日常診療の指針

乳房温存療法後の乳房内再発の意義

Implications of ipsilateral breast tumor recurrence (IBTR) after breast conserving therapy (BCT)

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乳房温存療法後の乳房内再発は，10年の経過観察で約10%程度みられ，近年遭遇する機会が増えてきた．乳房内再発をどう対処するかを考えるとき，乳房内再発の意義や特徴の理解が必要となる．

1．乳房内再発の定義

乳房内再発は，厳密には乳房温存療法後に原発巣の遺残が徐々に増大して認知される大きさになったものである．しかし温存療法の場合，原発巣がいったん根治したあとで，新たに同側乳房に発生した第二癌(new primary)もあり得る．いずれの場合であるかは，発生した部位や発症の時期などからある程度推測できる場合もあるが，正確な区別は困難である．また同時期に多発病巣が存在し，一方が顕在化した場合も考えられる．これらは本来別物として扱うべきものであるが，区別することが困難であり，欧米の報告の多くは乳房内再発(ipsilateral breast tumor recurrence；IBTR)ということばで同一のものと扱っている．本稿でも乳房内再発を同側乳房に発生した癌をすべて含めて扱った．

2．乳房内再発に対する理解とその変遷

古くは，乳房内再発は，生命予後を左右する遠隔再発と違って予後の良いものと考えられていた．それはStage I，II の乳癌に対して，温存療法と乳房切除の生存率が同等であること，乳房内再発の危険因子と遠隔再発の危険因子が異なることより両者は異質のものと考えられることなどが根拠となっていた．しかし現実には，乳房内再発を来した症例はそうでない症例よりも遠隔再発を来しやすく，その予後も悪いことが多くの大規模な臨床試験の解析から示された．すなわち近年では，乳房内再発はひき続き起こる遠隔再発の重要な予知因子であることが広く認知されている．なお，欧米の報告のいくつかは，領域リンパ節と乳房内再発を含めて扱っている(locoregional recurrence)．筆者らの理解では，領域リンパ節再発は乳房内再発と再発様式が異なっており，区別すべきものと考えられる．本稿でも乳房内再発のみのもの(isolated ipsilateral breast tumor recurrence)を対象とした．Isolated ipsilateral breast tumor recurrence だけに限った場合でもやはり乳房内再発は遠隔再発の予知因子であり，予後も悪い(図1)．しかし遠隔再発の予後や，領域リンパ節再発の予後と比べると比較的良好である．

3．乳房内再発のなかでどのようなもので予後が不良と考えられるか

乳房内再発の予後因子について，これまで報告されていることを述べる．原発巣に関与する因子としては，原発時のリンパ節転移の有無，組織学的異型度，腫瘍径などが報告されている．当然ではあるが転移陽性，異型度が高度，腫瘍径が大きいものの予後が悪い．再発巣については再発形式，腫瘍径，異型度，再発発見契機，再発部位などがあげられてい

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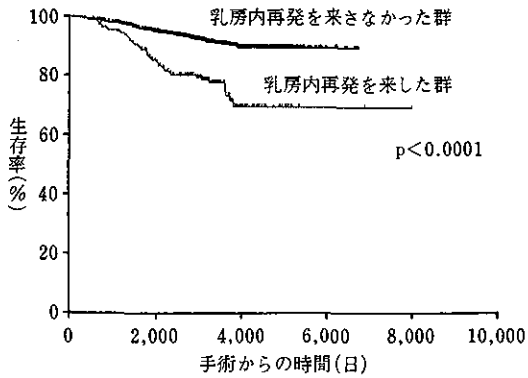

図1 厚生労働省がん研究助成金稲治班アンケート調査より (2002年6月)

る．とくに再発巣では，再発形式としてび漫性で手術不能な症例(炎症性乳癌型再発)や，皮膚や筋肉など乳腺組織以外からの再発は予後が不良である．また，乳腺内の再発巣が皮膚などに及ぶものも予後不良である．再発部位として，原発巣の近傍からの再発が不良とされる(再発部位は原発巣手術から8年くらいまでは原発巣の近傍の再発が多く，それを超えると他のquadrantからの再発が多いとされている)．それ以外の項目で重要なものは，初回手術から乳房内再発までの期間(DFI)である．多くの報告でDFIが短いものほど予後不良としている．これらの項目のなかで最もインパクトが高いものは再発形式(炎症性乳癌型再発はきわめて予後不良)であるが，手術可能な乳房内再発に限って考えると，恐らく原発巣におけるリンパ節転移とDFIが乳房内再発の予後を左右する最も重要な因子であろう．わが国においても，厚生労働省がん研究助成金稲治班において乳房内再発の意義が検証され，リンパ節転移とDFIが乳房内再発における遠隔転移の予知因子であった．

おわりに

乳房内再発は引き続き起こる遠隔再発の予知因子として重要な意義がある．それはとくに原発巣でリンパ節転移陽性，DFIが短い場合により重要である．現在，乳房内再発が遠隔転移の予知因子のみならず原因となり得るかどうかということが議論の対象となっている．また乳房内再発に対する治療法が問題となるが，このようなセッティングにおける至適な全身療法について検討した臨床試験はまだない(NSABPで乳房内再発を対象とした全身療法に関する試験を計画中とのことである)．局所治療については，一般的には残存乳房切除がなされている．再温存手術も一部のグループで試みられており良好な結果であるものの，その安全性は現在のところ明らかになっていない．以上，乳房温存療法後の乳房内再発の意義と今後の問題点について，これまでの報告とわれわれの私見を交えて述べた．

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Review Article

Breast-Conserving Treatment after Neoadjuvant Chemotherapy in Large Breast Cancer

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Several recent trials have demonstrated that neoadjuvant chemotherapy can allow more patients to successfully undergo breast-conserving treatment (BCT), and does not confer a survival disadvantage compared with standard adjuvant chemotherapy. In addition, the pathological response of primary breast tumors to neoadjuvant chemotherapy appears to be a surrogate marker for patient outcome.

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. The margin positive rate was 14.1% (9/64), similar to the rate after BCT for early-stage breast cancers, the largest diameter of which was smaller than 3 cm. At a median follow-up of 30 months, only 3 patients in the BCT group have developed local recurrence; the local recurrence rate appears to be comparable to that after BCT for early stage breast cancers. Long term follow-up is required, however, to establish whether this procedure is a safe alternative to mastectomy for patients with large breast cancers.

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Key words: Breast cancer, Neoadjuvant chemotherapy, Breast-conserving treatment, Local recurrence

Neoadjuvant chemotherapy has become the standard treatment for patients with locally advanced breast cancer, not only in western countries but also in Japan. Several recent studies, including that of the NSABP B-18 trial[1], have shown that breast cancer patients treated with neoadjuvant chemotherapy do not survive longer than those treated with conventional postoperative adjuvant chemotherapy. However, neoadjuvant chemotherapy seems to have several advantages over postoperative adjuvant chemotherapy. The most immediate advantage of neoadjuvant chemotherapy is that large breast cancers can be downstaged facilitating breast-conserving treatment (BCT) in patients for whom mastectomy is initially the only option for local control. In this review article, the feasibility of BCT for large breast cancer using neoadjuvant chemotherapy will be discussed.

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Breast Conservation after Neoadjuvant Chemotherapy: Studies and Trials

Since the early 1990s, a number of non-rondomized studies have evaluated breast-conserving treatment (BCT) after neoadjuvant chemotherapy in patients with locally advanced breast cancer or in patients with large breast cancer (usually larger than 3 cm)[2-11] (Table 1). Neoadjuvant chemotherapy is very effective for treating breast cancer with overall objective response rates generally higher than those reported previously for patients with metastatic disease; these range from 70% to more than 90%[1-11]. Regimens commonly used in neoadjuvant chemotherapy often contain anthracycline or methotrexate. Recently, docetaxel and paclitaxel were shown to be highly active not only in an adjuvant setting but also in a neoadjuvant setting[11, 12]. The NSABP implemented protocol B-27, a randomized trial, that evaluates the efficacy of docetaxel when administered in the preoperative or postoperative setting following doxorubicin and cyclophosphamide (AC) therapy.

Neoadjuvant chemotherapy was developed largely for a subgroup of patients with large breast cancer in the hope that downstaging would allow mas-

Table 1. Reported Rates of Breast Conservation after Neoadjuvant Chemotherapy: Non-Randomized Trials Performed within the Last 10 Years

Author (year)	Patient selection	Chemotherapy	n	BCT rate (%)	Median follow-up (mos)	Local recurrence (%)
Calais* (1994)	T≧3 cm	MxVCF or EVCF	158	49	38	8
Schwartz (1994)	stage ⅡB, Ⅲ	CMF	189	36	46	1
Veronesi (1995)	T≧3 cm	CMF	226	90	36**	6
Touboul* (1997)	stage Ⅱ-Ⅳ	AVCF	147	65	94	20
Merajver (1997)	stage Ⅲ	CAMF	89	28	54	14
Bonadonna (1998)	T≧3 cm	CMF or A	536	85	65	7
Danforth* (1998)	stage Ⅲ	CAMF	126	33	99	19
Mauriac* (1999)	T>3 cm	E	134	63	124	28
Kuerer (1999)	stage Ⅱ-Ⅳ	CAF	372	29	58	6
Bellino (2000)	T>3 cm	EP	48	65	NA	NA

*Some or all patients received radiation therapy as the only locoregional treatment.

