ANTICANCER RESEARCH *25*: 2519-2526 (2005)

Neoadjuvant Chemotherapy in Breast Cancer: Which Diagnostic Procedures Can be Used?

C.R. LOEHBERG[1], M.P. LUX[1], S. ACKERMANN[1], U.G. POEHLS[1], M.R. BANI[1], R. SCHULZ-WENDTLAND[2], T. PAPADOPOULOS[3], M. SCHMUCKER[4], M.W. BECKMANN[1] and P.A. FASCHING[1]

[1]Department of Obstetrics and Gynaecology and [2]Department of Gynaecological Radiology, University of Erlangen, Universitaetsstr. 21-23, 91054 Erlangen; [3]Institute of Pathology, University of Erlangen, Krankenhausstr. 8-10, 91054 Erlangen; [4]Institute of Psychology, University of Erlangen, Bismarckstr. 1, 91054 Erlangen, Germany

Abstract. *Background: To improve breast cancer treatment, the evaluation of predictive factors is in the focus of clinical research. Significant discrepancies between the clinical assessment of response to neoadjuvant chemotherapy (NACT) and the pathological assessment of response from post-therapy surgical specimens have been demonstrated. We focused on comparing the value of various diagnostic methods used in medical routine. Patients and Methods: A clinical evaluation of the primary tumour and regional lymph nodes before and after NACT was performed in 139 patients by physical examination, sonography and mammography. Results: Mammography and physical examination correlated best with pathological findings in the measurement of the tumour, whereas sonography was the most accurate predictor of the status for axillary lymph nodes. Conclusion: Mammography and physical examination are the best non-invasive predictors of the real size of the primary breast cancer, whereas sonography correlates better with the proven status of axillary lymph nodes.*

Many variables have been shown to correlate with the prognosis of patients with breast carcinoma, among the most useful being the presence and number of axillary lymph node metastases, tumour size and histological grade (Adjuvant Therapy for Breast Cancer. 2003 St. Gallen consensus statement), in particular after primary surgery. Much less is known about these factors after neoadjuvant chemotherapy (NACT) followed by surgery. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18 trial showed that NACT resulted in high rates of breast tumour response, axillary nodal downstaging and increased rates of breast preservation (1). A complete pathological response (pCR) conferred a survival advantage in patients with operable breast cancer after NACT (2, 3).

Of great interest are biological predictive factors of chemotherapy response. In the literature, histological or nuclear grade shows the strongest correlation with response (4, 5). Well-differentiated tumours seldom, if ever, achieve a pCR, whereas nearly all of the pCR occur in patients with poorly-differentiated tumours. In addition to high nuclear grade, high tumour proliferative rate assessed by immunohistochemical evaluation of proliferation-related proteins such as Ki67 has been reported to correlate with pCR (5, 6). Some reports have also found that patients with ER-negative tumours respond more often to NACT than patients with ER-positive tumours (4, 5, 7-10).

Besides the question of biological and pathological predictive factors, the optimal intensity and duration of NACT for breast cancer remain controversial due to the difficulty of evaluating response to therapy (11, 12).

Significant discrepancies between the clinical and the pathological assessment of response from post-therapy surgical specimens have been shown (13). Nearly 50% of the patients with a clinical complete response (CR) of the primary tumour were found to have macroscopic residual disease at surgery, whereas 20% of the patients with a clinical partial response (PR) had no macroscopic tumour at surgery (13-16). Because treatment decisions are often based on the assessment of the maximal response prior to the treatment, such difficulties complicate patients' management.

Accurate staging is of utmost importance to determine the extent of disease before and after NACT and thus

Correspondence to: P.A. Fasching, Department of Obstetrics and Gynaecology, University of Erlangen, Universitaetsstr. 21-23, 91054 Erlangen, Germany. Tel: +49-9131-8533508, Fax: +49-9131-8533839, e-mail: peter.fasching@gyn.med.uni-erlangen.de

Key Words: Neoadjuvant chemotherapy, breast cancer, mammography, sonography.

