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.

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.

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 8. Parameters for systemic therapy

	Total (n = 865)	National average
Tamoxifen was given to:		
ER (+) or PgR (+)	234/323 (72.5)	0.69*
	Missing: 7/323 (2.2)	
ER (−) and PgR (−)	68/130 (52.3)	0.55†
	Missing: 6/130 (4.6)	
Receptor status unknown/ missing	220/412 (53.4)	0.48§
	Missing: 21/412 (5.1)	
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)	0.64*
	N/A/Unk/Missing: 22/160 (13.8)	
Node negative	180/569 (31.6)	0.33*
	N/A/Unk/Missing: 86/569 (15.1)	
Node unknown/missing	52/136 (38.2)	0.20*
	N/A/unknown/missing: 25/136 (18.4)	
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
	6/865 (0.7)	U/C
Patients with Grade ≥3 acute/late toxicity	Missing 826/865 (95.5)	
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.

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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 locoregional 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.

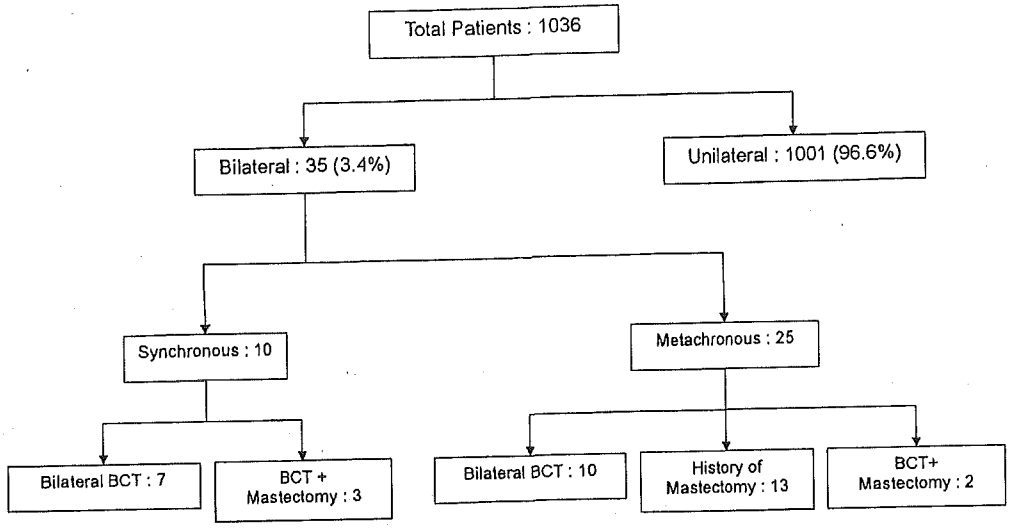

Fig 1. Total patients treated between July 1990 and December 1998.

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.

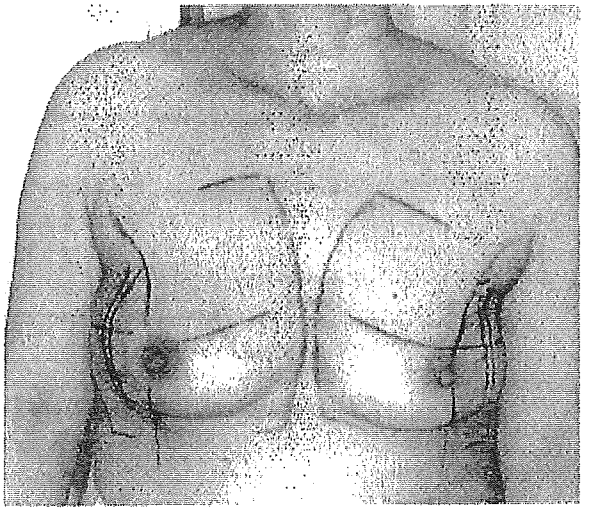

Fig 2. A case of simultaneous breast cancer: It is confirmed that there is no overlap by the skin markings.

