

ORIGINAL ARTICLE

The Impact of Local and Regional Recurrence on Distant Metastasis and Survival in Patients Treated with Breast Conservation Therapy

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Purpose: We evaluated the effect of local recurrence (LR) and regional recurrence (RR) on distant metastasis and survival in patients treated with breast conservation therapy (BCT). **Methods:** We analyzed 907 patients who were treated for invasive breast cancer between 1993 and 2006. With 53 months of follow-up, 28 patients (3.1%) developed LR in the breast and 12 patients (1.3%) developed RR before distant metastasis. LR and RR were separated into four patterns to determine the prognostic relevance of recurrence site and time to recurrence: LR within 3 years (early LR), LR after 3 years (late LR), RR within 3 years (early RR), and RR after 3 years (late RR). **Results:** Early LR (hazard ratio [HR], 4.76;

$p=0.003$) and early RR (HR, 18.16; $p<0.001$) were independent predictors of distant metastasis. In terms of overall survival, early LR (HR, 5.24; $p=0.002$), and early RR (HR, 18.80; $p<0.001$) were significantly related with poor survival. Patients with late LR/RR had a similar favorable prognosis compared with patients who never experienced LR/RR. **Conclusion:** The result suggests that time to LR/RR following BCT is a significant predictor developing a distant metastasis and surviving.

Key Words: Breast conservation therapy, Distant metastasis, Local recurrence, Regional recurrence, Survival

INTRODUCTION

A substantial increase in local recurrence (LR) of the treated breast has become a significant issue with the increased use of breast conservation therapy (BCT). The incidence of LR in the remnant breast varies between 2-10% after 5 years [1,2], and LR continues to occur at about 1% per year following BCT [3]. Isolated regional lymph node recurrence (RR) is an uncommon pattern of recurrence, and occurs in only 1-3% of patients with early stage breast carcinoma after a mastectomy or BCT [1,4,5]. Because of its rarity, relatively few data are available regarding the effect of LR and RR on the development of distant metastasis and survival in patients treated with BCT.

Studies on the prognostic effect of time on LR and RR after

BCT have reported conflicting results. While some studies have reported that prognosis of patients with late recurrence of more than 2-3 years is significantly better than that of patients with early recurrence within 2-3 years [6-8], another study found no significant effect of the interval from BCT to regional nodal recurrence on prognosis [9].

We hypothesized that the recurrence site (LR vs. RR) and time to recurrence (<3 vs. >3 years) might have prognostic relevance. In this study, the occurrence of LR and RR and time to LR and RR were considered together, and we tested for their ability to predict subsequent development of distant metastasis and survival.

METHODS

Study population

Between January 1993 and December 2006, 1,103 consecutive patients with breast cancer were treated with BCT at Severance Hospital, Yonsei University College of Medicine, Seoul, Korea. We retrospectively reviewed the data. Among the patients, we excluded 82 (7.4%) with ductal carcinoma *in situ*, one (0.1%) with a T4 lesion, four (0.4%) with stage IV disease at diagnosis, two (0.2%) with LR/RR diagnosed less than 3 months after initial surgery, and 32 (2.9%) with non-epithelial originating tumors (phyllodes, sarcoma, or lymphoma). Thir-

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ty-nine (3.5%) patients received neoadjuvant chemotherapy did not include to exclude the confounding effect of neoadjuvant chemotherapy. We also excluded 33 patients (3.0%) who did not receive radiation therapy, and three patients (0.2%) who did not receive appropriate axillary dissection. Finally, 907 patients comprised the study population.

BCT consisted of a wide resection of the primary tumor with an attempted margin of at least 1 cm and axillary staging followed by definitive breast radiation with or without systemic therapy. Microscopic margins were outperformed as routine clinical practice, and the primary site was re-excised for patients with microscopically involved margins. Sentinel lymph node biopsy (SLNB) using radioisotope was started in early 2000 at our medical center, so SLNB was performed in 279 patients (30.7%). Among them, we did not perform an axillary dissection in 209 patients with a negative sentinel lymph node, and they were considered N0.