Table I. *Patient characteristics before neoadjuvant chemotherapy, diagnosed and treated in the period 1999-2003: (N=139).*

Median (range) age in years of patients: 51 (26-79)					
Median (range) tumour size according to:			Physical examination:	3.4 cm (0 – 8.0 cm)	
			Sonography:	3.1 cm (1 – 7.0 cm)	
			Mammography:	3.2 cm (1 – 8.0 cm)	
Histological parameters:					
		N (%)		N	(%)
HR-positive		83 (60)	Mib1 <20%	69	(49)
HR-negative		56 (40)	Mib1 ≥20%	70	(51)
Her2/neu-positive		35 (25)	Invasive ductal	95	(69)
Her2/neu-negative		104 (75)	Invasive lobular	30	(21)
			other histological types	14	(10)
SBR grade	I	8 (5)			
	II	94 (68)			
	III	37 (27)			

Table II. *Clinical disease stage before neoadjuvant chemotherapy (N=139).*

Tumour status (T):	Physical examination		Sonography		Mammography	
	No.	(%)	No.	(%)	No.	(%)
cT0	0	(0)	0	(0)	0	(0)
cT1	15	(11)	15	(11)	17	(12)
cT2	93	(67)	101	(73)	103	(74)
cT3	10	(7)	8	(5)	5	(4)
cT4	21	(15)	15	(11)	14	(10)
Regional lymph node (N):	Physical examination		Sonography			
	No.	(%)	No.	(%)		
cN0	57	(41)	66	(48)		
cN+	82	(59)	73	(52)		

ascertain changes in tumour dimensions. Pathological staging of surgical specimens and lymph node dissection provides the most accurate information about currently accepted prognostic indicators. Two of these indicators, tumour size and axillary lymph node status, are used as a guide to select optimal adjuvant treatments in breast cancer patients following NACT and local therapy (17, 18). Clinical assessment of the primary breast tumour and regional lymph node status has been achieved by physical examination, sonography and mammography. Some reports have suggested that physical examination and mammography are complementary in the assessment of primary tumour response (13, 14, 19, 20), whereas other reports have concluded that sonography correlates best with pathological findings (21, 22). Fewer data are available on the clinical assessment of lymph node metastases (14, 23). Therefore, the preoperative evaluation of their response to NACT remains imprecise. This limits information about the differential impact of NACT on tumour and nodal status.

We focused on comparing the value of standard diagnostic methods, with regard to decision-making monitoring of therapy. The aims of our study were, first, to correlate physical examination, sonography and mammography measurements of tumours and regional lymph nodes after NACT with pathological findings. Secondly, we evaluated the effect of NACT on the clinical TNM stage and the difference in response of the primary tumours and lymph node metastases by comparing baseline and post-chemotherapy measurements for each of the three clinical assessment modalities.

Patients and Methods

Study design. From January 1999 to December 2003, 1578 patients with primary breast cancer were treated in the Department of Ob/Gyn of the University Hospital of Erlangen, Germany. According to the local protocol, 198 patients received NACT after histological confirmation by punch biopsy. One hundred and thirty-nine could be evaluated with complete measurements in a prospective analysis. The patients received NACT according to different protocols, *e.g.* Epirubicin (90 mg/m^2) and Cyclophosphamide (600 mg/m^2), q21d, 4 cycles or Epirubicin (90 mg/m^2) and Paclitaxel (175 mg/m^2), q21d, 4 cycles.

Methods. A clinical evaluation of the primary tumour and regional lymph nodes before and after NACT was performed by physical examination, sonography and mammography. All non-invasive tests considered for this analysis were performed at the Department of Ob/Gyn and the Department of Gynaecological Radiology of the University Hospital of Erlangen, Germany.

