Cancer Management and Research

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ORIGINAL RESEARCH

Locoregional recurrence-associated factors and risk-adapted postmastectomy radiotherapy for breast cancer staged in cT1-2N0-1 after neoadjuvant chemotherapy

This article was published in the following Dove Press journal:
Cancer Management and Research

Xin Wang
Liming Xu
Zhenzhen Yin
Daquan Wang
Qi Wang
Kunpeng Xu
Jinlin Zhao,
Lujun Zhao
Zhiyong Yuan
Ping Wang

Department of Radiation Oncology, Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Key Laboratory of Cancer Prevention and Therapy, Tianjin, Tianjin's Clinical Research Center for Cancer, Key Laboratory of Breast Cancer, Prevention and Therapy, Tianjin Medical University, Ministry of Education, Tianjin, 300060, China

Objective: In order to identify risk factors associated with locoregional recurrence (LRR) and assess the role of postmastectomy radiotherapy (PMRT) in early breast cancer (BC), managed with neoadjuvant chemotherapy (NAC) and mastectomy, a retrospective analysis of BC diagnosed with clinical stage T1-2N0-1 was conducted.

Patients and methods: A total of 217 patients were included in this analysis. The median age was 50 years (24–72 years). The clinical stage distributions were cT1 in 15 cases, cT2 in 202, cN0 in 53, and cN1 in 161 cases. All patients were treated with NAC and mastectomy, and 128 patients received PMRT.

Results: With a median follow-up time of 61 months, the 5-year cumulative LRR rate was 12%. Multivariate analysis demonstrated that pathological N stage, lymph-vascular invasion, and histological grade were independent prognostic factors associated with LRR. A nomogram model based on these factors was established, based on which the patients were deeply stratified into low- and high-risk group. In the low-risk group, radiotherapy did not decrease LRR (3.3% in PMRT group, 1.7% in no PMRT group, P=0.192). While in the high-risk group, PMRT significantly decreased LRR (21.8% in PMRT group, 42.2% in no PMRT group, P=0.031).

Conclusion: Lymph-vascular invasion, histological grade, as well as pathological N stage were important prognostic factors associated with LRR in BC patients staged in cT1-2N0-1, who were managed with NAC and mastectomy. In our cohort, not only clinical and pathological stage information but also other risk factors were taken into consideration when adjuvant PMRT was recommended. In the high-risk subgroup, PMRT significantly improved the prognosis.

Keywords: breast cancer, neoadjuvant chemotherapy, postmastectomy radiotherapy, prognosis

Introduction

In recent decades, neoadjuvant chemotherapy (NAC) has become common for treatment of breast cancer (BC). With the downstage of NAC, some inoperable diseases may regain chances of surgery, and those who would have originally required mastectomy maybe able to undergo breast-conserving surgery (BCS).[1–5] Therefore, NAC has been used for locally advanced diseases and also early-staged BC.[6,7] However, there were also some concerns of NAC such as cancer may progress, potential of over- or under-treatment, and limited evidence base to guide adjuvant treatment. Furthermore, upfront surgery followed by adjuvant chemotherapy assured an accurate assessment of disease at the time of initial treatment. Due to the inconsistency of clinical evaluation of the disease extent both at diagnosis and post-NAC, the evaluation of locoregional

Correspondence: Ping Wang
Department of Radiation Oncology, Tianjin Medical University Cancer Institute and Hospital, National Clinical Research Center for Cancer, Key Laboratory of Cancer Prevention and Therapy, Tianjin, Tianjin's Clinical Research Center for Cancer, Key Laboratory of Breast Cancer Prevention and Therapy, Tianjin Medical University, Ministry of Education, Huanhuxi Road, Tianjin 300060, China
Tel +86 186 2222 1112
Fax +86 22 2334 5607
Email wangping@tjmuch.com

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http://dx.doi.org/10.2147/CMAR.S173628

recurrence (LRR) risks becomes more complex. Though it is well established that patients with stage III/IV, or positive node ≥4, harboring high LRR rates and postmastectomy radiotherapy (PMRT) show significantly reduced LRR and improved survival,[8–12] there is little information available on stage I–II disease after NAC and mastectomy. For cT1-2N0-1 disease, even in the adjuvant settings, the value of PMRT has remained an issue of controversy until now. The addition of NAC in this subgroup will significantly mask the indication for PMRT and complicate the situation. LRR risks at the time of presentation and post-NAC, as well as biologic response to NAC, should be taken into consideration. This may lead to the recommendation of PMRT in early BC after NAC is determined on a case-by-case basis.

