Fig 7. CE-CT image of the right breast[32]. An enhanced mass lesion 0.6 cm in diameter in the upper inner quadrant was isolated from the left atrophic mammary gland. A skin marking is shown just above the lesion (arrow). Excisional biopsy revealed invasive ductal carcinoma, histological grade 3, 0.5 × 0.4 cm in diameter.

breast cancer in patients with metastatic axillary adenopathy in whom previous MMG and US yielded normal results[32]. We performed CE-CT to locate the primary tumors in five cases of occult breast cancer and succeeded in locating all five lesions (Fig 7).

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References

1) Muramatsu Y, Akiyama N, Hanai K: Medical exposure in lung cancer screening by helical computed tomography. *Jpn J Radiol Technol* 52:1-8, 1995.
2) Schnitt SJ, Connolly JL, Khettry U, *et al*: Pathologic findings in re-excision of the primary site in breast cancer patients considered for treatment by primary radiation therapy. *Cancer* 59:675-681, 1987.
3) Gage I, Schnitt S, Silver B, *et al*: Pathologic margin involvement and the risk of recurrence in patients treated with breast-conserving therapy. *Cancer* 78:1921-1928, 1996.
4) Healey EA, Osteen RT, Schnitt SJ, *et al*: Can the clinical and mammographic findings at presentation predict the presence of an intensive intraductal component in early stage breast cancer. *Int J Radiat Oncol Biol Phys* 17:1217-1221, 1989.
5) Tsunoda-Shimizu H, Ueno E, Tohno E, *et al*: Ultrasonographic evaluation for breast conservative therapy. *Jpn J Breast Cancer* 11:649-655, 1996 (in Japanese with English abstract).
6) Endo T, Ichihara S, Aoyama H, *et al*: The indications for breast conserving surgery on mammography. *Jpn J Breast Cancer* 11:643-648, 1996 (in Japanese with English abstract).
7) Akashi-Tanaka S, Fukutomi T, Miyakawa K, *et al*: Diagnostic value of contrast-enhanced computed tomography for diagnosing the intraductal component of breast cancer. *Breast Cancer Res Treat* 49:79-86, 1998.
8) Akashi-Tanaka S, Fukutomi T, Miyakawa K, *et al*: Diagnostic value of enhanced computed tomography in the detection of the widely spreading intraductal component of breast cancer: case reports. *Breast Cancer* 4:29-32, 1997.
9) Akashi-Tanaka S, Fukutomi T, Miyakawa K, *et al*: Clinical use of contrast-enhanced computed tomography for decision making in breast conserving surgery. *Breast Cancer* 4:280-284, 1997.
10) Uematsu T, Sano M, Homma K, *et al*: Three-dimensional helical CT of the breast: Accuracy for measuring extent of breast cancer candidates for breast conserving surgery. *Breast Cancer Res Treat* 65:249-257, 2001.
11) Akashi-Tanaka S, Fukutomi T, Miyakawa K, *et al*: Contrast-enhanced computed tomography for diagnosing the intraductal component and small invasive foci of breast cancer. *Breast Cancer* 8:10-15, 2001.
12) Hiramatsu H, Enomoto K, Ikeda T, *et al*: Three-dimensional helical CT for treatment planning of breast cancer. *Radiation Medicine* 17:35-40, 1999.
13) Furuhashi S, Karikomi M, Yano K: Contrast-enhanced helical CT of the breast cancer: (CT and histopathological correlation). *J Danso Eizo Kenkyuukai* 27:199-204, 2000 (in Japanese with English abstract).
14) Kanamaru H, Yokoyama H, Shirakawa H, *et al*: Value of helical computed tomography in diagnosing the extent of intraductal spread of breast cancer. *Jpn J Breast Cancer* 16:125-131, 2001 (in Japanese with English abstract).
15) Tozaki M, Yamashita A, Kawakami M, *et al*: Diagnosis of breast cancer extent using dynamic multidetector-row CT: correlation between MPR imaging and pathological cross-sections. *Nippon Acta Radiol* 60:560-567, 2000 (in Japanese with English abstract).
16) Ishida T: Preoperative detection of EIC and multifocal lesions of breast cancer; in comparison of 3-D CT and 3-D MRI as new modalities. *J Jap Surg Soc* 102:74, 2001 (in Japanese).
17) Hisamatsu K: 2001 personal communication
18) Fisher B, Bryant J, Wolmark N, *et al*: Effect of preoperative chemotherapy on the outcome of women with operative breast cancer. *J Clin Oncol* 16:2672-2685, 1998.
19) Hortobagyi GN: Treatment of locally advanced and inflammatory breast cancer. In: Harris JR, Lippman ME, Morrow M, Osborne CK eds, Diseases of the Breast, 2nd ed, Lippincott Williams & Wilkins, Philadelphia, pp645-650, 1999.
20) Akashi-Tanaka S, Fukutomi T, Watanabe T, *et al*: Accuracy of contrast-enhanced computed tomography in the prediction of residual breast cancer after neoadjuvant chemotherapy. *Int J Cancer (Radiat Oncol Invest)* 96:66-73, 2001.
21) Guiliano AE, Jones R, Brennan R, *et al*: Sentinel lym-

phadenectomy in breast cancer. *J Clin Oncol* 15:2345-2350, 1997.
22) Morrow M, Harris JR: Local management of invasive breast cancer. In: Harris JR, Lippman ME, Morrow M, Osborne CK eds, Diseases of the Breast, 2nd ed, Lippincott Williams & Wilkins, Philadelphia, pp549-550, 1999.
23) March D, Wechsler R, Kurtz A, *et al*: CT-pathologic correlation of axillary lymph nodes in breast carcinoma. *J Comput Assist Tomogr* 15:440-444, 1991.
24) Ogawa Y, Nishioka A, Hamada N, *et al*: Recent progress of imaging diagnosis for breast cancer. *Jpn J Breast Cancer* 11:243-253, 1996 (in Japanese with English abstract).
25) Suzuki M, Nagashima K, Yagata H, *et al*: Computed tomographic evaluation of axillary lymph node metastases from breast cancer. *J Jap Surg Associ* 60:898-903, 1999 (in Japanese with English abstract).
26) Nishie H, Hirooka Y, Kaibara N, *et al*: Preliminary study of diagnosis of lymph nodes metastasis of breast cancer by preoperative CT scan. *J Jap Surg Associ* 61:1118-1122, 2000 (in Japanese with English abstract).
27) Newman J: Recent advances in breast cancer imaging. *Radiologic Technol* 71:35-54, 1999.
28) Uematsu T, Sano M, Homma K: In vivo high-resolution helical CT of small axillary lymph nodes in patients with breast cancer. *AJR* 176:1069-1074, 2001.
29) Pierga J, Mouret E, Dieras V, *et al*: Prognostic value of persistent node involvement after neoadjuvant chemotherapy in patients with operable breast cancer. *Br J Cancer* 83:1480-1487, 2000.
30) Lluch A, Cervantes A, Pardo J, *et al*: Assessment of primary tumor and axillary involvement in breast cancer after neoadjuvant chemotherapy. A comparison of clinical examination, mammography, ultrasonography and CT-scan. *Proc Am Soc Clin Oncol* 14:135#240, 1995.
31) Hagay C, Cherel P, De-Maulmont C, *et al*: Contrast-enhanced CT: value for diagnosing local breast cancer recurrence after conservative treatment. *Radiol* 200:631-638, 1996.
32) Akashi-Tanaka S, Fukutomi T, Miyakawa K, *et al*: Contrast-enhanced computed tomography detection of occult breast cancers presenting as axillary masses. *Breast Cancer Res Treat* 55:97-101, 1999.

The Use of Contrast-Enhanced Computed Tomography Before Neoadjuvant Chemotherapy to Identify Patients Likely to Be Treated Safely With Breast-Conserving Surgery

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Objective: To select suitable candidates for breast-conserving treatment (BCT) after neoadjuvant chemotherapy (NAC), based on the classification of tumors into localized or diffuse types using contrast-enhanced computed tomography (CE-CT).

Summary Background Data: A relatively high rate of loco-regional failure after BCT has been reported with breast cancer downstaged by NAC. Accurate assessment of the suitability of BCT and the response to NAC, before the initiation of NAC, will allow the optimal selection of an appropriate therapeutic course.

Methods: We evaluated 110 consecutive patients with operable breast carcinomas measuring 3-cm or more in diameter by CE-CT after NAC treatment with doxorubicin and docetaxel at National Cancer Center Hospital, Tokyo, from May 1998 to November 2001. Lesions were classified as either localized or diffuse types by mammography (MMG), ultrasonography (US), and CE-CT.

Results: Tumors designated as localized type by MMG, US, and CE-CT were reduced to tumors less than 3.0 cm ($P < 0.0001$) in a concentric circle ($P < 0.0001$). Localized tumors by CE-CT were treated safely with BCT maintaining a negative margin status ($P = 0.01$). In contrast, diffuse type tumors shrunk into a mosaic pattern consisting of tumors larger than 3.1 cm. Tumors classified as localized by CE-CT responded better pathologically than diffuse tumors ($P = 0.0365$). Multivariate analysis demonstrated that morphologic type by CE-CT and histologic type were significant predictors of candidates for safe BCT.

