Clinical Studies

Figure 3 Scores of staining for oestrogen receptor and progesterone receptor before and after neoadjuvant chemotherapy in 29 patients whose lesions changed from being hormone receptor (HR)-negative to HR-positive. The size of the circle indicates the number of patients and the number is below the circle. (**A–C**) Proportion score, intensity score, total score of ER before and after NAC. (**D–F**) Proportion score, intensity score, total score of PgR before and after NAC.
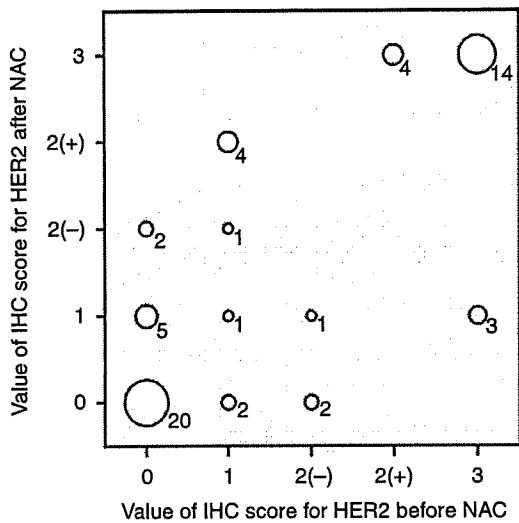

Figure 4 Bubble plot for immunohistochemistry score for HER2 before and after neoadjuvant chemotherapy in 59 patients with hormone receptor status conversion. The figures added to the bubbles are the number of patients and each bubble's size is determined by the number of patients in the category: the more the patients, the larger the bubble. The symbols (+) and (−), respectively, indicate the positive and negative status by fluorescent *in situ* hybridisation (FISH).
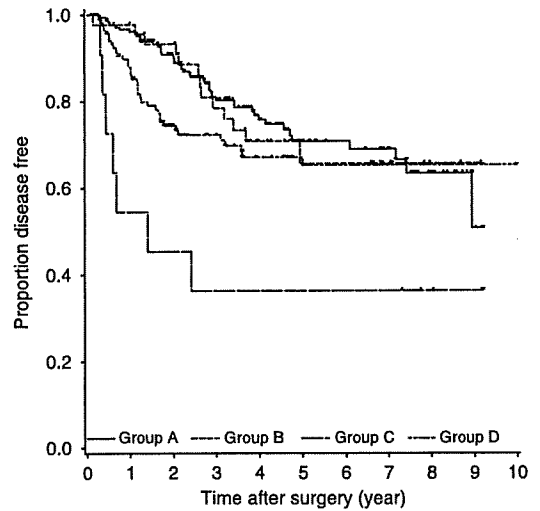
Figure 5 Kaplan–Meier curves of disease-free survival in four groups. Short vertical lines indicate censored data points. Log-rank test was significant for disease-free survival (DFS) ($P = 0.008$).

clinically not negligible. The poor prognosis of patients with HR status conversion not administered adjuvant ET indicates the necessity to determine the HR status of the lesions both before and

after NAC and to administer ET to patients with HR status conversion.

Despite yielding these clinically relevant findings, our study is limited in some aspects: (1) The patient groups studied were heterogeneous in terms of sample size and characteristics. (2) This study was retrospective and the results of the statistical tests were not based on randomisation, but were exploratory, although the

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Table 4 Results of multivariate Cox regression analysis of disease-free survival with stepwise selection

Variables	Hazard ratio (95% CI)	P-value
Group		
A	I	
B	1.16 (0.61, 2.19)	0.652
C	6.88 (3.00, 15.80)	<0.001
D	1.63 (1.01, 2.63)	0.045
Clinical stage		
IIA/IIB/IIIA	I	
IIIB/IIIC	1.56 (1.00, 2.42)	0.049
HER2		
Negative	I	
Positive	2.00 (1.30, 3.09)	0.002
Clinical response		
SD/PD	I	
PR/CR	0.56 (0.34, 0.92)	0.021
Number of lymph node metastases		
0	I	
1–3	2.09 (1.14, 3.83)	0.017
>4	6.49 (3.71, 11.37)	<0.001

Abbreviations: CI = confidence interval; CR = complete response; PR = partial response; SD = stable disease; PD = progression disease.

Table 5 Efficacy of endocrine therapy in patients with lesions showing hormone receptor status conversion after neoadjuvant chemotherapy in terms of disease-free survival

Variables	Hazard ratio (95% CI)	P-value
ET		
No	I	
Yes	0.19 (0.06, 0.60)	0.004
HER2		
Negative	I	
Positive	1.58 (0.46, 5.42)	0.467
Clinical response		
SD/PD	I	
PR/CR	0.75 (0.15, 3.93)	0.738
Clinical stage		
IIA/IIB/IIIA	I	
IIIB/IIIC	1.03 (0.26, 4.16)	0.968
Number of lymph node metastases		
0	I	
1–3	2.74 (0.63, 11.98)	0.181
>4	14.66 (3.24, 66.43)	0.001

Abbreviations: CI = confidence interval; CR = complete response; PR = partial response; SD = stable disease; PD = progression disease.

prognostic factors were adjusted using multivariate Cox regression analysis. Therefore, the impact of the change in the pre- and post-NAC HR statuses on the long-term outcomes and the efficacy of ET for patients with HR status conversion should be evaluated using a prospective study design. (3) The methods for measuring the ER

Figure 6 Kaplan–Meier curves of OS in four groups. Short vertical lines indicate censored data points. Log-rank test was significant for overall survival (OS) (*P* = 0.035).

and PgR status varied with the age of the patients, as shown in Table 1. Although the methods used for the determination of the HR statuses of the tumours of 36 patients among 368 patients were measured using different methods for the CNB and surgical specimens, only three of these tumours showed HR status conversion. A previous report showed that the HR status conversion occurred in 23% of the population in a study in which the same methods were used for the analysis of CNB and surgical specimens (Tacca *et al*, 2007), whereas HR status conversion was observed in 16.0% (59 patients) of the patients in this study. Therefore, the difference in the methods for measuring the ER and PgR statuses of the CNB and surgical specimens seems not to be the only reason for HR-status conversion.

