TABLE 1. Patient Demographics and Baseline Tumor Characteristics

Characteristic	No. of Patients (%)	
	Anastrozole Plus Goserelin	Tamoxifen Plus Goserelin
No. of patients	98	99
Age: Median [range]	44 [28-54]	44 [30-53]
Body mass index: Mean±SD, kg/m^2	22.2±3.5	22.1±3.3
Histology type		
Infiltrating ductal carcinoma	87 (88.8)	91 (91.9)
Infiltrating lobular carcinoma	3 (3.1)	3 (3)
Other[a]	8 (8.2)	5 (5.1)
Tumor grade		
1	42 (42.9)	48 (48.5)
2	36 (36.7)	26 (26.3)
3	4 (4.1)	14 (14.1)
Not assessable	1 (1)	0 (0)
Not done	15 (15.3)	11 (11.1)
Hormone receptor status		
ER positive	98 (100)	99 (100)
PgR positive	93 (94.9)	87 (87.9)
HER2 negative	98 (100)	99 (100)

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PgR, progesterone receptor; SD, standard deviation.
[a] Other included adenocarcinoma (n = 3).

baseline characteristics generally were well balanced between the treatment groups (Table 1). Paired samples for calculating changes in the Ki-67 index from baseline to week 24 were available for 89 patients in the anastrozole plus goserelin group and for 86 patients in the tamoxifen plus goserelin group.

Correlation of the Baseline Ki-67 Index and Best Overall Tumor Response

With a mean baseline Ki-67 index of 21.9% and 21.6% in the anastrozole and tamoxifen treatment groups, respectively, we used post hoc subset analyses to compare patients according to their baseline Ki-67 index (≥20 vs <20%). For anastrozole versus tamoxifen, best overall tumor response from baseline to week 24 was better with anastrozole plus goserelin versus tamoxifen plus goserelin both in patients who had a baseline Ki-67 index ≥20% (73.2% vs 44.8%; $P = .002$) and in patients who had a baseline Ki-67 index <20% (52.5% vs 29%; $P = .035$) (Fig. 2A).

Within the treatment groups, the best overall tumor response from baseline to 24 weeks, as measured by MRI or CT, was significantly better with anastrozole plus goserelin for patients who had a baseline Ki-67 index ≥20% than for those who had a baseline Ki-67 index <20% (73.2% vs 52.5%; $P = .036$). Among patients in the tamoxifen plus goserelin group, the best overall tumor response was 44.8% for patients who had a baseline Ki-67 index ≥20% and 29% for those who had a baseline Ki-67 index <20% ($P = .118$) (Fig. 2A).

Correlation of the Baseline Ki-67 Index and Histopathologic Response

There was no significant difference in the histopathologic response between patients who had a baseline Ki-67 index ≥20% versus patients who had a baseline Ki-67 index <20% in either treatment group (Fig. 2B).

Correlation of Change in the Ki-67 Index and Responders/Nonresponders

A waterfall plot of changes in the Ki-67 index for individual patients, illustrated according to responders or nonresponders, is provided in Figure 3. There was no apparent relation between a change in Ki-67 expression from baseline to week 24 for responders and nonresponders in either treatment group.

Correlation of the Baseline Ki-67 Index and Estrogen Receptor or Progesterone Receptor Status

In both treatment groups, positive ER status, as determined by the Allred score, was observed in 100% of patients at baseline and at week 24, and >90% of patients in both treatment groups were ER rich (baseline Allred score, ≥7). Therefore, it was not possible to determine any potential relation between the baseline ER Allred score and the percentage change in Ki-67 expression from baseline to week 24 in either treatment group.

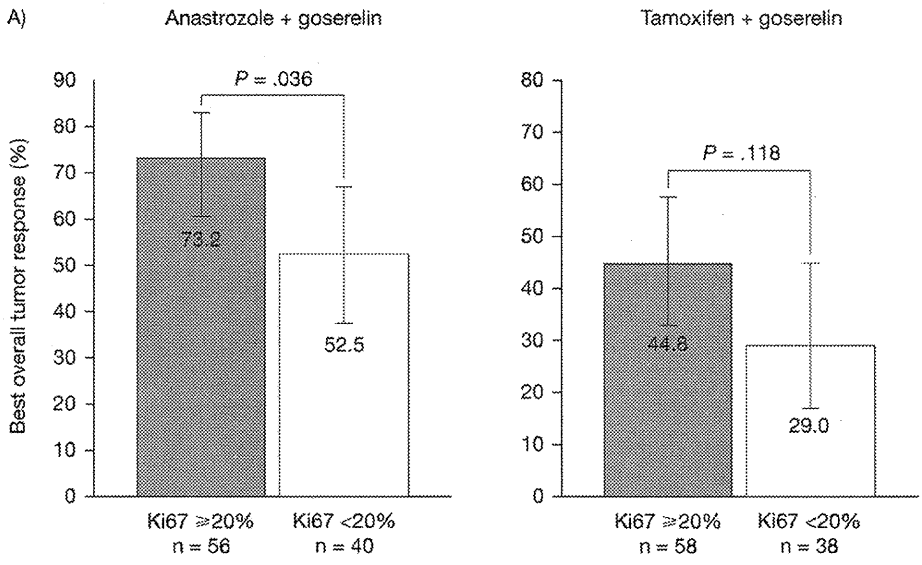
In the anastrozole plus goserelin group, 98.9% of patients were positive for PgR expression at baseline, and 34.4% were positive for PgR expression at week 24. The percentage of patients with positive PgR status was not altered from baseline (91.9%) to week 24 (89.5%) in the tamoxifen plus goserelin group (Fig. 4A). In both treatment groups, the mean decrease in the Ki-67 index was greater in patients who had a baseline PgR Allred score ≥7 (anastrozole group, −88.8%; tamoxifen group, −67.6%), compared with patients who had a baseline PgR Allred score <7 (anastrozole group, −74.1%; tamoxifen group, −32.8%) (Fig. 4B).

Preoperative Endocrine Prognostic Index Score

In the anastrozole treatment group, 33.3% of patients had a PEPI score of 0 compared with 11.4% in the tamoxifen group. Fewer patients (21.4%) had a PEPI score ≥4 in the anastrozole group compared with patients in the tamoxifen group (36.7%; $P = .002$) (Table 2).