Conclusions: The classification of tumors into either *localized* or diffuse types, using CE-CT before NAC administration, accurately predicts which tumors will be suitable candidates for BCT after NAC.

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A large randomized clinical trial confirmed the efficacy of neoadjuvant chemotherapy (NAC) in downstaging breast carcinomas and permitting the increased use of breast-conserving treatment (BCT), although no survival advantage was demonstrated.[1] The response rates of patients to NAC are generally high, ranging from 70 to 90%. Some patients, however, do not derive any benefit from NAC, and it would be advantageous to identify these patients before initiating NAC. In patients who were initially candidates for mastectomy but underwent BCT after NAC-mediated tumor downstaging, the incidence of ipsilateral breast tumor recurrence (IBTR) (14.5%) increased in comparison to patients undergoing BCT as initially planned (6.9%) ($P = 0.04$).[1] This may be due to the wide mosaic satellites of residual viable tumor cells in the original tumor-bearing area, despite tumor downstaging following NAC administration.[2,3] The reduction of a tumor into either a concentric circle or a wide mosaic-like pattern may be a critical factor for determining the suitability of BCT.[4]

The relationship between predictors of tumor shrinkage patterns and suitability of BCT has not been previously examined. Nakamura et al, however, reported in a small number of patients that papillotubular, estrogen receptor-positive, low nuclear grade, and negative c-erbB 2 tumors had a tendency to show mosaic-like patterns of residual tumor cells.[6] The morphologic tumor type prior to NAC may be a strong predictor of tumor shrinkage pattern and suitability of BCT. In this study, we investigated whether classifying tumors into diffuse or localized types, through the use of

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diagnostic imaging, can predict the safety of BCT and the response to NAC.

PATIENTS AND METHODS

Patients

One hundred ten consecutive patients with operable breast carcinomas measuring greater than 3-cm in diameter who were evaluated by palpation and contrast-enhanced computed tomography (CE-CT) before and after NAC at the National Cancer Center Hospital (NCCH) in Tokyo from May 1998 to November 2001 were enrolled in this study. They were also evaluated by mammography (MMG) and ultrasonography (US). The treatment protocol consisted of 4 cycles of doxorubicin and docetaxel at doses of 50 and 60 mg/m^2, respectively, with a 21-day cycle length, followed by mastectomy or breast-conserving surgery. Eligible women received initial pathologic confirmation of breast carcinoma by core needle biopsy. Complete staging was determined by chest x-ray, liver ultrasound, and bone scan for all patients prior to initiating NAC. All patients gave informed consent for study participation as approved by the institutional review board of NCCH.

Imaging Examinations

Helical CT scanning was performed using an X-Vigor scanner (Toshiba, Japan) at a current of 300 mA. Patients underwent one single spiral acquisition, during deep inspiratory apnea in the supine position, for up to 30 seconds. The first non-contrast-enhanced CT scan served as a baseline, imaged from the cranial end of the sternum to the inframammary fold. Subsequently, an enhanced zoomed scan visualized the whole breast, using a collimation of 5 mm and a pitch of 1 mm. One hundred milliliters of nonionic contrast material (300 mg I/mL) was injected at 2 mL/s. Fifty seconds elapsed between the administration of contrast material and the initiation of scanning. The reconstruction interval was 5 mm.[6]

A Mammomat 3000 (Siemens, Germany) was used for mammographic examination. In addition to standard oblique and cranio-caudal projections, cranio-caudal and medio-lateral spot views (5 cm in diameter) without magnification, were also obtained for most patients. Whole-breast US was performed using a SSA340A (Toshiba, Japan), possessing an annular array transducer. With all modalities in this study, tumor diameters were measured in the transverse direction.

To predict the shrinkage pattern, the diagnostic image findings were used to classify tumor morphology into either localized type or diffuse type (Fig. 1). By mammography, localized tumors were either devoid of microcalcifications or possessed microcalcifications contained within the tumor. Diffuse type tumors included density elevation type tumors (tumors whose border is not clearly defined), tumors with widespread microcalcifications beyond their edges, and multiple tumors. US findings also identified both localized and diffuse tumor types, including tumors with ducts, noticeable shadow formation, and multiple foci (Fig. 2). Enhanced CE-CT images classified these 2 types, with localized tumors visualized as single spots, while diffuse type tumors included those with surrounding spots, multiple spots, and glandular spreading (whole or part of a gland occupied by enhanced lesion) (Fig. 3).[7]

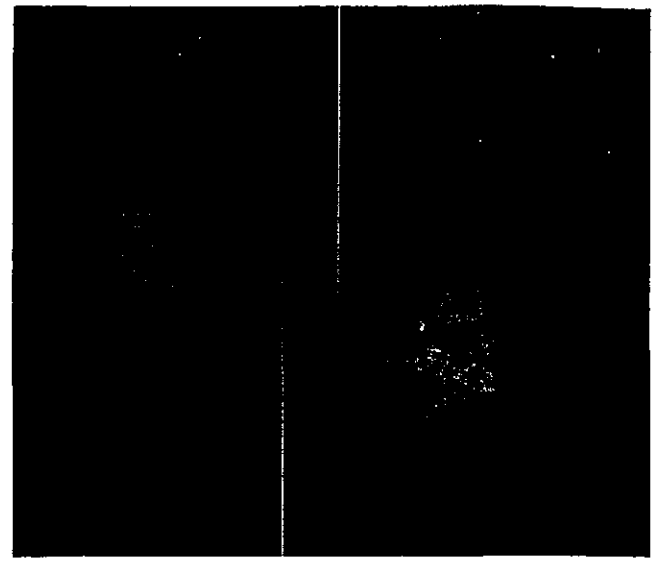

FIGURE 1. Localized tumor type (left) and diffuse type (right) by MMG.

MMG and CE-CT imaging studies were prospectively evaluated by 2 radiologists (K.M. and N.S.). US images were evaluated by 2 additional radiologists (H.M. and N.S.). Classifications of morphologic subtypes were made independently by N.S. and S.A. The coincidence rates of the classifications were 97% (107 of 110). Following discussion, cases without coincident interpretations were mutually agreed upon.

Histopathological Examinations

Surgical specimens were sectioned at approximately 7-mm to 10-mm intervals along a transverse axis, for analysis by breast pathologists. Margins were classified as negative if

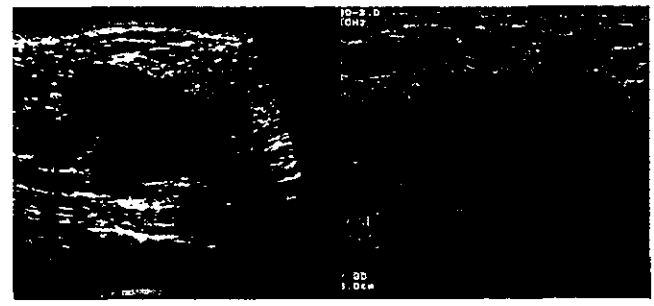

FIGURE 2. Localized tumor type (left) and diffuse type (right) by US.

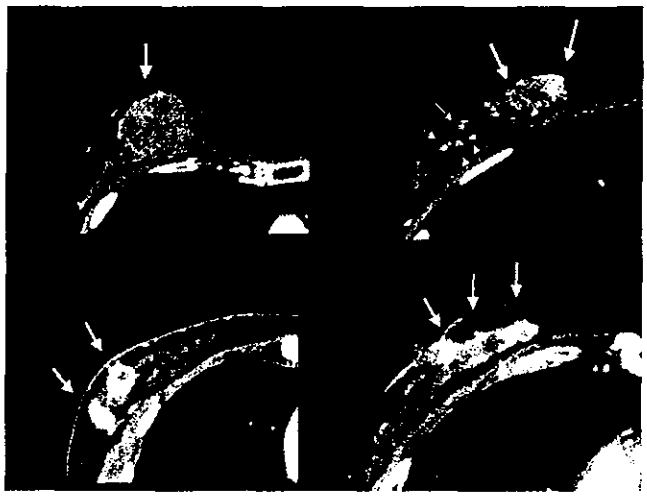

FIGURE 3. Localized tumor type (left upper) and diffuse type: tumor and spots (right upper), multiple spots (left lower), and glandular spreading type (right lower) by CE-CT.

no invasive or in situ ductal carcinoma was observed within 1 mm of the margin and positive when cancerous cells were observed at the margin. The response to NAC was classified according to the general rules for the clinical and pathologic recording of breast cancer.[8] For Grade 0, no response was observed; Grade 1a comprised those tumors with any degenerative change or severe degenerative change in less than one third of cancerous cells; for Grade 1b, severe degenerative changes were observed in one third to two thirds of the cancerous cells; Grade 2 tumors contained degeneration of more than two thirds of cancerous cells; Grade 3 tumors demonstrated a complete response, with no cancerous cells remaining.

Statistical Analysis

The χ^2 test was used for comparisons of sizes, histology, changes, and responses among morphologic groups. Differences with $P < 0.05$ were considered to be significant. A logistic regression model was used for univariate and multivariate analysis.

