

Locoregional recurrence of pT3N0M0 breast cancer after mastectomy is not higher than that of pT1-2N0M0: An analysis for radiotherapy

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The purpose of this study was to investigate the value of post-operative radiotherapy in the treatment of pT3N0M0 breast cancer after mastectomy. We analyzed the clinical data of 1390 patients with pT1-3N0M0 breast cancer who were admitted and treated from 1998 to 2007 at the Sun Yat-sen University Cancer Center. All patients underwent mastectomy and did not receive radiotherapy. The locoregional recurrence-free survival, distant metastasis-free survival and overall survival of different T stages of breast cancer were compared. The median follow-up duration was 72 months. The 10-year locoregional recurrence-free survival patients with pT1N0, pT2N0 and pT3N0 breast cancers were 95.3, 91.9 and 93.6%, respectively ($\chi^2 = 2.550$, $P = 0.279$). The 10-year distant metastasis-free survival rates of patients with pT1N0, pT2N0 and pT3N0 breast cancers were 88.1%, 81.0% and 78.4%, respectively ($\chi^2 = 8.254$, $P = 0.016$). The 10-year overall survival rates of patients with pT1N0, pT2N0 and pT3N0 breast cancers were 91.9%, 83.5% and 73.0%, respectively ($\chi^2 = 12.403$, $P = 0.002$). Univariate analyses failed to identify any prognostic factors for locoregional recurrence in pT3N0 patients. Multivariate analysis showed that the T stage had no effect on locoregional recurrence. The locoregional recurrence rate in patients with pT3N0M0 breast cancer who underwent mastectomy and did not receive postoperative radiotherapy was not higher than that in patients with pT1-2N0M0 breast cancer who received the same treatment, suggesting that routine adjuvant post-operative radiotherapy should not be recommended in this patient population. (*Cancer Sci* 2013; 104: 599–603)

Breast-conserving surgery and mastectomy are two of the standard surgical options for primary treatment of invasive breast cancers. Randomized trials have shown that patients with axillary lymph node-positive breast cancer benefit from post-operative radiotherapy,^(1–3) but the value of post-operative adjuvant radiotherapy for axillary lymph node-negative breast cancer remains controversial, particularly for pT3N0M0 patients. Existing clinical guidelines vary in therapeutic protocols for pT3N0M0 breast cancer patients. The American Society of Clinical Oncology recommended in 2001 that post-operative radiotherapy should be applied to patients with pT3N0M0.⁽⁴⁾ Some studies published by European, American and Chinese authors also support the use of post-operative radiotherapy for pT3N0M0 patients.^(5,6) However, the American College of Radiology expert panel for breast cancer recommended in 2009 that post-operative radiotherapy should be used for pT3N1M0 but not for pT3N0M0 patients.⁽⁷⁾ The National Comprehensive Cancer Network (NCCN) guidelines listed pT3N0M0 as an absolute indication for post-operative radiotherapy prior to 2010, but the wording has changed to “consider” since 2011. Therefore, further studies are required

to evaluate the value of post-mastectomy radiotherapy in pT3N0M0 breast cancers.

This study aimed to explore the value of post-mastectomy radiotherapy in patients with pT3N0M0 breast cancer undergoing mastectomy by comparing the locoregional recurrence and survival rates in patients with pT3N0M0 and pT1-2N0M0 breast cancers who underwent total mastectomy and did not receive post-operative radiation therapy.

Materials and Methods

Study subjects and inclusion criteria. We retrospectively analyzed the clinicopathological data of 3759 patients treated at the Sun Yat-sen University Cancer Center from January 1998 to December 2007. The subjects were selected based on the following criteria: female; unilateral breast cancer; completion of mastectomy and axillary lymph node dissection; post-mastectomy pathological stage of pT1-3N0M0 according to the 2009 Union for International Cancer Control/American Joint Committee on Cancer diagnosis criteria; complete dissection of tumor without positive surgical margins as indicated by pathological results; no pre-operative adjuvant therapy or post-operative adjuvant radiotherapy; and no serious accompanying disease. A total of 1390 patients were included in the study. All patients provided written informed consent for use of their clinicopathological data for research and the study was approved by the Ethics Committee of the Sun Yat-sen University Cancer Center.

