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SURGERY TODAY


*Original Articles*

# Clinical and Pathological Features of Intracystic Papillary Carcinoma of the Breast

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**Abstract**

***Purpose.*** To evaluate the clinicopathological features of intracystic papillary carcinoma (ICPC), which have not been established given its rarity and lack of standard diagnostic criteria.

***Methods.*** We reviewed the clinicopathological findings and treatment outcomes of 14 patients with ICPC diagnosed between 2002 and 2006.

***Results.*** Intracystic papillary carcinoma was diagnosed by fine-needle aspiration biopsy in three patients and by core-needle biopsy in six patients. A preoperative diagnosis was not made in five patients. Three patients underwent magnetic resonance imaging preoperatively, which helped to differentiate benign tumors and maintain free surgical margins. The final pathological diagnosis was invasive carcinoma in 2 (14.2%) of the 14 patients. The patients were followed up for 1–72 months, during which time only one died, of a cancer-unrelated cause.

***Conclusion.*** Our results show that ICPC is more difficult to diagnose than common breast cancer preoperatively. Excisional biopsy was necessary when fine-needle aspiration and core-needle biopsy could not provide a diagnosis. Magnetic resonance imaging is helpful to differentiate a benign tumor from invasive disease.

**Key words** Intracystic papillary carcinoma · Magnetic resonance imaging

## Introduction

Intracystic papillary carcinoma (ICPC) of the breast is a rare malignant tumor, accounting for fewer than 2% of breast cancers.[1] According to the Japanese Society for Breast Cancer, ICPC includes ductal carcinoma in situ (DCIS). Several reports have described invasive ICPC with synchronous liver metastases.[2–6] Intracystic papillary carcinoma is more difficult to diagnose than common breast cancer. Because of the lack of standard criteria for diagnosis and treatment, the clinicopathological features and treatments of this type of breast cancer have not been defined. We reviewed the clinical and pathological features of 14 patients who underwent surgery for ICPC between 2002 and 2006.

## Patients and Methods

Between 2000 and 2006, 2700 cases of primary breast cancer were diagnosed at the National Cancer Center Hospital, 14 of which were diagnosed as ICPC based on clinicopathological analysis. We reviewed the clinical features, pathological findings, and treatments of these 14 patients. Immunohistochemical evaluation was performed according to the DAKO criteria, with the ABC staining method. Immunohistochemical examinations for ER and PgR were defined as positive when there was positive nuclear reactivity. Positivity was scored as follows: 0, 0% positive cells; 1+, less than 10% positive cells; 2+, 10%–50% positive cells; and 3+, more than 50% positive cells. Immunohistochemical examinations for p53 were also defined as positive when there was positive nuclear reactivity. Positivity was scored as follows: 0, 0% of positive cells; +/–, less than 10%; 1+, 10 to 50%; and 2+, more than 50%. HER2 was defined as positive depending on the cytoplasmic membrane reactivity. The grading system for HER2 was also scored from 0 to 3+ by the immunohistological method reported by Bilous et al.[7]

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**Table 1.** Clinicopathological features of the 14 patients with intracystic papillary carcinoma

| No. | Age (years)/sex | Duration from detecting the tumor to operation (months) | Location | US cystic size (mm) | US solid size (mm) | US shape of solid component | MMG shape of mass | MMG calcification | MRI | FNA | CNB | Preoperative diagnosis |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 84/F | 2 | A | 22 | 5 | Irregular | Irregular | None | — | — | − | Not given |
| 2 | 83/F | 2 | D | 11 | 6 | Regular | Regular | None | — | Class 5 | − | DC |
| 3 | 75/F | 3 | A | 22 | 7 | Irregular | Irregular | A | — | Class 3 | + | Not given |
| 4 | 60/F | 4 | B | 36 | 10 | Regular | Regular | None | — | Class 2 | + | Not given |
| 5 | 43/F | 3 | A | 15 | 3 | Regular | Regular | None | — | — | + | Not given |
| 6 | 36/F | 9 | C | 34 | 17 | Irregular | No mass | None | — | — | + | ICPC |
| 7 | 57/F | 4 | E | 10 | 4 | Regular | Regular | None | — | Class 5 | − | DC |
| 8 | 70/M | 6 | E | 50 | 15 | Irregular | Irregular | None | — | — | + | ICPC |
| 9 | 75/F | 2 | A | 28 | 20 | Regular | Regular | A | — | Class 5 | − | DC |
| 10 | 48/F | 3 | A | 23 | 5 | Regular | Regular | P | — | Class 2 | + | Not given |
| 11 | 74/F | 8 | A | 14 | 14 | Regular | — | — | — | — | + | ICPC |
| 12 | 82/F | 24 | C | 200 | 30 | Regular | — | — | BCP | Class 2 | + | ICPC |
| 13 | 81/F | 2 | A | 170 | 52 | Irregular | Irregular | None | BCP | Class 2 | + | ICPC |
| 14 | 71/F | 2 | E | 60 | 21 | Irregular | Regular | None | BCP | — | + | ICPC |

US, ultrasonography; MMG, mammography; MRI, magnetic resonance imaging; FNA, fine-needle aspiration; CNB, core-needle biopsy; A, amorphous; P, pleomorphic; BCP, breast cancer type in MRI; DC, ductal carcinoma

## Results

The clinical data are summarized in Table 1. The patients consisted of one man and 13 women and their ages ranged from 36 to 82 years (median 72.5 years). The initial manifestation was a breast lump in all patients, 13 of whom noticed the breast lump, whereas it was detected by breast cancer screening in 1 patient. The time from tumor detection to treatment ranged from 2 to 24 months (median, 5.2 months). The size of the cystic component ranged from 1 to 20 cm (mean, 4 cm), and the size of the solid component ranged from 3 to 52 mm (median, 12 mm). The tumor was located in areas A, B, C, D, and E in seven, one, two, one, and three patients, respectively.

