*Curr Oncol*, Vol. 20, pp. e585-592; doi: http://dx.doi.org/10.3747/co.20.1540

ORIGINAL ARTICLE

# Irradiation after surgery for breast cancer patients with primary tumours and one to three positive axillary lymph nodes: yes or no?

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## ABSTRACT

### Objective and Methods

We retrospectively analyzed clinicopathologic features and survival in breast cancer patients who had T1 or T2 primary tumours and 1–3 histologically involved axillary lymph nodes and who were treated with modified radical mastectomy without adjuvant radiotherapy (RT). We also explored prognosis to find the high- and low-risk groups.

### Results

From May 2001 to April 2005, 368 patients treated at Tianjin Tumor Hospital met the study criteria. The 5- and 8-year rates were 7.2% and 10.7% for locoregional recurrence (LRR), 85.1% and 77.7% for disease-free survival (DFS), and 92.8% and 89.3% for overall survival (OS). Multivariate Cox regression analysis showed that age, tumour size, estrogen receptor (ER) status, and lymphovascular invasion (LVI) were independent prognostic factors for LRR and DFS. Based on 4 patient-related factors that indicate poor prognosis (age < 40 years, tumour > 3 cm, ER negativity, and LVI), the high-risk group (patients with 3 or 4 factors, accounting for 12.5% of the cohort) had 5- and 8-year rates of 24.3% and 36.9% for LRR, 57.2% and 39.2% for DFS, and 74.8% and 43.8% for OS compared with 5.0% and 7.1% for LRR, 88.9% and 83.1% for DFS, 91.6% and 83.4% for OS in the low-risk group (patients with 0–2 factors, accounting for 87.5% of the cohort; $p < 0.001$).

### Conclusions

Our study identified several risk factors that correlated independently with a greater incidence of LRR and distant metastasis in patients with T1 and T2 breast cancer and 1–3 positive nodes. Patients with 0–2 risk factors may not be likely to benefit from post-mastectomy RT, but patients with 3–4 risk factors may need RT to optimize locoregional control and improve survival.

## KEY WORDS

Breast cancer, prognostic group, axillary lymph nodes, radiotherapy

## 1. INTRODUCTION

Modified radical mastectomy (MRM) is an important treatment for a significant number of patients with breast cancer, especially for those with more diffuse local disease[1]. The roles of adjuvant chemotherapy and hormonal treatment in prolonging survival have been established in numerous randomized trials[2], and the addition of radiotherapy (RT) after definitive mastectomy and systemic chemotherapy was demonstrated to improve locoregional control and overall survival in patients who have high-risk breast cancer.

At present, post-mastectomy RT (PMRT) is indicated for patients with advanced primary tumours larger than 5 cm or with 4 or more positive axillary nodes. A decision on PMRT for intermediate-risk breast cancer patients with T1–2 N1 tumours is usually based on discrepancies in the prognostic factors considered by radiation oncologists, and determining the factors that should be considered prognostic for risk is difficult. The NCIC Clinical Trials Group MA.25 study randomly assigned patients with 1–3 positive nodes to receive either locoregional RT or no RT after MRM, but unfortunately, the study was closed because of lack of accrual. The Danish Breast Cancer Cooperative Group 82b and 82c studies showed a substantial survival benefit with RT after mastectomy, with patients having N1 breast cancer and those having more than N2 breast cancer achieving similar results[3]. Based on the results of a systematic review of node-positive

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breast cancer treated with mastectomy in trials conducted by the National Surgical Adjuvant Breast and Bowel Project, not only tumour size and number of positive lymph nodes, but also age, menopausal status, and number of dissected lymph nodes were significant predictors for locoregional failure[4]. However, the role of PMRT in patients with tumours 5 cm or less in size and 1–3 positive nodes has not been widely accepted, and the long-term effect on overall survival (OS) of local tumour control improved by adjuvant PMRT continues to be debated. The answer awaits the results of future randomized trials[5].