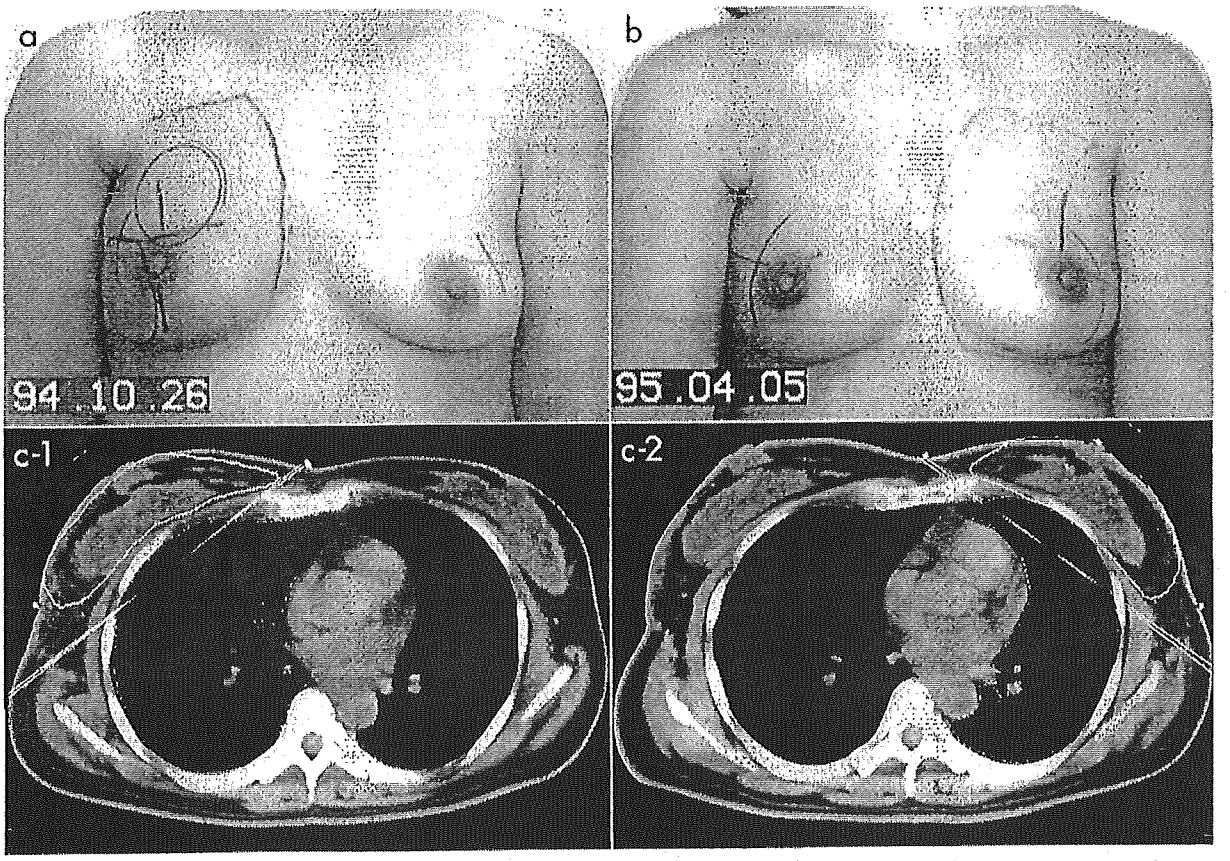

Fig 3. A case of metachronous breast cancer. (a) Radiation field for the first treatment. (b) Radiation field for the second treatment. Identifying the first field by the skin reaction is impossible. (c) We could recognize the first field accurately with the use of images from the previous CT simulation.

