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ORIGINAL ARTICLE

Risk factors for locoregional recurrence after postmastectomy radiotherapy in breast cancer patients with four or more positive axillary lymph nodes

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ABSTRACT

Background

We investigated risk factors for locoregional recurrence (LRR) in breast cancer patients with 4 or more positive axillary lymph nodes receiving postmastectomy radiotherapy (PMRT).

Methods

Medical records (1998–2007) were retrospectively reviewed for the population of interest. The Kaplan–Meier method was used to calculate the survival rate; Cox regression models were used for univariate and multivariate analysis of predictors of breast cancer LRR.

Results

The study enrolled 439 patients. Median duration of follow-up was 54 months. The 5-year rates of locoregional recurrence-free survival (LRRFS), distant metastasis–free survival (DMFS), and breast cancer–specific survival (BCSS) were 87.8%, 59.5%, and 70.7% respectively. In patients with LRR and no concomitant metastasis, and in those without LRR, the 5-year rates of DMFS were 21.1% and 65.7% respectively ($p < 0.001$), and the 5-year rates of BCSS were 34.5% and 76.4% respectively ($p < 0.001$).

Univariate analysis showed that menopausal status ($p = 0.041$), pN stage ($p = 0.006$), and positivity for HER2 [human epidermal growth factor receptor 2 ($p = 0.003$)] or the triple-negative disease subtype ($p < 0.001$) were determinants of LRRFS. Multivariate analysis showed that pN3 stage [hazard ratio (HR): 2.241; 95% confidence interval (CI): 1.270 to 3.957; $p = 0.005$], HER2 positivity (HR: 2.705; 95% CI: 1.371 to 5.335; $p = 0.004$), and triple-negative disease subtype (HR: 4.617; 95% CI: 2.192 to 9.723; $p < 0.001$) were independent prognostic factors of LRRFS.

Conclusions

In breast cancer patients with 4 or more positive axillary lymph nodes who undergo PMRT for breast cancer, LRR significantly influences survival. Patients who developed LRR carried a high risk for distant metastasis and death. Pathologic stage (pN3), HER2 positivity, and the triple-negative disease subtype are risk factors that significantly influence LRRFS.

KEY WORDS

Breast cancer, mastectomy, radiotherapy, locoregional recurrence, prognostic analysis

1. INTRODUCTION

Axillary lymph node metastasis is an important factor influencing the selection of postoperative radiotherapy for patients with breast cancer. Randomized trials have shown that postoperative radiotherapy can benefit patients by increasing local control[1]. Thus, for breast cancer patients with 4 or more metastatic axillary lymph nodes, radiotherapy is recommended after mastectomy[2,3]. Although postmastectomy radiotherapy (PMRT) can reduce locoregional recurrence (LRR) in two thirds of breast cancer patients at high risk, 6.2%–17.5% of patients with breast cancer still develop local recurrence after PMRT[4–7].

For patients with LRR who did not receive PMRT, comprehensive therapy still achieves a favourable rate of local control and survival[8]. Patients with LRR treated with chemotherapy experience improved disease-free survival (DFS) and overall survival, especially if the recurrence is negative for the estrogen receptor[9]. However, for patients with LRR after PMRT, local therapy (especially a second round of radiotherapy) usually has poor efficacy, and the survival of such patients is also significantly influenced by LRR[4]. Although all breast cancer patients with 4 or more positive axillary lymph nodes are staged in a similar manner, therapeutic outcomes can differ,

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which suggests that other factors determine therapeutic response or outcome. Thus, it is imperative to investigate the risk factors influencing LRR after PMRT, which might provide evidence for individualized breast cancer therapy. In the present study, we retrospectively studied clinical prognosis and explored risk factors influencing LRR in breast cancer patients with 4 or more positive axillary lymph nodes who underwent PMRT.

2. METHODS

2.1 Patient Selection

Clinicopathologic data for patients with breast cancer attending the Sun Yat-sen University Cancer Center from March 1999 to December 2007 were retrospectively reviewed. Patients were included if

- they had unilateral breast cancer (with neither ipsilateral supraclavicular lymph node metastasis nor distant metastasis), for which mastectomy and dissection of axillary lymph nodes was performed.
- a postoperative pathology examination showed 4 or more positive axillary lymph nodes (with pN2 being defined as 4–9 positive lymph nodes, and pN3, as 10 or more positive lymph nodes) and negative surgical margins.
- estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) had been ascertained by immunohistochemistry.
- chemotherapy had been administered for at least 4 weeks, and radiotherapy that included the ipsilateral chest wall and the supraclavicular and subclavian area had been administered.
- endocrine therapy had been administered when indications for endocrine therapy were present.