**Mean

BCT, breast-conserving treatment; NA, not available; Mx, mitoxantrone; V, vindesine; C, cyclophosphamide; F, 5-fluorouracil; E, epirubicin; M, methotrexate; A, adriamycin; P, paclitaxel

Table 2. Randomized Trials Comparing Neoadjuvant Chemotherapy with Postoperative Chemotherapy

Author (year)	Patient selection	Chemotherapy	n	BCT rate (%)	Median follow-up (mos)	Local recurrence (%)
Scholl (1994)	stage Ⅱ, Ⅲ	CAF→RT→S	200	82	54	10.6
		RT→S→CAF	190	77		8.2
Fisher (1998)	stage Ⅰ, Ⅱ	AC→S	752	68	60	7.9
		S→AC	743	60		5.8
Makris (1998)	stage Ⅰ-Ⅲ	MxM (Mi)→S	149	89	48	3.5
		S→MxM (Mi)	144	78		2.7

BCT, breast-conserving treatment; S, surgery; RT, radiation therapy; C, cyclophosphamide; A, adriamycin; F, 5-fluorouracil; Mx, mitoxantrone; M, methotrexate; Mi, mitomycin

tectomy to be avoided. Results from non-randomized studies suggest that this aim can be frequently achieved; the rates of BCT range from 28-90% (Table 1). However, it is meaningless to compare the BCT rates against each other, because none of these trials randomly assigned patients to BCT versus mastectomy after chemotherapy, the rate of BCT is usually related to the initial extent of the primary tumor, and not all the women in these studies desired BCT.

Currently, three randomized trials have compared these rates in patients treated with chemotherapy preoperatively versus postoperatively[1, 13, 14] (Table 2). Results from these trials confirmed that the need for mastectomy can be reduced with neoadjuvant chemotherapy, but the extent of the benefit is lower than in non-randomized studies. In the largest randomized series comparing neoadjuvant and adjuvant chemotherapy in patients with stage Ⅰ and Ⅱ breast cancer, the NSABP B-18 trial, BCT was achieved in 68% of patients in the group treated with neoadjuvant chemotherapy compared with 60% in the postoperative group ($p = 0.002$)[1]. The NSABP B-18 trial also demonstrates that in contrast to clinical CR, pathological CR is an excellent predictor of long-term outcome[1].

The Problem of Local Recurrence

Local recurrence rates are an important issue in the context of avoiding mastectomy. As shown in Table 2, none of the randomized trials have shown any significant difference in the local control rate between the two procedures[1, 13, 14]. In the NSABP B-18 trial, for example, 7.9% of 752 women randomly

assigned to the neoadjuvant chemotherapy arm developed local recurrence. This local recurrence rate was comparable to the 5.8% local recurrence rate found in 743 eligible women randomly assigned to postoperative adjuvant therapy[1]. However, when women in the neoadjuvant chemotherapy group who were downstaged were compared with those who underwent BCT as initially planned, the overall rate of local recurrence was twice as great in those who were downstaged. In this study, Fisher *et al.*[1] suggested that the rate of local recurrence might be reduced further if younger women with estrogen receptor (ER)-positive tumors were treated with tamoxifen, and a radiation boost to the lumpectomy site was given in patients whose tumors had been downstaged.

One way to potentially avoid local recurrence rates in the neoadjuvant setting is to obtain a clear surgical margin, because a positive surgical margin is a risk factor for local recurrences when conducting BCT[15]. It is important to remember, however, that an invasive tumor may shrink in the center, leaving small islands of tumor at the periphery[16]. Based on pathological assessment of the response, El-Didi *et al.*[17] demonstrated that only 26.7% of the patients who showed objective response were suitable candidates for BCT. Mammography and ultrasonography are important in the evaluation of response. However, ill-defined masses should be assessed with other imaging procedures[18]. Recently, magnetic resonance imaging or contrast-enhanced computed tomography have been shown to be useful in estimating the residual extent of disease after neoadjuvant chemotherapy[19,20].

Singletary *et al.*[21] established criteria for recommending BCT after neoadjuvant chemotherapy. They included the patient's desire for BCT, resolution of skin edema if initially present, residual tumor size < 5 cm, absence of extensive breast lymphatic invasion, absence of extensive suspicious microcalcifications, and no evidence of multicentricity. According to their criteria, women with residual tumors smaller than 5 cm are considered acceptable candidates for this procedure. In general, Japanese surgeons consider women with tumors smaller than 3 cm acceptable candidates for BCT.

Whether breast surgery after neoadjuvant chemotherapy is necessary in all patients remains controversial. Although most investigators advocate lumpectomy with or without axillary dissection, some authors indicate that surgery can be avoided if there is a complete clinical response. As can be seen in Table 1, local recurrence rates were highest in trials in which some or all patients received radiation therapy as the only form of locoregional treatment. In the Royal Marsden Hospital series, patients who had a complete or near complete response and electively underwent radiotherapy instead of surgery showed a significantly increased rate of local recurrence compared with those treated with surgery despite achieving clinical remission[22]. Kuerer *et al.*[23] recommend the placement of metallic clips early during neoadjuvant chemotherapy to facilitate later evaluation of the tumor site when tumor regression is marked.

Danforth *et al.*[8] suggested that inflammatory carcinoma at presentation may be an indicator of increased risk for local recurrence with breast-sparing radiotherapy, and that mastectomy may be more appropriate for this subset of patients. In their series, two of eight patients with local recurrence had diffuse skin involvement[8]. Inflammatory breast recurrence after BCT, the most dismal type of local recurrence, is considered to be an occult type of primary inflammatory breast cancer[24]. To avoid inflammatory breast recurrence, BCT should not be recommended for patients with inflammatory carcinoma even if downstaging is achieved.

Axillary Surgery after Neoadjuvant Chemotherapy

It has become clear that neoadjuvant chemotherapy has a significant effect on axillary lymph node metastases. In the NSABP B-18 trial, neoadjuvant chemotherapy resulted in a significant downstaging of axillary involvement, regardless of primary tumor size and clinical nodal status[1]. MD Anderson investigators[25] found that 23% of patients with locally advanced breast cancer and axillary metastases documented by fine needle aspiration cytology before treatment had completely pathologically negative nodes at dissection after four cycles of doxorubicin-containing neoadjuvant chemotherapy. Persistently involved pathological node after neoadjuvant chemotherapy is a predictor of poor outcome. In the Milan series, for example, 8-year disease-free survival was 75% for node-negative patients compared with 51% when 1-3 nodes were involved, and 35% when more than 3 nodes were involved[7].

To better gauge the necessity of axillary dissection, investigators at the MD Anderson Cancer Center have been enrolling patients whose disease has been clinically downstaged to T0-2, N0 and who

have become appropriate candidates for BCT in a prospective randomized trial of axillary dissection versus radiation therapy[23]. Until the results are available from the MD Anderson trial, axillary dissection after neoadjuvant chemotherapy remains the standard care.

The use of sentinel node biopsy in patients treated with neoadjuvant chemotherapy still remains controversial. Cox *et al.*[26] suggested that sentinel node biopsy be performed before neoadjuvant chemotherapy and that patients with detected axillary metastases be treated with axillary dissection after neoadjuvant chemotherapy. The combination of a gamma probe and fine needle aspiration, a potentially useful method for preoperative detection of sentinel node metastases[27], may be an alternative to sentinel node biopsy before chemotherapy. The role of sentinel node biopsy in patients treated with neoadjuvant chemotherapy is currently being prospectively evaluated by several investigators.

Experience at Osaka Medical Center for Cancer and Cardiovascular Diseases

Our own experience at the Osaka Medical Center for Cancer and Cardiovascular Diseases began in May 1995 with patients whose tumors were of sufficient size for mastectomy to be recommended. Between May 1995 and December 2000, 86 patients were enrolled. The criteria for inclusion were as follows: The largest tumor dimension between 3.1-6.0 cm, and N0-1, M0 disease. The pathological diagnosis of invasive breast cancer was confirmed on core biopsy specimen. Neoadjuvant chemotherapy consisted of four cycles of cyclophosphamide and epirubicin (CE), at 600 and 60 mg/m^2, respectively. The drugs were given intravenously on day 1 of the cycle, which was repeated every 21 days. Administration of CE was delayed as a result of hematologic toxicity on day 1 of any cycle. Early in the study, a regimen of cyclophosphamide, epirubicin and 5-fluorouracil (CEF) was given to 16 patients. The drug dosages of CEF were as follows: Cyclophosphamide, 100 mg/body/day for 14 days, epirubicin, 40 mg/m^2, and 5-fluorouracil, 500 mg/m^2. Patients were to receive all four cycles of chemotherapy, unless clinically progressive disease occurred before completion of therapy. Following neoadjuvant chemotherapy all patients underwent surgery. When technically and cosmetically feasible, breast-conserving surgery was performed. Those patients with minimal or no response to chemotherapy underwent mastectomy. All patients underwent axillary dissection.

Following surgery, all responders were given an additional 2 cycles of chemotherapy consisting of the same regimen as given before surgery. Radiation therapy was given to women who received breast-conserving surgery within 4 weeks after completion of their last course of chemotherapy. The dosage was 50 Gy over 5 weeks. Patients with a positive margin received a radiation boost to the tumor bed.