All images were obtained on dedicated mammography units, Siemens Mammomat 3000 N, resolution 14 lp/mm, screen-film combination AD Mammo Fine with ADM (Fuji), daylight printer FPM 2100 (Fuji). Areas of microcalcifications on mammograms were considered non-measurable tumour (14). The sonographic examinations were performed on a unit with high resolution transducers (Siemens Elegra Sonoline, 7.5 - 13 MHz). For tumour response assessment, sonographic measurement was performed on the hypoechoic core of the tumour (15). The patients underwent breast surgery and axillary dissection, according to the standard protocol, after completion of NACT. All surgical procedures were performed at the Department of Ob/Gyn of the University Hospital of Erlangen, Germany.

The histological type of the surgical specimen was defined according to the World Health Organization (WHO) classification. In immunohistochemistry (IHC), a tumour was considered steroid hormone receptor-positive (HR) with a staining >10% ER- and/or PR-positive cells. Her2/neu status was considered positive with a 3-fold positive result in IHC and with a 2-fold positive result in IHC, if confirmed in FISH analysis. Histological grading was

Table III. *Differences in response rate according to histological parameters and age (N=139).*

		Regression		No change		Progression		χ^2 and p values[a]
		No.	(%)	No.	(%)	No.	(%)	
All patients		86	(61)	47	(34)	6	(5)	
HR-positive		41	(53)	31	(40)	5	(7)	$\chi^2(2)=9.237$, $p=0.010$
HR-negative		42	(74)	13	(23)	2	(3)	
Mib1 <20%		32	(47)	35	(50)	2	(3)	$\chi^2(2)=12.006$, $p=0.002$
Mib1 ≥20%		51	(73)	15	(21)	4	(6)	
Her2/neu-positive		20	(55)	16	(45)	0	(0)	$\chi^2(2)=3.259$, $p=0.196$
Her2/neu-negative		63	(61)	33	(32)	7	(7)	
SBR grade	I	4	(45)	4	(45)	1	(10)	
	II	53	(57)	34	(37)	6	(6)	
	III	27	(73)	10	(27)	0	(0)	
	I, II, III:	$\chi^2(4)=5.839$, $p=0.211$		I, II:	$\chi^2(2)=1.122$, $p=0.571$			
	II,III:	$\chi^2(2)=3.945$, $p=0.139$		I, III:	$\chi^2(2)=6.434$, $p=0.040$			
Invasive ductal		58	(61)	33	(35)	4	(4)	$\chi^2(2)=0.338$, $p=0.825$
Invasive lobular		17	(57)	11	(36)	2	(7)	
Age ≤50 years		39	(59)	23	(35)	4	(6)	$\chi^2(2)=1.181$, $p=0.554$
Age >50 years		47	(64)	24	(33)	2	(3)	

[a]Pearson's Chi-square test

defined according to the modified Scarff, Bloom and Richardson (SBR) system (24). IHC, using the anti-Ki67 antibody Mib-1, was performed as an alternative to mitotic counts on the surgical specimens. Ki67 staining equal to or more than 20% was considered as high (5, 24-26). Information on the disease stage and other pre-treatment patient characteristics are summarized in Tables I and II.

The longest perpendicular dimension of the primary tumour was recorded in centimeters. The primary breast tumour measurements were obtained by physical examination, sonography and mammography performed before the first and after the last cycle of NACT. The largest dimension documented was considered for the analysis. During the therapy period, a reduction in tumour size of ≥25% was considered a clinical regression. Stable disease was defined as no measurable change in the longest perpendicular dimension, while progression was defined as an increase in tumour size of ≥25%. If more than one tumour was present in the same breast, only the size of the largest tumour mass was considered for the review.

The lymph node metastasis measurements were obtained by physical examination (positive = enlarged or well palpable) and sonography performed before the first and after the last cycle of NACT. Here, the lymph node status was documented as negative or positive according to the TNM system.

Sonography and mammography were obtained from the review of sonograms and mammograms by two persons, double review being the standard procedure for evaluation, and consensus measurement was documented. Pathological measurements were obtained from the surgical pathology report. Measurements were obtained at the time of the initial interpretation by the breast pathologist. If more than one tumour was present in the same breast, only the largest evaluation of the tumour was considered.