DISCUSSION

In this exploratory analysis, we investigated changes in Ki-67 expression among patients from the STAGE study, a



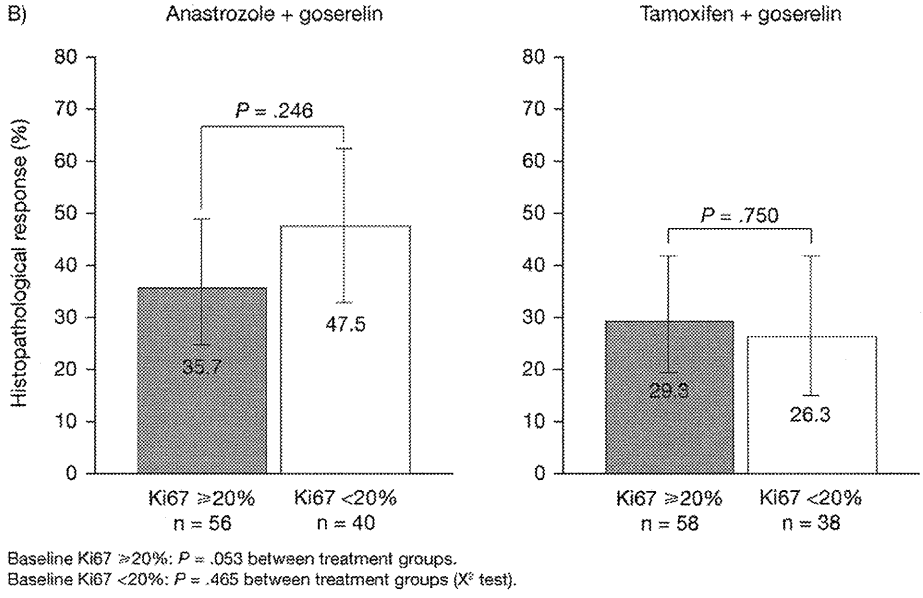


Figure 2. These charts illustrate the baseline Ki-67 index (≥20% vs <20%) according to (A) the best overall tumor response and (B) the histopathologic response at 24 weeks. Magnetic resonance imaging or computed tomography was used to measure responses. The best tumor response was defined a complete or partial response during the 24-week treatment period.

phase 3 randomized trial that compared tumor response for anastrozole plus goserelin versus response tamoxifen plus goserelin during 24 weeks of neoadjuvant treatment in premenopausal women with ER-positive breast cancer. The primary analysis indicated that the reduction in the Ki-67 index for patients who received goserelin was greater with anastrozole coadministration compared with tamoxifen, suggesting a greater inhibitory effect on tumor cell proliferation with this treatment combination.[20] Given the reported clinical prognostic value of Ki-67 expression after short-term neoadjuvant endocrine therapy for breast cancer,[19] this is in concordance with our finding that anastrozole combined with goserelin demonstrates a superior best overall tumor response compared with tamoxifen plus goserelin. Although Ki-67 is perceived as a reliable predictive endpoint, the outcomes of

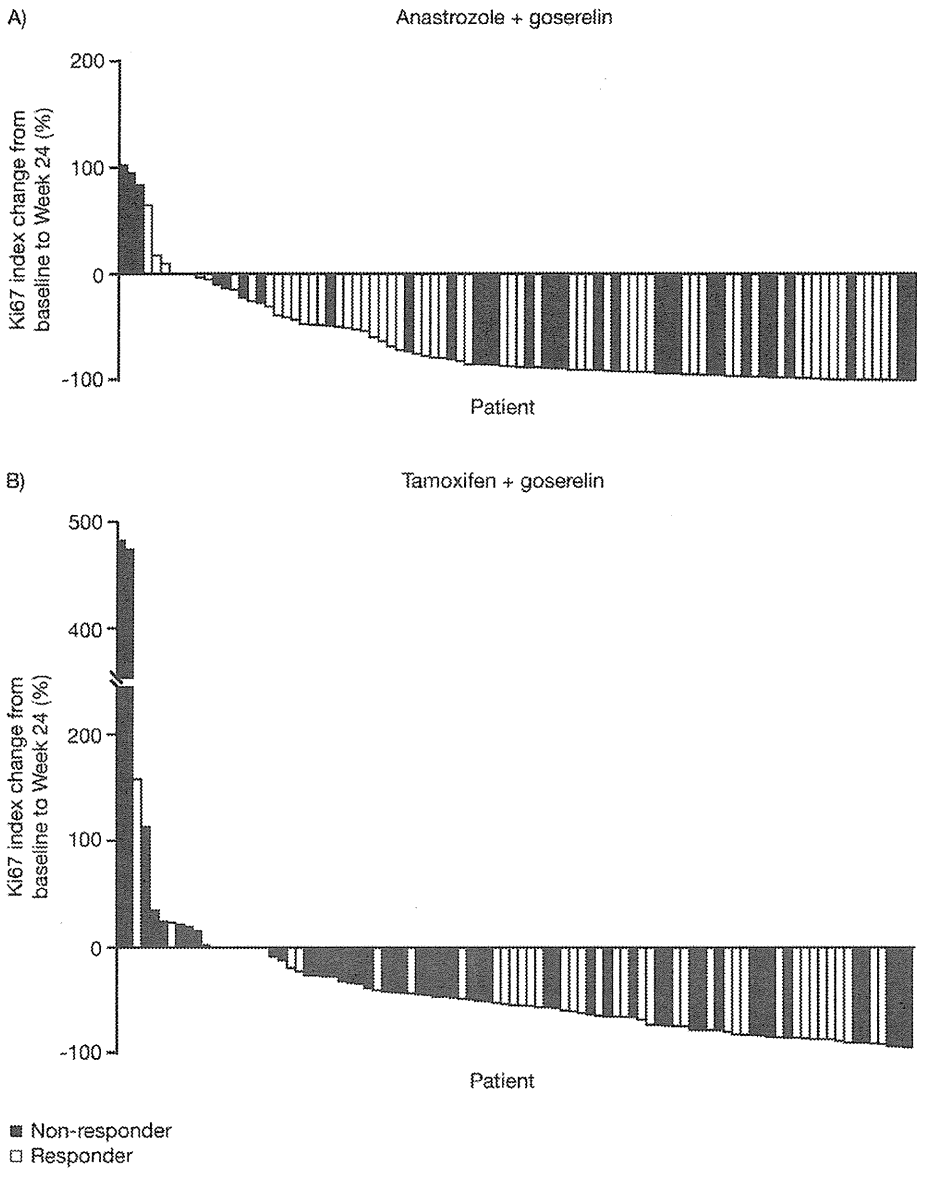


Figure 3. This is a waterfall plot of reductions in nuclear antigen Ki-67 levels in (A) the anastrozole plus goserelin treatment group and (B) the tamoxifen plus goserelin treatment group. Magnetic resonance imaging or computed tomography was used to measure responses. Responders were defined as those patients who had a complete or partial response during the 24-week treatment period.

the parallel adjuvant trial by the Austrian Breast and Colorectal Cancer Study Group (ABCSG) did not reflect outcomes related to the Ki-67 changes we observed: Results from the ABCSG-12 study indicated that there was no difference in disease-free survival between patients who received anastrozole versus tamoxifen (hazard ratio, 1.08; 95% CI, 0.81-1.44; $P = .591$).[26] The reason for this difference is not clear, although there were differences in the baseline characteristics of patients in each study: the STAGE study assessed a more hormone-dependent phenotype of tumor (ER-positive/HER2-negative in the STAGE study vs ER-positive/HER2-negative and ER-positive/HER2-positive in the ABCSG-12 trial), and the proportion of women with a body mass index >25 kg/m^2 was lower in the STAGE study (17% vs 33%). The ABCSG-12 group did not assess Ki-67 levels. It is also interesting to note that, as recently pointed out by Goncalves et al,[27] in our study, serum estradiol suppression