Ultrasonography showed a multicystic lesion in one patient, and a unicystic lesion in 13 patients. All patients had solid components with intracystic growth. The cystic component ranged from 11 to 220 mm (median, 22.5 mm), and the solid component ranged from 3 to 52 mm (median, 12 mm). The solid components were variable, regular, or irregular in shape.

Twelve patients underwent mammography, which showed a smooth mass in seven, an irregular mass in four, and no mass in one. Four patients had amorphous or pleomorphic calcifications. Magnetic resonance imaging (MRI) showed a breast cancer pattern in all three patients who underwent this examination. It also showed invasion of the cystic wall in one patient.

Fine-needle aspiration was done in 8 of the 14 patients and the tumor was designated as class 5 in 3 (37%) patients, class 3 in 1, and class 2 in 4. Core-needle biopsy was done of five of the tumors designated as class 3 or class 2. Five other patients underwent core-needle biopsy without fine-needle aspiration. A diagnosis of ICPC was made in six (60%) of these ten patients. A diagnosis was not able to be made by core-needle biopsy in four patients, who required excisional biopsy for a definite diagnosis. One patient did not undergo fine-needle aspiration or core-needle biopsy preoperatively.

The pathological features are summarized in Table 2. Thirteen patients underwent mastectomy or partial mastectomy; with axillary lymph node dissection in five, without axillary lymph node dissection in four, and with sentinel lymph node dissection in four. The intracystic fluid was either serous or bloody. Pathological findings revealed invasive ICPC in 2 (14.2%) patients and DCIS was detected around the ICPC in 3 (21.4%) patients. Axillary lymph node metastasis was found in one patient. Estrogen receptor, progesterone receptor, HER2, and p53 were positive in 14 (100%), 13 (92.8%), 3 (21.4%) and 2 (14.2%) patients, respectively.

Thirteen patients were treated with tamoxifen postoperatively, and three of the eight who underwent

**Table 2.** Pathological findings of intracystic papillary carcinoma (ICPC)

| No. | Proposed operation | Invasion of cystic wall | DCIS around ICPC | Lymph node metastasis | ER PgR HER2 | p53 | Histologic grade | Nuclear grade |
|---|---|---|---|---|---|---|---|---|
| 1 | Bp | – | – | No dissection | ER2 PgR2 HER2 1 | – | 1 | 1 |
| 2 | Bp | – | – | No dissection | ER2 PgR0 HER2 0 | – | 1 | 1 |
| 3 | Bt+sampling | – | – | 0/2 | ER2 PgR2 HER2 0 | + | 2 | 2 |
| 4 | Bq | – | – | No dissection | ER2 PgR1 HER2 0 | – | 2 | 2 |
| 5 | Bp+Ax | – | – | 0/11 | ER2 PgR2 HER2 0 | – | 2 | 2 |
| 6 | Bp+Ax | – | + | 0/22 | ER2 PgR2 HER2 0 | – | 1 | 1 |
| 7 | Bt+Ax | – | – | 0/20 | ER2 PgR2 HER2 1 | – | 2 | 2 |
| 8 | Bp | – | – | No dissection | ER2 PgR2 HER2 2 | 2+ | 2 | 2 |
| 9 | Bt+Ax | – | – | 0/18 | ER1 PgR1 HER2 0 | – | 2 | 3 |
| 10 | Bq+SLN | – | – | 0/4 | ER1 PgR2 HER2 0 | – | 1 | 1 |
| 11 | Bp | + | – | No dissection | ER2 PgR2 HER2 0 | – | 1 | 1 |
| 12 | Bt+SLN | – | – | 1/5 | ER3 PgR3 HER2 0 | – | 1 | 1 |
| 13 | Bt+SLN | – | + | 0/5 | ER3 PgR3 HER2 0 | – | 1 | 1 |
| 14 | Bt+SLN | + | + | 0/3 | ER3 PgR2 HER2 0 | – | 1 | 1 |

DCIS, ductal carcinoma in situ

partial mastectomy were also treated with radiation therapy. All 14 patients were followed up for 1–72 months. At the time of writing, 13 patients were alive without evidence of recurrence and one had died of a cause unrelated to cancer.

## Discussion

Intracystic papillary carcinoma is a rare type of breast cancer characterized by papillary growth within a macroscopic cyst. It accounts for fewer than 2% of all breast cancers.[1] Generally, ICPC shows no invasive growth outside of the cyst and is treated similarly to DCIS. However, there are reports of invasive ICPC with synchronous liver metastases.[2–6] Yet, because of its rarity and the lack of diagnostic criteria, the clinicopathological features and treatments of ICPC have not been established.

The average age of onset is higher than that for the more common types of breast cancer, at about 65 years old (range, 34–92 years).[8–10] The average age of onset in this series was 36–82 years old (median, 72.5). Some studies have reported a longer period from tumor detection to treatment for ICPC than for common breast cancer.[8,9] In our study, it ranged from 1 to 24 months (median, 5 months), which suggests that ICPC grows more slowly than common breast cancer, and that it has a lower pathological grade and a tendency not to form ulcerations.