Clinical data and treatment protocols. The median age of onset of breast cancer was 47 years (19–90 years). All patients underwent mastectomy and axillary lymph node dissection after a definite diagnosis was made. The median size of the primary tumor was 2.5 cm (0.5–10 cm). There were 557 cases (40.1%), 764 cases (55.0%) and 69 cases (4.9%) of pT1N0, pT2N0 and pT3N0, respectively. The median numbers of axillary lymph nodes removed in the patients with pT1N0, pT2N0 and pT3N0 breast cancers were 13 (1–34), 14 (1–36) and 12 (4–28), respectively. The following prognostic factors were evaluated: age (<35 years of age vs ≥ 35 years of age); menstruation status (pre-menopausal versus post-menopausal); estrogen receptor (ER) status (negative versus positive); progesterone receptor (PR) status (negative versus positive); human epidermal growth factor receptor 2 (Her2) status (negative versus positive); number of axillary lymph nodes removed (<10 vs ≥ 10); adjuvant chemotherapy regimen (cyclophosphamide, methotrexate and fluorouracil [CMF] regimen versus taxane-based and/or anthracycline-based regimen). The clinical

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Table 1. Patient and tumor characteristics (n = 1390)

Characteristics	n (%)	T1 n (%)	T2 n (%)	T3 n (%)	P
	1390	557 (40.1)	764 (55.0)	69 (4.9)	
Age (years)					
<35	110 (7.9)	35 (6.3)	69 (9.0)	6 (8.7)	0.183
≥ 35	1280 (92.1)	522 (93.7)	695 (91.0)	63 (91.3)	
Menopausal status					
Premenopausal	896 (64.5)	352 (63.2)	494 (64.7)	50 (72.5)	0.312
Postmenopausal	494 (35.5)	205 (36.8)	270 (35.3)	19 (27.5)	
ER status					
Negative	564 (40.6)	195 (35.0)	331 (43.3)	38 (55.1)	<0.001
Positive	826 (59.4)	362 (65.0)	433 (56.7)	31 (44.9)	
PR status					
Negative	500 (36.0)	180 (32.3)	287 (37.6)	33 (47.8)	0.016
Positive	890 (64.0)	377 (67.7)	477 (62.4)	36 (52.2)	
Her2 status					
Negative	1057 (76.0)	436 (78.3)	583 (76.3)	38 (55.1)	<0.001
Positive	333 (34.0)	121 (21.7)	181 (23.7)	31 (44.9)	
Chemotherapy					
CMF	236 (17.0)	88 (15.8)	135 (17.7)	13 (18.8)	0.870
Taxane and/or anthracycline	881 (83.0)	345 (84.2)	488 (82.3)	48 (81.2)	

CMF, cyclophosphamide, methotrexate and fluorouracil; ER, estrogen receptor; PR, progesterone receptor.

and pathological characteristics of the patients are shown in Table 1.

After surgery, 1117 patients (80.4%) received adjuvant chemotherapy, of which 236 cases (17.0%) were treated with CMF chemotherapy and 881 cases (63.4%) received anthracycline-based and/or taxane-based chemotherapy. The median number of chemotherapy cycles was 6 (1–8 cycles). Adjuvant chemotherapy was not carried out in 273 patients (19.6%). Endocrine therapies were adopted in 971 cases (69.9%), including all the ER-positive and/or PR-positive patients as well as some patients with negative receptor statuses. Herceptin-targeted therapy was applied in eight patients with Her2-positive tumors.

Follow up and method. All patients were followed up at the outpatient clinic or by phone consultation. The first day after surgery was the starting date of the follow up. The primary study endpoints included locoregional recurrence-free survival (LRFS; LRFS ± DMFS), distant metastasis-free survival (DMFS) and overall survival (OS). Locoregional recurrence referred to recurrent lesions in the ipsilateral chest wall and lymph nodes in the supra-clavicular and infra-clavicular fossa, the axillary area and the internal mammary region, confirmed by biopsy, the absence of distant metastasis, or occurrence of distant metastasis after at least 3 months. Distant metastasis refers to the spread of cancer to distant sites from locoregional recurrence sites, which was confirmed by two types of medical imaging tests, and pathology, if necessary. The mortality endpoint was defined as breast cancer-related death.