Table IV. *Correlation with pathology (tumour size in cm): clinical measurement obtained after neoadjuvant compared with pathological measurements.*

	Correlation with pathology[a]	
Mammography	r=0.628	$p<0.001$
Sonography	r=0.541	$p<0.001$
Physical examination	r=0.597	$p<0.001$

[a]Pearson's correlation (r)

Statistical analysis. Pearson Chi-square statistics, rank correlations (Kendall-Tau, τ) and Phi coefficient (Φ) were used to study associations between clinical and pathological assessments for the TNM stages and Pearson correlation for tumour sizes in cm. To evaluate the contribution of the different non-invasive measurement methods, a hierachical linear regression analysis was performed.

Results

Response was assessed by physical examination, imaging assessment and pathological assessment at the time of

Table V. *Pearson's correlation of the three evaluated non-invasive measurement methods.*

	Physical examination	Sonography	Mammography
Physical examination	1	0.774*	0.747*
Sonography	0.774*	1	0.888*
Mammography	0.747*	0.888*	1

*$p<0.001$

Table VI. *Summary of the effects of adding variables to the hierachical regression model.*

	change of R^2	p value
Step 1: Physical examination:	0.356	$p<0.001$
Step 2: adding Mammography only:	0.075	$p<0.001$
Sonography only:	0.016	$p=0.115$
Mammography+Sonography:	0.088	$p<0.001$

surgery. Regression could be detected in 61% of all evaluated patients and 62% of the registered patients received breast conserving therapy (Table III). A pathological complete remission was achieved in 13% of all patients.

A significantly better response rate was detected for HR-negative tumours ($p=0.010$), tumours with a higher proliferation rate (Mib1 ≥20%, $p=0.002$) and for poorly-differentiated tumours (SBR grade III, $p=0.040$) (Table III). No significant change in response rate could be shown either for age or for other histological parameters like Her2/neu status or histological type.

Measurements done after NACT by each of the three non-invasive methods were correlated separately with the pathological measurements. Mammography showed the best correlation with pathological size for the primary tumour ($r=0.628$, $p<0.001$); physical examination ($r=0.597$, $p<0.001$) was superior to sonography ($r=0.541$, $p<0.001$) (Table IV).

Furthermore, we examined the correlation of all three non-invasive measurement methods (Table V). Since all three measurement methods show a correlation with pathology in a similar order, this data is in harmony with the data given above, demonstrating a high correlation between the methods. The high correlations also pose the question of the unique diagnostic contribution of the individual measurement methods to determine tumour size. This question was addressed using a hierachical linear regression model. Routine clinical practice dictates that physical examination is performed first and this order was retained in the model (Table VI). This variable by itself accounts for 35.6% of the observed variance in tumour size. Adding mammography to the model in a second step significantly improves the prediction, explaining a further 7.5% of variance. In contrast, adding sonography to the model has only a small and non-significant impact on the predictive accuracy of the regression model. Consequently, the improved predictive power of the complete model (*i.e.*, adding both mammography and sonography) is mainly due to the unique contribution of mammography.

When tumour size is categorized in the TNM system, the above detected differences in measuring the tumour size are confirmed. Concerning the tumour status, mammography shows the best correlation to the pathological tumour status (Table VII). Fifty-two % of the 139 patients evaluated by mammography had no change in tumour status (TNM classification) after NACT, whereas 47% had a decrease of one or more stages. Twelve % had a two-stage or more decrease in tumour status; 1% had a one-stage increase (Table VIII). For the lymph node status, sonography (Phi-coefficient: 0.412, $p<0.001$) showed the best correlation to the pathological status. It was superior to physical examination (Phi-coefficient: 0.214, $p=0.022$) (Table VII). Eighty-three % of the 139 patients evaluated by sonography and 71% evaluated by physical examination had no change in lymph node status after NACT, whereas 17% and 28%, respectively, had a decrease of one stage (Table VIII).

The effects of NACT on the primary breast tumour and regional lymph node compartments could be evaluated in 73 patients, who had clinically evident primary breast tumours and enlarged lymph nodes on sonography at the time of diagnosis of breast cancer. Twenty-five % of these patients had concordant clinical downstaging of both the primary tumour and regional lymph node metastases. Thirty-five % had no appreciable decrease in either compartment; in 30%, the tumour decreased while the nodal metastases did not; in another 10%, the opposite occurred.