Intracystic papillomas are difficult to diagnose. Previous studies reported that the average age of onset was 40.7–47 years, and that 81% of intracystic papillomas in patients older than 60 years old were carcinoma.[8–10] Intracystic papillary carcinoma tumors tend to be larger than intracystic papillomas, but this does not necessarily help differentiate malignancy from benign growth.[11]

Ultrasonography was thought to be a useful modality to differentiate malignant from benign tumors, but as seen in this series, the shapes of the solid components can be variable, regular, or irregular in malignant and benign tumors. Thus, several studies have found that ultrasonography is not useful for identifying benign tumors.[11,12] Although ultrasonography can differentiate malignancy from benign tumors relatively easily when there is invasion, ICPC without invasion is difficult to diagnose with ultrasonography.

Magnetic resonance imaging is one of the most useful diagnostic techniques for common breast cancer, as it shows the patterns of the time–intensity curves of the lesion, allowing us to differentiate cancerous from benign tumors. Naoshige et al. reported that dynamic MRI imaging is very useful in the differential diagnosis of ICPC.[6] Kusuma et al. also reported that the MRI findings correlated with the pathological findings.[13] Only three of our patients underwent MRI, which showed malignant patterns in the time–intensity curve in all three. Moreover, in one patient it showed invasive growth outside of the cyst, corresponding to the pathological findings (Fig. 1). This finding demonstrates the strong potential of MRI to differentiate benign tumors from invasive disease.

Fine-needle aspiration or core-needle biopsy is important if the preoperative image indicates a potential malignancy. Fine-needle aspiration should be done initially, followed by core-needle biopsy, unless the fine-needle biopsy reveals class 5. In this series excisional biopsy was necessary when fine-needle aspiration or core-needle biopsy could not provide a diagnosis. It is more difficult to diagnose ICPC than common breast

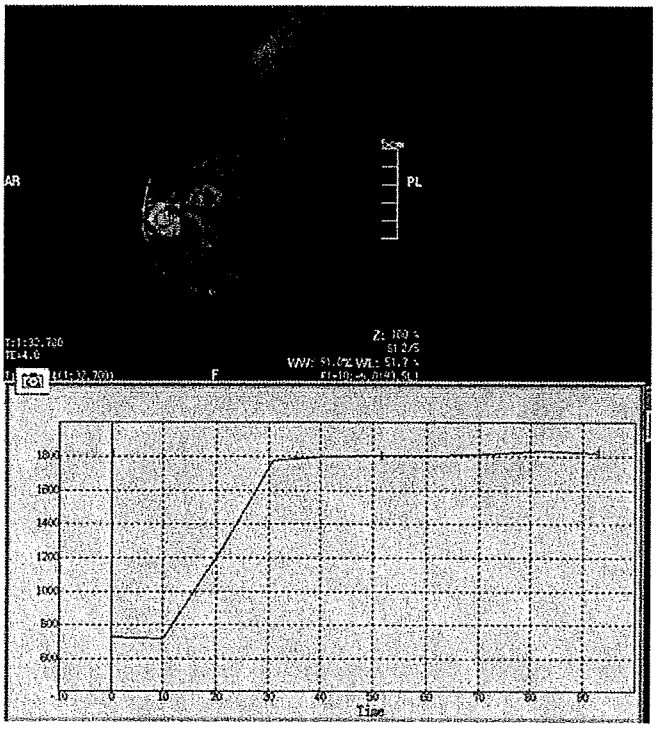


**Fig. 1.** Dynamic magnetic resonance imaging showed malignant patterns in the time–intensity curve of the lesion

cancer because nuclear atypicality of ICPC is not prominent. Therefore, a correct diagnosis is dependent on an adequate preoperative biopsy specimen.

The treatments for ICPC and DCIS are generally the same, although cases of invasive ICPC with synchronous liver metastases have been reported.[2–6] According to Yamashita et al., invasive ICPC is no longer rare and intraductal spread beyond 2 cm from the cystic wall is possible.[10] In this series, two patients had invasive ICPC and another patient had axillary lymph node metastases despite no evidence of invasion in any pathologic section. It is likely that this patient had invasive disease that was missed on the available pathologic sections. Thus, it is important to obtain negative pathological surgical margins. Intracystic papillary carcinoma has the potential to be invasive, which can be evaluated by MRI. Standard neoadjuvant and adjuvant treatments have not been established and surgical resection remains the first line of treatment. The frequency of lymph node metastasis of ICPC has been reported as 0%–36%, which is lower than that of common breast cancer.[9,14] Four patients in this series were treated with sentinel biopsy, which we have been performing in our department since 2004. It is now reasonable not to perform axillary lymph node dissection, as sentinel biopsy is an accepted indicator of ICPC.

All of the tumors in this series were positive for estrogen and progesterone receptors, and the patients were given tamoxifen as adjuvant therapy. Eight patients who underwent breast-conserving treatment received radiation. Although no definitive conclusions about adjuvant treatments have been made, ICPC should g enerally be treated like DCIS.

Based on our experience and review of the literature, we conclude that it is critical to evaluate the malignant potential of ICPC and to decide on the most appropriate adjuvant treatment for each individual patient.

