Breast Cancer
https://doi.org/10.1007/s12282-020-01158-0

ORIGINAL ARTICLE

Prognostic factors for breast cancer patients with T1–2 tumors and 1–3 positive lymph nodes and the role of postmastectomy radiotherapy in these patients

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Received: 9 February 2020 / Accepted: 11 September 2020

Abstract

Purpose The purpose of this study was to identify independent prognostic factors for breast cancer patients with T1–2 tumors and 1–3 positive lymph nodes, and discuss the role of postmastectomy radiotherapy(PMRT) in these patients.

Methods Between January 2005 and December 2015, the data on 840 eligible patients with breast cancer were retrospectively reviewed. Of these patients, 368 women received PMRT and 472 did not. The endpoints were locoregional recurrence (LRR) and distant metastasis (DM).

Results With a median follow-up of 62.0 months, multivariate analysis identified the following independent risk factors for increased LRR: tumor size ≥ 4 cm (HR: 2.994, 95% CI: 1.190–7.535, $P = 0.020$), ER- and PR-negative tumor (HR: 2.540, 95% CI: 1.165–5.537, $P = 0.019$), preoperative high neutrophil-to-lymphocyte ratio (NLR) (HR: 4.716, 95% CI: 1.776–12.528, $P = 0.002$)and low neutrophil-to-monocyte ratio (NMR) (HR: 0.231, 95% CI: 0.084–0.633, $P = 0.004$). And independent risk factors for increased DM: ER- and PR-negative tumor (HR: 2.540, 95% CI: 1.880–5.625, $P = 0.000$), high NLR (HR: 2.693, 95% CI: 1.426–5.084, $P = 0.002$) and low NMR (HR: 0.460, 95% CI: 0.257–0.824, $P = 0.009$). The high-risk patients (≥ 2 risk factors) had worse LRRFS and DFS than low-risk patients (0–1 risk factor) (all, $P < 0.05$). In the subgroup analysis, both low- and high-risk patients received PMRT had better LRRFS and DFS than those who without PMRT (all, $P < 0.05$), and the high-risk patients received PMRT had similar 5-year rates of LRRFS and DFS than low-risk patients who without PMRT (94.5 vs. 94.3%, $P = 0.402$; 83.4 vs.87.4%, $P = 0.877$, respectively).

Conclusions Tumor size, ER/PR status, preoperative NLR and NMR were independent predictors of risk of recurrence. PMRT could improve locoregional control even in low-risk subgroup of breast cancer patients with T1–2 tumors and 1–3 positive lymph nodes significantly.

Keywords Breast cancer · Neutrophil-to-lymphocyte ratio · Neutrophil-to-monocyte ratio · Prognosis · Radiotherapy

Introduction

Postmastectomy radiotherapy (PMRT) is one of the most important clinical treatments for breast cancer, and is of great benefit for reducing the rate of LRR and improving survival. Whether all breast cancer patients with T1–2 tumors and 1–3 positive lymph nodes (LNs) should receive PMRT remains controversial. In 2014, the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) reported that PMRT reduced both the recurrence and breast cancer mortality rates of patients with 1–3 positive LNs. It is worth noting that all the patients in their meta-analysis underwent treatment during an early era (1964–1986) [1]. Recent advances in systemic treatments such as chemotherapy, endocrine therapy, and targeted therapy have further reduced the rate of LRR in these patients [2–4]. The 2016 focused guideline update of the American Society of Clinical Oncology (ASCO) concluded that PMRT might be omitted for these patients who have a low risk of LRR [5]. Additionally, the problems of overtreatment and late complications in these patients are worth considering. Therefore, whether all breast cancer

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Published online: 17 September 2020

patients with T1–2 tumors and 1–3 positive LNs could benefit from PMRT in the modern era is worth investigating.

Previous studies on PMRT mostly selected patients with increased risk of recurrence, as did physicians in clinical practice [6–9]. The study investigators assessed various methods for identifying patients with increased risk, and developed prognostic models for evaluating the probability of recurrence that were based on clinicopathological factors such as age, lymphovascular invasion, tumor size, nuclear grade, lymph node status, and ER/PR status [10, 11]. New molecular markers included in the Amsterdam 70 gene signature, Mammaprint, and Oncotype Dx assays might provide additional information for the assessment of recurrence risk [12–15]. However, the high cost limits its clinical application.