In the present study, we investigated patterns of failure in patients with T1 or T2 N1M0 breast cancer treated with MRM but without PMRT, and we retrospectively analyzed the prognostic factors correlated with locoregional recurrence (LRR), distant metastasis, and survival to determine which patients do and do not benefit from PMRT. The institutional review board of Tianjin Tumor Hospital approved the study.

## 2. METHODS

Between May 2001 and April 2005, 723 female patients with unilateral stages 0–III T1 or T2 breast cancer with 1–3 positive axillary lymph nodes were treated with MRM at the Cancer Institute of Tianjin Tumor Hospital. Of those 723 patients, 355 (49%) received PMRT. Patients who had distant metastasis at diagnosis, those who had carcinoma *in situ,* those who had received neoadjuvant chemotherapy or PMRT, and those with less than 1 month of follow-up were excluded from the analysis. The remaining 368 patients were included.

The clinical records of the study patients were retrospectively reviewed to collect the necessary clinicopathologic data: age, primary tumour size, histologic type, nuclear grade, and estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) status. All patients had biopsy-proven invasive cancer, and all underwent MRM. When possible, re-excision was performed if margins were positive. Axillary lymph node dissection was performed in all patients, with a median of 19 nodes dissected (range: 5–53 nodes). The extent of the axillary lymph node dissection was usually confined to removal of level I and II nodes. If involved nodes at level II or III were suspected, dissection was extended to level III.

Systemic chemotherapy was given to 344 patients (93.5%). The regimens consisted of cyclophosphamide, methotrexate, and 5-fluorouracil; cyclophosphamide, doxorubicin or epirubicin, and 5-fluorouracil; or cyclophosphamide and doxorubicin. Hormonal therapy (tamoxifen in most cases) was given to patients whose tumours were positive for ER, PR, or both. If there was no evidence of recurrence during follow-up, hormonal therapy was routinely continued for 5 years.

Locoregional recurrence was defined as recurrence in the ipsilateral chest wall or in the axillary, supraclavicular, infraclavicular, or internal mammary lymph nodes. The LRR rates include all LRRs with or without previous or simultaneous distant metastasis. Disease at any other site was considered distant metastasis. Disease-free survival (DFS) was defined as the length of time before any evidence of LRR, distant metastasis, or breast cancer–related death by the end of follow-up. Overall survival was defined as the time from the date of MRM until death from any cause. Actuarial rates of total LRR, DFS, and OS were calculated by the Kaplan–Meier method. Comparisons of clinical and pathologic variables between patient groups were calculated using the log-rank test. The date of last follow-up was defined as the date of the last clinic visit at our centre, the date of the last clinical correspondence (letters and direct telephone calls to patients), or death. The Cox proportional hazards model was used for multivariate regression analyses. All $p$ values less than 0.05 were considered significant.

## 3. RESULTS

### 3.1 Patient Characteristics

Table I shows the clinical, pathologic, and treatment characteristics of the 368 study patients. Median age in the overall group was 50 years (range: 21–85 years). Median follow-up was 7.17 years (range: 0.75–10.5 years; 95% confidence interval: 7.23 to 7.52 years). Most patients (58.4%) had T2 tumours. The median number of lymph nodes removed in patients who underwent axillary dissection was 19 (range: 7–35; 95% confidence interval: 15.6 to 16.6). Tumours were ER-positive, PR-positive, or both in 226 patients; the remaining 142 patients had hormone receptor–negative disease. In 77 patients, tumours were HER2-positive, and in 238, they were HER2-negative. The remaining 53 patients were not tested for HER2 status. Most patients (93.5%) received adjuvant chemotherapy; 183 of the 226 patients with hormone receptor–positive disease received hormonal therapy. Only 14 patients received no systemic therapy.

