Kitakanto Med J
2007；57：221～224

True Local Recurrences or New Primary Tumors after Breast-Conserving Surgery and Radiation Therapy

Jun Horiguchi,[1] Yukio Koibuchi,[1] Nana Rokutanda,[1]
Rin Nagaoka,[1] Yuko Ishikawa,[1] Hiroki Odawara,[1]
Yuichi Iino,[2] Hideyuki Sakurai,[3] Tetsunari Oyama,[4]
and Izumi Takeyoshi [1]

Background & Aims : True local recurrences (TR) and new primary tumors (NP) in the conserved breast after breast-conserving surgery with radiation therapy are determined by the initial surgical margin, the location of recurrent tumors and the histological consistency between initial tumors and recurrent tumors. **Methods :** A total of 15 patients with breast recurrence out of a group of 389 women with breast cancer who underwent breast-conserving therapy between 1991 and 2003 were included in this study. The biological differences between TR and NP were examined. **Results :** Eight patients had TR, and seven had NP. The disease-free interval was 34.6 months in the TR group and 94.1 in the NP group. Breast-free survival was significantly better in the NP group than the TR group. The accumulated 10-year overall survival after salvage surgery in patients with TR or NP tumors was 85.1%. The accumulated overall survival after salvage surgery was better in the NP group than the TR group. **Conclusions :** Patients with NP tumors have a favorable prognosis compared to those with TR tumors. It is important to determine the type of breast recurrence in order to accurately predict the prognosis of patients with breast recurrence. (Kitakanto Med J 2007；57：221～224)

Key Words : Breast-conserving surgery, true local recurrence, new primary tumor, breast recurrence and breast cancer

Introduction

When evaluating ipsilateral breast tumor relapse (IBTR), it is important to consider that these relapses may represent two entities : either true local recurrences (TR) or new primary tumors (NP). It has been reported that NP results in more favorable outcomes compared to TR after breast-conserving surgery with radiation therapy.[1-3] TR and NP in the conserved breast following breast-conserving surgery with radiation therapy are determined by the initial surgical margin, the location of recurrent tumors and histology between initial tumors and recurrent tumors. We examined the biological differences between TR and NP.

Patients and Methods

A total of 15 patients with breast recurrence out of a group of 389 women with invasive breast cancer who underwent breast-conserving surgery with radiation therapy between 1991 and 2003 were evaluated in this study. Breast-conserving surgery consists of a wide excision of the primary tumor with a level II or III lymph node dissection. The tumor is widely excised with a 2-cm free margin as the minimum distance. Excised specimens are examined histopathologically in consecutive 5-mm slices. Negative margins are defined as no tumor cells within a 5-mm surgical margin. All patients undergoing breast-conserving surgery received whole breast irradiation. A daily dose of 2Gy calculated at the midplane of the breast is

1 Department of Thoracic and Viscera Organ Surgery, Gunma University Graduate School of Medicine 2 Department of Emergency, Gunma University Graduate School of Medicine 3 Department of Radiation Oncology, Gunma University Graduate School of Medicine 4 Department of Pathology, Dokkyo Medical University School of Medicine
Received : Mar 26. 2007
Address : JUN HORIGUCHI Department of Thoracic and Visceral Organ Surgery, Gunma University Graduate School of Medicine, Showa-machi 3-39-15, Maebashi, Gunma 371-8511, Japan

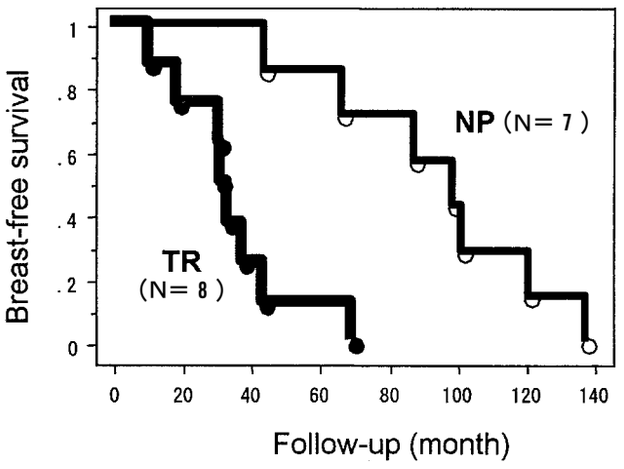

Fig. 1 Breast-free survival was significantly better in patients with new primary tumors (NP) than in those with true recurrence tumors (TR). ($p<0.01$, log-rank test)