As is well known, inflammation that damages specific tissues plays an essential role in the initiation of tumorigenesis [16, 17]. Inflammatory parameters in peripheral blood are associated with outcome in patients with various solid tumors, and NLR and platelet-to-lymphocyte ratio (PLR) has been regarded as independent prognostic markers for survival in breast cancer patients [18–21]. Compared with molecular markers, a preoperative peripheral blood inflammatory parameter is a more accessible and reliable prognostic marker, and might provide an additional approach for predicting the risk of recurrence and identifying the optimal patient for receiving PMRT.

Therefore, this study combined clinicopathological factors and preoperative peripheral blood inflammatory parameters to identify independent prognostic factors for breast cancer patients with T1–2 tumors and 1–3 positive lymph nodes, and discuss the role of PMRT in different risk subgroups.

Methods

Patients

From January 2005 to December 2015, a total of 840 women who were diagnosed at the Liaoning Cancer Hospital & Institute with invasive breast cancer and underwent mastectomy and sentinel lymph node biopsy (SLNB) and/or axillary lymph node dissection (ALND) were identified with pathologic T1–2 tumors and 1–3 positive LNs according to the 8th edition Union International Against Cancer and American Joint Committee on Cancer (UICC-AJCC) TNM system. We retrospectively collected information on the systemic treatment and PMRT of these patients, as well as their preoperative blood parameters. Exclusion criteria were as follows: metastatic breast cancer or bilateral breast cancer, received neoadjuvant therapy, and abnormal white blood cells (WBCs). None of the patients had a prior history of malignant disease.

Table 1 shows the clinicopathological and treatment characteristics of the 840 patients included in the analysis. In this study, the following cutoff values were used: PLR = 110.95; NLR = 2.76; NMR = 9.67; and monocyte-to-lymphocyte ratio (MLR) = 0.16. ER and PR positivity were classified as +, + +, + + + or ≥ 1% of tumor cells with nuclear staining. HER2 positivity was defined as tumors with an immunohistochemical staining score of + + + or + + with an amplification ratio by fluorescence-in-situ-hybridization analysis. A tumor with < 15% of cells being positive for Ki67 was considered to be low-Ki67 expressing and > 30% of Ki67-positive cells as high expressing.

Treatment

All patients underwent modified radical mastectomy, whether or not PMRT was subsequently administered depended on the choice of the doctor and/or the patient. A total of 368 (43.8%) patients received PMRT and 472 (56.2%) did not. The field and dose of irradiation were at the discretion of the radiation oncologist. Most treatment targets covered the ipsolateral chest wall and the supraclavicular area, 5 patients only covered the ipsolateral chest wall. Irradiation of the axillary and intermammary regional nodal basins was not routinely conducted, part of Level III axillary lymph nodes may be included in the field of supraclavicular area, and only 1 patient covered the axilla. The total dose was 46–50 Gy in 2 Gy per fraction. Of 799 (95.1%) patients receiving chemotherapy, most (644, 76.7%) received anthracyclines combined with paclitaxel. Of 563 (67.0%) patients receiving hormonal therapy, 241 (42.3%) received aromatase inhibitors. The few HER2-positive (35, 24.8%) patients were treated with trastuzumab.

Endpoint and follow-up

In this study, the endpoint was LRR and DM. LRR was defined as a clinically or pathologically confirmed recurrence in the ipsilateral chest wall, or metastatic lymph nodes in the axillary, supra-/subclavicular, or intermammary regional nodal basins. DM was defined as metastasis to the contralateral breast or other organs, as confirmed by clinical diagnosis or pathology. Follow-up began on the surgical date and ended on January 15, 2019. Follow-up data were collected from medical records, or telephoning every 3 months for 2 years postmastectomy, every 6 months for the next 3 years, and annually after 5 years. We defined LRRFS as the time from the date of mastectomy surgery to the date of first LRR or to the date of last follow-up for patients alive and free of recurrence (censored cases). Similarly, DFS was defined as the time to the date of LRR or DM. All patients

Table 1 Clinicopathological and treatment characteristics of the 840 pT1-2N1M0 breast cancer patients *N* (%)