The response to neoadjuvant chemotherapy was assessed preoperatively both clinically and mammographically and scored as follows: Complete response (CR), partial response (PR), no change (NC), or progressive disease (PD). The criterion adopted to assess pathological CR was disappearance of an invasive tumor from the breast.

The main adverse effects were leukopenia, nausea, vomiting and alopecia. Among the 86 patients who underwent neoadjuvant chemotherapy, Grade 2-4 leukopenia was observed in 29 patients (33.7%), nausea and vomiting in 22 patients (25.6%) and alopecia in 86 patients (100%). Of the 86 patients enrolled in the study, 55 patients (64.0%) achieved clinical response (CR or PR), including 9 patients (10.5%) with CR. Finally, 64 patients (74.4%) underwent BCT. These 64 patients corresponded to 5.3% of the total breast cancer surgeries (1,200 cases) during the study period, indicating that neoadjuvant chemotherapy resulted in a 5.3% increase of the BCT rate. Median follow-up was 30 months (range 7 to 73 months).

There was only one patient with pathological CR with non-invasive carcinoma only in the resected specimen. The low rate of pathological CR (1.2%) may result from the regimen of chemotherapy or the accuracy of pathological examination.

The rate of BCT, margin status, and follow-up results at a median follow-up of 30 months according to the primary tumor size are listed in Table 3. Depending on the initial size of the primary tumor, 58.3% to 83.3% of women treated with neoadjuvant chemotherapy underwent BCT: the smaller the tumor size, the higher the likelihood of BCT. Among the 64 patients, 9 patients (14.1%) showed a pathologically positive margin. The positive margin rate was similar to that after BCT for tumors measuring less than 3 cm in diameter in our series (Table 4). Powles *et al.*[28] also reported a randomized trial in which no significant difference was observed in positive margin rates between neoadju-

Table 3. Rate of BCT, Positive Margin Rate, and Follow-up Results after Neoadjuvant Chemotherapy

	Tumor Size			Total
	31-40 mm	41-50 mm	51-60 mm	
Eligible	42	32	12	86
BCT	35	22	7	64
BCT rate	83.3%	68.8%	58.3%	74.4%
Positive margin	5	4	0	9
Breast Rec.	1	1	0	2
Distant Rec.	3	3	1	7
Inflam. ca.	1	0	0	1

Breast Rec., breast recurrence; Distant Rec., distant recurrence; Inflam. ca., inflammatory breast recurrence

Table 4. Margin Status in Breast Cancer Treated with BCT after Neoadjuvant Chemotherapy Compared to that after BCT for Tumors Smaller than 3 cm

Tumor Size	Total	No. of positive Margin (%)	Histology of Positive Margins		
			DCIS	IDC	ly
≦3 cm	676	120 (17.8) *NS	97 (14.3) **NS	20 (3.0) ***	3 (0.4)
>3 cm (NACT)	64	9 (14.1) *	2 (3.1) **	6 (9.4) ***	1 (1.6)

*NS; **$p < 0.05$; ***$p < 0.01$; DCIS, ductal carcinoma *in situ*; IDC, invasive ductal carcinoma; ly, lymphatic invasion

vant and postoperative chemotherapy groups. However, it should be noted that of the 9 patients with positive margins in our series, 7 patients had positive margins caused by invasive lesions or lymphatic invasion.

At a median follow-up of 30 months, which is too brief to allow meaningful interpretation, local recurrence was observed in only 3 patients. This low recurrence rate appears to be comparable to that after BCT for early-stage breast cancers with a diameter less than 3 cm. It should be noted that one of the 3 patients with local recurrence had an inflammatory breast recurrence.

Long term follow-up is required, however, to allow adequate assessment of the real efficacy of this approach.

References

1) Fisher B, Bryant J, Wolmark N, *et al*: Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. *J Clin Oncol* 16:2672-2685, 1998.
2) 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.
3) 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.
4) 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.
5) Touboul E, Lefranc JP, 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.
6) 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.
7) 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.
8) Danforth DN Jr, Zujewski J, O'Shaughnessy J, *et al*: Selection of local therapy after neoadjuvant chemotherapy in patients with stage III A, B breast cancer. *Ann Surg Oncol* 5:150-158, 1998.
9) 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.

10) 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.
11) Bellino R, Cortese P, Danese S, *et al*: Epidoxorubicin and paclitaxel as primary chemotherapy for T > 3 cm and T4 breast cancer patients. *Anticancer Res* 20:4825-4828, 2000.
12) Gradishar WJ: Docetaxel as neoadjuvant chemotherapy in patients with stage Ⅲ breast cancer. *Oncol* 11 (supp 8):15-18, 1997.
13) Scholl SM, Fourquet A, Asselain B, *et al*: Neoadjuvant versus adjuvant chemotherapy in premenopausal patients with tumours considered too large for breast conserving surgery: Preliminary results of a randomized trial: S6. *Eur J Cancer* 30A:645-652, 1994.
14) 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.
15) Noguchi S, Koyama H, Kasugai T, *et al*: A case-control study on risk factors for local recurrences or distant metastases in breast cancer patients treated with breast-conserving surgery. *Oncol* 54:468-474, 1997.
16) Hunt KK, Buzdar AU: Breast conservation and tumor down-staging. In: Singletary S, ed. Breast Cancer. New York: Springer-Verlag, pp196-205, 1998.
17) 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* 30:249-254, 2000.
18) Huber S, Wagner M, Zuna I, *et al*: Locally advanced breast carcinoma: evaluation of mammography in the prediction of residual disease after induction chemotherapy. *Anticancer Res* 20:553-558, 2000.
19) 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* 17:110-119, 1999.
20) 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.
21) Singletary SE, Dhingra K, Yu DH: New strategies in locally advanced breast cancer. *Cancer Treat Res* 90:253-271, 1997.
22) Ellis P, Smith I, Ashley S, *et al*: Clinical prognostic and predictive factors for primary chemotherapy in operable breast cancer. *J Clin Oncol* 16:107-114, 1998.
23) 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.
24) Nishimura R, Koyama H, Kasumi F *et al*: A case control study on risk factors involved in inflammatory breast recurrence after breast-conserving surgery. *Oncol* 55:391-399, 1998.
25) Kuerer HM, Sahin AA, Hunt KK *et al*: Incidence and impact of documented eradication of breast cancer axillary lymph node metastases before surgery in patients treated with neoadjuvant chemotherapy. *Ann Surg* 230:72-78, 1999.
26) Cox CE, Haddad F, Bass S *et al*: Lymphatic mapping in the treatment of breast cancer. *Oncology* 12:1283-1298, 1998.
27) Motomura K, Inaji H, Komoike Y, *et al*: Gamma probe and ultrasonographically -guided fine needle aspiration biopsy of sentinel lymph node in breast cancer patients. *Eur J Surg Oncol* 27:141-145, 2001.
28) Powles TJ, Hickish TF, Makris HA, *et al*: Randomized trial of chemoendocrine therapy started before or after surgery for treatment of primary breast cancer. *J Clin Oncol* 13:547-552, 1995.

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Original Article

Long-Term Results of Breast Conserving Surgery for Stages I and II Breast Cancer: Experiences at Osaka Medical Center for Cancer and Cardiovascular Diseases

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Purpose: The purpose of this study is to summarize the long-term results of breast conserving surgery (BCS) for Japanese patients with stage I and II breast cancer at a single institute and to identify risk factors for local recurrence after BCS.

Patients and Methods: Between October 1986 and June 2000, 979 women underwent BCS with or without radiation therapy (RT). Overall survival, disease free survival and local recurrence rates were calculated by the Kaplan-Meier method. Risk factors for local recurrence were examined by multivariate analysis using the Cox proportional regression model.

Results: The 10-year overall survival rates were 90.9% for the surgery and radiation therapy (RT group) and 89.3% for the surgery only group with a median follow-up time of 46 months. The 10-year disease free survival rates were 85.1% in the RT group and 69.2% in the surgery only group ($p = 0.0001$). The positive margin rate was 14.1% (138/979). The 10-year overall survival rate of the patients with positive margins was 87.9%, compared with 90.8% for patients with negative margins (N.S.). The cumulative incidence of local recurrence at 10 years was significantly lower in the RT group (7.2%) than in the surgery only group (27.5%) ($p < 0.0001$). Multivariate analysis showed that positive margins and lack of post-operative irradiation or adjuvant endocrine therapy were risk factors for non-inflammatory local recurrence.

Conclusions: Our study indicates that BCS can be performed for Japanese women with early breast cancer. The margin status and post-operative irradiation had no influence on overall survival while but were significantly related to local recurrence.

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Key words: Breast cancer, Breast-conserving surgery, Local recurrence, Risk factor

Results of several randomized trials or meta-analyses have shown that lumpectomy or quadrantectomy with adequate post-operative breast irradiation produces survival rates similar to those of mastectomy for Stage I or II breast cancer[1-5]. Therefore, breast-conserving surgery (BCS) has become standard treatment for early breast cancer.

BCS was initiated in Japan in 1986, but there are few reports on the results for Japanese women with breast cancer[6-9]. The follow-up period was often rather short, or the study population was not large enough. Furthermore, the criteria for BCS, surgical procedures and post-operative treatment are different among hospitals. Thus it is difficult to evaluate the results of BCS in Japan. We initiated BCS for early breast cancer patients in October 1986. BCS was carried out by a small team of breast surgeons. The analysis of the results of BCS became possible due to a lengthened follow up period and an increase in the total number of patients. In this paper, we present the long-term results of BCS based on a large population at a single institute in Japan.

