The Breast (2007) 16, 482–488

ELSEVIER

THE BREAST

www.elsevier.com/locate/breast

ORIGINAL ARTICLE

# Favorable outcome in patients with breast cancer in the presence of pathological response after neoadjuvant endocrine therapy ☆

**Sadako Akashi-Tanaka[a,*], Mutsuko Omatsu[b,d], Chikako Shimizu[c], Masashi Ando[c], Kotoe Terada[a], Tadahiko Shien[a], Takayuki Kinoshita[a], Yasuhiro Fujiwara[c], Kunihiko Seki[b], Tadashi Hasegawa[b,d], Takashi Fukutomi[a,e]**

[a]*Division of Breast Surgery, National Cancer Center Hospital, 1-1 Tsukiji 5-chome, Chuo-ku, Tokyo 104-0045, Japan*
[b]*Division of Pathology, National Cancer Center Research Institute, Tokyo, Japan*
[c]*Division of Medical Oncology, National Cancer Center Hospital, Tokyo, Japan*
[d]*Department of Surgical Pathology, Sapporo Medical University School of Medicine, Sapporo, Japan*
[e]*Department of Breast and Endocrine Surgery, Aichi Medical University, Aichi, Japan*

Received 21 September 2006; received in revised form 6 January 2007; accepted 6 February 2007

**KEYWORDS**
Breast cancer;
Ki-67;
Neoadjuvant endocrine therapy;
Pathological response;
Prognostic factor

**Summary** Neoadjuvant endocrine therapy (NAET) can expand the number of breast cancer patients who can be treated with breast-conserving surgery and can predict benefit from adjuvant endocrine therapy. Because no validated surrogate markers for long-term outcome have been established, we conducted prospective trials to evaluate pathological response and Ki-67 index following treatment with tamoxifen or anastrozole. The study population included postmenopausal women with operable breast tumors that were both estrogen and progesterone receptor-positive and larger than 3 cm. Response was classified as pathological response (minimal response or better) and non-response. Non-responding (25.5%, vs. response 85.9%, $p = 0.002$), axillary node-positive (58.4% vs. node negative 100%, $p = 0.045$), and high pretreatment Ki-67 index (41.4% vs. low Ki-67 87.1%, $p = 0.03$) patients were significantly associated with poor 5-year relapse-free survival. Multivariate analysis of relapse-free survival indicated that pathological response was independent. Therefore, pathological response may be a favorable prognostic factor after NAET.


☆ Supported in part by Grants for Scientific Research from the Expenses for Health and Welfare Program (17-7) and for Research on Advanced Medical Technology (H-14 toxico–007) from the Ministry of Health, Labour and Welfare of Japan.
*Corresponding author. Tel.: +81 3 3542 2511; fax: +81 3 3542 3815.
*E-mail address:* sakashi@ncc.go.jp (S. Akashi-Tanaka).

0960-9776/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.breast.2007.02.003

## Introduction

With the recent development of aromatase inhibitors, neoadjuvant endocrine therapy (NAET) has attracted attention as a potentially effective therapy that might allow breast conservation even in women with large breast tumors[1–4]. In addition, NAET offers the possibility of testing therapeutic efficacy *in vivo*, which is of great importance for optimal adjuvant treatment. However, the short history of NAET leaves several questions to be answered. First, short-term surrogate markers of subsequent risk of relapse and death from breast cancer have not been established for NAET[5]. Recently, early changes in Ki-67 have been reported to be possible predictors of long-term outcome[6–8]. The short-term reduction in Ki-67 levels in NAET (in the IMPACT trial) paralleled that observed in patients who received the same endocrine therapy in the adjuvant setting (ATAC); this suggested that the changes in Ki-67 in NAET might be predictive of long-term outcome[7]. However, these data were not obtained in direct long-term follow-up studies of NAET. Second, classifications of pathological therapeutic response, which have been mainly produced based on pathological changes following chemotherapy or radiotherapy, have not been validated for tumors treated by NAET. We conducted a small study to clarify the significance of the classification of pathological therapeutic response and the Ki-67 index as prognostic factors of long-term outcome in response to NAET.

## Patients and methods

This analysis includes 45 postmenopausal women with operable estrogen and progesterone receptor (ER and PgR)-positive breast tumors that were larger than 3 cm as confirmed by core needle biopsy. These women were enrolled in two-phase II studies on NAET at the National Cancer Center Hospital (NCCH), Tokyo. Between February 1999 and July 2002, 31 patients were enrolled in a neoadjuvant tamoxifen study (neo TAM), in which they received tamoxifen for 4 months preoperatively. Between November 2002 and 2004, 17 patients were enrolled in a neoadjuvant anastrozole study (neo ANZ), in which they received anastrozole for 5 months preoperatively. Three patients in the neo TAM group were excluded from this analysis because they received preoperative chemotherapy following NAET and their tumors could not be evaluated for pathological response to endocrine therapy; two of these patients rejected mastectomy when there was no reduction of their tumors by NAET. These patients received chemotherapy with the hope that their tumors might shrink enough to allow breast-conserving surgery. Unfortunately, their tumors remained widespread in a mosaic pattern and they finally agreed to mastectomies. The third patient showed progressive disease, which led to skin invasion, and received chemotherapy before surgery. All patients provided written informed consent for study participation as approved by the institutional review board of the NCCH. Patients who responded to NAET continued the same endocrine therapy postoperatively for 5 years. Patients who showed clinically progressive disease or stable disease and pathological lymph node involvement after NAET received adjuvant chemotherapy, if tolerable, with a regimen containing anthracycline or classical CMF (cyclophosphamide, methotrexate, and 5-fluorouracil) following surgery. All patients who underwent breast-conserving surgery received postoperative radiotherapy to the ipsilateral breast.

### Tumor response

Primary tumors were clinically assessed every month. Clinical complete response (cCR) was defined as the clinical disappearance of the tumor at the end of NAET, and clinical partial response (cPR) was defined as a $\geqslant$70% decrease from baseline of the largest diameter[9]. Clinical progressive disease was defined as a $\geqslant$20% increase from the most reduced size of the largest diameter. If progressive disease was observed, patients immediately underwent radical mastectomy.

### Outcome measures

Relapse-free survival (RFS) was defined as the time from the initiation of treatment to local, regional, or distant treatment failure.

### Histological examination

Evaluation of ER and PgR status was by immunohistochemical studies using antibodies 1D5 and PgR636 (DAKO, Glostrup, Denmark), and tumors with more than 10% strongly stained nuclei were described as ER- or PgR-positive. Tumors obtained by core needle biopsy judged as positive for both receptors before treatment were eligible for this study. HER2 status was evaluated immunohistochemically using HercepTest (Dako), and 3+: strong complete membrane staining in >10% of tumor cells was defined as positive.

Ki-67 was stained using the MIB-1 antibody (DAKO) according to previously described methodology[10]. Ki-67 was scored as the percentage of positively stained cells among 1000 malignant cells in specimens obtained by either core needle biopsy before treatment (baseline) or by surgery after NAET. The cut-off value for Ki-67 positivity was defined as the median value of the Ki-67 index in this study population. The proportional change in Ki-67 expression from baseline was calculated as (residual Ki-67 index—pretreatment Ki-67 index) × 1/pretreatment Ki-67 index[7].

Histopathological therapeutic response was classified according to the General Rules for the Clinical and Pathological Recording of Breast Cancer 2005[11]. For Grade 0, no response was observed; Grade 1a comprised those tumors with mild changes in cancer cells regardless of the area, or marked changes seen in less than one-third of cancer cells; Grade 1b comprised tumors with marked changes seen in more than one-third but less than two-thirds of tumor cells; Grade 2 tumors contained marked changes in more than two-thirds of tumor cells; and Grade 3 tumors demonstrated a complete response, with no cancerous cells remaining. Mild changes include slight degenerative changes in cancer cells not suggestive of cancer cell death (including cancer cells with vacuolation of the cytoplasm, eosinophilic cytoplasm, swelling of the nucleus, etc). Marked changes include marked degenerative changes in cancer cells suggestive of cancer cell death (including liquefaction, necrosis, and disappearance of cancer cells). The pathological response group was defined as tumors with Grade1a, 1b, and 2 responses. The non-response group was defined as tumors with Grade 0 response.

## Statistical analysis

The $\chi^2$ test was used for comparisons of tumor characteristics and responses among groups. The Kaplan–Meier methods were used to generate RFS curves. The log rank test was used for the comparison of RFS between two groups. Differences with $p<0.05$ were considered to be significant.

**Table 1** Characteristics of patients and tumors treated with tamoxifen (neo TAM group) and anastrozole (neo ANZ group).

| | Neo TAM group ($n=28$) | Neo ANZ group ($n=17$) | |
|---|---|---|---|
| Age | 60 (51–75) | 61 (54–87) | |
| Tumor before NAET | | | |
| T2 | 18 | 11 | |
| T3 | 7 | 4 | NS |
| T4 | 3 | 2 | |
| Clinical response | | | |
| CR | 1 | 3 | |
| PR | 12 | 10 | |
| NC | 15 | 4 | $p=0.05$ |
| PD | 0 | 0 | |
| Surgery | | | |
| Mastectomy | 17 | 13 | |
| BCS | 11 | 4 | NS |
| Pathological response | | | |
| Grade 2 | 3 | 3 | |
| Grade 1b | 4 | 2 | |
| Grade 1a | 11 | 11 | $p=0.02$ |
| Grade 0 | 10 | 1 | |
| Axillary nodal status | | | |
| Negative | 7 | 6 | |
| 1–3 | 12 | 7 | NS |
| 4–9 | 7 | 3 | |
| >10 | 2 | 1 | |

NAET: neoadjuvant endocrine treatment; CR: complete response; PR: partial response; NC: no change; PD: progressive disease; NS: not significant; BCS: breast-conserving surgery.

## Results

Tumor and patient characteristics in the neo TAM and neo ANZ groups are shown in Table 1. The clinical response rates (cCR+cPR) for the neo TAM and neo ANZ groups were 46.4 and 76.5%, respectively. Of the neo ANZ group, only four patients underwent breast-conserving surgery, because some patients with good clinical responses chose mastectomies and refused postoperative radiotherapy. Patients treated with neo ANZ showed a statistically significantly higher rate of pathological

**Table 2** Tumor characteristics and responses to NAET stratified by patients with events and those without events.

| | Non-response group ($n = 11$) | Pathological response group ($n = 34$) | |
|---|---|---|---|
| Age | 57 (51–73) | 61 (52–87) | |
| Tumor before NAET | | | |
| T2 | 9 | 20 | |
| T3 | 1 | 10 | |
| T4 | 1 | 4 | NS |
| Histological grade before NAET | | | |
| Grade 1 | 1 | 8 | |
| Grade 2 | 6 | 15 | |
| Grade 3 | 4 | 9 | NS |
| Not available | 0 | 2 | |
| HER2 status before NAET | | | |
| Negative | 11 | 34 | |
| Positive | 0 | 1 | NS |
| NAET | | | |
| Tamoxifen | 10 | 18 | |
| Anastrozole | 1 | 16 | NS |
| Clinical response | | | |
| CR | 0 | 4 | |
| PR | 4 | 18 | |
| NC | 7 | 12 | NS |
| PD | 0 | 0 | |
| Ki-67 index before NAET | | | |
| High | 6 | 17 | |
| Low | 5 | 17 | NS |
| Residual Ki-67 index | | | |
| High | 7 | 16 | |
| Low | 4 | 18 | NS |
| Proportional reduction of Ki-67 index | | | |
| Median($Q_1$–$Q_3$) | −0.05 (−0.67–0.37) | −0.46 (−0.85–0.83) | NS |
| Lymphovascular invasion | | | |
| Negative | 9 | 28 | |
| Positive | 2 | 6 | NS |
| Axillary nodal status | | | |
| Negative | 2 | 11 | |
| 1–3 | 6 | 13 | |
| 4–9 | 1 | 9 | |
| >10 | 2 | 1 | NS |
| Adjuvant therapy | | | |
| Endocrine only | 5 | 20 | |
| Chemotherapy added | 6 | 14 | NS |

$Q_1$: first quartile; $Q_3$: third quartile.

response (Grades 1+2) than those treated with neo TAM ($p = 0.02$).

