (defined as: no spontaneous menses for > 1 year; LH levels > 30 IU/L; or bilateral oophorectomy prior to breast cancer diagnosis) with stage IIA–IIIA invasive ER- and/or PgR-positive breast carcinoma, as confirmed by immunohistochemical examination of core-needle biopsies (defined as: >10% endocrine receptor + nuclear staining). We further required that tumors be measurable by clinical palpation. Written informed consent was obtained from each patient.

Patients were ineligible if they had any severe coincident medical disease that would prevent them from receiving surgery, place them at unusual risk, or confound the study results; were unwilling or unable to discontinue using drugs affecting sex hormones (including hormone replacement therapy); had suffered from any invasive malignancy within the previous 5 years (other than carcinoma of the skin or carcinoma in situ of the cervix, adequately cone biopsied); had received any previous breast cancer treatment or tamoxifen as part of a breast cancer prevention study; or, had received treatment with non-approved drugs during the 3 months prior to randomization. Criteria for withdrawal from the study included patients who had completed the 5-year treatment course; did not begin randomized therapy; withdrew informed consent; had confirmed clinically significant disease before surgery or confirmed recurrence after surgery; had an adverse event; or, were withdrawn at the investigator's discretion.

Study design and setting

This study was conducted at three hospitals in Japan as a multicenter, open-label, double-arm, randomized, phase II clinical trial of pre-operative exemestane treatment in post-menopausal women with primary breast cancer. In order to optimally balance the patients in the two treatment arms with respect to prognostic factors, the patients were stratified by tumor factor, node factor, and age. The neoadjuvant endocrine treatment regimen consisted of one 25 mg exemestane tablet daily for 4 or 6 months. Fifty-one post-menopausal women with ER-positive and/or PgR-positive invasive breast cancer were randomly assigned to exemestane (25 mg/day) for 4 months (Group A) or exemestane



Setting: Multicenter study involving 3 hospitals in Japan

[a]CNB = core needle biopsy

[b]PD = Progressive Disease

The patient with PD canceled treatment and underwent immediate surgery.

Fig. 1. Study design.

(25 mg/day) for 6 months (Group B; Fig. 1). When antitumor effects were observed with progressive disease (PD), the treatment was canceled and patients underwent surgery immediately. All patient data was collected by UMIN (UMIN000005668) and analyzed at the National Cancer Center in Japan. Tumors were measured by caliper before exemestane treatment began, and again in the eighth week of therapy. Tumor regression by clinical examination, pathological response, decisions regarding breast-conserving surgery, and safety assessments were the main outcome measures. All patients provided written informed consent. This investigational registration period was planned three years from May 2008. The trial was conducted in accordance with the principles of Good Clinical Practice as specified in the Declaration of Helsinki (Edinburgh, 2000). The study protocol was guided by the current regulations governing clinical trials, and was approved by the Ethics Committees of the individual hospitals involved. All patients gave written informed consent before study enrollment.

Study endpoints

The primary endpoints were objective response rates (ORR) by caliper at 4 and 6 months of treatment using an intention to treat analysis. Secondary endpoints were the rates of breast-conserving surgery or mastectomy, and the pathological response rates.

Clinical assessments

The primary study objective was to compare the differences between exemestane treatment for 4 and 6 months, using objective complete responses (CRs) and partial responses (PRs) as defined by the Response Evaluation Criteria in Solid Tumors (RECIST),[9] which is based on caliper measurements of tumor size. Clinical response was assessed by comparing the longest diameter of the target lesions with the baseline measurement based on RECIST criteria. Every 4 weeks, patients underwent a physical examination, toxicity assessment, and tumor assessment using WHO criteria. If tumor progression was suspected, the tumor was further assessed by ultrasound or mammography. At baseline and immediately before surgery, the investigator recorded the extent of the least invasive feasible breast surgery option at that particular time: whether breast-conserving surgery or mastectomy was needed, or whether the tumor was inoperable.

Histological assessments

Histopathological therapeutic response was classified according to the General Rules for the Clinical and Pathological Recording of Breast Cancer 2005.[10] For Grade 0, no response was observed; Grade 1a comprised those tumors with mild changes in cancer cells regardless of the area, or marked changes seen in less than one-third of cancer cells; Grade 1b comprised tumors with marked changes seen in more than one-third but less than two-thirds of tumor cells; Grade 2 tumors contained marked changes in more than two-thirds of tumor cells; and Grade 3 tumors demonstrated a complete response, with no cancerous cells remaining. Mild changes included slight degenerative changes in cancer cells not suggestive of cell death (including cancer cells with vacuolation of the cytoplasm, eosinophilic cytoplasm, swelling of the nucleus, *etc.*). Marked changes include noticeable degenerative changes in cancer cells suggestive of cell death (including liquefaction, necrosis, and disappearance). The pathological response group was defined as tumors with Grade 1b and 2 responses. The non-response group was defined as tumors with Grade 0 and 1a responses.

Statistics

Based upon previous results, we assumed the response rate to be 40% and 60% after 4 and 6 months of exemestane, respectively (Table 1). To achieve an 80% statistical power, 46 examples were required to detect differences in both response rates with a 5% level of significance.[1] To account for attrition, we enrolled 50 patients.[11] Analysis was on an intention to treat (ITT) basis. The chi-squared test was used to compare tumor characteristics and responses, and rates of breast-conserving surgery between groups. Results with $p < 0.05$ were considered to be significant.

Results

Patient baseline characteristics

The study enrolled 52 post-menopausal women at 3 hospitals in Japan between April 25, 2008 and August 12, 2010. Of these, 26 patients were allocated to Group A, and 26 to Group B. One patient withdrew and did not complete the study (Group B). The main characteristics of the eligible patients are described in Table 2. The baseline characteristics were well balanced between the two treatment arms (Table 2).

Efficacy results

Evaluation of the primary efficacy endpoint (overall objective response as determined by clinical palpation) revealed that there was no statistically significant difference in the overall objective response (CR + PR) between the two treatment groups: Group A, 42.3%; Group B, 48.0%; $p = 0.89$ (Table 3). Clinically, 7.7% of Group A and 8.0% of Group B patients progressed while 50.0% and 44.0% of Group A and B patients, respectively, remained stable (not significant). As for the anti-tumor effect assessed by caliper at the eighth week, there were no differences between the two cohorts (Table 3). The pathological response rates of Groups A and B were 19.2% and 32.0%, respectively, a difference that was not statistically significant (Table 4, $p = 0.47$). Pathological CR in the primary breast lesion was only observed in one patient in Group B. Withdrawals from the trial due to side effects did not occur in either Group.

Table 2
Patients' baseline characteristics.

		Group A (4 months)	Group B (6 months)
Age, median (range)		66 (51–80)	64 (57–80)
Tumor stage, number (%)	T2	24 (92.3%)	24 (92.0%)
	T3	2 (7.7%)	2 (8.0%)
Nodal stage, number (%)	N0	21 (80.8%)	24 (92.0%)
	N1	5 (19.2%)	2 (8.0%)
Clinical stage, number (%)	IIA	19 (73.1%)	22 (84.0%)
	IIB	7 (26.9%)	4 (16.0%)
BMI[a]		23.9 (18.5–31.5)	24.5 (17.5–32.3)
Tumor diameter (caliper) Median (range) mm		30.5 (20–60)	30.0 (13–55)
Receptor status			
ER[b] positive/HER2[c] negative		25	22
ER[b] positive/HER2 positive		1	3
PgR[d]	Positive	20	18
	Negative	6	8

There were no differences between Groups A and B in these characteristics.
[a] BMI = body mass index.
[b] ER = estrogen receptor.
[c] HER2 = human epidermal growth factor receptor type 2.
[d] PgR = progesterone receptor.

Table 3
Clinical response (caliper).

Response[a]	Group A (4 months) number (26)		Group B (6 months) number (25)	
	8 weeks	16 weeks	8 weeks	24 weeks
CR	0	1	0	2
PR	7	10	5	10
SD	17	13	20	11
PD	2	2	0	2
Clinical ORR (CR or PR)	26.9%	42.3%	20.0%	48.0%

$p = 0.89$.
Complete Response: CR, Partial Response: PR, Stable Disease: SD, Progressive Disease: PD.
ORR: objective response rates.
[a] The RECIST methodology was used to assess response (Therasse et al., 2000).

Table 4
Clinical response (pathological response).

Pathological response[a]	Group A (4 months) number	Group B (6 months) number
3	0	1
2	0	1
1b	5	6
1a	15	13
0	6	4
Response rate (1b or 2 or 3)	19.2%	32.0%

$p = 0.47$.
0 no response, 1a mild response, 1b moderate response, 2 marked response, 3 complete response.
[a] Pathological response was defined as a Grade 1b, 2, or 3 lesion according to the following criteria.

Breast conservation

Of the 52 randomized patients, 32 would have required a mastectomy at baseline (17 in Group A and 15 in Group B; Table 5). For one of these patients, an operation was not performed. Surgery outcomes with respect to breast conservation improved in 4 of 26 patients in Group A (15.4%), as compared to 1 of 25 patients in Group B (4.0%). As compared to the intent-to-treat population, the increase in patients eligible for breast conserving surgery was numerically higher in Group A than Group B, although this difference did not reach statistical significance.

