Abstract. At present, the risk factors for distant recurrence among patients with early ipsilateral breast tumor recurrence (IBTR) require further investigation. Early IBTR is defined as occurring within 3 years following the initial surgery. In the current study, 40 patients with early IBTR were examined to determine the risk factors for distant recurrence. A node-positive status at the time of primary surgery and the administration of adjuvant chemotherapy following the primary surgery were significantly correlated with poorer distant disease-free survival (P=0.001 and P=0.002, respectively). Multivariate analyses revealed that the nodal status at the time of primary surgery was an independent predictive factor for distant recurrence (P=0.050). Therefore, the results of the current study revealed that the nodal status at the time of primary surgery was an independent predictive factor for distant recurrence among patients with early IBTR.

Introduction

Breast-conserving surgery is a standard treatment for stage I and II breast cancer; however, 5-10% of patients treated with breast-conserving surgery are diagnosed with ipsilateral breast tumor recurrence (IBTR) within 10 years (1,2). IBTR following breast-conserving surgery is associated with an elevated risk of mortality or of developing distant recurrence (3-7).

The time interval between the initial surgery and the occurrence of IBTR is defined as the disease-free interval (DFI), which is a predictor of disease recurrence following IBTR (3-6,8-12), and patients with early IBTR have a poorer prognosis, compared with those with late IBTR (8,10-12). However, irrespective of the DFI, the standard treatment for patients with IBTR is surgery is mastectomy. This treatment strategy must be modified if a subgroup of patients with early IBTR, with an equally poor prognosis as that of patients with regional or distant recurrence, is present (13). Therefore, it is important to estimate the risk of disease recurrence in such patients, as risk factors following early IBTR have not yet been elucidated. In the present study, the risk factors for distant recurrence following early IBTR were examined.

Patients and methods

Patients. The medical records of 3,793 patients with breast cancer who underwent breast-conserving surgery between January 1989 and December 2013 at the Osaka Medical Center for Cancer and Cardiovascular Diseases (Osaka, Japan) were reviewed. Of these patients (ages 28-89), 180 (4.7%) developed IBTR as the first event with no evidence of synchronous metastatic disease, and subsequently underwent salvage surgery. Within this group, the exclusion criteria were as follows: Patients with non-invasive tumors present in IBTR tissue specimens and patients who received neoadjuvant therapy as the initial treatment. A total of 153 patients with IBTR were eligible for the present study. A previous study examined the same patient group, focusing on patients with IBTR that occurred 5 years following the initial surgery (14), whereas, in the current study, 40 patients with IBTR that occurred within 3 years of the initial surgery were analyzed. The present study was approved by the local ethics committee of the Osaka Medical Center of Cancer and Cardiovascular Diseases, with waiver of informed patient consent.

Patients received a physical examination (palpation for breast, chest wall and regional lymph nodes) every 3-6 months for 5 years following primary or salvage surgery and annually thereafter, and also underwent mammograms annually following primary or salvage surgery. The estrogen receptor (ER) status of the surgical specimens obtained from patients was determined using immunohistochemistry (15), and tumors were classified as positive for ER expression if ≥10% of cells exhibited positive nuclear staining with monoclonal rabbit anti-human ERα (clone EP1, Dako; Agilent Technologies, Inc., Santa Clara, CA, USA). The human epidermal growth factor receptor 2 (HER2) status of patients' tissues was considered...
positive if the immunohistochemistry was 3+ or if the fluorescence in situ hybridization ratio (HER-2/chromosome 17) was >2.0 (16).

**Statistical analysis.** Distant disease-free survival (DDFS) rate was defined as the period of time between the date of surgery for patients with IBTR and the date of the appearance of distant recurrence, and was calculated using the Kaplan-Meier method. Log-rank tests were performed to evaluate the differences in DDFS among various patient subgroups. Univariate and multivariate analyses were performed using the Cox proportional hazards model.

All statistical tests were performed using SPSS version 21.0 (IBM SPSS, Armonk, NY, USA). All statistical tests and P-values were two tailed, and P<0.05 was considered to indicate a statistically significant difference.

**Results**

**Patient characteristics.** Patients’ clinical characteristics are presented in Table I. Some data was missing (such as HER2 status of primary tumor and IBTR). Within a median follow-up period of 2.2 years (range, 0.1-20.8 years) following salvage surgery for IBTR, distant recurrence occurred in 15/40 patients (37.5%), and the 3-year DDFS rate was 64.3%.