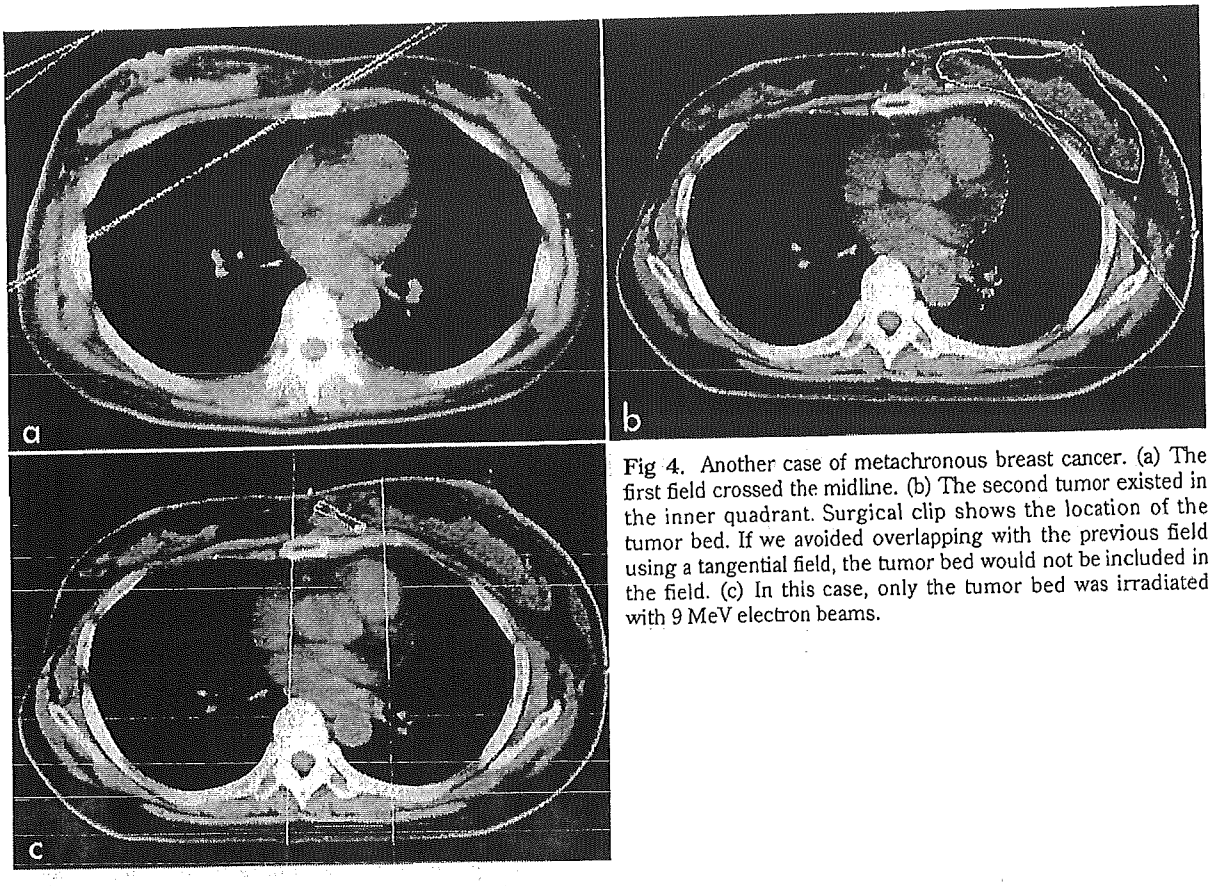

Fig 4. Another case of metachronous breast cancer. (a) The first field crossed the midline. (b) The second tumor existed in the inner quadrant. Surgical clip shows the location of the tumor bed. If we avoided overlapping with the previous field using a tangential field, the tumor bed would not be included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

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化学放射線療法

乳癌

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Point

切除可能な乳癌に対する術後補助療法

●放射線治療と化学療法の順序の問題は両者の同時併用により解決される。同時併用では毒性の増強が問題になるが、CMFと39.6Gyの放射線治療の同時併用では良好な局所制御が達成され、晩期障害も軽微であった。また、mitoxantroneを用いた同時併用化学放射線療法と逐次化学放射線療法のランダム化比較試験でも同時併用の実施可能性が示されている。

切除不能な局所進行乳癌・局所再発乳癌に対する化学放射線療法

●Anthracycline系薬剤は毒性の点で同時併用は勧められないが、taxane系薬剤では乳癌に対する同時併用化学放射線療法は実施可能と思われる。今後最適な化学療法レジメンや放射線治療の線量分割について研究が進むことが期待される。

切除可能乳癌に対する術前化学放射線療法

●術前化学療法に局所療法である放射線治療を付加しても生存率の向上は期待できないが、局所効果の上乗せは期待される。最近の臨床試験では40%を越えるpCR率も報告されており、画像診断技術の進歩や新しい予後因子の発見によってpCR例を高精度に予測することが可能になれば、手術無しに初回治療を完了するという、大きなパラダイムシフトがもたらされる可能性がある。

乳癌に対する化学放射線療法は、他疾患における化学放射線療法といくつかの点で異なっている。そもそも肺癌・食道癌・頭頸部癌などでは治療の基本方針として手術か非手術かというところに外科医と放射線・内科医の対決の図式が存在し、非手術治療において、局所効果を最大化し、かつ微小遠隔転移も根絶するという目的で化学放射線療法が行われてきた。一方、乳癌では手術・放射線治療・内分泌化学療法の役割分担がきわめて明確であり、現時点では放射

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線治療±化学療法による非手術治療という概念そのものがまだ認知されていない。そのほか、①強い有害事象のためにkey drugの一つであるanthracycline系の薬剤と放射線治療の同時併用が困難である、②乳癌の生存は遠隔微小転移の制御にかかっており、同時併用のために化学療法の強度を落とすことが好まれない、などの理由で化学放射線療法に対する関心は、他疾患におけるほど高くはないのが実情である。

