Table 3. Treatment Characteristics

Characteristics		No. of patients (%)
Surgery	Wide excision	604 (64)
	Quadrantectomy	231 (25)
	Tumorectomy	106 (11)
Margins	Focally positive	358 (38)
	Less than 2 mm	326 (35)
	2.1-5 mm	256 (27)
Whole breast	34-49.5 Gy	146 (16)
	50 Gy	740 (79)
	50.4-62 Gy	55 (6)
Tumor bed	34-59 Gy	252 (27)
	60 Gy	456 (48)
	61-70 Gy	233 (25)
Adjuvant Therapy		754 (80)

to 14.1 years, with a median of 4.9 years.

The patient characteristics are listed in Table 2. The median age of the patients was 48 years, with a range of 24-89 years. Among these, 514 (55%) patients were premenopausal and 319 (34%) were postmenopausal. The distribution of clinical stages according to the UICC criteria was 13 (1%) patients with stage 0 disease, 506 (54%) patients with stage I disease and 419 (45%) patients with stage II disease. Hormone receptor status was estrogen receptor (ER)-negative in 221 (23%), and ER-positive in 369 (39%) patients. The treatment characteristics are listed in Table 3. Regarding surgery, 604 (64%) patients underwent wide excision, 231 (25%) underwent quadrantectomy and 106 (11%) tumorectomy. Gross tumors were removed in all patients. Final pathological margin status was classified into 3 groups: 358 (38%) focally positive (cancer cells remained the surgical margin), 326 (35%) with equal or less than 2 mm free margins and 256 (27%) with 2.1-5 mm free margins. Radiation doses to the whole breast were less than 50 Gy in 146 (16%), 50 Gy in 740 (79%) and more than 50 Gy in 55 (6%) patients. Local boost irradiation was performed in 819 cases and the doses to the tumor bed were less than 60 Gy in 252 (27%), 60 Gy in 456 (48%) and more than 60 Gy in 233 (25%) patients. Adjuvant therapies were performed in 754 (80%) patients.

IBTR was defined as a recurrence in the treated breast at the first site of failure with or without a simultaneous regional node and/or distant metastasis. The cumulative rate of IBTC and overall survival were calculated by the Kaplan Meier method and were compared using log-rank tests. A p value of 0.05 or less was considered to be statistically significant.

Results

Recurrence was observed in 123 of 941 patients, and among them, IBTR was observed in 55 patients. The crude rates of IBTR were 5.8% for all patients, 7.8% for those with focally positive margins, 3.4% for those with equal or less than 2 mm margins and 6.3% for those with 2.1-5 mm margins. The time of IBTR was 0.6 to 9.0 years, with a median of 4.1 years. IBTR without other simultaneous sites of failure was recognized in 35 patients (3.7%) and IBTR with other sites of failure was rec-

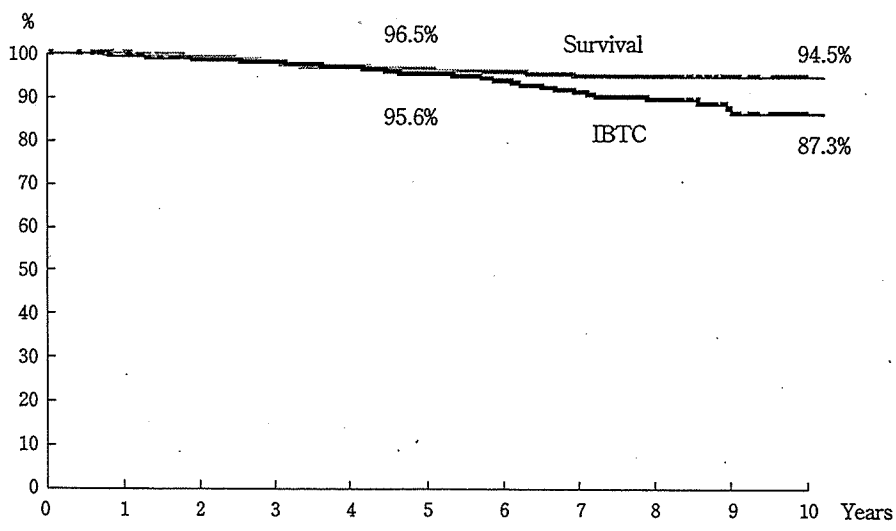

Fig 1. IBTC and survival in all cases. The total number of the patients was 941.

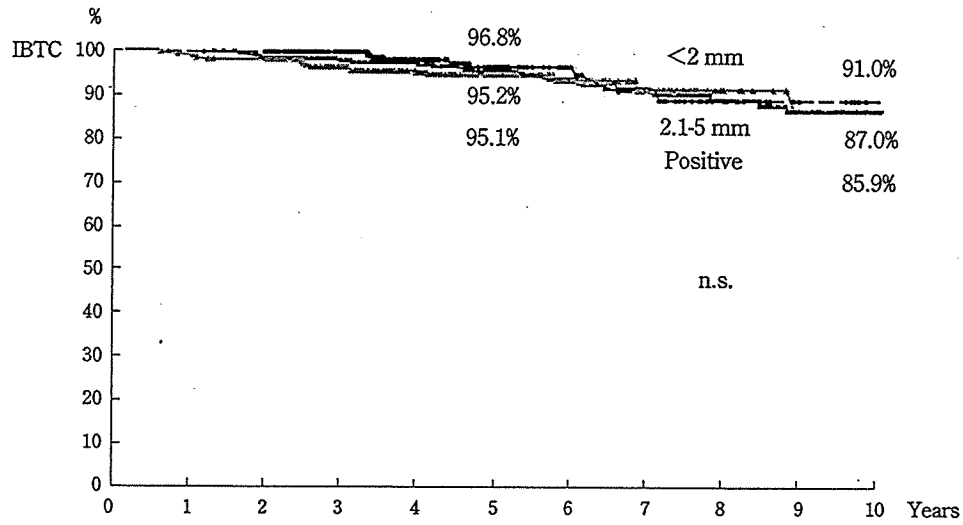

Fig 2. IBTC by marginal status. Final pathological margin status was classified into 3 groups: 358 (38%) focally positive (cancer cells remained the surgical margin), 326 (35%) with equal or less than 2 mm free margins and 256 (27%) with 2.1-5 mm free margins.

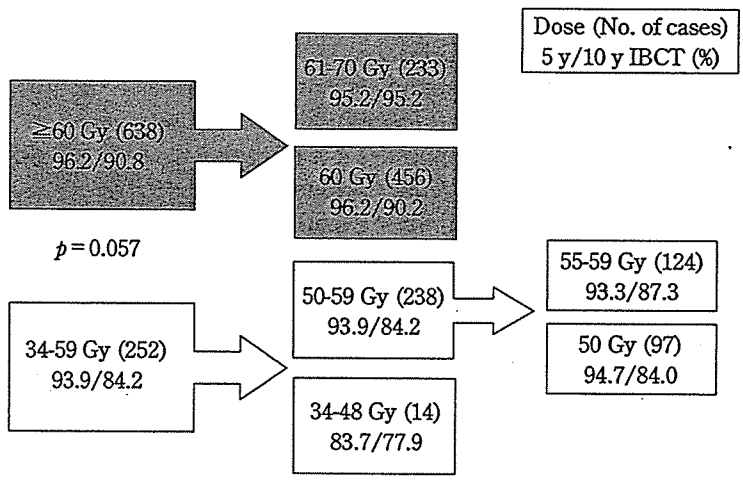

Fig 3. Five/ten years IBTC (%) by radiation dose of tumor bed.

ognized in 20 patients (2.1%). Distant metastasis was recognized in 88 patients (9.4%) and distant metastasis without IBTR in 68 patients (7.2%). Breast cancer death was observed in 33 cases (3.5%) among overall patients and 12 case (1.3%) among the IBTR patients. The cumulative IBTC rates at 5 and 10 years and the overall survival rates at 5 and 10 years were 95.6%, 87.3%, 96.5% and 94.5%, respectively (Fig 1).

The 10-year IBTC rates according to marginal status were 85.9% for those with focally positive margins, 91.0% for those with margins equal or less than 2 mm and 87.0% for those with 2.1-5 mm margins (Fig 2). There was no statistically significant difference between these three groups.

The influence of the radiation dose to the whole breast and the tumor bed was evaluated. In IBTR patients, radiation doses to the whole breast were less than 50 Gy in 12, 50 Gy in 37 and more than 50 Gy in 6 patients. The dose to the whole breast had no influence on IBTC. In IBTR patients, the doses to the tumor bed were less than 60 Gy in 27, 60 Gy in 21 and more than 60 Gy in 7 patients. The 10-year IBTC rates according to radiation doses to the tumor bed were 90.8% in doses equal to or more than 60 Gy and 84.2% in doses less than 60 Gy ($p = 0.057$). The relationship between the dose to the tumor bed and 5 and 10 year IBTC

rates is shown in Fig 3. A dose equal to or more than 60 Gy was given for 57% of focally positive margins, 86% for equal or less than 2 mm margins and 78% of 2.1-5 mm margins. This may be one reason why the patients with equal or less than 2 mm margins achieved the best IBTC rate of the three groups.

The 5 and 10 year IBTC rates according to marginal status and the doses to the tumor bed are listed in Table 4. In patients with focally positive margins, the IBTC of patients receiving radiation dose equal to or more than 60 Gy was significantly better ($p = 0.039$) (Fig 4).

The 10-year IBTC rates according to age were 65.7% for those younger than 35 years and 88.0% for those equal or older than 35 years ($p < 0.0001$) (Fig 5). Of IBTR patients, there were 17 (14%) younger than 35 years, 47 (38%) aged 35-44 years 36 (29%) aged 45-54 years, 18 (15%) aged 55-64 years, and 5 (4%) older than 65 years. The 10-year IBTC rates according to menopausal status were 91.0% for postmenopausal patients and 85.9% for

Table 4. IBTC by Tumor dose and Marginal Status

Dose	5/10 years IBTC (%) ≦59 Gy	60 Gy ≦	All
Positive	92.7/81.4	96.4/90.5	95.1/85.9
	$p = 0.039$		
<2 mm	92.5/86.6	97.4/92.6	96.8/91.0
	n.s.		
2.1-5 mm	98.1/88.7	94.3/92.0	95.2/87.0
	n.s.		