RESULTS

The mean age at surgery of 110 patients was 52 years, with a range from 29 to 69 years of age. Sixty patients (54.5%) presented with T2 tumors, 34 (30.9%) with T3 and 16 (14.5%) with T4b (skin involvement) tumors. Fifteen patients (13.6%) achieved a complete clinical response, while 68.1% (75 of 110) showed a partial clinical response. Pathologically, according to the general rules for the clinical and pathologic recording of breast cancer,[8] 6 tumors (5.5%) achieved a Grade 3 response, 33 (30%) achieved a Grade 2 response, 30 (27%) achieved a Grade 1b response, 35 (32%) achieved a Grade 1a response, and 6 (5.5%) did not demonstrate a response.

The relationships between the initial tumor characteristics and the morphologic types defined by diagnostic imaging are displayed in Table 1. Prior to NAC, 57 tumors were classified as localized by CE-CT, while 53 were designated as diffuse type. Based on physical examination, sizes of localized and diffuse tumors, as classified by all of the modalities, did not differ. When size was determined by each modality, however, localized tumors tended to be smaller. Invasive lobular carcinomas (ILC) tended to exhibit a diffuse morphology by US ($P = 0.05$). Of sixteen tumors showing skin involvement, 14 tumors were classified as localized by CE-CT. Five patients failed to be evaluated by breast US before NAC, and 2 were not evaluated after NAC. One patient failed to be evaluated by MMG before NAC, and another failed to be evaluated after NAC.

We compared the morphologic changes in the images before and after NAC (Table 2). According to all 3 modalities, localized tumors maintained their localized phenotype ($P < 0.0001$) (Fig. 4). Furthermore, diffuse tumors main-

TABLE 1. Initial Tumor Characteristics and Morphological Types

	Sizes by Palpation		Sizes by Each Modality		Histology			
	T ≤ 5.0 cm	T ≥ 5.1 cm	T ≤ 5.0 cm	T ≥ 5.1 cm	IDC	ILC	Others	Total
MMG								
Localized	40	24	54	10	55	7	2	64
Diffuse	23	22*	26	17†	39	4*	2	45
US								
Localized	31	20	46	5	48	2	1	51
Diffuse	30	24*	32	22†	43	8‡	3	54
CT								
Localized	32	25	48	9	51	3	3	57
Diffuse	31	22*	35	18#	43	8*	2	53

*NS; †$P = 0.01$; ‡$P = 0.05$; #$P = 0.02$.

TABLE 2. Morphological Changes in the Imaging Before and After NAC

	After			
Before	Localized	Diffuse	No Enhancement	
MMG				
Localized	53	6	6	
Diffuse	9	31	3	$P < 0.0001$
US				
Localized	38	7	5	
Diffuse	12	38	3	$P < 0.0001$
CT				
Localized	44	12	1	
Diffuse	15	36	2	$P < 0.0001$

FIGURE 4. A typical case with localized type tumor by CE-CT (left) decreased in size to form a concentric circle (right).

tained their diffuse phenotype (Fig. 5). This suggested that localized tumors shrink into a concentric circle, while diffuse tumors shrink into a mosaic-like pattern of tumor cells. The relationship between pathologic response and morphologic type is shown in Table 3. Localized tumors by CE-CT tended to respond better than diffuse type tumors ($P = 0.036$).

The results of univariate analysis on the initial histologic characteristics of the tumor on core biopsy, pathologic response to NAC, morphologic category, and prechemotherapy size based on diagnostic imaging and physical examination associated with safe BCT are listed in Table 4. Fifty-eight tumors (53%) measured less than 3.0 cm pathologically after NAC, while 52 (47%) remained larger than 3.0 cm. For BCT, we defined a residual tumor size of 3.0 cm as a safe upper limit. Significant associations were observed between almost all variables, except for initial size based on US. Localized tumors diminished in size to less than 3.0 cm ($P = 0.002$ for MMG, 0.0007 for US, and <0.0001 for CE-CT, respectively). Diffuse tumors did not consistently demonstrate reductions in size to less than 3.0 cm.

Multivariate regression analyses using a logistic regression model were conducted to identify independent factors for choosing candidates for safe BCT (Table 5). At the end of the multivariate analyses, the morphologic categories by CE-CT ($P = 0.0255$) and histology ($P = 0.0175$) remained significantly related to safe BCT following NAC.

Of 67 patients eligible for BCT (T< 3 cm), 38 patients chose BCT. Twelve patients had positive resection margins following BCT. Margin status was correlated with tumor type, as determined by CE-CT (Table 6). Diffuse tumors consistently exhibited positive margins ($P = 0.0096$). Of 7 patients eligible for BCT who had had skin involvement prior to NAC, 2 patients with localized tumor by CE-CT chose BCT and obtained negative margin status. No IBTRs were observed after a 2 year median follow-up.

FIGURE 5. A typical case with diffuse type tumor by CE-CT (left), which diminished to mosaic residue (right).

DISCUSSION

Appropriate use of NAC may allow BCT in patients who would otherwise be treated by mastectomy. Accurate

TABLE 3. Pathological Response to NAC and Morphological Types by Diagnostic Imaging Before NAC

	Pathological Response		
	Grade 0–1b	Grade 2–3	
MMG			
Localized	19	20	
Diffuse	46	24	$P = 0.093$
US			
Localized	23	28	
Diffuse	16	38	$P = 0.316$
CE-CT			
Localized	31	26	
Diffuse	39	14	$P = 0.0365$

TABLE 4. Univariate Analysis on Tumor Characteristics Associated With Safe BCT (Achieving t ≤ 3.0 cm)

		P-value	Relative Risk	95% CI
MMG	Localized/diffuse	0.0039	3.231	1.458–7.161
US	Localized/diffuse	0.0027	3.437	1.536–7.695
CT	Localized/diffuse	<0.0001	5.426	2.398–12.277
Palpable size	(cm)	0.0146	1.442	1.075–1.935
MMG size	(cm)	0.0043	0.717	0.570–0.901
US size	(cm)	0.2267	0.846	0.644–1.110
CT size	(cm)	0.0001	0.574	0.431–0.764
Histology	ILC/IDC	0.0127	0.070	0.009–0.566
Pathological Response Grade 2, 3/0, 1		0.0022	0.268	0.116–0.622

TABLE 5. Multivariate Analysis to Identify Independent Factors for Choosing Candidates for Safe BCT (Achieving t ≤ 3.0 cm)

		P-value	Relative Risk	95% CI
MMG	Localized/diffuse	0.1125	2.647	0.795–8.810
US	Localized/diffuse	0.8167	0.871	0.271–2.801
CT	Localized/diffuse	0.0255	3.806	1.178–12.303
Palpable size	(cm)	0.0511	0.652	0.424–1.002
MMG size	(cm)	0.5283	1.127	0.777–1.636
CT size	(cm)	0.1081	0.716	0.476–1.076
Histology	ILC/IDC	0.0177	0.054	0.005–0.601
Pathological response Grade 2, 3/0, 1		0.1358	0.422	0.136–1.312

prediction of the suitability of BCT and the response to NAC, prior to initiating NAC downstaging, would help in the optimal selection of treatment. The classification of tumors into either localized or diffuse types using diagnostic imaging provides a basis for making this determination. Localized tumors responded well to NAC and were reduced into smaller, concentric tumors that could be safely treated by wide excision, giving a negative margin status. Diffuse tumors, however, diminished into a mosaic pattern of residual tumor cells, giving a positive margin status when treated with BCT. Thus, they most likely would be more suitably treated by mastectomy or wide excision of the area corresponding to the original tumor size. Multivariate analysis demonstrated that classification by CE-CT was a powerful predictor of the safety of BCT. ILC was also an independent predictor of safe BCT, but the number of ILC was so small that the 95% confidence interval became wide.

TABLE 6. Margin Status of Breast-Conserving Treatment and Types by Diagnostic Imagings Before NAC

	Margin		
	Positive	Negative	
MMG			
Localized	8	20	
Diffuse	4	7	$P = 0.63$
US			
Localized	5	17	
Diffuse	7	9	$P = 0.17$
CE-CT			
Localized	4	20	
Diffuse	8	6	$P = 0.0096$

In this study, we defined a residual tumor size of 3.0 cm as a safe upper limit for BCT. Although larger tumor size is not an absolute contraindication for BCT,[9] tumors smaller than 3 or 4 cm by physical examination are eligible for BCT to facilitate cosmetically acceptable results and good local control.[10] As determined by the Japanese Breast Cancer Society, the current guidelines recommend tumors smaller than 3 cm as being safe for BCT.[11] Complete removal of tumor has been confirmed as crucial for BCT with good local control. Therefore, we have applied the guideline of 3 cm as a safe size limit for patients undergoing BCT.

Prediction of response to NAC has recently focused on expression of potential biologic markers such as estrogen receptor, p53, HER2/c-erbB-2, and Ki67 in the primary breast tumor.[12,13] ER-negative, poorly differentiated tumors were more likely to be associated with a higher response to NAC. The present study indicated that the morphologic category based on CE-CT was a significant predictor of pathologic tumor response to NAC. There are no reports that have associated morphology with the response to chemotherapy.