Characteristic	PMRT		no PMRT		*P*
	N = 368	%	*N* = 472	%	
Age, years					
< 40	56	(15.2)	35	(7.4)	0.000
41–50	146	(39.7)	178	(37.7)	
51–60	125	(34.0)	173	(36.7)	
> 60	41	(11.1)	86	(18.2)	
Quadrant					
Outer	202	(54.9)	296	(62.7)	0.023
Central and inner	160	(43.5)	174	(36.9)	
Other	6	(1.6)	2	(0.4)	
Tumor size, cm					
< 4	342	(92.9)	437	(92.6)	0.952
≥ 4	26	(7.1)	35	(7.4)	
Histological grade					
I	5	(1.4)	6	(1.3)	0.000
II	230	(62.5)	354	(75.0)	
III	62	(16.8)	63	(13.3)	
Unknown	71	(19.3)	49	(10.4)	
Vessel carcinoma embolus					
Yes	37	(10.1)	52	(11.0)	0.736
No	331	(89.9)	420	(89.0)	
Nodes removed					
< 10	74	(20.1)	116	(24.6)	0.221
11–15	177	(48.1)	232	(49.2)	
16–20	81	(22.0)	90	(19.1)	
> 20	36	(9.8)	34	(7.2)	
Positive LNs					
1	131	(35.6)	306	(64.8)	0.000
2	158	(37.5)	122	(25.8)	
3	99	(26.9)	44	(9.3)	
HER-2 status					
Negative	252	(68.5)	334	(70.8)	0.280
Positive	70	(19.0)	71	(15.0)	
Unknown	46	(12.5)	67	(14.2)	
ER/PR status					
Both Negative	87	(23.6)	79	(16.7)	0.016
Either Positive	281	(76.4)	393	(83.3)	
Ki67					
< 15%	76	(20.7)	137	(29.0)	0.000
15–30%	80	(21.7)	154	(32.6)	
> 30%	129	(35.1)	152	(32.2)	
Unknown	83	(22.6)	29	(6.1)	
Chemotherapy					
Yes	363	(98.6)	436	(92.4)	0.000
No	1	(0.3)	23	(4.9)	
Unknown	4	(1.1)	13	(2.8)	
Trastuzumab					
Yes	16	(4.3)	19	(4.0)	0.027
No	320	(87.0)	433	(91.7)	
Unknown	32	(8.7)	20	(4.2)	
Hormonal therapy					
Yes	267	(72.6)	296	(62.7)	0.000
No	87	(23.6)	101	(21.4)	
Unknown	14	(3.8)	75	(15.9)	
PLR					
Low	92	(25.0)	139	(29.4)	0.175
High	276	(75.0)	333	(70.6)	
NLR					
Low	294	(79.9)	392	(83.1)	0.278
High	74	(20.1)	80	(16.9)	
MLR					
Low	123	(33.4)	190	(40.3)	0.050
High	245	(66.6)	282	(59.7)	
NMR					
Low	171	(46.5)	185	(39.2)	0.041
High	197	(53.5)	287	(60.8)	

LNs lymph nodes, *HER2* human epidermal growth factor receptor 2, *ER* estrogen receptor, *PR* progesterone receptor, *PLR* platelet-to-lymphocyte ratio, *NLR* neutrophil-to-lymphocyte ratio, *MLR* monocyte-to-lymphocyte ratio, *NMR* neutrophil-to-monocyte ratio

without endpoint events were followed for at least one year after surgery.

Statistical analysis

We used X-tile software (https://medicine.yale.edu/lab/rimm/research/software.aspx) to determine the optimal cut-off values of inflammatory parameters. The chi-squared test was used to compare the clinicopathological and treatment characteristics between patients with and without PMRT. The Kaplan–Meier method was used to estimate LRRFS and DFS, and the log-rank test was used to compare the survival curves. Cox proportional hazards regression analysis was used to identify risk factors for LRR and DM in patients without PMRT. Those risk factors with $P < 0.1$ in univariate analysis were then evaluated by multivariate analysis to identify independent prognostic factors. LRRFS and DFS were compared after adjusting for treatment characteristics by propensity score matching (1:1 match, caliper 0.1). SPSS (version 22.0, IBM, Armonk, NY, USA) was used for analysis. A two-sided $P < 0.05$ was considered statistically significant.

Results

LRR and DM for all study patients

The median follow-up time was 62.0 months. LRR occurred in 45 of 840 (5.3%) patients in the following locations: 25 in the ipsilateral chest wall, 3 in the ipsilateral axillary fossa, 6 in the supraclavicular regional nodal basins, 2 in the intermammary regional nodal basins, and 9 occurred in two or more sites. DM occurred in 90 of the 840 (10.7%) patients in the following locations: 11 contralateral breast, and bones, lungs, liver, and brain, among others.