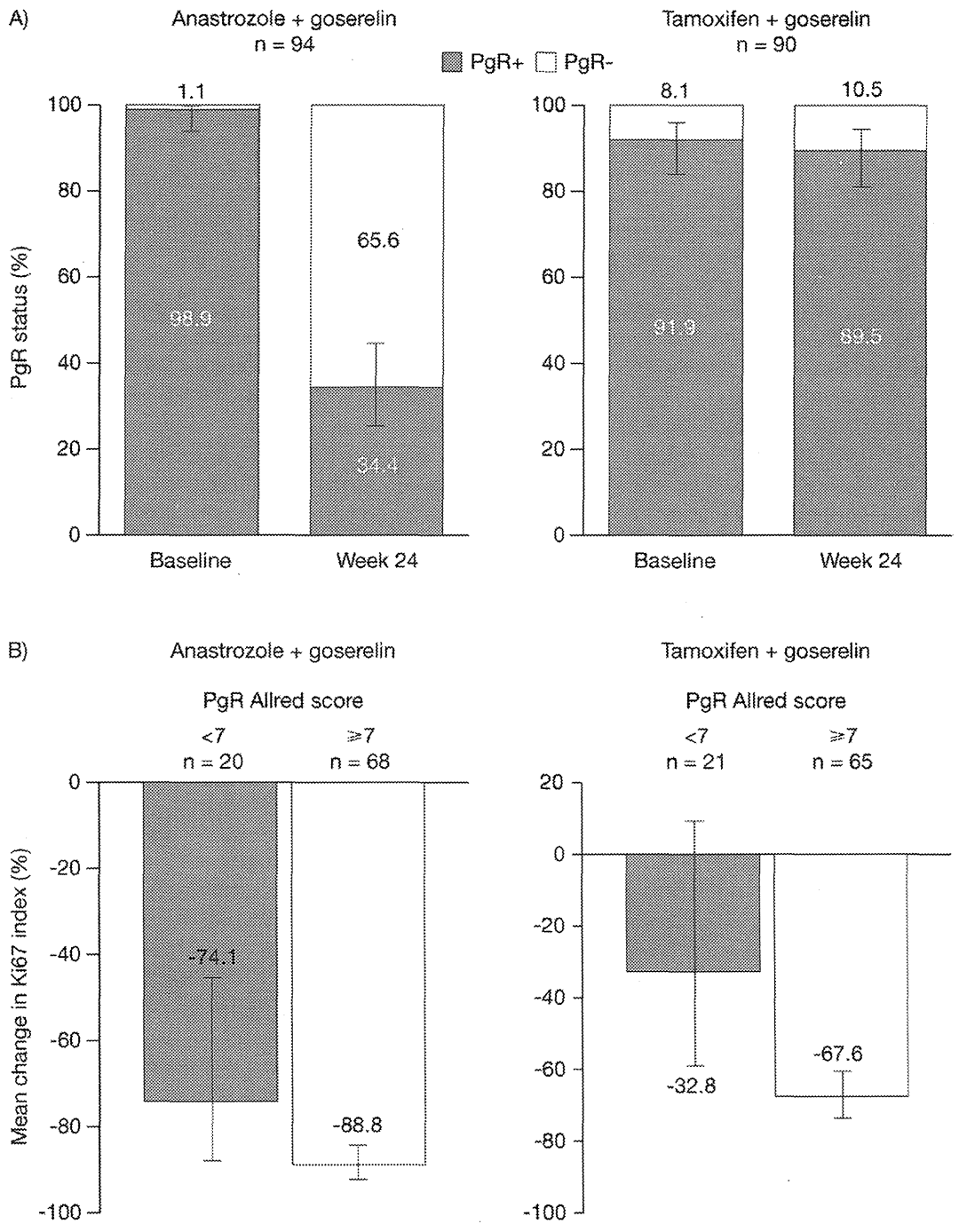


Figure 4. (A) Progesterone receptor status is illustrated at baseline and at 24 weeks. (B) Changes in the Ki-67 index and the baseline PgR Allred score are illustrated. PgR-positive (PgR+) indicates an Allred score >3; PgR-negative (PgR−), an Allred score <2.

appeared to decrease at week 24 compared with week 4, although the suppression was not statistically significant. This suggests the possibility of a gradual tachyphylaxis of the estrogen-suppressing effects of combined goserelin and anastrozole treatment, which potentially may explain the difference in outcomes between the ABCSG-12 and STAGE studies. However, further investigations would be required to confirm this.

TABLE 2. Preoperative Endocrine Prognostic Index Score

Treatment Group	No. of Patients	PEPI Score: No. of Patients (%)		
		0	1-3	≥4
Anastrozole plus goserelin	84	28 (33.3)	38 (45.2)	18 (21.4)
Tamoxifen plus goserelin	79	9 (11.4)	41 (51.9)	29 (36.7)
P for anastrozole vs tamoxifen		–	–	.002

Abbreviation: PEPI, Preoperative Endocrine Prognostic Index.
[a]*P* values were determined using the chi-square test.

In the current study, the best overall tumor response was superior with anastrozole compared with tamoxifen, irrespective of the baseline Ki-67 index. Within the anastrozole treatment group, we observed that the best overall tumor response was significantly better in patients who had a baseline Ki-67 index ≥20% versus patients who had a baseline Ki-67 index <20%. However, in the anastrozole group, we observed a numerically lower histopathologic response in patients who had a baseline Ki-67 index ≥20% compared with those who had a baseline Ki-67 index <20%. It was reported previously that baseline Ki-67 expression was not associated with outcome after neoadjuvant endocrine treatment (including anastrozole, letrozole, and tamoxifen) in ER-positive, postmenopausal women who had breast cancer.[19,25]

There was no apparent relation between a reduction in the Ki-67 index for responders and nonresponders in either treatment group. Although there tended to be more nonresponders among patients in the tamoxifen group who had less of a reduction in the Ki-67 index, the Spearman rank-correlation between the percentage change in the Ki-67 index and the best percentage change in greatest tumor dimension for the tamoxifen group was a modest 0.314. This observation is essentially consistent with what was reported previously by Dowsett et al, who conducted a similar analysis of postmenopausal patients who received neoadjuvant tamoxifen, anastrozole, and the tamoxifen/anastrozole combination.[28] This variation in the Ki-67 index change between responders and nonresponders indicates that the mechanism of estrogen-dependent growth is heterogeneous among breast tumors. Tumor growth is determined by a balance between cell proliferation and apoptosis. Stimulation of cell proliferation by estrogen may be dominantly implicated in tumor growth in some tumors, whereas inhibition of apoptosis by estrogen may be dominantly implicated in other tumors. Thus, a responder does not necessarily have a greater reduction in the Ki-67 index compared with a nonresponder if apoptosis is induced more strongly in the former than the latter after treatment.