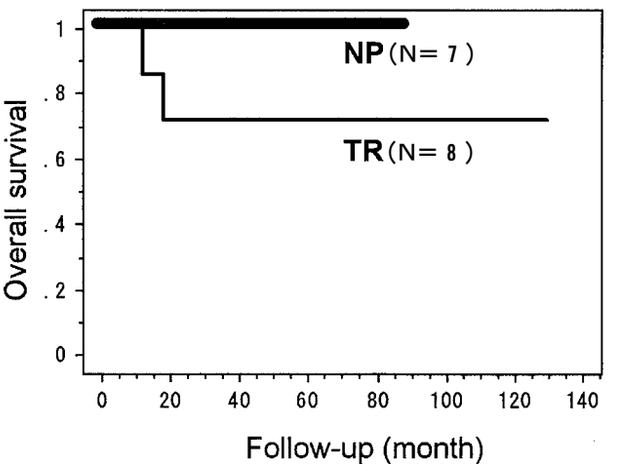

Fig. 2 Accumulated overall survival after salvage surgery was better in patients with new primary tumors (NP) than in those with true recurrence tumors (TR).

delivered through two opposing tangential fields (185°) which are designed to minimize lung exposure with high-energy photons (6-MV X-ray). A total dose of 50Gy is delivered in 25 fractions for five weeks. A radiation boost of 10Gy in 2 fractions to the tumor bed is delivered to margin-positive patients with electron beam radiation. All patients receive adjuvant chemotherapy and/or endocrine therapy. Patients with hormone-sensitive tumors are treated with 20mg tamoxifen every day for two years or longer. Patients are monitored every month for the first six or 12 months after surgery and at two or three-month intervals for the next two years, and at a minimum of six-month intervals thereafter. Biopsy is performed to confirm all local recurrences histologically.

An ipsilateral breast tumor recurrence (IBTR) was designated as TR if the surgical margin was positive and it was located within 3 cm of the primary tumor bed, or if the surgical margin was negative and the tumor was located within the primary tumor bed. If IBTR failed to meet either of these criteria or if the histologic subtype was apparently different from the primary tumor, it was designated as NP.

Clinicopathological factors and surgical treatment were analyzed using the Student's t-test or the chi-squared test. Actuarial result for breast-free survival was calculated using the Kaplan-Meier method. The log-rank test was used to compare the two survival curves.

Results

There were 15 invasive local recurrences (13 invasive ductal carcinomas and two invasive lobular carcinomas) after breast-conserving therapy including eight TRs and seven NPs. Histology of the ipsilateral breast recurent tumor was consistent with that of the primary tumor (Table 1). The age at primary surgery (mean±SE) was 53.3±5.3 in TR and 44.1±2.8 in NP. The tumor size at primary surgery (mean±SE) was 2.3±0.4 cm in TR and 2.5±0.4 cm in NP. Lymph node metastasis at primary surgery was observed in 2 out of 8 TRs and 2 out of 7 NPs. There was no significant difference in age, tumor size, nodal status, clinical stage, vascular invasion, lymphatic invasion, estrogen receptor or progesterone receptor between TR and NP (Table 2). The first local recurrence in TR and NP occurred 34.9±6.2 (mean±SE) months and 94.1±12.0 (mean±SE) months, respectively after breast-conserving-surgery. Breast recurrence-free survival was more favorable in patients with NP than those with TR (Fig 1). Two patients with NP developed contralateral breast cancer, and one with TR developed contralateral breast cancer. Two of the 15 patients showed inflammatory type of breast recurrence. A simple mastectomy was performed in six ipsilateral tumors, a subcutaneous mastectomy in one, and a partial mastectomy in eight cases. No subsequent local recurrence after salvage surgery occurred in seven patients with NP tumors. The accumulated 10-year overall survival after salvage surgery in patients with TR or NP tumors was 85.1%. The accumulated overall survival was better in the NP group than the TR group (Fig 2).

Discussion

In this study, we classified IBTR into either TR or NP, and clarified the biological differences between the two types of recurrence. Many researchers[1–6] have tried to distinguish NP from TR, including Huang et al[1] who classified IBTR as either NP or TR based on location and histology. We also classified IBTR as either TR or NP based on our histological findings