Discussion

Of great interest are biological predictive factors of chemotherapy response. In the literature, high nuclear grade, high tumour proliferative rate and ER-negative tumours show the strongest correlation with good response (4-10, 25). In our study, we showed similar results to the published data, demonstrating a significantly higher response rate in ER-negative tumours and tumours with a high proliferation rate and for poorly-differentiated tumours.

Based on this, the assessment of the primary tumour, physical examination measurements and mammography showed the highest correlation and the highest predictive value for the pathological findings in our study. We, therefore,

Table VII. *Tumour stage (T) and regional lymph node status (N) after neoadjuvant chemotherapy as assessed clinically and pathologically (N=139).*

Tumour stage (T):	Physical examination		Sonography		Mammography			Pathology	
	N	(%)	N	(%)	N	(%)		N	(%)
cT0	8	(5)	8	(5)	9	(6)	ypT0	18	(13)
cT1	70	(51)	66	(48)	59	(43)	ypT1	57	(41)
cT2	48	(36)	57	(42)	65	(47)	ypT2	45	(33)
cT3	4	(2)	5	(3)	3	(2)	ypT3	10	(7)
cT4	9	(6)	3	(2)	3	(2)	ypT4	9	(6)
	$\tau=0.420$[a] $p<0.001$		$\tau=0.367$[a] $p<0.001$		$\tau=0.443$[a] $p<0.001$				

Regional lymph node status (N):	Physical examination		Sonography			Pathology	
	N	(%)	N	(%)		N	(%)
cN0	103	(74)	93	(67)	ypN0	69	(49)
cN+	36	(26)	46	(33)	ypN+	70	(51)
	$\Phi=0.214$[b] $\chi^2(1)= 5.247$[c], $p=0.022$[c]		$\Phi=0.412$[b] $\chi^2(1)= 20.193$[c], $p<0.001$[c]				

[a]Kendall-Tau-b (τ) rank correlation
[b]Phi-coefficient (Φ)
[c]Pearson's Chi-square test

conclude that physical examination by experienced examiners and mammography interpreted by experienced radiologists remain the best non-invasive methods of assessing the size of the primary tumour in women with breast cancer. This result is interesting, given the fact that physical examination appeared superior to sonography and the latter did not add significantly to the predictive accuracy in determining tumour size. The result is, in part, compatible with the published data. The superiority of physical examination compared to mammography and sonography has been observed before (14). However, other investigators have published differing conclusions, such as the highest correlation for sonography (21, 22). Physical examination and mammography are both useful in the serial evaluation of breast cancers (19). Furthermore, it could be shown that the detectability of changes was not related to the type of treatment. Therefore, in this study we evaluated our patients independently of the chemotherapy regimen used (19). Even though we could determine a slightly better correlation for mammography and physical examination with the pathological tumour size, like other groups (35), the correlation between the three measurement methods was very high. Furthermore, none of the three measurement methods used in hospital routine could demonstrate a pCR in a reliable manner.

Determination of morphological tumour characteristics with regards to imaging methods was not in the focus of this investigation. However, phenomena like microcalcification,

Table VIII. *Changes in clinical TNM stages (downstaging) after neoadjuvant chemotherapy (N=139).*

Tumour status (T):	Physical examination		Sonography		Mammography	
	N	(%)	N	(%)	N	(%)
Decrease of one or more stages:	76	(55)	74	(54)	66	(47)
Decrease of one stage:	63	(45)	59	(43)	49	(35)
Decrease of two or more stages:	13	(10)	15	(11)	17	(12)
No change:	62	(44)	61	(44)	72	(52)
Increase of one stage:	1	(1)	4	(3)	1	(1)

Lymph node status (N):	Physical examination		Sonography	
	N	(%)	N	(%)
Decrease of one stage:	39	(28)	24	(17)
No change:	98	(71)	115	(83)
Increase of one stage:	2	(1)	0	(0)

architectural distortion, desmoplastic reaction and mixed density influence the diagnostic value of the examined imaging methods. In the published data, the extent of their influence is judged differently. The accuracy of physical examination could be reduced by fibrotic and necrotic masses mimicking a residual tumour mass. In other cases, the apparent clinical regression is due to resolution of post-biopsy phenomena such as hemorrhage and edema (15, 19, 27, 28). Furthermore, the influence of ductal carinoma *in situ* (DCIS) and further histological parameters remains unclear (15, 19, 27, 28).