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CLINICAL TRIAL

# Comparison among different classification systems regarding the pathological response of preoperative chemotherapy in relation to the long-term outcome

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**Abstract** Neoadjuvant chemotherapy (NAC) is increasingly used for operable disease. However there are several pathological response classification systems and the correlation between the pathological response to NAC according to each system and the patient outcome is still under debate. From 1998 to 2006, 370 primary breast cancer patients underwent curative surgical treatment after NAC containing both anthracycline and taxane at the National Cancer Center Hospital. We retrospectively evaluated the clinical and pathological response using the cTMN, Fisher's, Chevailler's, and the Japanese Breast Cancer Society classification systems (JBCS) respectively, and analyzed the correlation between each pathological response and disease free survival (DFS). Ninety-five (26%) patients had tumor recurrence. The five-year DFS according to Fisher's system was pCR, 80% and pINV, 63%. The five-year DFS according to Chevallier's system was Grade 1, 83%, Grade 2, 85%, Grade 3, 62%, and Grade 4, 65%. The five-year DFS according to the JBSC system was Grade 3, 77%, Grade 2, 68%, Grade 1a, 68%, Grade 1b, 58%, and Grade 0, 52%. None of the pathological response systems reached a statistically significant difference. In the classification by the post-treatment number of metastatic axillary lymph nodes, the 5-year DFS was $n = 0$, 86%; $n = 1$–3, 64%; $n = 4$–9, 44%; and $n > 10$ positive: 25% ($P < .0001$). In pathologically node negative patients, there were no significant differences in the DFS among all the classification systems. All three classifications analyzed were considered inadequate as the prognostic marker of the long-term outcome after NAC and further studies are warranted to optimize the prediction.

**Keywords** Breast cancer · Neoadjuvant · Chemotherapy · Response · Predictor

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## Introduction

Breast cancer has recently become the most common malignancy among Japanese women. Approximately 40,000 women are annually affected and breast cancer mortality has been increasing. National efforts to establish an early detection system by screening mammography has begun, but many of the primary cases still present with a palpable mass in the breast.

Neoadjuvant chemotherapy (NAC) has been accepted as one of the standards of care not only for locally advanced breast cancer but also for primary operable breast cancer. The disease free survival (DFS) and overall survival (OS) of patients treated with NAC is at least equivalent to those treated with post-operative adjuvant chemotherapy and the chance of breast conservation increases in patients with larger tumors [1, 2]. Although the benefit of the addition of taxane to anthracycline in the preoperative setting in terms of long-term outcome remains controversial, regimens that

combine both anthracycline and taxane, either sequentially or concomitantly, are widely used.

Prognostic factors after primary chemotherapy include the clinical and pathological response to primary chemotherapy, the cTNM stage, and axillary lymph-node status after chemotherapy. "Pathological complete response (pCR)" correlates with an improved DFS and OS and has often been used as the surrogate primary endpoint for NAC. However, the classification systems for pathological response vary among studies and the system that best reflects the long-term outcome remains unidentified. Thus in this study, we applied various pathological response systems in the published literature to the same patient cohort treated with NAC including anthracycline and taxane to compare their usefulness in the prediction of the long-term outcome after NAC.

## Patients and methods

### Patients and treatments

All breast cancer patients treated with NAC containing both anthracycline and taxane between May 1998 and October 2006 at the National Cancer Center Hospital were extracted from the surgical database to be included in this retrospective study. NAC was indicated in patients with clinical stage II or III primary breast cancer with tumors larger than 3 cm. Core needle biopsy was performed before NAC to obtain a pathological diagnosis. The NAC regimens included (1) four cycles of doxorubicin (DOX, 50 mg/m$^2$) and docetaxel (DOC, 60 mg/m$^2$) (AT) followed by additional adjuvant treatment with two cycles of AT or four cycles of iv CMF (cyclophosphamide, methotrexate and 5FU), (2) four cycles of fluorouracil (500 mg/m$^2$)/epirubicin (100 mg/m$^2$)/cyclophosphamide (500 mg/m$^2$) plus 12 weekly cycles of paclitaxel (80 mg/m$^2$) (FECT), (3) four cycles of doxorubicin (60 mg/m$^2$)/cyclophosphamide (600 mg/m$^2$) plus 12 weekly cycles of paclitaxel (80 mg/m$^2$) (ACT). After November 2002, in patients with HER2-overexpression tumors, trastsuzumab (initially 4 mg/kg and 2 mg/kg weekly) was administered with paclitaxel for 12 weeks in the ACT and FECT treated populations (ACTH and FECTH, respectively). Five years of endocrine therapy was scheduled when either the pretreatment biopsy specimen or surgical specimen post-chemotherapy were positive for the estrogen or progesterone receptor.

### Evaluation of pathological factors

Pretreatment diagnosis was established by pathologists from a core needle biopsy specimen. Surgical specimens were sectioned at about 7–10 mm and the pathological response was evaluated by pathologists. The expression levels of ER (1D5, Dako Cytomation), PgR (1A6, Novocastra) and HER2 (HercepTest®, Dako Cytomation) were examined with immunohistological staining. ER and PgR were classed as positive when more than 10% of cancer cell nuclei were stained, regardless of the intensity of the staining. HER2 was scored as follows: (0): negative for cells, (1+): slightly positive in more than 10% of cancer cells, (2+): moderately positive in more than 10% of cancer cells, (3+): markedly positive in more than 10% of cancer cells. Additional fluorescent in situ hybridization (FISH) for HER2 amplification (Pathvision, Vysis) was performed and when IHC (3+) or FISH-positive (HER2/CEP17 signal ratio $\geq$ 2.0) were defined as HER2-positive.

The response criteria used in this study included Fisher's system [1], Chevalier's system [3] and the histological response criteria of the Japanese Breast Cancer Society (JBCS) [4, 5]. The key definitions of each response classification system are described in Table 1. To summarize, Fisher's system evaluated only the histological evidence of invasive disease in the primary tumor, Chevallier's system incorporated nodal status and the JBSC system measured morphological changes in of the tumor cells and the proportion of histological changes in the primary tumor. The histological effect in both the primary tumor and axillary lymph node should be separately evaluated in the JBCS system, but the standard of how to combine the effect is not mentioned. Therefore we used the pathological response in only the primary lesion in the present study.