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Abbreviations:
BCS, Breast conserving surgery; RT, Radiation therapy

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Patients and Methods

Patients

Between October 1986 and June 2000, 1,037

Table 1. Characteristics of the Patients

tumor size	
T0	41 (pts)
T1	636
T2	302
nodal status	
0	682
n(+) 1-3	178
n(+) 4-9	36
n(+) 10≦	20
unknown	63
histology	
carcinoma *in situ*	97
invasive cancer	882
ER	
negative	285
positive	303
unknown	391
RT	
(−)	53
(+)	926
adjuvant therapy	
(−)	287
endocrine	595
chemo-endocrine	66
chemothrapy	31

patients underwent BCS at Osaka Medical Center for Cancer and Cardiovascular Diseases. Patients with distant metastasis (n = 3) or those who underwent primary chemotherapy (n = 55) were excluded from this study. Therefore, 979 patients without distant metastasis whose tumor size was less than 3 cm in diameter and without diffuse microcalcification on mammography were included in this study. The characteristics of these patients are summarized in Table 1.

Surgical Procedure and Pathological Examination

The mammary gland was resected roundly with at least 1.5 cm gross tumor-free margins. A level I and II axillary lymph node dissection was performed through a separate axillary incision. Pathological findings were examined by well trained pathologists. Exposure of cancer cells on the cut surface on pathologic examination was evaluated as positive margin. Histological subtype, lymphovascular invasion, histological grade and lymph node metastasis were evaluated as risk factors for local recurrence.

Post-Operative Irradiation

Post-operative irradiation was given at 50 Gy to the whole breast and an additional 13.2 Gy of boost irradiation was given to patients with positive margins. Nine hundred and twenty-six patients were treated with post-operative irradiation and 98 of these patients received boost irradiation. Fifty-three patients did not receive radiation therapy.

Adjuvant Therapy

A total of 595 patients (60.8%) were treated with adjuvant endocrine therapy, 66 (6.7%) with adjuvant chemo-endocrine therapy and 31 (3.2%) with adjuvant chemotherapy. The adjuvant therapy regimen was not uniform. As endocrine therapy, tamoxifen, LH-RH agonist or both was used for two years. Tamoxifen was used most frequently (569 patients). Chemotherapy included regimens such as CMF, doxorubicin-containing regimen or oral anti-cancer agents.

Analysis

Overall survival and disease-free survival rates were determined by the Kaplan-Meier method. Statistical analysis was done using a log-rank test. As for risk factors for local recurrence, we analyzed margin status, histological type, adjuvant endocrine therapy, adjuvant chemotherapy, post-operative irradiation, age, size, nodal status, lymphovascular invasion and histological grade. These factors were analyzed using the chi-square test for univariate analysis and the Cox proportional regression model for multivariate analysis.

Results

Fig 1 shows the follow-up results of BCS according to the margin status. The survival curves of patients treated with BCS with and without RT are shown in Fig 2. The 10-year overall survival was 90.9% in the RT group and 89.3% in the no RT group (Fig 2). The 10-year disease-free survival was 85.1% and 69.2%, respectively (Fig 3). Overall survival results were favorable regardless of the margin status or post-operative radiation therapy. Eighty-seven patients relapsed during a median follow-up time of 46 months. Recurrence consisted of local (44 patients), regional lymph node (10 patients) and recurrence in distant organ disease (33 patients). Local recurrence was further categorized into three types: in-breast recurrence (31 patients), skin or muscle recurrence in the ipsilat-

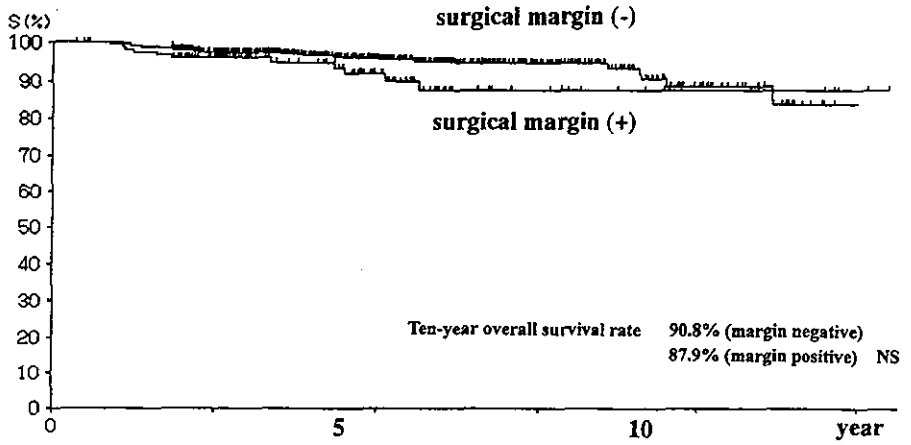

Fig 1. Overall survival curves of patients who underwent BCS according to margin status. There was no significant difference between the two groups. Ten-year overall survival was 90.8% in negative margin patients and 87.9% in positive margin patients.

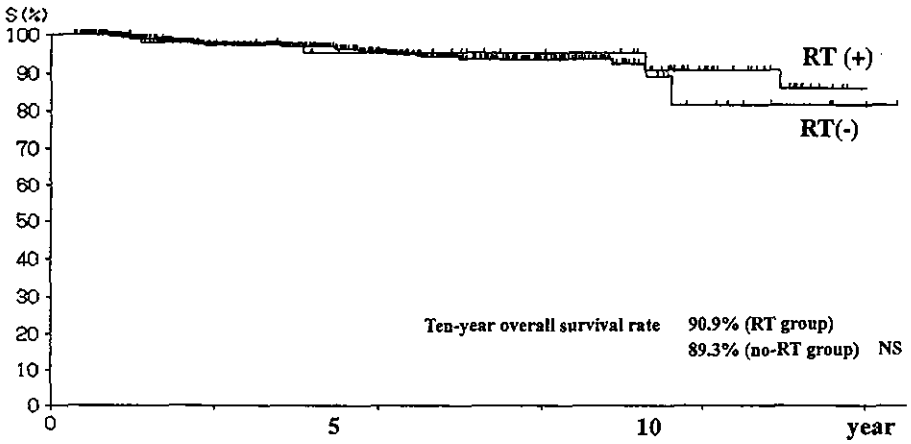

Fig 2. Overall survival curves of patients who underwent BCS with and without RT. There was no significant difference between the two groups. The survival rates of both groups were good. Ten-year overall survival was 90.9% in the RT group and 89.3% in the no RT group.

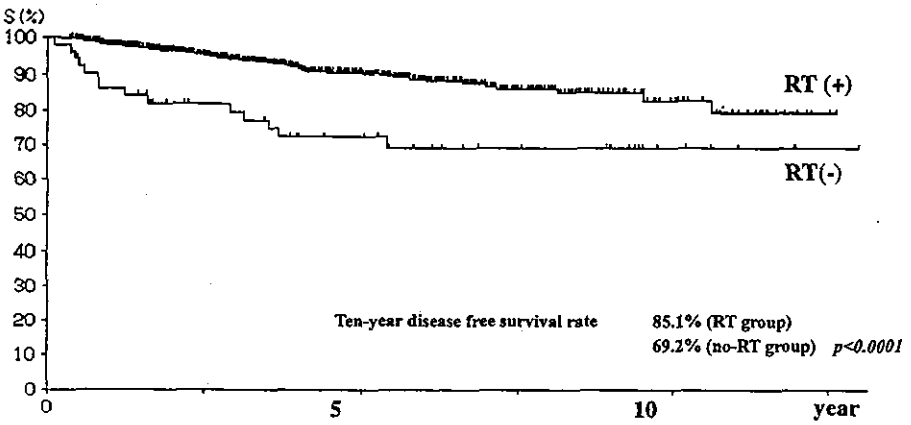

Fig 3. Disease free survival curves with and without RT. The RT group showed higher rates than the no RT group ($p < 0.0001$). Post-operative irradiation gave great advantage for disease free survival. However, the difference between the two groups became small over the 10-year follow-up.