All methods are restricted in the imaging of tumour residuals after neoadjuvant chemotherapy, because imaging of small microscopic foci of invasive or even non-invasive tumour residuals is hardly possible. Of special concern are tumour-specific microcalcifications, which can only be shown on mammograms. They do not regress under chemotherapy, even if the invasive tumour regresses, and they typically hint at non-invasive tumour residuals. For planning surgery, the pre-therapeutic tumour extent always has to be taken into account, because of the restricted ability to image small tumour residuals (15, 19, 27, 28).

More recent publications evaluate the relative value of magnetic resonance (MR) or scinti-mammography. MR mammography shows certain advantages like excellent reproducibility or independence of the structure and density of the breast (15, 28, 29). The aim of other studies was to assess the value of scintimammography in the evaluation of tumour response to NACT (30, 31). The question of whether MR or scinti-mammography gives better results in predicting response will be evaluated in future prospective trials.

In breast cancer patients, the number of surgically resected axillary lymph nodes has been considered to correlate closely with patient prognosis. Therefore, if metastatic lymph nodes could be treated by NACT pre-operatively, we would be able to select a more appropriate individual regimen of post-operative chemotherapy and expect prognostic advantages for patients with node-positive breast cancer. For the assessment of lymph node metastases, sonographic measurements showed the highest correlation with and the highest predictive value for pathological findings. Thus, we conclude that sonography is the best single non-invasive method of assessing the extent of nodal involvement based on nodal status.

In the published data, NACT induces axillary lymph node remission in approximately one-third of patients, which is confirmed by our data (32, 18). A negative axillary status after chemotherapy is reported not only to predict higher survival rates in these patients, but also makes them potentially suitable for non-surgical management of the axilla, particularly with sentinel lymph node (SLN) biopsy emerging as a reliable tool for determining axillary lymph node status (13, 18). Information regarding the post-chemotherapy axillary lymph node status, therefore, is vital and would facilitate a decision regarding axillary lymph node dissection at the time of initial surgery. To further improve the imaging of pre-operative lymph node status, other trials demonstrated that CT scan, performed to evaluate the therapeutic effect on metastatic lymph nodes following NACT, was the best method to detect axillary involvement. It can help to determine an appropriate regimen of post-operative chemotherapy and be of prognostic advantage in patients with node-positive breast cancer (33).

In our study, in almost two-thirds of the patients primary breast tumours and nodal metastases appeared to be equally affected by NACT. However, although these results are in accordance with other clinical observations, they need to be interpreted cautiously (14). The non-invasive determination of response to NACT is important to guide the choice of subsequent therapy. If no substantial response to NACT is seen, a different, non-cross-resistant chemotherapy regimen might be used preoperatively to increase the possibility of breast-conserving surgery.

Pathological complete remission continues to be the best prognostic factor for metastases-free survival. However, neither imaging method evaluated in this study is sensitive enough to identify, with certainty, the absence of residual malignant cells.

Many clinical trials with NACT have been performed and different recommendations made regarding indications, regimen, diagnosis before treatment, monitoring of efficacy, tumour localization, surgery, pathological evaluation and postoperative treatment (34). Here, we showed that physical examination, mammography and sonography are all three useful in the serial evaluation of breast cancer to determine the optimal approaches to preoperative and operative treatment, whereas findings on pathology are the major determinants to select postoperative systemic therapy and prognosis. Mammography showed the best correlation with pathological findings in tumour measurement, whereas sonography showed the best correlation in lymph node status. If other imaging methods like the MRI or CT scan are to become established in the clinical routine, further trials will have to show their value in comparison to these data.