It is expected that a tumor showing a better response to NAC and/or an initially smaller size would shrink into a smaller tumor that is more suitable for BCT. Multivariate analysis, however, suggested that the pathologic response and initial tumor size, as determined by palpation and diagnostic imaging, were not significant predictors of candidates for BCT. The morphologic type proved to be the more powerful predictor, probably due to shrinkage patterns.

After NAC, the major problem in the management of breast cancer is defining the extent of residual disease so that appropriate treatment may be undertaken. We reported that CE-CT could determine the extent of the residual cancerous lesions following NAC administration more accurately than other conventional diagnostic methods, such as MMG and US.[7] MRI may also prove to be valuable in defining the extent of

residual disease after NAC.[3,14–17] Many institutions, however, lack the appropriate expertise in breast MRI. CE-CT is advantageous over MRI, as it requires only approximately 5 min for examination. In addition, CE-CT breast images are obtained in the supine position used during surgery, providing precise information about the extent of cancerous tissue in the breast, in a context most useful to the surgeon. In MRI studies, on the other hand, patients are examined in the prone position, minimizing the motion of the breast during breathing. The breast can easily change shape in different positions. The image quality of MRI depends on the performance of the machine and additional complicated technical parameters, making this technique difficult to use as a universal diagnostic procedure. CE-CT also has higher spatial resolution and is less expensive. Finally, the presence of contraindications to MRI, such as patients with pacemakers or serious claustrophobia, makes CE-CT a preferable technique.[18]

Fisher et al showed that patients with IBTR exhibit more distant metastases than patients without IBTR and considered IBTR to be a marker of distant metastasis, rather than a cause.[19] Fortin et al, however, suggested that IBTR should be considered as a source for new distant metastases and an indicator of subsequent mortality by showing the difference in the time distribution of distant metastases for patients with and without IBTR.[20] Recently, a long follow-up retrospective study reported that a high frequency of IBTR occurrence (21.5% at 10 years) after BCT in downstaged patients, as well as IBTR following NAC, is a strong predictor of distant metastases.[21] Multiple re-excision after IBTR may increase the cost and associated trauma in women with breast cancer.[22] To achieve local control, careful selection of patients who may eligible for BCT was suggested. In this study, none of the patients developed IBTR, probably due to the short follow-up time and appropriate preoperative management using CE-CT.

In conclusion, the classification of tumors into either localized or diffuse types using CE-CT prior to NAC administration accurately predicts which tumors will be suitable candidates for BCT following NAC.

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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.* 1998;16:2672–2685.
2. El-Didi MH, Moneer MM, Khaled HM, et al. Pathological assessment of the response of locally advanced breast cancer to neoadjuvant chemotherapy and its implications for surgical management. *Surg Today.* 2000;30:249–254.
3. Abraham D, Jones R, Jones S, et al. Evaluation of neoadjuvant chemotherapeutic response and locally advanced breast cancer by magnetic resonance imaging. *Cancer.* 1996;78:91–100.
4. Ikeda T, Jinno H, Matui A, et al. The role of neoadjuvant chemotherapy for breast cancer treatment. *Breast Cancer.* 2002;9:8–14.
5. Nakamura S, Kenjo H, Nishio T, et al. Efficacy of 3D-MR mammography for breast conserving surgery after neoadjuvant chemotherapy. *Breast Cancer.* 2002;9:15–19.
6. Akashi-Tanaka S, Fukutomi T, Miyakawa K, et al. Diagnostic value of contrast-enhanced computed tomography for diagnosing the intraductal component of breast cancer. *Breast Cancer Res Treat.* 1998;49:79–86.
7. Akashi-Tanaka S, Fukutomi T, Watanabe T, et al. Accuracy of contrast-enhanced computed tomography in the prediction of residual breast cancer after neoadjuvant chemotherapy. *Int J Cancer (Radiat Oncol Invest).* 2001;96:66–73.
8. The Japanese Breast Cancer Society: *General Rules for Clinical and Pathological Recording of Breast Cancer.* 14th ed. Tokyo: Kanehara; 2000.
9. Morrow M, Harris JR: Local management of invasive breast cancer. In: Harris JR, Lippman ME, Morrow M, et al., eds. *Diseases of the Breast,* 2nd ed. Philadelphia: Lippincott Williams & Wilkins; 2000:526.
10. Heys D. Evaluation of breast cancer management: focus on neoadjuvant chemotherapy. *Breast Cancer.* 2001;8:339–350.
11. Fukutomi T. Breast cancer [in Japanese]. In: Kakizoe T, ed. *New Surgical Oncology Operative Techniques.* Tokyo: Medical View, 2001:57.
12. Kuerer HM, Newman LA, Smith TL, et al. Clinical course of breast cancer patients with complete pathologic primary tumor and axillary lymph node response to doxorubicin-based neoadjuvant chemotherapy. *J Clin Oncol.* 1999;17:460–469.
13. Makris A, Powles T, Dowsett M, et al. Prediction of response to neoadjuvant chemoendocrine therapy in primary breast carcinomas. *Clin Cancer Res.* 1997;3:593–600.
14. Gilles R, Guinebretiere J-M, Toussaint C, et al. Locally advanced breast cancer: contrast-enhanced subtraction MR Imaging of response to preoperative chemotherapy. *Radiology.* 1994;191:633–638.
15. Mumtaz H, Davidson T, Spittle M, et al. Breast surgery after neoadjuvant treatment. Is it necessary? *Eur J Surg Oncol.* 1996;22:335–341.
16. Trecate G, Ceglia E, Stabile F, et al. Locally advanced breast cancer treated with primary chemotherapy: comparison between magnetic resonance imaging and pathologic evaluation of residual disease. *Tumori.* 1999;85:220–228.
17. Tsuboi N, Ogawa Y, Inomata T, et al. Changes in the findings of dynamic MRI by preoperative CAF chemotherapy for patients with breast cancer of stage II and III: pathologic correlation. *Oncology.* 1999;6:727–732.
18. Akashi-Tanaka S, Fukutomi T, Miyakawa K, et al. Contrast-enhanced computed tomography diagnosing the intraductal component and small invasive foci of breast cancer. *Breast Cancer.* 2001;8:10–15.
19. Fisher B, Anderson S, Fisher E, et al. Significance of ipsilateral breast tumor recurrence after lumpectomy. *Lancet.* 1991;338:327–331.
20. Fortin A, Larochelle M, Laverdiere J, et al. Local failure is responsible for the decrease in survival for patients with breast cancer treated with conservative surgery and postoperative radiotherapy. *J Clin Oncol.* 1999;17:101–109.
21. Rouzier R, Extra J-M, Carton M, et al. Primary chemotherapy for operable breast cancer: Incidence and prognostic significance of ipsilateral breast tumor recurrence after breast-conserving surgery. *J Clin Oncol.* 2001;19:3828–3825.
22. Esserman L, Hylton N, Yassa L, et al. Utility of magnetic resonance imaging in the management of breast cancer: evidence for improved preoperative staging. *J Clin Oncol.* 1999;17:110–119.

●特 集● 乳癌治療の進歩

乳癌治療における術前化学療法の意義

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要旨 ある程度進行した乳癌を対象として術前化学療法を行うことは，生存率を低下させることなく一部の症例に乳房温存療法の機会を与え得る利点がある。

われわれも1995年5月から2000年12月の間に，腫瘍径3.1～6.0 cmの乳癌86例を対象としてepirubicin含有レジメンによる術前化学療法を行った。奏効例（CR＋PR）は55例（64.0%）で，最終的に64例（74.4%）に乳房温存療法を行い得た。そのうち，CR例は9例であったが，病理学的CRは非浸潤癌の遺残した1例のみであった。観察期間中央値39か月の時点で乳房内再発は9例であり，3 cm以下の乳癌に対する乳房温存療法の場合に比べて高率であった。術前化学療法後の乳房温存療法の局所コントロールに関する安全性については，今後さらに長期のフォローアップ成績の結果を待たねばならない。

The Role of Neoadjuvant Chemotherapy for Breast Cancer Treatment: Hideo Inaji*1, Yoshifumi Komoike*1, Kazuyoshi Motomura*1, Tsutomu Kasugai*2 and Hiroki Koyama*1 (*1*Dept. of Surgery III*, *2*Dept. of Pathology, Osaka Medical Center for Cancer and Cardiovascular Diseases*)

Summary

Neoadjuvant chemotherapy is being used increasingly in the management of patients with breast cancer, especially locally advanced cases. Such treatment is administered with the aim of of reducing the size of the primary tumor to increase the possibility of breast-conserving treatment (BCT). In our series, during the period from May 1995 to December 2000, 86 patients with tumors between 3.1 and 6.0 cm in diameter received epirubicin-based neoadjuvant chemotherapy. There were 55 (64.0%) responders and ultimately 64 patients (74.4%) were treated with BCT. With a median follow-up time of 39 months, 9 patients in the BCT group had developed local recurrence. Long-term follow-up is required to establish whether this procedure is a safe alternative to mastectomy for patients with large breast cancers. **Key words:** Breast cancer, Neoadjuvant chemotherapy, Breast-conserving treatment, Local recurrence, **Address request for reprints to:** Dr. Hideo Inaji, Department of Surgery III, Osaka Medical Center for Cancer and Cardiovascular Diseases, 3-3 Nakamichi 1-Chome, Higashinari-ku, Osaka 537-8511, Japan