Discussion

ER-positive tumors are generally less sensitive to chemotherapy than ER-negative tumors.[12,13] Some trials have shown that tamoxifen is an effective primary endocrine agent for the treatment of locally advanced[14] and operable ER-positive breast cancers, especially in the elderly population.[15,16] A combined analysis of the IMPACT and PROACT clinical trials showed a trend toward better objective response rates when patients received aromatase inhibitors, but no statistically significant difference was observed between treatments with aromatase inhibitors or tamoxifen.[2,3] However, in the P024 trial, the objective response rate for treatment with aromatase inhibitors was significantly greater than that for tamoxifen.[4] At present, the optimum duration of treatment for neoadjuvant endocrine treatment is not known. Ideally, the timing would be based on individual patient response. Clinical trials report a common duration period of preoperative endocrine therapy as 4–6 months. Likewise, the duration of many neoadjuvant chemotherapy treatments is 6 months. Therefore, we carried out this study to compare the use of exemestane for 4 and 6 months prior to surgery. We found no significant differences in outcomes between patients who received the drug for 4 or 6 months; however, the latter group tended to have higher anti-tumor responses. It is thought that this observation did not reach statistical significance because we set the significant difference of both groups at 20%.Our study results show that the maximum response of neoadjuvant hormone therapy by exemestane is around four months. These data are consistent with the study by Antonio Llombart-Cussac et al.,[18] in which the maximum response to therapy with letrozole was at 4.2 months. In addition, a randomized phase II study[17] compared 4–8 months of letrozole in a single arm; there tended to have higher anti-tumor responses. We think that these results indicate that the maximum response to neoadjuvant hormone therapy is also around four months. ER- and/or PgR-positive tumors are biologically heterogeneous. It is thought that biologically heterogeneous groups require detailed statistical adjustment. Krainick-Strobel UE et al.[17] found that 4 months of neoadjuvant exemestane therapy improved the rate of breast-conserving surgery. There was not a large difference in response rates for treatments of 3–6 month duration; however, the anti-tumor effects tended to be greater after 6 months of treatment as compared to shorter time points. In our study, neither treatment group experienced severe side effects as a result of the therapy. However, Group B tended to have a higher pathological response rate. It seems that the maximum anti-tumor effect may be reached at different time points for each patient over the course of 24 weeks of treatment. Therefore, we cannot expect a large antitumor effect by treating for longer than 4 months; however, we could extend the treatment period until the time of operation. Furthermore, in addition to using exemestane as preoperative treatment in post-menopausal women with ER-positive breast cancer, due to the mild side effects observed during the 6 month course of treatment, we envision administering the drug over the long term under careful clinical supervision.

Table 5
Rate of breast-conserving surgery.

Group A (4 months)			Group B (6 months)		
	Estimation (pre treatment)	Post treatment		Estimation (pre treatment)	Post treatment
Mastectomy	17	13	Mastectomy	14	13
BCS[a]	9	13	BCS	11	12
Rate of BCS	34.6%	50%	Rate of BCS	44.0%	48.0%

[a] BCS = Breast-conserving surgery.

Ethical approval

The present work has been approved by the ethical committee of each institutional.

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Conflict of interest statement

All authors declare that they have no conflict of interest.

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None.

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Original Study

Prognostic Factors for Triple-Negative Breast Cancer Patients Receiving Preoperative Systemic Chemotherapy

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Abstract

This study was aimed to identify significant prognostic factors for triple-negative breast cancer patients receiving preoperative systemic chemotherapy. Clinicopathologic backgrounds and prognosis of 135 patients were investigated. Statistical analysis demonstrated that better clinical response, fewer positive nodes, and lower histologic grades were significant favorable prognostic factors for the patients.

Background: Triple-negative breast cancer patients are more likely to achieve a pathologic complete response after preoperative chemotherapy but they have still poor prognosis. The aim of this study was to identify prognostic factors in triple-negative breast cancer patients receiving preoperative chemotherapy. **Patients and Methods:** Triple-negative breast cancer patients who underwent preoperative chemotherapy were retrospectively analyzed. Significant prognostic factors among clinical and pathologic variables were investigated with Kaplan–Meier analysis and Cox proportional hazards modeling for disease-free survival and overall survival. **Results:** Among the 135 triple-negative breast cancer patients, the median age was 54 years, median tumor diameter on palpation was 4.5 cm, and there were 62 clinically node positive patients. The clinical response rate was 76% (103 patients) and pathologic complete response rate was 21% (29 patients). Median disease-free survival was 44.4 months and median overall survival was 49.2 months. Univariate and multivariate analysis showed that that completion of chemotherapy, better clinical response, fewer positive nodes, and lower histologic grades were significant factors associated with both disease-free and overall survival. **Conclusions:** Our data demonstrated that clinical response of preoperative systemic chemotherapy is an important independent favorable prognostic factor for triple-negative breast cancer.

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Keywords: Clinical response, Histologic grades, Nodal status, Pathologic complete response, Prognosis

Introduction

Recent advances have changed the treatment strategy for breast cancer. The biological behavior of breast cancer has been investigated by molecular profiling with the use of array technology,[1] and breast cancers were divided into 3 major subtypes: luminal subtype, human epidermal growth factor receptor 2 (HER2) subtype, and basal and normal breast-like subtype.[1]

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Triple-negative breast cancer (TNBC), which is characterized by the lack of estrogen receptor (ER), progesterone receptor (PgR), and HER2 expression, is highly though not completely concordant with the basal subtype according to Sorlie's classification. It has no subtype-specific treatment and chemotherapy remains the only possible therapeutic option in the adjuvant or metastatic setting. Therefore, TNBC patients usually undergo adjuvant or neoadjuvant chemotherapy, but TNBC tends to develop visceral metastases and aggressive clinical behavior despite the clinical response.[2,3]

For patients receiving preoperative systemic chemotherapy (PST), previous studies involving patients with all breast cancer subtypes have shown that pathologic complete response (pCR) is a powerful surrogate marker of long-term disease-free (DFS) and overall survival (OS).[4–6] Thereafter, it was reported that pCR was also a surrogate marker of cancer-specific prognosis for TNBC patients.[7]

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On the other hand, patients who do not achieve pCR will have shorter survival and data on pathologic response can be obtained after PST. In order to resolve this issue, response-guided treatment has been examined in a phase III clinical trial.[8] This trial includes all breast cancer subtypes, but if response-guided treatment were applied to TNBC, it should be noted that TNBC tends to develop visceral metastases and aggressive clinical behavior despite clinical response.[2]

In this study, we retrospectively collected clinical, pathologic, and prognostic information on TNBC patients who underwent PST at our institution, and analyzed the data to identify any significant prognostic factors and to investigate what is the ideal treatment strategy for TNBC patients.

Patients and Methods

Among 4195 operable primary breast cancer patients, there were 135 patients who were diagnosed as TNBC by needle biopsy and then underwent systemic chemotherapy between 2000 and 2009 before surgery. The clinical tumor size, which was measured by magnetic resonance imaging (MRI) or computed tomography (CT) scans and ultrasonography (US), and clinical nodal status were recorded both before and after PST. Patients with more than International Union Against Cancer (UICC) T2 or N1 tumor underwent examination of CT and bone scintigram to rule out distant metastasis. The PST protocol and treatment of adverse effects were managed by clinical oncologists. The surgical procedure was determined by the surgeon in consultation with the radiologist on the radiologic findings after systemic chemotherapy. Patients underwent 1 or more of the following procedures: mastectomy, partial mastectomy, axillary lymph node dissection, and sentinel lymph node biopsy. Clinical response was based on clinical and radiologic findings as evaluated by surgeons, oncologists, and radiologists according to the Response Evaluation Criteria in Solid Tumors guidelines. Radiologic examinations of MRI or CT, and US for evaluation of clinical response were performed at least both before and after PST for every patient. Negative ER and PgR status were defined as < 1% of positive cells or an Allred score < 3, and negative HER2 status was defined as a HER2 score of 0 or 1 both before PST and after surgery by more than 2 pathologists. Patients with HER2 scores of 2 were excluded from this study. Pathologists also recorded the pathologic invasive tumor size, pathologic nodal status, histologic grades, the presence or absence of lymphovascular invasion, and pathologic response to PST based on the findings in the surgical specimen. The definition of pCR allowed for residual cancer of the intraductal component. Partial mastectomy or 4 or more positive lymph nodes were considered indications for radiation therapy.

All patients received physical examinations every 3–6 months, and blood tests and chest x-rays at least annually as outpatients after surgical treatment. Computed tomography and bone scintigraphy were performed according to patients' symptoms or abnormal findings on physical examination or blood tests. All patients were followed up until latest outpatient visit or death.

The association between clinicopathologic factors and 5-year DFS and OS was investigated using Kaplan–Meier analysis and Cox proportional hazards modeling, which was calculated from the date of PST initiation to the event. Clinicopathologic variables investigated included family history of breast cancer within second-degree relatives, menopausal status, body mass index (BMI), clinical T stage according to the UICC classification before PST, clinical nodal status before PST, chemotherapy regimen, completion of chemotherapy, surgical procedure, radiation therapy, histologic grade, pathologic invasive tumor size, pathologic nodal status according to the UICC classification, lymphatic invasion, vascular invasion, HER2 status (0 or 1), clinical response to PST, and pathologic response (pCR or non-pCR). JMP version 9.0 software was used for statistical analysis.

Table 1 Characteristics of the 135 TNBC Patients Before PST

	Patients (n)
Menopausal Status	
Pre	57
Post	78
Family History (Up to Second-Degree)	
Negative	118
Positive	17
BMI	
< 18.5	10
18.5–25	97
> 25	28
Clinical T Stage	
T1	6
T2	75
T3	34
T4	20
Clinical Nodal Status	
Negative	73
Positive	62

Abbreviations: BMI = body mass index; PST = preoperative systemic chemotherapy; TNBC = triple-negative breast cancer.

Results

Among the 135 TNBC patients, median tumor diameter on palpation was 4.5 cm (range, 1–15 cm), median age was 54 years (range, 23–77), and 73 patients had clinically positive lymph nodes before PST. There were 57 premenopausal and 78 postmenopausal patients. When patients were classified into 3 groups based on BMI, 10 patients were underweight (BMI < 18.5), 97 were within the normal range (BMI 18.5–25), and 28 were overweight or obese (BMI > 25). Patient characteristics are shown in Table 1. Of the 135 patients, 123 underwent both anthracycline (A) and taxane (T) containing (A+T) regimens, 5 patients had an A regimen only, and 7 patients had a T regimen only. The A+T regimen consisted of 4 cycles of doxorubicin (60 mg/m^2) plus cyclophosphamide (600 mg/m^2) followed by weekly paclitaxel (80 mg/m^2), 4 cycles of epirubicin (100 mg/m^2), cyclophosphamide (500 mg/m^2), and 5-fluorouracil (500 mg/m^2) followed by weekly paclitaxel (80 mg/m^2), and 4 cycles of concurrent doxorubicin (50 mg/m^2) plus docetaxel (50 mg/m^2). Concurrent regimens of A and T were terminated by 2002, T monotherapy was

Table 2 Clinical Response to PST

	CR	PR	SD	PD
Regimen				
A+T	43	52	13	15
A	0	3	1	1
T	1	4	2	0
Completion of Chemotherapy				
Yes	34	57	12	1
No	10	2	4	15
Total	44	59	16	16

Abbreviations: A = anthracycline regimen; A+T = regimen containing both anthracycline and taxane; CR = complete response; PD = progressive disease; PR = partial response; PST = preoperative systemic chemotherapy; SD = stable disease; T = taxane regimen.

terminated by 2005, and A regimens were terminated by 2007. Regarding treatment completion, 94 out of 123 patients (76%) receiving A+T regimens completed the scheduled treatment, 4 out of 5 patients (80%) given the A regimen and 6 out of 7 patients (86%) given the T regimen completed the treatment regimen. Seventeen patients discontinued chemotherapy because of adverse effects including febrile neutropenia and neuropathy. Fourteen patients discontinued chemotherapy because of progressive disease (PD). One patient each given a preoperative A regimen and T regimen received the other regimen after surgery; therefore a total of 125 patients received treatment containing both an A and a T (Table 2).