Tumor characteristics stratified by patients with pathological response or non-response are shown in Table 2. There were no statistically significant differences in tumor size, histological grade, HER2 status, clinical response, lymphovascular invasion, pathological nodal status, or addition of adjuvant chemotherapy between these groups. Reduction of Ki-67 was not significantly associated with either pathological or clinical response.

The median follow-up time after NAET was 44.7 months. There were 11 locoregional and/or metastatic events during this time. No ipsilateral breast tumor recurrence was observed after breast-conserving surgery. Patients with pathological non-response (25.5%, vs. response group 85.9%, $p = 0.002$; Fig. 1), axillary node positivity (58.4% vs. node negative 100%, $p = 0.045$), addition of adjuvant chemotherapy (41.2% vs. only endocrine therapy 77.5%, $p = 0.01$), and high pretreatment Ki-67 index (41.4% vs. low Ki-67 index 87.1%, $p = 0.03$; Fig. 2) were significantly associated with poor 5-year RFS. Initial T category, histological grade, clinical response, type of endocrine therapy, presence of reduction in Ki-67 values, and lymphovascular invasion was not associated with survival.

The median follow-up time for the neo TAM group was 65.8 months. In this group, patients with pathological non-response (28.0%, vs. response group 88.2%, $p = 0.006$; Fig. 3), axillary node positivity (59.9% vs. node-negative 100%), addition of adjuvant chemotherapy (43.2%, vs. only endocrine therapy 77.8%, $p = 0.03$), and high residual Ki-67 index (44.0%, vs. low Ki-67 index 100%, $p = 0.01$) were significantly associated with poor 5-year RFS.

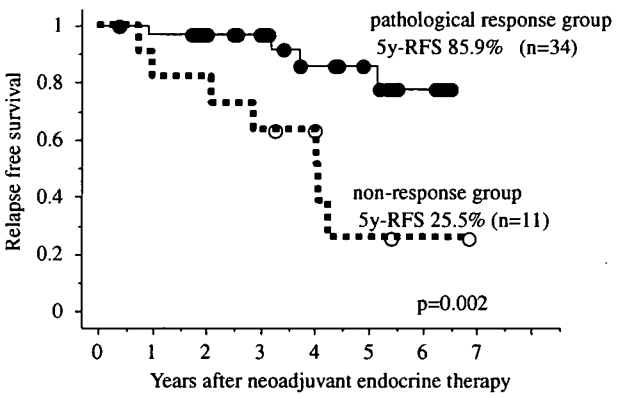


**Figure 1** Relapse-free survival curves following neoadjuvant endocrine therapy stratified into a pathological response group (—) and a non-response group (- - -). A statistically significant difference was observed between the groups ($p = 0.002$).

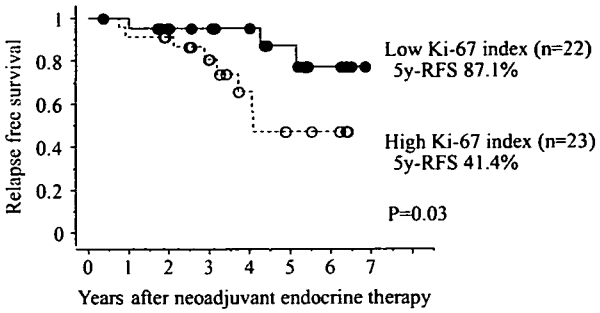


**Figure 2** Relapse-free survival curves following neoadjuvant endocrine therapy stratified into a low pretreatment Ki-67 index group (—) and a high Ki-67 index group (- - -). A statistically significant difference was observed between the groups ($p = 0.03$).

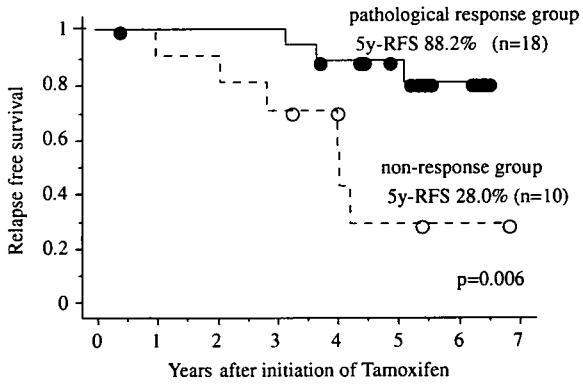


**Figure 3** Relapse-free survival curves following neoadjuvant endocrine therapy using tamoxifen stratified into a pathological response group (—) and a non-response group (- - -). A statistically significant difference was observed between the groups ($p = 0.006$).

The median follow-up time for the neo ANZ group was 30.0 months. The pathological response group achieved statistically better 3-year RFS than the non-response group (93.3% vs. 0%, $p < 0.0001$).

Multivariate regression analyses using a logistic regression model were conducted to identify independent prognostic factors for RFS (Table 3). These analyses indicated that pathological response ($p = 0.007$) was significantly related to RFS.

## Discussion

Although the sample sizes in this study are small, the pathological response group showed significantly more favorable outcomes than the non-pathological response group following NAET. This result is supported by all of the analyses conducted in this study and suggests that the pathological therapeutic response may be a prognostic factor for

**Table 3** Multivariate analysis for RFS after NAET.

| | | Hazard ratio (95%CI) | *p*-value |
|---|---|---|---|
| Pathological response | Non-response/response | 6.3 (1.6–23.8) | 0.0067 |
| Pretreatment Ki-67 | Low/high | 0.26 (0.055–1.17) | 0.079 |
| Residual Ki-67 | Low/high | 0.65 (0.14–2.98) | 0.58 |

RFS: relapse-free survival; CI: confidence interval.

long-term outcome following NAET. The response necessary for a favorable prognosis seems to differ between neoadjuvant chemotherapy and NAET. In the neoadjuvant cytotoxic chemotherapy setting, where response (pCR or not) is a clinically significant predictor of outcome[12], long-term outcome following treatment with cytostatic agents can be predicted based on the achievement of minimal pathological change. Using chemotherapy, total killing of cancer cells is necessary to improve prognosis; therefore, physicians should pursue regimens that will reach the highest pCR rates possible. On the other hand, only a few patients have been reported to achieve pCR following NAET[3]. This is one reason for hesitation in using endocrine agents in a neoadjuvant setting. However, with endocrine therapy, minimal pathological changes may have the same power to improve prognosis.

In this study, low Ki-67 index before NAET in all cases and low residual Ki-67 index in the neo TAM group were significant favorable prognostic factors. Ki-67 has been reported to carry modest prognostic significance and the residual (after treatment) level of Ki-67 may be a better predictor of response and/or absolute long-term outcome than the proportional reduction in Ki-67 because it is more likely to relate to the growth rate of the persistent disease[13]. The results of this study are concordant with these results. The results of the IMPACT trial supported the hypothesis that a reduction of Ki-67 in NAET might be predictive of long-term outcome, but this was not demonstrated in this study. As Urruticoechea has reported that a change in Ki-67 score of at least 32–50% between two determinations using core needle biopsies is required to consider the difference statistically different for an individual patient and attributable to treatment effects[13], the problem with the reproducibility of Ki-67 measurements must be overcome.

Patients who underwent additional adjuvant chemotherapy showed a statistically significant reduction in RFS compared with those who underwent only endocrine therapy. Selection bias must be considered, as most of the patients with positive lymph nodes were treated with chemotherapy. However, whether or not the chemotherapy was efficacious remains controversial because hormone-sensitive breast cancer is less responsive to chemotherapy[14,15]. Further investigations are required to determine the best treatment plan for such cases.

Neoadjuvant chemotherapy has now been established as one of the standard treatments for operable breast cancer. On the other hand, there is less evidence on NAET than on neoadjuvant chemotherapy, including long-term outcome. In this situation, NAET should be used to treat selected patients who will obtain great benefit from endocrine therapy and will not respond to chemotherapy and/or do not need chemotherapy. Without a doubt, hormone receptor status is the first eligibility criterion. Many studies on neoadjuvant chemotherapy have confirmed that hormone-sensitive tumors show worse responses to chemotherapy than hormone-resistant tumors[14,15]. However, not all hormone-sensitive tumors respond to endocrine therapy, underscoring the need for additional predictive tests. Gene analysis can be used as a second eligibility criterion. A multigene assay (Oncotype DX)™ succeeded in predicting that approximately half of the women with node-negative, hormone receptor-positive breast cancer who were treated with local therapy and tamoxifen have an excellent prognosis, with more than 90% having 10-year relapse-free survival; these patients are unlikely to benefit from chemotherapy[16,17]. A more favorable response and long-term outcome without severe adverse events may be achieved with only hormone therapy using gene expression profiles to select patients who are good candidates for NAET.

This study suggests that pathological response is a favorable prognostic factor following NAET. We await validation of these results in large studies such as the IMPACT trial or Letrozole P024 to establish the surrogate markers that predict the risk of recurrence.