**Association with DDFS.** Various clinical and pathological factors associated with DDFS among patients with early IBTR are listed in Table II. The nodal status at primary surgery and the use of adjuvant chemotherapy treatment following primary surgery were significantly correlated with DDFS (P=0.001 and P=0.002, respectively). Patients who were node-positive at primary surgery had a significantly poorer DDFS than node-negative patients (3-year DDFS, 33.5 vs. 93.3%, respectively; P=0.001; Fig. 1). Patients who received adjuvant chemotherapy (n=13; mainly anthracycline and/or taxane) following primary surgery exhibited a significantly poorer DDFS than those who did not receive chemotherapy (3-year DDFS, 34.4 vs. 77.9%, respectively; P=0.002; Table II). No significant differences were observed between any of the following groups: Negative or positive margin at primary surgery (P=0.58), radiotherapy or no radiotherapy following primary surgery (P=0.57) and basal (both ER- and HER2-negative) or non-basal type primary tumors (P=0.27) (Table II). Multivariate analyses demonstrated that the nodal status at primary surgery was an independent predictive factor of distant recurrence (P=0.050; Table III).

**Discussion**

The present study demonstrated that the nodal status at the time of primary surgery and the use of adjuvant therapy subsequent to primary surgery were risk factors for distant recurrence following early IBTR. It was hypothesized that the nodal status at primary surgery may interact with adjuvant therapy following primary surgery. Node-positive breast cancer patients have poorer prognosis compared with patients with negative lymph node metastasis. Therefore, patients with positive lymph node metastasis are more likely to be recommended for adjuvant chemotherapy compared with those with negative lymph node metastasis. Therefore, multivariate analysis incorporating these two factors was performed, which revealed that the nodal status at primary surgery was an independent prognostic factor in the present study group. At present, the risk factors that follow IBTR and are associated with the DFI require further investigation (8-10,14) and, to the best of our knowledge, no previous studies have been conducted to examine the risk factors following early IBTR. The nodal status at primary surgery and the use of adjuvant therapy following primary surgery, which were demonstrated to be prognostic factors among patients with early IBTR in the current study, were also associated with primary surgery, but not with recurrent tumors. By contrast, a previous study identified that the prognostic factors among patients with late IBTR were the ER and HER2 status of IBTR tissue specimens, which were associated with recurrent tumors, but not with primary surgery (14). Taken together, these findings suggest that early IBTR is associated with true recurrence, whereas late IBTR is associated with the presence of new primary tumors.

The 3-year DDFS rate in the present study was 33.5% among patients with early IBTR and a positive nodal status at the time of primary surgery. This DDFS rate is concordant with that reported by Wapnir et al (5), in which the 3-year DDFS was 44.9% among patients with early IBTR and a positive nodal status at the time of primary surgery. Furthermore, this DDFS rate is similar to that observed in patients with ipsilateral supraclavicular node recurrence (17) or lung metastases (18). Pergolizzi et al (17) reported that the median time to progression was 28 months in 44 patients with ipsilateral supraclavicular node recurrence from breast cancer (as a part of recurrent regional disease and without distant metastases) who received combined chemotherapy and radiotherapy treatment. Ludwig et al (18) observed that, during a retrospective analysis, the median DDFS following resection of lung metastatic tumors was 27.6 months.

The results of the current study suggest that patients with early IBTR and positive axillary nodes at the diagnosis of the primary tumor possess a high risk of distant recurrence and, therefore, should potentially receive more aggressive treatment compared with conventional treatment, including novel (neo)adjuvant systemic therapy or regional radiotherapy.
Table I. Characteristics of patients.

| Characteristics of patients | No. of patients (n=40) |
|-----------------------------|------------------------|
| Median age at initial diagnosis (range), years | 54 (30-81) |
| p-T stage of primary tumor |  |
| In situ | 3 |
| 1 | 7 |
| 2 | 30 |
| Grade of primary tumor |  |
| 1 | 0 |
| 2 | 18 |
| 3 | 19 |
| Unknown | 3 |
| Lymphovascular invasion of primary tumor |  |
| Negative | 19 |
| Positive | 20 |
| Unknown | 1 |
| Histological type of primary tumor |  |
| DCIS | 3 |
| Invasive ductal | 35 |
| Invasive lobular | 1 |
| Other | 1 |
| No. of positive lymph nodes of primary tumor |  |
| 0 | 18 |
| 1-3 | 12 |
| ≥4 | 4 |
| Unknown | 6 |
| ER status of primary tumor |  |
| Positive | 17 |
| Negative | 22 |
| Unknown | 1 |
| HER2 status of primary tumor |  |
| Positive | 10 |
| Negative | 18 |
| Unknown | 12 |
| Adjuvant chemotherapy following primary surgery |  |
| Yes | 13 |
| No | 27 |
| Adjuvant hormonal therapy following primary surgerya |  |
| Yes | 11 |
| No | 6 |
| Adjuvant trastuzumab following primary surgeryb |  |
| Yes | 0 |
| No | 10 |
| Median time interval between initial surgery and IBTR (range), years | 1.9 (0.1-2.9) |