In addition, we evaluated pretreatment clinical staging, the clinical response to preoperative chemotherapy and postoperative pathological lymph node status. The clinical response to preoperative chemotherapy was decided from the two greatest perpendicular diameters (before each chemotherapy treatment and before surgery) of tumors in the breast and axillary lymph nodes. No clinical evidence of palpable tumor in the breast and axillary lymph nodes was defined as a clinical complete response (cCR). A reduction in the total tumor size of 30% or greater was graded as clinical partial response (cPR). An increase in 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 the criteria for objective response and progression were considered as stable disease (cSD).

### Statistical analysis

Disease free survival (DFS) was calculated from the date that NC was initiated to the date of the first relapse including loco-regional recurrence or the last visit without

**Table 1** Pathological response classification systems

| Classification system | Key definitions |
|---|---|
| Fisher et al. [1] | Classification based on microscopic evidence |
| | pCR = no histological evidence of invasive tumor cells (specimens with only noninvasive cells included) |
| | pINV = histological evidence of invasive disease of any extent |
| Chevallier et al. [3] | Classification using both microscopic and macroscopic evidence |
| | Grade 1 (pCR) = disappearance of all tumor on either macroscopic or microscopic assessment |
| | Grade 2 = presence of in situ carcinoma in the breast, no invasive tumor, no tumor in the ALNs |
| | Grade 3 = presence of invasive carcinoma with stromal alteration |
| | Grade 4 = no/few modifications of the tumor appearance |
| JBCS | Classification using both microscopic and macroscopic evidence in primary tumor |
| | Grade 0 = no therapeutic effect |
| | Grade 1 = <66% therapeutic effect, but >33% effect evident |
| | Grade 2 = subjectively >66% therapeutic effect, but <near total therapeutic effect |
| | Grade 3 = disappearance of all tumor on either macroscopic or microscopic assessment |

pCR, pathological complete response; ALN, Axillary lymph node; pINV, pathological invasive disease; JBCS, Japanese breast cancer society

relapse. Kaplan–Meier plots and the log-rank test were used to assess the difference in survival. All comparisons were two-tailed. Cox-proportional hazards models were fitted for OS and DFS and included variables identified a priori as being associated with survival and the ALN status. Other variables not identified a priori were entered into the model one at a time and assessed for statistical significance. All pair-wise interactions were tested. The fit of the model and the proportional hazards assumption were assessed visually with residual plots. The statistical significance level ($P$) was taken as a measure of the strength of evidence against the null hypothesis, and $P < .05$ was considered statistically significant.

## Results

Three hundred and seventy patients with operable breast cancer were included in this study. Table 2 lists the patient and tumor characteristics. The median age was 50 years (26–71) and 192 (52%) patients were over the age of 50. Clinical staging at diagnosis was IIA in 104 (28%), IIB in 114 (31%), IIIA in 75 (20%) and IIIB in 77 (21%). ER and PgR positive patients were respectively 148 (40%) and 152 (41%). 183 (49%) patients were treated with AT, 73 (20%) with ACT and 90 (24%) with FECT. Trastuzumab as administered to four patients among the ACT-treated patients (ACTH) and 20 among the FECT-treated patients. Ten percent of patients with HER2-positive breast cancer received trastuzumab in this study.

Ninety-six patients (26%) had tumor recurrence with a median follow-up of 45 months (range 4–104). Nine patients had only loco-regional recurrence without distant metastasis. Only 42 patients died within this period.

The clinical and pathological response results are shown in Table 3. The overall clinical response rate to NAC was 88% (cCR + cPR) and the cCR rate was 28%. According to Fisher's classification, pCR and pINV was 65 (18%) and 305 (82%). According to Chevallier's classification, 30 (8%) patients achieved a Grade 1 (disappearance of all

**Table 2** Patient and tumor characteristics

| Parameter | No. of patients (%) |
|---|---|
| Total | 370 |
| Age | |
| Age <50 | 179 (48) |
| Age >51 | 191 (52) |
| Pretreatment pathology | |
| Invasive ductal carcinoma | 347 (94) |
| Invasive lobular carcinoma | 13 (4) |
| Mucinous carcinoma | 7 (2) |
| Others | 3 (1) |
| Hormone receptors | |
| ER positive | 148 (40) |
| PgR positive | 152 (41) |
| HER2 | |
| Positive (>2+) | 132 (36) |
| Neoadjuvant chemotherapy | |
| AT | 183 (49) |
| ACT | 73 (20) |
| ACTH | 4 (1) |
| FECT | 90 (24) |
| FECTH | 20 (5) |
| Surgery | |
| Partial mastectomy | 136 (37) |
| Total mastectomy | 234 (63) |