Statistical analysis. All data were analyzed using the spss 16.0 statistical software package (SPSS Inc., Chicago, IL, USA). The Kaplan–Meier method was used to generate the survival curves and to compare the survival rates. The differences between groups were evaluated using the log-rank test. Cox regression analysis was used for both univariate and multivariate analysis. The statistical significance level was set at 0.05.

Results

Overall survival. The median follow-up duration was 72 months (3–156 months). Locoregional recurrence occurred in 70 patients. There were 36 cases (51.4%) of relapse within the chest wall only, 19 cases (27.1%) in the supra-clavicular fossa only, four cases (5.7%) in the axillary only, two cases (2.9%) in

the infra-clavicular fossa only, and nine cases (12.9%) with relapses in more than two of the abovementioned locations. The 5- and 10-year LRFS rates were 95.2% and 93.3%, respectively. The median recurrence time was 29.6 months (5–98 months), with 35.2 months (9–79 months), 28.8 months (5–98 months) and 21.1 months (3–31 months) for patients with T1, T2 and T3 tumors, respectively. Distant metastasis occurred in 161 cases. The 5- and 10-year DMFS rates were 90.2% and 83.8%, respectively. The 5- and 10-year disease-free survival rates were 88.5% and 81.6%, respectively. A total of 119 patients died. The 5- and 10-year OS rates were 93.5% and 86.0%, respectively.

Survival of different T stages and prognosis analysis. There were no significant differences in LRFS among patients with pT1N0M0, pT2N0M0 and pT3N0M0 tumors. The corresponding 5- and 10-year LRFS rates were 95.7 and 95.3%, 94.9 and 91.9%, and 93.6 and 93.6%, in each patient group with pT1N0M0, pT2N0M0 and pT3N0M0 tumors, respectively ($\chi^2 = 2.550$, $P = 0.279$; Fig. 1). The 5- and 10-year DMFS rates in the three patient groups were 91.6 and 88.1, 89.5 and 81.0%, and 87.0 and 78.4%, respectively ($\chi^2 = 8.254$, $P = 0.016$; Fig. 2). The 5- and 10-year OS rates in the three patient groups were 94.4 and 91.9%, 93.4 and 83.5%, and 86.5 and 73.0%, respectively ($\chi^2 = 12.403$, $P = 0.002$; Fig. 3). The Cox univariate analysis (Tables 2,3) failed to identify any prognostic factors for LRFS in patients with pT3N0 tumors, but the results showed that the number of lymph nodes removed was a prognostic factor for improved OS. Hormone receptor status, age, number of lymph nodes removed and chemotherapy regimen were found to be prognostic factors for LRFS and better OS rates in patients with pT1N0M0 and pT2N0M0 tumors. The Cox multivariate analysis (Table 4) showed that age, instead of T stage, affected locoregional recurrence. Age, T stage and chemotherapy regimen were found to be independent prognostic factors for better OS.

Discussion

Adjuvant post-operative radiotherapy is currently recommended after mastectomy for pT3N0M0 breast cancer based on the results of the Danish Breast Cancer Cooperative Group 82b and 82c trials.^(1,2) In the present study, we found that the

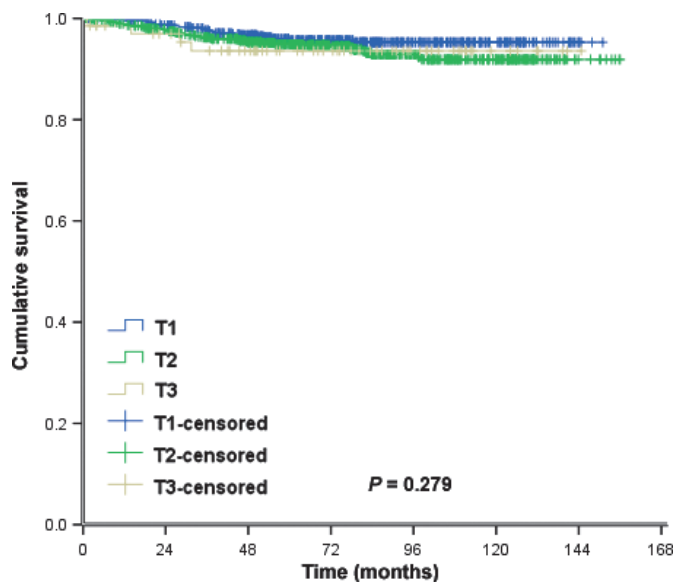


Fig. 1. Locoregional recurrence-free survival.