In conclusion, our study showed that the prognosis of patients with change in HR status after NAC but who did not receive ET was worse than that of the other groups. The hormone receptor status should be evaluated not only in the biopsy specimens obtained before the initiation of NAC but also in specimens obtained during post-NAC surgery; the pre- and post-NAC HR statuses will help determine the indication for adjuvant ET in patients. ET appears to be suitable for patients with tumours positive for HR status at least once, that is, either before or after NAC.

ACKNOWLEDGEMENTS

Conflict of interest

The authors declare that there are no competing financial interests.

REFERENCES

Adams AL, Eltoum I, Krontiras H, Wang W, Chhieng DC (2008) The effect of neoadjuvant chemotherapy on histologic grade, hormone receptor status, and Her2/neu status in breast carcinoma. *Breast J* 14: 141–146
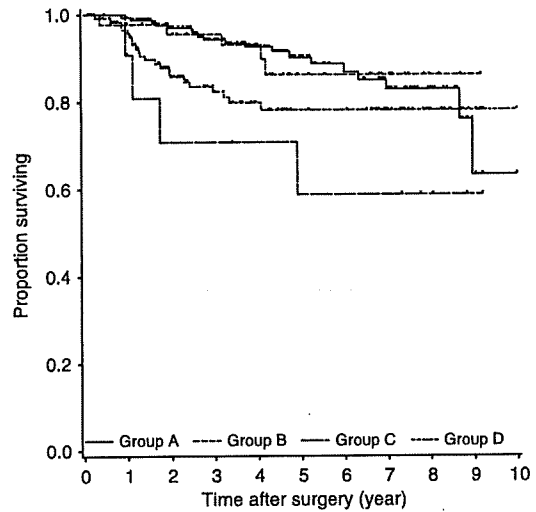
Allred DC, Harvey JM, Berardo M, Clark GM (1998) Prognostic and predictive factors in breast cancer by immunohistochemical analysis. *Mod Pathol* 11: 155–168

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1536

Arens N, Bleyl U, Hildenbrand R (2005) HER2/neu, p53, Ki67, and hormone receptors do not change during neoadjuvant chemotherapy in breast cancer. *Virchows Arch* 446: 489–496

Bottini A, Berruti A, Bersiga A, Brunelli A, Brizzi MP, Marco BD, Cirillo F, Bolsi G, Bertoli G, Alquati P, Dogliotti L (1996) Effect of neoadjuvant chemotherapy on Ki67 labelling index, c-erbB-2 expression and steroid hormone receptor status in human breast tumours. *Anticancer Res* 16: 3105–3110

Burcombe RJ, Makris A, Richman PI, Daley FM, Noble S, Pittam M, Wright D, Allen SA, Dove J, Wilson GD (2005) Evaluation of ER, PgR, HER-2 and Ki-67 as predictors of response to neoadjuvant anthracycline chemotherapy for operable breast cancer. *Br J Cancer* 92: 147–155

Colleoni M, Viale G, Zahrieh D, Pruneri G, Gentilini O, Veronesi P, Gelber RD, Curigliano G, Torrisi R, Luini A, Intra M, Galimberti V, Renne G, Nolè F, Peruzzotti G, Goldhirsch A (2004) Chemotherapy is more effective in patients with breast cancer not expressing steroid hormone receptors: a study of preoperative treatment. *Clin Cancer Res* 10: 6622–6628

Kasami M, Uematsu T, Honda M, Yabuzaki T, Sanuki J, Uchida Y, Sugimura H (2008) Comparison of estrogen receptor, progesterone receptor and Her-2 status in breast cancer pre- and post-neoadjuvant chemotherapy. *Breast* 17: 523–527

Kaufmann M, von Minckwitz G, Smith R, Valero V, Gianni L, Eiermann W, Howell A, Costa SD, Beuzeboc P, Untch M, Blohmer JU, Sinn HP, Sittek R, Souchon R, Tulusan AH, Volm T, Senn HJ (2003) International expert panel on the use of primary (preoperative) systemic treatment of operable breast cancer: review and recommendations. *J Clin Oncol* 21: 2600–2608

Lee SH, Chung MA, Quddus MR, Steinhoff MM, Cady B (2003) The effect of neoadjuvant chemotherapy on estrogen and progesterone receptor expression and hormone receptor status in breast cancer. *Am J Surg* 186: 348–350

Mauri D, Pavlidis N, Ioannidis JP (2005) Neoadjuvant versus adjuvant systemic treatment in breast cancer: meta-analysis. *J Natl Cancer Inst* 97: 188–194

Neubauer H, Gall C, Vogel U, Hornung R, Wallwiener D, Solomayer E, Fehm T (2008) Changes in tumour biological markers during primary systemic chemotherapy (PST). *Anticancer Res* 28: 1797–1804