Preoperative systemic chemotherapy resulted in a clinical response rate of 76%, including 44 patients (32%) with clinical complete response (CR) and 59 patients (44%) with partial response (PR). The correlation between completion of chemotherapy and clinical response is shown in Table 2. One hundred four patients completed the scheduled chemotherapy, resulting in 34 CR, 57 PR, 12 stable disease (SD), and 1 PD. On the other hand, 31 patients who did not complete chemotherapy were classified as 10 CR, 2 PR, 4 SD, and 15 PD. There was a significant difference in clinical response between patients who completed or discontinued PST ($P < .0001$).

All patients received successive surgical treatment. Total mastectomy was performed in 83 patients (61%) and partial mastectomy was performed in 52 patients (39%) (Table 3). Sentinel lymph node biopsy was performed in 37 patients (27%) who were clinically node negative before PST, of whom 26 had a negative sentinel node biopsy, and axillary lymph node dissection was omitted in 2 patients. All patients with positive sentinel nodes underwent axillary lymph node dissection.

Pathologic factors based on the surgical specimen findings are represented in Table 4. The median invasive pathologic size was 2 cm, and there were 71 pN0, 41 pN1, 15 pN2, and 8 pN3 patients. There were 87 patients with histologic Grade 3, 42 with Grade 2, and 6 with Grade 1 tumors. Lymphatic invasion was observed in 45 patients and vascular invasion was observed in only 9 patients. Pathologic chemotherapeutic effects among 135 patients consisted of 29 Grade 3 (pCR), 28 Grade 2, 15 Grade 1b, 52 Grade 1a, and 11 Grade 0 (Table 5). The correlation between clinical response and

Table 3 Treatment After PST of the 135 TNBC Patients

Treatment	Patients (n)
Surgical Procedure	
Total mastectomy	83
Wide resection	52
Radiation Therapy	
Yes	95
No	40

Abbreviations: PST = preoperative systemic chemotherapy; TNBC = triple-negative breast cancer.

Table 4 Pathologic Diagnosis of the 135 TNBC Patients

Pathologic Diagnosis	Patients (n)
Pathologic Invasive Size (pT)	
T1 (T ≤ 2.0 cm)	70
T2 (2.0 < T ≤ 5.0 cm)	35
T3 (T > 5.0 cm)	20
Pathologic Nodal Status (pN)	
N0	71
N1	41
N2	15
N3	8
Lymphatic Invasion	
Negative	90
Positive	45
Vascular Invasion	
Negative	126
Positive	9
Histologic Grade	
1	6
2	42
3	87
HER2 Score	
0	91
1	44

Abbreviation: TNBC = triple-negative breast cancer.

pathologic effect is shown in Table 5. Postoperative radiation therapy was administered to 95 patients (70%), including 66 patients who fulfilled the indication criteria, and 29 patients based on physician recommendation. One patient who underwent partial mastectomy declined radiation therapy.

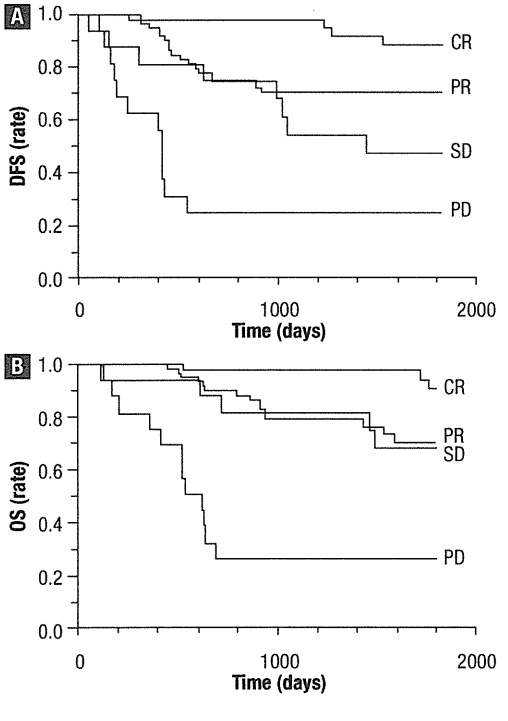
Recurrence occurred in 41 patients (30%) during the follow-up period, and breast cancer death was observed in 37 patients (27%). Median DFS was 44.4 months and median OS was 49.2 months. Five-year DFS and OS were calculated using the Kaplan–Meier method for patients based on clinical response and pathologic re-

Table 5 Correlation Between Pathologic and Clinical Response

Response	CR	PR	SD	PD	Total
Grade 3	19	4	1	0	24
Grade 2	10	20	3	0	33
Grade 1b	2	10	2	1	15
Grade 1a	12	23	9	8	52
Grade 0	1	2	1	7	11
Total	44	59	16	16	135

Abbreviations: CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease.

Figure 1 (A) Kaplan-Meier Disease-free Survival (DFS) Curves According to Clinical Response. There are Significant Differences in DFS According to Clinical Response. (B) Kaplan-Meier Overall Survival (OS) Curves According to Clinical Response. There are Also Significant Differences in OS According to Clinical Response.

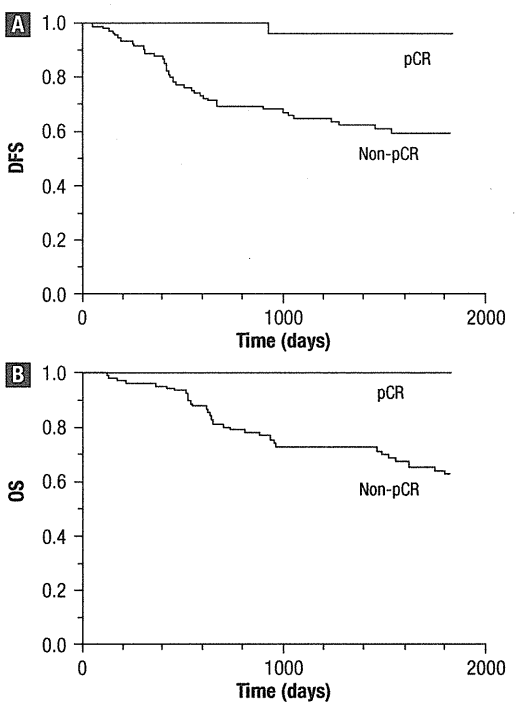


Abbreviations: CR = complete response; PD = progressive disease; PR = partial response; SD = stable disease.

sponse (Figures 1 and 2). There were no breast cancer deaths among patients who achieved pCR.

Results of univariate and multivariate analyses of clinicopathologic variables affecting 5-year DFS and OS are shown in Tables 6 and 7. Completion of chemotherapy, good clinical response, small

Figure 2 (A) Kaplan–Meier Disease-Free Survival (DFS) Curves for Patients With and Without a Pathologic Complete Response (pCR). Achieving pCR is Associated With a Significantly Better Prognosis than Non-pCR. (B) Kaplan–Meier Overall Survival (OS) Curves for pCR and Non-pCR Patients. Achieving pCR is Associated with a Significantly Better Prognosis than Non-pCR. The OS Rate is 100% in pCR Patients



pathologic invasive size, fewer positive nodes, no lymphatic invasion, no vascular invasion, low histologic grade, and pCR were significantly associated with both favorable 5-year DFS and 5-year OS. Multivariate analysis indicated that completion of chemotherapy ($P = .036$ for both DFS and OS), good clinical response ($P = .0007$ for DFS, .0002 for OS), fewer positive nodes ($P = .0004$ for DFS, .004 for OS), and lower histologic grades ($P = .025$ for DFS, .016 for OS) were significantly associated with both favorable 5-year DFS and 5-year OS. Vascular invasion ($P = .039$ for DFS, .061 for OS) were statistically significant for 5-year DFS only.