References

1 Fisher B, Bryant J, Wolmark N *et al*: Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. J Clin Oncol *16*: 2672-2685, 1998.

2 Chollet P, Amat S, Cure H *et al*: Prognostic significance of a complete pathological response after induction chemotherapy in operable breast cancer. Br J Cancer *86*: 1041-1046, 2002.

3 Cure H, Amat S, Peault-Llorca F *et al*: Prognostic value of residual node involvement in operable breast cancer after chemotherapy. Breast Cancer Res Treat *76*: 37-45, 2002.

4 Fisher ER, Wang J, Bryant J *et al*: Pathobiology of preoperative chemotherapy: findings from the National Surgical Adjuvant Breast and Bowel (NSABP) protocol B-18. Cancer *95*: 681-695, 2002.

5 Petit T, Wilt M, Velten M *et al*: 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(2)*: 205-211, 2004.
6 Aas T, Geisler S, Eide GE *et al*: Predictive value of tumour cell proliferation in locally advanced breast cancer treated with neoadjuvant chemotherapy. Eur J Cancer *39(4)*: 438-446, 2003.
7 Kuerer HM, Newman LA, Smith TL *et al*: Clinical course of breast cancer patients with complete pathologic primary tumour and axillary lymph node response to doxorubicin-based neoadjuvant chemotherapy. J Clin Oncol *17*: 460-469, 1999.
8 Colleoni M, Gelber S, Coates AS *et al*: Influence of endocrine-related factors on response to perioperative chemotherapy for patients with node-negative breast cancer. J Clin Oncol *19*: 4141-4149, 2001.
9 Colleoni M, Minchella I, Mazzarol G *et al*: Response to primary chemotherapy in breast cancer patients with tumours not expressing estrogen and progesterone receptors. Ann Oncol *11*: 1057-1059, 2000.
10 Mamounas EP: NSABP Protocol B-27. Preoperative doxorubicin plus cyclophosphamide followed by preoperative or postoperative docetaxel. Oncology *11*: 37-40, 1997.
11 Hortobagyi GN: Comprehensive management of locally advanced breast cancer. Cancer *66*: 1387-1391, 1990.
12 Bonadonna G, Valagussa P, Zucali R and Salvadori B: Primary chemotherapy in surgically resectable breast cancer. CA Cancer J Clin *45*: 227-243, 1995.
13 Buchholz TA, Hunt KK, Whitman GJ, Sahin AA and Hortobagyi GN: Neoadjuvant chemotherapy for breast carcinoma: multidisciplinary considerations of benefits and risks. Cancer *98(6)*: 1150-1160, 2003.
14 Herrada J, Iyer RB, Atkinson EN, Sneige N, Buzdar AU and Hortobagyi GN: Relative value of physical examination, mammography, and breast sonography in evaluating the size of the primary tumour and regional lymph node metastases in women receiving neoadjuvant chemotherapy for locally advanced breast carcinoma. Clin Cancer Res *3(9)*: 1565-1569, 1997.
15 Junkermann H and von Fournier D: Imaging methods for evaluating the response of breast carcinoma to preoperative chemotherapy. Radiologe *37(9)*: 726-732, 1997.
16 Moscovic EC, Mansi JL, King DM, Murch CR and Smith E: Mammography in the assessment of response to medical treatment of large primary breast tumour. Clin Radiol *47*: 339-344, 1993.
17 Newman LA, Pernick NL, Adsay V *et al*: Histopathologic evidence of tumour regression in the axillary lymph nodes of patients treated with preoperative chemotherapy correlates with breast cancer outcome. Ann Surg Oncol *10(7)*: 734-739, 2003.
18 Kuerer HM, Sahin AA, Hunt KK *et al*: Incidence and impact of documented eradication of breast cancer axillary lymph node metastases before surgery in patients treated with neoadjuvant chemotherapy. Ann Surg *230*: 72-78, 1999.