Patients were treated with radiotherapy using tangential fields directed at the whole breast after conservative surgery. The whole breast dose was 50.4 Gy (range, 45-55.8 Gy) with 1.8-2 Gy per fraction. A tumor bed boost was performed with a 9-12 MeV electron beam. The median boost dose was 10 Gy (range, 10-20 Gy). In cases with a close or positive resection margin, the total radiation dose including the boost dose was increased to 65 Gy. As a rule, the irradiated volume involved the breast alone in patients with less than three positive lymph nodes. Cases with extracapsular lymph node extension or more than four positive lymph nodes were irradiated in the axilla or subclavicular fossa. The internal mammary lymph node was not routinely irradiated if there was no evidence of tumor involvements by radiological tests.

Adjuvant chemotherapy was indicated for patients who were node positive and had high-risk node negative disease. Between 1993 and 2004, patients with node negative disease received six cycles of cyclophosphamide, methotrexate, and 5-fluorouracil (CMF), whereas those with node positive disease received six cycles of 5-fluorouracil, doxorubicin, and cyclophosphamide (FAC). From 2005 until the end of the study, four cycles of doxorubicin plus cyclophosphamide (AC) were administered to those with node positive disease and four cycles of doxorubicin plus cyclophosphamide followed by four cycles of taxane (AC→T) were administered to those with node positive disease. Among 798 patients with positive estrogen (ER) or progesterone receptors (PR), only 539 patients (63.0%) received adjuvant endocrine therapy, because premenopausal women were excluded from endocrine therapy in the early period of this study.

Tested variables

We retrospectively reviewed the patients' clinicopathological

data including age, tumor stage, lymph node status, histological type, histological grade, ER/PR status, adjuvant systemic therapy, and follow-up data. LR was defined as histological evidence of a new tumor occurring in the treated breast or overlying skin more than 3 months after the completion of definitive surgery. The definition of RR was any biopsy-proven carcinoma found in the axilla or supraclavicular lymph nodes. Patient diagnosed with both LR and RR simultaneously were defined as RR. To evaluate the prognostic effect of LR and RR and time to recurrence, LR and RR were separated into four patterns: LR within 3 years (early LR), LR after 3 years (late LR), RR within 3 years (early RR), and RR after 3 years (late RR). Clinicopathological variables and patterns of LR and RR were tested for their ability to predict distant relapse free survival (DRFS) and overall survival (OS). All data were extracted from the Severance Hospital breast cancer registry which is a prospectively maintained database and includes clinical information, pathological information, treatment modalities, and outcome details.

Statistics

The primary end points of this analysis were DRFS and OS. Events determining DRFS were distant recurrence and death before recurrence. OS was death from any cause. Survival time was defined as the length of time from the date of surgery to the date of an event or the date last known to be alive. Survival rates were calculated by the Kaplan-Meier method, and the log-rank test was used to compare the groups. Multivariate analyses were performed using Cox proportional hazard regression model to determine whether LR and RR patterns were independent predictors of DRFS and OS. All reported *p*-values were two-sided, and a *p*-value < 0.05 was considered significant.

RESULTS

Patient characteristics

The clinicopathological characteristics of the study population and LR and RR patterns are summarized in Table 1. At the time of initial diagnosis, 96 patients (10.6%) were under the age of 35, and 272 patients (30.0%) had T2 lesions. At the time of initial surgery, 254 patients (28.0%) had a positive axillary lymph node. Almost 90% of patients had invasive ductal carcinoma (808 of 907, 89.9%). Information on histological grade, ER and PR status, and adjuvant chemotherapy was available in 732, 846, 847, and 903 patients, respectively. Approximately two-thirds of patients received adjuvant systemic chemotherapy and endocrine therapy. No significant differences were observed in the clinicopathological characteristics between LR and RR.