しかしながら乳癌治療においても化学放射線療法は模索されていることは事実であり、それらについて考察してみたい。

切除可能な乳癌に対する術後補助療法としての同時併用化学放射線療法

乳房温存療法では温存乳房内再発を抑えるために、術後の放射線治療が必須とされている。また乳房切除術症例においてもハイリスク症例では、放射線治療（PMRT）が推奨されている。ここで術後補助化学療法を行う症例では、放射線治療と化学療法の順序が問題になる。化学療法開始の遅れは遠隔転移のリスクを増やす、あるいは放射線治療開始の遅れは局所再発のリスクを増やすという意見もあったが[1]、長期観察ではこの傾向は薄れており[2]、結論が出ないまま実地臨床としては化学療法先行が広く行われているようである。このような問題を解決する一つの手段として化学療法と放射線療法の同時併用が試みられている。これらの多くは化学療法の減量や放射線治療の中断を評価基準として同時併用は実施可能であると結論している。しかし逐次併用に較べて急性毒性は明らかに高度であり、特に現在標準的な術後化学療法として最も広く受け入れられているACレジメンの同時併用では、実に70%の症例にgrade 3～4の皮膚毒性を認めた報告もある[3]。長期成績について、乳房温存症例に対してCMFと39.6Gyの放射線治療を同時併用したHarvardのトライアルでは、対象症例に局所再発のハイリスク症例が多く、放射線の線量が通常よりも低かったにもかかわらず、良好な局所制御が達成され、晩期障害も軽微であったとしている[4,5]。ただし現在ではCMFレジメンは、術後補助療法の主流とは言えなくなってきており、新しい化学療法レジメンを用いた臨床試験によってその実施可能性と有用性を検証していく必要がある。Calaisらは706例を対象としてanthracyclineとしてdoxorubicinのかわりにmitoxantroneを用いた同時併用化学放射線療法と逐次化学放射線療法のランダム化比較試験を行った。まだ観察期間の中央値は37ヵ月と短いが、リンパ節転移陽性群では同時併用群において有意に局所再発が少ない結果となっており、同時併用の有用性が示唆されている[6]（表1）。

切除不能な局所進行乳癌・局所再発乳癌に対する同時併用化学放射線療法

切除不能な局所進行乳癌に対する標準的なアプローチとしては導入化学療法によって腫瘍を縮小させたうえで可能であれば乳房切除および必要に応じて胸壁の再建術が行われることが多い。導入化学療法に放射線治療を同時併用することにより局所効果の上乗せが期待されるが、化学療法単独でも75%程度の奏効率が得られること、およびkey drugであるanthracycline系薬剤と放射線治療の同時併用で毒性が著しく増強することから、これまで積極的に追求されてこなかったという経緯がある。一方、もう一つの乳癌key drugであるtaxane系の薬剤にも放射線増感作用があることが知られており、すでに肺癌、頭頸部癌、食道癌などで同時併用化学放射線療法の成績が報告されている。乳癌について、Formentiらは44例のstage ⅡB（T3N0M0）～stage

著者	患者数	化学療法レジメン	放射線量	特記すべき毒性（RT中あるいは術後）
Dubeyら 1999[4]	BCT：112	Classic CMF ×6コース	全乳房：39.6 Gy/1.8 Gy Boost：16Gy/2 Gy	湿性落屑：50% 皮膚毒性による放治中断：4% grade4 好中球減少：15% 放射線肺炎：1例 化学療法85%以上完遂：93%
Isaacら 2002[9]	BCT：151 MRM：51	Classic CMF ×6～12コース or i.v. CMF×8コース	全乳房/胸壁：40 Gy/2.5 Gy Boost：12.5 Gy/2.5 Gy (151/202)	湿性落屑：1% 皮膚毒性による放治中断：なし 他の毒性による放治中断：4% relative dose intensity ：0.87
Calaisら 2002[6]	BCT：706	Mitoxantrone (12mg/m²) 5FU (500mg/m²) Cyclophosphamide (500mg/m²)×6コース	A群：化学療法6コース終了後 B群：最初の化学療法3コースと同時 全乳房：50Gy/5週 Boost：10～20Gy	皮膚の急性毒性は両群で同等 食道炎（>Grade 1）はA群7%、b群23%
Faulら 2003[10]	BCT：73	Classic CMF×6コース or i.v. CMF ×6～8コース	全乳房＋Boost：59.58 Gy (50～63) 1回線量1.8 Gy～2.0 Gy	grade3 皮膚毒性：51% 放治遅延日数：1.32日（0～15） Nadir顆粒球数：1,207 Nadir血小板数：18万3千
Fietsら 2003[3]	BCT：71 MRM：41	Classic CMF×6コース or AC (60/600m/m²) ×4コース	全乳房：50Gy＋Boost ：14～20Gy/2 Gy 胸壁＋鎖上＋傍胸骨＋腋窩 ：50Gy/2 Gy* (*ボーラスで表面線量100%)	grade 3～4 皮膚毒性： AC：70%　CMF：47% 広範囲照射でより強い傾向 化学療法85%以上完遂： AC：90%　CMF：88%