Discussion

The primary aim of our study was to clarify which factors are prognostic indicators for TNBC patients who receive preoperative systemic chemotherapy. Univariate analysis showed both clinical and pathologic responses were significant factors, in addition to other clinicopathological factors, but multivariate analysis showed that pCR was not an independent prognostic factor. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18 and B-27 multiinstitutional randomized clinical trials of pre- and postopera-

Table 6 Univariate Analysis of Clinicopathological Factors for DFS and OS

	DFS		OS	
	Hazard Ratio (95% CI)	*P*	Hazard Ratio (95% CI)	*P*
Menopausal Status				
Pre	1	.157	1	.133
Post	0.62 (0.33–1.14)		0.63 (0.32–1.22)	
Familial History				
Negative	1	.988	1	.939
Positive	1.03 (0.35–2.40)		0.99 (0.29–2.50)	
BMI				
< 18.5	1	.931	1	.801
18.5–25	1.00 (0.36–4.17)		0.71 (0.25–2.98)	
> 25	0.76 (0.21–3.54)		0.70 (0.20–3.27)	
UICC Stage				
I	1	.318	1	.449
II	0.24 (0.05–4.33)		0.20 (0.04–3.60)	
III	0.42 (0.09–7.61)		0.32 (0.06–5.78)	
PST Regimen				
A+T	1	.891	1	.796
A	0.72 (0.04–3.33)		0.98 (0.05–4.59)	
T	0.82 (0.13–2.69)		NA	
Completion of PST				
Yes	1	.025	1	.0044
No	2.10 (1.07–3.94)		2.44 (1.19–4.78)	
Clinical Response				
CR	1	< .0001	1	< .0001
PR	3.61 (1.33–12.5)		4.25 (1.40–18.4)	
SD	6.56 (2.07–24.6)		4.66 (1.14–22.7)	
PD	19.6 (6.71–70.7)		28.0 (8.67–125.1)	
Surgical Procedure				
Mastectomy	1	.556	1	.546
WLR	0.86 (0.45–1.61)		0.88 (0.43–1.73)	
Radiation Therapy				
Yes	1	.296	1	.934
No	0.71 (0.33–1.40)		0.81 (0.36–1.66)	
pT (Except pCR)				
T1	1	.0009	1	.0024
T2	1.88 (0.81–4.46)		2.14 (0.86–5.52)	
T3	3.93 (1.84–8.88)		4.07 (1.79–10.1)	
pN				
N0	1	< .0001	1	< .0001
N1	4.58 (2.11–10.7)		4.05 (1.76–10.1)	
N2	4.88 (1.74–13.1)		4.65 (1.53–13.4)	
N3	15.4 (5.47–41.9)		10.7 (3.50–30.7)	
Lymphatic Invasion				
No	1	< .0001	1	< .0001
Yes	4.60 (2.46–8.91)		4.06 (2.07–8.28)	

Table 6 Continued

	DFS		OS	
	Hazard Ratio (95% CI)	*P*	Hazard Ratio (95% CI)	*P*
Vascular Invasion				
No	1	< .0001	1	< .0001
Yes	7.56 (3.18–16.0)		6.23 (2.48–13.7)	
Histologic Grade				
1	NA	.0047	NA	.0063
2	1		1	
3	2.84 (1.34–7.01)		3.45 (1.46–10.1)	
HER2 Status				
Score 0	1	.933	1	.613
Score 1	1.00 (0.51–1.88)		0.83 (0.39–1.66)	
Pathologic Response				
pCR	1	.001	NA	.0044
Non-pCR	13.5 (2.94–239.8)			

Abbreviations: A = anthracycline regimen; A+T = regimen containing both anthracycline and taxane; BMI = body mass index; CR = complete response; DFS = disease-free survival; OS = overall survival; pCR = pathologic complete response; PD = progressive disease; pN = pathologic nodal status; PR = partial response; PST = preoperative systemic chemotherapy; pT = pathologic invasive size; SD = stable disease; T = taxane regimen; UICC = International Union Against Cancer; WLR = wide local resection.

Table 7 Multivariate Analysis of Clinicopathologic Factors for DFS and OS

Factor	DFS (*P*)	OS (*P*)
Completion of PST (Yes or No)	.015	.039
Clinical Response (CR, PR, SD, PD)	.0007	.0002
pT (T1, T2, > T3)	.266	.099
pN (N0, N1, N2, N3)	.0003	.0022
Lymphatic Invasion (yes or no)	.562	.513
Vascular Invasion (yes or no)	.039	.061
Histologic Grade (1, 2, or 3)	.025	.016
Pathologic Response (CR or non-CR)	.428	.548

Abbreviations: CR = complete response; DFS = disease-free survival; OS = overall survival; PD = progressive disease; PR = partial response; pT = pathologic invasive size; SD = stable disease.

tive chemotherapy showed that pCR was a favorable prognostic factor for patients who underwent preoperative chemotherapy.[5,9,10] Kaplan–Meier analysis for DFS and OS demonstrated that both good clinical response with PST and pCR were correlated with a favorable prognosis. Our data also show that both DFS and OS of patients who achieve pCR is much better than that of patients who did not achieve pCR by Kaplan–Meier analysis. In addition, there were no breast cancer recurrences and no deaths among patients with pCR, although most recent metaanalysis has shown that prognosis of triple-negative breast cancer is worse than luminal types even if pCR is achieved.[11] However, pCR is not an independent prognostic indicator according to the multivariate analysis. This might be caused by relatively small sample size of our study, and of course, it cannot be concluded that pCR is not a surrogate marker for prognosis of TNBC patients. This implies that there is a strong relationship between pCR and clinical response and clinical response offsets the prognostic value of pCR. We emphasize that some other factors, such as clinical response and histologic grades are also important for TNBC as well as pCR.

In this study, statistical analysis was done with a median follow-up period of 49.2 months, which is too short to evaluate 10-year survival rates. Triple-negative breast cancer has biologically aggressive features, and the DFS curve plateaus 5 years after diagnosis and the OS curve plateaus 8 years after diagnosis.[12] Furthermore, in this study, because there were only 2 patients with UICC stage I disease, our study population included patients with more advanced disease that might result in earlier recurrence and breast cancer death. This is the reason why we analyzed the prognostic factors for TNBC with the current median follow-up time. In contrast, recurrence and breast cancer death in the current study were observed in about one-third of the TNBC patients in the previous study.[10] More recurrences or breast cancer deaths might occur with more time in our study group; therefore, we need to continue observing these patients and reanalyze the prognostic factors in the future.

A recent report[13] showed that women with T1–2 N0 TNBC treated with mastectomy without radiation therapy have a significantly increased risk of locoregional recurrence compared with those treated with partial mastectomy; however, distant metastasis-free survival or OS were not evaluated. Our data demonstrated that the type of surgical procedure, mastectomy or partial mastectomy, did not affect DFS or OS, perhaps because relatively few cases of locoregional recurrence were observed in our study (5.9%) compared with the previous report (10%).

We also found that completion of chemotherapy was a significant prognostic factor among TNBC patients. Multivariate analysis demonstrated that completion of chemotherapy was an independent prognostic factor despite the relationship with clinical response. Pre-

operative systemic chemotherapy should be finished not only in clinical trials but also in routine practice unless unmanageable severe adverse events or obvious disease progression occurs. Furthermore, considering the poor prognosis of patients with clinical PD, another regimen should be considered for patients to avoid a PD clinical response.

There were 16 patients of PD (12%) and 16 of SD (12%) in our study. The rate of clinical nonresponders in our study was higher than that of a previous multiinstitutional randomized phase III trial, NSABP B-27.[14] Our group included 112 of invasive ductal (83%), 9 of invasive lobular (7%), and 14 were special histologic types such as squamous cell carcinoma or spindle cell carcinoma (10%). Preoperative systemic chemotherapy for 7 out of 14 patients (50%) of special types resulted in PD. This might affect the higher PD rate and our results of statistical analysis.

We demonstrated the prognostic data of TNBC patients with PST, but there were 2 out of the 135 patients who received systemic chemotherapy after surgery as well. One patient received A regimen before surgery and T regimen after surgery. The other received T before and A after surgery. These 2 patients were included the 'A+T' group for analysis of prognosis. This might not affect the results because a randomized clinical trial showed that there was no difference in prognosis between preoperative AC-T and preoperative AC plus postoperative T.[10]

Family history is a not significant factor for prognosis. It has been reported that there is a strong correlation between the triple-negative subtype and *BRCA* mutations.[15] Among Japanese women, hereditary breast cancer is strongly associated with the triple-negative phenotype[16] and aggressive behavior. These reports suggest that TNBC patients with a family history of breast cancer have a poorer prognosis than patients with no family history. Our data suggest that the prognosis of TNBC patients with a family history of breast cancer is similar to those with sporadic TNBC. Of course, this might be because of the relatively low numbers of patients with a positive family history in our study, but our findings are supported by a previous report describing that the overall prognosis of breast cancer in *BRCA* carriers receiving PST is similar to patients with sporadic breast cancers receiving PST.[17]

Conclusion

Our study demonstrated that multivariate analysis demonstrates that pCR is not an independent significant prognostic marker for TNBC patients receiving PST. Clinical response is a stronger surrogate marker than pCR for a favorable prognosis. The importance of clinical response should be further investigated in multicenter clinical trials, and as well, novel treatment procedures need to be established for TNBC patients with unfavorable responses to PST.

Clinical Practice Points

- Previous clinical studies have revealed that pCR is a surrogate marker for prognosis after PST, and pCR is usually used as the primary end point of clinical trials involving PST instead of OS or DFS.
- However, there is no report focused on triple-negative breast cancer receiving PST.
- From the current study, Kaplan–Meier analysis demonstrated that patients achieving pCR have more favorable prognosis than the others, but multivariate analysis of characteristics after adjustment for confounders showed that clinical response, nodal status, and vascular invasion instead of pCR were the significant for patients' prognoses.
- Metaanalysis demonstrates that triple-negative patients have a relatively poor prognosis compared with patients with luminal types even if pCR is achieved,[11] and to our knowledge, this is the first report that pCR is not an independent prognostic marker for triple-negative breast cancer patients.
- We believe these findings will be of great interest to oncologists, and particularly to researchers working on breast cancer clinical trials.

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Disclosures

The authors have stated that they have no conflicts of interest.