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はじめに

ある程度進行した乳癌に対する治療のオプションの一つに術前化学療法 neoadjuvant chemotherapy (primary chemotherapy, preoperative chemotherapy, induction chemotherapy などの用語も同義語として用いられる)が登場してきた。National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18 トライアルの結果，術前化学療法は生存率や健存率を低下させることなく乳房温存療法の適応拡大の機会を増加させ得ることが示され[1]，広く認知されるに至った。わが国でも比較的大きな腫瘍径 (通常 3 cm 以上) の乳癌に対して術前化学療法を取り入れる施設が増えてきた。本稿では，海外での臨床試験の成績ならびにわれわれの行ってきた術前化学療法の preliminary な成績について述べる。

なお，以下に述べる各種臨床試験の成績は，①対象が比較的早期例か，炎症性乳癌を含めた局所進行乳癌 (病期III以上) か？ ②評価対象病変は原発巣のみか，腋窩リンパ節を含むのか？ ③効果判定が触診のみか，画像所見を優先しているか？ ④乳房温存療法の適応拡大を主要評価項目としたトライアルか？ などの点でまちまちであり，相互間の比較は慎重であらねばならないことを最初に断っておきたい。

I．術前化学療法の意義と臨床試験の成績

術前化学療法について，その長所および欠点と考えられる事項を表 1 に列記した。同じ内容の化学療法レジメンを術前あるいは術後に投与する無作為化比較試験として代表的なもの[1-5]を表 2 に整理した。なかでも，NSABP B-18 トライアル[1]は，現時点で最もエビデンスレベルの高いものである。その結果は，術前化学療法が，①生存率，健存率，無遠隔再発生存率 (distant disease free survival) の向上には寄与しない，②局所効果が予後因子として有用である，③乳房温存療法の施行

表 1 術前化学療法の利点と欠点

利　点	欠　点
1）微小転移巣の早期コントロール (理論上)	1）n 状況など病理学的予後因子の欠除
2）化学療法剤の感受性試験	2）PD 例での患者に与えるストレス
3）乳房温存療法の適応拡大	3）over-treatment の可能性

表 2 術前化学療法と術後補助化学療法の無作為化比較試験

報告者 (年)	対　象	レジメン	症例数	BCT 施行率(%)	観察期間 中央値(月)	生存率
Scholl (1994)	stage II, III	CAF → RT → S	200	82	54	p=0.039
		RT → S → CAF	190	77		
Fisher (1998)	stage I, II	AC → S	752	68	60	NS
		S → AC	743	60		
Makris (1998)	stage I～III	MxM (Mi) → S	149	89	48	NS
		S → MxM (Mi)	144	78		
Mauriac (1999)	T>3 cm	EVcM → MiThV → S	134	63	124	NS
		S → EVcM → MiThV	138	0		
Jakesz (2001)	T>3 cm	CMF → S	214	—	—	NS
		S → CMF	209	—		

S: 手術, RT: 放射線治療, BCT: 乳房温存療法, C: cyclophosphamide, A: adriamycin, F: 5-fluorouracil, Mx: mitoxantrone, M: methotrexate, Mi: mitomycin C, E: epirubicin, Vc: vincristine, Th: thiotepa, V: vindesine

表3 術前化学療法でのpCRと健存率

報告者（年）	pCRの率（%）	観察期間	健存率		p
			pCR	pCR以外	
Cameron（1997）	4	8年	88%*	35%*	0.05
Bonadonna（1998）	4（1%DCIS）	8年	86%	37%	0.03
Fisher（1998）	13（4%DCIS）	5年	85%	58%	0.0001
Kuerer（1999）**	12	5年	87%	58%	<0.01
Rouzier（2002）	14	5年	86%	48%	<0.05

*：生存率，**：原発巣，転移リンパ節ともにpCRのもののみをpCRと判定

頻度増加につながる，の3点に要約される。ただ，①に関してはScholl ら[2]のみが術前化学療法群で有意に生存率が高かった（ただし健存率では有意差なし）としているが，一般に生存率の向上には寄与しないとみるべきである。

なお，術前化学療法のレジメンとしてはanthracyclineやmethotrexateをキードラッグとしたレジメンが中心であったが，最近の趨勢としてtaxaneが使用されることが多く，従来のレジメンより高い奏効率が期待されている[6,7]。

なかでも注目されるのはAberdeenグループのトライアルであり，anthracycline含有レジメンによる術前化学療法耐性例にdocetaxelの効果が期待し得る結果を示している[8]。

II. 局所効果と予後

前述のように，術前化学療法の効果判定に当たって，NSABP B-18[1]などのように原発巣のみの二次元的計測により評価しているものもあれば，腋窩リンパ節も評価対象に含める評価基準を採用しているもの[9]もあるので注意を要する。

さて，NSABP B-18でも示されているように臨床的なCR（cCR）群，とりわけ病理学的にCR（pCR）の得られた例での予後が極めて良好であり，同様な結果は他のグループ[10-13]からも報告されている（表3）。なお，腋窩リンパ節転移陽性例で腋窩リンパ節の病理学的CR，すなわち転移リンパ節が消失した例では特に予後が良好であり，腋窩リンパ節への反応性をより重視する報告[13]もある。

術前化学療法の効果予知因子に関する研究も多数のものがあり[14]，有望視されているものも少なくない[14-16]が，未だ決定打といえるものはない。

III. 術前化学療法と乳房温存療法

いうまでもなく術前化学療法の魅力は乳房温存療法に持ち込める症例があることである。2001年開催のSt. GallenでのInternational Consensus Panelでも局所進行乳癌を別にして，やや進行した程度の乳癌に対してはダウンステージング後に乳房温存療法を期待し得る場合にのみその対象を限定すべきであるとしている[17]。

術前化学療法後の乳房温存療法の施行率と局所再発率[4,11-13,18-23]を表4に示す。対象の設定や乳房温存療法を意識したトライアルかどうかでずいぶん内容に差はあるが，腫瘍径3cm以上を対象とした臨床試験に限ると49～90%が乳房温存療法可能となっている。また，局所再発率も一般の乳房温存療法に比べるとやや高率とする報告が多いが許容範囲とみることはできる。

表2に掲げた無作為化比較試験の結果でも，術前・術後化学療法両群の間で局所再発率に有意の差を認めていない。しかし，ここには落とし穴があり，NSABP B-18トライアルでもダウンステージングにより乳房温存し得た症例は，もともと乳房温存療法の適応であった症例に比べて約2倍の局所再発があった点が指摘されている[1]。Institute Curieの最近の報告[24]でも，術前化学療法後の乳房温存療法例での局所再発率は5年16%，10年21.5%であり，やはり通常の乳房温存療法に比べると高率といえる。また，彼ら[24]によると局所再発が遠隔再発の強力な予後因子になり得るとしている。

われわれは，1995年5月以降触診腫瘍径が3.1～

表 4 術前化学療法後に乳房温存療法を行った乳癌の局所再発率

報告者（年）	対象	症例数	乳房温存療法施行率（%）	観察期間中央値（月）	局所再発率（%）
Calais (1994)*	T≧3 cm	158	49	38	8
Schwartz (1994)	stage IIB, III	189	36	46	1
Veronesi (1995)	T≧3 cm	226	90	36**	6
Touboul (1997)*	stage II～IV	147	65	94	20
Merajver (1997)	stage III	89	28	54	14
Bonadonna (1998)	T≧3 cm	536	85	65	7
Danforth (1998)*	stage III	126	33	99	19
Mauriac (1999)*	T>3 cm	134	63	124	28
Kuerer (1999)	stage II～IV	372	29	58	6
Rouzier (2002)***	T>3 cm	174	65	120	24

*: 局所療法として放射線療法単独の例を含む，**: 平均，***: T 1～3 を対象としているが T>3 cm のサブセットに限定した

表 5 大阪府立成人病センターにおける術前化学療法の成績

	化学療法開始前の腫瘍径（cm）			計
	3.1～4.0	4.1～5.0	5.1～6.0	
症例数	42	32	12	86
奏効例（%）	25 (59.5%)	22 (68.8%)	8 (66.7%)	55 (64.0%)
乳房温存例（%）	35 (83.3%)	22 (68.8%)	7 (58.3%)	64 (74.4%)
断端陽性例（%）*	5 (14.3%)	4 (18.2%)	0 (0%)	9 (14.1%)

*: 乳房温存例中の比率 （文献[25]より引用改変）

6.0 cm で，N0～1，M0 の乳癌を対象に術前化学療法を施行し，ダウンステージングが得られた症例に対しては乳房温存療法を施行してきた[25]。術前化学療法の内容は cyclophosphamide 600 mg/m²＋epirubicin 60 mg/m²（CE 療法）であり，一部の症例は 5-FU を追加（CEF 療法）し，原則として 4 サイクル投与した。2000 年 12 月までに登録された症例は 86 例であり，奏効率（CR＋PR）は 55 例（64.0%）で，最終的に 64 例（74.4%）に乳房温存療法を行い得た（表 5）。なお，この 64 例という数字は同期間の乳癌手術総数 1,200 例の 5.3%に該当し，術前化学療法の導入が乳房温存療法の適応拡大につながったと考えられた。大阪府立成人病センターにおける 1986 年以降の乳癌手術術式の変遷と術前化学療法による温存療法施行例の率を図 1 に示す。