Quddus RM, Sung JC, Zhang C, Pasqueriello T, Eklund M, Steinhoff MM (2005) HER-2/neu expression in locally advanced breast carcinomas: Pre-and post-neoadjuvant chemotherapy. *Breast Cancer* 12: 294–298

Shet T, Agrawal A, Chinoy R, Havaldar R, Parmar V, Badwe R (2007) Changes in the tumor grade and biological markers in locally advanced breast cancer after chemotherapy-implications for a pathologist. *Breast J* 13: 457–464

Tacca O, Penault-Llorca F, Abrial C, Mouret-Reynier MA, Raoelfils I, Durando X, Achard JL, Gimbergues P, Curé H, Chollet P (2007) Changes in and prognostic value of hormone receptor status in a series of operable breast cancer patients treated with neoadjuvant chemotherapy. *Oncologist* 12: 636–643

Taucher S, Rudas M, Gnant M, Thomanek K, Dubsky P, Roka S, Bachleitner T, Kandioler D, Wenzel C, Steger G, Mittlböck M, Jakesz R (2003) Sequential steroid hormone receptor measurements in primary breast cancer with and without intervening primary chemotherapy. *Endocr Relat Cancer* 10: 91–98

Clinicopathological Features of Tumors as Predictors of the Efficacy of Primary Neoadjuvant Chemotherapy for Operable Breast Cancer

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Abstract

Background Neoadjuvant chemotherapy (NC) is standard therapy for patients with locally advanced breast cancer and is increasingly used for early-stage operable disease. Clinical and pathological responses are important prognostic parameters for NC, which aims to achieve a pathological complete response or tumor reduction to reduce the volume of subsequent breast resection. Clinicopathological markers that predict patient response to NC are needed to individualize treatment.

Methods From 1998 to 2006, 368 patients with primary breast cancer underwent curative surgical treatment after NC (anthracycline and/or taxane without trastuzumab). We retrospectively evaluated the clinicopathological features and classification of the tumors using computed tomography (CT) before NC and analyzed the correlation with the pathological complete response (pCR) and reduction of tumor size after treatment.

Results The overall response and pCR rates in these patients were 86% and 17%, respectively. In multivariate analysis, classification as a scirrhous-type tumor was an independent predictor of reduced likelihood of pCR ($p = 0.0115$; odds ratio 0.21). For tumor reduction, histological grade 3 ($p = 0.0002$; odds ratio 3.3) and localized tumors identified by using CT imaging ($p = 0.0126$; odds ratio 2.4) were independent predictors in multivariate analysis.

Conclusions In this study, NC often did not result in pCR for breast cancers classified as scirrhous. Furthermore, tumor type classification using CT imaging and histological grading was effective to predict tumor reduction in response to NC that included an anthracycline and/or a taxane.

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Introduction

Neoadjuvant chemotherapy (NC) is used to reduce the size of locally advanced breast cancer tumors, and hence, the area to be resected, or to enable breast conservation for cases in which it was otherwise not possible. In clinical practice, because currently available anticancer drugs are extremely effective, these goals are achieved in many patients and the primary tumors completely disappear (i.e., pathological complete response (pCR)) in some patients by the end of NC. Data from large-scale studies have revealed that the patients who achieved pCR after preoperative administration of anticancer drugs have significantly better prognoses than other patients. These preoperative chemotherapy regimens primarily consist of an anthracycline. A

taxane may be added for some patients and additionally, trastuzumab is included for HER-2-positive patients. Indeed, the percentage of patients who experienced pCR increased when an anthracycline was added to their treatment regimens, and further increased with the addition of a taxane [1, 2]. With NC, limited surgery is assumed to be performed after the volume of the advanced breast cancer tumor is reduced, whereas NC is designed to extend the survival of patients by causing tumors to disappear solely by using anticancer drugs. Therefore, even those patients with breast cancer who have relatively small tumors close to their early-stage are currently treated first with anticancer drugs. Although preoperative chemotherapy has been used in wider range of cases, there are no practical criteria for its indications in terms of the results from clinicopathological examinations. Clinically, some patients show excellent responses to anticancer drugs and NC should be performed proactively, whereas other patients do not significantly benefit from these drugs and NC may not be necessary. Thus, individually predicting the efficacy of NC used for different purposes and deciding whether it should be performed is a current clinical goal.

In recent translational research, the efficacy of anticancer or hormone drugs were predicted by immunologically examining the sensitivity of the patients to these drugs [3]. As the indications of NC continue to expand, it is necessary to precisely select therapeutic methods, including the type of anticancer drugs, based on small tissue samples and laboratory test results that are available before surgeries. In the present study, we retrospectively examined cases treated at our clinic to determine whether it is possible to predict the efficacy of NC used for different purposes based on pretreatment tissue samples and the tumor shape observed using pretreatment CT imaging.