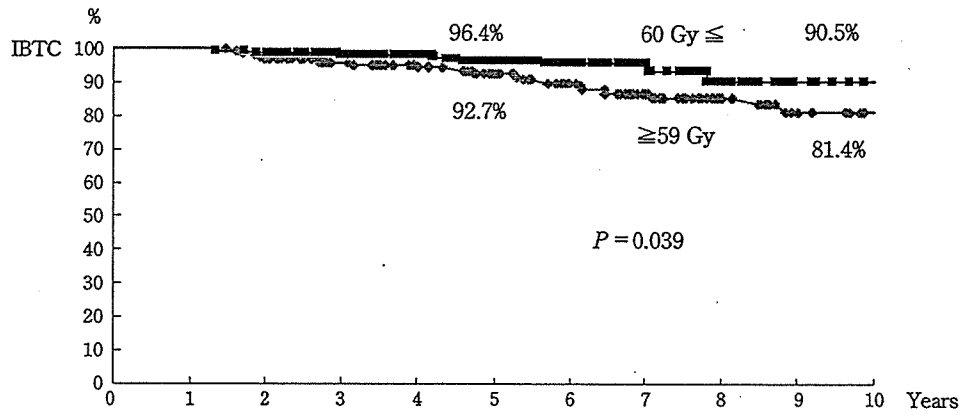

Fig 4. IBTC of margin positive patients by tumor dose. The doses to the tumor bed were less than 60 Gy in 252 (27%), 60 Gy in 456 (48%) and more than 60 Gy in 233 (25%).

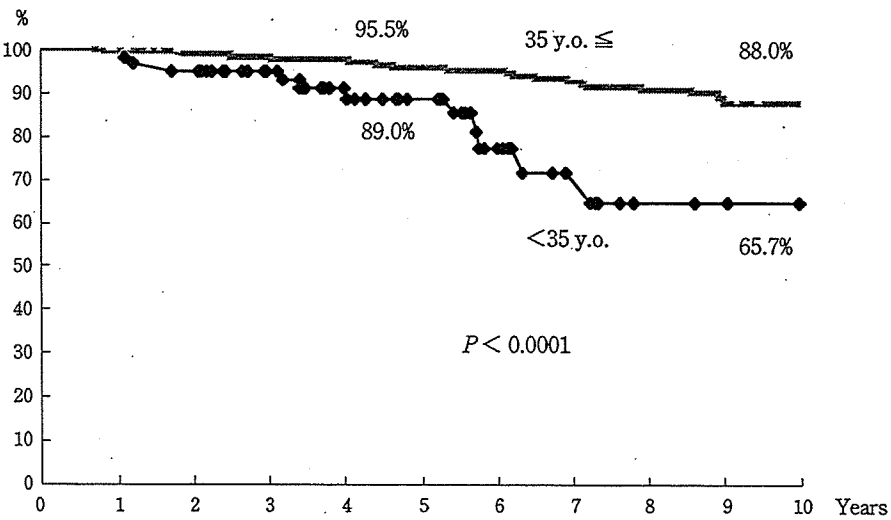

Fig 5. IBTC by age. The median age of the patients was 48 years, with a distribution of 64 (7%) in younger than 35 years.

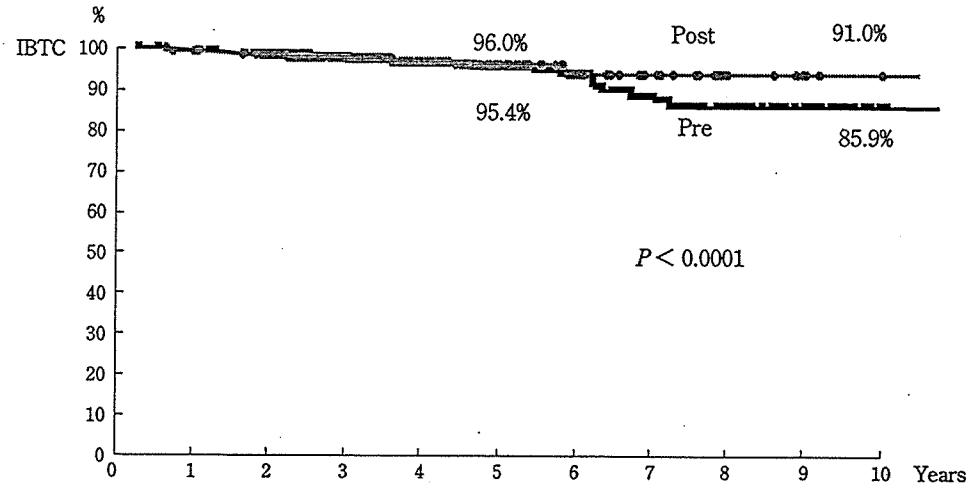

Fig 6. IBTC by menopausal status. Five hundred fourteen patients (55%) were premenopausal and 319 (34%) were postmenopausal.

Table 5. IBTC by dose and Other Factors

	5/10 years IBTC (%)		
Dose	≦59 Gy	60 Gy ≦	All
Age <35 y.o.	79.4/65.0	93.8/68.2	88.9/71.3
	n.s.		
Premenopause	94.3/83.3	95.8/88.0	95.4/85.9
	n.s.		
t2	91.0/76.6	95.2/89.3	92.8/84.1
	$p=0.016$		

premenopausal patients ($p < 0.0001$) (Fig 6). The 10-year IBTC rates according to tumor size were 90.4% in t1 and 84.1% in t2 ($p = 0.023$) patients. The other factors, such as nodal status, ER status, and use of adjuvant therapy, had no statistically significant differences in IBTC. The 5 and 10 year IBTC rates according to age, menopausal status, tumor size and radiation dose to the tumor bed are listed in Table 5. The tumor bed dose equal to or more than 60 Gy was significantly better for achieving IBTC in t2 cases ($p = 0.016$). However, there was no improvement with a tumor bed dose equal or more than 60 Gy for younger age or premenopausal patients.

Discussion

Breast conserving therapy has been recognized as a standard treatment of early stage breast cancer. Randomized trials have demonstrated that survival rates after BCT are equivalent to those obtained after mastectomy. However, IBTR is a lifelong risk and source of anxiety for the patients. To reduce the risk of IBTR, one can remove more breast tissue at BCS, but cosmesis can be unacceptably affected by more extensive surgery. To optimize the balance between the risk of IBTR and cosmesis, the volume of residual cancer cells near the resection margin is regarded as important. Many retrospective studies have demonstrated that positive resection margins were one of the most significant factors impacting IBTR[1,2]. To minimize IBTR in BCT, the surgical oncologist strives for clear resection margins. Although the clinical assessment of resection margin analysis is delicate, many specific issues have been discussed. Even in patients with negative margins, IBTR occurred in more than 40% of patients without postoperative breast radiotherapy in NSABP B06[3]. This means that a negative margin does not equivalent no residual cancer cells in the conserved breast. In the cases with positive margins, it is nearly certain that cancer cells have been left in the breast, and IBTR is likely unavoidable without postoperative radiotherapy and/or chemoendocrine therapy.

It is an undeniable fact that radiotherapy reduces IBTR in negative and positive margin patients. Nevertheless, the balance between the residual cancer volume and radiation tumor control is not fully delineated. It is also not clear which patient and tumor characteristics affect IBTC in positive or close margin cases.

Many authors have suggested that a high boost

dose of radiation reduced IBTR in patients with positive resection margins. Heimann *et al.* reported 5-year a IBTC rate in patients with positive margins of 91% with a boost of >60 Gy compared to 76% with a ≦60 Gy dose[4]. Spivack *et al.* reported that IBTC was 8% with a boost of >60 Gy compared to 22% with a dose of ≦60 Gy[5]. Slotman *et al.* reported that IBTC in patients with positive or close margins was 5% with an interstitial boost of ≧75 Gy compared to 10-13% with external beam 65-70 Gy[6]. Schmidt-Ullrich *et al.* reported that dose escalation of the tumor bed is effective in margin positive patients. They irradiated 70 Gy in case with margin <2 mm, 65 Gy in 2-5 mm margin cases and 60 Gy in >5 mm margin cases[7]. Neuschatz *et al.* reported a margin radiation dose escalation trial. They irradiated a boost dose of 10 Gy in disease-free margin (DFM) cases greater than 5 mm, 14 Gy in DFM cases greater than 2-5 mm, 20 Gy in DFM cases greater than 2-0 mm or positive margin cases followed by 50-50.4 Gy irradiated of whole breast. The 5 year ITBC rate is very low, however, close or positive margins had significantly increased IBTR after 5 years. They thought that represented this a mixture of true recurrences and new primary cases[8]. Freedman *et al.* reported that dose escalation of the tumor bed is effective in 5 year results, but is not effective 10 years. They irradiated 66 Gy in margin positive cases , 64 Gy in cases with ≦2 mm margins and 60 Gy in cases with >5 mm margins. Systemic therapy reduced 5-year recurrence results, but not 10-year result[2]. These were retrospective studies and consisted of a relatively small number of patients. It is impossible to determine the effect of the radiation dose with a nonrandomized study.

The EORTC 'boost versus no boost' trial is a randomized trial for radiation dose effect. After tumorectomy followed by whole breast irradiation of 50 Gy, 5318 patients with a microscopically complete excision were randomized to no boost or a 16 Gy boost, while 251 patients with an incomplete excision were randomized to a boost dose of 10 Gy or 26 Gy. In margin negative patients, a boost dose of 16 Gy reduced the relative risk of IBTR and slight impaired cosmesis[9]. The results of positive margin patients are not yet reported.

Some authors reported that the extent of the positive margins influenced IBTR[10-15]. Gage *et al.* reported IBCR of focally positive margins was acceptably low compared with more than focally positive margins. Park *et al.* reported that the rate of local recurrence was 7% in patients with close or negative margins, 14% in those with focally-positive margins and 27% in those with extensively positive margins[11]. DiBiase *et al.* reported the degree of margin positives influences IBTC[13]. A high dose of boost irradiation in patients with positive or close margins does not appear to confer the same risk of IBTR as patients with negative margins, however, when positive margins are focal or minimal, the impact on IBTR may be significant.

Other factors associated with IBCR were young age, premenopausal status and tumor size in our cohort. Obedian *et al.* and Tartter *et al.* reported that positive margins were significantly associated with large tumor size and young age[16,17]. Neuschatz *et al.* reported that patients 45 years or younger had a significantly lower rate of IBTC and that dose escalation did not fully overcome the influence of young age[8]. Leong *et al.* and Kini *et al.* reported that patients 35 years or younger had a significantly lower IBTC[18,19]. Leong *et al.* concluded that this was regardless of margin status. DiBiase *et al.* reported that stage, menopausal status and the use of chemotherapy were significant factors for IBTR[20]. Nixon *et al.* showed that younger patients have a higher frequency of adverse pathologic factors (including grade 3 histology, lymphatic vessel invasion, necrosis, and ER negativity) and that this was the reason for the poor prognosis compared with older patients[21].

Our series was a retpospective analysis, but the number of registered patients with positive or close margins was more than one thousand and the total number of patients analyzed was 941. We think no other series has accumulated this number of patients with positive or close margins, and the number of patients is advantageous for analyzing prognostic factors. The 10-year IBTC rates were 90.8% with doses of equal to or more than 60 Gy and 84.2% in doses of less than 60 Gy in the entire cohort ($p=0.057$) (Fig 3). However, in 358 patients with positive margins, the 10-year IBTC rates were 90.5% in doses of equal to or more than 60 Gy and 81.4% in doses less than 60 Gy ($p=0.039$) (Fig 4). Young age and premenopausal status had the most influence on IBTC regardless of the radiation dose to the tumor bed. Pathological t-stage was significantly associated with IBTC and depended on the radiation dose.