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Histological factors for accurately predicting first locoregional recurrence of invasive ductal carcinoma of the breast

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The accurate assessment of the risk of first locoregional recurrence is very important for improving the survival of patients with invasive ductal carcinoma of the breast. The present study investigated which histological factors (both well-known histological factors and factors that we have proposed) were the most capable of accurately predicting first locoregional recurrence among 1042 patients with invasive ductal carcinoma and various tumor statuses (overall, nodal status, Union Internationale Contre le Cancer pathological TNM stage, adjuvant therapy status, and adjuvant radiotherapy status) using multivariate analyses by the Cox proportional hazard regression model. The present study clearly demonstrated that the best factor for accurately predicting locoregional recurrence was grade 3 lymph vessel tumor embolus (>4 mitotic figures and >6 apoptotic figures in tumor embolus), followed by type 2 invasive ductal carcinoma (negative for fibrotic foci but positive for atypical tumor-stromal fibroblast), grade 2 lymph vessel tumor embolus (1–4 mitotic figures and >0 apoptotic figures in tumor embolus; >0 mitotic figures and 1–6 apoptotic figures in tumor embolus), primary invasive tumor cell-related factors (>19 mitotic figures, presence of tumor necrosis, presence of skin invasion) and >5 mitotic figures in metastatic carcinomas to the lymph node. Our proposed factors were superior to well-known histological factors of primary invasive tumors or clinicopathological factors for the accurate prediction of first locoregional recurrence in patients with invasive ductal carcinoma of the breast. (*Cancer Sci* 2013; 104: 1252–1261)

Locoregiocal recurrence is an important prognostic factor for patients with invasive ductal carcinoma of the breast,[1] and several studies have been performed to clarify factors that are significantly associated with locoregional recurrence.[2,3] These studies demonstrated that lymph vessel invasion, histological grade, tumor size, hormone receptor status, and HER2 status are very important predictors of locoregional recurrence in patients with invasive ductal carcinoma. We have already reported histological factors that are significantly associated with distant-organ metastasis or the tumor-related death of patients with invasive ductal carcinoma of the breast.[4] Since the publication of our previous study,[4] we have performed additional studies that identified the following new histological factors as predictors of the outcome of patients with invasive ductal carcinoma of the breast[5]: (i) type of invasive ductal carcinoma;[6] (ii) grading system for lymph vessel tumor emboli;[7] (iii) number of apoptotic figures in blood vessel tumor emboli;[8] (iv) number of mitotic figures in metastatic carcinomas to the lymph node;[9] and (v) maximum dimension of metastatic carcinomas to the lymph node.[8] Although our studies clearly demonstrated that the factors we previously reported were very useful for accurately predicting tumor recurrence, distant-organ metastasis or tumor-related death,[4–9] we have not yet investigated whether these factors are significantly associated with the locoregional recurrence of invasive ductal carcinoma of the breast. We are confident that clarification of the recurrent or metastatic patterns of invasive ductal carcinomas based on their histological features will provide clinicians, pathologists, and scientists with very important clues for accurately evaluating the true biological characteristics of invasive ductal carcinomas. Such a result would likely contribute to the establishment of targeted therapies for patients with invasive ductal carcinoma of the breast.

The purpose of the present study was to investigate which histological factors were most capable of accurately predicting first locoregional recurrence in patients with invasive ductal carcinoma of the breast.

Materials and Methods

Patients and histological examinations. The subjects of this study were 1042 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 same case series as that used in our previous study).[5] The invasive ductal carcinomas were diagnosed preoperatively using needle biopsy, aspiration cytology, mammography, or ultrasonography. All the patients were Japanese women, ranging in age from 23 to 72 years old (median, 55 years). All the tumors were classified according to the pathological UICC-TNM (pTNM) classification.[10] The protocol (20–112) for this study was reviewed by the institutional review board of the National Cancer Center.

The clinicopathological factors, well-known histological factors and the eight factors that we previously proposed were evaluated and we arranged the above mentioned factors into five groups (Table 1). The eight factors that we previously proposed are as follows (Tables 1 and 2): (i) fibrotic focus;[11,12] (ii) type of invasive ductal carcinoma (Fig. 1a–c);[6] (iii) grading system for lymph vessel tumor emboli (Fig. 1d–f);[7] (iv) number of apoptotic figures in blood vessel tumor emboli;[8] (v) grade of stromal fibrosis in metastatic carcinomas to the lymph node;[8] (vi) maximum dimension of metastatic carcinomas to the lymph node;[8] (vii) number of extranodal blood vessel tumor emboli;[8] and (viii) number of mitotic figures in

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Table 1. Groups and factors

Clinicopathological group				
1	Adjuvant therapy			
	None	Endocrine therapy	Chemoendocrine therapy	Chemotherapy
2	Adjuvant radiotherapy			
	Not received		Received	
3	Age (year)			
	≤39		>39	
4	Allred scores for estrogen receptors in tumor cells			
	0 or 2	3 to 6	7 or 8	
5	Allred scores for progesterone receptors in tumor cells			
	0 or 2	3 to 6	7 or 8	
6	HER2 category			
	0 or 1	2	3	
Primary invasive tumor cell-related group				
1	Histologic grade			
	Grade 1	Grade 2	Grade 3	
2	Invasive tumor size (mm)			
	≤20	>20 to ≤50	>50	
3	Nuclear feature of primary invasive tumors			
	Small	Moderate	Marked	
4	Number of mitotic figures in the primary invasive tumors			
	≤9	>9 to ≤19	>19	
5	Skin invasion			
	Absent		Present	
6	Tumor necrosis			
	Absent		Present	
Primary tumor-stromal fibroblast-related group				
1	Fibrotic focus, dimension (mm)			
	Absent	≤8	>8	
2	Types of invasive ductal carcinoma			
	Type 1	Type 2	Type 3	Type 4
Tumor embolus-related group				
1	Grading system for lymph vessel tumor embolus			
	Grade 0	Grade 1	Grade 2	Grade 3
2	Number of apoptotic figures in blood vessel tumor emboli			
	Absent	≤2	>2	

Table 1. (continued)

Metastatic carcinomas to the lymph node-related group					
1	UICC pN category				
	pN0	pN1mi	pN1	pN2	pN3
2	Grade of stromal fibrosis in metastatic carcinomas to the lymph node				
	No nodal metastasis	None, mild and moderate		Severe	
3	Maximum dimension of metastatic carcinomas to the lymph node (mm)				
	No nodal metastasis	≤20		>20	
4	Number of extranodal blood vessel tumor emboli				
	No nodal metastasis	≤2		>2	
5	Number of mitotic figures in metastatic carcinomas to the lymph node				
	No nodal metastasis	≤5		>5	

pN0, no nodal metastasis, but including lymph node with isolated tumor cell clusters (single tumor cells or small clusters of cells not more than 0.2 mm in greatest dimension); pN1mi, cases with micrometastasis (larger than 0.2 mm, but none larger than 2.0 mm in greatest dimension); pN1, 1–3 nodal metastases; pN2, 4–9 nodal metastases; pN3, 10 or more nodal metastases; no nodal metastasis, pN0 cases excluding the seven cases with lymph nodes containing isolated tumor cell clusters; Grade 0 of grading system for lymph vessel tumor embolus, no lymph vessel invasion.

metastatic carcinomas to the lymph node.[9] In the present study, seven of the 598 pN0 cases had isolated tumor cell clusters (ITC)[10] (Table 3). We excluded these seven cases from the pN0 cases and these cases showed no stromal fibrosis in metastatic carcinomas to the lymph node, showed a ≤20 mm maximum dimension in metastatic carcinomas to the lymph node, showed ≤2 extranodal blood vessel tumor emboli, or showed ≤5 mitotic figures in metastatic carcinomas to the lymph node (Table 3). Thus, we classified these seven cases as cases with no grade of stromal fibrosis, those with a ≤20 mm maximum dimension, those with ≤2 extranodal blood vessel tumor emboli, or those with ≤5 mitotic figures in metastatic carcinomas to the lymph node (Table 3).

The following antibodies were used for immunohistochemistry: anti-estrogen receptor mouse monoclonal antibody ER88 (BioGenex, Fremont, CA, USA), anti-progesterone receptor mouse monoclonal antibody PR88 (BioGenex), and anti-HER2 mouse monoclonal antibody CB11 (BioGenex). Allred scores for estrogen receptor or progesterone receptor were assessed according to our previously study.[13] We defined an Allred score of 0 or 2 for ER or PR as being negative for ER or PR and Allred scores of 3 or more for ER or PR as being positive for ER or PR. HER2 expression in tumor cells was categorized according to the definition of Wolf.[14] All types 2 and 4 invasive ductal carcinomas were immunohistochemically studied using monoclonal antibodies to keratins (AE1/3) to confirm that the atypical tumor-stromal fibroblasts were not modified invasive tumor cells, and fibroblasts that were negative for keratins were considered as atypical tumor-stromal fibroblasts (Fig. 1b). We also performed immunohistochemical staining for alpha-smooth muscle actin for types 2 and 4 invasive ductal carcinomas to investigate whether atypical tumor-stromal fibroblasts are myofibroblasts (Fig. 1c). Some invasive ductal carcinomas contained large lymph vessel tumor emboli, especially in invasive ductal carcinomas containing a grade 2 or grade 3 lymph vessel tumor emboli, and it was difficult to determine whether they were true lymph vessel tumor emboli or a non-invasive ductal carcinoma component by hematoxylin and eosin staining alone. We therefore performed immunohistochemical staining with D2-40 antibody (monoclonal mouse antibody, Signet, Dedham, MA, USA, 1:200) to confirm that the lymph vessel tumor emboli identified by hematoxylin and eosin staining were true tumor emboli in some invasive ductal carcinomas with grade 2 or grade 3 lymph vessel tumor emboli (Fig. 1e). Histologic grade, nuclear feature of primary invasive tumors, and mitotic activity index in primary invasive tumors were evaluated according to the criteria of Elston and Ellis.[15] Tumor necrosis in primary invasive tumors was evaluated according to the definition of Gilchrist.[16]

Patient outcome and statistical analysis. Survival was evaluated using a median follow-up period of 98 months (range: 63–134 months) until March 2011. Of the 1042 invasive ductal carcinoma patients, first locoregional recurrence was observed in 47 out of 1042 patients with invasive ductal carcinoma. The first locoregional recurrence-free survival period was calculated using the time of surgery as the starting point. The factors that were significantly associated with first locoregional recurrence in the univariate analyses were then entered together into multivariate analyses using the Cox proportional hazard regression model. In addition, we conducted to compare the power of grading system for lymph vessel tumor emboli with that of the following three lymphatic parameters for accurately predicting the first locoregional recurrence in multivariate analysis using the Cox proportional hazard regression model: (i) the presence or absence of lymph vessel invasion; (ii) real numbers of lymph vessel invasion;[17] and (iii) location of lymph vessel tumor emboli[18] (inside area of the tumor, advanced area within the tumor and outside area of the tumor). In this study, we were unable to perform multivariate analyses for first locoregional recurrence because of a small sample size (fewer than 10 patients) in patients who did not receive adjuvant therapy. The case-wise and step-down method was applied until all the remaining factors were significant at a P-value of <0.05. First locoregional recurrence-free survival curves were drawn by the Kaplan–Meier method. All the analyses were performed using Statistica/Windows software (StatSoft, Tulsa, OK, USA).