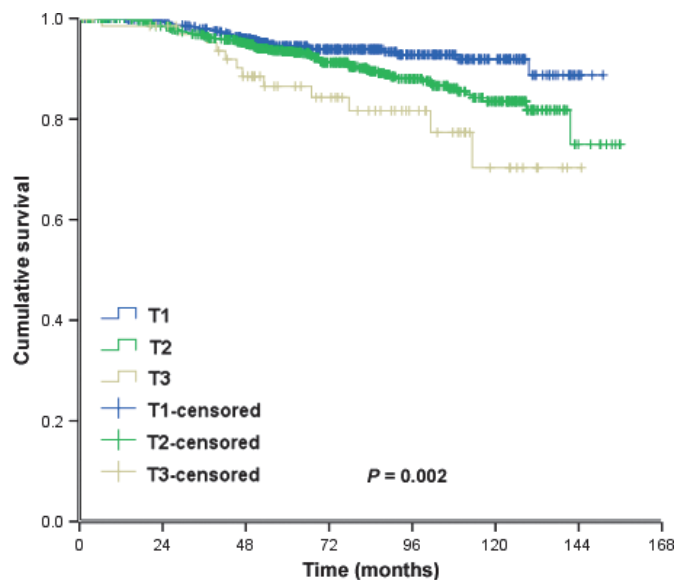


Fig. 3. Overall survival.

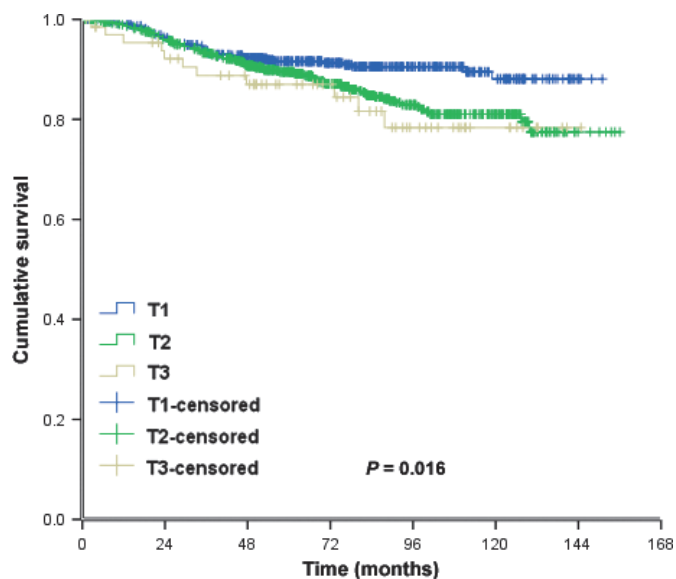


Fig. 2. Distant recurrence-free survival.

locoregional recurrence rates were similar in patients with pT3N0 and pT1-2N0 tumors. The 10-year locoregional recurrence rates in both groups were less than 10%. Our results also showed no increase in the locoregional recurrence rate with enlargement of the primary tumor, whereas the OS of the patients was affected primarily by distant failure.

At present, research is focused on the effect of positive lymph node status on local recurrence in patients with large tumors (≥ 5 cm), instead of the increased locoregional recurrence caused by the large tumors themselves. The American College of Radiology expert panel for breast cancer has recommended radiotherapy for only the patients with pT3N1M0, but not those with pT3N0M0, tumors. Nagao *et al.*⁽⁷⁾ report that in patients with tumor sizes ≥ 5 cm, the locoregional recurrence rate was lower in axillary lymph node-negative patients than in lymph node-positive patients (1.6 vs 10.1%).⁽⁸⁾ Our study compared the locoregional recurrence rate in

patients with pT1N0 M0, pT2N0M0 and pT3N0M0 tumors and found that the size of primary tumor did not have any effect on the locoregional recurrence rate. The 10-year locoregional recurrence rates were less than 10% in all groups, which is consistent with the report of Mignano *et al.*⁽⁹⁾ In addition, in a study reported by Goulart *et al.*⁽¹⁰⁾ on the effect of adjuvant post-operative radiotherapy in axillary lymph node-negative breast cancer patients with tumor sizes ≥ 5 cm, the 10-year locoregional recurrence rate was 2.3 and 8.9% ($P = 0.2$), and the 10-year breast cancer survival rate was 85.8 and 74.6% ($P = 0.24$) in the radiotherapy and non-radiotherapy groups, respectively.