Methods

Patients and treatments

All patients diagnosed with operable breast cancer and treated between May 1998 and July 2006 at the National Cancer Center Hospital (NCCH; Tokyo, Japan) with NC, including an anthracycline and a taxane, were included this retrospective study. NC was indicated for clinical stage II tumors and tumors >3 cm or stage III breast cancer tumors. Core-needle biopsy was performed before NC to allow a pathological diagnosis. Doxorubicin (DOX, 50 mg/ m^2) and docetaxel (DOC, 60 mg/m^2) (AT regimen) were administered in four cycles every 3 weeks before surgery. Additional adjuvant treatment with DOX/DTX was given if the patients achieved complete or partial remission after preoperative chemotherapy or were otherwise treated with

four cycles of intravenous cyclophosphamide, methotrexate, and 5-fluorouracil. FECT treatment was four cycles of 5-fluorouracil (500 mg/m^2)/epirubicin (100 mg/m^2)/cyclophosphamide (500 mg/m^2) plus 12 weekly cycles of paclitaxel (80 mg/m^2) followed by surgery. The ACT regimen was 4 cycles of doxorubicin (60 mg/m^2)/cyclophosphamide (600 mg/m^2) plus 12 weekly cycles of paclitaxel (80 mg/m^2) followed by surgery. The T regimen was 12 weekly cycles of paclitaxel (80 mg/m^2) followed by surgery. Recently, patients with breast cancer that showed an HER-2 overexpression phenotype have received trastuzumab as PST. However, in this study we excluded these patients because we have only recently begun to use trastuzumab, and many HER-2–positive patients did not receive this treatment. Tamoxifen (20 mg/day) or anastrozole (10 mg/day) was administered for 5 years when pretreatment biopsy specimens or surgical postchemotherapy specimens were positive for estrogen receptor (ER) or progesterone receptor (PgR). The surgical treatment employed was mastectomy or breast-conserving surgery with axillary lymph node dissection (level 2) and that was decided from both of preoperative general diagnosis (palpation, MMG, US, and MDCT findings) and intraoperative pathological findings.
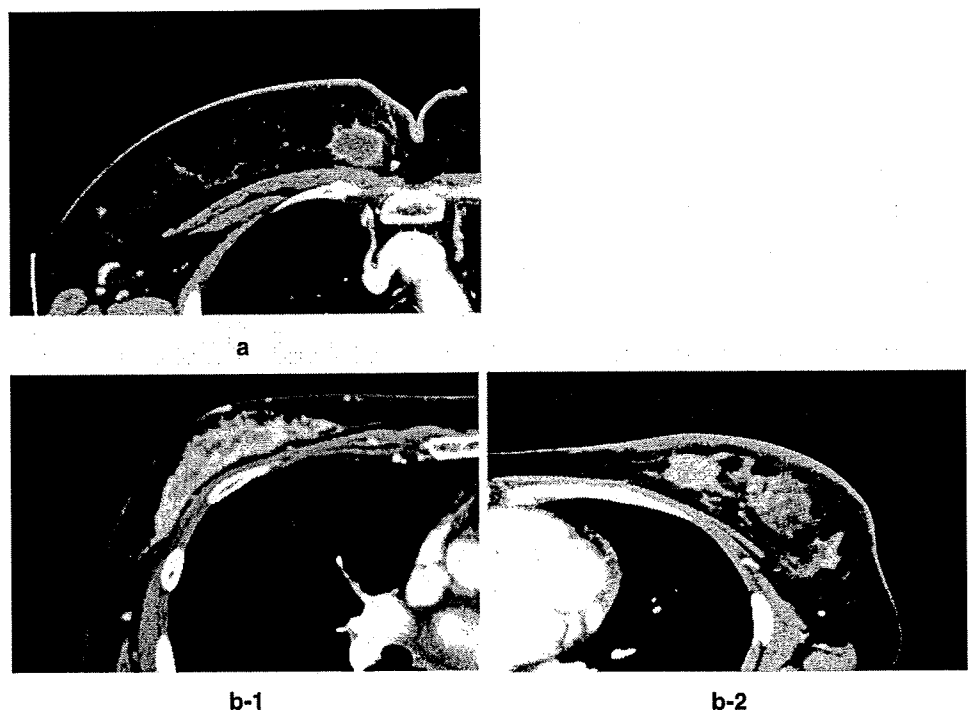
Evaluation of pathological factors

Pretreatment diagnoses were established by our pathologists using a core-needle biopsy or a surgical resection. The expression levels of hormone receptors and HER-2 were determined by using immunohistological examinations. Surgical specimens were sectioned to an approximately 7–10-mm thickness and pathologically classified by pathologists. Pathologic features were noted and invasive ductal carcinomas (IDCs) were classified as one of three subtypes (papillotubular, solid-tubular, and scirrhous) according to the General and Pathological Recording of Breast Cancer guideline established by the Japanese Breast Cancer Society [4]. The diagnosis of invasive lobular carcinoma was based on tumor histology showing the absence of E-cadherin by immunohistological examination on the pretreatment specimens. The criteria for histological grading of IDCs were based on a modification of those recommended by the World Health Organization [5, 6]. The response criteria used in this study include Fisher's system [7]; pCR means no histological evidence of invasive tumor cells (specimens with only noninvasive cells were included), whereas pINV indicated the presence of invasive tumor cells. The criterion for ER- and PgR-positive samples was specific signals in more than 10% of the cancer cell nuclei, regardless of intensity. HER-2 positivity was defined as 3+ , i.e., markedly positive in more than 10% of the cancer cells.

Clinical responses to preoperative chemotherapy were reflected by the two greatest perpendicular diameters (before each chemotherapy treatment and before surgery) of tumors in the breast and an axillary lymph node. No clinical evidence of palpable tumor in the breast and axillary lymph nodes was defined as a clinical complete response (cCR). Reduction in the total tumor size by 30% or more was graded as a clinical partial response (cPR). An increase in the total tumor size of more than 20% or appearance of new suspicious ipsilateral axillary adenopathy was considered progressive disease (cPD). Tumors that did not meet any of the criteria for response or progression were considered unchanged (cNC).