**Table 3** Response to neoadjuvant chemotherapy, Cox proportional hazards model for disease free survival

| Parameter | No. of patients (%) | Hazard ratio (95% CI) |
|---|---|---|
| Fisher's classification | | |
| pCR | 65 (18) | 1.00 |
| pINV | 305 (82) | 1.07 (0.56–2.73) |
| Chevallier's classification | | |
| Grade 1 | 30 (8) | 1.00 |
| Grade 2 | 21 (6) | 1.03 (0.18–5.85) |
| Grade 3 | 172 (46) | 1.00 (0.43–2.26) |
| Grade 4 | 147 (40) | 1.31 (0.27–5.66) |
| JBCS classification | | |
| Grade 3 | 34 (9) | 1.00 |
| Grade 2 | 102 (28) | 1.39 (0.54–3.39) |
| Grade 1b | 81 (22) | 0.96 (0.36–2.32) |
| Grade 1a | 141 (38) | 0.61 (0.21–1.71) |
| Grade 0 | 12 (3) | 0.50 (0.56–2.73) |
| Pathological lymph node status | | |
| $n = 0$ | 174 (47) | 1.00 |
| $n = 1$–3 | 102 (28) | 0.78 (0.54–1.10) |
| $n = 4$–9 | 57 (15) | 1.57* (1.07–2.24) |
| $n > 10$ | 37 (10) | 2.71* (1.83–3.95) |
| Clinical stage | | |
| IIA | 104 (28) | 1.00 |
| IIB | 114 (31) | 0.68 (0.45–1.01) |
| IIIA | 75 (20) | 1.23 (0.86–1.74) |
| IIIB | 77 (21) | 1.22 (0.85–1.74) |
| Clinical response | | |
| CCR + cPR | 324 (88) | 1.00 |
| CSD + cPD | 46 (12) | 1.44* (1.10–1.87) |

CI, Confidence interval, * $P < .001$

tumors in either breast or lymph node) pathological response. According to the JBCS classification, there were 34 (9%) patients with Grade 3 pathological response (pathologically no residual tumor in the breast). Post-treatment pathological nodal status was negative in 174 (47%), 1–3 positive in 102 (28%), 4–9 positive in 57 (15%), and >10 positive in 37 (10%) patients, respectively. In the Cox proportional hazards model, the classification of pathological lymph node status and clinical response were identified as being independently significantly associated with patient outcomes (Table 3). Pretreatment hormone receptor status was not associated with pathological response or DFS. Inclusion of trastuzumab in NAC was associated with the pathological response in HER2-positive tumors ($P = 0.04$), but there was no statistical difference in the DFS (data not shown).

Figure 1 illustrates the Kaplan–Meier curves of the patient cohort of DFS according to each pathological response classification system (Fisher's, Chevallier's, JBCS). Among these classification systems, Fisher's tended to show a correlation with DFS, however, it did not reach a statistically significant difference ($P = .067$). The five-year DFS rates in Grade 3, Grade 2, Grade 1a, Grade 1b and Grade according to the JBCS system were 77%, 68%, 68%, 58%, and 52%, respectively ($P = .525$). According to Chevallier's system, the five-year DFS rates for Grade 1, Grade 2, Grade 3 and Grade 4 were 83%, 85%, 62% and 65%, respectively ($P = .16$).

The five-year DFS according to the number of post-treatment axillary node metastases was $n = 0$, 86%; $n = 1$–3, 64%; and $n = 4$–9, 25%. Figure 2 shows the DFS according to the pre-treatment cTMN classification, post-treatment pathological nodal status and clinical response to NAC. The pre-treatment clinical stage, clinical response to NAC and post-treatment pathological nodal status were strong predictors of DFS ($P < .0001$, $P = .0005$, $P < .0001$, respectively).

The pathological response results in post-treatment pathological node negative patients are shown in Fig. 3. Pathological node-negative patients accounted for 174 (47%) out of 370 patients. Since the number of Grade 0 patients according to the JBCS system was only two, they were excluded from the analysis. There were no significant relationships between the three pathological response classification systems and the DFS in pathologically node-negative patients. Neither clinical response ($P = .142$) nor pre-treatment clinical stage ($P = .231$) predicted DFS in node-negative patients.

## Discussion

Pathological and biological markers predicting "pCR" in NAC have been evaluated in several studies [6, 7], but there is no consensus on the definition of pathological response. It is particularly unclear whether the classification needs the measurement of the extent of therapeutic effect including the disappearance of tumor cells and decrease of tumor cellularity [1–3, 8, 9]. The frequency distribution of residual tumor size was altered markedly by the inclusion of tumor cellularity, and the accurate pathologic response information may be provided the product of pathologic size and tumor cellularity [10]. The results in our study showed that the evaluation of tumor cellularity and tumor size by both Chevallier's and he JBCS classification systems was not useful for predicting prognosis in both all patients and node-negative patients. This result was in contrast to another study, where the reduction of tumor cellularity significantly correlated with the overall and disease free survival [11]. The negative finding in our study may be due to the small sample size of the study and limited number of events in each category of the