Twenty-eight patients (3.1%) developed LR and 12 patients

Table 1. Clinicopathologic, treatment characteristics, and patterns of local/regional recurrence

Characteristics	No locoregional recurrence, No. (%)	Local recurrence, No. (%)	Regional recurrence, No. (%)	p-value
Age (yr)				0.002
≤35 (n=96)	84 (87.5)	9 (9.4)	3 (3.1)	
>35 (n=811)	783 (96.5)	19 (2.3)	9 (1.1)	
Tumor stage				0.580
T1 (n=635)	606 (95.4)	19 (3.0)	10 (1.6)	
T2 (n=272)	261 (95.9)	9 (3.3)	2 (0.7)	
Lymph node metastasis				0.242
Negative (n=653)	621 (95.1)	24 (3.7)	8 (1.2)	
Positive (n=254)	246 (96.9)	4 (1.6)	4 (1.6)	
Histologic type				0.064
Ductal (n=808)	774 (95.8)	26 (3.2)	8 (1.0)	
Lobular (n=15)	14 (93.3)	1 (6.7)	0 (0)	
Others (n=84)	79 (94.0)	1 (1.2)	4 (4.8)	
Histologic grade (n=732)*				0.441
I (n=212)	203 (96.2)	5 (2.4)	3 (1.4)	
II/III (n=520)	501 (96.2)	17 (3.3)	3 (0.6)	
ER status (n=846)*				0.204
ER(-) (n=305)	289 (94.7)	13 (4.3)	3 (1.0)	
ER(+) (n=541)	521 (96.3)	12 (2.2)	8 (1.5)	
PR status (n=847)*				0.390
PR(-) (n=367)	349 (95.1)	11 (3.0)	7 (1.9)	
PR(+) (n=480)	462 (96.3)	14 (2.9)	4 (0.8)	
Adjuvant chemotherapy (n=903)*				0.003
Not done (n=306)	282 (92.2)	17 (5.6)	7 (2.3)	
Done (n=597)	581 (97.3)	11 (1.8)	5 (0.8)	
Endocrine therapy (n=907)				0.011
Not done (n=367)	343 (93.5)	19 (5.2)	5 (1.4)	
Done (n=540)	524 (97.0)	9 (1.7)	7 (1.3)	

ER=estrogen receptor; PR=progesterone receptor.

*Histologic grade, ER and PR status, and adjuvant chemotherapy did not know whole data. The numbers in parentheses are data that can be known as the chart review.

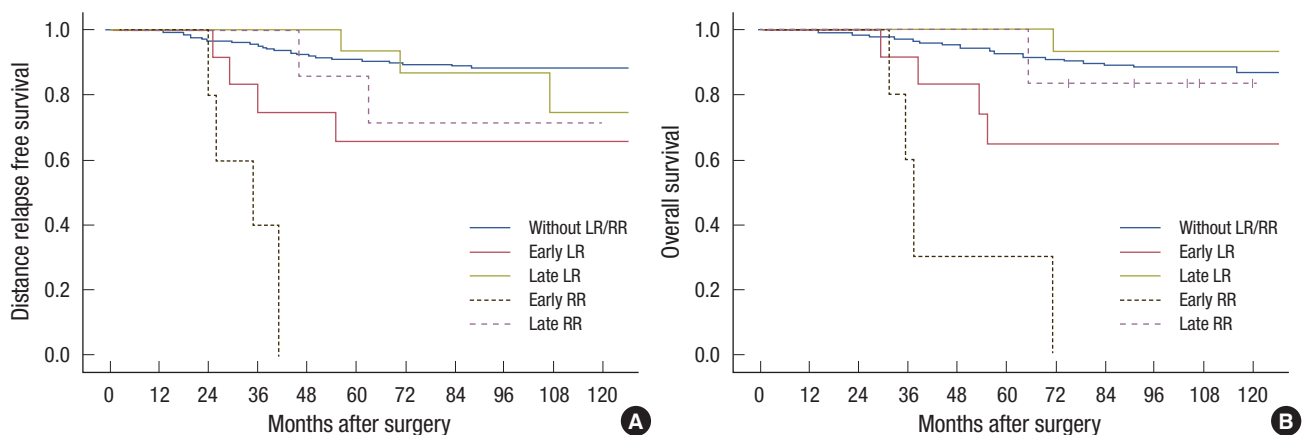


Figure 1. Kaplan-Meier 5-year distant relapse free survival (A) and overall survival (B) estimate according to the patterns of local recurrence and regional recurrence. Early local recurrence (LR), local recurrence within 3 years; Late LR, local regional after 3 years; Early regional recurrence (RR), regional recurrence within 3 years; Late RR, regional recurrence after 3 years.