In order to evaluate the LRR rate and identify associated risk factors, a retrospective analysis of cT1-2N0-1 BC post-NAC and mastectomy was conducted, helping to provide some evidence for the recommendation of adjuvant PMRT.

Patients and methods

Patient characteristics

Patients with BC staged in cT1-2N0-1M0 and treated with mastectomy after NAC in our institute between 2011 and 2013 were retrospectively analyzed. All patients underwent mammography and breast ultrasonography prior to chemotherapy. Clinical nodal status was determined by physical examination and ultrasound. Patients with distant metastasis, inflammatory or bilateral breast cancer, and previous or concurrent malignancy were excluded. A total of 217 patients met the inclusion criteria. The clinical stage was determined according to American Joint Committee on Cancer criteria (seventh edition). The clinical stage distributions were cT1 in 15, cT2 in 202, cN0 in 53, and cN1 in 164 patients. This study was approved by Tianjin Medical University Cancer Institute and Hospital's Ethics Committee. And a waiver for individual patients' consent for this retrospective study was also obtained from this committee. To maintain confidentiality, relevant medical records, laboratory results, images, and histopathological data were collected anonymously. The records of patients were kept confidential, and individuals outside this research team had no access to them.

Treatment details

NAC regimes consisted of anthracycline and taxane chemotherapy (82% of cases) and cyclophosphamide, methotrexate, and fluorouracil (12% of cases). All patients underwent mastectomy after NAC, with a median dissected lymph node number of 22. PMRT was determined by patient and her radiation oncologist; 128 (59%) patients received PMRT and 89 (41%) patients did not. Treatment volumes included the chest wall and regional nodal basins (high axilla and supraclavicular fossa, with or without the internal mammary chain). Dose prescription was 50 Gy in 25 fractions. Additionally, 213 cases (98%) received adjuvant chemotherapy and the median number of chemotherapy (NAC + adjuvant chemotherapy) cycles was 6. In cases of hormone receptor positive (estrogen and/or progesterone receptor positive), 122 cases (73%) were treated with endocrine therapy.

Statistical analysis

LRR was defined as disease recurrence on the ipsilateral chest wall or ipsilateral axillary, supraclavicular, infraclavicular, or internal mammary lymph nodes. Time to follow-up was calculated from the date of diagnosis. The LRR rates were calculated using the Kaplan–Meier method. Univariate and multivariate analyses were performed using the Cox proportional hazards model. Factors with P-value <0.05 were included in multivariate analysis. According to the final set of the Cox regression model, a prognostic nomogram to predict risks of LRR was developed, and the accuracy of the prognostic model was evaluated using the concordance index (C-index). SPSS version 20.0 software and R version 3.3.2 were used for all statistical analyses.

Results

Patient characteristics and treatment data

Patient characteristics and treatment data are summarized in Table 1. When compared with patients who did not receive PMRT, a greater percentage of irradiated patients had more advanced clinical N-stage (P=0.004), clinical stage (P=0.040), and ypN stage (P=0.000). No difference between the two groups was observed in other clinical–pathological factors (Table 1).

Follow-up and patterns of failures

With a median follow-up of 61 months, the 5-year cumulative rate of locoregional recurrence-free survival (LRFS), distant metastasis-free survival, disease-free survival, and overall survival rates were 88%, 79%, 73%, and 81%, respectively. Twenty-six patients (12%) developed LRR, and the most common site of LRR was chest wall (17 patients, 65%), followed by the supraclavicular lymph node (nine patients, 35%). Axillary nodal and inner mammary nodal failure occurred in three patients each. Eleven patients presented with isolated LRR, and other 15 patients also experienced distant metastases (Figure 1).