We recommend that the tumor bed should be irradiated with at least 60 Gy in the patients with

positive margins. The median follow up time was 4.9 years at analysis, therefore further follow-up is necessary to draw final conclusions.

Acknowledgement

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References

1) Singletary SE: Surgical margins in patients with early-stage breast cancer treated with breast conservation therapy. *Am J Surg* 184:383-393, 2002.
2) Freedman G, Fowble B, Hanlon A, Nicolaou N, Fein D, Hoffman J, Sigurdson E, Boraas M, Goldstein L: Patients with early stage invasive cancer with close or positive margins treated with conservative surgery and radiation have an increased risk of breast recurrence that is delayed by adjuvant systemic therapy. *Int J Radiat Oncol Biol Phys* 44:1005-1015, 1999.
3) Fisher B, Anderson S, Bryant J, Margolese RG, Deutsch M, Fisher ER, Jeong JH, Wolmark N: 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* 347:1233-1241, 2002.
4) Heimann R, Powers C, Halpem HJ, Michel AG, Ewing CA, Wyman B, Recant W, Weichselbaum RR: Breast preservation in stage I and II carcinoma of the breast. The University of Chicago experience. *Cancer* 78:1722-1730, 1996.
5) Spivack B, Khanna MM, Tafra L, Juillard G, Giuliano AE: Margin status and local recurrence after breast-conserving surgery. *Arch Surg* 129:952-956, 1994.
6) Slotman BJ, Meyer OW, Njo KH, Karim AB: Importance of timing of radiotherapy in breast conserving treatment for early stage breast cancer. *Radiother Oncol* 30:206-212, 1994.
7) Schmidt-Ullrich R, Wazer DE, Tercilla O, Safaii H, Marchant DJ, Smith TJ, Homer MA, Robert NJ: Tumor margin assessment as a guide to optimal conservation surgery and irradiation in early stage breast carcinoma. *Int J Radiat Oncol Biol Phys* 17:733-738, 1989.
8) Neuschatz AC, DiPetrillo T, Safaii H, Price LL, Schmidt-Ullrich RK, Wazer DE: Long-term follow-up of a prospective policy of margin-directed radiation dose escalation in breast-conserving therapy. *Cancer* 97:30-39, 2003.
9) Bartelink H, Horiot JC, Poortmans P, Struikmans H, Van den Bogaert W, Barillot I, Fourquet A, Borger J, Jager J, Hoogenraad W, Collette L, Pierart M; European Organization for Research and Treatment of Cancer Radiotherapy and Breast Cancer Groups: Recurrence rates after treatment of breast cancer with standard radiotherapy with or without additional radiation. *N Engl J Med* 345:1378-1387, 2001.
10) Gage I, Schnitt SJ, Nixon AJ, Silver B, Recht A, Troyan SL, Eberlein T, Love SM, Gelman R, Harris JR, Connolly JL: Pathologic margin involvement and the risk of recurrence in patients treated with breast-conserving therapy. *Cancer* 78:1921-1928, 1996.
11) Park CC, Mitsumori M, Nixon A, Recht A, Connolly J, Gelman R, Silver B, Hetelekidis S, Abner A, Harris JR, Schnitt SJ: 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 Clinic Oncol* 18:1668-1675, 2000.
12) Smitt MC, Nowels KW, Zdeblick MJ, Jeffrey S, Carlson RW, Stockdale FE, Goffinet DR: The importance of the lumpectomy surgical margin status in long-term results of breast conservation. *Cancer* 76:259-267, 1995.
13) DiBiase SJ, Komarnicky LT, Schwartz GF, Xie Y, Mansfield CM: The number of positive margins influences the outcome of women treated with breast preservation for early stage breast carcinoma. *Cancer* 82:2212-2220, 1998.
14) Peterson ME, Schultz DJ, Reynolds C, Solin LJ: 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* 43:1029-1035, 1999.
15) Wazer DE, Jabro G, Ruthazer R, Schmid C, Safaii H, Schmidt-Ullrich RK: Extent of margin positivity as a predictor for local recurrence after breast conserving irradiation. *Radiat Oncol Investig* 7:111-117, 1999.
16) Obedian E, Haffty BG: Negative margin status improves local control in conservatively managed breast cancer patients. *Cancer J Sci Am* 6:28-33, 2000.
17) Tartter 1997 Tartter PI, Kaplan J, Bleiweiss I, Gajdos C, Kong A, Ahmed S, Zapetti D: Lumpectomy margins, reexcision, and local recurrence of breast cancer. *Am J Surg* 179:81-85, 2000.
18) Leong C, Boyages J, Jayasinghe UW, Bilous M, Ung O, Chua B, Salisbury E, Wong AY: Effect of margins on ipsilateral breast tumor recurrence after breast conservation therapy for lymph node-negative breast carcinoma. *Cancer* 100:1823-1832, 2004.
19) Kini VR, Vicini FA, Frazier R, Victor SJ, Wimbish K, Martinez AA: Mammographic, pathologic, and treatment-related factors associated with local recurrence in patients with early-stage breast cancer treated with breast conserving therapy. *Int J Radiat Oncol Biol Phys* 43:341-346, 1999.
20) DiBiase SJ, Komarnicky LT, Heron DE, Schwartz GF, Mansfield CM: Influence of radiation dose on positive surgical margins in women undergoing breast conservation therapy. *Int J Radiat Oncol Biol Phys* 53:680-686, 2002.
21) Nixon AJ, Neuberg D, Hayes DF, Gelman R, Connolly JL, Schnitt S, Abner A, Recht A, Vicini F, Harris JR: Relationship of patient age to pathologic features of the tumor and prognosis for patients with stage I or II breast cancer. *J Clin Oncol* 12:888-894, 1994.

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Original Article

Bilateral Breast-Conserving Therapy for Bilateral Breast Cancer: Results and Consideration of Radiation Technique

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Background: Although breast-conserving surgery followed by definitive irradiation is an established treatment for patients with early breast cancer, the role of breast-conserving therapy (BCT) for patients with bilateral breast cancer has not been well studied and the radiation therapy technique is still under investigation. We examined the feasibility of breast-conserving therapy for bilateral breast cancer and present here our radiation therapy technique with CT simulator.

Methods: Between July 1990 and December 1998, we treated 17 patients with bilateral breast cancer who underwent bilateral breast-conserving surgery followed by definitive irradiation. Seven patients had synchronous bilateral breast cancer and ten had metachronous bilateral breast cancer. Radiation therapy consisted of 50 Gy to the bilateral whole breast in all patients but one. A CT simulator was used to plan a tangential radiation field to the breast in all patients. Boost irradiation of 10 Gy was administered to 8 tumors with close or positive margins.

Results: With a median follow-up periods of 95 months from each operation, no patients showed loco-regional recurrence on either side, and none suffered distant metastasis. Furthermore no serious late adverse effects were observed.

Conclusion: This study demonstrated that BCT is feasible for bilateral breast cancer and the CT simulator is useful for determining the radiation field, especialy when lesions are metachronous.

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Key words: Bilateral breast cancer, Breast-conserving therapy, BCT, Breast-conserving surgery, Radiation therapy

The incidence of clinically observed bilateral breast cancer is reported to range from 1.4 to 11.8%[1-3], small but significant. Although breast-conserving surgery followed by irradiation is an established treatment for patients with early breast cancer, the frequency of patients receiving bilateral breast irradiation ranges from 0.4% to 5.5%[4-6]. The role of breast-conserving therapy for patients with bilateral breast cancer has not been well studied and scant attention has been devoted to the techniques for radiation therapy. We herein present our technique, which utilizes a CT simulator, and analyze the outcome of treatment for patients with bilateral breast cancer treated with breast-conserving therapy (BCT).

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Abbreviations:
BCT, Breast -conserving therapy

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Materials and Methods

Between July 1990 and December 1998, a total of 1036 patients with breast cancer were treated with BCT, defined as breast-conserving surgery and axillary lymph node dissection followed by definitive radiation therapy at the Department of Radiology at Kyoto University Hospital. Among them, 35 patients (3.4%) had bilateral breast cancer, and 17 of them were treated with bilateral BCT (Fig 1). Therefore, 17 patients treated with bilateral BCT were analyzed in the present study.

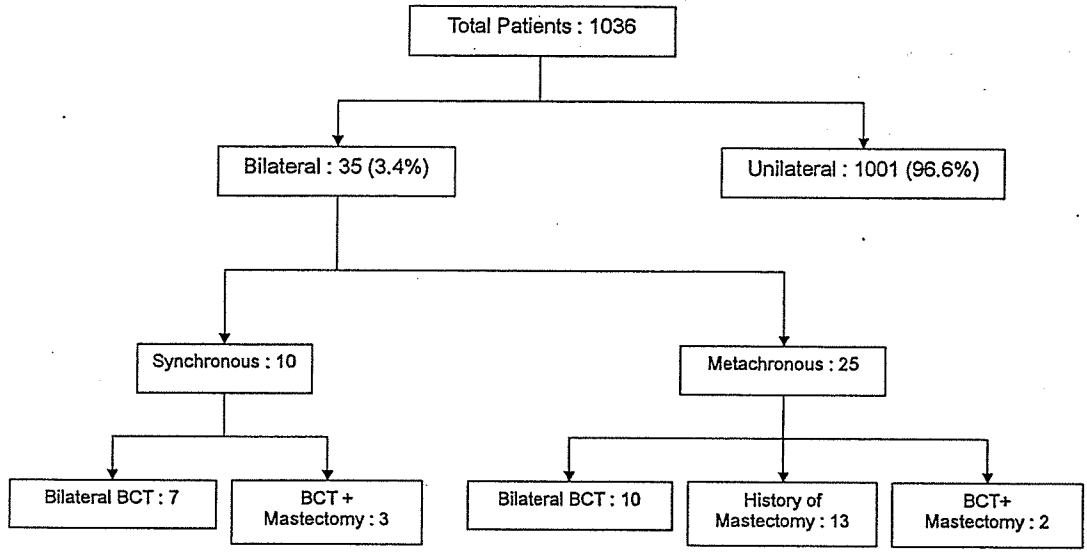

Fig 1. Total patients treated between July 1990 and December 1998.

Table 1. Patient Characteristics

	Synchronous (7 Pt.)	Metachronous (10 Pt.)
Age at diagnosis	Median 53 (43-68)	Median 45 (28-54)*
Family history		
1st degree	0	3
2nd degree	1	0
Menstrual status		
Premenopausal	2	8
Perimenopausal	0	0
Postmenopausal	2	2
Unknown	1	

* age at the diagnosis of the 1st tumor

Table 2. Tumor Characteristics of the 34 Treated Breasts

	Number	%
Pathology		
DCIS	1	
Invasive ductal	32	94
Invasive lobular	1	
Clinical T Stage		
T0	1	3
T1	22	65
T2	11	32
Clinical UICC Stage		
I	22	65
IIA	9	26
IIB	3	9
Pathologic N stage		
N0	31	91
N1	3	9
Estrogen receptor status		
Negative	11	32
Positive	13	38
Not done/unknown	10	30

Seven patients had synchronous bilateral breast cancer and 10 patients had metachronous bilateral breast cancer. They developed the newly diagnosed contralateral breast cancer 4 to 70 months after the first BCT with a median interval of 29 months. Synchronous breast cancer was defined as the diagnosis of both tumors within 1 month. The patients' characteristics and the characteristics of the 34 breast cancers are summarized in Tables 1 and 2.