奏効例のうち 9 例（10.5%）が cCR であった。pCR は腫瘍消失例のみならず，非浸潤癌巣のみの遺残もその範疇に含めることが多い[1,9]が，そのような広義の pCR 例が 1 例みられた。pCR ではないが病理学的に著効を認めた 1 例の組織像を図 2 に示す。なお，断端陽性率は 14.1%であり（表 5），3 cm 以下の乳癌に対する乳房温存手術の場合とほぼ同率であったが，浸潤癌やリンパ管侵襲での断端陽性例が多いのが特徴であった[25]。観察期間中央値 39 か月の時点で局所再発例は 9 例であり，当センターでの 3 cm 以下の乳癌での乳房温存例の局所再発率（放射線療法併用例で 7.2%）[27]に比べると明らかに高率である。

術前化学療法の効果判定には腫瘍体積の減少だけでなく，乳房温存手術の対象となり得る症例の選別にはその縮小パターンが重要であり，求心性

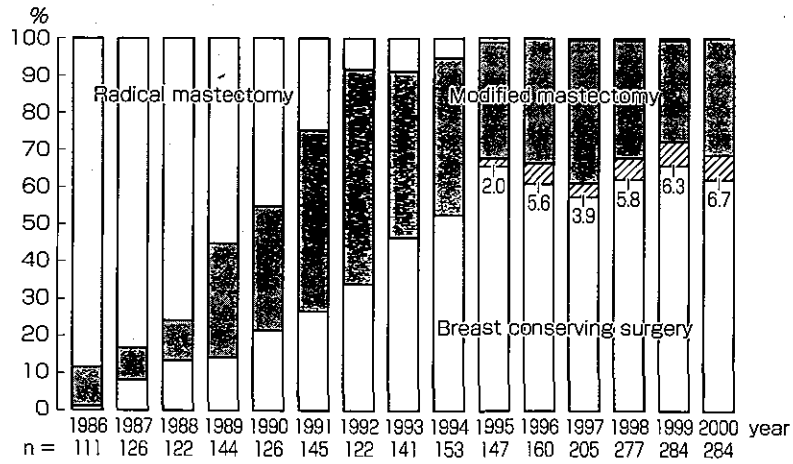

図 1 術前化学療法の乳房温存療法適応拡大への寄与
―大阪府立成人病センターにおける乳癌手術術式の変遷―
▨: 術前化学療法後の乳房温存療法施行頻度

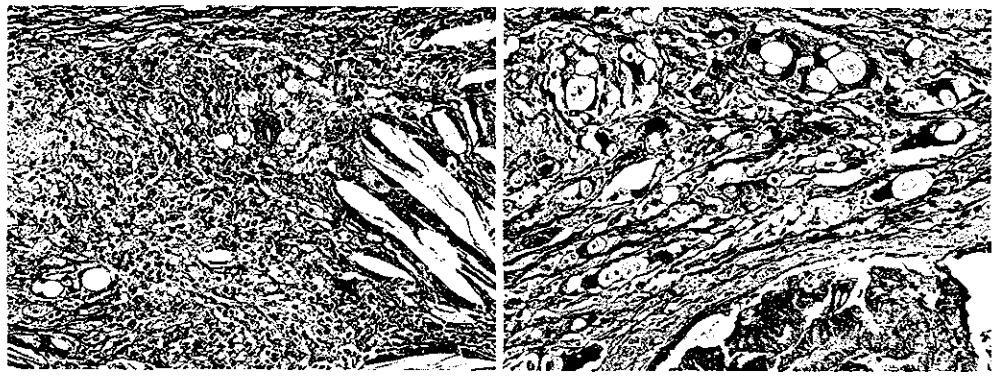

図 2 術前化学療法により病理学的に高度の変化が認められた例
症例は24歳。CE 4サイクル後手術を行ったが，病理学的に高度の変性が認められ組織学的効果は1bと判定された[26]。

の縮小パターンが求められる。微細病変の遺残有無を評価するためにはMRI[28]，CT[29]などの手助けを必要とすることが多い。

なお，局所進行乳癌で術前化学療法後に乳房切除術を行った場合に胸壁への放射線療法なしでは局所・領域リンパ節再発が高頻度でみられるが，特に化学療法後のリンパ節転移個数が重要な予後因子であり，高危険群では胸壁への放射線療法が望ましいとされる[30]。

おわりに

術前化学療法に関して，NSABP B-18での評価項目に沿って，その意義を考察した。術前化学療法の効果判定自体一定の指針はないが，乳癌学会規約委員会でも治療効果判定基準小委員会（大川智彦委員長）を設け，RECIST基準[31]の導入に向けての作業が進行中であることを最後に述べておく。

文 献

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) Scholl SM, Fourquet A, Asselain B, *et al*: Neoadjuvant vs adjuvant chemotherapy in premenopausal patients with tumours considered too large for breast conserving surgery:

preliminary results of a randomised trial: S 6. *Eur J Cancer* **30 A**: 645-652, 1994.
3) Makris A, Powles TJ, Ashley SE, *et al*: A reduction in the requirements for mastectomy in a randomized trial of neoadjuvant chemoendocrine therapy in primary breast cancer. *Ann Oncol* **9**: 1179-1184, 1998.
4) Mauriac L, MacGrogan G, Avril A, *et al*: Neoadjuvant chemotherapy for operable breast carcinoma larger than 3 cm: a unicentre randomized trial with a 124-month median follow-up. *Ann Oncol* **10**: 47-52, 1999.
5) Jakesz R: Comparison of pre -vs. postoperative chemotherapy in breast cancer patients: four-year results of Austrian Breast & Colorectal Study Group (ABCSG) Trial 7. *Proc ASCO # 125, 2001.*
6) Coste D, von Minokwitz G, Raab G, *et al*: The role of docetaxel (taxotere) in neoadjuvant chemotherapy of breast cancer. *Semin Oncol* **26**: 24-31, 1999.
7) Bellino R, Cortese P, Danese S, *et al*: Epidoxorubicin and paclitaxel as primary chemotherapy for T>3 cm and T 4 breast cancer patients. *Anticancer Res* **20**: 4825-4828, 2000.
8) Smith IC, Heys SD, Hutcheon AW, *et al*: Neoadjuvant chemotherapy in breast cancer: Significantly enhanced response with docetaxel. *J Clin Oncol* **20**: 1456-1466, 2002.
9) Kuerer HM, Hunt KK, Newman LA, *et al*: Neoadjuvant chemotherapy in women with invasive breast carcinoma: conceptual basis and fundamental surgical issues. *J Am Coll Surg* **190**: 350-363, 2000.
10) Cameron DA, Anderson EDC, Levack P, *et al*: Primary systemic therapy for operable breast cancer-10-year survival data after chemotherapy and hormone therapy. *Br J Cancer* **76**: 1099-1105, 1997.
11) Bonadonna G, Valagussa P, Brambilla C, *et al*: Primary chemotherapy in operable breast cancer: eight-year experience at the Milan Cancer Institute. *J Clin Oncol* **16**: 93-100, 1998.
12) Kuerer HM, Newman LA, Smith TL, *et al*: Clinical course of breast cancer patients with complete pathologic primary tumor and axillary lymph node response to doxorubicin-based neoadjuvant chemotherapy. *J Clin Oncol* **17**: 460-469, 1999.
13) Rouzier R, Extra J-P, Klijanienko J, *et al*: Incidence and prognostic significance of complete axillary downstaging after primary chemotherapy in breast cancer patients with T1 to T3 tumors and cytologically proven axillary metastatic lymph nodes. *J Clin Oncol* **20**: 1304-1310, 2002.
14) Bhalla K and Harris WB: Molecular and biologic determinants of neoadjuvant chemotherapy of locoreginal breast cancer. *Semin Oncol* **25**: 19-24, 1998.
15) Mankoff DA, Dunnwald LK, Gralow JR, *et al*: Monitoring the response of patients with locally advanced breast carcinoma to neoadjuvant chemotherapy using [technetium 99 m]-sestamibi scintimammography. *Cancer* **85**: 2410-2423, 1999.
16) Takamura Y, Kobayashi H, Taguchi T, *et al*: Prediction of chemotherapeutic response by collagen gel droplet embedded culture-drug sensitivity test in human breast cancers. *Jnt J Cancer* **98**: 450-455, 2002.
17) Goldhirsch A, Glick JH, Gelber RD, *et al*: Meeting highlights: International Consensus Panel on the Treatment of Primary Breast Cancer. *J Clin Oncol* **19**: 3817-3827, 2001.
18) Calais G, Berger C, Descamps P, *et al*: Conservative treatment feasibility with induction chemotherapy, surgery, and radiotherapy for patients with breast carcinoma larger than 3 cm. *Cancer* **74**: 1283-1288, 1994.
19) Schwartz GF, Birchansky CA, Komarnicky LT, *et al*: Induction chemotherapy followed by breast conservation for locally advanced carcinoma of the breast. *Cancer* **73**: 362-369, 1994.
20) Veronesi U, Bonadonna G, Zurrida S, *et al*: Conservation surgery after primary chemotherapy in large carcinomas of the breast. *Ann Surg* **222**: 612-618, 1995.
21) Touboul E, Lefranc J-P, Blondon J, *et al*: Primary chemotherapy and preoperative irradiation for patients with stage II larger than 3 cm or locally advanced non-inflammatory breast cancer. *Radiother Oncol* **42**: 219-229, 1997.
22) Merajver SD, Weber BL, Cody R, *et al*: breast conservation and prolonged chemotherapy for locally advanced breast cancer: The University of Michigan experience. *J Clin Oncol* **15**: 2873-2881, 1997.
23) Danforth DN, Zujewski J, O'Shaughnessy J, *et al*: Selection of local therapy after neoadjuvant chemotherapy in patients with stage IIIA, B breast cancer. *Ann Surg Oncol* **5**: 150-158, 1998.
24) Rouzier R, Extra J-P, Carton M, *et al*: Primary chemotherapy for operable breast cancer: incidence and prognostic significance of