Of the 3636 breast cancer patients treated with mastectomy at Sun Yat-sen University Cancer Center between March 1999 and December 2007, 1947 were node-positive. Of the 521 patients with 4 or more positive lymph nodes, 439 met the criteria for inclusion in the study.

2.2 Clinicopathologic Factors

The clinicopathologic factors used to evaluate risk of breast cancer LRR included age, menopausal status, pT stage, pN stage, lymphovascular invasion, molecular disease subtypes, neoadjuvant chemotherapy, and PMRT. For the ER and PR, positivity was defined as more than 10% positive cells; HER2 positivity was defined as 3+ by immunohistochemistry, or 2+ by immunohistochemistry plus positivity by fluorescence *in situ* hybridization. In the present study, the molecular subtypes were not determined according to the criteria developed at the St. Gallen International Breast Cancer Conference, because immunohistochemistry for Ki-67 was missing for some patients[10]. Breast cancer subtypes were therefore categorized as follows:

- ER- or PR-positive and HER2-negative (HR+, HER2–)
- HR-positive or -negative and HER2-positive (HER2+)
- ER-, PR-, and HER2-negative (triple-negative)

2.3 Follow-Up and Endpoints of Survival

Follow-up was initiated on the first postoperative day and was performed once every 3–6 months. The major endpoint of follow-up was LRR-free survival (LRRFS). Distant metastasis–free survival (DMFS) and breast cancer–specific survival (BCSS) served as secondary endpoints. "Locoregional recurrence" refers to pathologically confirmed recurrence at the ipsilateral chest wall or within the supraclavicular and subclavian lymph nodes, axillary lymph nodes, or internal mammary lymph nodes. "Distant metastasis" refers to recurrence at a site distant from the primary cancer, confirmed by two imaging examinations or by pathology assessment. "Disease-free survival" refers to the absence of LRR or distant recurrence. "Breast cancer–specific survival" was defined as the time until death from breast cancer.

2.4 Statistical Analysis

Statistical significance was determined using the log-rank test. Univariate and multivariate analysis used Cox regression. Factors in the univariate analysis that were significant indicators of endpoints were included in the multivariate analysis. Statistical significance was determined using the log-rank test. Values of p less than 0.05 were considered significant.

3. RESULTS

3.1 Clinicopathologic Information and Therapy

Table I shows clinicopathologic information for the 439 enrolled patients. Median age at diagnosis was 45 years (range: 24–78 years). Each patient underwent mastectomy and dissection of the axillary lymph nodes. The median number of dissected axillary lymph nodes was 18 (range: 5–73). The median number of positive lymph nodes was 9 (range: 4–67). An anthracycline- or taxane-based protocol was used for chemotherapy. Neoadjuvant chemotherapy was given to 86 patients for a median of 2 cycles (range: 1–6 cycles), with 52 patients (60.5%) receiving anthracycline-based regimens, and 34 (39.5%) receiving regimens with both an

TABLE I Univariate analysis of clinicopathologic factors and factors influencing locoregional recurrence of breast cancer

Characteristic	*Value [*n *(%)]*	*Hazard ratio*	*95% CI*	p *Value*
Patients	439			
Age				
<35 Years	52 (11.8)	Reference		
≥35 Years	387 (88.2)	0.843	0.380 to 1.868	0.673
Menopausal status				
Premenopausal	288 (65.6)	Reference		
Postmenopausal	151 (34.4)	1.769	1.025 to 3.054	0.041
Pathologic T stage				
pT1–2	315 (71.8)	Reference		
pT3–4	124 (28.2)	1.577	0.896 to 2.773	0.114
Pathologic N stage				
pN2	233 (53.1)	Reference		
pN3	206 (46.9)	2.197	1.249 to 3.864	0.006
Lymphatic invasion				
No	416 (94.8)	Reference		
Yes	23 (5.2)	1.174	0.365 to 3.770	0.788
Breast cancer subtype				
HR-positive, HER2-negative	219 (49.9)	Reference		
HER2-positive	159 (36.2)	2.773	1.412 to 5.449	0.003
Triple-negative	61 (13.9)	4.871	2.315 to 10.248	<0.001
Type of radiotherapy				
Tangential field	199 (45.3.)	Reference		
Electrons	240 (54.7)	1.067	0.613 to 1.857	0.818
Neoadjuvant chemotherapy				
No	353 (80.4)	Reference		
Yes	86 (19.6)	1.686	0.914 to 3.113	0.095