Two database analyses of Surveillance, Epidemiology and End Results showed that post-operative radiotherapy was unable to improve the survival rate, with only one subgroup analysis suggesting that radiotherapy may increase the 10-year OS (70.7 vs 58.4%, $P < 0.001$) in patients over 50 years.^(11,12) Goulart *et al.*⁽¹⁰⁾ show that recurrence in the non-radiotherapy group occurs primarily in patients with pathologic stage III tumors who did not receive endocrine therapies. In a study conducted by Hamamoto *et al.* (2010), the locoregional recurrence rate was only 7% in patients with pT3N0 tumors, and the 8-year locoregional recurrence rate was significantly higher in patients ≤ 40 years than in those >40 years (27 vs 2%, $P = 0.0135$), suggesting that adjuvant post-operative radiotherapy may be appropriate for some pT3N0 patients with a high risk of recurrence.⁽¹³⁾ However, the risk factors vary in different studies. The present study did not identify any risk factor for recurrence. Therefore, further studies are needed to identify risk factors for recurrence in specific subsets of patients.

Based on the data from the above studies, the locoregional recurrence rate is not high in pT3N0 patients, and post-operative radiotherapy cannot enhance the survival rate. This might explain why the NCCN changed the wording from “indication” to “recommendation” for radiotherapy for patients with pT3N0M0 tumors. Although significant progress has been made in modern radiation therapy, long-term cardiopulmonary function impairment induced by radiotherapy after breast cancer surgery should not be ignored. The 10-year locoregional recurrence rate was $<10\%$ in patients with pT3N0M0 tumors in the present study. Following the recommendation that post-operative

Table 2. Univariate analysis of the impact of locoregional recurrence-free survival according to different pT stage

Characteristics	T1		T2		T3	
	HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>
Age (years)						
≥ 35 vs <35	0.395 (0.117–1.336)	0.135	0.370 (0.178–0.771)	0.008*	0.410 (0.179–1.335)	0.668
Menopausal status						
Pre versus post	0.834 (0.340–2.045)	0.691	0.784 (0.410–1.499)	0.462	0.029 (0.001–27.21)	0.450
ER status						
Positive/unknown versus negative	0.595 (0.340–2.045)	0.225	0.596 (0.329–1.079)	0.088	0.417 (0.043–4.006)	0.448
PR status						
Positive/unknown versus negative	0.383 (0.166–0.887)	0.025*	0.541 (0.300–0.978)	0.042*	2.746 (0.286–26.406)	0.382
Her2 status						
Positive/unknown versus negative	1.438 (0.563–3.676)	0.448	0.558 (0.236–1.321)	0.184	0.326 (0.034–3.144)	0.332
Nodes removed (n)						
≥ 10 vs <10	0.848 (0.313–2.299)	0.746	0.466 (0.244–0.890)	0.021*	0.257 (0.036–1.827)	0.175
Chemotherapy						
Taxane and/or anthracycline versus CMF	0.633 (0.243–1.651)	0.350	0.749 (0.356–1.576)	0.446	0.248 (0.035–1.769)	0.164

**P* < 0.05, indicates a significant difference. CI, confidence interval; CMF, cyclophosphamide, methotrexate and fluorouracil; ER, estrogen receptor; HR, hazards ratio; PR, progesterone receptor.

Table 3. Univariate analysis of the impact of overall survival according to different pT stages

Characteristics	T1		T2		T3	
	HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>	HR (95% CI)	<i>P</i>
Age (years)						
≥ 35 vs <35	0.632 (0.193–2.072)	0.449	0.657 (0.326–1.321)	0.238	0.653 (0.142–3.008)	0.584
Menopausal status						
Pre versus post	0.917 (0.444–1.892)	0.814	1.561 (0.986–2.472)	0.058	1.028 (0.275–3.851)	0.967
ER status						
Positive/unknown versus negative	0.383 (0.192–0.765)	0.007*	0.688 (0.436–1.086)	0.108	0.302 (0.081–1.135)	0.076
PR status						
Positive/unknown versus negative	0.414 (0.208–0.822)	0.012*	0.579 (0.367–0.915)	0.019*	0.363 (0.108–1.217)	0.101
Her2 status						
Positive/unknown versus negative	2.027 (0.978–4.201)	0.057	1.218 (0.703–2.098)	0.486	0.886 (0.271–2.893)	0.841
Nodes removed (n)						
≥ 10 vs <10	1.403 (0.541–3.634)	0.486	0.554 (0.331–0.926)	0.024*	0.226 (0.072–0.706)	0.010*
Chemotherapy						
Taxane and/or anthracycline versus CMF	1.327 (0.524–3.360)	0.550	0.468 (0.264–0.830)	0.009*	0.704 (0.192–2.573)	0.595