Table I. Continued.

| Characteristics of patients | No. of patients (n=40) |
|-----------------------------|------------------------|
| Median age at IBTR diagnosis (range), years | 56.5 (32.0-82.0) |
| p-T stage of IBTR |  |
| In situ | 0 |
| 1 | 26 |
| ≥2 | 13 |
| Unknown | 1 |
| Grade of IBTR |  |
| 1 | 3 |
| 2 | 10 |
| 3 | 21 |
| Unknown | 6 |
| Lymphovascular invasion of IBTR |  |
| Negative | 19 |
| Positive | 17 |
| Unknown | 4 |
| Histological type of IBTR |  |
| DCIS | 0 |
| Invasive ductal | 37 |
| Invasive lobular | 1 |
| Other | 1 |
| Unknown | 1 |
| ER status of IBTR |  |
| Positive | 17 |
| Negative | 20 |
| Unknown | 3 |
| HER2 status of IBTR |  |
| Positive | 9 |
| Negative | 22 |
| Unknown | 9 |
| Adjuvant chemotherapy following salvage surgery |  |
| Yes | 15 |
| No | 22 |
| Unknown | 3 |
| Adjuvant hormonal therapy following salvage surgerya |  |
| Yes | 9 |
| No | 5 |
| Unknown | 3 |
| Adjuvant trastuzumab following salvage surgeryb |  |
| Yes | 4 |
| No | 5 |

*aIncluding only patients with ER-positive tumors. bIncluding only patients with HER2-positive tumors. DCIS, ductal carcinoma in situ; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; IBTR, ipsilateral breast tumor recurrence; p-T, pathological tumor.
In addition to the DFI, previous studies have demonstrated that the nodal status at the time of primary surgery was a prognostic factor among patients with IBTR (4, 19). The association between the DFI and the nodal status of the primary tumor, and its prognostic relevance among patients with IBTR, has yet to be elucidated. In addition, the small sample size, short follow-up period and high frequency of missing data.

Table II. Three-year DDFS rates according to various clinico-pathological factors among patients with early IBTR (n=40).

| Characteristics of patients | 3-year DDFS rates, % | P-value |
|----------------------------|---------------------|--------|
| Age at initial diagnosis, years |                     |        |
| <50 | 48.9 | 0.870 |
| ≥50 | 70.3 |
| p-T stage of primary tumor |                     |        |
| In situ or 1 | 80.2 | 0.110 |
| 2 | 50.3 |
| Margin of primary tumor |                     |        |
| Negative | 66.0 | 0.58 |
| Positive | 53.3 |
| Grade of primary tumor |                     |        |
| 1 or 2 | 66.5 | 0.770 |
| 3 | 58.0 |
| Lymphovascular invasion of primary tumor |             |        |
| Negative | 74.9 | 0.190 |
| Positive | 51.9 |
| Lymph node status of primary tumor |             |        |
| Negative | 93.3 | 0.001 |
| Positive | 33.5 |
| ER status of primary tumor |             |        |
| Positive | 72.2 | 0.400 |
| Negative | 55.9 |
| HER2 status of primary tumor |             |        |
| Positive | 71.1 | 0.220 |
| Negative | 50.2 |
| Basal type of primary tumor |             |        |
| Yes | 43.8 | 0.27 |
| No | 66.2 |
| Radiotherapy following primary surgery |             |        |
| Yes | 66.5 | 0.57 |
| No | 61.4 |
| Adjuvant chemotherapy following primary surgery |             |        |
| Yes | 34.4 | 0.002 |
| No | 77.9 |
| Adjuvant hormonal therapy following primary surgery |             |        |
| Yes | 71.6 | 0.460 |
| No | 75.0 |
| Age at IBTR diagnosis, years |             |        |
| <50 | 48.9 | 0.870 |
| ≥50 | 70.3 |
| p-T stage of IBTR |             |        |
| 1 | 67.3 | 0.450 |
| ≥2 | 54.9 |
| Grade of IBTR |             |        |
| 1 or 2 | 75.0 | 0.490 |
| 3 | 55.1 |