## References

1. Smith IE, Dowsett M, Ebbs SR, et al. Neoadjuvant treatment of postmenopausal breast cancer with anastrozole,

tamoxifen, or both in combination: the Immediate Preoperative Anastrozole, Tamoxifen, or Combined with Tamoxifen (IMPACT) multicenter double-blind randomized trial. *J Clin Oncol* 2005;**23**(22):5108–16.
2. Ellis MJ, Coop A, Singh B, et al. Letrozole is more effective neoadjuvant endocrine therapy than tamoxifen for ErbB-1- and/or ErbB-2-positive, estrogen receptor-positive primary breast cancer: evidence from a phase III randomized trial. *J Clin Oncol* 2001;**19**(18):3808–16.
3. Semiglazov VF, Semiglazov VV, Ivanov VG, et al. Neoadjuvant endocrine therapy: exemestane(E) vs tamoxifen (T) in postmenopausal ER+ breast cancer patients. *Breast Cancer Res Treat* 2003;**82**(Suppl 1):S22.
4. Cataliotti L, Buzdar A, Noguchi S, et al. Comparison of anastrozole versus tamoxifen as preoperative therapy in postmenopausal women with hormone receptor-positive breast cancer: the pre-operative "Arimidex" compared to Tamoxifen (PROACT) trial. *Cancer* 2006;**106**(6):2095–103.
5. Dixon JM. Role of endocrine therapy in the neoadjuvant surgical setting. *Ann Surg Oncol* 2004;**11**(1 Suppl):18S–23S.
6. Ellis MJ. Neoadjuvant endocrine therapy for breast cancer: more questions than answers. *J Clin Oncol* 2005;**23**(22): 4842–4.
7. Dowsett M, Smith IE, Ebbs SR, et al. Short-term changes in Ki-67 during neoadjuvant treatment of primary breast cancer with anastrozole or tamoxifen alone or combined correlate with recurrence-free survival. *Clin Cancer Res* 2005;**11**:951s–8s.
8. Tao Y, Klause A, Vickers A, et al. Clinical and biomarker endpoint analysis in neoadjuvant endocrine therapy trials. *J Steroid Biochem Mol Biol* 2005;**95**:91–5.
9. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. *J Natl Cancer Inst* 2000;**92**(3):205–16.
10. Johnston SR, Boeddinghaus IM, Riddler S, et al. Idoxifene antagonizes estradiol-dependent MCF-7 breast cancer xenograft growth through sustained induction of apoptosis. *Cancer Res* 1999;**59**(15):3646–51.
11. Japanese Breast Cancer Society. General rules for clinical and pathological recording of breast cancer 2005. Histopathological criteria for assessment of therapeutic response in breast cancer. *Breast Cancer* 2005;**12 Suppl**:s12.
12. Fisher B, Bryant J, Wolmark N, Mamounas E, Brown A. Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. *J Clin Oncol* 1998;**16**:2672–85.
13. Urruticoechea A, Smith IE, Dowsett M. Proliferation marker Ki-67 in early breast cancer. *J Clin Oncol* 2005;**23**(28): 7212–20.
14. Kaufmann M, von Minckwitz G, Rody A. Preoperative (neoadjuvant) systemic treatment of breast cancer. *Breast* 2005;**14**(6):576–81.
15. Chang J, Powles TJ, Allred DC, et al. Biologic markers as predictors of clinical outcome from systemic therapy for primary operable breast cancer. *J Clin Oncol* 1999;**17**(10): 3058–63.
16. Paik S, Shak S, Tang G, et al. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. *N Engl J Med* 2004;**351**(27):2817–26.
17. Paik S, Tang G, Shak S, et al. Gene expression and benefit of chemotherapy in women with node-negative, estrogen receptor-positive breast cancer. *J Clin Oncol* 2006;**24**(23): 3726–34.

原著

2007.3.5受付

# Intracystic papillary carcinoma (ICPC) の診断と臨床的特徴
## —自験例14例からの検討—

赤木智徳*1　木下貴之*1　枝園忠彦*1　北條　隆*1
明石定子*1

**Clinical and Pathological Features of Intracystic Papillary Carcinoma (ICPC) of The Breast**：Akagi T*1, Kinoshita T*1, Shien T*1, Hojo T*1 and Akashi S*1 (*1Breast surgery division, National cancer center hospital)

Background：Intracystic papillary carcinoma (ICPC) of the breast is rare and preoperative diagnosis is difficult. Materials and Methods：This study investigated the clinical and pathological features of ICPC. Fourteen ICPC were included in this study. We reviewed their clinicopathological findings and treatments. Results：In 9 cases, diagnoses of ICPC were obtained using fine needle aspiration and core needle biopsy. In 5 cases, a diagnosis could not be obtained preoperatively. MRI in addition to sonography helped to establish the differential diagnosis from benign tumor and maintain disease-free surgical margins. Conclusion：Preoperative diagnosis of ICPC is difficult and excisoinal biopsy was necessary unless fine needle aspiration and core needle biopsy can obtain the diagnosis. MRI is available to diagnose the invasiveness of this disease.

**Key words**：Intracystic papillary carcinoma, Preoperative diagnosis
*Jpn J Breast Cancer* **22** (4)：280～285, 2007

## はじめに

Intracystic papillary carcinoma (ICPC) は乳癌全体の約2％弱[1]とまれな疾患である．現在の乳癌取扱い規約では非浸潤性乳管癌ductal carcinoma *in situ* (DCIS) に含まれ，線維性の壁に囲まれた内腔へ乳頭状に突出し発育する乳癌で，通常周囲間質に高度の浸潤を伴わないとされる[2]．しかし，組織学的に嚢胞壁外や乳管内での高度の進展を示す例[3]や，同時性肝転移例[4]などの報告もある．また良性嚢胞腫瘍との鑑別が困難である．今回われわれは，ICPCの14例を経験したので臨床病理学的検討とともに若干の文献的考察を加えて報告する．

## 1. 対象と方法

2000年10月から2006年12月まで当科で経験した原発性乳癌は約2,700症例，そのうちICPCと診断されたのは14例0.51％であった．この14例において臨床病理学的特徴，予後を検討し，さらに免疫組織染色によりホルモンレセプター，HER2，p53を評価した．

## 2. 結　果

### 1) 臨床的特徴（表1）

年齢は中央値72.5歳（36～82歳）で，14人のうち1人が男性，女性13人のうち3例が閉経前，10例は閉経後であった．主訴は全例乳房腫瘤で，自己発見が13例，検診発見が1例で，腫瘍径の中央値は25.5mm（11～220mm）であった．占拠部位はA領域に7例，B領域に1例，C領域に2例，D

*1 国立がんセンター中央病院乳腺外科

表1　Intracystic papillary carcinomaの臨床的特徴および診断

| 症例 | 年齢・性 | 病悩期間(月) | 部位 | US最大径(嚢胞mm) | US最大径(充実内腫瘤mm) | US充実腫瘤形状 | MMG腫瘤陰影 | MMG石灰化 | MRI | FNA | CNB | 術前病理診断 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 84・F | 2 | 右A | 22 | 5 | 不整型 | 辺縁不整 | なし | ／ | ／ | ／ | なし |
| 2 | 83・F | 2 | 左D | 11 | 6 | 整型 | 辺縁平滑 | なし | ／ | class 5 | ／ | DC |
| 3 | 75・F | 3 | 右A | 22 | 7 | 不整型 | 辺縁不整 | A | ／ | class 3 | ＋ | なし |
| 4 | 60・F | 4 | 右B | 36 | 10 | 整型 | 辺縁平滑 | なし | ／ | class 2 | ＋ | なし |
| 5 | 43・F | 3 | 左A | 15 | 3 | 整型 | 辺縁平滑 | なし | ／ | ／ | ＋ | なし |
| 6 | 36・F | 9 | 左C | 34 | 17 | 不整型 | はっきりせず | なし | ／ | ／ | ＋ | ICPC |
| 7 | 57・F | 4 | 左E | 10 | 4 | 整型 | 辺縁平滑 | なし | ／ | class 5 | ／ | DC |
| 8 | 70・M | 6 | 左E | 50 | 15 | 不整型 | 辺縁不整 | なし | ／ | ／ | ＋ | ICPC |
| 9 | 75・F | 2 | 右A | 28 | 20 | 整型 | 辺縁平滑 | A | ／ | class 5 | ／ | DC |
| 10 | 48・F | 3 | 左A | 23 | 5 | 整型 | 辺縁平滑 | P | ／ | class 2 | ＋ | なし |
| 11 | 74・F | 8 | 左A | 14 | 14 | 整型 | ／ | ／ | ／ | ／ | ＋ | ICPC |
| 12 | 82・F | 24 | 右C | 200 | 30 | 整型 | ／ | ／ | BCP | class 2 | ＋ | ICPC |
| 13 | 81・F | 2 | 右A | 170 | 52 | 不整型 | 辺縁不整 | なし | BCP | class 2 | ＋ | ICPC |
| 14 | 71・F | 2 | 左E | 60 | 21 | 不整型 | 辺縁平滑 | なし | BCP | ／ | ＋ | ICPC |

＊US：乳腺超音波検査．A：amorphous集簇．P：pleomrphic集簇．BCP：乳癌造影パターン
FNA：Fine needle aspiration．CNB：Core needle biopsy．DC：ductal carcinoma．

表2　手術・病理所見

| 症例 | 術式 | 嚢胞壁外浸潤 | 周囲DCIS | リンパ節転移 | 各種レセプター | p53 | G | NG |
|---|---|---|---|---|---|---|---|---|
| 1 | Bp | なし | なし | 郭清なし | ER 2 PgR 2 HER 2＋ | － | 1 | 1 |
| 2 | Bp | なし | なし | 郭清なし | ER 2 PgR 0 HER 2－ | － | 1 | 1 |
| 3 | Bt＋sampling | なし | なし | 0/2 | ER 2 PgR 2 HER 2－ | ＋ | 2 | 2 |
| 4 | Bq | なし | なし | 郭清なし | ER 2 PgR 1 HER 2－ | － | 2 | 2 |
| 5 | Bp＋Ax | なし | なし | 0/11 | ER 2 PgR 2 HER 2－ | － | 2 | 2 |
| 6 | Bp＋Ax | なし | あり | 0/22 | ER 2 PgR 2 HER 2－ | － | 1 | 1 |
| 7 | Bt＋Ax | なし | なし | 0/20 | ER 2 PgR 2 HER 2＋ | － | 2 | 2 |
| 8 | Bp | なし | なし | 郭清なし | ER 2 PgR 2 HER 2＋ | 2＋ | 2 | 2 |
| 9 | Bt＋Ax | なし | なし | 0/18 | ER 1 PgR 1 HER 2－ | － | 2 | 3 |
| 10 | Bq＋SLN | なし | なし | 0/4 | ER 1 PgR 2 HER 2－ | － | 1 | 1 |
| 11 | Bp | あり | なし | 郭清なし | ER 2 PgR 2 HER 2－ | － | 1 | 1 |
| 12 | Bt＋SLN | なし | なし | 1/5 | ER 3 PgR 3 HER 2－ | － | 1 | 1 |
| 13 | Bt＋SLN | なし | あり | 0/5 | ER 3 PgR 3 HER 2－ | － | 1 | 1 |
| 14 | Bt＋SLN | あり | あり | 0/3 | ER 3 PgR 2 HER 2－ | － | 1 | 1 |

領域に1例で，E領域に3例に存在した．病悩期間は中央値5.2カ月（2～24カ月）であった．

**2) 診断**

超音波検査では1例は多房性の嚢胞であったが，他13例はすべて単房性の嚢胞であり，いずれの症例も内部に充実性成分を認めた．腫瘍径は中央値25.5mm（11～220mm）で，充実成分径は中央値12mm（3～52mm）であった．内部の充実成分の形状は整，不整とさまざまであった．

マンモグラフィー（MMG）は12例に施行，7例が辺縁平滑で，4例は辺縁不整の腫瘤陰影として描出され，1例はMMG上腫瘤陰影を認めなかった．amorphousおよびpleomorphicな集簇する石灰化を3例にみとめた．MRIは3例に施行，嚢胞内容液はいずれも血性所見を呈した．ダイナミックスタディーでは3例（100%）ともに乳癌の造影パターンを示した．また嚢胞壁外進展を1例(症例14)に認めた．8例にFine needle aspiration施行，class5が3例，class3が1例，class2が4例であった．class5であった3例はいずれもductal carcinoma疑いという結果であった．Fine needle aspirationの細胞診陽性率は8例中3例（37.5%）であった．class3以下の5例にはCore needle biopsy 追加施行した．また5例はFine needle biopsy施行せずに，はじめからCore needle biopsyを施行．計10例のCore needle biopsyを施行，