### 3.2 Patterns of Recurrence

Breast cancer recurred in 72 patients, including 34 patients with LRR. The median time to LRR was 3.84 years (95% confidence interval: 3.26 to 3.84 years). Location of the LRR was the chest wall in 15 patients (44.1%); the supraclavicular lymph nodes in 10 patients (29.4%); the internal mammary chain in 2 patients (5.9%); and multiple synchronous locations in 7 patients (20.6%, 3 in the chest wall and supraclavicular region, 2 in the supraclavicular region and internal mammary chain, 1 in the chest wall and internal mammary chain, and 1 in the axillary nodal basin and supraclavicular region). In 16 patients

TABLE I Clinicopathologic characteristics of patients treated with modified radical mastectomy with and without adjuvant radiotherapy

| *Characteristic* | *Value* |
|---|---|
| Age (years) | |
| Median | 50 |
| Range | 21–85 |
| Age distribution [*n* (%)] | |
| ≤40 Years | 78 (21.2) |
| >40 Years | 290 (78.8) |
| Menopausal status [*n* (%)] | |
| Premenopausal | 160 (43.5) |
| Postmenopausal | 208 (56.5) |
| Tumour classification [*n* (%)] | |
| T1 | 153 (41.6) |
| T2 | 215 (58.4) |
| Pathologic type [*n* (%)] | |
| Invasive ductal carcinoma | 273 (74.2) |
| Others | 95 (25.8) |
| Positive lymph nodes [*n* (%)] | |
| Number positive | |
| 1 | 198 (53.8) |
| 2 | 94 (25.5) |
| 3 | 76 (20.7) |
| Axillary nodes positive | |
| ≤20% | 335 (91.0) |
| >20% | 33 (9.0) |
| Receptor status [*n* (%)] | |
| Estrogen | |
| Negative | 178 (48.4) |
| Positive | 190 (51.6) |
| Progesterone | |
| Negative | 195 (53.0) |
| Positive | 173 (47.0) |
| HER2 | |
| Negative | 238 (64.7) |
| Positive | 77 (20.9) |
| Not tested | 53 (14.4) |
| Lymphovascular invasion [*n* (%)] | |
| No | 296 (80.4) |
| Yes | 72 (19.6) |
| Grade [*n* (%)] | |
| I | 39 (10.6) |
| II | 259 (70.4) |
| III | 70 (19.0) |
| Adjuvant therapy [*n* (%)] | |
| Chemotherapy | |
| Yes | 344 (93.5) |
| No | 24 (6.5) |
| Hormonal therapy | |
| Yes | 183 (49.3) |
| No | 185 (50.3) |

HER2 = human epidermal growth factor receptor 2.

(47.1%), the LRR was the only recurrence event. In the other 18 patients, the LRR was diagnosed concurrently with distant metastasis (9 patients, 26.5%), before distant metastasis (8 patients, 23.5%), or after distant metastasis (3 patients, 8.8%). In the 56 patients with distant metastasis, the metastasis occurred in lung in 20 patients (35.7%), in bone in 13 patients (23.2%), in the contralateral breast in 3 patients (5.4%), in liver in 1 patient (1.8%), in brain in 1 patient (1.8%), and in multiple synchronous locations in 18 patients (32.1%).

### 3.3 Prognostic Factors for LRR and DFS

The 5- and 8-year cumulative rates of LRR in the entire patient cohort were 7.2% and 10.7% respectively; the 5- and 8-year cumulative rates of distant metastasis were 85.1% and 77.7% respectively; and the 5- and 8-year cumulative rates of OS were 92.8% and 89.3% respectively.

Univariate testing for the statistical significance of factors with prognostic implications (Table II) included age, T classification, tumour size, number of nodes examined, number of involved axillary nodes, ER status, PR status, HER2 status, presence of LVI in the primary tumour, nuclear grade, treatment with adjuvant chemotherapy, and treatment with adjuvant hormonal therapy. Factors of significance for LRR were age less than 40 years ($p = 0.047$), T2 classification ($p = 0.032$), ER negativity ($p = 0.021$), HER2 positivity ($p = 0.024$), and presence of LVI ($p = 0.001$). Factors of significance for DFS were age less than 40 years ($p = 0.014$), T2 classification ($p = 0.019$), ER negativity ($p = 0.015$), presence of LVI ($p = 0.019$), 3 positive nodes ($p = 0.045$), and no tamoxifen treatment ($p = 0.014$).