Table II. Continued.

| Characteristics of patients | 3-year DDFS rates, % | P-value |
|----------------------------|---------------------|--------|
| Lymphovascular invasion of IBTR |             |        |
| Negative | 69.1 | 0.170 |
| Positive | 52.1 |
| ER status of IBTR |             |        |
| Positive | 56.4 | 0.540 |
| Negative | 64.7 |
| HER2 status of IBTR |             |        |
| Positive | 77.8 | 0.270 |
| Negative | 58.0 |
| Adjuvant chemotherapy following salvage surgery |             |        |
| Yes | 55.8 | 0.210 |
| No | 69.2 |
| Adjuvant hormonal therapy following salvage surgerya |             |        |
| Yes | 64.8 | 0.071 |
| No | 26.7 |
| Adjuvant trastuzumab following salvage surgeryb |             |        |
| Yes | 75.0 | 0.800 |
| No | 80.0 |

Table III. Multivariate analysis of predictors of distant recurrence following early ipsilateral breast tumor recurrence.

| Characteristics of patients | HR | 95% CI | P-value |
|-----------------------------|----|--------|--------|
| Lymph node status of primary tumor (positive vs. negative) | 5.281 | 1.002-27.833 | 0.050* |
| Adjuvant chemotherapy following primary surgery (positive vs. negative) | 2.983 | 0.750-11.856 | 0.120 |
| Age at IBTR diagnosis, years |    |        |        |
| <50 | 48.9 | 0.870 |
| ≥50 | 70.3 |
| p-T stage of IBTR |    |        |        |
| 1 | 67.3 | 0.450 |
| ≥2 | 54.9 |
| Grade of IBTR |    |        |        |
| 1 or 2 | 75.0 | 0.490 |
| 3 | 55.1 |

*P<0.05 indicates a statistically significant difference. HR, hazard ratio; CI, confidence interval.

In addition to the DFI, previous studies have demonstrated that the nodal status at the time of primary surgery was a prognostic factor among patients with IBTR (4, 19). The association between the DFI and the nodal status of the primary tumor, and its prognostic relevance among patients with IBTR, has yet to be elucidated. In addition, the small sample size, short follow-up period and high frequency of missing data,
particularly for the HER2 status of patients [primary tumor, 30.0% (12/40); IBTR, 22.5% (9/40)] were limitations of the present study. For ER-positive tumors, the annual breast cancer mortality rates are similar during years 0-4 and 5-14 (20).

In conclusion, the nodal status at primary surgery was demonstrated to be an independent predictive factor of distant recurrence among patients with early IBTR in the current study; however, further studies are required to support this association.

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References

1. Fisher B, Anderson S, Bryant J, Margolese RG, Deutsch M, Fisher ER, Jeong JH and 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.

2. Veronesi U, Cuginielli N, Mariani L, Greco M, Saccozzi R, Luini A, Agullar M and Murubini E: Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. N Engl J Med 347: 1277-1232, 2002.

3. Haffty BG, Reiss M, Beinfeld M, Fischer D, Ward B and McKhann C: Ipsilateral breast tumor recurrence as a predictor of distant disease: Implications for systemic therapy at the time of local relapse. J Clin Oncol 14: 52-57, 1996.

4. Komoike Y, Akiyama F, Iino Y, Ikeda T, Akashi-Tanaka S, Ohsumi S, Kusama M, Sano M, Shin E, Suemasu K, et al: Ipsilateral breast tumor recurrence (IBTR) after breast-conserving treatment for early breast cancer: Risk factors and impact on distant metastases. Cancer 106: 35-41, 2006.

5. Wapnir IL, Anderson SJ, Mamounas EP, Geyer CE Jr, Jeong JH, Tan-Chiu E, Fisher B and Wolmark N: Prognosis after ipsilateral breast tumor recurrence and locoregional recurrences in five national surgical adjuvant breast and bowel project node-positive adjuvant breast cancer trials. J Clin Oncol 24: 2028-2037, 2006.

6. Anderson SJ, Wapnir I, Dingam JJ, Fisher B, Mamounas EP, Jeong JH, Geyer CE Jr, Wickerham DL, Costantino JP and Wolmark N: Prognosis after ipsilateral breast tumor recurrence and locoregional recurrences in patients treated by breast-conserving therapy in five national surgical adjuvant breast and bowel project protocols of node-negative breast cancer. J Clin Oncol 27: 2466-2473, 2009.