CT imaging

CT examinations were performed with the patient in the supine position using a helical CT scanner (X-Vigor; Toshiba Medical Systems, Japan) between January and June 2000 or using an MDCT scanner (Aquilion, Toshiba) beginning in July 2000. The first noncontrast-enhanced CT scan served as the baseline with scanning performed from the cranial end of the sternum to the inframammary fold. Subsequently, an enhanced zoomed scan was obtained to visualize the entire breast. A bolus of 100 ml of nonionic contrast material (300 mgI/ml) was injected intravenously at a rate of 3 ml per second via an antecubital vein on the side opposite the affected breast using an automated injector. Image acquisition was started 40 s after the start of the bolus injection. The reconstruction interval was 5 mm.

The tumor shape was classified into two types: localized tumors visualized as single lesions and nonlocalized tumors, including those with surrounding lesions, multiple lesions, or glandular spreading (Fig. 1). CT imaging was used before both NC and surgery. The maximum tumor size measurements and the tumor shape classification were obtained using the CT images and compared with the size measured during the pathological examination.

Results

From May 1998 to July 2006, 403 patients were administered an anthracycline and/or a taxane as NC at the NCCH. Excluding the patients who received trastuzumab, the indication of which was not clear at the time of the study, concomitantly with a taxane, 368 patients who were diagnosed with breast cancer using pretreatment cutting needle biopsies were included in this study. The patient backgrounds are shown in Table 1. Among the patients, 194 (53%) were aged 50 years or younger and 174 (47%) were aged 51 years or older. The clinical stages of the patients at the first visit were IIA, IIB, IIIA, and IIIB for 29%, 31%, 13%, and 20%, respectively. According to the histological examinations of pretreatment cutting needle biopsies, 333 patients (90%) had an IDC, 19%, 36%, and 36% of which were classified as papillotubular type, solid-tubular type and scirrhous type, respectively. Other than IDC, 14 patients (4%) had an invasive lobular carcinoma (ILC) and 7 patients (2%) had a mucinous carcinoma.

Fig. 1 Classification of tumor by CT imaging. a Localized type. b-1 Nonlocalized type: glandular spreading. b-2 Nonlocalized type: tumor with surrounding lesions

a

b-1   b-2

Table 1 Patient and disease characteristics ($N = 368$)

Parameter	No. of patients	%
Age (years)		
≤50	194	53
≥51	174	47
Clinical stage		
IIA	105	29
IIB	114	31
IIIA	74	13
IIIB	75	20
Pretreatment pathology		
Invasive ductal carcinoma	333	90
Papillotubular type	68	19
Solid-tubular type	131	36
Scirrhous type	134	36
Invasive lobular carcinoma	14	4
Mucinous carcinoma	7	2
Other	14	4
Hormone receptors		
ER positive	150	41
PgR positive	218	59
HER2		
Positive	57	15
Histological grade		
G1	18	5
G2	169	46
G3	181	49
Neoadjuvant chemotherapy		
AC	3	1
ACT	75	20
AT	185	50
FECT	92	25
T	13	4
Surgery		
Partial mastectomy	136	37
Total mastectomy	232	63
Clinical response		
CR	99	27
PR	218	59
NC	46	13
PD	5	1
Pathological response		
pCR	64	17
pINV	304	83
Postoperative pathological tumor size (mm)		
Median	24	
Range	0–130	
No. of pathological LN metastases		
0	164	45
1–3	108	29

Table 1 continued

Parameter	No. of patients	%
4–9	58	16
≥10	38	10

PgR, progesterone receptor; *ER*, estrogen receptor; *CR*, complete response; *PR*, partial response; *NC*, neoadjuvant chemotherapy; *pCR*, pathological complete response; *LN*, lymph node

Immunohistological examinations revealed that 41%, 59%, and 15% of the patients were positive for ER, PgR, and HER-2, respectively. The histological grade was G2 and G3 in 46% and 49% of the patients, respectively, indicating that many patients had relatively high-grade disease. As NC regimens, AC, ACT, AT, FECT, and T were used in 1%, 20%, 50%, 25%, and 4% of the patients, respectively. The clinical response rate to NC was 86% (27% for cCR and 59% for cPR), and 64 patients (17%) achieved a pCR pathological response. The median postoperative pathological tumor size was 24 (range, 0–130) mm. Whereas 45% of the patients were node-negative, 16% of the patients had four or more and approximately 10% of the patients had ten or more metastatic lymph nodes. Among the 368 patients, we further examined 267 patients who underwent CT imaging before treatment (Table 2). Classification of the tumor shape based on CT imaging showed localized tumors in 65 patients (24%). The median maximum tumor size measured using pretreatment CT was 40 (range, 15–120) mm. When we compared pretreatment maximum tumor size and the postoperative pathological tumor size in these patients, the treatment reduced the maximum tumor size by 30% or more in 146 patients (55%).

Table 3 shows the results of univariate analysis performed to evaluate the relationship between the efficacy of

Table 2 Tumor characteristics in CT images ($N = 267$)

Parameter	No. of patients	%
Tumor type		
Localized type	65	24
Nonlocalized type	202	76
Pretreatment tumor size (mm)		
Median	40	
Range	15–120	
Tumor reduction rate[a]		
>30%	146	55
<30%	121	33

[a] x100 (Pretreatment tumor size − pathological tumor size)/pretreatment tumor size); pretreatment tumor sizes were measured in imaging from computed tomography

Table 3 Univariate analysis of predictive markers in pathological response and tumor reduction