Results

Patients. All of the patients had a solitary lesion; 498 patients were premenopausal, and 544 were postmenopausal. A partial mastectomy had been performed in 458 patients, and a

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Table 2. Histological features, criteria or assessing methods of the five factors that we have proposed

1 *Histological features of atypical tumor-stromal fibroblasts and the type of invasive ductal carcinoma*

(1) The presence of atypical tumor-stromal fibroblasts was defined based on the presence of one or more atypical tumor-stromal fibroblasts in the tumor stroma inside and outside of the fibrotic foci in invasive ductal carcinoma. Although atypical tumor-stromal fibroblasts are occasionally distributed at random locations in the tumor stroma, they tend to exist within the cellular area of the tumor-stromal fibroblasts

(2) The number of nuclei in an atypical tumor-stromal fibroblast is one or more. The nuclear size of an atypical tumor-stromal fibroblast is two or more times larger than that of an ordinary tumor-stromal fibroblast. The nuclear features of an atypical tumor-stromal fibroblast include an irregular or convoluted shape, and also include various bizarre shapes

(3) An obvious small to large size nucleolus or nucleoli are seen in the nucleus or nucleoli of atypical tumor-stromal fibroblasts and some atypical tumor-stromal fibroblasts show a coarsely granulated nuclear chromatin pattern

Type	Fibrotic focus	Atypical tumor-stromal fibroblast not forming a fibrotic focus	Atypical tumor-stromal fibroblast forming a fibrotic focus
1	Absent	Absent	Not applicable
2	Absent	Present	Not applicable
3	Present	Not assessed	Absent
4	Present	Not assessed	Present

2 *Grading system for lymph vessel tumor embolus*

Grade 0 Invasive ductal carcinomas with no lymph vessel tumor embolus

Grades 1–3 Invasive ductal carcinomas with lymph vessel tumor embolus or emboli

	No. of mitotic figures	No. of apoptotic figures
Grade 1	0	0
	0	Any
	Any	0
Grade 2	1–4	>0
	>0	1–6
Grade 3	>4	>6

(1) The numbers of tumor cell mitotic figures and apoptotic figures in lymph vessels are counted in 20 high-power fields. In carcinomas containing a small number of lymph vessel tumor emboli, the mitotic figures and apoptotic figures are counted in fewer than 20 high-power fields

(2) A large lymph vessel tumor emboli located far from the stroma-invasive tumor margin is selected and the mitotic figures and apoptotic figures in the lymph vessel tumor emboli or embolus are counted

(3) The numbers of mitotic figures and apoptotic figures in tumor cells composing the lymph vessel tumor embolus or emboli in the high-power field containing the largest number of mitotic figures, and/or the largest number of apoptotic figures are recorded as the number of mitotic figures and apoptotic figure in the lymph vessel tumor emboli or embolus. The cumulative numbers of tumor cell mitotic figures and apoptotic figures in the lymph vessel tumor emboli in all 20 high-power fields are not used

3 *Grade of stromal fibrosis in metastatic carcinomas to the lymph node*

None Metastatic carcinoma with no tumor-stromal fibrosis

Mild Metastatic carcinoma occupied by ≤30% tumor-stromal fibrosis

Moderate Metastatic carcinoma occupied by >30 to ≤80% tumor-stromal fibrosis

Severe Metastatic carcinoma occupied by >80% tumor-stromal fibrosis

4 *Extranodal blood vessel tumor embolus or emboli*

Tumor embolus or emboli in blood vessel or vessels with a smooth muscle-supported endothelial lining in perinodal adipose tissues was/were assessed as extranodal blood vessel tumor embolus or emboli

5 *Mitotic figures in metastatic carcinomas to the lymph node*

(1) A random search for mitotic figures in metastatic mammary carcinoma to the lymph nodes is performed using high-power magnification fields (×10 or ×20) of the tumor area

(2) Next, one high-power magnification field (×40) of the tumor area containing the highest number of mitotic figures is selected to determine the largest number of metastatic mammary carcinoma to the lymph nodes exhibiting mitotic figures

modified radical mastectomy had been performed in 584. The surgical margins of all the partial mastectomy materials were histologically examined to confirm whether tumor cells were absent or present at the surgical margins of the materials; we confirmed that all the materials had been completely resected because the outermost edges of the tumors were 5 mm or further from the surgical margin of the materials. A Level I and 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 1042 patients, 873 received adjuvant therapy, consisting of chemotherapy in 217 patients, endocrine therapy in 281 patients, and chemoendocrine therapy in 375 patients. The chemotherapy regimens used were anthracycline-based with or without taxane and

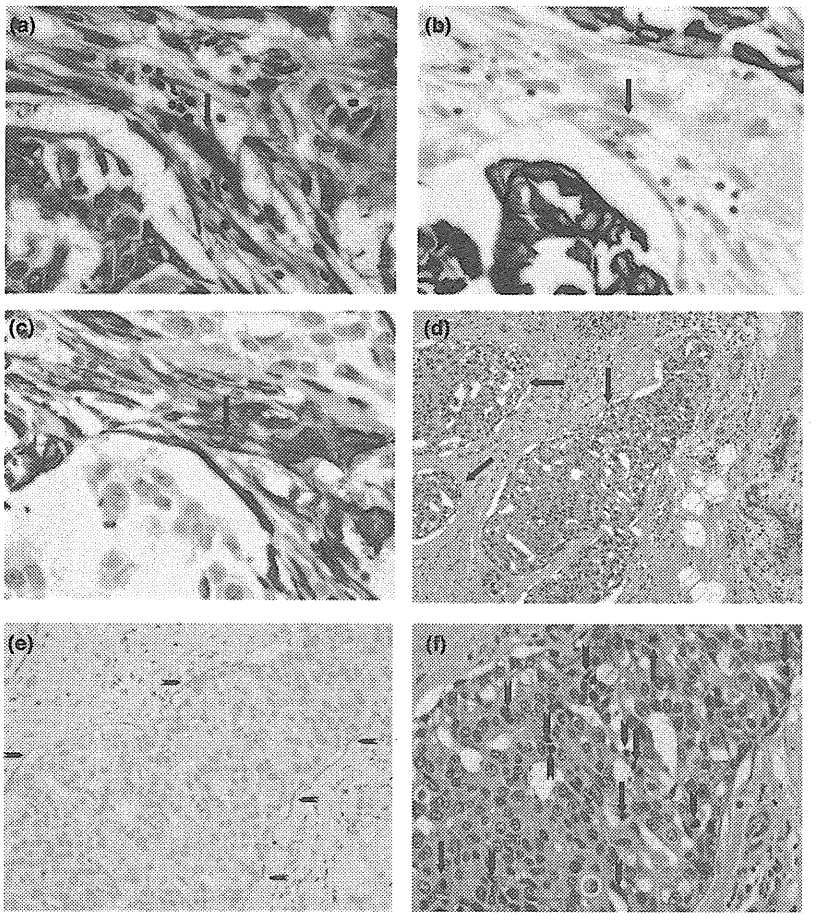

Fig. 1. (a–c) Type 2 invasive ductal carcinoma. One atypical tumor-stromal fibroblast with a large spindle nucleus is visible in the tumor stroma (arrow). The fibroblast was stained negative for AE1/3 (arrow, b) and positive for smooth muscle actin (arrow, c). The invasive tumor cells were stained positive for AE1/3 (b). (d–f) Grade 3 lymph vessel tumor emboli. Three large lymph vessel tumor emboli are present, and the wall of one of the tumor lymph vessels containing the embolus was positive for D2–40 (arrowheads, e). Five mitotic tumor cells (arrows) and eight apoptotic tumor cells (arrowheads) are visible within the tumor embolus (f).

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. Of the 1042 patients, 466 patients received adjuvant radiotherapy.

Univariate analyses for first locoregional recurrence. Overall, age (P = 0.026), the Allred score for estrogen receptors in the tumor cells (P = 0.017), the histologic grade (P = 0.009), the invasive tumor size (P < 0.001), nuclear features of the primary-invasive tumor cells (P < 0.001), the number of mitotic figures in the primary-invasive tumor cells (P = 0.002), tumor necrosis (P = 0.019), the type of invasive ductal carcinoma, the grading system for lymph vessel tumor emboli, the UICC pN category, the grade of stromal fibrosis in metastatic carcinomas to the lymph node, the maximum dimension of metastatic carcinomas to the lymph node, the number of extranodal blood vessel tumor emboli, and the number of mitotic figures in metastatic carcinomas to the lymph node were significantly associated with first locoregional recurrence in the univariate analyses (Table 3). The fibrotic focus dimension (Table 3), the number of apoptotic figures in blood vessel tumor emboli (Table 3), adjuvant therapy, adjuvant radiotherapy, the Allred score for progesterone receptors in the tumor cells, the HER2 category, and the skin invasion were not significantly associated with first locoregional recurrence in the univariate analyses (data not shown). Atypical tumor-stromal fibroblast was observed in 69 (7%) cases (type 2 and 4 invasive ductal carcinoma cases) among 1042 cases (Table 3). The presence of atypical tumor-stromal fibroblasts stained positive for alpha-smooth muscle actin was observed in 60 (87%) out of 69 types 2 and 4 invasive ductal carcinomas (type 2: 35/40 cases, 88%; type 4: 25/29 cases, 86%).[6]

Multivariate analysis for clarifying the best lymphatic factor for accurately predicting first locoregional recurrence. Number of lymph vessel invasion ranged from 0 to 494 (median number and standard error: 0 and 1.1) in the present study. Only the grading system for lymph vessel tumor emboli significantly increased the hazard ratio for first locoregional recurrence in the multivariate analysis (P = 0.002). The presence of lymph vessel invasion (P = 0.158), real number of lymph vessel tumor emboli (P = 0.144), or location of lymph vessel tumor emboli (inside area of the tumor: P = 0.227; advanced area within the tumor: P = 0.512; outside area of the tumor: P = 0.425) failed to significantly increase the hazard ratio for first locoregional recurrence in the multivariate analysis.