Multivariate Cox regression analysis showed that age (<40 years), tumour size (>3 cm), ER status (negative), and presence of LVI were independent prognostic factors for LRR and DFS (Table III).

### 3.4 Prognostic Groups for LRR, DFS, and OS

Using the 4 patient-related factors revealed to be prognostic by multivariate regression analysis, we allocated the patients to a high-risk (presence of 3 or 4 factors) and a low-risk group (presence of 0–2 factors). The 5- and 8-year LRR rates were 24.3% and 36.9% respectively in the high-risk group and 5.0% and 7.1% in the low-risk group ($p < 0.001$). The 5- and 8-year DFS rates were 57.2% and 39.2% respectively in the high-risk group and 88.9% and 83.1% in the low-risk group ($p < 0.001$). The 5- and 8-year OS rates were 74.8% and 43.8% respectively in the high-risk group and 91.6% and 83.4% in the low-risk group ($p < 0.001$, Table IV, Figure 1).

## 4. DISCUSSION

Postoperative irradiation including the supraclavicular area is a standard treatment for N2 breast cancer

patients after breast-conserving treatment or MRM[6,7]. However, the indications for PMRT in patients with pT1 or pT2 breast cancer and 1–3 positive lymph nodes is still controversial. So far, no trial dedicated to solving this issue has been conducted. Recent studies seem to suggest that there are subgroups at moderately high risk and at low risk for locoregional failure among patients with T1 or T2 breast cancer

TABLE II Univariate analysis of prognostic factors for locoregional recurrence (LRR) and disease-free survival (DFS)

| *Factor* | *LRR (%)* | | p *Value* | DFS (%) | | p *Value* |
|---|---|---|---|---|---|---|
| | *5-Year* | *8-Year* | | *5-Year* | *8-Year* | |
| Age distribution | | | | | | |
| ≤40 | 13.3 | 16.6 | 0.047 | 76.1 | 68.9 | 0.014 |
| >40 | 5.6 | 9.1 | | 87.6 | 80.3 | |
| Menopausal status | | | | | | |
| Yes | 8 | 12.5 | 0.224 | 84.2 | 78.4 | 0.863 |
| No | 6.7 | 9.2 | | 85.8 | 77.3 | |
| Tumour classification | | | | | | |
| T1 | 5.7 | 5.7 | 0.032 | 89.7 | 84.6 | 0.019 |
| T2 | 8.4 | 14.5 | | 81.8 | 72.5 | |
| Pathologic type | | | | | | |
| Invasive ductal carcinoma | 9.1 | 13 | 0.407 | 83.5 | 76.8 | 0.358 |
| Others | 6.6 | 9.8 | | 89.7 | 80.5 | |
| Positive lymph nodes | | | | | | |
| Number positive | | | | | | |
| 1 or 2 | 6.3 | 9.7 | 0.201 | 87.7 | 79.9 | 0.045 |
| 3 | 10.9 | 14.6 | | 75.5 | 69.8 | |
| Axillary nodes positive | | | | | | |
| ≤20% | 7 | 9.9 | 0.175 | 85.3 | 78.4 | 0.349 |
| >20% | 10.3 | 18.8 | | 83.1 | 70.5 | |
| Receptor status | | | | | | |
| Estrogen | | | | | | |
| Negative | 10.3 | 16 | 0.021 | 80.3 | 70.5 | 0.015 |
| Positive | 4.4 | 5.9 | | 89.6 | 84.1 | |
| Progesterone | | | | | | |
| Negative | 6.5 | 10.2 | 0.786 | 83.1 | 75.8 | 0.356 |
| Positive | 8 | 11.1 | | 87.3 | 80 | |
| HER2[a] | | | | | | |
| Negative | 5.8 | 8 | 0.024 | 86.2 | 79.7 | 0.208 |
| Positive | 11.1 | 19.7 | | 79.7 | 72 | |
| Lymphovascular invasion | | | | | | |
| No | 5.4 | 7.7 | 0.001 | 76.6 | 67.1 | 0.019 |
| Yes | 15.1 | 22.8 | | 87.2 | 80.4 | |
| Grade | | | | | | |
| I or II | 6.9 | 10.1 | 0.463 | 86.6 | 78.8 | 0.281 |
| III | 8.9 | 13 | | 78.9 | 73.4 | |
| Adjuvant therapy | | | | | | |
| Chemotherapy | | | | | | |
| Yes | 4.3 | 4.3 | 0.437 | 85 | 77.5 | 0.818 |
| No | 7.4 | 11.1 | | 87.5 | 82 | |
| Hormonal therapy | | | | | | |
| No | 7.5 | 12.3 | 0.254 | 83.2 | 71.5 | 0.014 |
| Yes | 7 | 9 | | 87 | 83.7 | |