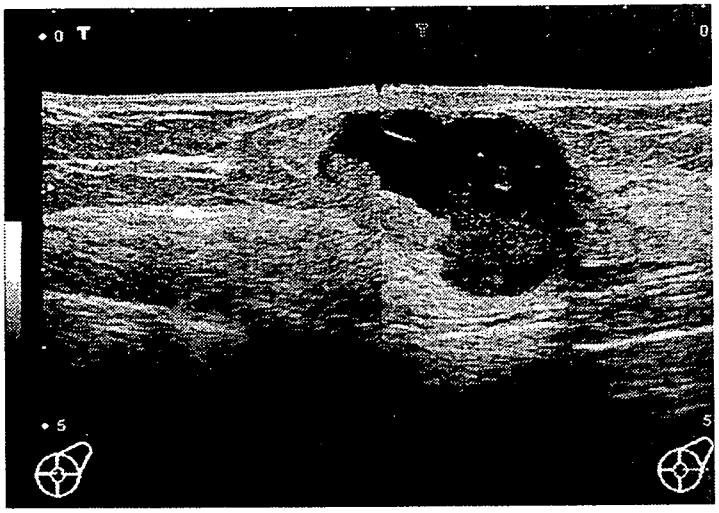

**図1　超音波所見**

後方エコーの増強を伴った50×43×26 mmの嚢胞と，嚢胞壁の一部から内腔に突出する21×18×7 mm大の乳頭状腫瘍を認めた．

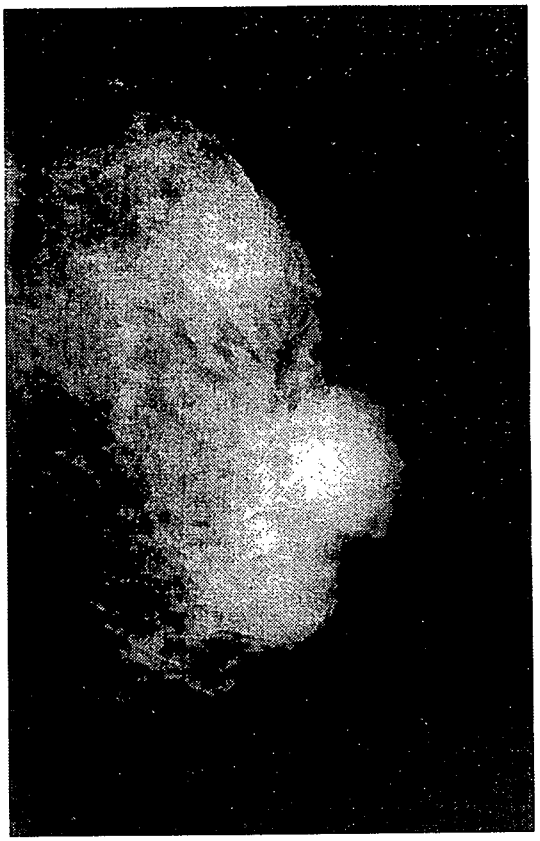

**図2　マンモグラフィー所見**

medio-lateral viewでE領域に辺縁平滑で，ほぼ均一な腫瘤陰影を認めた．石灰化は認めなかった．

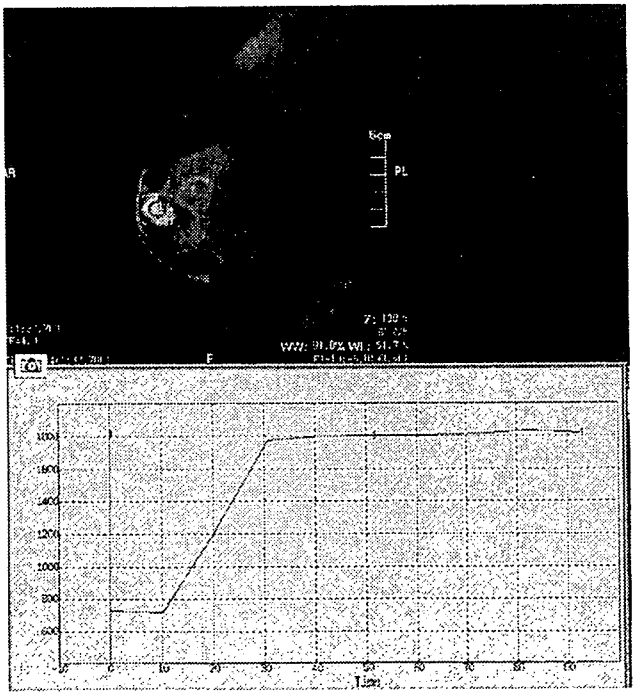

**図3　MRI**

ダイナミックスタディーにて乳癌の造影パターンを示した．

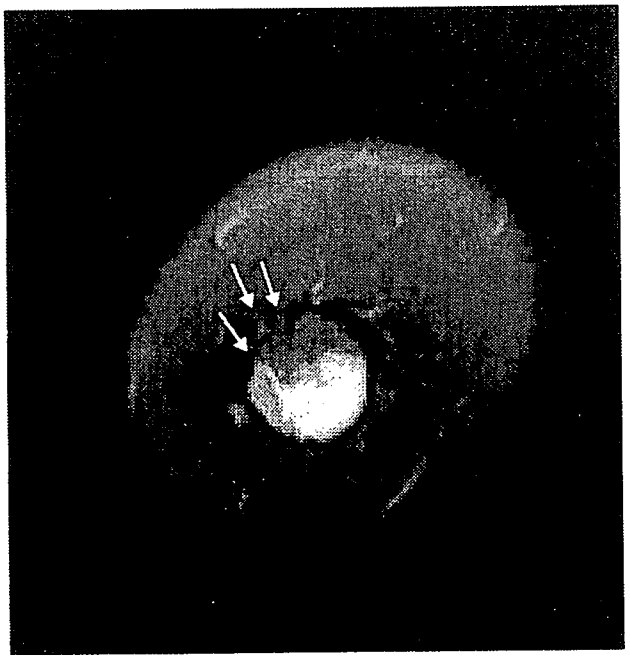

**図4　MRI**

T2W1において嚢胞壁と考えられる低信号域の断裂が認められ，MRI上，腫瘍の嚢胞壁外進展がみられた．

ICPCの術前病理学的診断を得た症例は計6例(60%)であり，残りの4例はCore needle biopsyでも確定できず切除生検にて乳癌の診断を得た．なお1例はFine needle aspirationおよびCore needle biopsyをともに施行せずに切除生検を行った．

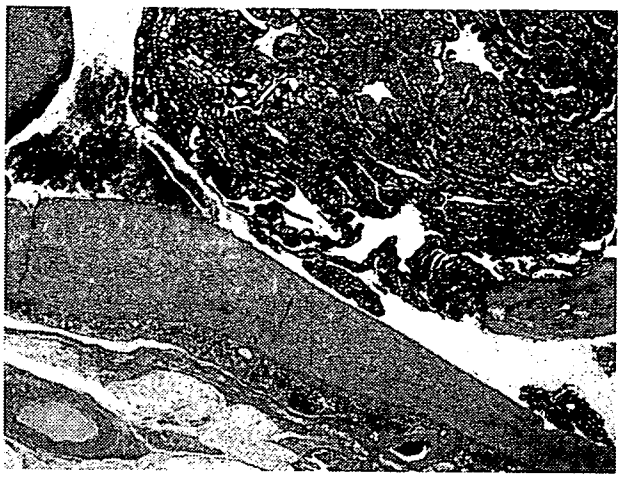

**図5　病理組織所見**
径5cm大の嚢胞内に2cm大の乳頭状隆起性病変を認め，嚢胞液は暗赤色であった．この隆起性病変は中等度の核異型，核分裂像を有する腫瘍細胞が乳頭状，cribriform patternを呈して増殖．

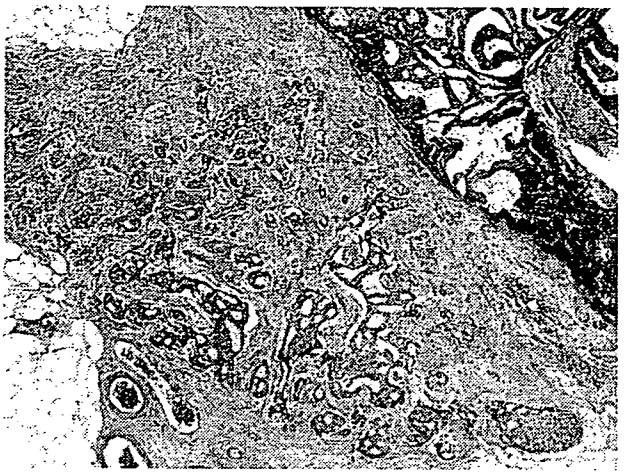

**図6　病理組織所見**
腫瘍細胞の間質への浸潤が認められた．

**3) 手術・病理（表2）**

5例に腋窩郭清を伴う乳房切除術および乳房部分切除術を施行，4例は腋窩郭清を伴わない乳房部分切除術を施行した．さらに2004年以降の4例はセンチネルリンパ節生検を伴う乳房切除術および乳房部分切除術を施行した．嚢胞内容液の性状はいずれもきわめて淡い血性から濃い暗赤色を呈し，14例のうち2例（14.2%）に間質浸潤を認めた．また3例に嚢胞壁外にDCISを認め，1例に腋窩リンパ節転移を認めた．G1とG2がそれぞれ8例（57%）6例（43%），NG1とNG2とNG3がそれぞれ8例（57%）5例（36%）1例（7%）であった．またホルモンレセプターはERが全例（100%），PgRは13例が陽性（92.8%）で，HER2は3例（21.4%），p53は2例（14.2%）が陽性であった．

**4) リンパ節転移症例**

ICPC14例のうち1例に腋窩リンパ節転移を認めた．本症例は82歳女性，病悩期間が24カ月，腫瘍径が20cmであった．Core needle biopsyでICPCの診断を得，乳房切除術およびセンチネルリンパ節生検を施行，術中迅速病理診断にてセンチネルリンパ節転移はなかったが，永久標本にてリンパ節1個にmicrometastasisを認めた．ER，PgRはともに陽性，HER2，p53はいずれも発現していなかった．作成標本上，嚢胞壁外への浸潤はみとめていない．

**5) 補助療法・予後**

13例にTAM投与，温存術8例中3例に残存乳房に対する術後照射を行った．男性症例の1例の他因死を除き，13例すべて再発の所見なく生存中である．次に代表的な1例（症例14）を提示する．