As regards conservative surgery, 14 tumors were treated by quadrantectomy, while 20 tumors were treated by wide excision. All patients underwent axillary dissection bilaterally. Twenty-six tumors had negative margins of resection, 6 had close margins of resection, that is, within 5 mm from the resected margin, and 1 had positive margins of resection, defined as microscopic involvement at the resected margin on the histological examination.

Following breast conserving surgery, a total dose of 50 Gy in daily fractions of 2 Gy was delivered over 5 weeks to the whole breast via opposing tangential fields. We used a CT simulator (Shimadzu Corp. CT-S, Kyoto) to plan the tangential

fields. We selected the beam energy for the tangential fields according to the breast size: twenty-seven unilateral breasts were treated with cobalt-60 gamma rays, 1 with 4-MV photons, and 5 with 6-MV photons for the tangential fields. One breast was irradiated with an en-face electron beam. Seven patients with simultaneous breast cancer were treated by matched midline technique with bilateral tangential fields using the CT simulator (Fig 2). On the other hand, we referred to the CT simulation images of the first tumors to avoid field overlapping when we determined the tangential fields for the second tumors in the patients with metachronous breast cancers (Fig 3). The primary site was boosted in the 7 patients with close or positive surgical margins. This boost irradiation comprised to a total dose of 10 Gy in 5 fractions of electron beams through a field 6 to 8 cm in diameter, including the tumor bed. The ipsilateral supraclavicular and ipsilateral internal mammary nodal areas were not included in the target volume.

All patients received oral 5-fluorouracil (5-FU) or its derivatives, and also received tamoxifen for 2 years after the operation, regardless of the axillary node status or estrogen receptor (ER) status.

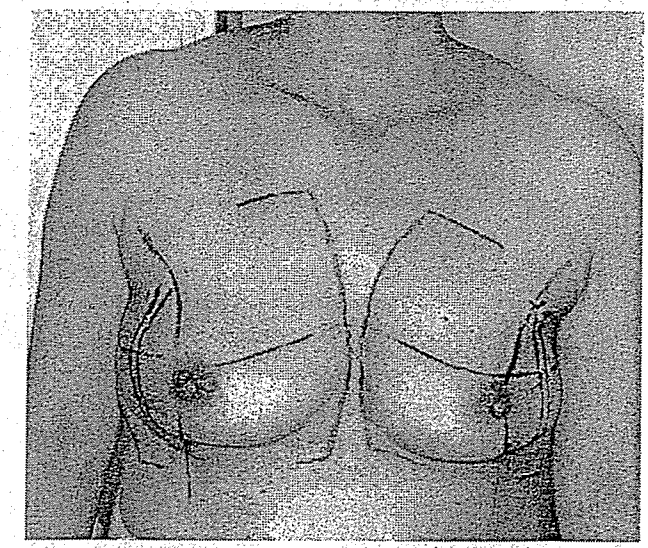

Fig 2. A case of simultaneous breast cancer: It is confirmed that there is no overlap by the skin markings.

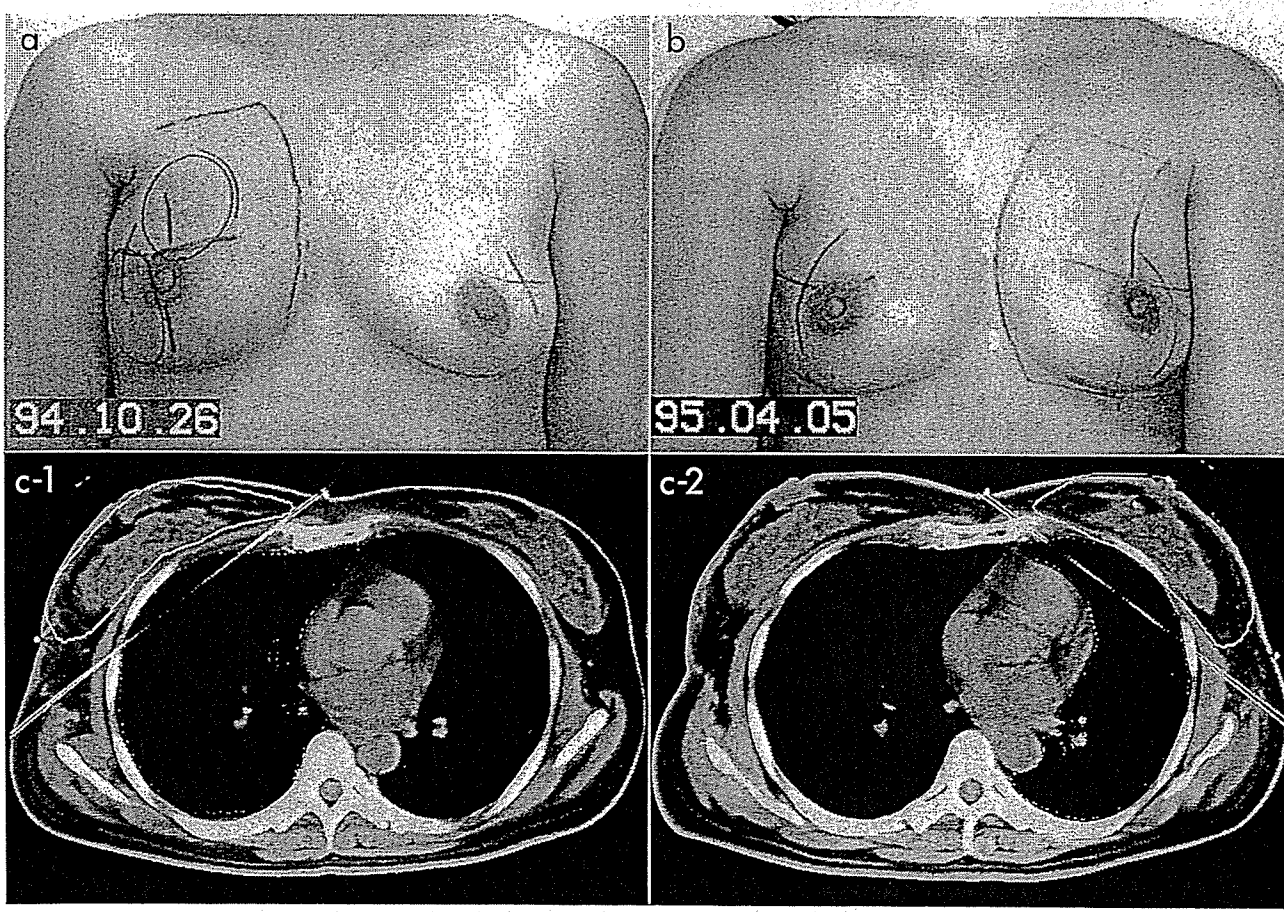

Fig 3. A case of metachronous breast cancer. (a) Radiation field for the first treatment. (b) Radiation field for the second treatment. Identifying the first field by the skin reaction is impossible. (c) We could recognize the first field accurately with the use of images from the previous CT simulation.

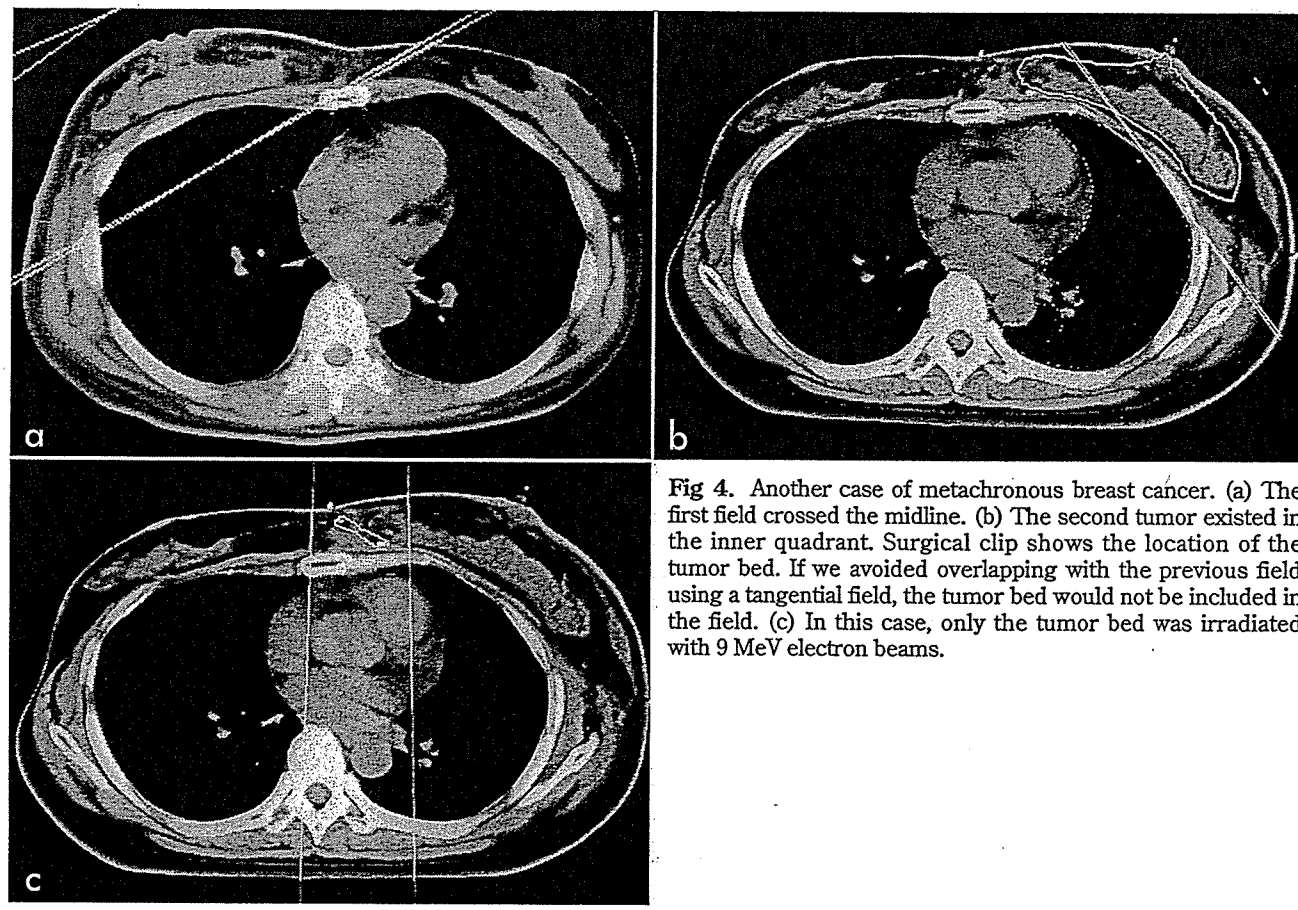

Fig 4. Another case of metachronous breast cancer. (a) The first field crossed the midline. (b) The second tumor existed in the inner quadrant. Surgical clip shows the location of the tumor bed. If we avoided overlapping with the previous field using a tangential field, the tumor bed would not be included in the field. (c) In this case, only the tumor bed was irradiated with 9 MeV electron beams.