In the neoadjuvant setting, endocrine therapy has demonstrated greater (or equivalent) efficacy in postmenopausal women with a lower Ki-67 index.[29,30] In contrast, in our study, both anastrozole and tamoxifen produced greater response rates in premenopausal women with a higher Ki-67 index. It is therefore possible that the main pathways of proliferative stimulation (and the effectiveness of endocrine treatments) may differ between premenopausal and postmenopausal women with ER-positive breast cancer, according to their level of Ki-67 expression. In general, high Ki-67 expression is traditionally is believed to offer a poor prognosis and is predictive of response to chemotherapy regimens.[31] However, our results suggest that endocrine therapy has at least comparable effectiveness for premenopausal patients with ER-positive breast cancer who have a high Ki-67 index.

No correlation could be determined between a change in the Ki-67 index and baseline ER status in either treatment group. However, the number of patients who were identified as PgR-positive decreased at week 24 in the anastrozole treatment group, an effect that was not observed in the patients who received tamoxifen plus goserelin. PgR expression also was reduced under neoadjuvant AI treatment for breast cancer in the ABCSG 17 study, although it remains to be determined whether the down-regulation of PgR may be used as a marker of clinical efficacy.[32] In our study, the reason why the positive rate of PgR was reduced in the anastrozole plus goserelin arm compared with the tamoxifen plus goserelin arm is most likely because of the estrogenic action of tamoxifen, which would induce PgR expression.

Although there may be a potential correlation between a reduction in Ki-67 and the baseline PgR Allred score in patients who receive anastrozole plus goserelin versus tamoxifen plus goserelin, further analyses will be required to determine whether a Ki-67 reduction in patients with high baseline PgR expression translates into a clinical benefit.

After treatment with anastrozole, a lower proportion of patients had a PEPI score ≥4 (indicating a high risk of

recurrence) compared with the tamoxifen treatment group. The PEPI model has been validated previously and has indicated significant differences in recurrence-free survival in the adjuvant setting between 3 PEPI risk groups (PEPI risk scores of 0, 1-3, and $\geq$4), with a PEPI score of 0 indicating a very low risk of relapse.[25] Data from the adjuvant treatment setting will provide added knowledge for the individualization of future adjuvant treatments after neoadjuvant therapy for breast cancer.

Currently, very little is known about the prognostic effect of Ki-67 in premenopausal women. However, in 1 recent study, the prognostic significance of Ki-67 was investigated in women with ER-positive breast cancer who had received short-term presurgical tamoxifen, and Decensi and colleagues reported that the Ki-67 response was a good predictor of recurrence-free survival and overall survival.[33]

To our knowledge, this is the first randomized study to investigate the potential of Ki-67 as a clinical biomarker for AI efficacy in premenopausal women with ER-positive breast cancer. It has been demonstrated that a reduction in Ki-67 expression as a result of neoadjuvant AI treatment can be a potentially useful marker of improved surgical outcomes in postmenopausal women with ER-positive breast cancer, and such a reduction has been identified as predictive of favorable outcomes in the adjuvant treatment period.[34] A reduction in Ki-67 expression during neoadjuvant treatment reportedly was greater with anastrozole versus tamoxifen in postmenopausal women who had ER-positive breast cancer,[18] and a parallel result also was observed in the corresponding adjuvant trial, in which recurrence-free survival also was greater for those who received anastrozole.[8] Yet another similar result was observed for letrozole, in which a greater Ki-67 reduction was observed compared with tamoxifen in the neoadjuvant setting.[35] Greater clinical effectiveness also was observed for letrozole in the neoadjuvant setting, both in terms of the objective response rate and the rate of breast-conserving surgery.[36]

In conclusion, tumor response was greater with anastrozole compared with tamoxifen, regardless of the baseline Ki-67 index, in premenopausal women who received goserelin as neoadjuvant therapy for ER-positive, early stage breast cancer. The current results indicate that endocrine therapy may offer a more tolerable treatment option than cytotoxic chemotherapy as neoadjuvant treatment for these patients, and further studies of the anastrozole plus goserelin treatment combination in this setting are warranted.

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CONFLICT OF INTEREST DISCLOSURES

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ORIGINAL ARTICLE

Locoregional recurrence risk factors in breast cancer patients with positive axillary lymph nodes and the impact of postmastectomy radiotherapy

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Abstract
Background Locoregional recurrence (LRR) after mastectomy reduces the patient's quality of life and survival. There is a consensus that postmastectomy radiotherapy (PMRT) helps establish locoregional control and reduces LRR in patients with ≥4 metastatic nodes. However, in patients with 1–3 metastatic nodes, the incidence of LRR and the role of PMRT have been the subject of substantial controversy. This study assessed the risk factors for LRR and the efficacy of PMRT in Japanese breast cancer patients with metastatic nodes.
Methods This study analyzed 789 cases of invasive breast carcinoma with metastatic nodes from 1998 to 2008. We divided the study population into 4 groups: 1–3 positive nodes with/without chemotherapy and ≥4 positive nodes with/without chemotherapy. Risk factors for LRR were identified and the relationship between LRR and PMRT was analyzed.
Results During the median follow-up of 59.6 months, 61 (7.7%) patients experienced LRR. In patients who received chemotherapy, independent LRR risk factors were high nuclear grade, severe lymphatic invasion, vascular invasion, and progesterone receptor-negative status in patients with 1–3 positive nodes, and severe lymphatic invasion and estrogen receptor-negative status in patients with ≥4 nodes. Although patients treated with PMRT had good outcomes, there was no significant difference, and PMRT did not significantly improve the outcome of the patients with all risk factors.
Conclusions With systemic therapy and adequate dissection, PMRT by itself was of limited value in establishing locoregional control. The indication for PMRT in patients with 1–3 positive nodes remains controversial.

Keywords Breast cancer · Locoregional recurrence · Postmastectomy radiotherapy · Outcome

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Introduction

For breast cancer patients and oncologists alike, locoregional recurrence (LRR) is still a clinical problem with regard to control of the disease and outcome after mastectomy. To achieve locoregional control and reduce LRR, the role of postmastectomy radiotherapy (PMRT) has been established by several randomized clinical trials (RCT) [1–4]. Based on these results, PMRT has become the standard adjuvant therapy for patients with 4 or more metastatic lymph nodes. Recently, some RCT demonstrated that PMRT improves outcome in all patients with metastatic lymph nodes, regardless of the number of positive nodes [5, 6]. However, the role of PMRT in patients with 1–3 positive nodes remains controversial [7, 8].

This study is a retrospective analysis to evaluate which clinicopathological features are predictive factors for LRR, such as the number of metastatic nodes. We also analyze the role and efficacy of PMRT in Japanese breast cancer patients.

Materials and methods

Patients and treatments

This study is a retrospective analysis of 789 patients with invasive breast carcinoma with metastatic lymph nodes

who were treated with total mastectomy and axillary lymph node dissection (level II or level III) at the National Cancer Center Hospital, Tokyo, Japan, from 1998 to 2008.