Multivariate analyses for first locoregional recurrence. Overall (n = 1042), lymph vessel tumor embolus grade 2 (P < 0.001, Fig. 2a) and 3 (P < 0.001, Fig. 2a), and type 2 invasive ductal carcinoma (P < 0.001, Fig. 2b) significantly increased the hazard ratios for first locoregional recurrence in the multivariate analyses (Table 8). Lymph vessel tumor embolus grade 3 was significantly associated with first locoregional recurrence in a manner that was independent of almost all the tumor statuses, except for adjuvant radiotherapy status (received adjuvant radiotherapy) (Tables 4–8). Type 2 invasive ductal carcinoma was significantly associated with first locoregional recurrence among the overall patients who had received adjuvant therapy (P < 0.001), the UICC pN0 patients (Tables 4 and 8), the UICC pN1-3 patients (Tables 4 and 8), the UICC

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Table 3. Frequencies of first locoregional recurrence of the eight histological factors that we have proposed and UICC pN category

	Cases (%) 1042	No. patients (%) First locoregional recurrence Present 47	Absent 995	*P*-value
Primary tumor-stromal fibroblast-related group				
Fibrotic focus, dimension (mm)				
Absent	667	30 (5)	637 (95)	0.624
≤8	221	9 (4)	212 (96)	
>8	154	8 (5)	146 95)	
Types of invasive ductal carcinoma				
Type 1	627	23 (4)	604 (96)	<0.001
Type 2	40	7 (18)	33 (82)	
Type 3	346	15 (4)	331 (96)	
Type 4	29	2 (7)	27 (93)	
Tumor embolus-related group				
Grading system for lymph vessel tumor embolus				
Grade 0	666	20 (3)	646 (97)	<0.001
Grade 1	250	6 (2)	244 (98)	
Grade 2	97	12 (12)	85 (88)	
Grade 3	29	9 (31)	20 (69)	
Number of apoptotic figures in blood vessel tumor emboli				
Absent	890	36 (4)	854 (96)	0.071
≤2	78	6 (8)	72 (92)	
>2	74	5 (7)	5 (93)	
Metastatic carcinomas to the lymph node-related group				
UICC pN category				
pN0	598	17 (3)	581 (97)	<0.001
pN1mi	20	0	20 (100)	
pN1	291	16 (6)	275 (94)	
pN2	85	6 (7)	79 (93)	
pN3	48	8 (17)	40 (83)	
Grade of stromal fibrosis in metastatic carcinomas to the lymph node				
No nodal metastasis	591	17 (3)	574 (97)	<0.001
None, mild and moderate	415	25 (6)	390 (94)	
Severe	36	5 (14)	31 (86)	
Maximum dimension of metastatic carcinomas to the lymph node (mm)				
No nodal metastasis	591	17 (3)	574 (97)	<0.001
≤20	396	26 (7)	370 (93)	
>20	55	4 (7)	51 (93)	
Number of extranodal blood vessel tumor emboli				
No nodal metastasis	591	17 (3)	574 (97)	<0.001
≤2	423	25 (6)	398 (94)	
>2	28	5 (18)	23 (82)	
Number of mitotic figures in metastatic carcinomas to the lymph node				
No nodal metastasis	591	17 (3)	574 (97)	<0.001
≤5	286	12 (4)	274 (96)	
>5	165	18 (11)	147 (89)	

NA, not available; pN0, no nodal metastasis, but including lymph node with isolated tumor cell clusters (single tumor cells or small clusters of cells not more than 0.2 mm in greatest dimension); pN1mi, cases with micrometastasis (larger than 0.2 mm, but none larger than 2.0 mm in greatest dimension); pN1, 1–3 nodal metastases; pN2, 4–9 nodal metastases; pN3, 10 or more nodal metastases; no nodal metastasis, pN0 cases excluding the seven cases with lymph nodes containing isolated tumor cell clusters; Grade 0 of grading system for lymph vessel tumor embolus, no lymph vessel invasion.

Table 4. Multivariate analyses for first locoregional recurrence in invasive ductal carcinoma patients who received adjuvant therapy according to UICC pN category

	First locoregional recurrence			
	pN0 (n = 453)		pN1-3 (n = 420)	
	Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value
Grading system for lymph vessel tumor embolus				
Grade 0	1.0		1.0	
Grade 1	1.0		1.5 (0.5–4.5)	0.503
Grade 2	11.9 (3.0–46.6)	<0.001	2.2 (0.7–6.7)	0.163
Grade 3	11.9 (3.0–46.6)	<0.001	11.7 (3.4–39.9)	<0.001
Types of invasive ductal carcinoma				
Type 1	1.0		1.0	
Type 2	6.1 (1.2–29.9)	0.025	6.3 (2.0–20.0)	0.002
Type 3	2.0 (0.5–8.6)	0.362	0.9 (0.4–2.2)	0.810
Type 4	9.8 (0.9–105.8)	0.059	NA	
Number of mitotic figures in the primary invasive tumors				
≤9	1.0		1.0	
>9 to ≤19	3.4 (0.3–40.1)	0.323	–	
>19	4.7 (1.2–18.4)	0.023	–	

–, not significant; NA, not available; no nodal metastasis, pN0 cases excluding the seven cases with lymph nodes containing isolated tumor cell clusters.

Table 5. Multivariate analyses for first locoregional recurrence in invasive ductal carcinoma patients who received adjuvant therapy according to UICC pTNM stage

	First locoregional recurrence			
	Stages I and II (n = 692)		Stage III (n = 181)	
	Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value
Grading system for lymph vessel tumor embolus				
Grade 0	1.0		1.0	
Grade 1	1.8 (0.6–5.4)	0.319	0.3 (0.03–2.10)	0.210
Grade 2	7.9 (2.9–20.9)	<0.001	0.7 (0.1–3.2)	0.596
Grade 3	15.8 (3.2–77.3)	<0.001	8.1 (2.4–28.1)	<0.001
Types of invasive ductal carcinoma				
Type 1	1.0		1.0	
Type 2	6.4 (2.3–18.2)	<0.001	–	
Type 3	1.2 (0.5–3.3)	0.685	–	
Type 4	NA		–	
Tumor necrosis				
Absent	1.0		1.0	
Present	2.4 (1.0–5.8)	0.045	–	

–, not significant; NA, not available.

pTNM stages I and II patients (Tables 5 and 8), the patients who had received endocrine therapy (Tables 6 and 8), the patients who had received chemotherapy (Tables 6 and 8), the patients who had not received adjuvant radiotherapy (Tables 7 and 8) and the patients who had received adjuvant radiotherapy (Tables 7 and 8). Lymph vessel tumor embolus grade 2 was significantly associated with first locoregional recurrence among the overall patients who had received adjuvant therapy ($P < 0.001$), the UICC pN0 patients (Tables 4 and 8), the UICC pTNM stages I and II patients (Tables 5 and 8) and the patients who had received chemoendocrine therapy (Tables 6 and 8). Twenty or more mitotic figures in primary invasive tumors, the presence of tumor necrosis, and the presence of skin invasion were significantly associated with first locoregional recurrence among the UICC pN0 patients (Tables 4 and 8), among the UICC pTNM stages I and II patients (Tables 5 and 8) and among the patients who had

Table 6. Multivariate analyses for first locoregional recurrence in invasive ductal carcinoma patients who received adjuvant therapy according to adjuvant therapy status

	First locoregional recurrence					
	Endocrine (n = 281)		Chemoendocrine (n = 375)		Chemotherapy (n = 217)	
Grading system for lymph vessel tumor embolus						
Grade 0	1.0		1.0		1.0	
Grade 1	0.6 (0.1–3.4)	0.602	1.7 (0.3–9.1)	0.545	0.8 (0.09–6.40)	0.795
Grade 2	1.6 (0.2–12.0)	0.667	6.8 (1.3–36.8)	0.026	0.8 (0.09–7.30)	0.866
Grade 3	25.8 (1.2–560.0)	0.038	9.8 (1.4–70.8)	0.024	27.5 (6.3–119.1)	<0.001
Types of invasive ductal carcinoma						
Type 1	1.0		1.0		1.0	
Type 2	37.2 (3.6–369.7)	0.002	–		18.6 (3.6–90.7)	<0.001
Type 3	7.4 (0.9–59.0)	0.058	–		1.5 (0.4–6.1)	0.579
Type 4	NA		–		5.4 (0.6–52.6)	0.145
Number of mitotic figures in metastatic carcinomas to the lymph node						
No nodal metastasis	1.0		1.0		1.0	
≤5	3.1 (0.7–12.9)	0.120	–		–	
>5	20.1 (1.3–312.3)	0.032	–		–	
Skin invasion						
Absent	1.0		1.0		1.0	
Present	–		–		5.4 (1.4–21.6)	0.014

–, not significant; NA, not available.

Table 7. Multivariate analyses for first locoregional recurrence in invasive ductal carcinoma patients who received adjuvant therapy according to adjuvant radiotherapy status

	First locoregional recurrence			
	No adjuvant radiotherapy (n = 576)		Adjuvant radiotherapy (n = 466)	
	Hazard ratio (95% CI)	P-value	Hazard ratio (95% CI)	P-value
Types of invasive ductal carcinoma				
Type 1	1.0		1.0	
Type 2	3.2 (1.1–9.5)	0.041	6.0 (1.2–29.3)	0.026
Type 3	1.3 (0.5–3.4)	0.563	0.9 (0.2–3.3)	0.843
Type 4	3.1 (0.3–29.8)	0.334	NA	
Grading system for lymph vessel tumor embolus				
Grade 0	1.0		1.0	
Grade 1	1.7 (0.5–5.1)	0.366	–	
Grade 2	3.5 (0.9–16.7)	0.051	–	
Grade 3	129.8 (29.1–578.0)	<0.001	–	
Number of mitotic figures in metastatic carcinomas to the lymph node				
No nodal metastasis	1.0		1.0	
≤5	–		1.6 (0.3–8.4)	0.603
>5	–		5.6 (1.8–17.4)	0.003

–, not significant; NA, not available.

received chemotherapy (Tables 6 and 8), respectively. Six or more mitotic figures in metastatic carcinomas to the lymph node were significantly associated with the first locoregional recurrence among the patients who had received endocrine therapy (Tables 6 and 8), and the patients who had received adjuvant radiotherapy (Tables 7 and 8).