Table 1 Patients' clinical–pathological characteristics and treatment data

Characteristics	Total	No PMRT (89 patients)		PMRT (128 patients)		*P*-value
		No.	(%)	No.	(%)	
Age group (years)						0.218
≤50	111	41	46.1	70	54.7	
>50	106	48	53.9	58	45.3	
Menopausal status						0.213
Premenopause	126	49	55.1	77	60.2	
Postmenopause	89	38	42.7	51	39.8	
Unknown	2	2	2.2	0	0.0	
Clinical T stage						1.000
T1	15	6	6.7	9	7.0	
T2	202	83	93.3	119	93.0	
Clinical N stage						0.004
N0	53	31	34.8	22	17.2	
N1	164	58	65.2	106	82.8	
Clinical stage						0.040
I	5	4	4.5	1	0.8	
IIa	58	29	32.6	29	22.7	
IIb	154	56	62.9	98	76.6	
NAC cycles						0.214
<4	105	48	53.9	57	44.5	
≥4	112	41	46.1	71	55.5	
ypT stage						0.069
ypT0–2	200	86	96.6	114	89.1	
ypT3–4	17	3	3.4	14	10.9	
ypN stage						0.000
ypN0	58	42	47.2	16	12.5	
ypN1	61	38	42.7	23	18.0	
ypN2–N3	98	9	10.1	89	69.5	
Histological grade						0.257
1	2	2	2.2	0	0.0	
2	178	69	77.5	109	85.2	
3	17	8	9.0	9	7.0	
Unknown	20	10	11.2	10	7.8	
LVI						0.252
Yes	21	6	6.7	15	11.7	
No	196	83	83.3	113	88.3	
ER status						0.923
Positive	167	68	76.4	99	77.3	
Negative	49	21	23.6	28	21.9	
Unknown	1	0	0.0	1	0.8	
PR status						0.790
Positive	157	63	70.8	94	73.4	
Negative	59	26	29.2	33	25.8	
Unknown	1	0	0.0	1	0.8	
Her-2 receptor status						0.616
Positive	23	11	12.4	12	9.4	
Negative	142	60	67.4	82	64.1	
IHC (2+)a	47	17	19.1	30	23.4	
Unknown	5	1	1.1	4	3.1	
Cycles of chemotherapy						0.139
<6	36	19	21.3	17	13.3	
≥6	181	70	78.7	111	86.7	
Hormonal therapy						0.851
Yes	122	48	53.9	74	57.8	
No	90	39	43.8	51	39.8	
Unknown	5	2	2.2	3	2.3	
Targeted therapy						0.810
Yes	12	6	6.7	6	4.7	
No	202	82	92.1	120	93.8	
Unknown	3	1	1.1	2	1.6	

Abbreviations: PMRT, postmastectomy radiotherapy; NAC, neoadjuvant chemotherapy; LVI, lymph-vascular invasion; ER, estrogen receptor; PR, progesterone receptor.

Univariable and multivariable analyses

All clinical–pathological factors were included in univariate analysis (Table 2). Factors with *P*-value <0.05 in univariate analysis were then included in multivariate analysis. Pathological stage (*P*=0.004), histological grade (*P*=0.001), and lymph-vascular invasion (LVI) (*P*=0.044) were identified as independent prognosis factors associated with LRR (Table 3). The LRR curves were plotted by Kaplan–Meier method (Figure 2). The 5y-LRR rates were significantly different according to pathological N stage (ypN0, ypN1, and ypN2-3: 2%, 5%, and 25%, respectively, *P*=0.000), LVI (yes and no: 33% and 11%, respectively, *P*=0.001), and histological grade (grade 3 and non-grade 3: 42% and 11%, respectively, *P*=0.000).