Parameter	pCR		Tumor reduction rate >30%	
	n (%)	p value	n (%)	p value
Age (years)				
≥51	42[a] (22)	0.022	61 (52)	N.S.
≤50	22 (13)		85 (56)	
Invasive ductal carcinoma				
Solid-tubular type	35[a] (27)	0.0006	60[a] (67)	0.005
Scirrhous type	12[a] (8)	0.0006	50 (52)	N.S.
Papillotubular type	8 (12)	N.S.	29 (54)	N.S.
ER-negative	53[a] (24)	<0.0001	96 (59)	N.S.
ER-positive	11 (7)		50 (48)	
PgR-negative	50[a] (23)	0.0005	92 (58)	N.S.
PgR-positive	14 (9)		54 (50)	
HER2 3+	19[a] (33)	0.004	24 (55)	N.S.
HER2 2+	6 (11)		27 (66)	
HER2 <1+	39 (15)		95 (52)	
Histological grade G3	45[a] (25)	0.001	89[a] (70)	<0.0001
G2	17 (10)		49 (39)	
G1	2 (11)		7 (58)	
Clinical response				
CR + PR	62[a] (20)	0.0017	138[a] (60)	<0.0001
NC + PD	2 (3)		8 (22)	
CT tumor type				
Localized type	16 (24)	0.063	48[a] (74)	0.0003
Nonlocalized type	29 (14)		98 (49)	

[a] p < 0.05

CT, computed tomography; ER, estrogen receptor; PgR, progesterone receptor; CR, complete response; PR, partial response; NC, neoadjuvant chemotherapy

NC and the clinicopathological examination results. Significantly higher percentages of patients achieved pCR if they were aged 50 years or older, had solid-tubular type disease, were negative for ER or PgR, were positive for HER-2, had histological grade 3 disease, demonstrated positive clinical sensitivity (CR [complete response] + PR [partial response]), or were classified as having localized disease using pretreatment CT imaging. Conversely, significantly lower percentages of patients experienced pCR if their tumors were histologically classified as scirrhous. When the pretreatment maximum tumor size and the postoperative pathological maximum tumor size were compared, the clinicopathological factors that were significantly associated with 30% or more reductions in tumor size were having solid tubular-type disease, testing negative for ER, classification of histological grade 3, positive clinical sensitivity (CR + PR), and classification as localized tumors based on pretreatment CT imaging. Table 4 shows the results of multivariate analysis of these factors. In this analysis, the factor that was significantly associated with reduced rates of pCR was tumors classified as scirrhous. Other factors did not significantly influence the pathological response. Histological grade 3, positive clinical sensitivity (CR + PR), and classification as localized tumors were significantly associated with tumor size reduction.

Discussion

In recent years, NC has been used not only for locally advanced breast cancer but also for relatively early-stage breast cancer. This type of therapy is used to (1) achieve pCR; (2) enable breast conservation by reducing the size of the tumor; and (3) evaluate the sensitivity of the breast cancer to anticancer drugs.

The primary purpose of NC is to achieve pCR, which is based on the understanding that patients who experience pCR after NC have better prognoses relative to other patients [8]. To accomplish this purpose, it is necessary to characterize the cases of breast cancer that are more likely to achieve pCR and to select anticancer drugs that are appropriate for each case. Immunohistological examinations, including analyses of hormone receptors, HER-2 and

Table 4 Multivariate analysis

Parameter	pCR		Tumor reduction rate >30%	
	p value	Odds ratio	p value	Odds ratio
Age >51 years	NS		NS	
Solid-tubular type	NS		NS	
Scirrhous type	0.008	0.2 (−1.441 to −0.239)	NS	
ER-negative	NS		NS	
PgR-negative	NS		NS	
HER2 3+	NS		NS	
Histological grade G3	NS		<0.0001	3.76 (0.349–0.989)
CR + PR	NS		0.0003	5.28 (0.405–1.309)
Localized type	NS		0.012	2.42 (0.104–0.796)

CR, complete response; PR, partial response; NS, not significant

Ki-67, have been reported to relate to the efficacy of PST [9–12]. In our study, we examined the characteristics of breast cancer tumors that made it easier to achieve pCR with NC. In univariate analysis, histological grade 3 and solid-tubular type tumors as well as lack of ER and PgR overexpression and the presence of HER-2 overexpression were shown to be significantly associated with improved treatment efficacy. However, multivariate analysis revealed that cases classified as scirrhous type were significantly less likely to achieve pCR. Interestingly, PST has been reported to be less effective for ILC [13–15]. In this study ILC had few effect of tumor size reduction of NC and there was no pCR case in ILCs (data not shown). However, ILC was rare in Japan formerly and there were few ILC patients in this study. One of the reasons for this low efficacy may be that tumor cells from ILCs are relatively isolated and are distributed among the fibrous stroma, leading to less blood flow to the tumor and less drug accessibility. Scirrhous-type tumors, which were associated with less NC efficacy, are histologically similar to ILCs growing as the stroma grows with relatively isolated tumor cells. Therefore, these histological features may be related to the efficacy of NC for these tumors.