CI = confidence interval; HR = hormone receptor; HER2 = human epidermal growth factor receptor 2.

anthracycline and a taxane. Adjuvant chemotherapy was administered to all patients for a median of 5 cycles (range: 2–8 cycles), with 272 patients (62.0%) receiving anthracycline-based regimens, and 167 (38.0%) receiving regimens with both an anthracycline and a taxane. For the 353 patients who did not receive neoadjuvant chemotherapy, adjuvant chemotherapy was given after surgery for a median of 6 cycles (range: 4–8 cycles).

All patients received PMRT after chemotherapy. The PMRT was delivered mainly to the ipsilateral chest wall and supraclavicular and subclavian lymph drainage regions. The chest wall was irradiated with a 6-MeV electron-beam field ($n = 240$) or a tangential 6-MV X-ray field ($n = 199$). A bolus (0.5–1.0 cm) was used to compensate for the chest wall. At the supraclavicular and subclavian lymph drainage regions, 6-MV X-rays and 12–15 MeV electron-beam fields were used for irradiation. The total radiation dose was 50 Gy in 25 fractions. Patients with tumours positive for the ER or PR (or both) received endocrine therapy, mainly with tamoxifen and aromatase inhibitors. Patients with HER2+ tumours were not treated with trastuzumab.

3.2 Survival and Patterns of Therapeutic Failure

Among the study patients, the median duration of follow-up was 54 months (range: 5–138 months). Locoregional recurrence was noted in 52 patients, with a median time to LRR of 21 months (range: 6–110 months). The 5-year LRRFS was 87.8% (Figure 1). Recurrence was found only on the chest wall in 19 patients, only in the supraclavicular and subclavian area in 13 patients, and only in the axilla in 4 patients. Recurrence was noted on the chest wall and in the axilla in 1 patient, on the chest wall and in the supraclavicular area in 2 patients, and at multiple sites in 13 patients. In 12 patients with LRR, distant metastasis was also observed, with 169 patients in the entire study cohort developing distant metastasis. The overall 5-year rates of DMFS and BCSS were 59.5% (Figure 1) and 70.7% respectively, and 129 women died of their breast cancer (Figure 1). One patient died of cardiovascular disease.

In patients with LRR (no concomitant metastasis) and without LRR, the 5-year rates of DMFS were 21.1% and 65.7% respectively ($p < 0.001$). The 5-year rates of BCSS were 34.5% and 76.4% respectively ($p < 0.001$, Figure 2).

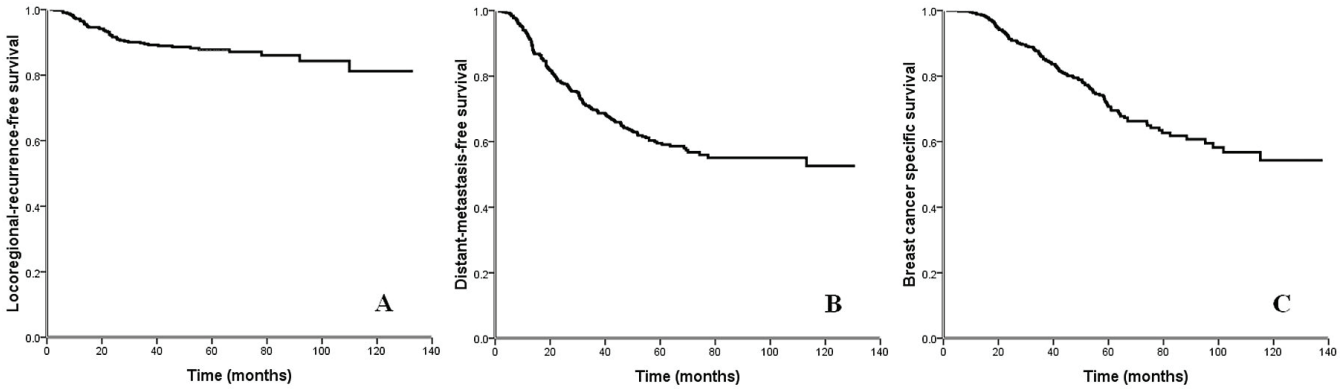

FIGURE 1 Cumulative patient survival. (A) Locoregional recurrence-free survival. (B) Distant metastasis-free survival. (C) Breast-cancer-specific survival.