表1●切除可能乳癌に対する術後補助療法としての同時併用化学放射線療法

BCT：乳房温存療法

MRM：胸筋温存乳房切除術

CMF：Cyclophosphamide, Methotrexate, 5-FU

AC：Doxorubicine, Cyclophosphamide

Ⅲ患者に対してpaclitaxel 30mg/m²の週2回投与と同時に総線量45Gy/1回線量1.8Gyの放射線治療を行い、grade 3の皮膚毒性が7%、臨床的奏効率が91%、乳房切除の標本における病理学的完全奏効（pCR）率が16%であったとしている[7]。また、唐澤らは11例の局所進行乳癌（stageⅢB～Ⅳ）および24例の局所再発乳癌に対してdocetaxel 20～40mg/m²の隔週投与あるいは15～20mg/m²の毎週投与に放射線治療（総線量の中央値60Gy）を同時併用し、臨床的奏効率が96%（完全奏効68%、部分奏効28%）、grade 3以上の皮膚毒性が6%、grade 3以上の好中球減少が17%であったとしている[8]。このように、taxane系薬剤では乳癌に対する同時併用化学放射線療法は実施可能と思われ、今後最適な化学療法レジメンや放射線治療の線量分割について研究が進むことが期待される。

切除可能乳癌に対する術前療法としての逐次併用化学放射線療法

NSABP-B18をはじめとするランダム化比較試験において、術前化学療法と術後化学療法で同等の生存率が得られることが示され、術前化学療法は乳癌に対する標準治療の一つとして位置づけられている。乳癌に対する術前化学療法の

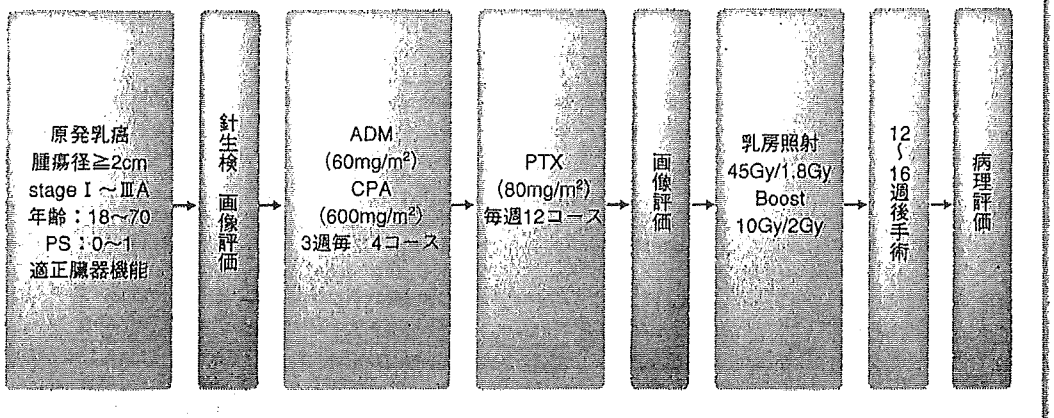

図1 腫瘍径2cm以上のⅠ～ⅢA期 原発乳癌に対する術前化学療法とそれに続く放射線照射の有効性・安全性試験コンセプト図

ADM：Adriamycin　CPA：Cyclophosphamide　PTX：Paclitaxel

うよりはむしろ放射線治療の早期開始と化学療法も含めた総治療期間の短縮である。また、術前化学放射線療法の試みは新しい乳癌治療戦略につながるものとして注目される。いずれにおいても放射線治療と同時併用が可能でありかつ効果的な化学療法レジメンの確立が急がれる。