7. Ishitobi M, Ohsumi S, Inaji H, Ohno S, Shigematsu H, Akiyama F, Iwase T, Akashi-Tanaka S, Sato N, Takahashi K and Oura S: Ipsilateral breast tumor recurrence (IBTR) in patients with operable breast cancer who undergo breast-conserving treatment after receiving neoadjuvant chemotherapy: Risk factors of IBTR and validation of the MD Anderson prognostic index. Cancer 118: 4385-4393, 2012.

8. Kurz JM, Spirialier JM, Amalric R, Brandone H, Ayme Y, Jacquelien J, Hans D and Bressac C: The prognostic significance of late local recurrence after breast-conserving therapy. Int J Radiat Oncol Biol Phys 18: 87-93, 1990.

9. Elkhuizen PH, Hermans J, Leer JW and van de Vijver MJ: Isolated late local recurrences with high mitotic count and early local recurrences following breast-conserving therapy are associated with increased risk on distant metastasis. Int J Radiat Oncol Biol Phys 50: 387-396, 2001.

10. van der Sangen MJ, van de Poll-Franse LV, Roumen RM, Rutten HJ, Coebergh JW, Vreugdenhil G and Voogd AC: The prognosis of patients with local recurrence more than five years after breast conservation therapy for invasive breast carcinoma. Eur J Surg Oncol 32: 34-38, 2006.

11. van Laar C, van der Sangen MJ, Poortmans PM, Nieuwenhuijzen GA, Roukema JA, Roumen RM, Tjän-Heijnen VC and Voogd AC: Local recurrence following breast-conserving treatment in women aged 40 years or younger: Trends in risk and the impact on prognosis in a population-based cohort of 1143 patients. Eur J Cancer 49: 3093-3101, 2013.

12. Ishitobi M, Okumura Y, Arima N, Yoshida A, Nakatsukasa K, Iwase T, Shen T, Masuda N, Tanaka S, Tanabe M, et al: Breast cancer subtype and distant recurrence after ipsilateral breast tumor recurrence. Ann Surg Oncol 20: 1886-1892, 2013.

13. Allkner S, Tang MH, Bruefler C, Dahlgren M, Chen Y, Olsson E, Winter C, Baker S, Ehinger A, Rydén L, et al: Contralateral breast cancer can represent a metastatic spread of the first primary tumor: Determination of clonal relationship between contralateral breast cancers using next-generation whole genome sequencing. Breast Cancer Res 17: 102, 2015.

14. Ishitobi M, Okuno J, Kittaka N, Nakayama T, Koyama H and Tamaki Y: Distant recurrence risk after late ipsilateral breast tumor recurrence: Results of a retrospective, single-institution study. Oncology 89: 269-274, 2015.

15. Umemura S, Kurosumi M, Moriya T, Oyama T, Arihiro K, Yamashita H, Umekita Y, Komokite Y, Shimizu C, Fukushima H, et al: Immunohistochemical evaluation for hormone receptors in breast cancer: A practically useful evaluation system and handling protocol. Breast Cancer 13: 232-235, 2006.

16. Wolff AC, Hammond ME, Hicks DG, Dowsett M, McShane LM, Allison KH, Allred DC, Bartlett JM, Bilous M, Fitzgibbons P, et al: Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American society of clinical oncology/collaborative of American pathologists clinical practice guideline update. J Clin Oncol 31: 3997-4013, 2013.

17. Pergolizzi S, Adamo V, Russi E, Santacaterina A, Maisano R, Numico G, Palazzolo C, Ferrari F, Settineri N, Altavilla G, et al: Prospective multicenter study of combined treatment with chemotherapy and radiotherapy in breast cancer women with the rare clinical scenario of ipsilateral supraclavicular node recurrence without distant metastases. Int J Radiat Oncol Biol Phys 65: 25-32, 2006.

18. Ludwig C, Stoeblen E and Hasse J: Disease-free survival after resection of lung metastases in patients with breast cancer. Eur J Surg Oncol 32: 34-38, 2006.

19. Voogd AC, van Tienhoven G, Peterec HL, Crommelin MA, Rutgers EJ, van de Velde CJ, van Geel BN, Slot A, Rodrigus PT, Janssen JJ, et al: Local recurrence after breast conservation therapy for early stage breast cancer: Detection, treatment and outcome in 266 patients. Dutch study group on local recurrence after breast conservation (Borst). Cancer 85: 437-446, 1999.

20. Early Breast Cancer Trialists’ Collaborative Group (EBCTCG): Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: An overview of the randomised trials. Lancet 365: 1687-1717, 2005.