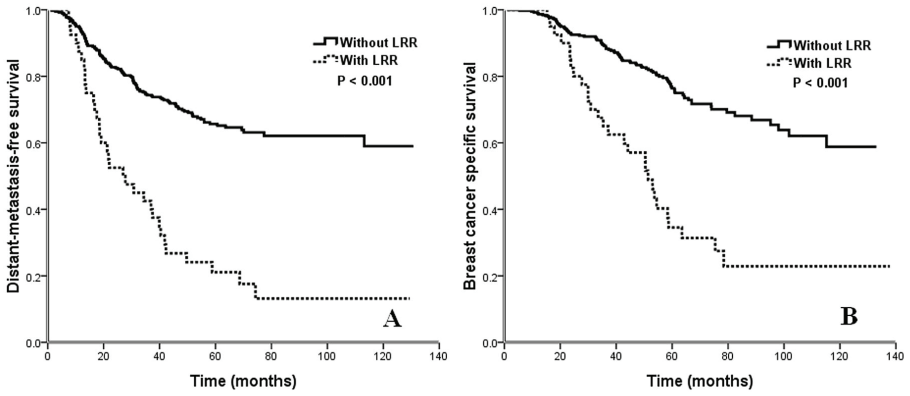

FIGURE 2 (A) Distant metastasis-free survival and (B) breast-cancer-specific survival in patients with and without locoregional recurrence (LRR).

3.3 Analysis of Prognostic Factors

Univariate analysis showed that menopausal status ($p = 0.041$), pN stage ($p = 0.006$), HER2 positivity ($p = 0.003$), and the triple-negative disease subtype ($p < 0.001$) were factors influencing LRRFS. Age, lymphovascular invasion, pT stage, type of PMRT, and type of neoadjuvant chemotherapy had no effect on prognosis ($p > 0.05$, Table I). Cox regression analysis showed that pN3 stage ($p = 0.005$), HER2 positivity ($p = 0.004$), and the triple-negative disease subtype ($p < 0.001$) were independent predictors of LRRFS (Table II). Kaplan–Meier analysis showed that the 5-year rates of LRRFS were 92.0% and 82.9% for stages pN2 and pN3 respectively ($p = 0.005$). The 5-year rates of LRRFS were 94.3%, 84.0%, and 72.2% in patients with the HR+, HER2–; HER2+; and triple-negative disease subtypes respectively ($p < 0.001$).

4. DISCUSSION

In the present study, the 5-year rate of LRRFS was 12.2% in patients who had 4 or more positive axillary lymph nodes and who received PMRT. Patients with LRR had a poor prognosis. In addition, in patients who received standard anthracycline- or taxane-based chemotherapy and PMRT, the 5-year LRRFS was still about 20% when the patients were classified as having stage pN3, HER2+, or triple-negative breast cancer. Our study demonstrated that pN3 stage, HER2 positivity, and the triple-negative disease subtype were independent predictors of LRR.

After completion of radiotherapy, LRR is an important risk factor for death from breast cancer. In the present study, patients who developed LRR experienced significantly lower rates of DMFS and BCSS than did patients without LRR. A recent study by Bantema–Joppe *et al.*[11] demonstrated that, compared with patients without LRR, patients with LRR experienced a higher risk of distant metastasis [hazard ratio: 5.5; 95% confidence interval (CI): 2.1 to 14.5]. A similar report noted that LRR after mastectomy was the most important prognostic factor for distant metastasis[12]. The origin of the LRRS in those patients might be related to systemic disease. However, correlation is not causation, and it is just as probable that patients with aggressive tumours are more likely to experience both LRR and distant metastasis.