ipsilateral breast tumor recurrence after breast-conserving surgery. *J Clin Oncol* **19**: 3828-3835, 2001.
25) Inaji H, Komoike Y, Motomura K, *et al*: Breast-conserving treatment after neoadjuvant chemotherapy in large breast cancer. *Breast Cancer* **9**: 20-25, 2002.
26) Commitee for Production of Histopathological Criteria, Japanese Breast Cancer Society: Histopathological criteria for assessment of therapeutic response in breast cancer. *Breast Cancer* **8**: 1-2, 2001.
27) Komoike Y, Motomura K, Inaji H, *et al*: Long-term results of breast conserving surgery for stage I and II breast cancer. *Breast Cancer* (in press).
28) Nakamura S, Kenjo H, Nishio T, *et al*: Efficacy of 3 D-MR mammography for breast conserving surgery after neoadjuvant chemotherapy. *Breast Cancer* **9**: 15-19, 2002.
29) Akashi-Tanaka S, Fukutomi T, Miyakawa K, *et al*: Contrast-enhanced computed tomography for diagnosing the intraductal component and small invasive foci of breast cancer. *Breast Cancer* **8**: 10-15, 2001.
30) Buchholz TA, Tucker SL, Masullo L, *et al*: Predictors of local-regional recurrence after neoadjuvant chemotherapy and mastectomy without radiation. *J Clin Oncol* **20**: 17-23, 2001.
31) Therasse P, Arbuck SG, Eisenhauer EA, *et al*: New guidelines to evaluate the response to treatment in solid tumors. *J Natl Cancer Inst* **92**: 205-216, 2000.

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特　集

乳癌手術の現況とその根拠

5. 乳房円状部分切除術

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キーワード　乳癌，乳房円状部分切除術，乳房温存療法，乳房内再発

I. 内容要旨

比較的早期の乳癌に対する乳房温存療法がわが国において開始されすでに10数年が経過し，わが国独自の長期追跡結果もぽつぽつ出されるようになってきた．その細部においてはなおバリエーションがあるもののおおむね「乳房温存療法ガイドライン（1999)」に準拠して，乳房円状部分切除術＋腋窩リンパ節郭清＋放射線療法が標準的乳房温存療法として定着しつつある．ただ，乳房円状部分切除術では無視しえない頻度で断端陽性となりうるので乳房内再発を回避するため万全の策を講ずるべきである．

II. はじめに

乳癌取扱い規約[1]では，乳房温存手術を，乳房扇状部分切除術（以下，扇状部分切除術と略す），乳房円状部分切除術（以下，円状部分切除術と略す），腫瘤摘出術に分類し，円状部分切除術の定義として，「術中の触診上，腫瘤縁より一定の距離をおいて肉眼上正常と思われる乳腺組織に切除線をおく乳腺部分切除で，wide excisionに相当する」と定義されている．海外ではwide excision以外にも多数の用語が使用されるが，その内容が上記定義に該当するものであれば円状部分切除術と同等とみなして扱った．たとえばVeronesiらの言うtumourectomyは事実上free margin 1cmの円状部分切除術（Bp (1cm)）に該当するし，lumpectomy（取扱い規約上は円状部分切除術か腫瘤摘出術か判然としないので用いない方がよいとされている）も通常は円状部分切除術を意味する用語として繁用されている．

本稿では自験例での円状部分切除術の長期成績や，次項で述べられる扇状部分切除術との功罪について述べる．なお手技的な面は「乳房温存療法ガイドライン（1999)[2]」に詳しいので割愛した．

III. 円状部分切除術による乳房温存療法の実状—日本と欧米の比較

わが国における乳房温存療法の施行頻度は今なお増加傾向にあり，乳癌学会の全国調査によると2000年その施行頻度が全乳癌の40.8%に達した[3]．米国では乳房温存療法の対象となりうるI, II期乳癌（全乳癌の約75%）のうち実際に乳房温存療法を受けたものは1994年度の手術例で42.6%と予想外に低率[4]であり，わが国での温存療法の急速な普及には目をみはるものがある．

施行頻度や乳房温存療法の内容自体に施設間格差が依然大きいものの，おおむね乳房温存療法ガイドライン（1999)[2]に準拠して症例の選択や治療内容が決定されるようになってきた．このガイドラインでの適応規準を表1に示すが，腫瘍径（3cm以下）を除き米国で1992年出された乳房温存療法ガイドライン[5]（1998年改定されている[6]が内容はほとんど変わっていない）とほぼ合致した内容である．

術式に関して，欧米の趨勢は円状部分切除術であり，乳房温存手術＝円状部分切除術＋腋窩リンパ節郭清（最近ではセンチネルリンパ節転移陰性例に対して非郭清の選択肢もありうる）と理解して間違いない．その理由は生存率に差がなく美容上円状部分切除術がより有

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表1　乳房温存療法の適応（乳房温存療法ガイドライン（1999）[2]より抜粋）

1. 腫瘤の大きさが3cm以下
2. 各種画像診断で広範な乳管内進展を示す所見（マンモグラフィで広範な悪性石灰化を認めるなど）のないもの
3. 多発病巣のないもの
4. 放射線照射が可能なもの
5. 患者が乳房温存療法を希望すること

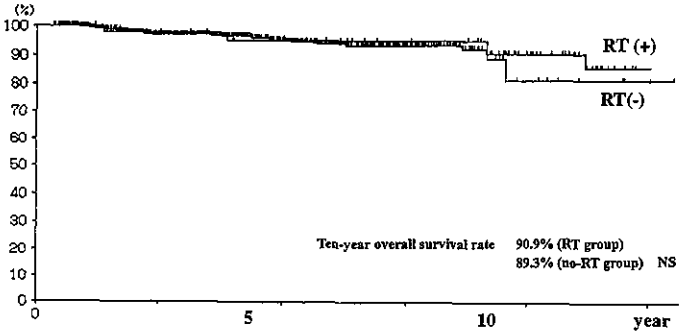

図1　乳房温存療法を行った乳癌の生存率（自験例）
RT(+)：放射線療法併用群
RT(−)：放射線療法非併用群
（文献11）より引用）

利だからである[7]．わが国においては乳房温存療法が開始された当初扇状部分切除術を採用する施設が多かったが，ガイドラインで円状部分切除術が推奨されたこともあって，現在では円状部分切除術（Bp（1〜2cm））＋腋窩リンパ節郭清＋放射線療法が標準的乳房温存療法として位置づけられるようになった．乳癌学会アンケート調査結果[3]で放射線療法併用例が漸増傾向にあるが，これは乳房円状部分切除術が大多数を占めてきていることを裏付けるものであろう．

IV. 円状部分切除術による乳房温存療法の成績

今さら言うまでもないが，National Surgical Adjuvant Breast and Bowel Project（NSABP）B-06[8]をはじめとしたいくつかの無作為化比較試験の結果，円状部分切除術＋腋窩リンパ節郭清±放射線療法からなる乳房温存療法が乳房切除術と同等の生存率をもたらす[6]ことが広く認識されるようになった．また，放射線療法により乳房内再発が有意に減少することもNSABP　B-06のみならず複数の無作為化比較試験のメタアナリシス[9]でも確認されている．円状部分切除術＋放射線療法からなる乳房温存療法での乳房内再発率は10年でおよそ10%前後，すなわち年率約1%であり[6]，この程度を許容範囲とみるべきであろう．

最近の乳房温存療法に関する話題のひとつに乳房内再発と遠隔再発との関係があり，乳房内再発例ではその後の遠隔再発率が有意に高いことが示されている[10]．乳房内再発が遠隔再発の原因になりうるとする直接的根拠はないが，極力局所コントロールも目指すべきことは自明のことである．