**症　例**：71歳，女性．

**家族歴**：特記事項なし．

**既往歴**：特記事項なし．

**現病歴**：2006年10月，左乳房腫瘤に気づき前医受診し，当科紹介となる．

**入院時血液検査所見**：末梢血，生化学検査ともに正常範囲内で，腫瘍マーカー（CEA 0.9ng/m*l*，CA15-3 14U/m*l*，ST439<1.0）の上昇もみられなかった．

**入院時現症**：左乳房E領域を中心にBD領域に及ぶ60mm大のやや弾性硬の腫瘤を認めた．胸筋，皮膚への固定は認めなかった．乳頭分泌なく，腋窩リンパ節も触知しなかった．

**超音波所見（図1）**：後方エコーの増強を伴った60×43×26mmの嚢胞と，嚢胞壁の一部から内腔に突出する21×18×7mm大の乳頭状腫瘍を認めた．

**MMG所見（図2）**：E領域に辺縁平滑で，ほぼ均一な腫瘤陰影を認めた．石灰化は認めなかった．

**MRI**：ダイナミックスタディーにて乳癌の造影パターンを示した（**図3**）．また，T2W1において嚢胞壁と考えられる低信号域の断裂が認められ，

MRI上，腫瘍の嚢胞壁外進展がみられた（**図4**）．

**経　過**：以上の所見より，2006年11月Core needle biopsy施行し，ICPCの診断を得て，乳房切除術＋センチネルリンパ節生検を施行した．術中迅速病理診断にてセンチネルリンパ節に転移は認めなかった．

**病理組織所見**：径5cm大の嚢胞内に2cm大の乳頭状隆起性病変を認め，嚢胞液は暗赤色であった．この隆起性病変は中等度の核異型，核分裂像を有する腫瘍細胞が乳頭状，cribriform patternを呈して増殖（**図5**），一部間質への浸潤が認められた（**図6**）．リンパ節転移は認めず(0/3)，G2，NG2および免疫組織学的検索にてER，PgRはともに陽性，HER2，p53はいずれも発現していなかった．

## 3. 考　察

ICPCは嚢胞内腔へ乳頭状に突出し発育する乳癌で，乳癌全体の約2％弱[1]といわれている．一般的にductal carcinoma *in situ*の範疇で浸潤を伴うことはほとんどなく，現在の乳癌取扱い規約によれば，病巣が嚢胞内に限局し，非浸潤性嚢胞内乳癌とすることが記載されている．しかし，組織学的にも嚢胞壁外への浸潤や乳管内で広く進展を示す例[3]や，同時性肝転移例[4]などの報告もあり，定義についてはいまだコンセンサスを得られていない．したがって今回われわれは，浸潤の有無を問わず病理学的検索にて，ICPCと診断された14例を検討した．通常の乳癌と比較すると，平均年齢65歳（範囲34～92歳）[1]と高齢者に多いとされ，今回の14例でも中央値72.5歳（36～82歳）であり通常乳癌より高齢であった．また病悩期間も長いことも報告[2,5]されており，今回も中央値5カ月（1～24カ月）であった．腫瘍の性質として通常乳癌より発育が緩徐で，潰瘍を形成せずにGradeが低いため，放置されやすいと考えられる．良悪性の鑑別として，嚢胞内乳頭腫と鑑別は困難である．鑑別点としては嚢胞内乳頭腫の平均年齢は40.7～47歳で低く，60歳以上の嚢胞内腫瘍では，癌は81％に認めたという報告がある[7,8,9]．また腫瘍径は悪性であれば良性より大きい傾向にあるが，良悪性鑑別において診断的価値は低い[7,8]と報告されている．超音波検査は良悪性の鑑別検査としてあげられるが，嚢胞内腫瘤部分の辺縁など良悪性とも不整なものが多く鑑別にあまり有用でないといわれている[8,9]．通常乳癌における良悪性の鑑別としてMRIは有用であり，MRI所見が乳癌病理組織像を反映するという報告もある[10]．われわれは症例12以降の3例においてMRIを施行しいずれもダイナミックスタディーにて悪性を示す造影パターンを呈した．ICPCにおいても良悪性鑑別のため画像診断の1つとしてMRIは重要であると考えられる．またさらに，症例14においてMRIで腫瘍の嚢胞壁外浸潤を認めたように，MRIは進展度診断にも有用であり，嚢胞壁進展の評価にもきわめて有効である．以上より，少しでも悪性が疑われる場合はFine needle aspirationを行い，さらにCore needle biopsyをエコーガイド下に充実性部分を確実に穿刺することが必要である．しかし本検討症例においてもそうであるが，嚢胞内充実成分への針生検は難しく，Fine needle aspirationおよびCore needle biopsyにても診断の得られない症例では積極的に切除生検を考慮するべきと思われる．治療は原則として非浸潤性乳管癌(DCIS)治療に沿って行うことが可能である．しかし，嚢胞壁外浸潤を示す例[3]や，同時性肝転移例[4]などの報告もあることを把握しておく必要がある．報告によると浸潤癌はまれではなく，乳管内進展についても嚢胞壁より2cm以上超えて乳管内を進展するものも報告されている[6]．今回の14例中2例に浸潤部分を認め，さらに別の1例に作成標本には浸潤部は認めなかったが，リンパ節転移を認め，標本作成外に浸潤部分が存在したことが推察された．このように切除範囲決定には，MRIによる進展度評価を参考にし，広範な腫瘍進展を念頭において断端陰性となることが重要である．術前化学療法，術後化学療法の報告はなく，統一された指針はないが，第一選択治療は切除療法と考える．リンパ節転移に関しては0～25％と報告に幅があるが，通常の乳癌より頻度は低いとされている[8,9]．われわれは2004年以降よりセンチネルリンパ節生検を開始し，4例にセンチネルリンパ節生検を伴う乳房切除，乳房部分切除術を施行した．通常乳癌と同様，郭清省略には慎重であるべきで，センチネルリンパ節生検はよい適応と思われる．

今回14例すべてホルモン感受性を認め，乳房部分切除は8例に施行した．補助療法としては，明確な指針はないがDCIS治療にしたがって，症例を選びホルモン療法，残存乳房放射線照射などを考慮する必要があると思われる．

## 4. 結　語

ICPCの14例につき臨床病理学的検討を加え報告した．良悪性の鑑別は困難であり，Fine needle aspiration, Core needle biopsyに加え切除生検が必要である．切除範囲決定には，MRIによる進展度評価を参考に，広範な腫瘍進展を念頭において断端陰性となることが重要である．また，腋窩リンパ節の評価は病変の大きさに関わらず必要であり，現在広く施行されているセンチネルリンパ節生検は腋窩リンパ節転移の少ないICPCによい適応と考えられる．

### 文　献


1) WHO Classification Tumors of the Breast and Female Genital Organs
2) Czernobilsky B：Intracystic carcinoma of the female breast. *Surg Gynecol Obstet* **124**：93-98, 1967
3) 橋本幸直, 仁尾義則, 小池　誠, 他：嚢胞内乳癌の4例, 外科 **68**：365-370, 2006
4) Okita R, Ohsumi S, Takashima S, et al：Synchronous liver metastasese of intracystic papillary carcinoma with invasion of the breast. *Breast Cancer* **12**：327-330, 2005
5) McKittrick JE, Doane WA, Failing RM：Intracystic papillary carcinoma of the breast. *Am Surg* **35**：195-202, 1969
6) 山下晃徳, 吉本賢隆, 岩瀬拓士, 他：乳腺内乳癌の臨床病理像, 日臨外医会誌 **55**：2726-2731, 1994
7) 林　剛, 西田正之, 佐藤一彦, 他：乳腺嚢胞内腫瘍性病変の検討, 日臨外医会誌 **57**：2355-2359, 1996
8) 稲吉　厚, 小城左明, 澤田俊彦, 他：嚢胞内乳腺腫瘍に対する超音波診断および穿刺吸引細胞診の検討, 日臨外医会誌 **60**：893-897, 1999
9) 才川義明, 小坂昭夫：嚢胞内乳癌8例の検討. 日臨外医会誌 **52**：2887-2890, 1991
10) Kusuma R, Takayama F, Tsuchiya S：MRI of the breast：comparison of MRI signals and histological characteristics of the same slices. *Med Mol Morphol* **38**：204-215, 2005

# Ipsilateral Breast Tumor Recurrence (IBTR) after Breast-Conserving Treatment for Early Breast Cancer

## *Risk Factors and Impact on Distant Metastases*

**Yoshifumi Komoike, M.D.**[1]
**Futoshi Akiyama, M.D.**[2]
**Yuichi Iino, M.D.**[3]
**Tadashi Ikeda, M.D.**[4]
**Sadako Akashi-Tanaka, M.D.**[5]
**Shozo Ohsumi, M.D.**[6]
**Mikihiro Kusama, M.D.**[7]
**Muneaki Sano, M.D.**[8]
**Eisei Shin, M.D.**[9]
**Kimito Suemasu, M.D.**[10]
**Hiroshi Sonoo, M.D.**[11]
**Tetsuya Taguchi, M.D.**[12]
**Tsunehiro Nishi, M.D.**[13]
**Reiki Nishimura, M.D.**[14]
**Shunsuke Haga, M.D.**[15]
**Keiichi Mise, M.D.**[16]
**Takayuki Kinoshita, M.D.**[17]
**Shigeru Murakami, M.D.**[18]
**Masataka Yoshimoto, M.D.**[19]
**Hideaki Tsukuma, M.D.**[20]
**Hideo Inaji, M.D.**[1]

**BACKGROUND.** The clinical features of ipsilateral breast tumor recurrence (IBTR) after breast conserving therapy (BCT) for early stage breast cancer were analyzed from long-term follow-up of BCT in Japan. The purpose of this study was to clarify risk factors of IBTR and the impact of IBTR on development of distant metastases in this ethnic group.

**METHODS.** Patients ($N$ = 1901)with unilateral breast cancer ≤ 3 cm in diameter who underwent BCT at 18 Japanese major breast cancer treatment institutes from 1986 to 1993 were registered in this study. Survival rates, the incidences of IBTR and distant metastases, and annual rates of IBTR and distant metastases after primary operation were calculated by the Kaplan–Meier method. A Cox proportional hazards model was used to estimate the risks of IBTR and distant metastases. A Cox model was also used to estimate the risks of distant metastases after IBTR in the group of IBTR.

**RESULTS.** At a median follow-up time of 107 months, the 10-year overall and disease-free survival rates were 83.9% and 77.8%, respectively. The 10-year cumulative rates of IBTR were 8.5% in the patients with postoperative irradiation and 17.2% in the patients without irradiation. The 10-year cumulative distant metastasis rate was 10.9%. On multivariate analysis, young age, positive surgical margin, and omission of radiation therapy were significant predictors of IBTR. In addition, IBTR significantly correlated with subsequent distant metastases (hazard ratio, 3.93; 95% confidence interval, 2.676–5.771; $P < 0.0001$). Among patients who

[1] Department of Surgery, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, Japan.

[2] Department of Breast Pathology, Cancer Institute Hospital, Tokyo, Japan.

[3] Department of Emergency and Critical Care Medicine, Gunma University Faculty of Medicine, Gunma, Japan.

[4] Department of Surgery, Keio University School of Medicine, Tokyo, Japan.

[5] Division of Breast Surgery, National Cancer Center Hospital, Tokyo, Japan.

[6] Department of Surgery, National Shikoku Cancer Center, Ehime, Japan.

[7] Third Department of Surgery, Tokyo Medical University, Tokyo, Japan.