Risk factors of LRR and DM

Univariate analysis of LRR revealed that tumor size ≥ 4 cm, ER- and PR-negative tumor, and low NMR were significantly associated with a high LRR rate ($P = 0.028$, $P = 0.002$, and $P = 0.015$, respectively). Additionally, Ki67 > 30%, high NLR, and high MLR were marginally associated with a high LRR rate ($P = 0.072$, $P = 0.053$, and $P = 0.080$, respectively). Thus, we included these 6 factors in the multivariate analysis of LRR. Multivariate analysis identified tumor size ≥ 4 cm (HR: 2.994, 95% CI: 1.190–7.535, $P = 0.020$), ER- and PR-negative tumor (HR: 2.540, 95% CI: 1.165–5.537, $P = 0.019$), high NLR (HR: 4.716, 95% CI: 1.776–12.528, $P = 0.002$) and low NMR (HR: 0.231, 95% CI: 0.084–0.633, $P = 0.004$) as independent risk factors of the LRR rate (Table 2). Similarly, independent risk factors for increased DM were: ER- and PR-negative tumor (HR: 2.540, 95% CI: 1.880–5.625, $P = 0.000$), high NLR (HR: 2.693, 95% CI: 1.426–5.084, $P = 0.002$) and low NMR (HR: 0.460, 95% CI: 0.257–0.824, $P = 0.009$). (Table 3).

Subgroup analysis of the benefit of PMRT

The main purpose of this study was to evaluate whether all breast cancer patients with 1–3 positive LNs would benefit from PMRT, we defined two risk subgroups according to the number of independent risk factors and then compared the rates of LRRFS and DFS between the two subgroups. We used 1:1 matching to adjust for systemic treatments (chemotherapy, hormonal therapy, trastuzumab) of the patients. Survival analysis showed that the differences of the 5-year rates of LRRFS and DFS between the two risk subgroups were significant (94.7 vs. 84.0%, $P = 0.001$; 88.2 vs. 72.4%, $P = 0.000$, respectively) (Fig. 1).

In subgroup analysis, both low- and high-risk patients who received PMRT had better 5-year rates of LRRFS than those without PMRT (97.0 vs. 94.3%, $P = 0.007$; 94.5 vs. 78.2%, $P = 0.010$, respectively), and the high-risk patients who received PMRT had similar 5-year rates of LRRFS than low-risk patients without PMRT (94.5 vs. 94.3%, $P = 0.402$). Similarly, both low- and high-risk patients who received PMRT had better 5-year rates of DFS than those without PMRT (89.1 vs. 87.4%, $P = 0.049$; 83.4 vs. 54.9%, $P = 0.008$, respectively), and the high-risk patients who received PMRT had similar 5-year rates of DFS than low-risk patients without PMRT (83.4 vs. 87.4%, $P = 0.877$) (Fig. 2).

Discussion

Breast cancer is a malignant tumor with obvious heterogeneity. Tumor molecular subtypes, pathological stage, and recurrence risk are important factors for comprehensive treatment planning. Additionally, the risk of postoperative recurrence is the main factor affecting whether or not PMRT is performed after surgery. Patients with a primary tumor ≥ 5 cm or ≥ 4 positive LNs have a high risk of recurrence and should be considered for PMRT [5, 22]. However, for patients with a primary tumor ≤ 5 cm and 1–3 positive LNs, individualized treatment planning is necessary, and different medical centers employ different treatment choices [23–26].

Previously, PMRT was selectively administered to patients with 1–3 positive LNs who were considered to have a relatively high risk of recurrence [5, 6]. Currently, with improvements surgical procedures, the use of new chemotherapeutic and endocrine agents, and the promotion of targeted therapy, the recurrence rate of breast cancer after surgery has been further reduced [3, 27], and the clinicopathological factors affecting LRR may have changed. It is necessary for us to re-evaluate the prognostic factors for breast cancer patients with T1–2 tumors and 1–3 positive LNs.