The patients were periodically followed-up at our clinic. They were examined every 3 to 6 months in the first 2 years, and every 6 to 12 months thereafter according their pathological status. Loco-regional recurrence, distant metastasis, complications and cosmetic outcomes were evaluated.

Results

Of 17 patients, 15 patients were irradiated with matched tangential fields without overlapping, 1 patient was irradiated iwith matched tangential fields with overlapping of 1.2 cm, and 1 patient with a medially located metachronous tumor received en-face electron beam alone because overlapping with the previous field could not be avoided with tangential field (Fig 4).

No patients were lost to follow-up. The median follow-up period after each operation was 95 months. No patients showed loco-regional recurrence on either side or distant metastasis.

Regarding complications associated with treatment, severe arm edema was observed in one patient whose upper arms showed a 4 cm difference in circumference. One patient developed moderate fibrosis at the site of overlapping, but this did not affect cosmetic outcome. The patient who was irradiated with overlapping of 1.2 cm did not develop any skin or soft tissue complications. In other cases, complications were none or slight.

We also evaluated cosmetic outcome using the cosmetic score[7]. Six patients (35%) were scored as excellent and 10 (59%) were scored as good. Only one patient (6%) was graded fair because of unilateral breast contracture.

Discussion

Although as many as 10% of the patients with breast cancer may develop bilateral cancer[1-3] and radiation therapy is essential to breast conserving therapy, there is scant information on the technical aspects of such irradiation[8,9]. To minimize late damage to skin and soft tissue, overlapping of bilateral tangential fields should be avoided. On the other hand, maintaining good coverage of breast tissue is important to minimize the risk of intra-breast recurrence. In the patients with meta-

chronous breast cancer patients, which account for 2/3 of all bilateral cases, it is necessary to reproduce the previous tangential field before planning the contralateral tangential beam. In a conventional X-ray simulator, it is almost impossible to reproduce the medial margin accurately. Tattooing, which is commonly used in Western countries and might be useful in such situations, is seldom used in Japan. CT-simulation is quite useful because the overlapping of bilateral tangential fields can be evaluated much more accurately than conventional simulation, although there are some limitations derived from the change of the patient's figure and the difference in positioning. In patients with thick subcutaneous tissue at the midline, or those with tumors located very near to the midline, overlapping may be unavoidable despite the use of a CT simulator. However, it is still possible to explore the use of a CT for planning tangential fields for irradiation of metachronous breast cancer patients.

Conclusion

This study demonstrated that BCT is feasible for bilateral breast cancer and the CT simulator is useful for determining the radiation field, especially when they are metachronous. It is helpful in minimizing overlap of the radiation fields and provides the best possible treatment plan.

References

1) Donovan AJ: Bilateral breast cancer. *Surg Clin North Am* 70:1141-1149, 1990.
2) Gogas J, Markopoulos C, Skandalakis P, *et al*: Bilateral breast cancer. *Am Surg* 59:733-735, 1993.
3) Michowitz M, Noy S, Lazebnik N, *et al*: Bilateral breast cancer. *J Surg Oncol* 30:109-112, 1985.
4) van Limbergen E, van den Bogaert W, van der Schueren E, *et al*: Tumor excision and radiotherapy as primary treatment of breast cancer. Analysis of patient and treatment parameters and local control. *Radiother Oncol* 8:1-9, 1987.
5) Chu AM, Cope O, Russo R, *et al*: Patterns of local-regional recurrence and results in Stages I and II breast cancer treated by irradiation following limited surgery. An update. *Am J Clin Oncol* 7:221-229, 1984.
6) Bedwinek JM, Brady L, Perez CA, *et al*: Irradiation as the primary management of stage I and II adenocarcinoma of the breast: analysis of the RTOG breast registry. *Cancer Clin Trials* 3:11-18, 1980.
7) Harris JR, Levene MB, Svensson G, *et al*: Analysis of cosmetic results following primary radiation therapy for stages I and II carcinoma of the breast. *Int J Radiat Oncol Biol Phys* 5:257-261, 1979.
8) Kopelson G, Munzenrider JE, Doppke K, *et al*: Bilateral breast cancer: radiation therapy results and technical considerations. *Int J Radiat Oncol Biol Phys* 7:335-341, 1981.
9) Fung MC, Schultz DJ, Solin LJ: Early-stage bilateral breast cancer treated with breast-conserving surgery and definitive irradiation: the University of Pennsylvania experience. *Int J Radiat Oncol Biol Phys* 38:959-967, 1997.

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CLINICAL INVESTIGATION **Breast**

THE PATTERNS OF CARE STUDY FOR BREAST-CONSERVING THERAPY IN JAPAN: ANALYSIS OF PROCESS SURVEY FROM 1995 TO 1997

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Purpose: To present the results of a process survey on breast-conserving therapy (BCT) in Japan from 1995 to 1997.
Methods and Materials: From September 1998 to December 1999, data on the treatment process of 865 randomly selected BCT patients were collected by extramural audits.
Results: For primary surgery, wide excision or tumorectomy was performed in 372 patients (43.0%), and quadrantectomy or segmental mastectomy was performed in 493 patients (57%). The extent of axillary dissection was equal or beyond Level II in 590 patients (68.2%). Systemic chemotherapy was administered to 103 of 160 node-positive patients (64.4%) and 180 of 569 node-negative patients (31.6%). Tamoxifen was administered to 234 of 323 hormone receptor–positive patients (72.5%) and 68 of 130 hormone receptor–negative patients (52.3%). Photon energy of 10 MV was administered for whole breast irradiation in 38 patients (4.4%) without bolus.
Conclusions: The extent of surgical resection for BCT was large in Japan. Pathologic assessment and the technique of radiation therapy were apparently suboptimal in some cases. Information on prognostic/predictive factors was not fully utilized to individualize systemic adjuvant therapy. Establishment and widespread use of guidelines for BCT for in Japan are desirable. Repeated surveys will demonstrate how such guidelines affect clinical practices. © 2005 Elsevier Inc.

Patterns of Care Study, Breast-conserving therapy, Radiation therapy.

INTRODUCTION

Breast-conserving therapy (BCT) has been proved by many randomized clinical trials to produce survival results equivalent to those of mastectomy (1–6) and is now the treatment of choice for early breast cancers in Western countries. In Japan, BCT was incorporated into practice in the mid-1980s and has recently become increasingly established. The national survey conducted by the Japanese Breast Cancer Society (JBCS) indicated that in 2000 approximately 40% of patients with breast cancer received BCT (7). However, its indication and implementation were not standardized until 1999, when the JBCS published a guideline for BCT, and there still exists considerable variation around the country.

The patterns of care study (PCS) was originally developed in the United States in the mid-1970s. Such studies evaluate the structure of the facility, including both personnel and equipment, and the process of treatment and then feed back the outcome to improve the quality of cancer treatment (8–10). The Japanese version of PCS began in 1996, and treatment processes and outcomes have been reported for uterine cervical cancer, esophageal cancer, and lung cancer to date (11–13).

This study surveyed the treatment process for BCT in Japan between 1995 and 1997 and identified national averages for important factors.

METHODS AND MATERIALS

Eligibility criteria for this analysis were as follows: (1) the patient was treated between January 1995 and December 1997, (2) the patient was female, (3) there were no gross multiple tumors, (4)

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there was no diffuse microcalcification on pretreatment mammography, (5) there were no distant metastases, (6) the patient did not have bilateral lesions, (7) there were no prior or concurrent malignancies, (8) there was no prior history of irradiation of the breast, and (9) the patient did not have any collagen vascular disease other than rheumatoid arthritis.

In 1995, a total of 556 institutions nationwide were stratified into four classifications according to the Japanese facility master list, and 72 institutions were randomly sampled. Then, the subjects of this survey were randomly sampled from the lists of eligible patients supplied by these institutions (two-staged cluster method [10]). Between September 1998 and December 1999, extramural audits of institutions were conducted by the Japanese PCS Working Group. The audits were performed by member physicians of the working group. Consequently, data for the treatment process of 865 BCT patients were collected (Table 1). Although it was our initial intent to collect equal numbers of patients from equal numbers of facilities in each stratum, there were some problems, such as difficulty in getting approval of an external audit from the institutional review board or an unexpectedly large number of ineligible patients in the list provided by the facility. However, the resultant imbalance did not affect the results of this study because calculation of the national average takes these imbalances into account.

A newly developed data format based on the fifth PCS data format developed in the United States was used for this survey. The original format was provided courtesy of the American College of Radiology and modified by the Japanese PCS Working Group to accommodate the staging system of JBCS. The data format is a FileMaker Pro (version 4.0) database (FileMaker, Santa Clara, CA), installed on portable computers. It consists of 316 items, which cover all aspects of the initial treatment of breast cancer. Data were collected primarily from charts of the radiation oncology department. In addition, best efforts were made to obtain required information by using all available resources at the location. In this analysis, the extent of surgery, precision of pathologic evaluation, the technique for postoperative radiation therapy, indication and usage of systemic chemo-endocrine therapy, and the result of functional–cosmetic assessment were evaluated. National averages were calculated where applicable with Sedransk's equation (14). The details of the calculation were described by us previously (15, 16). Of note, national averages were not calculated if the amount of missing data exceeded 20%.

In the tables presented, "unknown" indicates that the item in the format was filled with data "unknown," whereas "missing" means the item in the format was left empty. We combined "unknown" and "missing" in the tables because their meanings are the same in most cases: no valid data were found in the given resources. "Unknown/missing" data for categoric data were included in the ratio calculation, whereas those data for continuous variables were excluded from the ratio calculation, as seen in a corresponding report from the U.S. PCS (17).

RESULTS

Patient backgrounds and the results of pretreatment evaluation are shown in Table 2. Of the entire group of patients, 36.2% were postmenopausal. Approximately 70% of the patients had tumor with a clinical size no larger than 2.0 cm. Approximately 90% of patients were clinically node negative.

Table 1. Definition of facility categories and the number of patients registered in each category

	No. of facilities visited	No. of patients registered
A facilities: university hospitals and cancer centers		
A1 facility (≥300 patients per year)	20	296
A2 facility (<300 patients per year)	19	193
B facilities: community-based hospitals		
B1 facility (≥120 patients per year)	18	256
B2 facility (<120 patients per year)	15	121
Total	72	865

Type and extent of breast-conserving surgery are shown in Table 3. Fifty-seven percent of patients received breast surgery equivalent to quadrantectomy. The most common procedure for the axilla was Level I/II dissection, which was used in 59.7% of patients. The mean number of dissected lymph nodes was 14.3 ± 7.1.