(1.3%) developed RR as the first event, with a median follow-up time of 53 months (range, 4-179 months). None of the patients showed histological or radiological signs of distant metastasis

at the time of LR and RR diagnosis (Table 1). The distribution of early LR, late LR, early RR, and late RR was 12 (1.3%), 16 (1.8%), 5 (0.6%), and 7 (0.8%), respectively. Recurrent sites

were an ipsilateral breast (n = 28, 70.0%), axillary lymph node (n = 2, 5.0%), supraclavicular lymph node (n = 9, 22.5%), and internal mammary lymph node (n = 1, 2.5%).

Among 653 patients with axillary node-negative disease, 209 patients (32.0%) performed only SLNB and the rest 444 patients (68.0%) underwent axillary node dissection. Early LR, late LR, early RR, and late RR occurred in 1, 1, 0, and 1 patient among those who performed only SLNB, respectively, and 9, 13, 2, and 4 patients among those who underwent ALND, respectively. Among patients with node-negative disease, SLNB alone did not lead to inferior locoregional control than ALND.

At the time of the LR and RR diagnosis, 30 patients (75%) underwent surgical treatment including simple mastectomy with or without axillary dissection, or axillary dissection alone. Twelve patients (30%) were treated with additional radiotherapy to regional lymph node. Chemotherapy was administered to 22 patients (55%), and 16 patients (40%) received endocrine therapy. Two patients (5%) received herceptin.

Effect of LR and RR on DRFS and OS

Of the 40 patients who underwent LR and RR, 13 (32.5%) experienced subsequent distant recurrence. The distribution of early LR, late LR, early RR, and late RR was four (5.0%), three (3.8%), four (5.0%), and two (2.5%). The distance metastatic sites were bone (n = 5), lung (n = 7), liver (n = 4), central nervous system (n = 4), and other visceral organ (n = 3). Eleven patients (27.5%) died after detection of LR and RR. Of 867 patients who did not undergo LR and RR, 67 (7.7%) experienced distance recurrence. Distance metastasis sites were bone (n = 38), lung (n = 37), liver (n = 18), central nervous system (n = 7), and other visceral organ (n = 7). Fifty-seven patients (6.7%) died during the following-up period. The following factors were analyzed for their ability to predict DRFS and OS: age, T stage, lymph node status, histological type, histological grade, ER/PR status, adjuvant chemotherapy, endocrine therapy, and LR and RR patterns.

In a univariate analysis, younger age (≤ 35 years) at diagnosis ($p = 0.003$), larger tumor size of more than 2 cm ($p = 0.008$), positive lymph node ($p < 0.001$), and early LR and early RR development ($p < 0.001$) had a significant effect on DRFS. Positive lymph node status ($p = 0.005$) and early LR and early RR development ($p < 0.001$) had a significant effect on poor survival (Table 2, Figure 1). The 5-year DRFS for patients presenting with early LR and early RR was 65.6% and 0%, respectively. The 5-year OS of early LR and early RR was 66.8% and 30.0%, respectively. The 5-year DRFS and OS of late LR and late RR were similar compared with patients who never experienced LR and RR (Table 2).

In multivariate analysis, younger age (≤ 35 years) (hazard

Table 2. Univariate analysis for predicting 5 year distant relapse free survival and overall survival

Characteristics	5-yr DRFS (%)	p-value	5-yr OS (%)	p-value
Age (yr)				
≤ 35	81.9	0.003	87.3	0.140
> 35	91.1		92.3	
Tumor stage				
T1	92.1	0.008	92.3	0.536
T2	86.0		90.6	
Lymph node metastasis				
Negative	92.9	< 0.001	93.8	0.005
Positive	83.5		86.9	
Histologic type				
Ductal	89.8	0.555	91.6	0.998
Lobular	100		100	
Others	91.4		91.9	
Histologic grade (n = 732)*				
I	93.0	0.095	93.1	0.312
II/III	88.2		90.0	
ER status (n = 846)*				
Negative	90.8	0.873	92.4	0.940
Positive	90.0		91.8	
PR status (n = 847)*				
Negative	90.6	0.511	91.9	0.648
Positive	90.1		92.1	
Adjuvant chemotherapy (n = 903)*				
Not done	89.5	0.934	91.2	0.385
Done	90.3		91.9	
Adjuvant endocrine therapy				
Not done	89.6	0.895	90.4	0.301
Done	90.4		92.8	
Patterns of LR/RR				
No LR/RR	90.9	< 0.001	92.4	< 0.001
Early LR	65.6		66.8	
Late LR	93.8		100	
Early RR	0		30.0	
Late RR	85.7		100	