Table 1 Patients with ipsilateral breast recurrence

Case	Age	Clinical Stage	Histology of Primary Tumor	Surgical Margin	Margin-positive Factor	Breast-free survial Interval (month)	Distance from Primary Tumor Bed to Breast Recurrent Tumor (cm)	Histology of Recurrent Tumor	TR or NP	Salvage Surgery	Surgical Margin at Salvage surgery	Subsequent Breast-Recurrence	Survival time after Breast Recurrence (month)
1	62	IIA	IDC	+	Ductal	31M	≦3	IDC	TR	Bt	—	—	130M alive
2	64	I	IDC	+	Ductal	44M	≦3	IDC	TR	Bt	—	—	113M alive
3	45	IIA	IDC	—	—	67M	≦3	IDC	NP	Bp	—	—	89M alive
4	54	IIA	IDC	+	Invasive	19M	0	IDC	TR	Bt	+	+	18M dead
5	38	I	IDC	—	—	44M	≦3	IDC	NP	Glt	—	—	82M alive with recurrence
6	78	IIA	IDC	+	Ductal+Invasive	32M	≦3	IDC	TR	Bp	+	+	37M dead
7	30	I	IDC	+	Ductal	70M	≦3	IDC	TR	Bp	+	+	65M alive
8	47	IIA	IDC	+	Invasive	121M	3<	IDC	NP	Bp	—	—	47M alive
9	38	I	ILC	—	—	88M	≦3	LOB	NP	Bp	—	—	41M alive
10	46	I	IDC	—	—	99M	≦3	IDC	NP	Bp	+	—	35M alive
11	42	I	ILC	+	Lobular	38M	≦3	LOB	TR	Bp	—	—	34M alive
12	45	I	IDC	+	Ductal	32M	≦3	IDC	TR	Bt	—	—	27M alive
13	58	IIA	IDC	—	—	138M	≦3	IDC	NP	Bp	+	—	19M alive
14	52	IIB	IDC	—	—	11M	0	IDC	TR	Bt	—	—	12M dead
15	37	I	IDC	—	—	102M	≦3	IDC	NP	Bt	—	—	13M alive

IDC : Invasive ductal carcinoma, ILC : Invasive lobular carcinoma, TR : True recurrence, NP : New primary, Bt : Mastectomy, Bp : local excision, Glt : Total glandectomy

Table 2 Characteristics of patients at initial surgery

Factors		TR N=8	NP N=7
Age	mean±SE	53.3±5.3	44.1±2.8
Tumor size (cm)	mean±SE	2.3±0.4	2.5±0.4
Lymph node metastasis	negative	6	5
	positive	2	2
Lymphatic invasion	0, 1	3	6
	2, 3	3	1
	unknown	2	0
Venous invasion	0	1	3
	1	5	4
	unknown	2	0
Clinical stage	I	4	4
	IIA	3	3
	IIB	1	0
Histology	IDC	7	6
	ILC	1	1
ER (EIA)	negative	6	4
	positive	0	2
	unknown	2	1
PgR (EIA)	negative	6	5
	positive	0	1
	unknown	2	1

TR : True recurrence, NP : New primary, IDC : Invasive ductal carcinoma, ILC : Invasive lobular carcinoma, EIA : Enzyme immuno-assay

and tumor location between the primary tumors and recurrent tumors. Huang et al[1] did not evaluate the surgical margins of primary tumors in order to classify IBTR as NP or TR. Theoretically, TR develops from residual surviving tumor clonogens. Risk factors for developing TR thus should be related to issues of the primary tumor surgical margin status. We took surgical margin status into consideration in classification of recurrent tumors. Smith et al[6] also classified IBTR as either NP or TR. Specifically, patients were classified as NP if the recurrence was distinctly different from the primary tumor with respect to the histologic subtype, if the recurrence location was in a different location, or if the flow cytometry had changed from aneuploid to diploid. Sixty patients were classified as TR, seventy were classified as NP, and 6 were unable to be classified. NP relapses developed at a rate of 0.6%/year for the first 5 years, increasing to 0.9%/year between 6 and 10, steadily increasing at approximately 1%/year after 10 years. TR relapses started out highest and then steadily declined at 0.86%/year for the first 5 years, decreasing to 0.625%/year from 6 to 10 years and then leveled off with no increase after 10 years. The TR/NP ratio varies among researchers.[1-6] The TR/NP+TR ratio was reported to be 81% by Recht et al,[4] 62% by Huang et al,[1] 44% by Smith et al,[6] and 75% by

Krauss et al.[2] The TR/NP+TR ratio in our study was 53%. The follow-up period and the classification of failure pattern may be related with the TR/NP+TR ratio.

Huang et al[1] reported that patients with NP had significantly higher rates of carcinoma in the contralateral breast adds. This data indicated that patients with NP tumors were likely to develop second primary breast cancer irrespective of ipsilateral or contralateral breasts. The NSABP P-1 trial[7] showed that the administration of tamoxifen for 5 years reduced the 5-year risk of developing contralteral breast carcinoma by much as 50% in all age groups. This data suggested that tamoxifen might reduce developing NP after breast-conserving therapy. In our study, two patients with NP tumors and one with TR tumors developed a second contralateral breast cancer. We could not draw a definitive conclusion in this aspect because of the small number of breast recurrent patients.