なお，大阪府立成人病センターにおける乳房温存療法の成績[11]について触れておくが，術式は円状部分切除術＋腋窩リンパ節郭清であり，大部分の症例に放射線療法がなされた．観察期間中央値は46カ月である．2000年6月までの979例についての10年生存率は放射線療法併用群90.9%，非併用群89.3%で両群間に差を認めず（図1），historical controlと比較して遜色のない結果であった．また，乳房内再発に関与するリスクファクターの多変量解析による検討では，断端陽性，放射線療法非併用および補助内分泌療法非併用が有意の因子であった（表2）．若年者は通常ハイリスクとされるが，自験例では年齢は有意の因子でなかった．有意のリス

表2　乳房内再発に関する有意のリスクファクター（多変量解析）

factors	risk/reference factor	R.R.	p value
surgical margin	positive/negative	5.02	$p < 0.0001$
radiation therapy	yes/no	0.23	$p = 0.0005$
adjuvant endocrine therapy	yes/no	0.25	$p = 0.0019$

RR: relative risk　　（文献[11]より引用）

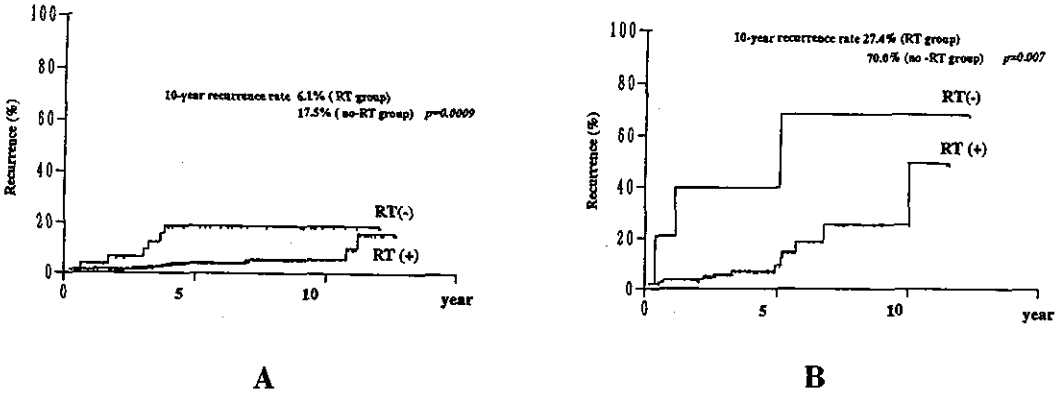

図2　乳房温存療法を行った乳癌の累積乳房内再発率（自験例）
A：断端陰性例　B：断端陽性例
RT(+)：放射線療法併用群
RT(−)：放射線療法非併用群
（文献11）より引用）

クファクターのなかでも断端状況のインパクトは特に大きく，断端陽性例では放射線療法を行ってもなお乳房内再発率は高率であった．断端陽性群および陰性群における累積乳房内再発率を放射線療法の有無別に図2に示す．なお，両群間での生存率に差は認めていない．

V. 乳房切除範囲と癌遺残

Hollandら[12]は乳房切除術を行った腫瘍径2cm以下の乳癌での病理学的検索から主病巣から2cm以上はなれた部位に癌が存在したものが42%あり，その1/3が浸潤癌であったと報告している．したがって，surgical marginを大きくすることにより癌遺残の可能性は小さくなるが美容的にはより不利になるというtrade-offの現象は乳房温存療法のひとつのジレンマといえよう．

円状部分切除術と扇状部分切除術との無作為化比較試験としてはMilan IIトライアル[13]が有名であり，この比較試験では生存率こそ両群間で差はなかったものの乳房内再発は年率で，扇状部分切除術＋放射線療法(QUA. RT)の群0.46%に対して円状部分切除術＋放射線療法(T.A.RT)の群では2.45%と有意に高率であった．ただ，このトライアルでは両群とも断端を陰性とするための追加切除等は一切なされておらず（事実T.A. RT群において断端陽性率が高い），断端陰性を心がけるならば，乳房内再発率はさらに低率に抑えられるはずと考えられる．

VI. より高い局所コントロールを目指して

生存率に差がない以上局所コントロールに乳房温存療法の成否がかかっているわけであり，局所コントロールには腫瘍側因子よりもむしろ治療側因子（断端陽性となることも含めて）の影響が大きいことをすでに述べた．局所コントロールに向けて重要なことは，まず組織学的断端陰性を心がけることであり，MRIなどを含む術前画像診断での正確な拡がり診断や，術中・術後の適切な断端診断（病理，細胞診）が要求される．ただ，断端陽性の定義にもよるが厚生労働省がん研究

助成金坂元班での共同研究では断端陽性率19.0%(判定は各施設の基準による)であり[4]，自験例でも14.1%[11]であることから，やはり10～20%程度の断端陽性例が出ることは覚悟せねばならない．それでもなお遺残する微小病変に対しては放射線療法でのブースト照射や補助療法（ことに内分泌療法）の効果に期待をかけるべきであるが，勿論断端陽性の程度次第では再切除(乳房切除への変更も含めて）もありうる．最近，腫瘍床へのブースト照射の意義がEuropean Organization for Research and Treatment of Cancer（EORTC）無作為化比較試験で実証された[15]ので断端陽性例は当然その対象とすべきであろう．

VII. おわりに

わが国における乳房温存療法は今なお増加の傾向にあるが，その根幹をなす乳房温存手術の内容自体が縮小の傾向にある．畢竟，乳房切除範囲の大小というよりは断端をいかに陰性に近づけるかにその成否がかかっていることをあらためて銘記すべきであろう．

厚生労働省がん研究助成金「長期の追跡結果に基づく乳癌に対する適正な乳房温存療法の確立に関する研究」班（稲治班）においてわが国の乳房温存療法の長期成績が出される予定であるが，その成績をみながら，さらに改良を重ねていくべきであろう．現行の乳房温存療法ガイドラインの表題の後にあえて（1999）と付記されているように，このガイドラインはあくまで1999年の時点での指針であり，今後とも流動的に軌道修正してゆくべきものであろう．

文　献

1) 日本乳癌学会：臨床・病理　乳癌取扱い規約（第14版）金原出版，東京，2000.
2) 日本乳癌学会学術委員会：乳房温存療法ガイドライン（1999）教育広報社，1999.
3) The Japanese Breast Cancer Society : Results of questionnaires concerning breast cancer surgery in Japan : an update in 2000. Breast Cancer, 9 : 1, 2002.
4) Morrow M, White J, Moughan J, et al. : Factors predicting the use of breast-conserving therapy in stage I and II breast carcinoma. J Clin Oncol 19:2254—2262, 2001.
5) Winchester DP, Cox JD : Standards for breast-conservation treatment. CA Cancer J Clin, 42 : 134—176, 1992.
6) Winchester DP, Cox JD : Standards for diagnosis and management of invasive breast carcinoma. CA Cancer J Clin. 48 : 83—107, 1998.
7) Clough KB : Surgical techniques in breast conservation. Eur J Cancer, 38 (suppl 3) : S16—18, 2002.
8) Fisher B, Anderson S, Redmond C, et al. : Reanalysis and results after 12 years of follow-up in a randomized clinical trial comparing total mastectomy with lumpectomy with or without irradiation in the treatment of breast cancer. N Engl J Med, 333 : 1456—1461, 1995.
9) Early Breast Cancer Trialists' Collaborative Study Group : Favorable and unfavorable effects on long-term survival of radiotherapy for early breast cancer: An overview of the randomized trials. Lancet, 355 : 1757—1770, 2000.
10) Fisher ER, Anderson S, Tan-Chiu E, et al. : Fifteen-year prognostic discriminants for invasive breast carcinoma. National Surgical Adjuvant Breast and Bowel Project Protocol-06. Cancer, 91 : 1679—1687, 2001.
11) Komoike Y, Motomura K, Inaji H, et al. : Long-term results of breast conserving surgery for stage I or II breast cancer. Experiences at Osaka Medical Center for Cancer and Cardiovascular Diseases. Breast Cancer, 9 : 248—253, 2002.
12) Holland R, Veling SHJ, Mravunac M, et al. : Histologic multifocality of Tis, T1—2 breast carcinoma. Implications for clinical trials of breast-conserving surgery. Cancer, 56 : 979—990, 1985.
13) Veronesi U, Salvadori B, Luini A, et al. : Breast conservation is a safe method in patients with small cancer of the breast. Long-term results of three randomized trials on 1973 patients. Eur J Cancer, 31A : 1574—1579, 1995.
14) 大住省三：わが国の放射線治療併用の乳房温存療法．臨外，57 : 289—295, 2002.
15) Bartelink H, Horiot J-C, Poortmans P, et al. : Recurrence rates after treatment of breast cancer with standard radiotherapy with or without additional radiation. N Engl J Med, 345 : 1378—1387, 2001.

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Breast-conserving treatment has become the standard treatment for early breast cancer, not only in Western countries but also in Japan. Wide excision is perferred to quadrantectomy because the former results in better cosmesis than the latter. However, the margin status may be positive more frequently in the former than in the latter. The results of our study indicated that positive margins and the absence of radiotherapy or endocrine therapy proved to be independent risk factors for local recurrence. Because margin status influences local control, tumor margins after wide excision should be accurately determined, and higher doses of radiotherapy and adjuvant therapy are indicated for patients with positive margins.