DRFS = distant relapse free survival; OS = overall survival; ER = estrogen receptor; PR = progesterone receptor; Early LR = local recurrence within 3 years; Late LR = local regional after 3 years; Early RR = regional recurrence within 3 years; Late RR = regional recurrence after 3 years.

*Histologic grade, ER and PR status, and adjuvant chemotherapy did not know whole data. The numbers in parentheses are data that can be known as the chart review.

ratio [HR], 1.79; 95% confidence interval [CI], 1.01-3.15; $p = 0.043$), positive lymph node (HR, 2.34; 95% CI, 1.47-3.71; $p < 0.001$), early LR (HR, 4.76; 95% CI, 1.69-13.34; $p = 0.003$), and early RR (HR, 18.16; 95% CI, 6.34-52.00; $p < 0.001$) were significantly related with lower DRFS, whereas tumor size (HR, 1.58; 95% CI, 1.00-2.51; $p = 0.05$) had marginal significance. In terms of OS, a positive lymph node (HR, 2.10; 95% CI, 1.28-3.45; $p = 0.003$), early LR (HR, 5.24; 95% CI, 1.86-14.74; $p = 0.002$), and early RR (HR, 18.80; 95% CI, 6.24-55.05; $p < 0.001$) were significantly related to lower OS. No apparent difference

Table 3. Hazard ratios and 95% confidence intervals by multivariate Cox model

Variables	DRFS			OS		
	HR	95% CI	p-value	HR	95% CI	p-value
Age (>35 vs. ≤35 yr)	1.79	1.01-3.15	0.043	1.29	0.66-2.52	0.437
Tumor stage (T1 vs. T2)	1.58	1.00-2.51	0.050	1.09	0.65-1.82	0.724
Node metastasis (negative vs. positive)	2.34	1.47-3.71	<0.001	2.10	1.28-3.45	0.003
Without LR/RR	Ref.			Ref.		
Early LR	4.76	1.69-13.34	0.003	5.24	1.86-14.74	0.002
Late LR	1.319	0.40-4.35	0.650	0.97	0.22-4.19	0.977
Early RR	18.16	6.34-52.00	<0.001	18.80	6.42-55.05	<0.001
Late RR	2.89	0.70-11.86	0.141	1.43	0.19-10.39	0.722

DRFS=distance relapse free survival; OS=overall survival; HR=hazard ratio; CI=confidence interval; LR=local recurrence; RR=regional recurrence; Early LR=local recurrence within 3 years; Late LR=local regional after 3 years; Early RR=regional recurrence within 3 years; Late RR=regional recurrence after 3 years; Ref.=reference.

in DRFS and OS was found between patients who experienced late LR and RR and those who did not (Table 3).

DISCUSSION

The magnitude of problem of LR is substantial as many women choose BCT for initial management. RR is a relatively uncommon event, and few data are available regarding the association among RR, DRFS, and OS. However, as the number of long term survivors has increased, analysis of treatment outcomes has revealed that the LR and RR problem has a potential impact on DRFS and OS [10,11]. Evaluation of the prognostic effect of LR and RR on the development of DR and survival following BCT may help to determine the treatment modality.

Several studies have focused on LR and RR as the first event after BCT and reported that LR and RR are significant predictors of subsequent distant metastases and survival [4,12-16]. Additionally, it seems that the prognosis after RR is much worse than that after LR. According to an analysis of five trials conducted by the National Surgical Adjuvant Breast and Bowel Project, the risks of distant disease and death were greater after RR than LR in each trial [17]. However, whether time to recurrence is a marker for distant metastasis remains controversial. Several studies have identified the time to LR and RR from initial surgery as an additional important prognostic factor for DRFS and OS [5,12-14,17-20], whereas another study reported that the time to regional nodal recurrence did not have a significant effect on prognosis [9].