Table 2. Result of Univariate Analysis Concerning Risk Factors for Local Recurrence after BCS

risk factors	*category*	*p* value
surgical margin	positive/negative	$p < 0.0001$
radiation therapy	yes/no	$p < 0.0001$
adjuvant endocrine therapy	yes/no	$p < 0.0001$
adjuvant chemotherapy	yes/no	$p = 0.69$
histological grade	Ⅲ/Ⅰ, Ⅱ	$p = 0.18$
histology	DCIS/IDC	$p = 0.09$
lymphovascular invasion	positive/negative	$p = 0.72$
size	>2 cm/$\leqq 2$ cm	$p = 0.19$
age	>40 y.o./$\leqq 40$ y.o.	$p = 0.31$

Table 3. Result of Multivariate Analysis on Risk Factors for Local Recurrence after BCS

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	$p = 0.0019$

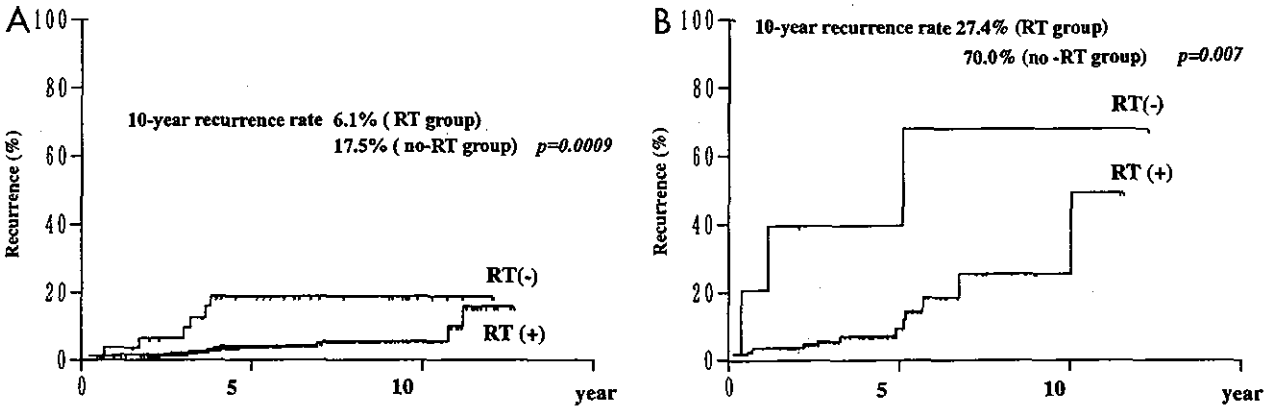

Fig 4. Cumulative incidences of local recurrence with and without RT. A) Patients with positive margin status. B) Patients with negative margin status. The effect of RT was greater in cases with positive margins. It was useful for the prevention of local recurrence even in negative margin status patients.

eral breast (8 patients) and inflammatory local recurrence (5 patients). If limited to non-inflammatory local recurrence, the cumulative 10-year recurrence rate was better in the RT group (7.2%) than the no RT group (27.5%) ($p < 0.0001$). Table 2 shows the result of univariate analysis of risk factors for local recurrence. Positive margin status, lack of post-operative irradiation and omission of adjuvant endocrine therapy were significantly related to local failure. As shown in Table 3, these three factors independently correlated with local recurrence by multivariate analysis. Cumulative incidences of local recurrence with or without RT are shown in Fig 4. For patients with negative margin status, the 10-year cumulative incidence of local failure was 6.1% in the RT group and 17.5% in the no RT group (Fig 4a). For the patients with positive margins, the 10-year cumulative incidence of local failure was 27.4% in the RT group and 70.0% in the no RT group (Fig 4b). There were significant differences between the two groups. The degree of the difference between the RT

group and the no RT group was greater in positive margin cases.

Discussion

On the basis of large randomized trials for early stage breast cancer in Europe and the USA[1, 2], BCS has become standard surgical treatment in Japan. However BCS for Japanese women has not been evaluated. In this retrospective study, we evaluated the long-term results of BCS for stage I and II breast cancer at a single institute, treated according to a uniformed protocol. The 10-year overall survival rate was 90.4%. Although a randomized control study for BCS has not been carried out in Japan, this rate was higher than that in Europe or the USA[2, 3, 5]. Compared with the results of mastectomy for Stage I and II breast cancer at our institute in the same period, the overall survival rate was also higher (data not shown).

Approximately 10 to 20% of patients who underwent BCS are reported to have residual cancer[10]. Questions continue about the influence of positive margins on survival. Local recurrence rates obviously increase if the surgical margin is positive[11, 12]. Recent studies reported that local recurrence was not only a marker for distant metastasis but also the cause of it[13]. In our study, the overall survival of positive margin patients was similar to that of negative margin patients (Fig 1). There were no significant differences between the RT group and the no RT group (Fig 2). Though the number of the patients who relapsed with their breast was low, the survival rate after local recurrence was not poor (data not shown). It is important to avoid local recurrence. Thus we analyzed local recurrence. Forty-four patients (4.5%) had recurrence in their breast. In-breast recurrence occurred in at a rate of 1 to 2 percent every year. Inflammatory recurrences generally recurred within 2 years. The incidence of recurrence in distant organs or regional lymph nodes was highest at 3 years after surgery and recurrence after 5 years postoperatively was very rare (data not shown). These results were similar to those of previous reports. The 10-year cumulative local recurrence rates were 7.2% in the RT group and 27.5% in the no RT group. There was a significant difference between the two groups. Ten cases (33% of the local recurrent case in the RT group) recurred over 5 years after surgery in the RT group while most of the recurrences occurred within 5 years in patients in the no RT group. Only one case (7% of the local recurrence in the no RT group) recurred more than 5 years after surgery in the no RT group. The local recurrence rates of the two groups tended to equalize after long-term observation (Fig 3). Post-operative irradiation is, therefore, thought to be very important for local control, especially in the first 10 years after surgery.

Many studies[11, 12, 15-22] have shown that margin status, omission of post-operative irradiation or adjuvant endocrine therapy were significant risk factors for local recurrence by univariate analysis. Adjuvant chemotherapy did not significantly influence local recurrence in our study. The NSABP B-06 trial showed that CMF was effective for the prevention of distant failures and local recurrences. In our study, various regimens were used, such as oral drugs, CMF or doxorubicin-containing regimens. We did not analyze each patient group individually. Thus it is difficult to evaluate the significance of adjuvant chemotherapy for local recurrence. As for endocrine therapy, our results confirmed its significance for local control. The cumulative incidence of local failure was significantly lower in the patients receiving adjuvant endocrine therapy. Of interest, adjuvant endocrine therapy had a significant effect on the risk of local recurrence regardless of the ER status (data not shown). This effect was also observed regardless of whether RT was given or not (data not shown). Nodal status, lymphatic invasion or histological grade were not significant risk factors for local recurrence. They were more likely to be risk factors for distant metastasis. The impact of age, tumor size or past history of breast cancer on local recurrence is controversial. Our findings showed no statistically significant correlation between these factors and local failure. Several biomarkers, such as Ki-67 and p53, can predict local recurrence[20, 21]. However, among therapeutic factors, positive margin, lack of RT, and lack of adjuvant therapy may be more important. Indeed these three factors proved to be independent risk factors for local recurrence by multivariate analysis. Therefore, it is important to exclude these factors to prevent local recurrence.

Our study found that BCS had no effect on patients' survival. Adjuvant therapies, new drugs, early detection and chemoprevention have become more important for the improvement of survival of breast cancer patients. However, BCS is very important to ensure quality of life after

surgery. Selecting patients who can undergo BCS and achieve optimal results without local failure is important, as are criteria expansion and solutions for local recurrence after BCS. More detailed analysies and well designed clinical trials are needed.

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References

1) Veronesi U, Saccozzi R, Del Vecchio M, *et al*: Comparing radical mastectomy with quadrantectomy, axillary dissection, and radiotherapy in patients with small cancers of the breast. *N Engl J Med* 305:6-11, 1981.
2) Fisher B, Anderson S, Redmond CK, *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.
3) 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 randomised trials on 1,973 patients. *Eur J Cancer* 31A:1574-1579, 1995.
4) Clark RM, Whelan T, Levine M, *et al*: Randomized clinical trial of breast irradiation following lumpectomy and axillary dissection for node-negative breast cancer: an update. Ontario Clinical Oncology Group. *J Natl Cancer Inst* 88:1659-1664, 1996.
5) van Dongen JA, Voogd AC, Fentiman IS, *et al*: Long-term results of a randomized trial comparing breast-conserving therapy with mastectomy: European Organization for Research and Treatment of Cancer 10801 trial. *J Natl Cancer Inst* 92:1143-1150, 2000.
6) Kasumi F, Iwase T, Yoshimoto M, *et al*: Experience of quadrantectomy with axillary dissection without radiotherapy sustained by serial pathological examination for stage I breast cancer. *J Cancer Res Clin Oncol* 121:549-554, 1995.
7) Koyama H, Inaji H, Noguchi S, *et al*: Recent Progress in Breast Conserving Therapy: From Experiences in Japan. *Breast Cancer* 3:151-160, 1996.
8) Noguchi M, Yagasaki R, Kawahara F, *et al*: Breast conserving treatment versus modified radical mastectomy in Japanese patients with operable breast cancer. *Int Surg* 82:289-294, 1997.
9) 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 Radiation Oncology Biol Phys* 49:1311-1316, 2001.
10) Morimoto T, Okazaki K, Komaki K, *et al*: Cancerous residue in breast-conserving surgery. *J Surg Oncol* 52:71-76, 1993.
11) Gage I, Schnitt SJ, Nixon AJ, *et al*: Pathological margin involvement and the risk of local recurrence in patients treated with breast conserving therapy. *Cancer* 78:1921-1928, 1996.
12) Renton SC, Gazet JC, Ford HT, *et al*: The importance of resection margin in conservative surgery for breast cancer. *Eur J Surg Oncol* 22:17-22, 1996.
13) Fortin A, Larochelle M, Laverdiere J: Local failure is responsible for the decrease in survival for patients with breast cancer treated with conservative surgery and postoperative radiotherapy. *J Clin Oncol* 17:101-109, 1999.
14) Holli K, Saaristo R, Isola J, *et al*: Lumpectomy with or without postoperative radiotherapy for breast cancer with favourable prognostic features: results of a randomized study. *Br J Cancer* 84:164-169, 2001.
15) Locker AP, Ellis IO, Morgan DA, *et al*: Factors influencing local recurrence after excision and radiotherapy for primary breast cancer. *Br J Surg* 76:890-894, 1989.
16) Kurtz JM: Factors influencing the risk of local recurrence in the breast. *Eur J Cancer* 28:660-666, 1992.
17) Clarke DH, Martinez AA: Identification of patients who are at high risk for locoregional breast cancer recurrence after conservative surgery and radiotherapy: a review article for surgeons, pathologists, and radiation and medical oncologists. *J Clin Oncol* 10:474-483, 1992.
18) van Dongen JA, Bartelink H, Fentiman IS, *et al*: Factors influencing local relapse and survival and results of salvage treatment after breast-conserving therapy in operable breast cancer: EORTC trial 10801, breast conservation compared with mastectomy in TNM stage I and II breast cancer. *Eur J Cancer* 28A:801-805, 1992.
19) Bethke KP: Breast conservation: predictors and treatment of local recurrence. *Sem Surg Oncol* 12:332-338, 1996.
20) Dalberg K, Eriksson E, Kanter L, *et al*: Biomarkers for local recurrence after breast-conservation-a nested case-control study. *Breast Cancer Res Treat* 57:245-259, 1999.
21) Noguchi S, Koyama H, Motomura K, *et al*: The possible prognostic significance of p53 immunostaining status of the primary tumor in patients developping local recurrence after breast-conserving surgery. *Oncology* 55:450-455, 1998.
22) Buchholz TA, Tucker SL, Erwin J, *et al*: Impact of systemic treatment on local control for patients with lymph node-negative breast cancer treated with breast-conservation therapy. *J Clin Oncol* 19:2240-2246, 2001.
23) Kurtz JM, Spitalier JM, Amalric R: Mammary recurrences in women younger than forty. *Int J Radiat Oncol Biol Phys* 15:271-276, 1988.
24) Harrold EV, Turner BC, Matloff ET: Local recurrence in the conservatively treated breast cancer patients: a correlation with age and family history. *Cancer J Sci Am* 4:302-307, 1998.