[a] Testing for HER2 was not performed in 53 patients.
HER2 = human epidermal growth factor receptor 2.

TABLE III Multivariate analysis of prognostic factors for locoregional recurrence (LRR) and disease-free survival (DFS)

| *Factor* | *Comparison* | *LRR (%)* | | p *Value* | *DFS (%)* | | p *Value* |
|---|---|---|---|---|---|---|---|
| | | *HR* | *95% CI* | | *HR* | *95% CI* | |
| Age | >40 vs. ≤40 | 0.355 | 0.165 to 0.762 | 0.008 | 0.455 | 0.267 to 0.775 | 0.004 |
| Tumour classification | T2 vs. <T1 | 1.923 | 0.835 to 4.428 | 0.124 | 1.960 | 1.108 to 3.467 | 0.021 |
| Positive nodes (*n*) | 1 or 2 vs. 3 | 0.967 | 0.886 to 1.056 | 0.454 | 0.943 | 0.889 to 1.000 | 0.051 |
| ER status | Positive vs. negative | 0.355 | 0.161 to 0.783 | 0.010 | 0.441 | 0.262 to 0.740 | 0.002 |
| HER2 status | Positive vs. negative | 2.052 | 0.967 to 4.356 | 0.061 | 1.905 | 0.670 to 2.008 | 0.596 |
| Lymphovascular invasion | Positive vs. negative | 3.029 | 1.454 to 6.309 | 0.003 | 1.905 | 1.099 to 3.303 | 0.022 |

ER = estrogen receptor; HER2 = human epidermal growth factor receptor 2.

TABLE IV Five-year and eight-year locoregional recurrence (LRR), disease-free survival (DFS), and overall survival (OS) for the low-risk and high-risk patient groups

| *Risk group* | *Patients [n (%)]* | *LRR (%)* | | p *Value* | DFS (%) | | p *Value* | *OS (%)* | | p *Value* |
|---|---|---|---|---|---|---|---|---|---|---|
| | | *5-Year* | *8-Year* | | *5-Year* | *8-Year* | | *5-Year* | *8-Year* | |
| Low | 322 (87.5) | 5.0 | 7.1 | <0.001 | 88.9 | 83.1 | <0.001 | 91.6 | 83.4 | <0.001 |
| High | 46 (12.5) | 24.3 | 36.9 | | 57.2 | 39.2 | | 74.8 | 43.8 | |

and 1–3 positive lymph nodes. Various clinical and pathologic risk factors for such locoregional failure have been reported[8–12]: hormone receptor negativity[8,10,11], younger age (<40 or <45 years of age)[8,9], ratio of positive lymph nodes to dissected lymph nodes (25%)[8,12], presence of LVI[11], pT2[10], 2 or 3 positive lymph nodes (compared with 1 positive node)[10], and a medial tumour location[8].