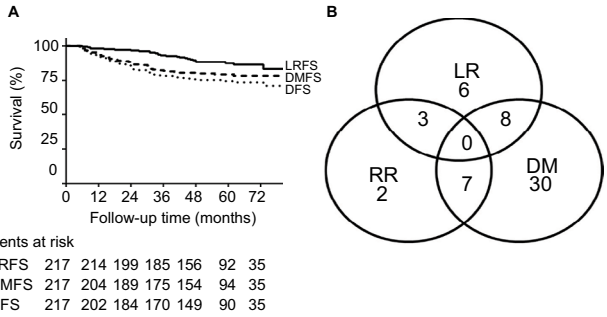

Figure 1 (**A**) Survival curves of the whole cohort of patients; (**B**) failure pattern of the whole cohort of patients.

Abbreviation: LRFS, locoregional recurrence-free survival; DMFS, distant metastasis free survival; DFS, disease free survival; LR, local recurrence; RR, regional recurrence; DM, distant metastasis.

Nomogram model for predicting LRR risk and risk-adapted PMRT

Based on the prognostic factors, a nomogram predicting locoregional failure for early staged BC after NAC and mastectomy was developed (Figure 3A). The C-index was 0.784. Risk scores were calculated for each patient and a cutoff value of 80 was selected according to ROC curve. Patients were deeply stratified into low risk (risk scores <80, 48%) and high-risk subgroups (risk scores >80, 52%) according to the nomogram. Low-risk patients had significantly lower LRR rate than high-risk patients (5y-LRR: 3% vs 27%, *P*=0.000).

Table 2 Univariate analysis of factors associated with LRFS

Variables	No. of patients	5-Year LRFS rate	*P*-value	Variables	No. of patients	5-Year LRFS rate	*P*-value
Age group			0.232	LVI			0.001
≤50	111	90.7		Yes	21	67.3	
>50	106	83.8		No	196	90.5	
Menopausal status			0.139	ER status			0.190
Premenopause	126	92.3		Positive	167	90.3	
Postmenopause	89	82.6		Negative	49	81.4	
Clinical T stage			0.488	PR status			0.530
T1	15	93.3		Positive	157	89.7	
T2	202	89.2		Negative	59	84.8	
Clinical N stage			0.329	Her-2 receptor status			0.160
N0	53	84.5		Positive	23	68.9	
N1	164	87.1		Negative	142	88.6	
Clinical stage			0.238	Adjuvant radiotherapy			0.181
I	5	80.0		Yes	128	86.7	
IIa	58	86.7		No	89	90.7	
IIb	154	86.2		Adjuvant chemotherapy			0.589
NAC cycles			0.579	Yes	213	89.4	
<4	105	86.8		No	4	100.0	
≥4	112	88.0		Cycles of chemotherapy			0.272
ypT stage			0.000	<6	36	93.8	
ypT0–2	200	90.1		≥6	181	87.5	
ypT3–4	17	56.0		Hormonal therapy			0.120
ypN stage			0.000	Yes	122	90.4	
ypN0	58	98.3		No	90	82.2	
ypN1	61	94.7		Targeted therapy			0.152
ypN2–3	98	75.0		Yes	12	71.3	
Histological grade			0.000	No	202	89.2	
1+2	180	89.6					
3	17	58.2					

Abbreviations: NAC, neoadjuvant chemotherapy; LVI, lymph-vascular invasion; LRFS, locoregional recurrence-free survival; ER, estrogen receptor; PR, progesterone receptor.

Additionally, we evaluated the benefits of PMRT in different risk groups. In the low-risk group, PMRT did not influence 5y-LRR (3.3% in PMRT group, 1.7% in no PMRT group, *P*=0.192). In the high-risk group, PMRT significantly decreased 5y-LRR (21.8% in PMRT group vs 42.2% in no PMRT group, *P*=0.031) (Figure 3B). Similar benefit trends were also found in overall survival; PMRT significantly decreased deaths in high-risk group, but not in low-risk group (Figure S1).