Neoadjuvant chemotherapy (NAC) was indicated for clinical stage II tumors that were larger than 3 cm in diameter, and for all stage III tumors. Adjuvant chemotherapy and/or hormone therapy were given in cases based on the most current recommendations from the St. Gallen's Consensus Meeting at the time [9–13]. Anthracycline-based chemotherapy included 4 cycles of CEF (cyclophosphamide 500 mg/m^2, epirubicin 100 mg/m^2, and fluorouracil 500 mg/m^2) every 3 weeks or 4 cycles of AC (doxorubicin 60 mg/m^2 and cyclophosphamide 600 mg/m^2). Taxane chemotherapy included 12 cycles of weekly paclitaxel (wPTX, 80 mg/m^2). Concurrent anthracycline and taxane chemotherapy included 4 cycles of AT (doxorubicin 50 mg/m^2 and docetaxel 60 mg/m^2) every 3 weeks. Sequential anthracycline and taxane chemotherapy included 2 cycles of AT followed by 12 cycles of wPTX, AC followed by wPTX, or CEF followed by wPTX. Trastuzumab (first cycle 4 mg/kg, subsequent cycles 2 mg/kg) was added to anthracycline and taxane chemotherapy regimens in patients with overexpression of human epidermal growth factor receptor 2 (HER2).

Radiation therapy (RT) was offered to patients with 4 or more metastatic lymph nodes and/or tumors >5 cm. RT was delivered to the chest wall, including the surgical scar and regional lymph nodes (i.e., supraclavicular, infraclavicular, and axillary), by bilateral X-irradiation using the tangential technique. Because level I and II axillary dissection was performed, RT was performed in the axillary apical area (level III). The parasternal region was not included in the field. The patients were treated using a linear accelerator, and the intended dose was a median absorbed dose in the target volume of 50 Gy, given in 25 fractions over a period of 5 weeks. All patients were simulated with a conventional simulator.

Histopathological analysis

Surgical specimens were examined to determine histological subtype, histological grade (HG), nuclear grade (NG), and the presence or absence of lymphatic or vascular space invasion. Histological subtype was classified using the World Health Organization histological classification of breast tumors [14]. HG was assessed using the Scarff–Bloom–Richardson classification [15]. NG was assessed using the General Rules for Clinical and Pathological Recording of Breast Cancer, 16th Edition [16, 17]. Immunohistochemistry was used to examine tissue samples for the expression of estrogen receptor (ER), progesterone receptor (PgR), and HER2. The cutoff values for ER and PgR were 10% positive cells. HER2 status was defined based on immunohistochemical staining (IHC). The specimens that were HER2 2+ by IHC were then subjected to fluorescence in-situ hybridization (FISH). HER2-positive samples were defined as those that were HER2 3+ in IHC or HER2 2+ in IHC with an amplification ratio in FISH of ≥2.0. The degree of lymphatic invasion (ly) was classified by hematoxylin and eosin staining as follows: absent, no lymphatic invasion; ly1+, minimal lymphatic invasion; ly2+, moderate lymphatic invasion; and ly3+, marked lymphatic invasion. The degree of venous invasion (v) was classified as follows: absent, no venous invasion; present, venous invasion. These evaluations were performed by two qualified pathologist.

Follow-up and statistical analysis

The duration of follow-up was calculated from the first day of treatment (NAC or surgery) to the most recent medical visit on record. LRR was defined as tumor recurrence in chest wall or regional lymph nodes with or without synchronous distant metastasis.

For comparison of categorical variables, the chi-squared test was used. Locoregional recurrence-free survival (LRFS) was calculated using the Kaplan–Meier method and compared using the log-rank test. Cox's proportional hazards regression models were used to assess the prognostic significance of tumor clinicopathological characteristics on the evaluated outcomes, which were expressed as hazard ratios (HR) with 95% confidence intervals (CI). Factors that were significant at $p \leq 0.05$ in the univariate analysis were entered into the multiple regression models. All data were analyzed using SPSS software (SPSS Inc., Chicago, IL, USA).

Results

Associations between patient and tumor characteristics and LRR

The patients, divided into 2 groups based on the number of positive nodes, and their chemotherapy treatment status are shown in Table 1. All patients had 6 or more dissected lymph nodes; the median number of dissected lymph nodes was 18.6. The median number of positive nodes per patient was 3.0.

In patients with 1–3 positive nodes (n 1–3), the mean age and the proportion of postmenopausal patients were significantly higher in those who did not receive chemotherapy. The patients who received chemotherapy had tumors that were significantly higher in HG and were more likely to be ER-negative. In patients with 4 or more

Table 1 Patient and tumor characteristics

	1–3 positive lymph nodes ($n = 479$)			≥4 positive lymph nodes ($n = 310$)		
	Chemotherapy ($n = 370$)	No chemotherapy ($n = 109$)	p	Chemotherapy ($n = 268$)	No chemotherapy ($n = 42$)	p
Age (years), mean ± SD	52.8 ± 10.5	64.0 ± 12.1	<0.001	54.0 ± 10.6	62.2 ± 13.8	<0.001
Menopausal status			<0.001			0.064
Premenopausal (%)	172 (46.5)	20 (18.3)		105 (39.2)	10 (23.8)	
Postmenopausal (%)	198 (53.5)	89 (81.7)		163 (60.8)	32 (76.2)	
Tumor size (cm), mean ± SD	3.4 ± 2.1	3.2 ± 1.8	0.308	4.8 ± 2.9	4.0 ± 2.0	0.109
Tumor size (mm)			0.297			0.471
<21 (%)	114 (30.8)	33 (30.3)		49 (18.3)	6 (14.3)	
21–50 (%)	196 (53.0)	66 (60.6)		119 (44.4)	23 (54.8)	
>50 (%)	60 (16.2)	10 (9.2)		100 (37.3)	13 (31.0)	
Histological subtype			0.175			0.423
IDC (%)	327 (88.4)	97 (89.0)		237 (88.4)	32 (76.2)	
ILC (%)	24 (6.5)	3 (2.8)		17 (6.3)	2 (4.8)	
Other (%)	19 (5.1)	9 (8.3)		14 (5.2)	4 (9.5)	
Histological grade			0.008			0.598
G1 (%)	19 (5.1)	8 (7.3)		11 (4.1)	3 (7.1)	
G2 (%)	153 (41.4)	62 (56.9)		91 (34.0)	15 (35.7)	
G3 (%)	192 (51.9)	39 (35.8)		160 (59.7)	24 (57.1)	
Nuclear grade			0.052			0.017
G1 (%)	29 (7.8)	13 (11.9)		23 (8.6)	2 (4.8)	
G2 (%)	156 (42.2)	58 (53.2)		80 (29.9)	23 (54.8)	
G3 (%)	176 (47.6)	38 (34.9)		165 (61.5)	17 (40.5)	
Lymphatic invasion			0.954			0.252
Absent (%)	106 (28.6)	33 (30.3)		37 (13.8)	4 (9.5)	
1+ (%)	219 (59.2)	64 (58.7)		116 (43.3)	22 (52.4)	
2+ (%)	43 (11.6)	12 (11.0)		65 (24.3)	15 (35.7)	
3+ (%)	2 (0.5)	1 (0.9)		30 (11.2)	1 (2.4)	
Vascular invasion			0.148			0.254
Absent (%)	340 (91.9)	97 (89.0)		218 (81.3)	38 (90.5)	
Present (%)	30 (8.1)	12 (11.0)		50 (18.7)	4 (9.5)	
No. of dissected lymph nodes, mean ± SD	17.4 ± 5.8	16.0 ± 6.8	0.110	20.7 ± 7.4	20.8 ± 6.8	0.933
No. of positive nodes, mean ± SD	1.8 ± 0.8	1.6 ± 0.9	0.119	10.9 ± 7.9	9.1 ± 6.3	0.186
ER positive (%)	250 (67.6)	95 (87.2)	<0.001	169 (63.1)	32 (76.2)	0.136
PgR positive (%)	247 (66.8)	80 (73.4)	0.204	161 (60.1)	30 (71.4)	0.231
HER2 positive (%)	76 (20.5)	18 (16.5)	0.294	62 (23.1)	8 (19.0)	0.450
Radiotherapy (%)	55 (14.9)	1 (0.9)	<0.001	174 (64.9)	12 (28.6)	<0.001
LRR (%)	18 (4.9)	6 (5.5)	0.109	32 (11.9)	5 (11.9)	0.776