[8] Department of Surgery, Niigata Cancer Center Hospital, Niigata, Japan.

[9] Department of Surgery, National Osaka Hospital, Osaka, Japan.

[10] Department of Surgery, Saitama Cancer Center, Saitama, Japan.

[11] Department of Breast and Thyroid Surgery, Kawasaki Medical School, Okayama, Japan.

[12] Department of Surgical Oncology, Osaka University Graduate School of Medicine, Osaka, Japan.

[13] Department of Surgery, Mitsui Memorial Hospital, Tokyo, Japan.

[14] Department of Surgery, Kumamoto City Hospital, Kumamoto, Japan.

[15] Department of Surgery, Tokyo Women's Medical University Daini Hospital, Toyko, Japan.

[16] Kodama Clinic, Fukuoka, Japan.

[17] Department of Surgery, National Tokyo Medical Center Hospital, Tokyo, Japan.

[18] Department of Breast Oncology, National Kyushu Cancer Center 1, Kyoto, Japan.

[19] Department of Breast Surgery, Cancer Institute Hospital, Tokyo, Japan.

[20] Department of Cancer Control and Statistics, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, Japan.

Supported by a Grant-in-Aid for research of cancer treatment from the Ministry of Health, Labour and Welfare of Japan (No.13-9).

Address for reprints: Yoshifumi Komoike, Department of Surgery, Osaka Medical Center for Cancer and Cardiovascular Diseases, 1-3-3 Nakamichi, Higashinari-ku, Osaka 537-8511, Japan; Fax: (011) 81-6-6981-8055; E-mail: komoike-yo@mc.pref.osaka.jp

Received June 29, 2004; revision received June 16, 2005; accepted July 19, 2005.


DOI 10.1002/cncr.21551
Published online 6 December 2005 in Wiley InterScience (www.interscience.wiley.com).

developed IBTR, initial lymph node metastases and short interval to IBTR were significant risk factors for subsequent distant metastasis.

**CONCLUSIONS.** Young age, positive surgical margin, and omission of radiation therapy seemed to be important factors in relation to local control. The authors' results also indicated that IBTR is significantly associated with subsequent distant metastasis. Patients with positive nodal status at primary operation or with short interval from primary operation to IBTR are at especially high risk of distant metastasis. It remains unclear, however, whether IBTR is an indicator or a cause of subsequent distant metastases. ***Cancer* 2006;106:35–41.**



**KEYWORDS: breast cancer, breast-conserving treatment, ipsilateral breast tumor recurrence, distant metastases.**

A long time has passed since breast-conserving therapy (BCT) became the standard treatment modality for early stage breast cancers.[1–2] The increasing number of patients treated with BCT resulted in a corresponding increase of ipsilateral breast tumor recurrence (IBTR). The main concern for both physicians and patients is, therefore, the risk of IBTR in the preserved breast.

Postoperative irradiation to the remaining breast has significantly reduced the incidence of IBTR.[1–5] The results of the recent National Surgical Adjuvant Bowel and Breast Project (NSABP) B-21, showed that radiation therapy was so effective that it would even benefit early breast cancers at minimal risk for IBTR.[6] Therefore, postoperative irradiation was thought to be an important part of standard procedure for BCT.

In addition to radiation therapy, some factors were reported to have an influence on IBTR. For example, young women were generally thought to have a higher frequency of local recurrence.[7–11] Kroman et al. recently reported a relation between young age and increasing risk of IBTR, from a study of BCT with over 2000 patients.[12] The European Organization for Research and Treatment of Cancer (EORTC) trial also confirmed the impact of age.[13]

The presence or absence of cancer cells at the resection margin, and their quantity, are also major factors affecting IBTR.[14–19] Park et al. reported that the 8-year accrued rate of IBTR was 7% in patients with negative and close margins, 14% in those with focally positive margins, and 27% in those with extensively positive margins.[14] Although the definitions of positive margin are obscure, the importance of pathologic margin status in relation to the risk of IBTR has been shown.

Many studies have shown that IBTR is associated with subsequent distant metastases (DM) and worse survival.[20–28] Whether IBTR is an indicator or a cause of subsequent DM is debatable.[26,29–33] It has been proposed that IBTR is not the cause but is simply a significant indicator of subsequent DM. Other groups have recently suggested that IBTR may be a cause of DM.[32,34,35]

In the current study, we summarized the long-term follow-up results of BCT for Japanese women with breast cancer, and we focused on IBTR, particularly its incidence, risk factors, and predictive significance for subsequent DM. In Japan, BCT was adopted later than in western countries. Therefore, there are few studies summarizing the results of BCT for Japanese women.[36,37] This is the first long-term report of large-scale results of BCT in this ethnic group.

## MATERIALS AND METHODS

Included in this study were 1901 patients with unilateral breast cancer ≤ 3 cm in diameter who underwent BCT at 18 major institutes from 1986 to 1993. Patients who had received primary systemic therapy, and those with past history of breast cancer, were excluded. Postoperative irradiation or adjuvant therapy were not exclusion criteria. The surgical procedure consisted of wide excision or quadrantectomy plus axillary lymph node dissection.

Questionnaire forms were sent to the members of this study in November 2001 to collect clinical patient data. The questionnaire asked for data as follows: age at primary operation, menopausal status, date of primary operation, initial tumor size by palpation, histologic type, pathologic lymph node status, histologic margin status, lymphovascular invasion, nuclear grade, extensive intraductal component (EIC), estrogen receptor status (ER), progesterone receptor status (PgR), adjuvant endocrine therapy, adjuvant chemotherapy, postoperative irradiation, boost radiation, date of IBTR, method of salvage operation, systemic therapy after IBTR, secondary local recurrence and its date, distant metastases, date of distant metastases, contralateral breast cancer, death, cause of death, and date of death or last visit. Serial sections of resected specimens were meticulously examined at all institu-

tions. Margins ≤ 5 mm from the cut edge of the specimen were usually regarded as positive margins. Measurement methods and cutoff levels of the hormone receptors were not standardized, and they varied between institutions.

IBTR was defined as all events which occurred in the remaining breast after BCT. No distinction was made between recurrence because of residual cancer cells or because of new primary cancer.

Local-free, disease-free, distant disease-free, and overall survival rates were calculated using the Kaplan–Meier method. The statistical differences of local, distant, disease-free rates, and overall survival were proved using a log-rank test for univariate analysis. Multivariate analyses for local free and distant disease-free rates were performed using the Cox proportional hazards model. In univariate and multivariate analysis, age was dealt with as a serial variable and was not categorized at a certain point, such as ≤ 35 years or older. All statistical analyses were performed with Stat View 5.0 software (SAS Institute, Cary, NC).

## RESULTS

### Systemic Recurrence and IBTR

There were 1901 patients available for analysis of survival and recurrence rates. The median follow-up period was 107 months(range, 2–184 mos). Patient characteristics are shown in Table 1. There were 172 patients who developed IBTR, and 179 patients had recurrences in distant organs or regional lymph nodes. During follow-up, 182 patients died; of these, 128 patients died of their breast cancers. The 10-year overall and cause-specific survival rates were 83.9% and 92.2%, respectively. The 10-year distant disease-free survival was 77.8%. The 10-year cumulative rate of IBTR was 9.6% (8.5% in the group with postoperative irradiation and 17.2% in the group without RT). There was a significant difference between these two groups ($P < 0.0001$).

TABLE 1
Patient Characteristics

| Characteristic | No. of patients |
|---|---|
| Age, yrs | |
| Median | 49 |
| Range | 21–89 |
| ≤ 35 | 135 |
| > 36 | 1766 |
| Clinical tumor size, cm | |
| Median | 17 |
| Range | 0–30 |
| Lymph node metastasis | |
| Positive | 380 |
| Negative | 1476 |
| Unknown | 45 |
| ER status | |
| Positive | 779 |
| Negative | 482 |
| Unknown | 640 |
| PgR status | |
| Positive | 510 |
| Negative | 430 |
| Unknown | 961 |
| Surgical margin | |
| Positive | 263 |
| Negative | 1503 |
| Uncertain | 135 |

ER: estrogen receptor; PgR: progesterone receptor.

### Risk Factors for IBTR

Factors influencing IBTR are shown in Table 2. In a univariate analysis, younger age at primary operation, tumor size, positive margin status, high nuclear grade, EIC, PgR, omission of endocrine therapy, and omission of postoperative irradiation were significantly associated with IBTR. Of these, younger age, positive margin status, and omission of postoperative irradiation were independently associated with IBTR on a multivariate Cox proportional hazards model analysis.

### Time Course of IBTR and Distant Metastasis

The annual rate and cumulative incidence of IBTR after primary operation is shown in Figure 1. The peak of IBTR was seen at 3 to 4 years after primary operation, and the annual rate decreased gradually thereafter. Figure 2 shows the clinical outcome of patients with and without IBTR. Patients who developed IBTR had a significantly greater risk of developing DM ($P < 0.0001$).

### Risk Factors for Distant Metastasis

Both distant disease-free and overall survival rates were significantly lower in the IBTR group. To determine whether IBTR is related to DM and patient prognosis, we verified risk factors for DM. Univariate analysis showed that initial age, lymph node metastases, margin status, lymphovascular invasion, nuclear grade, EIC, PgR, and IBTR were all significantly correlated with DM (Table 3). In a multivariate analysis, IBTR was independently associated with DM as well as with lymph node metastases. The hazard ratio (HR) associated with distant metastasis was 3.93 (95% confidence interval [CI], 2.676–5.771) in IBTR, and 3.34 (95% CI, 2.365–4.724) in node-positive patients (Table 3).

Of 1901 patients, 172 developed IBTR, and 51 developed subsequent DM after IBTR; 27 of these patients developed distant metastases within 1 year after IBTR.

TABLE 2
Factors Influencing Ipsilateral Breast Tumor Recurrence (IBTR), Results of Univariate and Multivariate Analysis

| Variable | Univariate analysis *P* value | Multivariate analysis HR | *P* value | 95% CI |
|---|---|---|---|---|
| Age | < 0.0001 | 0.943 | < 0.0001 | 0.917–0.970 |
| Size | 0.0257 | 1.017 | 0.2557 | 0.988–1.047 |
| Histologic type | | | | |
| DCIS/IDC/special | 0.6053 | | | |
| Lymph node metastasis | | | | |
| +/− | 0.141 | | | |
| Surgical margin | | | | |
| +/− | < 0.0001 | 2.849 | 0.0004 | 1.587–5.012 |
| ly +/− | 0.8768 | | | |
| v +/− | 0.5236 | | | |
| Nuclear grade | | | | |
| 3/1, 2 | 0.0650 | | | |
| EIC +/− | 0.0106 | 1.422 | 0.1857 | 0.847–2.398 |
| ER −/+ | 0.0493 | 0.696 | 0.1464 | 0.427–1.135 |
| PgR −/+ | 0.0036 | | | |
| Chemotherapy | | | | |
| −/+ | 0.0878 | | | |
| Endocrine therapy | | | | |
| −/+ | 0.0180 | 1.543 | 0.0824 | 0.397–1.057 |
| Radiation therapy | | | | |
| −/+ | < 0.0001 | 3.861 | < 0.0001 | 0.155–0.433 |

HR: hazard ratio; CI: confidence interval; DCIS: ductal carcinoma in situ; IDC: invasive ductal carcinoma; Special: lobular carcinoma, medullary carcinoma, squamous cell carcinoma, etc.; ly: lymphatic invasion; v: vascular invasion; EIC: extensive intraductal component; ER: estrogen receptor; PgR: progesterone receptor.