著者	患者数	化学療法レジメン	放射線量	pCR rate	特記すべき毒性 (RT併用と術後)
Jacquillatら 1990[11]	250	Vinblastine+Thiotepa +MTX+5FU×3～6 コース	45Gy	＊cCR rate：30%	1例に肋骨骨折
Semiglazovら 1994[12]	271	Thiotepa+MTX+5FU ×1～2コース	60Gy	pCR rate：29%	リンパ漏 18% 術後感染 4% 放射性肺臓炎 3%
Colleoniら 1998[13]	32	AC（60/600mg/m^2） ×3コース	50Gy+10Gyp	pCR rate：22%	術後感染 16% 創部離開 13%
Aryusら 2000[14]	55	EC（90/600m/m^2） ×4コース	50Gy+6～11Gy	pCR rate：43%	Moderate（詳細不明）

表2●切除可能乳癌に対する術前療法としての逐次併用化学放射線療法

＊：pCR rateの記載なし

利点として、以下が挙げられる。

①乳房温存率が増加する。

治療が奏効することにより、当初乳房温存の適応外とされた腫瘍でも乳房温存が可能となる。

②術前化学療法に対する腫瘍の反応により予後を予測することができる。

原発病巣に対する抗腫瘍効果と全身の微小転移に対する抗腫瘍効果との間に相関があり、pCR例では長期の無病生存が期待できる。

③化学療法のコンプライアンスが高まる。

術後補助化学療法と異なり、患者が腫瘍の退縮を自覚することができ、治療に対する意欲が高まる。

特に①の乳房温存率の増加については、すでに多くの施設で積極的に取り組まれている。術前化学療法単独の場合、現時点で最も強力なレジメンはanthracycline系の薬剤とtaxane系の薬剤を逐次的に使用するものであり、Greenらは30%近いpCR達成率を報告している。ここで術前化学療法に局所療法である放射線治療を付加しても生存率の向上は期待できないが、局所効果の上乗せは期待される。このような試みは1990年代から行われており、最近のanthracycline系薬剤を用いた臨床試験では40%を越えるpCR率も報告されている（表2）。上述のように化学療法としてさらに強力なレジメンが出現しており、わが国でもanthracycline系の薬剤とtaxane系の薬剤の逐次的使用に放射線治療を加える臨床試験の症例登録が完了している（図1）。

現在の診断技術ではpCRの診断は手術によってはじめて得られるため、例え原発巣の癌細胞が根絶されていても手術を省略することは不可能である。しかし、PETやダイナミックCT、ダイナミックMRといった画像診断技術の進歩や新しい予後因子の発見によってpCR例を高精度に予測することが可能になれば、手術無しに初回治療を完了するという、大きなパラダイムシフトがもたらされる可能性がある。

まとめ

乳癌における化学放射線療法の位置づけは他の癌と異なる。特に最も頻度の高い術後照射の場合、同時併用の目的は局所効果の上乗せとい

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Treatment Outcome of Breast-Conserving Therapy in Patients with Positive or Close Resection Margins: Japanese Multi Institute Survey for Radiation dose Effect

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Background: The relationship between a positive resection margin and the risk of ipsilateral breast tumor recurrence (IBTR) is controversial. To evaluate the radiation dose and other factors influencing the ipsilateral breast tumor control (IBTC) in patients with positive or close resection margins after breast conserving surgery (BCS), the Japanese Radiation Oncology Study Group (JROSG) S-99-3 study group conducted a multi-institute survey of these patients.

Methods: The patients with less than 5 mm tumor-free margins after BCS were eligible for this study. A total of 971 patients from 18 institutes were enrolled in the analysis. The final pathological margin status was classified into 3 groups. Radiation doses to the tumor bed were less than 60 Gy in 252 patients, 60 Gy in 456 patients and more than 60 Gy in 233 patients.

Results: IBTR was observed in 55 patients (5.8%). The IBTC rates at 5 and 10 years by the Kaplan Meier method were 95.6% and 87.3%, respectively. There was no significant difference in 10-year IBTC rates according to marginal status; 85.9% in positive margin patients, 91.0% in equal or less than 2 mm margin patients and 87.0% in 2.1-5 mm margin patients. Radiation dose to the tumor bed was a marginally significantly associated with the 10-year IBTC rate (≧60 Gy 90.8% vs <60 Gy 84.2%, $p = 0.057$). In patients with positive margins, IBTC with radiation dose equal to or more than 60 Gy was significantly better ($p = 0.039$). The other factors influencing the IBTC were age (≧35 years vs <35 years: $p < 0.0001$), menopausal status ($p < 0.0001$) and tumor size ($p = 0.023$).

Conclusions: In patients with positive margins, IBTC with radiation dose equal to or more than 60 Gy was significantly better than the others. We recommend that the tumor bed be irradiated with at least 60 Gy in the patients with positive margins. Further follow-up is necessary to draw final conclusions.