SD standard deviation, *IDC* invasive ductal carcinoma, *ILC* invasive lobular carcinoma, *G* grade, *ER* estrogen receptor, *PgR* progesterone receptor, *HER2* human epidermal growth factor receptor 2, *LRR* locoregional recurrence

positive nodes ($n \geq 4$), the mean age was higher in the subgroup who did not receive chemotherapy; however, there was no difference in menopausal status. NG was higher in those who received chemotherapy. There was no difference with regard to hormone receptor status. Nevertheless, the number of metastatic nodes and the use of RT were higher in those who received chemotherapy.

During the median follow-up of 59.6 months, a total of 61 (7.7%) patients suffered LRR. In the 61 cases of LRR, 40 occurred in the skin and/or chest wall and 21 occurred in the regional lymph nodes. The patients were classified into four groups according to the number of lymph node metastases, and chemotherapy. There were 24/479 (5.0%) cases of LRR in the n 1–3 group and 37/310 (11.9%) in the

$n \geq 4$ group. In particular, in the patients who received chemotherapy, the incidence of LRR was 13/370 (3.5%) in the n 1–3 group and 26/268 (9.7%) in the $n \geq 4$ group.

The relationship between clinicopathological characteristics and the incidence of LRR was analyzed (Table 2). In the univariate analysis, NG 3, the severity of lymphatic invasion, the presence of vascular invasion, and hormone receptor-negative status were significant predictors of LRR in the n 1–3 patients who received chemotherapy. In the $n \geq 4$ patients who received chemotherapy, a tumor size >50 mm, the severity of lymphatic invasion, the presence of vascular invasion, and hormone receptor-negative status were significantly associated with LRR. However, in patients who did not receive chemotherapy, there were no factors significantly associated with LRR among the variables tested, regardless of the number of metastatic nodes.

The independent association between tumor characteristics and the risk of LRR, analyzed using Cox's proportional hazards regression models, is shown in Table 3. In the multivariate analysis, among the n1–3 patients who received chemotherapy, the severity of lymphatic invasion (HR 3.938; 95% CI 1.275–12.163), NG 3 (3.118; 1.001–9.730), the presence of vascular invasion (4.433; 1.384–14.202) and PgR-negative status (0.177; 0.060–0.521) were correlated with worse LRFS. For the $n \geq 4$ patients who received chemotherapy, the severity of lymphatic invasion (HR 4.861; 95% CI 1.896–12.462) and ER-negative status (0.402; 0.161–0.998) were correlated with worse LRFS.

The role of radiotherapy and incidence of LRR

LRR occurred in 40/547 (7.3%) patients who were not treated with RT and 21/242 (8.7%) patients who were treated with RT. There was no significant difference.

Figures 1, 2, and 3 show the Kaplan–Meier curves for outcomes among patients stratified by the number of positive nodes and treatment status. There was no statistically significant difference in the LRFS rate according to RT treatment status, although there was a trend towards better outcomes in the patients who received RT. There were 2/370 (0.5%) and 112/268 (41.8%) patients who received chemotherapy in the n 1–3 and $n \geq 4$ groups, respectively, who had all risk factors for LRR from the multivariate analysis. Figure 4 shows the outcomes among the patients with 4 or more positive nodes who received chemotherapy, considered a high-risk group. There was again a non-significant trend towards better prognosis with RT.

Discussion

Adjuvant therapy has been demonstrated to improve the outcomes of breast cancer patients. In addition to chemotherapy, PMRT has been shown to significantly reduce the risk of LRR and improve survival from several randomized control trials [1–4]. Following the consensus, we treated patients with massive lymph node metastasis and/or large tumor volume with RT. This report is the retrospective analysis of the role and efficacy of PMRT and the factors associated with LRR in Japanese patients.

To determine the LRR risk factor for each patient's background, we separated patients into four groups according to the number of positive nodes and whether chemotherapy was given. Irrespective of the number of lymph node metastases, the presence of lymphovascular invasion and hormone receptor-negative status were independent risk factors for LRR. The severity of lymphatic invasion was the common factor. NG was an independent factor in patients with 1–3 positive nodes. These variables were also reported in several other studies [18–21]. Therefore, the incidence of LRR was dependent on the malignancy of the tumor and the invasion of the lymphovascular space. The purpose and role of chemotherapy and RT was changed by the patient's status. For the patients with 1–3 metastatic nodes, chemotherapy was performed because of their hormone receptor-negative and/or high-grade tumor basis of the consensus at the time, and the purpose and role of RT were the prevention of chest wall recurrence after the removal of a large tumor rather than regional lymph node recurrence. On the other hand, most of the patients with more than 4 metastatic nodes were eligible for chemotherapy for systemic control of their metastasis and the purpose and role of RT were the control of their lymphovascular invasion.

RCT studies have shown the incidence of LRR to be 8–10% in patients who received chemoradiotherapy and 24–35% in patients who received chemotherapy without RT [1–4]. However, in our institute, the rate of LRR was 8.7% in patients who received RT and 7.3% in those who did not; the significant benefit of RT was not found in all subgroups. Although our patient population was similar to those of other studies, the incidence of LRR was very low in this study, especially in the patients who did not receive RT. Potential reasons for the low incidence of LRR in this study are the differences in the number of dissected lymph nodes and the duration of follow-up. In other studies, level I and/or partial level II lymph node dissection was performed, with the median number of dissected nodes ranging from 7 to 17 [22]. These numbers are lower than the number of dissected nodes at our institute, where level II or III dissection is the standard procedure. Though the role of PMRT for patients with more than 4 metastatic nodes has been established, it cannot be denied that adequate lymph node dissection is essential for locoregional control. Moreover, if it is considered that LRR is one expression of systemic organ metastasis, the role of RT might be limited

Table 2 Hazard ratio of locoregional recurrence-free survival by patient and tumor characteristics at presentation (univariate analysis)