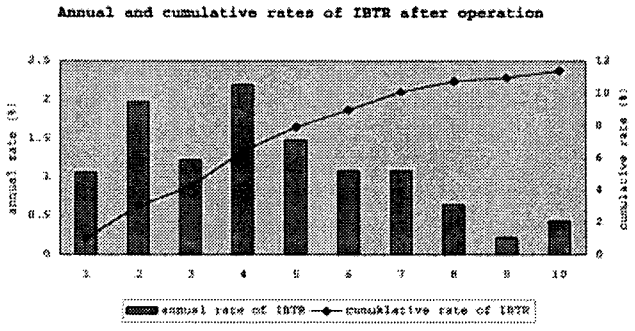


**FIGURE 1.** Annual and cumulative rates of ipsilateral breast tumor recurrence (IBTR) after primary operation are represented. The bar graph shows annual rates of IBTR. It was 1 to 2% up to 7 years from primary operation. After that, the incidences decreased slightly, but they did not reach zero. The incidence was highest at 4 to 5 years after primary operation. The line graph shows cumulative incidence of IBTR. It was linear to 7 years and a little flattened thereafter.

Factors associated with distant metastases among patients who developed on IBTR were analyzed. Univariate analysis showed that nodal status, lymphovascular invasion, and period to IBTR were potential risk factors for DM. Initial nodal status and interval to IBTR were independent risk factors for DM by Cox proportional hazard model (Table 4). Annual rates of DM for primary operation in patients with or without IBTR were compared (Fig. 3). The incidences of DM in the group of patients with IBTR were higher than those in the group of patients without IBTR regardless of the time after operation. More interestingly, the annual rates of distant metastases in the group of patients with IBTR showed two

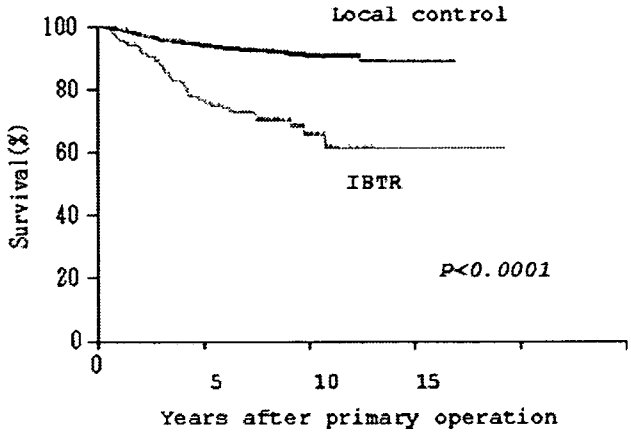


**FIGURE 2.** Distant-free survival after primary operation is shown according to local relapse. The distant-free survival curve shows that patients with IBTR are more likely to develop subsequent distant metastases. There was a statistically significant difference between the two groups ($P < 0.0001$). The actuarial distant-free survival rate at 10 years was 89.7% in the local control group and 70.3% in the IBTR group.

TABLE 3
Risk Factors for Distant Metastases After Breast Conserving Surgery, Results of Univariate and Multivariate Analysis

| Variable | Univariate analysis HR | *P* value | Multivariate analysis HR | *P* value | 95% CI |
|---|---|---|---|---|---|
| Age | 0.979 | 0.004 | 0.99 | < 0.30 | 0.978–1.008 |
| Size | 1.013 | 0.10 | | | |
| Lymph node metastasis | | | | | |
| +/− | 3.55 | < 0.0001 | 3.34 | < 0.0001 | 2.365–4.724 |
| Surgical margin | | | | | |
| +/− | 1.46 | 0.03 | 1.30 | 0.20 | 0.873–1.926 |
| ly +/− | 2.16 | < 0.0001 | | | |
| v +/− | 1.98 | 0.002 | | | |
| Nuclear grade | | | | | |
| 3/1, 2 | 3.32 | 0.006 | | | |
| EIC +/− | 0.57 | 0.03 | | | |
| ER −/+ | 0.79 | 0.16 | | | |
| PgR −/+ | 0.64 | 0.01 | | | |
| IBTR +/− | 3.72 | < 0.0001 | 3.93 | < 0.0001 | 2.676–5.771 |

HR: hazard ratio; CI: confidence interval; ly: lymphatic invasion; v: vascular invasion; EIC: extensive intraductal component; ER: estrogen receptor; PgR: progesterone receptor; IBTR: ipsilateral breast tumor recurrence.

TABLE 4
**Risk Factors for Subsequent Distant Metastases After IBTR, Results of Univariate and Multivariate Analysis**

| Variable | Univariate analysis *P* value | Multivariate analysis HR | *P* value | 95% CI |
|---|---|---|---|---|
| Age | 0.1724 | | | |
| Size | 0.5618 | | | |
| Lymph node metastasis | | | | |
| +/− | < 0.001 | 2.68 | 0.008 | 1.291–5.574 |
| Surgical margin | | | | |
| +/− | 0.3113 | | | |
| ly +/− | 0.0161 | 1.21 | 0.599 | 0.888–2.506 |
| v +/− | < 0.0001 | | | |
| Nuclear grade | | | | |
| 3/1, 2 | NE | | | |
| EIC +/− | 0.2134 | | | |
| ER −/+ | 0.4057 | | | |
| PgR −/+ | 0.2230 | | | |
| DFI | < 0.0001 | 0.99 | 0.008 | 0.999–1.000 |

HR: hazard ratio; CI: confidence interval; ly: lymphatic invasion; v: vascular invasion; EIC: extensive intraductal component; ER: estrogen receptor; PgR: progesterone receptor; DFI: disease free interval.

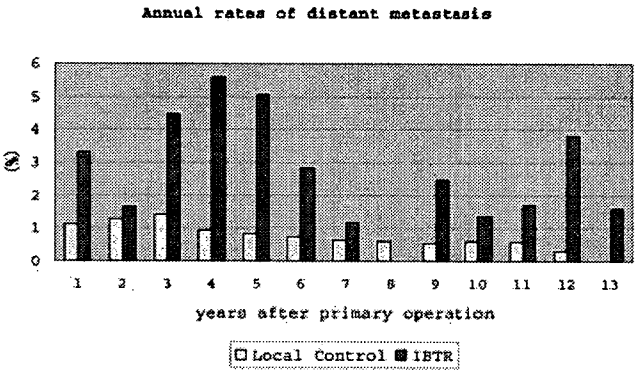


**FIGURE 3.** The time distribution of distant metastases after primary operation compares the local control group (LC) and IBTR group. In the group of patients without IBTR, the incidence of DM was high at 2 to 4 years after primary operation, and it gradually decreased thereafter. By contrast, in the group of patients with IBTR, the annual rates of distant metastases showed two peaks, 4 to 5 years and 12 to 13 years after primary operation. The proportion of DM after 9 years was remarkably high.

peaks, and the incidence of DM after 9 years was remarkably high. By contrast, in the group of patients without IBTR, the incidence of DM was high at 2–4 years after primary operation and subsequently decreased.

## DISCUSSION

The current study was conducted to clarify the risk factors for IBTR, as well as the impact of IBTR on distant metastases in patients with early stage breast cancer treated with BCT. We first summarized the results of BCT cases in Japan with long-term follow-up. As previously reported,[36,37] the survival rates and local control rates of BCT in Japan were favorable. Risk factors of IBTR were younger age, positive margin status, and omission of postoperative irradiation. These results were consistent with previous reports.

The 10-year cumulative rates of IBTR were 8.5% and 17.2% in patients with and without radiation therapy, respectively. On a Cox proportional hazards model, postoperative irradiation decreased the risk of IBTR by about one-fourth (HR, 0.259, 95% CI, 0.214–0.431, $P < 0.0001$). This result is similar to the result of Early Breast Cancer Trialists' Collaborative Group (EBCTCG) metaanalysis.[38]

In the current study, positive surgical margins were also associated with an increased risk of IBTR as previously reported.[14–18] However, definitions of margin status are not standardized. Some researchers defined it only as "positive" or "negative".[16,20] Other studies have assessed surgical margin according to distance from the cut edge,[17] but these distances varied by < 1 mm, < 2mm, or < 10mm.[14,19,39] In the current study, the majority of close margins (≤ 5 mm from the cut edge of the specimen) were regarded as positive margins. Although judgment of margin status depends on each institution, meticulous histologic assessment was done in all institutions. (The removed specimens are examined by expert pathologists at each institute, by using 5 mm sections.)

The influence of young age on the risk of IBTR is striking. It has been supported by many previous studies.[7–11] Jobsen et al. reported that age < 40 years was the only significant predictor of IBTR for women treated with BCT with pathologic T1 tumors and negative lymph node status.[10] Harrold et al. showed a correlation with young age and IBTR by using a cut-point age of 40 years.[40] Freedman et al. also found age to be a risk factor of IBTR, but their cut-point age was 55 years.[9] Fourquet et al. categorized patients into 4 age groups (< 32, 32–45, 46–55, > 55).[7] In our series, age was analyzed as a serial variable. The results are that the younger the patient, the higher the risk of IBTR. It was noteworthy that younger age was a risk factor of IBTR regardless of age cut-point.

Our results also showed that IBTR was significantly correlated with DM, as shown by several other reports.[19–24] The HR was 3.93 by multivariate analysis. This ratio was very similar to that of NSABP B-06.[20] When compared with the relative risk (3.34) of lymph node metastasis for distant metastasis, IBTR has almost the same impact on DM.

One of the aims of this study was to clarify what type of IBTR is likely to develop subsequent DM. Univariate analysis showed that initial lymph node metastases,

lymphovascular invasion, nuclear grade, and the interval from primary operation to IBTR were significantly associated with DM. Short DFI was reported to be highly correlated with subsequent DM.[21,25,26,31,41-44] These risk factors appear to reflect the inherent aggressive characteristics of primary tumors.[38,39] Thus the risk of developing DM would be predetermined before treatment, with local recurrence being a manifestation of this risk.

The time distribution of annual rates of DM among patients with IBTR showed a noteworthy pattern. Two peaks in the incidence of DM were observed; 4 to 5 years and 12 to 13 years after primary operation. In patients without IBTR, a peak of incidence was seen 3 to 4 years after primary operation, with a gradual decrease thereafter. Our results agreed with the long-term results of NSABP B-06 and some other studies.[32,33] Some groups have presumed that the second peak of DM was due to IBTR.[28,29] Considering that late distant metastases are not likely to develop so frequently after mastectomy, IBTR may be a cause of DM in such cases. Up to now, many investigators thought that IBTR was only a marker for DM[19,20,23,24] because many cases of IBTR that subsequently developed DM had more aggressive primary tumor characteristics. Recently, however, it appears that additional radiation may lead to a survival benefit, suggesting IBTR may, in part, be a cause of DM, especially in cases of IBTR who develop late DM.[45]

Classifying IBTR into true recurrence (TR) or new primary tumor (NP) is one of the concerns. The finding that cumulative incidence of IBTR is linear to 7 years and flattens slightly thereafter (Table 1. line graph) suggests that not a few cases of late recurrence may be NP recurrence. In the current study, we did not distinguish a second primary breast cancer from true recurrence because it is difficult to correctly diagnose. Some studies suggest the prognostic significance of IBTR from this viewpoint. True recurrence is generally thought to have worse prognosis than a new primary tumor.[46-48] Haffty and colleagues speculated that a certain portion of IBTR contained new primary tumor and biologic behaviors were quite different.[48,49] So it is noteworthy that IBTR represent two distinct entities, and classifying IBTR may help our understanding of the complicated behavior of IBTR.