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Key words: Breast conserving therapy, Resection margin, Radiotherapy

Breast conserving therapy that consisting of gross tumor excision followed by breast irradiation is a well-recognized standard therapy for local treatment of early-stage breast cancer. There continues to be controversy as to which factors predict an increased risk of IBTR. The association between pathologic resection margin status and IBTR is a well discussed but controversial matter. Many retrospective studies have reported a significantly increased rate of IBTR in positive margin patients compared with negative margin patients, but some have not. Singletary and Freedman *et al.*

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Abbreviations:
IBTR, Ipsilateral breast tumor recurrence; IBTC, Ipsilateral breast tumor control; BCS, Breast conserving surgery; JROSG, Japanese Radiation Oncology Study Group; EIC, Extensive intraductal component; UICC, Union Internationale Centre le Cancer; ER, Estrogen receptor; BCT, Breast conserving therapy; n.s., not significant; DFM, Disease-free margin

reviewed the articles examining the relationship between resection margins and IBTR[1,2]. Singletary reported that margin detections were very heterogeneous, as some assessments were based on gross assessment during surgery, and some were based on detailed microscopic examination. Furthermore, it is also unclear what factors are associated with positive margins and IBTR in margin positive or close margin patients. Some authors reported that positive margins were associated with large tumor size, young age, axillary node-positive status, presence of lymphovascular invasion, and the presence of extensive intraductal component (EIC)[1]. It is also unclear whether high doses of boost radiation influence outcome in margin positive or close patients. Optimal breast irradiation after BCS remains an unresolved issue in those cases.

JROSG was established in 1997 as a multi-institutional cooperative organization, a national cancer study research group that studies radiotherapy either alone or in conjunction with surgery and/or chemotherapy. The members consisted of radiation oncologists nation-wide in Japan.

To evaluate the effect of the radiation dose and the other factors influencing IBTC in patients with positive or close resection margins after BCS, the JROSG S-99-3 study group conducted a multi-institutional survey of these patients. This protocol has been studied since 1999. This article evaluates the results of the study.

Materials and Methods

Since 1999, registration forms were sent to the members of JROSG. Patients were eligible for this study if they met the following entry criteria: histological documentation of carcinoma of the breast, clinical stage 0 to II, tumor diameter less than 3 cm, no extensive intraductal spread or multiple tumor foci, focally positive or close (less than 5 mm) resection margins after BCS, whole breast irradiation was performed and a follow-up period longer than 2 years or until the time of recurrence. The clinical, pathological and treatment features investigated in this study were age, menopasal status, primary tumor size, UICC clinical stage, pathologic nodal status, histologic type, hormone-receptor status, marginal status (focally positive, less than 2 mm, 2.1-5 mm), surgical method, total radiation dose to the whole breast, total radiation dose to the tumor bed and the use of adjuvant systemic therapy.

Table 1. Participating Institutes and Person in Charge

Kyoto Univ.	Mitsumori M., Yamauchi C.
Cancer Institute	Gomi K.
Shikoku Cancer Center	Kataoka M.
Tokyo Women's Medical Univ.	Karasawa Ku.
Niigata Cancer Center	Uematsu T., Sugita T.
Aichi Cancer Center	Kodaira T.
Gunma Univ.	Yamakawa M., Sakurai H.
Tokyo Met. Komagome Hosp.	Karasawa Ka.
Saku Gentral Hosp.	Watanabe T.
Hyogo Medical Center for Adults	Tsujino K.
Isezaki Municipal Hosp.	Shiojima K.
Tohoku Univ.	Kakutou Y.
Tokyo Met. Fucyu Hosp.	Kita M.
Okayama Univ.	Kobayashi Ma.
Shiga Uni. of Medical Science	Syo K.
Tokai Univ.	Oizumi Y.
Rinku General Medical Center	Shioura H.
Jikei Univ.	Kobayashi Mi

Table 2. Patients' Characteristics

Characteristics		No. of patients (%)
Age	24-35	64 (7)
	35-44	236 (25)
	45-54	391 (42)
	55-64	166 (18)
	65-74	68 (7)
	75-83	16 (2)
Menopause	Pre	514 (55)
	Term	108 (11)
	Post	319 (34)
Stage	0	13 (1)
	I	506 (54)
	II	419 (45)
T Stage	Tis	13 (1)
	T1	506 (54)
	T2	419 (45)
n Stage	n0	663 (70)
	n1	278 (30)
ER	Negative	221 (23)
	Positive	369 (39)
	Unknown	351 (37)