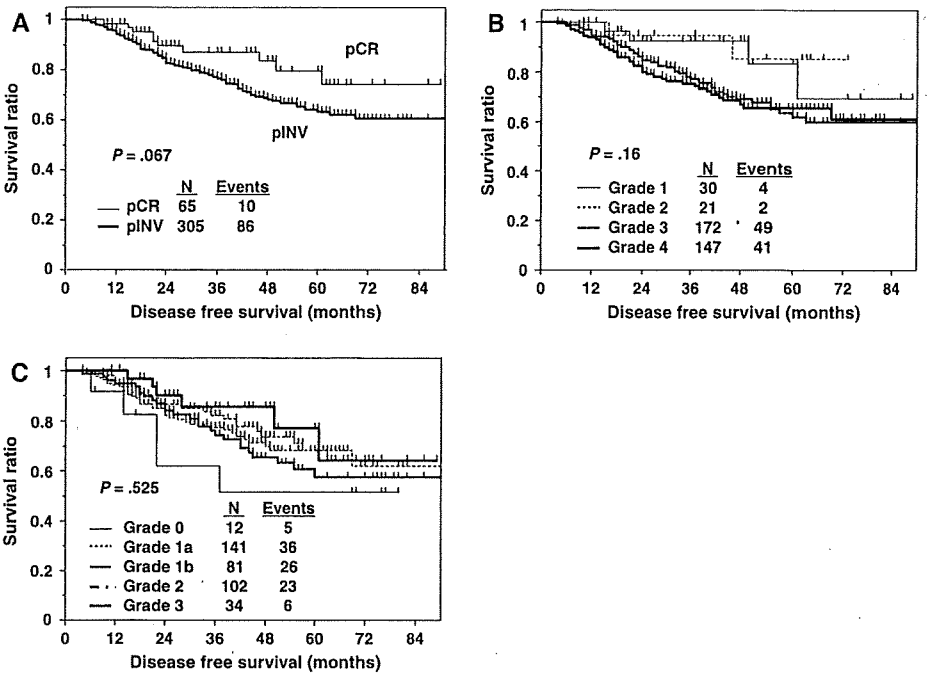


**Fig. 1** Kaplan–Meier curves of disease free survival according to pathological response classification systems examined. (a) Fisher's classification; (b) Chevallier's classification; (c) JBCS classification

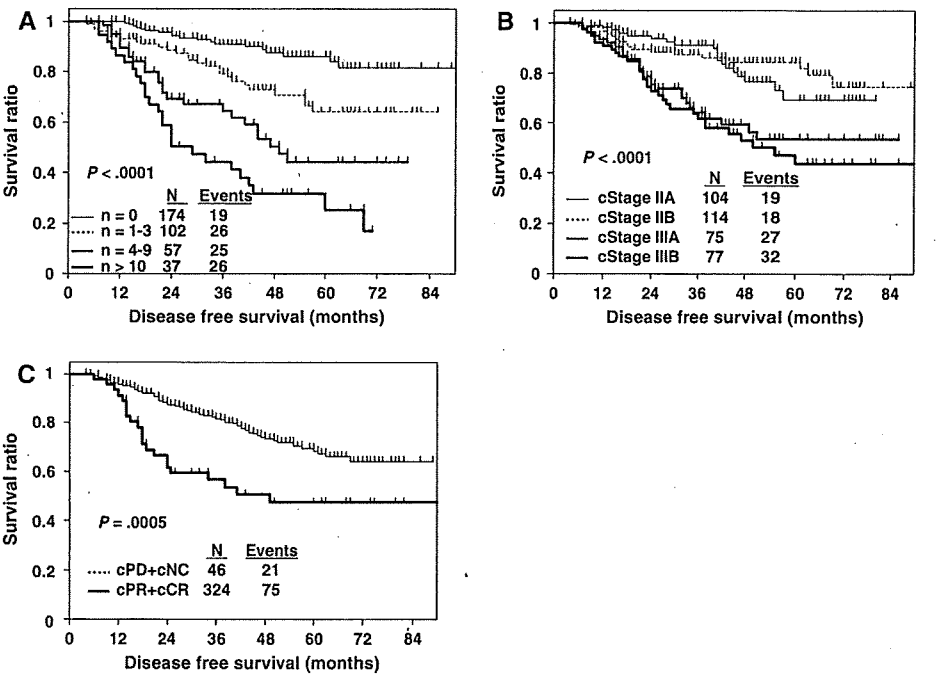


**Fig. 2** Kaplan–Meier curves of disease free survival according to (a) Pathologic nodal status; (b) Clinical staging and (c) Clinical response

classification. Moreover the variety of chemotherapy regimens used as NAC may have affected the result. Particularly, trastuzumab was used only in the recent HER2-positive patient cohort.

However, studies including ours indicate the importance of incorporating the pathological nodal status in the prediction of prognosis for patients after NAC [12–15]. Fisher's classification is the most popular classification system using major clinical trials such as NSABP trials, but this classification system is diagnosed simply based on the disappearance of invasive tumor cells, regardless of non-invasive tumor cells, only in the primary tumor. Although Fisher's system is simple, objective and its usefulness as a predictive marker has been validated [1–3, 9, 14], incorporation of the therapeutic effect in axillary lymph nodes may be necessary for more precise outcome prediction.