	1–3 positive nodes					
	Chemotherapy (n = 370)			No chemotherapy (n = 109)		
	HR	95% CI	p	HR	95% CI	p
Menopausal status			0.052			0.716
Premenopausal	1			1		
Postmenopausal	3.037	0.990–9.318		0.663	0.073–6.056	
Tumor size (mm)			0.544			0.696
≤50	1			1		
>50	1.472	0.423–5.132		1.044	0.323–290133	
Histological subtype			0.926			0.672
IDC	1			1		
ILC	0.945	0.291–3.073		0.137	0.001–1346.73	
Histological stage			0.500			0.999
G1/2	1			1		
G3	1.391	0.529–3.655		1.001	0.167–5.996	
Nuclear grade			0.030			0.368
G1/2	1			1		
G3	3.448	1.124–10.575		2.277	0.380–13.645	
Lymphatic invasion			0.046			0.518
Absent/1+	1			1		
2+/3+	2.894	1.019–8.216		2.035	0.342–914.885	
Vascular invasion			0.002			0.583
Absent	1			1		
Present	6.141	1.976–19.092		1.766	0.232–13.547	
Estrogen receptor			0.028			0.270
Negative	1			1		
Positive	0.330	0.123–0.867		0.259	0.023–2.860	
Progesterone receptor			0.004			0.674
Negative	1			1		
Positive	0.239	0.091–0.631		0.597	0.054–6.599	
HER2			0.825			0.540
Negative	1			1		
Positive	0.868	0.247–3.048		0.038	0.021–133.590	
	≥4 positive nodes					
	Chemotherapy (n = 268)			No chemotherapy (n = 42)		
	HR	95% CI	p	HR	95% CI	p
Menopausal status			0.321			0.588
Premenopausal	1			1		
Postmenopausal	0.691	0.333–1.434		0.674	0.322–1.243	
Tumor size (mm)			0.049			0.495
≤50	1			1		
>50	1.544	1.002–3.424		1.875	0.308–11.405	
Histological subtype			0.385			0.574
IDC	1			1		
ILC	1.275	0.648–2.509		4.453	0.879–17.831	
Histological stage			0.094			0.465
G1/2	1			1		
G3	2.070	0.883–4.848		1.969	0.319–12.148	

Table 2 continued

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

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

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

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

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

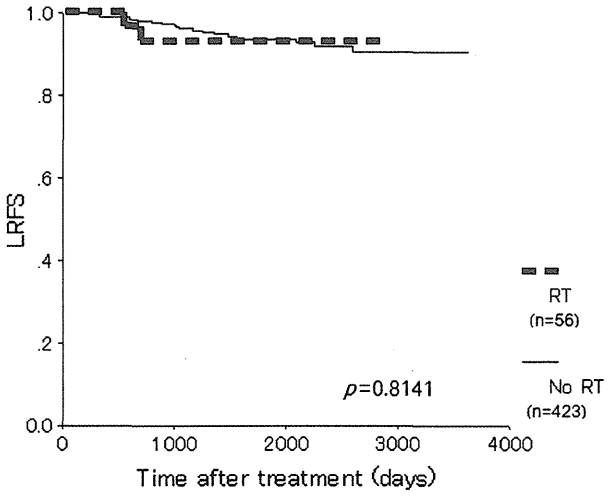

Fig. 1 Locoregional recurrence-free survival (*LRFS*) in patients with 1–3 positive nodes who received chemotherapy. *RT* radiation therapy

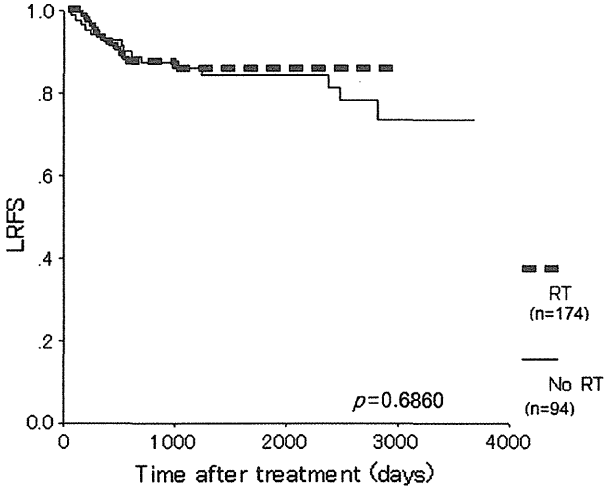

Fig. 2 Locoregional recurrence-free survival (*LRFS*) in patients with ≥4 positive nodes who received chemotherapy. *RT* radiation therapy

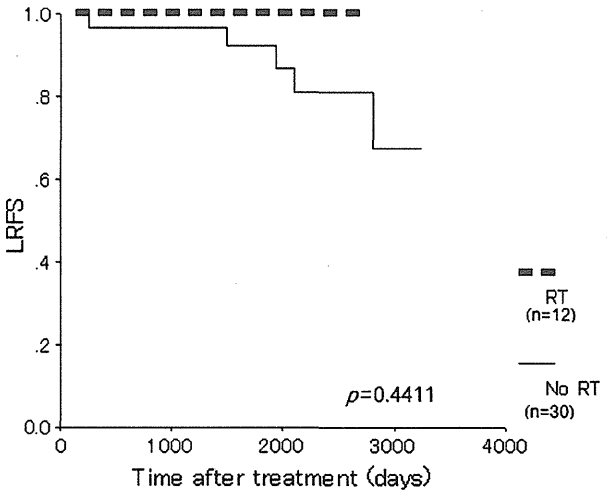

Fig. 3 Locoregional recurrence-free survival (*LRFS*) in patients with ≥4 positive nodes who did not receive chemotherapy. *RT* radiation therapy

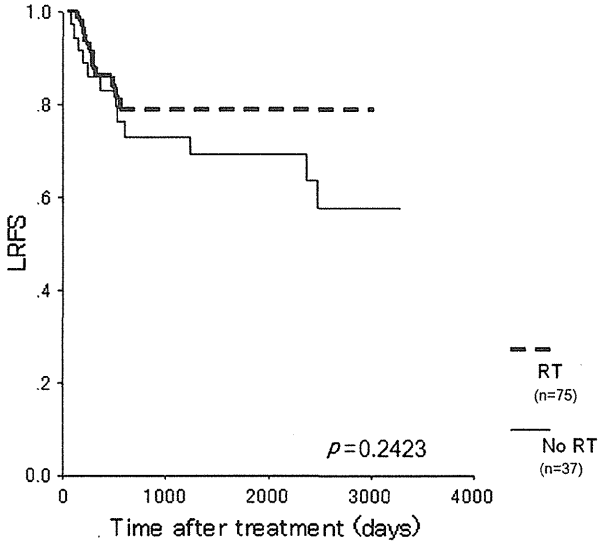

Fig. 4 Locoregional recurrence-free survival (*LRFS*) in the high-risk group of patients with ≥4 positive nodes who received chemotherapy. *RT* radiation therapy

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

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

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

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

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

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

Conflict of interest None.