Table 3 Multivariate analysis of LRFS

Variable	HR	95% CI	*P*-value
ypN			0.004
ypN stage N1 vs N0	3.602	0.401–32.309	0.252
ypN stage N2–3 vs N0	13.730	1.832–102.903	0.011
Histological grade 3 vs 1–2	4.598	1.808–11.693	0.001
LVI yes vs no	2.654	1.029–6.847	0.044

Abbreviations: LRFS, locoregional recurrence-free survival; LVI, lymph-vascular invasion.

Discussion

To our knowledge, this retrospective study, including a highly selective subgroup of BC, presents the largest single cohort of stage cT1–2N0–1 cases after NAC and mastectomy. NAC is increasingly used in early BC, making more patients eligible for BCS. For cases with poor response to chemotherapy, mastectomy is still the main treatment of choice.[3] However, the LRR rate and value of PMRT in early-stage BC after NAC and mastectomy remain contentious. In our cohort, the 5-year LRR rate was 12%. ypN stage, histological grade, and LVI were identified as independent prognostic factors associated with LRR. A nomogram model for predicting LRR was established, and patients were divided into low- and high-risk groups. PMRT significantly reduced LRR rates in the high-risk group, but not in the low-risk group.

Until now, early staged BC after NAC had been poorly studied. In the adjuvant settings, the LRR rates ranged from 3% to 20% in patients with T1–2 with 1–3 positive axillary

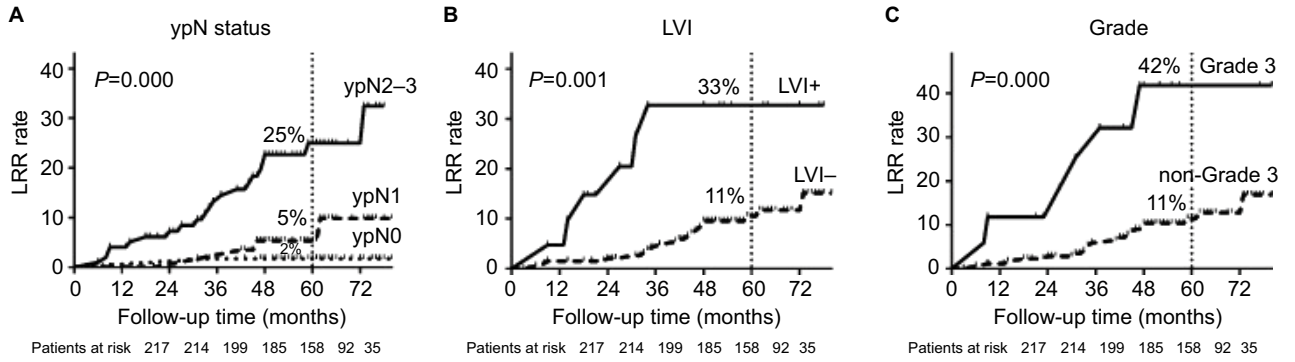

Figure 2 (**A**) LRR rates of patients in ypN0, ypN1, and ypN2–3; (**B**) LRR rates of patients with or without LVI; (**C**) LRR rates of patients with or without histological grade 3.
Abbreviations: LRR, locoregional recurrence; LVI, lymph-vascular invasion.