The results of histopathologic assessment are shown in Table 4. Approximately 80% of the patients had invasive ductal cancer. Final microscopic margin was negative in 76.7%. Of note, margin status was not documented in 9.5% of the patients. Only 14.6% of patient records showed quantification of the intraductal component of the specimen. Axillary lymph node was pathologically negative in 78.1%, and only 4.7% of patients had ≥4 positive axillary lymph nodes.

Parameters for treatment planning of tangential fields are shown in Table 5. A fixation system, such as cast or shell, was used in 32.6%. X-ray simulation was the most common method of treatment planning and was used in 67.5% of the patients. Of note, 44% of those X-ray simulations were performed without information from diagnostic CT. Dorsal margins of the tangential fields were matched in 78.7%, and the tilting technique was more commonly used than the half beam technique. Specialized fields, such as the axilla, parasternal, and supraclavicular, were seldom used.

Parameters for treatment delivery of the tangential field are listed in Table 6. The mean interval between final breast surgery and the initiation of radiation therapy was 28.5 ± 21.9 days. Approximately 60% of the patients received photons at an energy level <6 MV. There were 38 patients (4.4%) who received tangential breast irradiation with a 10-MV photon without bolus. Of note, 2.7% of the patients received whole breast irradiation with electron beam alone. The mean cranio–caudal size of the initial radiation field was 17.7 ± 2.6 cm. The most commonly used dose and fractionation was 50 Gy for 25 fractions and 50.4 Gy for 28 fractions. Consequently, overall treatment time for the initial field was 36.4 ± 8.9 days. Of note, 18.6% of the patients received treatment to only one tangential field each day.

Parameters for boost field irradiation are shown in Table 7. Boost to the tumor bed was given in 53.9%, 45.0%, and 11.9% of patients showing positive, close, and negative pathologic margins, respectively. The most commonly used

Table 2. Patient characteristics and the results of pretreatment evaluation

	Total (n = 865)	National average
Age (y)	51.5 ± 11.2	N/A
Missing	8	
Height (cm)	154.2 ± 5.6	N/A
Missing	331	
Body weight (kg)	54.0 ± 8.4	N/A
Missing	313	
Menstrual status		N/A
Pre	312/865 (36.1)	
Peri	86/865 (9.9)	
Post	313/865 (36.2)	
Unknown/missing	154/865 (17.8)	
Family history of breast cancer		N/A
No	534/865 (61.7)	
Yes	46/865 (5.3)	
Unknown/missing	285/865 (33.0)	
Mammography performed		N/A
Not done	11/865 (1.3)	
≤3 months before surgery	539/865 (62.3)	
After excision	8/865 (0.9)	
Before and after initial excision	20/865 (2.3)	
Unknown	287/865 (33.2)	
Clinical tumor size (cm)	1.9 ± 0.9	1.9
≤1.0	140/713 (19.64)	
1.1–2.0	361/713 (50.63)	
2.1–3.0	171/713 (23.98)	
3.1–4.0	28/713 (3.93)	
4.1–5.0	7/713 (0.98)	
≥5.1	6/713 (0.84)	
Missing	152	
Nipple–tumor distance (cm)	3.9 ± 1.9	U/C
≤2.0 cm	58/287 (20.2)	
2.1–4.0	119/287 (41.5)	
4.1–6.0	85/287 (29.6)	
≥6.1	25/287 (8.7)	
Missing	578	
Clinical N stage (UICC 1997)		N/A
N0	741/831 (89.2)	
N1	87/831 (10.5)	
N2	8/831 (0.4)	
Missing	34	

Abbreviations: N/A = not applicable; U/C = unable to calculate owing to the excessive amount of missing data; UICC = Union Internationale Contre Cancre.

Data are presented as n or mean ± standard deviation. Numbers in parentheses are percentages.

dose and fractionation for boost irradiation was 10 Gy for 5 fractions.

Systemic chemo-endocrine therapy is summarized in Table 8. Tamoxifen was given to 72.5% of receptor-positive patients. However, 52.3% of receptor-negative patients also received tamoxifen. When tamoxifen was given, it was initiated during radiation therapy in 82.2%. Chemotherapy was given to 64.4% and 31.6% of node-positive and node-negative patients, respectively. However, intensive chemotherapy was given to 36.9% node-positive patients (38 of 103) and 15.6% node-negative patients (28 of 180). (Intensive chemotherapy was defined as incorporating at least one of the following: doxorubicin, cyclophosphamide, methotrexate, mitomycin, mitoxantrone, paclitaxel, vinblastine, or vincristine.) The most common regimen for chemotherapy was single-agent oral administration of 5-fluorouracil or its derivatives and was administered to 52.4% (54 of 103) of node-positive patients and 76.7% of node-negative patients (138 of 180).

Toxicity of the treatment and functional–cosmetic results are listed in Table 9. Whole treatment was well tolerated, and there were only 6 patients (0.7%) with Grade 3 or greater acute/late toxicity. The results of objective functional–cosmetic evaluation were documented in only 31.9% of the cases, of which 80.0% were excellent to good. Similarly, patient satisfaction was documented only in 23.1% of the cases and showed that 66.5% of patients were satisfied with the functional–cosmetic results.

DISCUSSION

Approximately 10 years after it was initiated in Western countries, BCT was introduced in Japan in the mid-1980s (7). In the period when the patients in this study were treated, physicians were still developing an optimal implementation of BCT in Japan, and it was not until 1999 that the JBCS published a guideline for BCT.

The current study demonstrates that the indication for BCT was fairly conservative, and most of the patients were Union Internationale Contre Cancre (UICC) Clinical Stage I.

Table 3. Type and extent of breast-conserving surgery

	Total (n = 865)	National average
Extent of final breast surgery		N/A
≤Tumorectomy*	47/865 (5.4)	
Wide excision†	325/865 (37.5)	
Quadrantectomy‡	493/865 (57)	
Missing	0	
Extent of axillary dissection		N/A
Level I	177/865 (20.5)	
Level I/II	516/865 (59.7)	
Level I/II/III	74/865 (8.6)	
Unknown/Missing	98/865 (11.3)	
Number of axillary lymph nodes in specimen	14.3 ± 7.1	U/C
0	10/584 (1.7)	
1–5	19/584 (3.3)	
6–9	116/584 (19.9)	
10–19	323/584 (55.3)	
≥20	116/584 (19.9)	
Missing	281	
Maximum	48	

Abbreviations as in Table 2.

Data are presented as n or mean ± standard deviation. Numbers in parentheses are percentages.

* Includes incisional biopsy, excisional biopsy, microdochectomy (single duct excision), and tumorectomy.

† Includes wide excision and partial mastectomy.

‡ Includes segmental resection and quadrantectomy.

Table 4. Results of histopathologic assessment

	Total (n = 865)	National average
Pathology report on chart		0.71*
Yes	564/865 (65.2)	
No	260/865 (30.1)	
Unknown/missing	41/865 (4.7)	
Histology of the tumor		N/A
Carcinoma, NOS	2/865 (0.2)	
Adenocarcinoma, NOS	4/865 (0.5)	
Ductal carcinoma in situ	29/865 (3.4)	
Lobular carcinoma in situ	1/865 (0.1)	
Invasive ductal carcinoma	676/865 (78.2)	
Mucinous carcinoma	26/865 (3.0)	
Medullary carcinoma	17/865 (2.0)	
Invasive lobular carcinoma	18/865 (2.1)	
Squamous cell carcinoma	2/865 (0.2)	
Apocrine carcinoma	2/865 (0.2)	
Tubular carcinoma	57/865 (6.6)	
Unknown/missing	31/865 (3.6)	
Final microscopic margin		N/A
Positive	65/865 (7.5)	
Close (≤2 mm)	40/865 (4.6)	
Negative	663/865 (76.7)	
Unknown or not stated/ missing	97/865 (11.2)	
Intraductal cancer quantified		U/C
No	154/865 (17.8)	
Yes	126/865 (14.6)	
Unknown/missing	585/865 (67.6)	
Estrogen receptor status		
Not done	96/865 (11.1)	
Positive	269/865 (31.1)	
Negative	199/865 (22.9)	
Insufficient tissue	7/865 (0.8)	
Unknown/missing	295/865 (34.1)	
Progesterone receptor status		N/A
Not done	114/865 (13.2)	
Positive	252/865 (29.1)	
Negative	170/865 (19.7)	
Insufficient tissue	7/865 (0.8)	
Unknown/missing	322/865 (37.2)	
No. of pathologically positive axillary lymph nodes		N/A
0	569/729 (78.1)	
1–3	126/729 (17.3)	
≥4	34/729 (4.7)	
Missing	136	
Maximum	37	

Abbreviation: NOS = not otherwise specified. Other abbreviations as in Table 2.

Data are presented as *n*. Numbers in parentheses are percentages.

* "Yes" = 1, others = 0.

In BCT, the balance between surgery and radiation therapy depends on the extent of surgery. For example, if mastectomy is performed for T1–T2 tumor, postoperative radiation therapy is not necessary for local control. As the extent of surgery decreases, the importance of radiation therapy increases, and the radiation dose to achieve adequate local control also increases. The strategy for BCT in Japan in this study period was to surgically remove as much of the cancer cells as possible rather than to remove grossly recognizable tumor and let radiation therapy do the rest. Consequently, the ratio of patients with microscopically positive/close margin was only 12.4%. The same trend was observed in the treatment of the axilla. Although it was generally accepted that axillary dissection for clinically node-negative patients does not improve survival, 68.3% of the patients received Level I/II or more axillary dissection.

Histopathologic evaluation is the most important part of BCT because it influences all aspects of subsequent treatment. The number of positive lymph nodes determines the necessity of chemotherapy. Hormone receptor status is important for endocrine therapy. To reduce the extent of surgery while maintaining sufficient local control, meticulous treatment planning based on a full understanding of the pathologic features of the tumor is mandatory. However, in the current study, margin status was unknown, at least in the departmental chart for radiation therapy, in 11.2% of the patients. The quality of the pathologic report showed some room for improvement in that nuclear grading and quantification of the intraductal component were missing from most case reports. This might reflect a lack of pathologists specializing in breast cancer in Japan.

Radiation therapy was also suboptimal in some aspects. A fixation system is recommended to increase the reproducibility of daily treatment. However, such a system was used

Table 5. Parameters for radiotherapy treatment planning

	Total (n = 865)	National average
Cast or shell was used		0.30
Yes	282/865 (32.6)	
No	578/865 (66.8)	
Unknown/N/A/missing	5/865 (0.6)	
Simulation		N/A
Clinical set-up only	87/865 (10.1)	
X-ray simulation without diagnostic CT	257/865 (29.7)	
X-ray simulation with diagnostic CT	327/865 (37.8)	
CT simulation	192/865 (22.2)	
Missing	2/865 (0.2)	
Reference point for tangential fields		N/A
Isocenter of the field	614/637 (96.4)	
Upper 1/3 of nipple and lower margin of RT field	3/637 (0.5)	
Others	2/637 (0.3)	
Missing	18/637 (2.8)	
Matching of dorsal margin of tangential fields		N/A
None	108/637 (17.0)	
Half beam used	121/637 (19.0)	
Tilting	380/637 (59.7)	
Unknown/N/A/missing	28/637 (4.4)	
Specialized fields irradiated	11/865 (1.3)	N/A
Axilla	1/865 (0.1)	
Internal mammary	8/865 (0.9)	
Supraclavicular	17/865 (2.0)	

Abbreviation as in Table 2.