In the present study, we found that age less than 40 years, tumour larger than 3 cm, ER negativity, and presence of LVI had a statistically significant effect on LRR and DFS. At our centre, the 8-year rates of LRR and DFS for younger patients (<40 years) were 16.6% and 68.9% respectively, which were higher than those in the group 40 years of age and older. Several other groups have found younger age to be associated with a significantly higher predicted risk of LRR[13,14]. Sharma and colleagues[15] and Yildirim and Berberoglu[16] reported that younger age was the only independent factor associated with the risk of LRR. In fact, older patients are known to be at less risk of relapse than are younger patients, because their tumours have more favourable biology[17,18]. The protective effect of hormone receptor positivity correlates closely with administration of hormonal therapy. In our research, ER positivity was also a protective factor with respect to both LRR and DFS. The 8-year rates for LRR and DFS in T2 disease at our centre were 17.5% and 72.5%, which imply that patients with T2 disease were more likely to experience LRR and distant metastasis. The T classification exerted a significant effect on LRR in multivariate analysis in studies originating from the Eastern Cooperative Oncology Group and the Netherlands[19,20]. Additional analysis for patients with a T1 or T2 primary tumour and 1–3 involved nodes again revealed the significant impact of tumour size on LRR[21–23]. The presence of LVI in the primary tumour in our study was significantly associated with a doubling of the 5- and 8-year local recurrence rates. Three studies from England, in which patients were treated with either mastectomy or lumpectomy followed by RT, all demonstrated that LVI was predictive of local recurrence[24], and patients with LVI were reported to frequently experience supraclavicular recurrence[25].

The number of prognostic factors was well correlated with observed risk. We analyzed the LRR rate and survival by risk group (high or low) and found that survival in the high-risk group was quite poor, with overall 8-year LRR, DFS, and OS rates of 36.9%, 39.2%, and 43.8%. In contrast, survival in the low-risk group was relatively optimistic, with an 8-year LRR of just 7.1% and an 8-year DFS of 83.1%.

It is generally assumed—and was well-described by the Early Breast Cancer Trialists' Collaborative Group—that a threshold of more than 10% for an absolute gain in the local recurrence rate within the first 5 years is needed before a survival benefit can be expected[2,26,27]. Considering its toxicity, PMRT could be skipped in the group of patients unlikely to achieve such a benefit[28–30]. Whether a reduction in LRR results in a reduction in distant metastasis is uncertain, but several reports have shown that a reduction in LRR is associated with a lower rate of distant metastasis.