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ORIGINAL ARTICLE

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

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Abstract
Background The purpose of this work was identify potential prognostic factors for survival in patients with primary metastatic hormone receptor-positive breast cancer undergoing endocrine therapy (ET) as first-line treatment.
Methods We investigated the clinical and pathological characteristics of 69 newly diagnosed stage IV hormone receptor-positive breast cancer patients undergoing ET between 1999 and 2009, and correlated these factors with disease progression and overall survival.
Results Multivariate regression analysis revealed that progesterone receptor (PgR) positivity (hazard ratio (HR) 0.248; $p = 0.001$) and clinical benefits of first-line ET (HR 0.386; $p = 0.008$) were significant prognostic factors for survival. When first-line ET was not effective, patients for whom second-line ET was effective survived significantly longer than those for whom second-line ET was not effective (median survival time, 45.3 vs. 25.8 months; $p = 0.0411$).
Conclusions PgR positivity and clinical benefits of first-line ET were independent prognostic factors for patients with hormone receptor-positive stage IV breast cancer. Moreover, the benefits of second-line ET in patients with a tumor resistant to first-line ET suggests the existence of drug-specific resistance to ET.

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

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Introduction

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

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

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

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

Patients and methods

Patients

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

Methods

All patients had invasive carcinoma histologically confirmed by core needle biopsy of the primary site. In 2000–2002, ER and PgR were detected by use of the specific antibodies 1D5 (Dako, Glostrup, Denmark) and 1A6 (Ventana Medical Systems, Tucson, AZ, USA) respectively; in 2003–2004, clones ER88 and PgR88 (Kyowa Medex, Tokyo, Japan); and in 2005–2009, clones 1D5 and PgR636 (Dako) were used. Levels of hormone receptor positivity were defined as positive staining in more than 1% or more than 10% of the tumor cell nuclei. HER2 expression was measured by use of HercepTest™ (Dako) in 2000–2002 and 2005–2009, and by use of Nichirei (Tokyo, Japan) anti-HER2/neu polyclonal antibodies in 2003–2004. HER2 positivity was defined as an immunohistochemistry (IHC) score of 3+ (intense staining of the cell membrane in more than 10% of the cancer cells) or positive fluorescence in situ hybridization (FISH) HER2 amplification signals (HER2/CEP17 signal ratio of 2 with IHC score of 2+).

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

Statistical analysis

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

Results

Characteristics of the patients

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

Table 1 Patients' characteristics

Characteristic	Number of patients	%
All patients	69	100
Age at diagnosis		
Median (range)	53 (27–86)	–
<50 years	22	32
≥50 years	47	68
Menopausal status		
Premenopause	22	32
Postmenopause	47	68
Clinical T factor (UICC sixth edition)		
T0	1	1
T1	2	3
T2	11	16
T3	16	23
T4	39	57
Clinical N factor (UICC sixth edition)		
N0	16	23
N1	31	45
N2	12	17
N3	6	9
Site of metastasis		
Liver	16	23
Lung	26	38
Bone	48	70
Brain	1	1
Skin	3	4
Lymph node	13	19
Bone and soft tissue only	31	45
Histology		
Invasive ductal carcinoma	65	94
Invasive lobular carcinoma	3	4
Others	1	1
Histological grade		
1 (well differentiated)	2	3
2 (moderately well or partially differentiated)	39	57
3 (poorly differentiated)	22	32
Unknown	5	7
ER status		
≥10% of positively stained nuclei	63	91
<10% but ≥1% of positively stained nuclei	1	1
<1% of positively stained nuclei (negative)	2	3
Uninterpretable/missing	3	4
PgR status		
≥10% of positively stained nuclei	44	64
<10% but ≥1% of positively stained nuclei	12	17
<1% of positively stained nuclei (negative)	12	17
Uninterpretable/missing	1	1
HER2 status		
Positive	8	12
Negative	60	87
Uninterpretable/missing	1	1
First-line ET		
TAM + LHRH analog	23	33
AI	40	58
TAM	6	9

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

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

OS and associated prognostic factors

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

Relationship between responsiveness to ET and survival

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

Table 2 Univariate analysis of prognostic factors

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

* $p < 0.05$

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

immediate second-line ET because of the absence of visceral metastases and the patient's own desire to receive ET. Four of the 9 patients who had initial resistance to first-line ET experienced clinical benefits with second-line ET; 2 had received anastrozole and 1 had received letrozole as first-line ET and TAM as second-line ET, whereas another had received TAM plus LHRH analog as first-line ET and medroxyprogesterone (MPA) as second-line ET (Table 4). In this population, patients who benefitted from second-line ET had significantly longer OS than those who did not (MST 45.3 vs. 19.9 months; $p = 0.0002$).

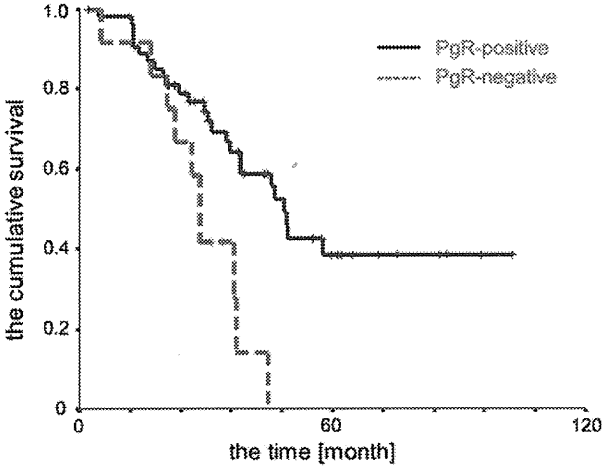

Fig. 1 Overall survival as a function of the progesterone receptor status. *Solid line*: progesterone receptor-positive patients, median 48.4 months (43.3–53.5). *Dashed line* progesterone receptor-negative patients, median 28.5 months (25.3–31.7). $p = 0.0036$

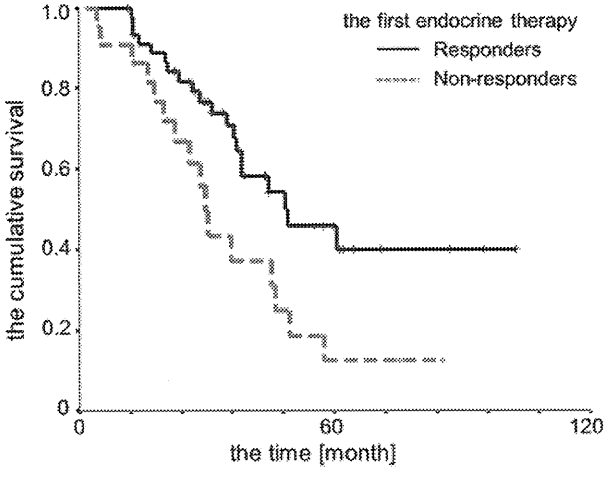

Fig. 2 Overall survival as a function of the clinical benefit rate of the first endocrine therapy. *Solid line*: responders to the first endocrine therapy, median 49.0 months (26.9–71.1). *Dashed line* non-responders to the first endocrine therapy, median 29.6 months (26.3–32.9). $p = 0.0170$

Table 3 Multivariate analysis of prognostic factors

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

HR hazard ratio, *CI* confidential interval, *ET* endocrine therapy

Discussion

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

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

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

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

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