Data are presented as *n* (%).

Table 6. Parameters for tangential field irradiation

	Total (n = 865)	National average
Interval between final breast surgery and radiation therapy (d)	28.5 ± 21.9	28.3
<7	8/852 (0.9)	
7–13	79/852 (9.3)	
14–20	266/852 (31.2)	
21–27	180/852 (21.1)	
28–55	257/852 (30.2)	
≥56	62/852 (7.3)	
Missing	13	
Maximum	253	
Beam type for whole breast irradiation		N/A
60 Co.	124/865 (14.4)	
Photons <4 MV	5/865 (0.6)	
Photons ≥4 MV, <6 MV	406/865 (46.9)	
Photons ≥6 MV, <8 MV	217/865 (25.1)	
Photons ≥8 MV, <10 MV with bolus	0/865 (0.0)	
Photons ≥8 MV, <10 MV without bolus	1/865 (0.1)	
Photons ≥10 MV with bolus	39/865 (4.5)	
Photons ≥10 MV without bolus	38/865 (4.4)	
Photons ≥10 MV, bolus unknown	2/865 (0.2)	
Electrons	23/865 (2.7)	
Mixed	1/865 (0.1)	
Missing	9/865 (1.0)	
Wedges		N/A
On both fields	386/781 (49.4)	
On lateral fields only	2/781 (0.3)	
No beam modifiers	392/781 (50.2)	
Unknown/missing	1/781 (0.1)	
Cranio–caudal size of the field (cm)	17.7 ± 2.6	17.4
<10	8/846 (1.0)	
10.0–11.9	7/846 (0.8)	
12.0–13.9	24/846 (2.8)	
14.0–15.9	106/846 (12.5)	
16.0–17.9	209/846 (24.7)	
18.0–19.9	286/846 (33.8)	
20.0–21.9	146/846 (17.3)	
22.0–23.9	50/846 (5.9)	
≥24	10/846 (1.2)	
Missing	0/846 (0.0)	
Max	25.5	
Total dose for whole breast (cGy)	4882.45 ± 327.25	4867.76
<4400	12/852 (1.4)	
4400–4599	79/852 (9.3)	
4600–4799	91/852 (10.7)	
4800–4999	29/852 (3.4)	
5000–5199	630/852 (73.9)	
≥5200	11/852 (1.3)	
Missing	13	
Maximum	6000	
Fraction size (cGy)	204 ± 22	207.72
<160	2/816 (0.3)	
160–179	0/816 (0.0)	
180–199	46/816 (5.6)	
200–219	708/816 (86.8)	
220–239	2/816 (0.3)	
≥240	58/816 (7.1)	
Missing	49	
Maximum	500	
Overall treatment time for whole breast irradiation (d)	36.4 ± 8.9	35.9
≤35	314/847 (37.1)	
36–41	453/847 (53.5)	
42–48	60/847 (7.1)	
≥49	20/847 (2.4)	
Missing	18	
Maximum	125	
No. of tangents treated per day		0.74*
Both	637/845 (75.4)	
One only	157/845 (18.6)	
Unknown/N/A/missing	51/845 (6.0)	

Abbreviation as in Table 2.

Data are presented as n or mean ± standard deviation. Numbers in parentheses are percentages.

* Both = 1; the others = 0.

only in 32.6% of cases. Matching of the dorsal margin of the tangential field reduces unnecessary radiation to the lung; however, 17.0% of patients were irradiated without such a

Table 7. Parameters for boost field irradiation

	Total (n = 865)	National average
Boost was given to:		N/A
Margin positive	35/65 (53.9)	
	Missing: 2/65 (3.1)	
Margin close (≤2 mm)	18/40 (45.0)	
	Missing: 0/40 (0.0)	
Margin negative	79/663 (11.9)	
	Missing: 46/663 (6.9)	
Margin unknown/missing	14/97 (14.4)	
	Missing: 11/97 (11.3)	
Boost dose (cGy)	1004 ± 393	997.14
<400	0/130 (0.0)	
400–599	6/130 (4.6)	
600–799	5/130 (3.9)	
800–999	7/130 (5.4)	
1000–1199	103/130 (79.2)	
1200–1399	4/130 (3.1)	
1400–1599	5/130 (3.9)	
1600–1799	0/130 (0.0)	
1800–1999	0/130 (0.0)	
2000–2199	0/130 (0.0)	
≥2200	0/130 (0.0)	
Missing	16	
Maximum	1400	
Electron energy for boost (MeV)		0.67
6–8	29/127 (22.8)	
9–11	69/127 (54.3)	
12–14	15/127 (11.8)	
≥15	7/127 (5.5)	
Unknown/Missing	7/127 (5.5)	
Max	18MeV	

Abbreviation as in Table 2.

Data are presented as n or mean ± standard deviation. Numbers in parentheses are percentages.

Table 8. Parameters for systemic therapy

	Total (n = 865)	National average
Tamoxifen was given to:		
ER (+) or PgR (+)	234/323 (72.5) Missing: 7/323 (2.2)	0.69*
ER (−) and PgR (−)	68/130 (52.3) Missing: 6/130 (4.6)	0.55†
Receptor status unknown/ missing	220/412 (53.4) Missing: 21/412 (5.1)	0.48§
Tamoxifen was given:		N/A
With RT	429/522 (82.2)	
Post-RT	491/522 (94.1)	
Timing unknown/missing	11/522 (2.1)	
Chemotherapy† was given to:		
Node positive	103/160 (64.4) N/A/Unk/Missing: 22/160 (13.8)	0.64*
Node negative	180/569 (31.6) N/A/Unk/Missing: 86/569 (15.1)	0.33*
Node unknown/missing	52/136 (38.2) N/A/unknown/missing: 25/136 (18.4)	0.20*
Chemotherapy given to node positive:	103/160 (64.4)	N/A
Nonintensive‡	54/103 (52.4)	
Intensive§	38/103 (36.9)	
Others	0/103 (0)	
Unknown/Missing	11/103 (10.7)	
Chemotherapy given to node negative:	180/569 (31.6%)	N/A
Nonintensive‡	138/180 (76.7)	
Intensive§	28/180 (15.6)	
Others	0/180 (0.0)	
Unknown/missing	14/180 (7.8)	
Chemotherapy given to node missing:	52/136 (38.2)	N/A
Nonintensive‡	19/52 (36.5)	
Intensive§	7/52 (13.5)	
Others	0/52 (0.0)	
Unknown/missing	26/52 (50.0)	
Chemotherapy† was given:		N/A
Pre-RT	142/375 (37.9)	
Post-RT	213/374 (57.0)	
Concurrent with RT	140/370 (37.8)	
Alternating with RT	22/345 (6.4)	

Abbreviations: ER = estrogen receptor; PgR = progesterone receptor, RT = radiation therapy. Other abbreviation as in Table 2.

Data are presented as n (%).

* "Yes" = 1, others = 0.

† Includes all kinds of chemotherapy.

‡ Includes single-agent, oral administration of 5-fluorouracil or its derivative.

§ Includes chemotherapy that incorporated at least one of the following: doxorubicin, cyclophosphamide, methotrexate, mitomycin, mitoxantrone, paclitaxel, vinblastine, and vincristine.

plan. A wedge filter is often necessary to ensure dose homogeneity within the treatment volume; however, 50.2% were treated without wedges. In as many as 18.6% of patients, only one of the two tangent fields was treated per day. Such treatment does not guarantee equivalent biologic effect within the treatment volume. Moreover, discordance with existing guidelines in some treatment characteristics might lead to more serious deterioration of treatment outcome. For example, treatment with a 10-MV photon without bolus might cause significant underdosage in the shallow part of breast tissue in average-sized Japanese women. Although it is difficult to statistically prove the impact of these suboptimal treatments on outcome, such underdosage should be corrected to provide the best possible local tumor control.

The current study has some limitations derived from its methodology. First, patients receiving breast-conserving surgery without radiation therapy were not included because there were only patients who received radiation therapy in the sample source. Considering the fact that there were approximately 25–30% of such patients in the study period (7), the results presented here might not reflect the whole of BCT practice in Japan. It is mandatory to join forces with other disciplines to comprehensively depict the patterns of care for diseases like breast cancer, in which multidisciplinary treatment is established.

Second, extensive data were missing for certain items in the database. Although the absence of the data itself might have some implication, it is difficult to differentiate whether the data did not exist at all or whether the auditor could not find existing data at the time of review. Therefore, the items with extensive missing data should be interpreted with caution. For example, approximately 70% of the data for the item "Cosmetic score at 1 year" were "unknown/missing." This finding itself provides vital information that the cosmetic outcome was seldom evaluated by the physician. However, if these patients had been evaluated, they would have fallen into one of the four scoring categories. Therefore, it might be misleading to report that only 3.7% showed

Table 9. Toxicity of the treatment and functional–cosmetic results

	Total (n = 865)	National average
Patients with Grade ≥3 acute/late toxicity	6/865 (0.7) Missing 826/865 (95.5)	U/C
Cosmetic score at 1 y		N/A
Excellent	30/865 (3.5)	
Good	191/865 (22.1)	
Fair	49/865 (5.7)	
Poor	6/865 (0.7)	
Unknown/N/A/missing	589/865 (68.1)	
Patient satisfaction at 1 y		N/A
Satisfactory	133/865 (15.4)	
Fair	63/865 (7.3)	
Unsatisfactory	4/865 (0.5)	
Unknown/missing	665/865 (76.9)	

Abbreviations as in Table 2.

Data are presented as n (%).

excellent cosmetic outcome without referring to the excessive percentage of "unknown/missing" data.

In conclusion, BCT in Japan was still in the developmental phase during the period when this first national survey was conducted. Repeated surveys and point-by-point comparisons with results from other countries will demonstrate how BCT has been developed and optimized for patients in Japan.