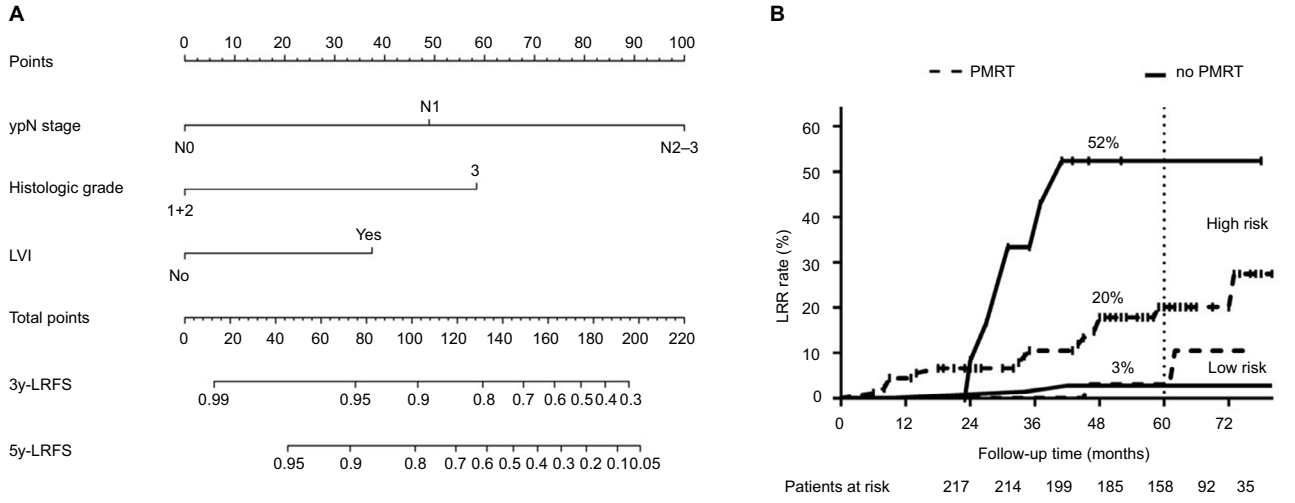

Figure 3 (**A**) A nomogram model was established according to our dataset. (**B**) The LRR curves in low- and high-risk group treated with or without PMRT.
Abbreviations: LRR, locoregional recurrence; PMRT, postmastectomy radiotherapy, LRFS, locoregional recurrence-free survival.

lymph nodes (ALN).[13,14] Various risk factors such as age, grade, LVI, numbers of positive lymph node, and so on affect LRR. Similar results were also observed in NAC settings from retrospective analyses. Variables, including initial clinical stage, age, extent of residual disease, and risk factors (LVI, extra-capsular extension [ECE], and triple-negative phenotype), impacting LRR after NAC have been reported. Fowble et al[15] suggested that in clinical stage II disease, age, estrogen receptor status, chemotherapy response, LVI, and ECE affect LRR after NAC. Another study focused on stage I–II disease identified clinical stage T3N0, ≥4 positive lymph nodes after NAC, and young age as poor predictors for LRR.[16] In another series of stage II patients, young age, LVI, and high grade were associated with an increased risk of LRR.[11,17] Our analysis found similar results: pathological N stage, LVI, and tumor grade were independent factors influencing LRR in cT1-2N0-1 patients after NAC and mastectomy.

In order to establish a valid method to predict LRR risk, a nomogram model was developed based on risk factors. Several nomogram models have been proposed to predict the response of ALN, pCR, and DFS.[18–20] In the present study, we presented the first nomogram model to predict LRR in clinical stage I–II patients after NAC and mastectomy, showing a high degree of accuracy with a C-index of 0.78. Patients with risk scores <80, namely, patients with none or only one of the three risk factors (ypN1, LVI, or grade 3) were categorized as low-risk group that disclosed LRR rate of 3%. This is in accordance with a report,[15] which suggested that patients in cT1-2N0-1 with pathologically N0, or 1–3 positive nodes and with ER+ disease, aged >40 years with no LVI or ECE presented the lowest risk category, with LRR rate <10%. Similar results were observed from Vila, for clinical stage II patients with ypN0 or ypN1: the 5y-LRR rate was 5%.[21] In contrast, patients with a risk score >80 were grouped as high risk with LRR rates emerging at 27%. Our nomogram model was highly efficient in discriminating different LRR risks in cT1-2N0-1 after NAC and mastectomy.