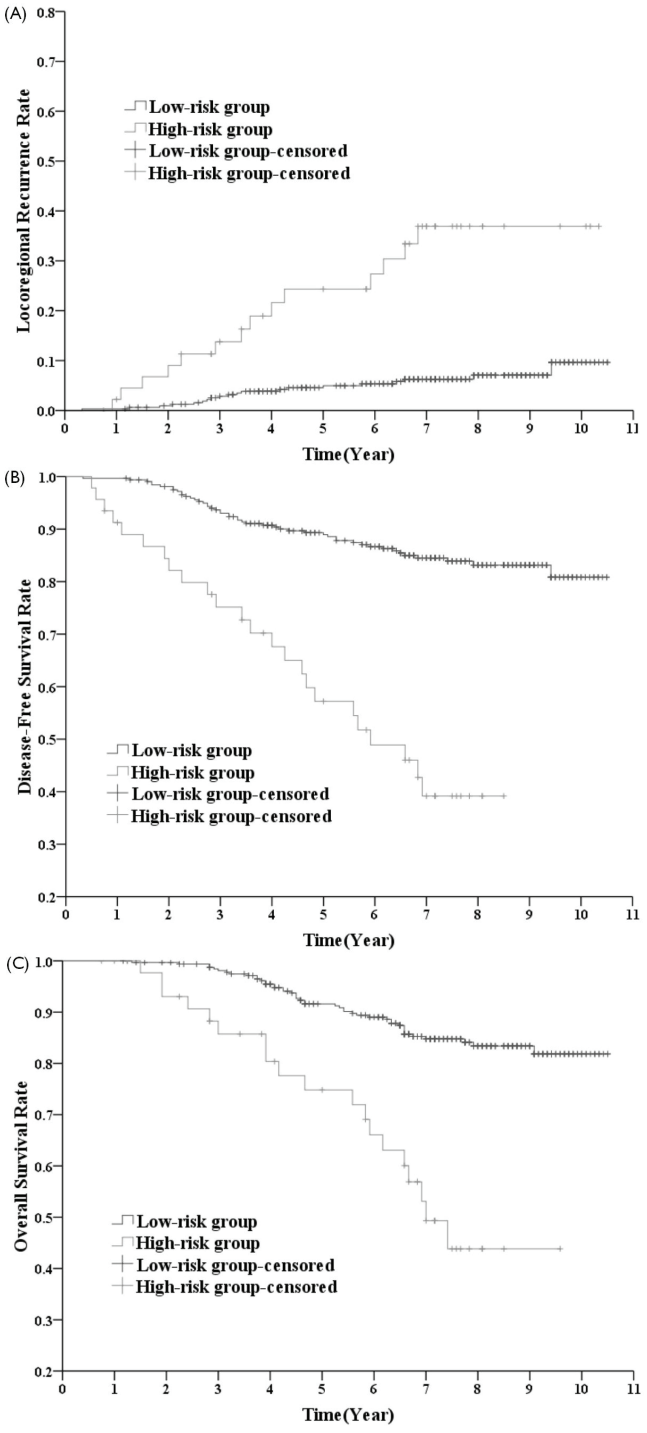


FIGURE 1 *Rates of (A) locoregional recurrence, (B) disease-free survival, and (C) overall survival for patients in the low- and high-risk groups.*

We believe that PMRT might reduce LRR in high-risk N1 patients and that it might therefore also reduce distant metastasis and improve survival.

Our study has certain limitations. First, it has inherent selection biases because of its retrospective nature, and in our centre, about 50% of patients with T1 and T2 breast cancer and 1–3 positive nodes received PMRT, which might influence the analysis. Second, other risk factors, such as high Ki-67 or extracapsular spread, were not taken into account in the regression analysis because their detection rates are still relatively low in our centre. However, because of the small sample size, none of those factors is likely to have emerged as significant in the study cohort. Third, patients in our study received level I–II axillary dissections, with a median of 19 nodes identified. Our results might therefore not be applicable to the new era of dissection guided by a sentinel node.

## 5. CONCLUSIONS

Our population-based study identified a subset of patients with T1 and T2 breast cancer and 1–3 positive nodes in whom the 8-year rate of LRR was more than 30%, which contrasts with the 10% incidence seen in the overall population at our centre. The risk factors of younger age (<40 years), larger tumour (>3 cm), ER negativity, and the presence of LVI are significant for post-mastectomy LRR, and patients with 3 or 4 of those factors have a significantly higher risk of LRR and DFS.

With respect to treatment morbidity and the costs of PMRT in this specific disease group, patients at low risk (0–2 of the factors) might not be likely to benefit from such therapy. Patients at high risk (3–4 of the factors) might need PMRT to optimize locoregional control and to improve survival. Randomized trials are warranted to determine the potential benefit of PMRT on locoregional control and survival in patients with a T1 or T2 primary tumour and 1–3 positive nodes.

## 6. ACKNOWLEDGMENT

This study was supported by the Anticancer Key Technologies R&D Program of Tianjin (grant no. 12ZCDZSY16200).

## 7. CONFLICT OF INTEREST DISCLOSURES

The authors have no financial conflicts of interest to declare.

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