Distant recurrence risk following early ipsilateral breast tumor recurrence

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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

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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).

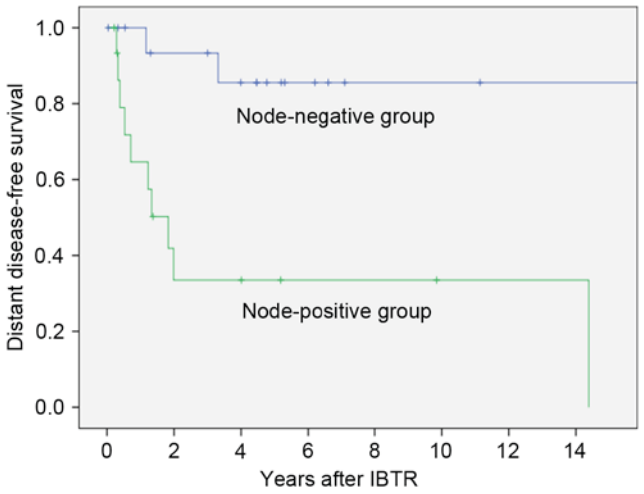

Figure 1. Distant disease-free survival rate following early IBTR according to the nodal status at primary surgery. IBTR, ipsilateral breast tumor recurrence.

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 surgery[a]	
Yes	11
No	6
Adjuvant trastuzumab following primary surgery[b]	
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 surgery[a]	
Yes	9
No	5
Unknown	3
Adjuvant trastuzumab following salvage surgery[b]	
Yes	4
No	5

[a]Including only patients with ER-positive tumors. [b]Including 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.

Table II. Three-year DDFS rates according to various clinicopathological 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[a]		
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	
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 surgery[a]		
Yes	64.8	0.071
No	26.7	
Adjuvant trastuzumab following salvage surgery[b]		
Yes	75.0	0.800
No	80.0	

[a]Including only patients with ER-positive tumors. [b]Including only patients with HER2-positive tumors. DDFS, distant disease-free survival; IBTR, ipsilateral breast tumor recurrence; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; p-T, pathological tumor.

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[a]
Adjuvant chemotherapy following primary surgery (positive vs. negative)	2.983	0.750-11.856	0.120

[a]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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