Next, we attempted to make sense of recommendation of PMRT in early BC after NAC as a risk-adapted therapeutic strategy in the context of existing clinical knowledge. LRR plays a vital role in determining whether PMRT should be considered or not. It is generally accepted that risks <10% do not warrant PMRT, whereas >20% do. Unfortunately, due to limited information with relatively small sample size, controversies arise about the benefits of PMRT in BC staged I–II after NAC and mastectomy. In clinical practice, PRMT was determined on a case-by-case basis by patient's radiation oncologist, usually based on the maximum stage from the pre-therapy clinical and pathological stage. According to our model, 5y-LRR rate reached at 27% in high-risk group and PMRT significantly decreased 5y-LRR rates from 42% to 22%. Huang et al[9] also demonstrated that PMRT significantly lowered LRR rates for patients with stage IIb, or with four or more positive nodes, which was consistent with high-risk patients in our cohort. In our analysis, low-risk patients presented 3% of LRR and showed no benefit from PMRT. Le Scodan et al[22] analyzed patients with clinical stage II (63%)–III (27%) and ypN0 after NAC, observing no significant difference in LRFS for patients treated with or without PMRT (96.2% vs 92.5%). Shim et al[23] also identified 151 BC patients with clinical stage II (60%)–III (40%) and ypN0 disease: the 5-year LRFS rates were 98.1% with PMRT and 92.3% without PMRT. PMRT showed no correlation with LRFS. However, another report concluded that in cT1-2N1 patients, who received NAC and mastectomy,[24] PMRT significantly improved LRFS (96.9% vs 78.6%), even in ypN0 patients (94.7% vs 72.9%). Therefore, prospective randomized trials are urgently warranted, and we look forward to the result of an ongoing Phase III clinical trial NSABP B-051/RTOG 1304 (NCT01872975), which is focused on cT1-3N1 BC with N-negative after NAC treated with or without RT. This trial may provide strong clinical evidence to support decisions on PMRT after NAC in low-risk subgroup.

As a retrospective study, we acknowledge that our study has several limitations. First, bias exists between patients who received PMRT and those who did not. In addition, although NAC regimens are relatively standardized, chemotherapy cycles were inconsistent and might compromise chemotherapy response rates, and the follow-up time may not be long enough for BC. However, our study included relatively large sample sizes of cT1–2N0 BC after NAC and mastectomy and established a valid nomogram model to provide a risk-adapted recommendation of PMRT in this most disputable subgroup. We believe that the current analysis provides some evidence for risk-adapted PMRT and will be important in future validation from larger and prospective data sets.

Conclusion

In our cohort, LVI, histological grade, as well as pathological N stage were independently important prognostic factors associated with LRR in BC staged in cT1-2N0-1 after NAC and mastectomy. Risk-adapted PMRT is recommended according to our nomogram model, which could be a valuable tool for predicting risk of LRR and guiding optimal clinical decisions, and validations from other independent data sets are warranted.

Acknowledgments

A part of this work was accepted for presentation in the poster viewing session in ESTRO 37th Annual Meeting in Spain.

This study is supported by the National Natural Science Foundation of China (Grant No. 81502656).

Disclosure

The authors report no conflicts of interest in this work.

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Supplementary material

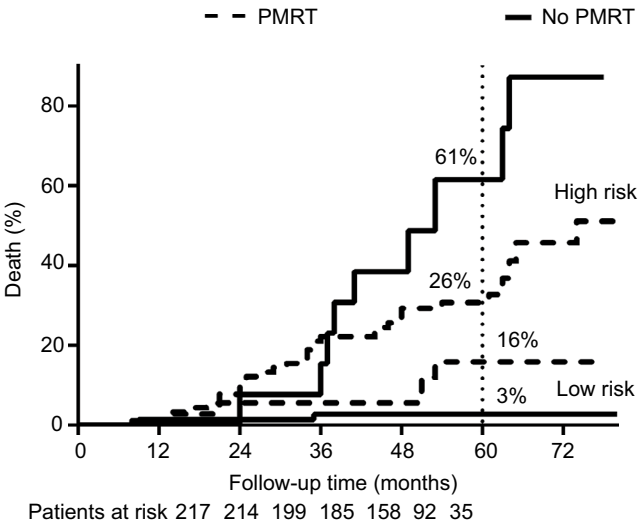

Figure S1 Mortality curves in low-risk and high-risk groups.
Notes: PMRT decreased mortality in high-risk group, but not in low-risk group.
Abbreviation: PMRT, postmastectomy radiotherapy.