In the present study, we found that the LRR rate was higher in patients with HER2+ tumours than in those with tumours of other molecular subtypes, which is consistent with previous reports[13–15]. Those

TABLE II Multivariate analysis of factors influencing locoregional recurrence of breast cancer

Characteristic	*Hazard ratio*	*95% CI*	p *Value*
Pathologic N stage			
pN2	Reference		
pN3	2.241	1.270 to 3.957	0.005
Breast cancer subtype			
HR-positive, HER2-negative	Reference		
HER2-positive	2.705	1.371 to 5.335	0.004
Triple-negative	4.617	2.192 to 9.723	
Menopausal status			
Premenopausal	Reference		
Postmenopausal	1.737	1.002 to 3.010	0.049

CI = confidence interval; HR = hormone receptor; HER2 = human epidermal growth factor receptor 2.

findings suggests that HER2+ breast cancer is a relatively resistant subtype of the disease. Studies have shown that trastuzumab can increase sensitivity to radiotherapy in patients with HER2+ breast cancer[16]. Panoff *et al.* found that the 5-year rate of LRRFS was significantly lower in patients with HER2+ breast cancer treated with trastuzumab than in patients with HER2– disease (1.7% vs. 7.5%, $p = 0.032$)[6]. In the present study, patients with HER2+ disease were not treated with trastuzumab.

Triple-negative breast cancer is highly heterogeneous in its clinical, pathologic, and molecular features. Our results also revealed that the LRR rate was greater in patients with triple-negative breast cancer than in patients with breast cancers of other molecular subtypes, which accords with results in previous reports[14]. Thus, we speculate that triple-negative breast cancer is a relatively radiotherapy-resistant subtype of breast cancer. To date, no targeted protocol has been developed for the treatment of triple-negative breast cancer. Although studies show that PARP1 (poly[ADP-ribose] polymerase-1) inhibitor can potentially increase the sensitivity of triple-negative breast cancer to radiotherapy[17,18], treatment of triple-negative breast cancer with PARP1 inhibitor and irradiation is still in its infancy.

Lee *et al.*[19] found that the addition of radiotherapy to other treatment did not improve the DFS of patients with breast cancer at stage pN3 (44.4% vs. 40.3%, $p = 0.618$) and that the LRR rate was still as high as 26.3%. In addition, Chang *et al.*[20] and Koca *et al.*[21] reported that the 5-year LRR rate was 13%–24% in patients with breast cancer at stage pN3 after PMRT, and the 5-year DFS was only about 46%. Those results are consistent with our finding that patients with pN3 breast cancer had a high risk of LRR after PMRT. It is possible that, after node dissection, patients with pN3 tumours have residual disease in the axilla that contributes to their higher rate of LRR.

Some investigators experimented with altering the patterns of radiotherapy in breast cancer patients with a high risk of LRR, applying targeted biologic therapy[6,16–18] and an increase in the radiation dose. Panoff *et al.*[22] used chest irradiation at the recommended dose of more than 50 Gy and found that the 5-year LRR rate was 5.7% for patients receiving a radiation dose of more than 50.4 Gy (median: 60.4 Gy) and 12.7% for those receiving 50.4 Gy or less (median: 50.4 Gy, $p = 0.054$). Moreover, DFS ($p < 0.001$) and overall survival ($p < 0.001$) were shorter in the 50.4 Gy or less group than in the more than 50.4 Gy group[22]. In addition, in patients undergoing breast-conserving therapy, irradiation at a high dose was found to further reduce LRR[23].

Our study has some limitations: It was a retrospective single-centre study, and eligible patients were not treated with trastuzumab. Whether targeted therapy would have influenced therapeutic outcomes in the present study is unclear. However, studies have demonstrated that trastuzumab significantly reduces the likelihood of LRR in patients with HER2-overexpressing tumours[6,24].

5. CONCLUSIONS

In patients undergoing PMRT for breast cancer and having 4 or more positive axillary lymph nodes, LRR was observed to significantly influence survival. The development of LRR carries a high risk of distant metastasis and death. In addition, pN3 stage, HER2 positivity, and the triple-negative disease subtype were found to be risk factors influencing LRRFS. Every effort should be made to lower the locoregional failure rate in breast cancer.

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7. CONFLICT OF INTEREST DISCLOSURES

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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