Clinical Study

Oncology

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Repeat Lumpectomy for Patients with Ipsilateral Breast Tumor Recurrence after Breast-Conserving Surgery

Preliminary Results

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Key Words
Breast cancer · Breast-conserving surgery · Ipsilateral breast tumor recurrence · Salvage treatment · Repeat lumpectomy

Abstract
In this study, we assessed the appropriateness of conducting repeat lumpectomy for ipsilateral breast tumor recurrence (IBTR) based on the characteristics of recurrence after primary breast conserving surgery (BCS). Of 41 patients who had developed IBTR from October 1986 to June 2000 at our institute, 11 underwent mastectomy of the remaining breast and 30 underwent repeat lumpectomy. The 5-year overall survival rate at a median follow-up of 43 months after salvage surgery was 90.9% for the mastectomy group and 90.0% for the lumpectomy group. The 5-year distant disease-free survival rate was 70.1% for the mastectomy group and 83.0% for the lumpectomy group. The survival rates were remarkably high in both treatment groups, with no significant difference between them. IBTRs in the majority of our patients were small lesions less than 1 cm in diameter. They did not feature lymphatic invasion and had low histological grade. Compared with that of primary lesions, the malignancy of recurrent tumors was not increased in many patients. In contrast to these preferable features, 9 of 30 patients who underwent repeat lumpectomy developed second local relapse within 3 years after salvage operation. Young age (≤35 years), positive family history and omission of adjuvant systemic therapy were found to exhibit trends as a discriminate for further local recurrences. In view of the relatively good prognosis of IBTRs and excellent results of repeat lumpectomy, we consider this method a treatment option that deserves serious consideration if we can select the patients who will not likely develop second local relapse.

Introduction

With long-term follow-up of breast cancer patients after breast conserving surgery, the method of treatment of IBTR has become an important problem. It has been clarified that IBTR is an important predictive factor for subsequent distant recurrence, suggesting the need for systemic therapy [1–6]. Even in such cases, many patients survive for a long period after recurrence [7–10], and the selection of local therapy is an important issue regarding the patient's quality of life (QOL).

It has not been clarified whether mastectomy should be performed for local treatment of IBTR or whether repeat lumpectomy can be performed. In previous reports, mas-

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tectomy of the remaining breast was generally performed [3–5, 9, 11–13]. The 5-year survival rate after salvage mastectomy varied from 50 to 90% among reports, and survival of patients was favorable in many reports. However, there have been few reports on repeat lumpectomy, and little is known regarding its postoperative results. In recent years, several studies have found no difference in survival rate between repeat lumpectomy and salvage mastectomy [14, 15].

Since long-term survival can be expected after salvage surgery for IBTR, it is necessary to determine the feasibility of conducting repeat lumpectomy for recurrence. In this study, we clarify the characteristics of IBTR at our institute and discuss the feasibility of conducting repeat lumpectomy.

Patients and Methods

From October 1986 to June 2000, 979 patients with stage I or II breast cancer underwent breast-conserving surgery at our institute. 926 patients were treated with post-operative irradiation and 53 did not receive radiation therapy. Among these patients, 47 developed IBTR. Without differentiating the development of new tumor from the recurrence of primary tumor, all tumors that had occurred in the ipsilateral breast after primary operation were handled as IBTRs. Axillary lymph node recurrence was excluded from the subjects of this study. Of these, 41 patients underwent salvage surgery and were all included in analysis. Of the patients who had not undergone salvage surgery, 5 were not operable due to recurrence of inflammatory breast cancer and the remaining 1 patient did not give consent for surgery and received systemic therapy alone. Of the 41 patients treated by salvage surgery, 33 had tumor recurrence limited to the remaining mammary gland and 8 had tumor recurrence in regions including the breast skin or muscle tissue. As salvage surgery, mastectomy of the remaining breast was performed in 11 patients and repeat lumpectomy was performed in 30 patients. Primary lesions of these patients were examined for clinico-pathological factors such as tumor size, histological type, presence or absence of extensive intraductal component (EIC), lymphatic invasion, histological grade and lymph node metastasis. Recurrent lesions were also examined for tumor size, histological type, presence or absence of EIC, lymph vessel invasion, histological grade and time to recurrence. Pathological evaluation of tumors was conducted by specialized pathologists. The histological grade was determined according to Bloom Richardson classification. The survival curve was obtained by the Kaplan-Meier method. The significance of differences between the two treatment groups was determined by the log-rank test.

Results

Mean interval between initial treatment and IBTR was 37 months (range of 1–139). Positive margin status at primary operation was seen in 15 patients and negative margin status in 32 patients. The background factors for the 41 patients treated by salvage surgery are presented in table 1. The number of patients with an initial age of 35 years or younger was greater in the repeat lumpectomy group. And the number of patients with secondary tumor smaller than 1 cm in diameter was also greater in the repeat lumpectomy group. However, there were no significant differences between the two treatment groups in primary tumor size, lymphatic invasion, lymph node metastasis or histological grade of atypia. Similarly, there was no significant difference in postoperative adjuvant therapy between the two groups. Table 2 summarizes the method of detection of recurrence, tumor size, location of recurrence, presence or absence of multiple tumors and time to recurrence. Most recurrences were detected by palpation and many recurrent lesions were small masses less than 1 cm in diameter. The location of recurrence was within 3 cm from the site of primary lesion in 29 patients and more than 3 cm from the primary lesion in 10 patients. Five patients had multiple lesions. Pathological characteristics of the recurrent tumors were compared with those of the corresponding primary tumors. Non-invasive cancer was found for 9 patients (22%) with pri-

Table 1. Patients' background

	Repeat lumpectomy	Mastectomy	
Initial age, years			
≤35	7	0	p = 0.09
>35	23	11	
Primary tumor size			
≤2 cm	21	5	
>2 cm	9	6	
Nodal status at primary operation			
0	21	10	
1–3	4	1	
≥4	3	0	
Unknown	2	0	
Adjuvant therapy after primary operation			
Endocrine	8	2	
Chemo	2	1	
Chemo-endocrine	1	0	
None	19	8	
Treatment after salvage operation			
Endocrine	17	5	
Chemo	4	2	
Chemo-endocrine	1	0	
None	8	4	

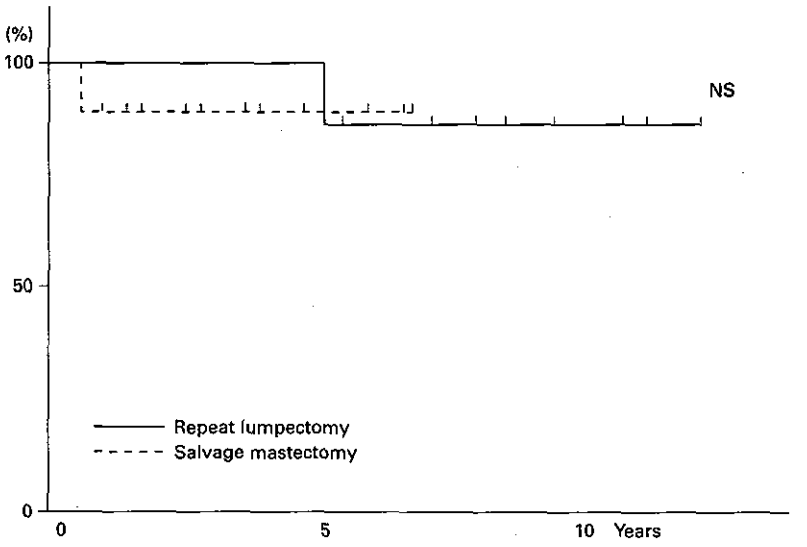

Fig. 1. Overall survival curves after salvage surgery were shown in this figure. In our cases, the prognosis after IBTR was quite good. The 5-year survival rates were 90.9% in the salvage mastectomy group and 90.0% in the repeated lumpectomy group. There was no significant difference between the two groups. Many patients could live long (at least over 5 years) after IBTR. NS = Not significant.