REFERENCES

1. Blichert-Toft M, Rose C, Andersen JA, *et al.* Danish randomized trial comparing breast conservation therapy with mastectomy: Six years of life-table analysis. Danish Breast Cancer Cooperative Group. *J Natl Cancer Inst Monogr* 1992;19–25.
2. Arriagada R, Le MG, Rochard F, *et al.* Conservative treatment versus mastectomy in early breast cancer: Patterns of failure with 15 years of follow-up data. Institut Gustave-Roussy Breast Cancer Group. *J Clin Oncol* 1996;14:1558–1564.
3. 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.
4. Jacobson JA, Danforth DN, Cowan KH, *et al.* Ten-year results of a comparison of conservation with mastectomy in the treatment of stage I and II breast cancer. *N Engl J Med* 1995;332:907–911.
5. van Dongen JA, Bartelink H, Fentiman IS, *et al.* Randomized clinical trial to assess the value of breast-conserving therapy in stage I and II breast cancer, EORTC 10801 trial. *J Natl Cancer Inst Monogr* 1992;15–18.
6. Veronesi U, Luini A, Galimberti V, *et al.* Conservation approaches for the management of stage I/II carcinoma of the breast: Milan Cancer Institute trials. *World J Surg* 1994;18:70–75.
7. Japanese Breast Cancer Society. Results of questionnaires concerning breast cancer surgery in Japan: An update in 2000. *Breast Cancer* 2002;9:1.
8. Coia LR, Hanks GE. Quality Assessment in the USA: How the Patterns of Care Study Has Made a Difference. *Semin Radiat Oncol* 1997;7:146–156.
9. Hanks GE, Coia LR, Curry J. Patterns of Care Studies: Past, Present, and Future. *Semin Radiat Oncol* 1997;7:97–100.
10. Owen JB, Sedransk J, Pajak TF. National Averages for Process and Outcome in Radiation Oncology: Methodology of the Patterns of Care Study. *Semin Radiat Oncol* 1997;7:101–107.
11. Uno T, Sumi M, Sawa Y, *et al.* Process of care and preliminary outcome in limited-stage small-cell lung cancer: Results of the 1995-1997 patterns of care study in Japan. *Int J Radiat Oncol Biol Phys* 2003;55:626–632.
12. Teshima T, Abe M, Ikeda H, *et al.* Patterns of care study of radiation therapy for esophageal cancer in Japan: Influence of the stratification of institution on the process. *Jpn J Clin Oncol* 1998;28:308–313.
13. Teshima T, Abe M, Ikeda H, *et al.* Patterns of care study of radiation therapy for cervix cancer in Japan: The influence of the stratification of institution on the process. *Jpn J Clin Oncol* 1998;28:388–395.
14. Sedransk N, Sedransk J. Distinguishing among distributions using data from complex sample designs. *J Am Stat Assoc* 1979;74:754–760.
15. Tanisada K, Teshima T, Ohno Y, *et al.* Patterns of Care Study quantitative evaluation of the quality of radiotherapy in Japan. *Cancer* 2002;95:164–171.
16. Tanisada K, Teshima T, Inoue T, *et al.* National average for the process of radiation therapy in Japan by Patterns of Care Study. *Jpn J Clin Oncol* 1999;29:209–213.
17. Shank B, Moughan J, Owen J, *et al.* The 1993-94 patterns of care process survey for breast irradiation after breast-conserving surgery-comparison with the 1992 standard for breast conservation treatment. The Patterns of Care Study, American College of Radiology. *Int J Radiat Oncol Biol Phys* 2000;48:1291–1299.

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Case Report

A Case of Metachronous Bilateral Breast Cancer with Bilateral Radiation Pneumonitis After Breast-conserving Therapy

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We report a patient with metachronous bilateral breast cancer who has twice developed radiation pneumonitis after breast-conserving therapy for each breast. The patient was a 48-year-old woman, who presented with Stage I right breast cancer. After wide excision of the right breast tumor and dissection of level I axillary lymph nodes, systemic therapy with oral 5-FU and tamoxifen was started. Subsequently, tangential irradiation with a total dose of 50 Gy in 25 fractions was given. Seven months after irradiation, she developed respiratory symptoms and radiation pneumonitis was diagnosed. The symptoms resolved with oral prednisolone. Thirty months after the right breast cancer treatment, Stage I left breast cancer was diagnosed. After wide excision of the left breast tumor and partial removal of the level I axillary lymph nodes, the same oral systemic chemo-hormonal therapy was initiated. Thereafter, tangential irradiation with a total dose of 50 Gy in 25 fractions was given. Four months after irradiation, she developed respiratory symptoms. A chest X-ray showed an area of increased density in the left lung consistent with radiation pneumonitis. The symptoms were mild and they improved spontaneously without medication. Although there is insufficient evidence to justify or withhold whole breast radiation therapy from patients with a history of contralateral breast cancer and radiation pneumonitis, it is essential to discuss the adequacy of whole breast irradiation and the possibility of alternative approaches, such as breast-conserving surgery without irradiation or partial breast irradiation for this rare condition.

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Key words: Bilateral breast cancer, Breast-conserving therapy, Radiation pneumonitis

We recently encountered a rare patient with metachronous bilateral breast cancer, who twice developed radiation pneumonitis after each breast-conserving therapy (BCT). We herein report the clinical course and review the literature.

Case Report

The patient was a 48-year-old woman. She underwent wide excision and level I dissection of the right axillary lymph nodes for Stage I (T1N0M0: UICC 5th edition) breast cancer of the right breast. Systemic chemo-hormonal therapy with 200 mg/day oral 5-FU and 20 mg/day oral tamoxifen was started immediately after surgery. Thereafter, she underwent tangential irradiation to the whole breast. The 50 Gy radiation dose was given in 25 fractions with $^{60}Co\gamma$ rays (Fig 1). Seven months after the irradiation, she developed sore throat, fever and severe coughing. Because the symptoms did not resolve with oral antibiotics, chest X-ray showed a ground-glass appearance (Fig 2), and she had a history of radiation therapy, radiation-induced pneumonitis was diagnosed and treated with 30 mg/day oral prednisolone and antibiotics. After three weeks of treatment, the symptoms resolved and prednisolone was tapered. One month later, a chest X-ray showed a new shadow in the upper field of the ipsilateral lung (Fig 3). Both 45 mg/day oral prednisolone and antibiotics were resumed. After two weeks of medication, the symptoms resolved and prednisolone

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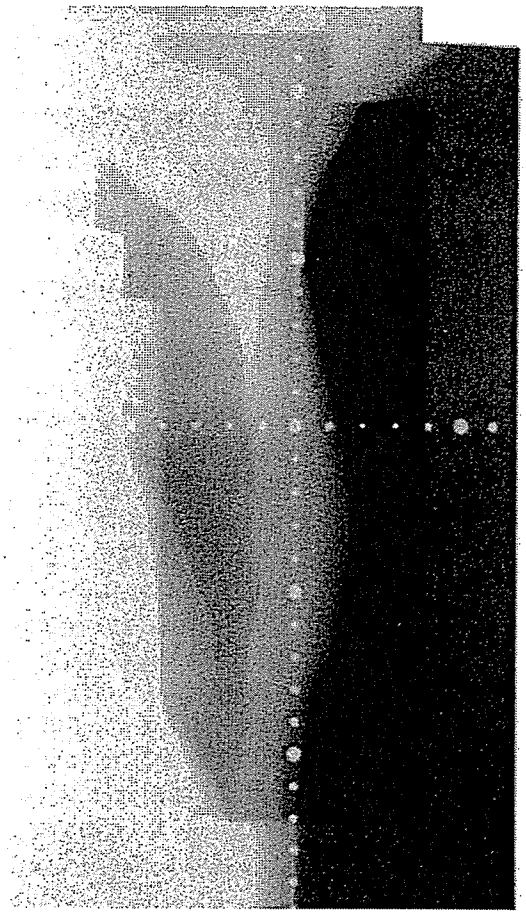

Fig 1. The irradiated field of the whole right breast with $^{60}Co\gamma$ rays.

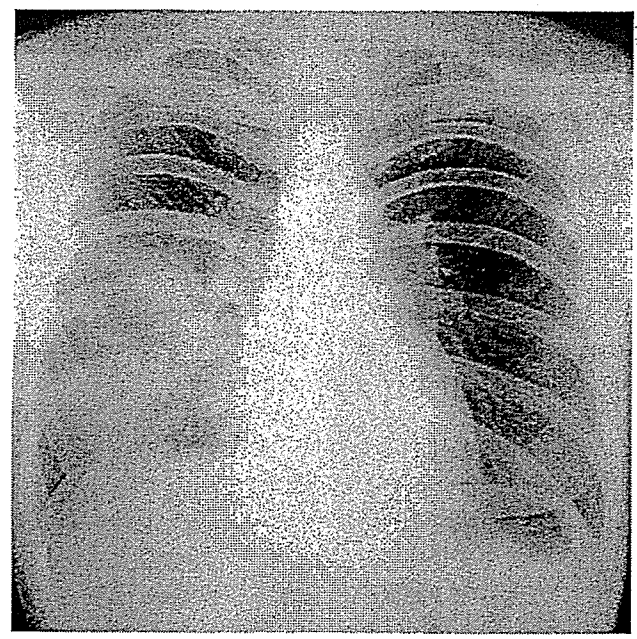

Fig 2. Seven months after irradiation, chest X-ray showed a ground-glass appearance in the middle to lower lung fields of the right lung.

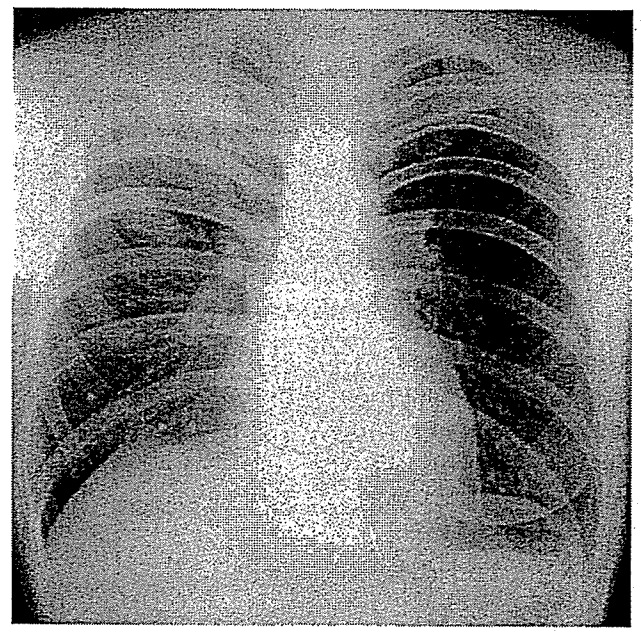

Fig 3. Eight months after irradiation, chest X-ray showed a new shadow in the upper field of the ipsilateral lung.

was tapered. Of note, oral 5-FU and tamoxifen were continued throughout the treatment for radiation pneumonitis until two years after the surgery. Thirty months after the treatment of the right breast cancer, she was diagnosed with left breast cancer. Subsequently, she underwent wide excision of the left breast tumor and partial removal of the level I axillary lymph nodes for Stage I (T1N0M0: UICC 5th edition) breast cancer. The same systemic chemo-hormonal therapy of 200 mg/day oral 5-FU and 20 mg/day oral tamoxifen was initiated immediately after surgery. She underwent 50 Gy of tangential irradiation to the left breast in 25 fractions with 6 MV X rays, which were shaped to prophylactically irradiate the level I axillary lymph nodes that had not been completely dissected (Fig 4). Four months after irradiation, she again developed symptoms of a common cold. Chest X-ray showed increased density in the left lung consistent with radiation pneumonitis (Fig 5). This time, the symptoms were mild and she was followed without prednisolone and improved a few days later.

Discussion

The overall incidence of bilateral breast cancer,