It has been reported that NC is useful for breast conservation after a reduction of tumor size [16–18]. In the EORTC10902 study, NC enabled breast conservation in 57 of 246 (23%) patients who were scheduled to undergo total mastectomies [16]. In the present study, we characterized the tumor sizes, which tended to be reduced by NC, using pretreatment CT imaging as well as clinicopathological examinations. Magnetic resonance imaging (MRI) is more widely used to plan adequate surgical treatment for early breast cancer than CT probably because of the risk of radiation exposure. However, CT scan has an important advantage compared with MRI because CT breast images are obtained in the supine position used during surgery, thus providing precise information about the tumor extent; in contrast, in most previous studies of MRI, patients were examined in the prone position to minimize motion of the breast during breathing. There are helical CT scanners in many medium and small Japanese hospitals. Therefore, we can use CT without circumstance. As a result, a significant reduction of tumor size was observed in cases classified as localized tumors, as well as those categorized as histological grade 3 disease and those that achieved CR or PR in terms of clinical efficacy. There are previous reports about NC reducing the sizes of tumors and the safety of breast-conserving therapy, including one from our institution [18–20]. When the tumors show sporadic shrinkage, they need to be resected carefully after NC because the remaining tumor cells can be diffusely distributed. In contrast, when the shrinkage pattern is concentric, NC is thought to be more effective for reducing the tumor size, making breast-

conserving therapy safer. Therefore, localized tumors may achieve a favorable degree of reduction because they often shrink in a concentric manner. In evaluation of the tumor reduction rate, we classified the tumor shape, measured the pretreatment tumor size, and compared it with the postoperative pathological tumor size. The classification of tumors into localized or nonlocalized types using CT imaging provides a basis for making this determination. Localized tumors responded well to NC and were reduced into smaller, concentric tumors that could be safely treated by wide excision, giving a negative margin status. However, nonlocalized tumors diminished into a mosaic pattern of residual tumor cells, giving a positive margin status when treated with breast conserving therapy and tumor reduction rate were low. Multivariate analysis demonstrated that classification by CT was a powerful predictor of the tumor reduction rate by NC in this study. To the best of our knowledge, this is the first report to show that the tumor shape is useful as a predictive criterion for the efficacy of NC.

Breast cancer therapy with anticancer drugs is thought to result in equivalent survival rates when performed before or after surgery [8, 16]. Currently, both anthracyclines and taxanes are sufficiently used to increase the percentage of patients achieving pCR; however, there are no definitive criteria that detail the proper indications of various anticancer drugs for different types of tumors. Therefore, unnecessary drugs may be administered to patients in excessive doses. The postoperative adjuvant therapy for primary breast cancer is provided in accordance with the recommendations from the St. Gallen consensus meeting [21]. Although adjuvant chemotherapy is considered to be standard for node-positive patients, many aspects concerning the administration of anticancer drugs to node-negative patients have not been clarified. In particular, whether the anthracyclines and taxanes used for NC are necessary for these node-negative patients is not clear, and thus, these drugs may be used excessively for these patients. We believe that it is critical to predict the efficacy of drugs used for different purposes to determine which drugs and doses should be for each patient. In the NSABPB-27 study, the addition of a taxane to an anthracycline did not result in a significantly improved survival rate, which suggested that more specific criteria are needed to identify the cases in which taxanes produce an additive effect [1]. In recently published studies, the sensitivity of a certain drug was evaluated and then therapy was continued only for patients who experienced efficacy by adding the drug, whereas surgeries were performed for those who did not benefit from the medication. In fact, there are patients who do not benefit from widely used anticancer drugs, including anthracyclines and taxanes [21, 22]. Performing NC aggressively in these patients is disadvantageous. Thus,

it is important to identify tumors resistant to NC before the treatment and to exclude such cases from NC.

We have examined the predictability of NC efficacy, which has no current definitive indication. Regarding the prediction of efficacy to achieve pCR, high degrees of responsiveness is reportedly obtained with the concomitant use of trastuzumab in patients who have HER-2 overexpression [2]. At our institution, trastuzumab has been administered to these patients in recent years, leading to a markedly high pCR rate, which surpassed that achieved using NC with anthracyclines and taxanes. These patients, however, were not included in this study because we only recently started routinely using trastuzumab and many patients who showed HER-2 expression did not receive this agent early in the study. The examination of both pCR and tumor size reduction in the present study identified several factors that are useful to determine the indications of NC. This study indicated that pCR of scirrhous type for NC was difficult and the primary tumor with localized tumor type in CT imaging or histological grade 3 will be fairly reduced by NC. However, these features could not predict the response completely and terminate the NC premature in nonresponders. Additional cases and prospective studies that are focused on particular types of cases are necessary.

References

1. Bear HD, Anderson S, Smith RE et al (2006) Sequential preoperatrive or postoperative docetaxel added to preoperative doxorubicin plus cyclophosphamide for operable breast cancer: National Surgical Adjuvant Breast and Bowel Project Protocol B-27. J Clin Oncol 24:1–9

2. Buzdar AU, Ibrahim NK, Francis D, Booser DJ, Thomas ES, Theriault RL, Pusztai L, Green MC, Arun BK, Giordano SH, Cristofanilli M, Frye DK, Smith TL, Hunt KK, Singletary SE, Sahin AA, Ewer MS, Buchholz TA, Berry D, Hortobagyi GN (2005) Significantly higher pathologic complete remission rate after neoadjuvant therapy with trastuzumab, paclitaxel, and epirubicin chemotherapy: results of a randomized trial in human epidermal growth factor receptor 2-positive operable breast cancer. J Clin Oncol 23:3676–3685

3. Hayes DF, Thor AD, Dressler LG, Weaver D, Edgerton S, Cowan D, Broadwater G, Goldstein LJ, Martino S, Ingle JN, Henderson IC, Norton L, Winer EP, Hudis CA, Ellis MJ, Berry DA (2007) HER2 and response to paclitaxel in node-positive breast cancer. N Engl J Med 357:1496–1506

4. Japanese Breast Cancer Society (2005) General rules for clinical and pathological recording of breast cancer. Breast Cancer 12:S12–S14