In summary, young age, positive surgical margin, and omission of radiation therapy are independent risk factors for IBTR, and IBTR was certainly correlated with subsequent DM. Initial nodal status and the interval to IBTR were significantly associated with DM after IBTR. It remains unclear whether IBTR is an indicator of DM or a cause of it. Further study is needed to solve this question.

## REFERENCES


1. Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med.* 2002;347:1233-1241.
2. Veronesi U, Cascinelli N, Mariani L, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. *N Engl J Med.* 2002;347:1227-1232.
3. Clark RM, Whelan T, Levine M, et al. Randomized clinical trial of breast irradiation after lumpectomy and axillary dissection for node-negative breast cancer: an update. *J Natl Cancer Inst.* 1996;88:1659-1664.
4. Liljegren G, Holmberg L, Adami HO, et al. Sector resection with or without postoperative radiotherapy for stage I breast cancer: five-year results of a randomized trial. Uppsala-Orebro Breast Cancer Study Group. *J Natl Cancer Inst.* 1994; 86:717-722.
5. Forrest AP, Stewart HJ, Everington D, et al. Randomised controlled trial of conservation therapy for breast cancer: 6-year analysis of the Scottish trial. Scottish Cancer Trials Breast Group. *Lancet.* 1996;348:708-713.
6. Fisher B, Bryant J, Dignam JJ, et al. Tamoxifen, radiation therapy, or both for prevention of ipsilateral breast tumor recurrence after lumpectomy in woman with invasive breast cancers of one centimeter or less. *J Clin Oncol.* 2002;20: 4141-4149.
7. Fourquet A, Campana F, Zafrani B, et al. Prognostic factors of breast recurrence in the conservative management of early breast cancer: A 25-year follow-up. *Int J Radiat Oncol Biol Phys.* 1989;17:719-725.
8. Locker AP, Ellis IO, Morgan DAL, et al. Factors influencing local recurrence after excision and radiotherapy for primary breast cancer. *Br J Surg.* 1989;76:890-894.
9. Freedman GM, Hanlon AL, Fowble BL, et al. Recursive partitioning identifies patients at high and low risk for ipsilateral tumor recurrence after breast-conserving surgery and radiation. *J Clin Oncol.* 2002;20:4015-4021.
10. Jobsen JJ, van der Palen J, Meerwaldt JH. The impact of age on local control in women with pT1 breast cancer treated with conservative surgery and radiation therapy. *Eur J Cancer.* 2001;37:1820-1827.
11. Arriagada R, Le MG, Contesso G, et al. Predictive factors for local recurrence in 2006 patients with surgically resected small breast cancer. *Ann Oncol.* 2002;13:1404-1413.
12. Kroman N, Holtveg H, Wohlfahrt J, et al. Effect of breast-conserving therapy versus radical mastectomy on prognosis for young women with breast carcinoma. *Cancer.* 2004;15: 688-693.
13. Vrieling C, Collette L, Fourquet A, et al. Can patient-, treatment- and pathology-related characteristics explain the high local recurrence rate following breast-conserving therapy in young patients? *Eur J Cancer.* 2003;39:932-944.
14. Park CC, Mitsumori M, Nixon A, et al. Outcome at 8 years after breast-conserving surgery and radiation therapy for invasive breast cancer: influence of margin status and systemic therapy on local recurrence. *J Clin Oncol.* 2000;18: 1668-1675.
15. Renton SC, Gazet J-C, Ford HT, et al. The impact of the resection margin in conservative surgery for breast cancer. *Eur J Surg Oncol.* 1996;22:17-22.

16. Mansfield CM, Komarnicky LT, Schwartz GF, et al. Ten-year results in 1070 patients with stages I and II breast cancer treated by conservative surgery and radiation therapy. *Cancer.* 1995;75:2328–2336.
17. Singletary SE. Surgical margins in patients with early-stage breast cancer treated with breast conservation therapy. *Am J Surg.* 2002;184:383–393.
18. Smitt MC, Nowels K, Carlson RW, et al. Predictor of reexcision findings and recurrence after breast conservation. *Int J Radiot Oncol Biol Phys.* 2003;57:979–985.
19. Peterson ME, Schultz DJ, Reynolds C, et al. Outcomes in breast cancer patients relative to margin status after treatment with breast-conserving surgery and radiation therapy: the University of Pennsylvania experience. *Int J Radiat Oncol Biol Phys.* 1999;15:1029–1035.
20. Fisher B, Anderson S, Fisher ER, et al. Significance of ipsilateral breast tumour recurrence after lumpectomy. *Lancet.* 1991;338:327–331.
21. Veronesi U, Marubini E, Del Vecchio M, et al. Local recurrences and distant metastases after conservative breast cancer treatments: partly independent events. *J Natl Cancer Inst.* 1995;87:19–27.
22. Kurtz JM, Spitalier JM, Amalric R, et al. The prognostic significance of late local recurrence after breast-conserving therapy. *Int J Radiat Oncol Biol Phys.* 1990;18:87–93.
23. Whelan T, Clark R, Roberts R, et al. Ipsilateral breast tumor recurrence postlumpectomy is predictive of subsequent mortality: results from a randomized trial. *Int J Radiat Oncol Biol Phys.* 1994;30:11–16.
24. Kemperman H, Borger J, Hart A, et al. Prognostic factors for survival after breast conserving therapy for stage I and II breast cancer. The role of local recurrence. *Eur J Cancer.* 1995;31A:690–698.
25. Haffty BG, Reiss M, Beinfield M, et al. Ipsilateral breast tumor recurrence as a predictor of distant disease: implications for systemic therapy at the time of local relapse. *J Clin Oncol.* 1996;14:52–57.
26. Freedman GM, Fowble B. Local recurrence after mastectomy or breast-conserving surgery and radiation. *Oncology (Huntingt).* 2000;14:1561–81.
27. Fowble BL. Ipsilateral breast tumor recurrence following breast-conserving surgery for early-stage invasive cancer. *Acta Oncol.* 1999;38(Suppl 13):9–17.
28. Meric F, Mirza NQ, Vlastos G, et al. Positive surgical margins and ipsilateral breast tumor recurrence predict disease-specific survival after breast-conserving therapy. *Cancer.* 2003; 97:926–933.
29. Della Rovere GQ, Benson RJ. Ipsilateral breast tumor recurrence of breast cancer: determinant or indicator of poor prognosis. *Lancet Oncol.* 2002;3:183–187.
30. Vicini FA, Kestin L, Huang R, Martinez A. Does local recurrence affect the rate of distant metastases and survival in patients with early-stage breast carcinoma treated with breast-conserving therapy? *Cancer.* 2003;15:910–919.
31. McBain CA, Young EA, Swindell R, et al. Local recurrence of breast cancer following surgery and radiotherapy: incidence and outcome. *Clin Oncol (R Coll Radiol).* 2003;15:25–23.
32. 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.* 2001;91:1679–1687.
33. Recht A, Silen W, Schnitt SJ, et al. Time-course of local recurrence following conservative surgery and radiotherapy for early stage breast cancer. *Int J Radiat Oncol Biol Phys.* 1988;15:255–261.
34. 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.
35. Cowen D, Houvenaeghel G, Bardou V, et al. Local and distant failures after limited surgery with positive margins and radiotherapy for node-negative breast cancer. *Int J Radiat Oncol Biol Phys.* 2000;47:305–312.
36. Kodaira T, Fuwa N, Itoh Y, et al. Aichi Cancer Center 10-year experience with conservative breast treatment of early breast cancer: retrospective analysis regarding failure patterns and factors influencing local control. *Int J Radiat Oncol Biol Phys.* 2001;49:1311–1316.
37. Ohsumi S, Sakamoto G, Takashima S, et al. Long-term results of breast-conserving treatment for early-stage breast cancer in Japanese women from multicenter investigation. *Jpn J Clin Oncol.* 2003;33:61–67.
38. Early Breast Cancer Trialists' Collaborative Group. Favourable and unfavourable effects on long-term survival of radiotherapy for early breast cancer: an overview of the randomized trials. *Lancet.* 2000;355:1757–1770.
39. Silverstein MJ, Lagios MD, Groshen S, et al. The influence of margin width on local control of ductal carcinoma in situ of the breast. *N Engl J Med.* 1999;13:1455–1461.
40. Harrold EV, Turner BC, Matloff ET, et al. Local recurrence in the conservatively treated breast cancer patients: a correlation with age and family history. *Cancer J Sci Am.* 1998;4:302–307.
41. Le MG, Arriagada R, Spielmann M, et al. Prognostic factors for death after an isolated local recurrence in patients with early-stage breast carcinoma. *Cancer.* 2002;94:2813–2820.
42. Schmoor C, Sauerbrei W, Bastert G, et al. Role of isolated locoregional recurrence of breast cancer: results of four prospective studies. *J Clin Oncol.* 2000;18:1696–1708.
43. Touboul E, Buffat L, Belkacemi Y, et al. Local recurrences and distant metastases after breast-conserving surgery and radiation therapy for early breast cancer. *Int J Radiot Oncol Biol Phys.* 1999;43:25–38.
44. Haffty BG, Fischer D, Beinfield M, et al. Prognosis following local recurrence in the conservatively treated breast cancer patient. *Int J Radiat Oncol Biol Phys.* 1991;21:293–298.
45. Vinh-Hung V, Verschraegen C. Breast-conserving surgery with or without radiotherapy: pooled-analysis for risks of ipsilateral breast tumor recurrence and mortality. *J Natl Cancer Inst.* 2004;96:115–121.
46. Smith TE, Lee D, Turner BC, et al. True recurrence vs. new primary ipsilateral breast tumor relapse: an analysis of clinical and pathologic differences and their implications in natural history, prognoses, and therapeutic management. *Int J Radiat Oncol Biol Phys.* 2000;48:1281–1289.
47. Huang E, Buchholz TA, Meric F, et al. Classifying local disease recurrences after breast conservation therapy based on location and histology: new primary tumors have more favorable outcomes than true local disease recurrences. *Cancer.* 2002;95:2059–2067.
48. Haffty BG, Carter D, Flynn SD, et al. Local recurrence versus new primary: clinical analysis of 82 breast relapses and potential applications for genetic fingerprinting. *Int J Radiat Oncol Biol Phys.* 1993;27:575–583.
49. Lannin D, Haffty BG. End results of salvage therapy after failure of breast-conservation surgery. *Oncology.* 2004;18:272–279.