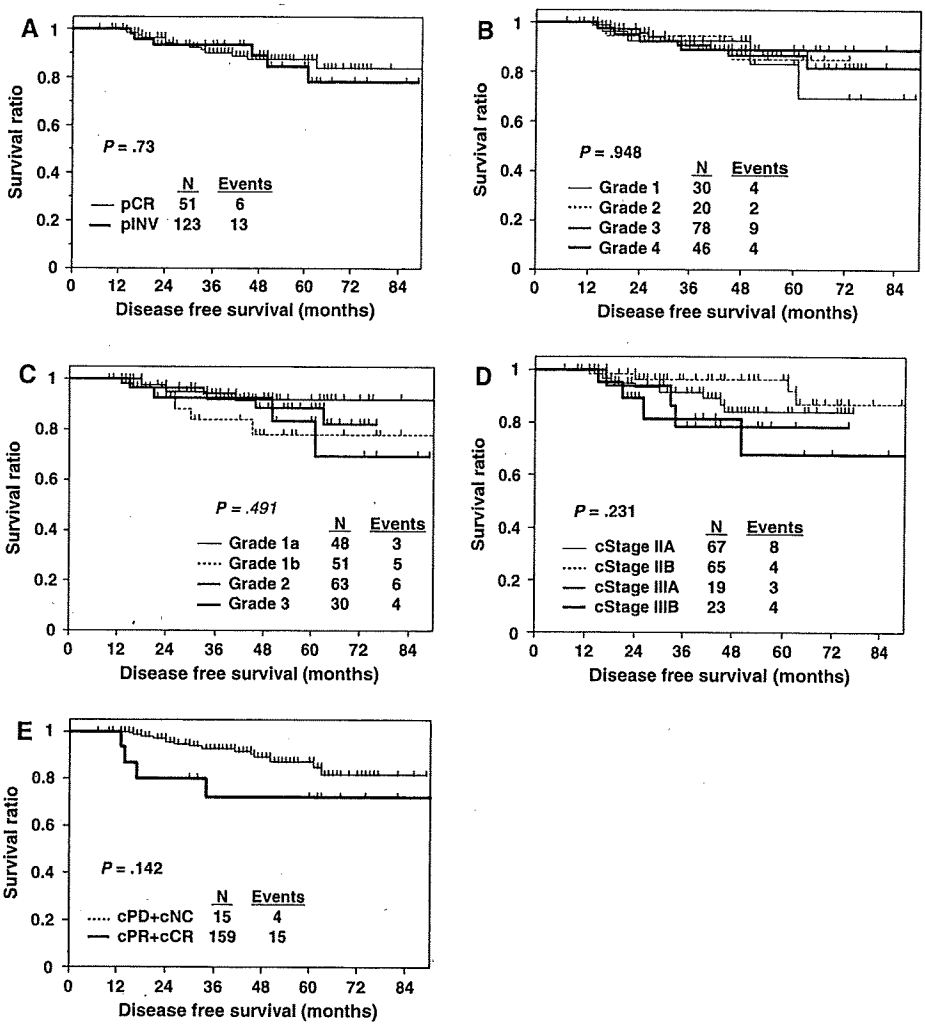


**Fig. 3** Kaplan–Meier curves of disease free survival in node negative patients (a) Fisher's classification; (b) Chevallier classification; (c) JBCS classification; (d) Clinical staging; (e) Clinical response

On the other hand, clinical response was the significant predictor of the disease free survival in this study as reported in several other papers [13, 16–19]. Clinical response reflects the activity of chemotherapeutic agents. Clinical responders had a better prognosis compared with non-responders. The pretreatment clinical stage correlated with disease free survival, but there were good responders among the patients with advanced primary lesions and clinically positive axillary lymph nodes. Although pCR significantly correlated with the clinical response, the importance of the clinical response in outcome prediction may remain in patients with residual tumor or pathologically negative axillary lymph node after NAC.

In conclusion, we think that all three classifications analyzed in this study were not adequate as a prognostic marker of long-term outcome after NAC. The evaluation of the therapeutic effect in primary tumors warrants further study, especially in pathologically node-negative patients after NAC. Given the suggestion that the benefit of certain chemotherapy regimens might be different depending on the biological tumor characteristics (e.g. hormone responsive, HER2, triple negative), the validity of pCR as a prognostic marker might better be tested independently in each biological subset. Moreover, the validity of pCR with NAC including biologically targeted drugs such as trastuzumab should also be revisited.

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# 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.

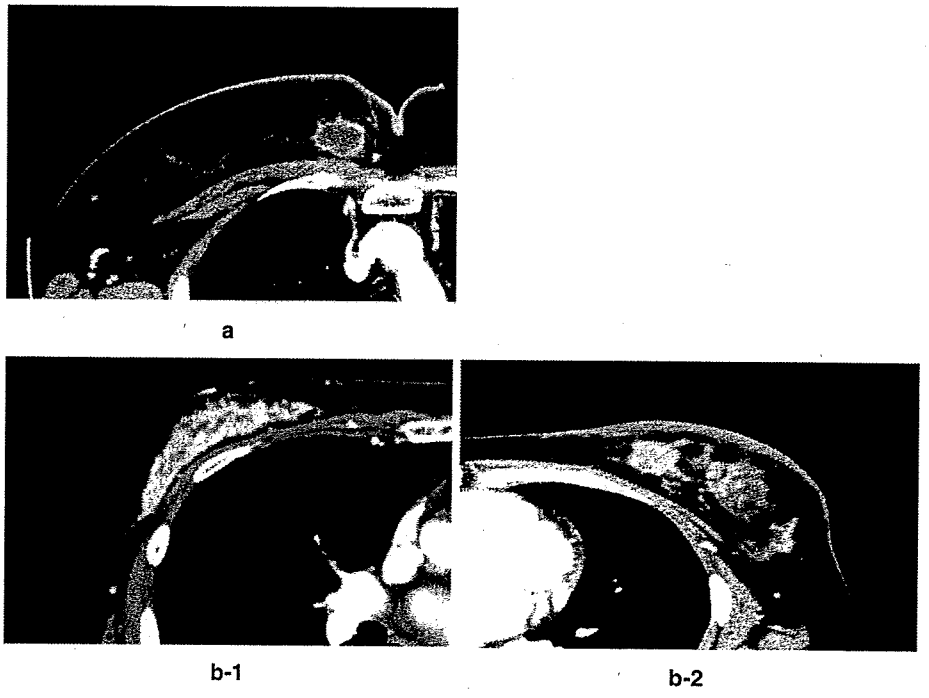


**Fig. 1** Classification of tumor by CT imaging. **a** Localized type. **b-1** Nonlocalized type: glandular spreading. **b-2** Nonlocalized type: tumor with surrounding lesions

**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 |
| 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 post-operative 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.

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