Between 1999 and 2002, 1007 patients from 18 institutions were registered (Table 1). Among them, 66 were ineligible due to a short follow-up period or a tumor more than 3 cm, so a total of 941 were enrolled in this analysis. The years of treatment for the study population were 1986 to 2000. The range of follow-up for surviving patients was 2

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-

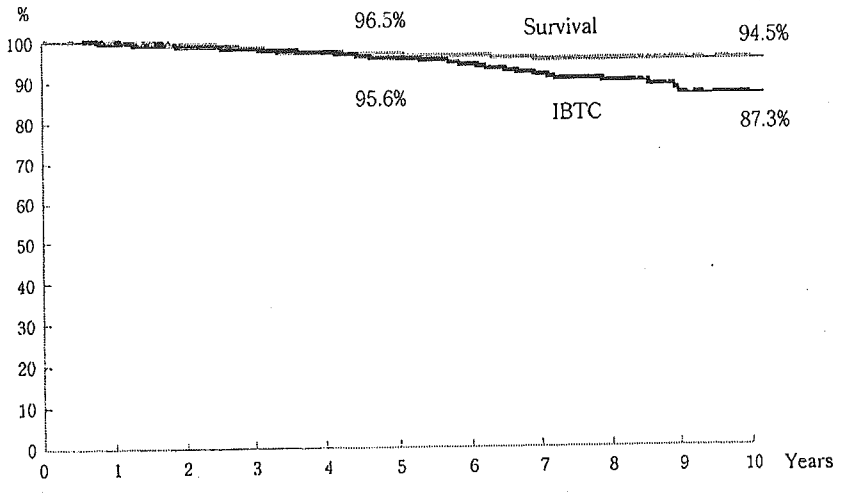

Fig 1. IBTC and survival in all cases. The total number of the patients was 941.

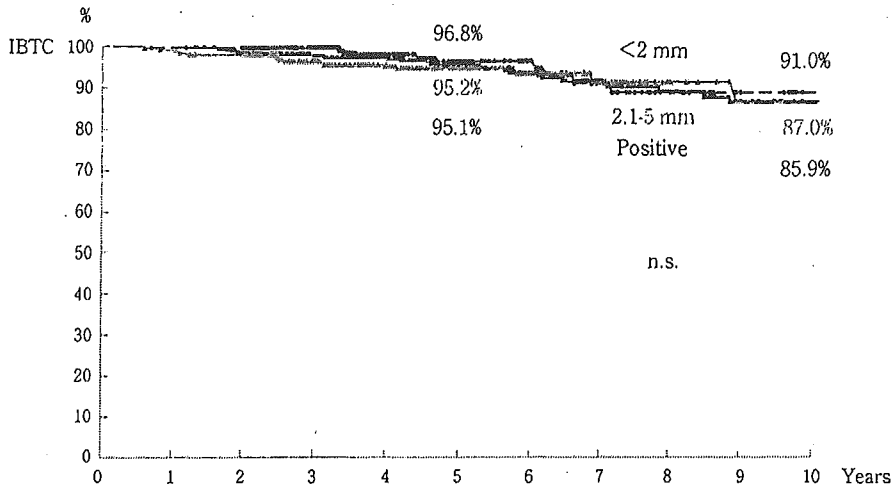

Fig 2. IBTC by marginal status. Final pathological margin status was classified into 3 groups: 358 (38%) focally positive (cancer cells remained the surgical margin), 326 (35%) with equal or less than 2 mm free margins and 256 (27%) with 2.1-5 mm free margins.

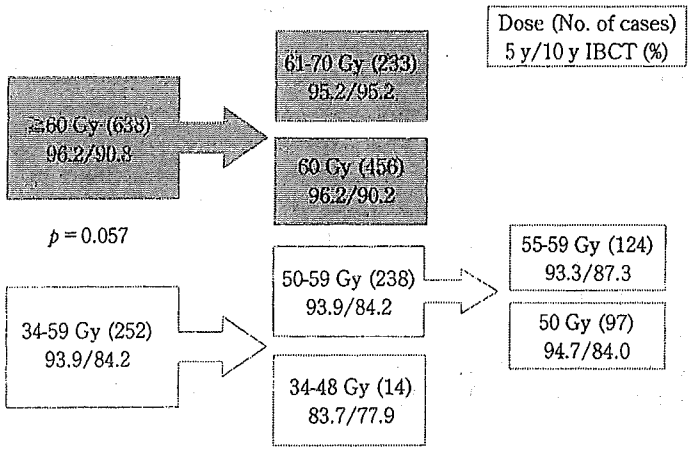

Fig 3. Five/ten years IBTC (%) by radiation dose of tumor bed.

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