5. (1981) Histological Typing of Breast Tumours. International Histological Classification of Tumours. No. 2. World Health Organization, Geneva, pp 18–22

6. Tsuda H, Sakamaki C, Tsugane S, Fukutomi T, Hirohashi S (1998) Prognostic significance of accumulation of gene and chromosome alterations and histological grade in node-negative breast carcinoma. Jpn J Clin Oncol 28:5–11

7. Fisher B, Bryant J, Wolmark N (1998) Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. J Clin Oncol 16:2672–2685

8. Wolmark N, Wang J, Mamounas E, Bryant J, Fisher B (2001) Preoperative chemotherapy in patients with operable breast cancer: nine-year results from National Surgical Adjuvant Breast and Bowel Project B-18. J Natl Cancer Inst Monographs 30:96–102

9. Pierga JY, Mouret E, Laurence V, Dieras V, Savigioni A, Beuzeboc P, Dorval T, Palangie T, Jouve M, Pouillart P (2003) Prognostic factors for survival after neoadjuvant chemotherapy in operable breast cancer: the role of clinical response. Eur J Cancer 39:1089–1096

10. Bollet MA, Sigal-Zafrani B, Gambotti L, Extra JM, Meynier M, Nos C, Dendale R, Campana F, Kirova YM, Dieras V, Fourquet A, for Institute Curie Breast Cancer Study Group (2006) Pathological response to preoperative concurrent chemo-radiotherapy for breast cancer: results of a phase II study. Eur J Cancer 42:2286–2295

11. Petit T, Wilt M, Velten M, Millon R, Rodier JF, Borel C, Mors R, Haegele P, Eber M, Ghnassia JP (2004) Comparative value of tumour grade, hormonal receptors, Ki-67, HER-2 and topoisomerase II alpha status as predictive markers in breast cancer patients treated with neoadjuvant Anthracycline-based chemotherapy. Eur J Cancer 40:205–211

12. Amat S, Abrial C, Penault-Llorca F, Delva R, Bougnoux P, Leduc B, Mouret-Reynier M-A, Mery-Mignard D, Bleuse J-P, Dauplat J, Cure H, Chollet P (2005) High prognostic significance of residual disease after neoadjuvant chemotherapy: a retrospective study in 710 patients with operable breast cancer. Breast Cancer Res Treat 94:255–263

13. Tubiana-Hulin M, Stevens D, Lasry S, Guinebretiere M, Bouita L, Cohen-Solal C, Cherel P, Rouesse J (2006) Response to neoadjuvant chemotherapy in lobular and ductal breast carcinomas: a retrospective study on 860 patients from one institution. Ann Oncol 17:1228–1233

14. Cocquyt VF, Blondeel PN, Depypere HT, Praet MM, Scelfhout VR, Silvia OE, Hurler J, Serreyn RF, Daems KK, Van Belle SJ (2003) Different response to preoperative chemotherapy for invasive lobular carcinoma and invasive ductal carcinoma. Eur J Surg Oncol 29:361–367

15. Matieu MC, Rouzier R, Llombart-Cussac A, Sideris L, Koscielny S, Travagli JP, Contesso G, Delaloge S, Spielmann M (2004) The poor responsiveness of infiltrating lobular breast carcinomas to neoadjuvant chemotherapy can be explained by their biological profile. Eur J Cancer 40:342–351

16. van der Hage JA, van der Velde CJ, Julien JP, Tubiana-Hulin M, Vanderveiden C, Duchateau L, Cooperating Investigators (2001) Preoperative chemotherapy in primary operable breast cancer: results from the European oeganization for research and treatment of cancer trial 10902. J Clin Oncol 19:4224–4237

17. Maklis A, Powles TJ, Ashley SE, Chang J, Hickish T, Tidy VA, Nash AG, Ford HT (1998) A reduction in the requirements for mastectomy in a randomized trial of neoadjuvant chemoendocrine therapy in primary breast cancer. Ann Oncol 9:1179–1184

18. Moneer M, El-Didi M, Khaled H (1999) Breast conservative surgery: is it appropriate for locally advanced breast cancer following downstaging by neoadjuvant chemotherapy? A pathological assessment. Breast 8:315–319

19. Akashi-Tanaka S, Fukutomi T, Sato N, Iwamoto E, Watanabe T, Katsumata N, Ando M, Miyakawa K, Hasegawa T (2004) The use of contrast-enhanced computed tomography before neoadjuvant chemotherapy to identify patients likely to be treated safely with breast-conserving surgery. Ann Surg 239:238–243

20. Puglisi F, Mansutti M, Aprile G, Minisini AM, Di Loreto C, Bazzocchi M, Londero V, Cedolini C, Gentile G, Pizzolitto S, Piga A, Sobrero A (2004) Tumor shrinkage evaluation during and

after preoperative doxorubicin and cyclophosphamide followed by docetaxel in patients with breast cancer. Anticancer Res 24:2487–2494

21. Goldhirsch A, Wood WC, Gelber RD et al (2007) Progress and promise: highlights of the international expert consensus on the primary therapy of early breast cancer 2007. Ann Oncol 18: 1133–1144

22. Shien T, Tashiro T, Omatsu M, Masuda T, Furuta K, Sato N, Akashi-Tanaka S, Uehara M, Iwamoto E, Kinoshita T, Fukutomi T, Tsuda H, Hasegawa T (2005) Frequent overexpression of epidermal growth factor receptor (EGFR) in mammary high grade ductal carcinomas with myoepithelial differentiation. J Clin Pathol 58:1299–1304