19 Dershaw DD, Drossman S, Libermann L and Abramson A: Assessment of response to therapy of primary breast cancer by mammography and physical examination. Cancer *75*: 2093-2098, 1995.
20 Vinnicombe SJ, MacVicar AD, Guy RL *et al*: Primary breast cancer: mammographic changes after neoadjuvant chemotherapy, with pathologic correlation. Radiology *198(2)*: 333-340, 1996.
21 Serrano-Migallon JA, Sandoval-Guerrero FJ, Miranda-Hernandez H *et al*: Estudio comparativo entre clinica, mastografia y ultrasonido, para determinar el tamano de las lesions mamarias. Rev Inst Nal Cancerol *39*: 1931-1936, 1993.
22 Fornage BD, Toubas O and Morel M: Clinical, mammographic, and sonographic determination of preoperative breast cancer size. Cancer *60*: 765-771, 1987.
23 Lluch A, Cervantes A, Pardo JD *et al*: Assessment of primary tumour and axillary involvement in breast cancer after neoadjuavnt chemotherapy. A comparison of clinical examination, mammography, ultrasonography and CT-scan. Proc Am Soc Clin Oncol *14*: 135, 1995.
24 Elston CW and Ellis IO: Pathological prognostic factors in breast cancer. I. The value of histological grade in breast cancer: experience from a large study with long-term follow-up. Histopathology *19*: 403-410, 1991.
25 Trihia H, Murray S, Price K, Gusterson BA *et al*: Ki-67 expression in breast carcinoma. Cancer *97*: 1321-1331, 2003.
26 Gerdes J, Lemke H, Baisch H, Wacker HH, Schwab U and Stein H: Cell cycle analysis of a cell proliferation-associated human nuclear antigen defined by the monoclonal antibody Ki-67. J Immunol *133(4)*: 1710-1715, 1984.
27 Huber S, Wagner M, Zuna I, Medl M, Czembirek H and Delorme S: Locally advanced breast carcinoma: evaluation of mammography in the prediction of residual disease after induction chemotherapy. Anticancer Res *20*: 553-558, 2000.
28 Balu-Maestro C, Chepellier C, Bleuse A *et al*: Imaging in evaluation of response to neoadjuvant breast cancer treatment benefits MRI. Breast Cancer Res Treat *72(2)*: 145-152, 2002.
29 Kneeshaw PJ, Turnbull LW and Drew PJ: Current applications and future direction of MR mammography. Br J Cancer *88(1)*: 4-10, 2003.
30 Wilczek B, von Schoultz E, Bergh J, Eriksson E, Larsson SA and Jacobsson H: Early assessment of neoadjuavnt chemotherapy by FEC-courses of locally advanced breast cancer using 99m-Tc-MIBI. Acta Radiol *44(3)*: 284-287, 2003.
31 Cayre A, Cachin F, Maublant J *et al*: Single static view 99mTc-sestamibi scintimammography predicts response to neoadjuvant chemotherapy and is related to MDR expression. Int J Oncol *20(5)*: 1049-1055, 2002.
32 Fisher B, Brown A, Mamounas E *et al*: Effect of preoperative chemotherapy on local-regional disease in women with operable breast cancer: findings from National Surgical Adjuvant Breast and Bowel Project B-18. J Clin Oncol *15*: 2483-2493, 1997.
33 Akashi-Tanaka S, Fukutomi T, Sato N and Miyakawa K: The role of computed tomography in the selection of breast cancer treatment. Breast Cancer *10(3)*: 198-203, 2003.
34 Kaufmann M, von Minckwitz G, Smith R *et al*: International Expert Panel on the Use of Primary (Preoperative) Systemic Treatment of Operable Breast Cancer: Review and Recommendations. J Clin Oncol *21(13)*: 2600-2608, 2003.
35 Golshan M, Fung BB, Wiley E *et al*: Prediciton of breast cancer size by ultrasound, mammography and core biopsy. The Breast *13*: 265-271, 2004.

Received November 4, 2004
Accepted April 4, 2005