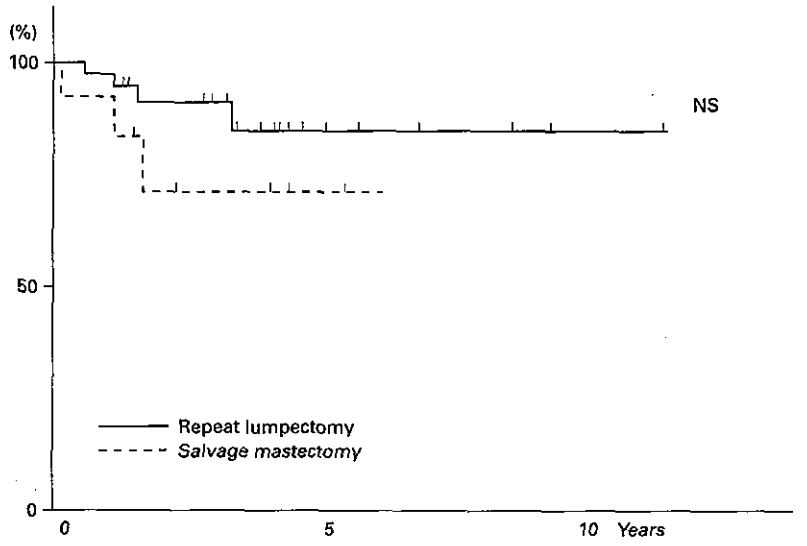

Fig. 2. Distant disease-free survival curves after salvage surgery were shown in this figure. Four out of 10 patients with salvage mastectomy and 4 out of 31 patients with repeated lumpectomy developed distant metastasis. The 5-year distant disease-free survival rates were 70.1% in the salvage mastectomy group and 83.0% in the repeated lumpectomy group. Repeated lumpectomy group was superior to salvage mastectomy group about distant failure but there was significant difference between them (p = 0.09). NS = Not significant.

mary lesions and 7 patients (17%) with recurrent lesions. Of these, non-invasive cancer progressed to invasive cancer in 5 patients (55%), whereas invasive cancer became non-invasive in 3 patients (9.4%). Lymph vessel invasion was present in both primary and recurrent lesions in the same 8 patients (19%), with no change in the status of lymph vessel invasion from negative to positive. Histological grade of atypia increased from grade I to II in 2 patients and from grade II to III in 1 patient. On the other hand, histological atypia decreased from grade II to I in 3 patients and from grade III to II in 1 patient. In many patients, however, there were no changes in histological grade or status of lymph vessel invasion between primary and recurrent lesions. The 5-year overall survival was remarkably high in both salvage surgery groups, at 90.9% for the mastectomy group and 90% for the lumpectomy group, with no significant difference between the two groups (fig. 1). The 5-year distant disease-free survival rates were also high, at 70.1% for the mastectomy group and 83.0% for the lumpectomy group, again with no significant difference between the two groups (fig. 2). However, 9 of 30 patients treated by repeat lumpectomy devel-

Table 2. Clinical characteristics of ipsilateral breast tumor recurrence (IBTR)

Initial age, years	47 (27–74)
Detection methods	
Palpation	37 patients
Mammography	2
Others[1]	2
Recurrent tumor, size in cm	1.1 (0–6.7)
Disease free interval, months	54 (1–138)
Distance from primary site	
≤3 cm	29 patients
>3 cm	10
Not determined	2
Type	
Solitary	36
Multiple	5

[1] Cases of bloody nipple discharge.

Table 3. Univariate analysis of possible risk factors for second local relapse

Possible risk factors for second local failure	Number of patients			p value[1]
	second relapse	total	%	
Age				
≤35 years	5	7	71.4	0.031
>35 years	4	23	17.4	
Family history				
Yes	2	3	66.7	0.006
No	7	27	25.9	
Contralateral breast cancer				
Yes	3	5	60.0	0.68
No	6	19	24.0	
Disease free interval				
≤2 years	4	6	66.7	0.22
>2 years	6	24	20.8	
Primary tumor size				
≤2 cm	3	21	14.3	0.09
>2 cm	6	9	66.7	
Recurrent tumor size				
≤1 cm	9	21	42.9	0.07
>1 cm	0	9	0	
Margin at salvage operation				
Positive	1	1	100	0.38
Negative	8	29	27.6	
Adjuvant therapy				
Yes	4	23	17.4	0.05
No	3	7	42.9	

[1] Detected by log-rank test.

oped second local recurrence within 3 years. The 3-year local disease-free survival rate was 62.9% (fig. 3). All the patients with second local recurrence could be successfully treated by second salvage surgery. Two of 9 patients developed subsequent distant metastasis. None of these patients developed uncontrolled local failure. In order to avoid second local relapse, some possible risk factors for local recurrence were examined. Age of 35 or younger at the primary operation, having familial history of breast cancer and omission of systemic therapy after salvage operation were considered to be risk factors for second local recurrence by univariate analysis. The results are shown in table 3.

Discussion

In this study, we assessed surgical treatment, repeat lumpectomy in particular, for patients with local recurrence after BCS. Many researchers have reported that local recurrence after BCS is an important marker of subsequent distant recurrence [1–6]. Fisher et al. reported based on NSABPB-06 data that patients with local recurrence are 3.41 times more likely to develop distant metastasis than those without recurrence [1]. Among patients treated by BCS at our institute, the distant recurrence rate was slightly higher in the local control group than in the local failure group (data not shown), although the difference between these groups was not as great at that reported by other researchers [3, 6, 7, 17]. However, at a median follow-up of 42 months there was no significant difference in overall survival between these groups. Thus, even if patients with IBTR subsequently develop distant recurrence, their long-term survival can be expected, especially with the cases of non-inflammatory local failure [18, 19]. Therefore, it is desirable to select treatment for IBTR that provides good QOL. However, since there has been no clinical trial comparing repeat lumpectomy and salvage mastectomy for IBTR, the safety of repeat lumpectomy has not been confirmed. Accordingly, at present the standard surgical treatment for IBTR is mastectomy [9–12, 20, 21]. There are many unanswered questions concerning repeat lumpectomy, such as the incidence of IBTR again after repeat lumpectomy, whether second salvage surgery can be performed for subsequent recurrence, whether malignancy increases with repeated recurrence and whether the survival rate after repeat lumpectomy is less than that after salvage mastectomy. One-third of our patients treated by repeat lumpectomy subsequently developed local recurrence. Also, a local recurrence rate of

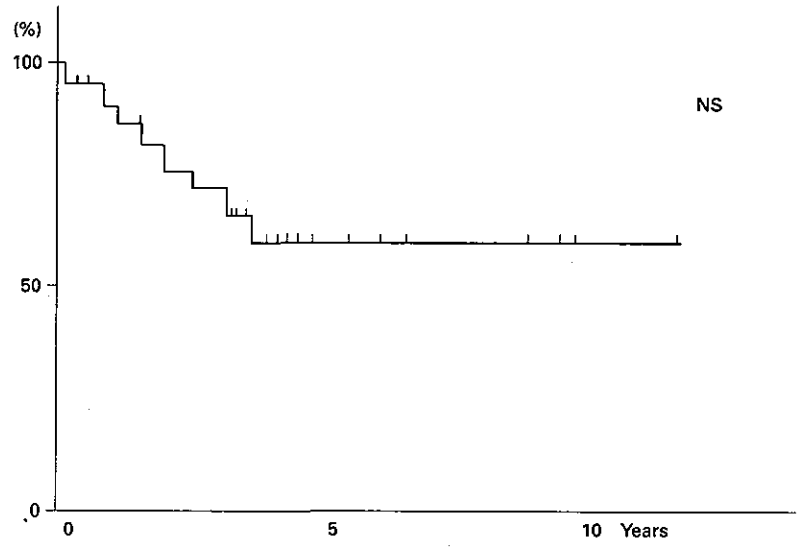

Fig. 3. Local disease-free survival after repeated lumpectomy was shown in this figure. About one third of patients developed second local recurrences within 3 years. The 3-year local disease-free survival rate was 62.9%. NS = Not significant.