It took a significant amount of time for patients with NP tumors before disease recurrence, this was similar to the data of Huang et al[1] and Smith et al.[6] Smith et al[6] also reported that it took a significant amount of time for NP patients to develop a breast relapse compared to TR patients (7.3 years vs. 3.7 years), suggesting that the time until breast relapse is significantly longer in NP than TR. In previous investigations, local recurrence after repeat conservative surgery was between 19-50% of in-breast recurrent patients.[5,8-11] Abner et al.[10] reported a local recurrence rate of 31% at a median follow-up of 39 months, and Voogd et al.[5] reported a local recurrence rate of 38% at a median follow-up of 52 months. In our study, the local recurrence rate was 25% (two of eight patients) after local excision alone for in-breast local recurrence at a median follow-up of 39 months. The surgical margin at local salvage excision was positive in these two patients. These two recurrences may be classified as a second TR. On the other hand, patients with NP tumors underwent completely local resection, resulting in favorable local control. These patients may develop second NP tumors during the longer follow-up period.

TR with pathological evidence of skin involvement usually results in poor prognosis after salvage surgery. Voogd et al[5] reported that skin involvement, the extent of recurrence and both lymph node status, and histologic grade of the primary disease were strong predictors for distant metastases in patients with invasive recurrence. Gage et al.[12] also reported that associated simultaneous skin recurrence occurred in approximately 1% of local recurrence cases and was associated with rapid distant metastases and a poor overall survival rate. The infammatory type of local recurrence showed skin involvement and large extent of recurrence. We experienced two cases of the inflammatory type of breast recurrence, which developed rapid distant metastases resulting in death.

In conclusion, it is important to determine the type of breast recurrence in order to accurately predict the prognosis of patients with breast recurrence. Patients with NP tumors have a favorable prognosis compared to those with TR tumors.

References

1. Huang E, Buchholtz TA, Meric F, et al. Classifying local disease recurrences after breast conservation therapy based on location and histology : New primary tumors have more favorable outcomes than true local disease recurrences. *Cancer* 2002 ; 95 : 2059-2067.
2. Krauss DJ, Kestin LL, Mitchell C, et al. Changes in temporal patterns of local failure after breast-conserving therapy and their prognostic implications. *Int J Radiat Oncol Biol Phys* 2004 ; 60 : 731-740.
3. Komoike Y, Akiyama F, Iino Y, et al. Analysis of ipsilateral breast tumor recurrences after breast-conserving treatment based on the classification of true recurrences and new primary tumors. *Breast Cancer* 2005 ; 12 : 104-111.
4. RechtA, Silen W, Schnitt SJ, et al. Time-course of local recurrence following conservative surgery and radiotherapy for early stage breast cancer. *Int J Radiat Oncol Biol Phys* 1988 ; 15 : 255-261.
5. Voogd AC, van Tienhoven G, Peterse HL, et al. Local recurrence after breast conservation therapy for early stage breast carcinoma : Detection, treatment, and outcome in 266 patients. *Cancer* 1999 ; 85 : 437-446.
6. Smith TE, Lee D, Turner BC, et al. True recurrence vs. new primary ipsilateral breast tumor relapse : An analysis of clinical and pathologic differences and their implications in natural history, prognoses, and therapeutic management. *Int J RAdiat Oncol Biol Phys* 2000 ; 48 : 1281-1289.
7. Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for prevention of breast cancer : Report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. *J Natl Cancer Inst* 1998 ; 90 : 1371-1388.
8. Kuerer HM, Arthur DW, Haffty BG, et al. Repeat breast-conserving surgery for in-breast local breast carcinoma recurrence : The potential role of partial irradiation. *Cancer* 2004 ; 100 : 2269-2280.
9. Salvadori B, Marubini E, Miceli R, et al. Reoperation for locally recurrent breast cancer in patients previously treated with conservative surgery. *Br J Surg* 1999 ; 86 : 84-87.
10. Abner AL, Recht A, Eberlein T, et al. Prognosis following salvage mastectomy for recurrence in the breast after conservative surgery and radiation therapy for early-stage breast cancer. *J Clin Oncol* 1993 ; 11 : 44-48.
11. Dalberg K, Mattsson A, Sandelin K, et al. Outcome of treatment for ipsilateral breast tumor recurrence in early-stage breast cancer. *Breast Cancer Res Treat* 1998 ; 49 : 69-78.
12. Gage I, Schnitt SJ, Recht A, et al. : Skin recurrences after breast-conserving therapy for early-stage breast cancer. *J Clin Oncol* 1998 ; 16 : 480-486.