Discussion

The results of the present study clearly exhibited an excellent power for the tumor embolus-related group for the accurate prediction of first locoregional recurrence in patients with invasive ductal carcinoma since this group was significantly associated with the first locoregional recurrence independent of the tumor-status categories except among patients who had received adjuvant radiotherapy (Table 8). Especially, the results of the present study clearly exhibited an excellent power for lymph vessel tumor embolus grade 3 for the accurate prediction of first locoregional recurrence in patients with invasive ductal carcinoma independent of the tumor statuses (Table 8). In contrast, a grade 1 lymph vessel tumor embolus was not a significant predictor for first locoregional recurrence and had a similar predictive power to grade 0 lymph vessel tumor embolus (Fig. 2a); more than half of the 376 patients with lymph vessel invasion were classified as having lymph vessel tumor embolus grade 1 (Table 3). These results suggest that the lymph vessel tumor embolus grade was capable of selecting not only patients with the worst prognosis, but also patients with a good prognosis among patients with lymph vessel invasion. Although many studies have already reported that the presence or absence of lymph vessel invasion or the number of invaded lymph vessels is an important factor for accu-

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Table 8. Groups and factors significantly associated with first locoregional recurrence in patients with invasive ductal carcinoma

First locoregional recurrence											
A		B: Patients who received adjuvant therapy (n = 873)									
Total	All	All	UICC pN category		UICC pTNM stage		Adjuvant therapy status			Adjuvant radiotherapy status	
11			pN0	pN1–3	I and II	III	Endocrine therapy	Chemoendocrine therapy	Chemotherapy	None	Yes
Tumor embolus-related group											
10	G3	G3	G3	G3	G3	G3	G3	G3	G3	G3	•
	G2	G2	G2		G2			G2			
Primary tumor-stromal fibroblast-related group											
9	T2	T2	T2	T2	T2	•	T2	•	T2	T2	T2
Primary invasive tumor cell-related group											
3	•	•	MF19	•	Tumor necrosis	•	•	•	Skin invasion	•	•
Metastatic carcinomas to the lymph node-related group											
2	•	•	•	•	•	•	MF5	•	•	•	MF5
Clinicopathological group											
0	•	•	•	•	•	•	•	•	•	•	•

•, not significant; A, overall patients; G3, grade 3; G2, grade 2; T2, type 2 invasive ductal carcinoma; MF19, number of mitotic figure, >19; MF5, number of mitotic figures, >5.

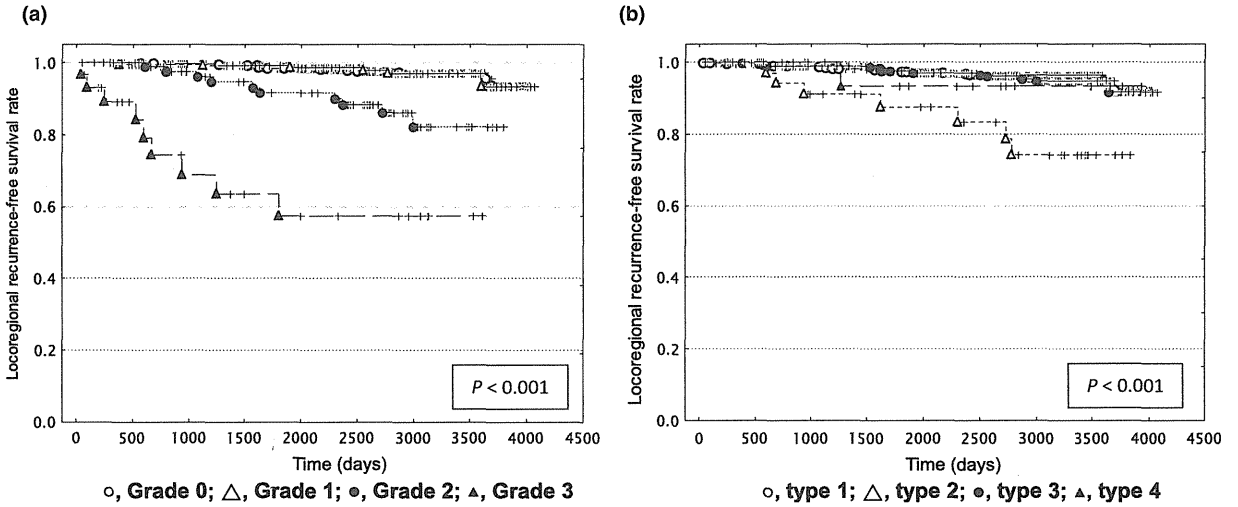

Fig. 2. First locoregional recurrence-free survival curves for overall patients with invasive ductal carcinoma (a and b). (a) Patients with grade 3 lymph vessel tumor emboli had the shortest locoregional recurrence-free survival curve. Patients with grade 2 lymph vessel tumor emboli also had a significantly shorter locoregional recurrence-free survival curve than patients with grade 1 lymph vessel tumor emboli or patients with grade 0 lymph vessel tumor emboli. (b) Patients with type 2 invasive ductal carcinoma had a significantly shorter first locoregional recurrence-free survival curve than patients with type 1 invasive ductal carcinoma, patients with type 3 invasive ductal carcinoma and patients with type 4 invasive ductal carcinoma.

rately predicting the locoregional recurrence of invasive ductal carcinoma,[19,20] we confirmed that the grading system for lymph vessel tumor emboli is superior to the presence or absence of lymph vessel invasion, the number of invaded lymph vessels or the location of lymph vessels invaded for accurately predicting first locoregional recurrence in this study. Thus, we can conclude that the lymph vessel tumor embolus grade is the only lymph vessel assessment parameter that can accurately divide patients with lymph vessel invasion into a good prognosis group and a poor prognosis group. However, the locoregional predictive power of the lymph vessel tumor embolus grade was inferior to type 2 invasive ductal carcinoma or >5 mitotic figures in metastatic carcinomas to the lymph node in patients who had received adjuvant radiotherapy; this finding strongly suggests that adjuvant radiotherapy prevents locoregional recurrence in patients with lymph vessel tumor embolus grades 3 or 2.[21] Since the lymph vessel tumor embolus grade is assessed based on the numbers of mitotic figures and apoptotic figures in tumor cells in the lymph vessel,[7] adjuvant radiotherapy probably inhibits the acceleration of the cell cycle in tumor cells in the lymph vessel. Thus, adjuvant radiotherapy may contribute to improving the outcome of patients with lymph vessel tumor embolus grade 3 or those with lymph vessel tumor embolus grade 2. From these, we can conclude that the lymph vessel tumor embolus grade in the tumor embolus-related group was the best grade for accurately predicting first locoregional recurrence among patients with invasive ductal carcinoma of a low-risk, intermediate-risk or high-risk

class. In addition, the results of the study also exhibited no predictive power for number of apoptotic figures in blood vessel tumor emboli for the accurate prediction of first locoregional recurrence in patients with invasive ductal carcinoma.

The next most-important group was the primary tumor-stromal fibroblast-related group, because this group accurately predicted first locoregional recurrence in nine of the 13 tumor statuses (Table 8). Especially, the results of the present study clearly exhibited a useful power for type 2 invasive ductal carcinoma for the accurate prediction of first locoregional recurrence in patients with invasive ductal carcinoma independent of the tumor statuses (Table 8). Type 2 invasive ductal carcinoma and type 4 invasive ductal carcinoma have atypical tumor-stromal fibroblasts, and the former does not have a fibrotic focus within them but the latter has a fibrotic focus with atypical tumor-stromal fibroblasts.[7] Thus, the presence of atypical tumor-stromal fibroblasts alone probably plays an important role in the establishment of first locoregional recurrence under the condition of the absence of fibrotic foci in invasive ductal carcinomas. We have previously reported that atypical tumor-stromal fibroblasts exhibit a significantly higher frequency of p53 protein expression than ordinary tumor-stromal fibroblasts;[6,22] this finding clearly indicates that the presence of atypical nuclear features is closely associated with p53 expression in tumor-stromal fibroblasts. p53 mutations in tumor-stromal fibroblasts are relatively common among primary breast cancers and have been reported to exert a positive effect on cancer growth.[23,24] p53 gene abnormalities or specific reactive changes in p53 immunoreactivity in tumor-stromal fibroblasts produced by tumor cell-stromal cell interactions inside and outside of the fibrotic foci probably lead to the expression of p53 in tumor-stromal fibroblasts. Consequently, some tumor-stromal fibroblasts expressing p53 inside and outside of fibrotic foci probably transform into atypical tumor-stromal fibroblasts. Furthermore, since many atypical tumor-stromal fibroblasts were also stained for smooth muscle actin,[6] one can conclude that many of the atypical tumor-stromal fibroblasts have the biological characteristics of myofibroblasts.[25,26] Thus, these atypical tumor-stromal fibroblasts likely play important roles in the first locoregional recurrence of invasive ductal carcinomas of the breast.

In conclusion, the present study clearly demonstrated that the following factors that we have proposed play very important roles in the establishment of first locoregional recurrence: (i) lymph vessel tumor embolus grade; and (ii) atypical tumor-stromal fibroblast outside a fibrotic focus, and also clearly demonstrated that the primary invasive tumor cell-related group, the metastatic carcinomas to the lymph node-related group, and the clinicopathological group were strikingly inferior to the above two factors for the prediction of first locoregional recurrence (Table 8). Thus, we can conclude that the above two factors are very useful surrogate markers for accurately predicting first locoregional recurrence of patients with invasive ductal carcinoma of the breast. Clinicians usually plan the follow-up care of patients after the initial operation has been completed, deciding whether patients should be treated with adjuvant therapy and which type of adjuvant therapy should be performed based on pathological reports of the clinicopathological findings for the invasive ductal carcinomas. Thus, pathology reports of invasive ductal carcinomas that are based on the assessment of our proposed factors would probably provide clinicians with more important clues for the selection of patients with a high likelihood of locoregional recurrence among patients with invasive ductal carcinoma, compared with ordinary pathology reports of invasive ductal carcinomas, throughout the follow-up period after the initial operation. Since it has recently been reported that the gene expression profile and protein expression profile of the tumor stroma play a very important role in tumor progression in carcinoma,[27,28] key proteins that are expressed in tumor cells with highly-accelerating cell cycle in the lymph vessels, but also by atypical tumor-stromal fibroblasts should be carefully investigated to develop targeted therapies that eradicate tumor cells with highly-accelerating cell cycle or atypical tumor-stromal fibroblast expressing key proteins, resulting in the improved outcome of patients with invasive ductal carcinoma of the breast.

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Disclosure Statement

The authors have no conflict of interest.

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