35% after repeat lumpectomy was reported by Kurtz et al. [14], and was considerably higher than that after lumpectomy for primary lesions. A possible reason for this high rate of recurrence is that postoperative irradiation had already been performed in combination with lumpectomy for primary lesions whereas radiation therapy could not be performed in many patients after repeat lumpectomy. Another possible reason is that originally tumors were predisposed to local recurrence. Second recurrent tumor could be removed again in many cases [22]. And all of our patients were eligible for second salvage surgery after second local recurrence. Considering the physical burden of repeat surgery on patients and psychological burden of recurrence, however, second recurrence must to the extent possible be avoided. To identify some risk factors for second local relapse, we examined some clinical or pathological findings. As shown in table 3, young age at primary operation, positive family history of breast cancer and omission of adjuvant systemic therapy after repeat lumpectomy seemed to lead to second local relapse. Though data is not shown in table 3, 3 patients did not receive radiation therapy both after primary and secondary operations. Two out of these developed second local relapse. As it is clear that postoperative irradiation is useful for local control, we should apply radiation therapy to repeat lumpectomy patients who have not received radiation therapy yet. In our study, most of the patients with IBTR had already received post-operative irradiation and we did not apply additional irradiation for fear of some radiation-induced damages such as fat necrosis. However, additional focused radiation via electron beam or brachytherapy might certainly decrease the rate of second local relapse. It is generally believed that additional focused radiation is not proper for the patients with early relapse because such case is considered to be radiation resistant. But it may be worthwhile applying for the patients with late relapse.

Dalbarg et al. [13] reported cases of locally uncontrollable recurrence after repeat lumpectomy, and recommended mastectomy for salvage surgery to prevent it. Patients with a large size of primary lesion, a primary lesion with advanced lymph node metastases and short interval from primary operation to first local relapse were reported to be at high risk of developing locally uncontrollable second recurrence [8, 13, 14, 19, 23]. To determine whether tumor malignancy increases with recurrence, the pathological characteristics of primary and recurrent lesions were compared in our patients. We found that the characteristics of primary and recurrent lesions were similar in many cases, suggesting lack of change in malignancy with recurrence. However, in some patients non-invasive cancer progressed to invasive cancer and the histological grade increased with recurrence. In contrast, in some patients invasive cancer became non-invasive on recurrence and the histological grade decreased with recurrence. Thus, no specific trend was observed in change of malignancy with recurrence. There have been very few reports comparing malignancy between primary and recurrent tumors. However, since non-invasive cancer progressed to invasive cancer in about one-half of patients with recurrence [24], we must

treat carefully especially in the case of DCIS. At present no conclusion can be drawn regarding survival rate and distant recurrence rate after repeat lumpectomy. Kurtz et al. [25] presented data demonstrating equivalent survival rates after repeat lumpectomy and salvage mastectomy of remaining breast for the first time. And recently, some reports supported their results. Salvadori et al. [15] showed high survival rate of repeat lumpectomy. Also, Solin et al. [16] reported remarkably satisfactory results with repeat lumpectomy for very early breast cancer. The results of repeat lumpectomy were also excellent in our study.

Although a greater number of patients and a longer follow-up period are needed than those in our study, we believe that the time has come to consider comparative studies of repeat lumpectomy and salvage mastectomy for IBTR. It is necessary to perform optimal surgery for local recurrence by determining those patients who are at low risk of developing second recurrence and those at high risk of developing locally uncontrollable second recurrence, and thereby identifying patients who can be treated by repeat lumpectomy without reduction of survival rate. Of course more studies must be needed to answer these questions.

References

1 Fisher B, Anderson S, Fisher ER, Redmond C, Wickerham DR, Wolmark N, Mamounas EP, Deutsch M, Margolese R: Significance of ipsilateral breast tumour recurrence after lumpectomy. Lancet 1991;338:327–331.

2 Whelan T, Clark R, Roberts R, Levin M, Forster G, investigators of the Ontario Clinical Oncology Group: Ipsilateral breast tumor recurrence postlumpectomy is predictive of subsequent motility: Results from a randomized trial. Int J Radiot Oncol Biol Phys 1994;30:11–16.

3 Veronesi U, Marubini E, Vecchio MD, Manzari A, Andreola S, Greco M, Luini A, Merson M, Soccozzi R, Rilke F, Salvadori B: Local recurrence and distant metastasis after conservative breast cancer treatments: Partly independent events. J Natl Cancer Inst 1995;87:19–27.

4 Haffty BG, Reiss M, Beinfield M, Fischer D, Ward B, McKhann C: 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.

5 Voogd AC, van Tienhoven G, Peterse HL, Crommelin MA, Rutgers EJ, van de Velde CJ, van Geel BN, Slot A, Rodrigus P, Jobsen JJ, et al: Local recurrence after breast conservation therapy for early stage breast carcinoma. Detection, treatment, and outcome in 266 patients. Cancer 1999;85:437–446.

6 Schmoor C, Sauerbrei W, Bastert G, Martin Schumacher for the German Breast Cancer Study Group: Role of isolated locoregional recurrence of breast cancer: Results of four prospective studies. J Clin Oncol 2000;18:1696–1708.

7 Stotter AT, Atkinson EN, Fairston BA, McNeese MD, Oswald MJ, Balch CM: Survival following locoregional recurrence after breast conservation therapy for cancer. Ann Surg 1990;212:166–172.

8 Stotter At, McNeese MD, Ames FC, Oswald MJ, Ellerbroek NA: Predicting the rate and extent of locoregional failure after breast conservation therapy for early breast cancer. Cancer 1989;64:2217–2225.

9 Fowble B, Solin LJ, Schultz DJ, Rubenstein J, Goodman R: Breast recurrence following conservative surgery and radiation: Patterns of failure, prognosis, and pathologic finding from mastectomy specimens with implications for treatment. Int J Radiot Oncol Biol Phys 1990;19:833–842.

10 Haffty BG, Fischer D, Beinfield M, McKhann C: Prognosis following local recurrence in the conservatively treated breast cancer patient. Int J Radiot Oncol Biol Phys 1991;21:293–298.

11 Osborne MP, Borgen PI, Wong GY, Rosen PP, McCormick B: Salvage mastectomy for local and regional recurrence after breast-conserving operation and radiation therapy. Surg Gynecol Obstet 1992;174:189–194.

12 Cajucom CC, Tsangaris TN, Nemoto T, Driscoll D, Penetrante RB, Holyoke ED: Results of salvage mastectomy for local recurrence after breast-conserving surgery without radiation therapy. Cancer 1993;71:1774–1779.

13 Dalberg K, Mattsson A, Sandelin K, Rutqvist LE: Outcome of treatment for ipsilateral breast tumor recurrence in early-stage breast cancer. Breast Cancer Res Treat 1998;49:69–78.

14 Kurtz JM, Jacquemier J, Amalric R, Brandone H, Ayme Y, Hans D, Bressac C, Spitalier J-M: Is breast conservation after local recurrence feasible? Eur J Cancer 1991;27:240–244.

15 Salvadori B, Marubini E, Miceli R, Conti AR, Cusumano F, Andreola S, Zucali R, Veronesi U: Reoperation for locally recurrent breast cancer in patients previously treated with conservative surgery. Br J Surg 1999;86:84–87.

16 Solin LJ, Fourquet A, Vicini FA, Haffty B, Taylor M, McCormick B, McNeese M, Pierce LJ, Landmann C, Olivotto IA, et al: Salvage treatment for local recurrence after breast-conserving surgery and radiation as initial treatment for mammographically detected ductal carcinoma in situ of the breast. Cancer 2001;91:1090–1097.

17 Kemperrman H, Borger J, Hart A, Peterse H, Bartrlink H, van Dongen J: Prognostic factors for survival after breast conserving therapy for stage I and II breast cancer: The role of local recurrence. Eur J Cancer 1995;31:690–698.

18 Clarke DH, Le MG, Sarrazin D, Lacombe M-J, Fontaine F, Travagli J-P, May-Levin F, Contesso G, Arriagada R: Analysis of local-regional relapses in patients with early breast cancers treated by excision and radiotherapy: Experience of the institut Gustave-Roussy. Int J Radiot Oncol Biol Phys 1985;11:137–145.

19 Haffty BG, Goldberg NB, Fischer D, McKhann C, Beinfield M, Weissberg JB, Carter D, Gerald W: Conservative surgery and radiation therapy in breast carcinoma: Local recurrence and prognostic implications. Int J Radiot Oncol Biol Phys 1989;17:727–732.

20 Kennedy MJ, Abeloff MD: Management of locally recurrent breast cancer. Cancer 1993;71:2395–2409.

21 Bethke KP: Breast conservation: Predictors and treatment of local recurrence. Semi Surg Oncol 1996;12:332–338.

22 Kurtz JM, Amalric R, Brandone H, Ayme Y, Jacquemier J, Pietra J-C, Hans D, Pollet J-F, Bressac C, Spitalier J-M: Local recurrence after breast-conserving surgery and radiotherapy. Frequency, time course, and prognosis. Cancer 1989;63:1912–1917.

23 Kurtz JM, Spitalier J-M, Amalric R, Brandone H, Ayme Y, Jacquemier J, Hans D, Bressac C: The prognostic significance of late local recurrence after breast-conserving therapy. Int J Radiot Oncol Biol Phys 1990:18:87–93.

24 Fisher B, Dignam J, Wolmark N, Mamounas E, Costantino J, Poller W, Fisher ER, Wickrham DL, Deutsch M, Margolese R, et al: Lumpectomy and radiation therapy for the treatment of intraductal breast cancer: Findings from National Surgical Adjuvant Breast and Bowel Project B-17. J Clin Oncol 1998;16:441–452.

25 Kurtz JM, Amalric R, Brandone H, Ayme Y, Spitalier J-M: Results of salvage surgery for mammary recurrence following breast-conserving therapy. Ann Surg 1988;207:347–351.