We separated LR and RR into four patterns-(early LR, late LR, early RR, and late RR) to evaluate the prognostic relevance of site of recurrence (LR vs. RR) and time to LR and RR (early vs. late) after BCT. The data presented here confirm that patients who experience early LR and early RR within the first few years following their original diagnosis have a poor prognosis.

LR and RR within 3 years was a strong predictor of developing distant recurrence and death. Early RR showed the worst prognostic patterns and the outcomes in these patients at 5 years showed a DRFS of 0% and an OS of 30%, followed by an early LR. Although a trend was seen for higher rates of distant metastases in patients with late RR, it was not statistically significant (HR, 2.89; 95% CI, 0.70-11.86; $p = 0.141$). These findings suggest that time to LR and RR is a more important prognostic factor for distant metastases and survival than site of recurrence. We assumed that more rapidly recurring tumors have higher biological aggressiveness, and that patients who sustain early LR and early RR tend to display worse clinical behavior and a relatively unfavorable prognosis.

Interestingly, the prognosis of patients who experienced late LR was not that different from that of patients who never experienced recurrence. A possible explanation for this finding is that a significant portion of patients who experience late LR following BCT develop new primary tumors as opposed to true LR [21]. True recurrence and a new primary tumor may have a different natural history, different biological behavior and a different prognosis. Theoretically, true recurrent tumors may be more radio-resistant and more drug-insensitive than a new primary tumor [17,21].

Prevention and prediction of LR and RR at the time of initial diagnosis of primary tumor might be an important issue if LR and RR, as the first event after BCT, influences DRFS and OS. Patients at high risk for LR and RR can benefit from initial aggressive surgery [22], but, no robust marker predicts the risk of locoregional failure, which would be helpful when selecting an ideal initial therapy [23]. A major effort is underway to predict LR and RR using molecular markers in genome-wide association studies.

In the absence of data from prospective randomized trials, we suggest that the decision should be tailored to the risk of the individual patient based on the knowledge of a demonstrated

benefit of adjuvant systemic therapy in patients with primary cancer. Our data suggests that patients with early LR and early RR need to be considered as a clinically distinct group compared with those who develop late LR and late RR. The high incidence of distant metastasis and death in patients who experienced early LR and early RR justifies considering more aggressive systemic therapy at the time of the LR and RR diagnoses. Age, tumor size, and axillary lymph node status were also significantly related to distant recurrence and all should be considered for further adjuvant therapy.

We noted that patients who experienced late RR had a greater than 2.89 fold relative risk of developing distant metastasis without statistical significance. Because the limited power of this study with a small number of patients was a possible cause for the failure to demonstrate a difference, our data could not provide definitive answers regarding the role of systemic treatment for patients with late RR. It seems reasonable to select systemic treatment strategies on an individual basis for patients who experience late LR and late RR.

We included patients who had received appropriate radiation, and standard axillary surgery and excluded patients who were administered inappropriate locoregional treatment. However, similar to other studies, an important limitation of this retrospective study was the small number of patients, as is apparent from the broadness of the confidence intervals. Interpretation of the results is also hampered by the heterogeneity of the study population because of the long study duration and different adjuvant systemic therapies used after initial surgery. Additionally, treatment strategies at the time of LR and RR were highly individualized given the lack of prospective data to make decisions regarding patients with LR and RR.

Early LR and early RR within 3 years following BCT was a strong independent predictor of DRFS and OS, whereas survival of patients with late LR and late RR was not significantly different from those who never experienced LR and RR. Other prognostic factors (age, tumor size, positive axillary lymph node) were also important predictors of DRFS and OS. Aggressive systemic treatment should be considered for patients who experience early LR and early RR, whereas systemic treatment for patients with late LR and late RR could be determined on an individual basis. A multi-institutional study is necessary to establish a standard treatment protocol for patients who suffer from LR and RR following BCT. It may be possible in the future to tailor initial surgery for a primary tumor using biological marker that estimates the risk of local and regional failure.

CONFLICTS OF INTEREST

All authors declare no conflicts of interest.

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