**P* < 0.05, indicates a significant difference. CI, confidence interval; CMF, cyclophosphamide, methotrexate and fluorouracil; ER, estrogen receptor; HR, hazards ratio; PR, progesterone receptor.

Table 4. Multivariate Cox regression analysis for locoregional recurrence-free survival and overall survival

Characteristic	LRFS			OS		
	HR	95% CI	<i>P</i>	HR	95% CI	<i>P</i>
Age (years)						
≥ 35 vs <35	0.431	0.212–0.875	0.020*	0.491	0.266–0.907	0.023*
Menopausal status						
Pre versus post	0.926	0.492–1.746	0.813	1.269	0.784–2.053	0.333
Tumor stage						
T2 versus T1	1.110	0.635–1.941	0.715	1.105	0.695–1.757	0.673
T3 versus T1	1.356	0.456–4.039	0.584	2.372	1.169–4.814	0.017
ER status						
Positive/unknown versus negative	0.600	0.293–1.231	0.164	0.685	0.381–1.234	0.208
PR status						
Positive/unknown versus negative	0.772	0.375–1.591	0.483	0.731	0.404–1.320	0.298
Her2 status						
Positive/unknown versus negative	0.642	0.323–1.278	0.207	1.157	0.705–1.899	0.563
Nodes removed (n)						
≥ 10 vs <10	0.668	0.364–1.227	0.194	0.685	0.421–1.112	0.126
Chemotherapy						
Taxane and/or anthracycline versus CMF	0.677	0.379–1.209	0.188	0.593	0.372–0.945	0.025*

**P* < 0.05, indicates a significant difference. CI, confidence interval; CMF, cyclophosphamide, methotrexate and fluorouracil; ER, estrogen receptor; HR, hazard ratio; LRFS, locoregional recurrence-free survival; OS, overall survival; PR, progesterone receptor.

radiotherapy should be performed in patients with a locoregional recurrence rate >20%,⁽¹⁴⁾ adjuvant post-operative radiotherapy should not be recommended for patients with pT3N0M0 breast cancers. However, our study was a retrospective analysis with a limited number of study subjects. Large randomized clinical trials are still needed to determine the exact value of post-operative radiotherapy for pT3N0M0 breast cancer patients.

The adjuvant chemotherapy and endocrine therapy regimens of the Danish Breast Cancer Cooperative Group 82b and 82c trials are currently inadequate for invasive breast cancers.^(1,2) Taghian *et al.*⁽¹⁵⁾ applied adjuvant chemotherapy and endocrine therapies, achieving a 10-year locoregional recurrence rate of 7.0 and 7.2% in patients with tumor size <5 cm and >5 cm, respectively ($P = 0.9$). Mignano *et al.*⁽⁹⁾ report that no locoregional recurrence was found in patients who received adjuvant chemotherapy. In this study, the majority of patients with pT3N0 were treated with taxane-based and/or anthracycline-

based chemotherapy, and the 10-year locoregional recurrence rate was only 6.4%. Treatment failure was mostly due to distant metastasis that affected the OS. Therefore, adjuvant treatment may exert more significant beneficial effects in pT3N0M0 patients with the advance in such treatment.

In summary, our results show that the locoregional recurrence rate in patients with pT3N0M0 breast cancer who underwent mastectomy and did not receive post-mastectomy radiotherapy was not higher than that in pT1-2N0M0 patients who received the same treatment, suggesting that it might be inappropriate to routinely recommend adjuvant post-operative therapy in this patient population. However, large randomized clinical trials are needed to confirm this conclusion.

Disclosure Statement

The authors have no conflict of interest to declare.

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