Inflammatory mediators are important local constituents of the environment of tumors, and inflammatory cells such as neutrophils play an important role in tumor growth and metastasis [16, 28]. Increasing numbers of studies have recently explored the relationship between inflammatory parameters and the outcomes of patients with tumors to develop new therapeutic approaches and prognostic evaluation methods, and to identify new molecular targets that could lead to improvements in the diagnosis and treatment of tumors [17]. The inflammatory parameters of interest in breast cancer typically include PLR, NLR, MLR, and NMR. Several studies have shown that breast cancer patients with elevated NLR and PLR levels can have poor survival outcomes [19–21]. However, certain inflammatory parameters studied in relation regard to various endpoints have led to conflicting results about the prognostic significance of inflammatory parameters in breast cancer patients. The conflicting results might be accounted for by the different cutoff

Table 2 Univariate and multivariate analysis of factors associated with LRRFS

Characteristic	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P*	HR	95% CI	*P*
Age, years						
< 40	1		0.144			
41–50	1.4	(0.318,6.169)	0.656			
51–60	0.606	(0.126,2.920)	0.533			
> 60	1.882	(0.406,8.718)	0.419			
Quadrant						
Outer	1.024	(0.640,1.637)	0.922			
Central and Inner						
Tumor size, cm						
< 4	2.731	(1.117,6.680)	0.028	2.994	(1.190,7.535)	0.02
≥ 4						
Histological grade						
I + II	1.108	(0.636,1.852)	0.764			
III						
Vessel carcinoma embolus						
Yes	1.472	(0.350,6.199)	0.598			
No						
Nodes removed						
< 10	1		0.269			
11–15	1.351	(0.523,3.493)	0.534			
16–20	2.331	(0.845,6.431)	0.102			
> 20	0.596	(0.071,4.979)	0.633			
Positive LNs						
1 + 2	1.406	(0.905,2.354)	0.121			
3						
HER2 status						
Negative	1.009	(0.906,1.121)	0.873			
Positive						
ER/PR status						
Both Negative	3.108	(1.492,6.477)	0.002	2.54	(1.165,5.537)	0.019
Either Positive						
Ki67						
< 15%	1		0.02	1		0.185
15–30%	2.154	(0.646,7.180)	0.212	1.947	(0.581,6.520)	0.28
> 30%	2.861	(0.910,8.994)	0.072	2.351	(0.712,7.763)	0.161
PLR						
Low	2.093	(0.859,5.100)	0.104			
High						
NLR						
Low	2.1	(0.990,4.453)	0.053	4.716	(1.776,12.528)	0.002
High						
MLR						
Low	2.122	(0.914,4.929)	0.08	0.977	(0.378,2.526)	0.963
High						
NMR						
Low	0.41	(0.200,0.840)	0.015	0.231	(0.084,0.633)	0.004
High						

Table 3 Univariate and multivariate analysis of factors associated with DFS

Characteristic	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P*	HR	95% CI	*P*
Age, years						
< 40	1		0.604			
41–50	0.714	(0.311,1.643)	0.656			
51–60	0.386	(0.160,0.931)	0.533			
> 60	0.846	(0.344,2.079)	0.419			
Quadrant						
Outer	0.945	(0.647,1.381)	0.771			
Central and Inner						
Tumor size, cm						
< 4	1.946	(0.987,3.837)	0.055	1.781	(1.190,7.535)	0.104
≥ 4						
Histological grade						
I + II	1.101	(0.770,1.573)	0.598			
III						
Vessel carcinoma embolus						
Yes	3.288	(0.803,13.473)	0.098	3.694	(0.892,15.294)	0.071
No						
Nodes removed						
< 10	1		0.048	1		0.052
11–15	1.058	(0.523,3.493)	0.86	1.04	(0.548,1.974)	0.905
16–20	1.851	(0.845,6.431)	0.072	1.886	(0.948,3.751)	0.071
> 20	0.198	(0.071,4.979)	0.119	0.169	(0.022,1.298)	0.087
Positive LNs						
1 + 2	1.234	(0.852,1.786)	0.266			
3						
HER2 status						
Negative	0.988	(0.913,1.070)	0.765			
Positive						
ER/PR status						
Both Negative	3.21	(1.915,5.381)	0	3.252	(1.880,5.625)	0
Either Positive						
Ki67						
< 15%	1		0.022	1		0.366
15–30%	1.372	(0.658,2.862)	0.399	1.343	(0.637,2.831)	0.438
> 30%	1.767	(0.889,3.511)	0.104	1.359	(0.662,2.790)	0.403
PLR						
Low	1.436	(0.826,2.495)	0.199			
High						
NLR						
Low	1.921	(1.126,3.278)	0.017	2.693	(1.426,.5.084)	0.002
High						
MLR						
Low	1.268	(0.753,2.136)	0.372			
High						
NMR						
Low	0.656	(0.406,1.060)	0.085	0.46	(0.257,0.824)	0.009
High						

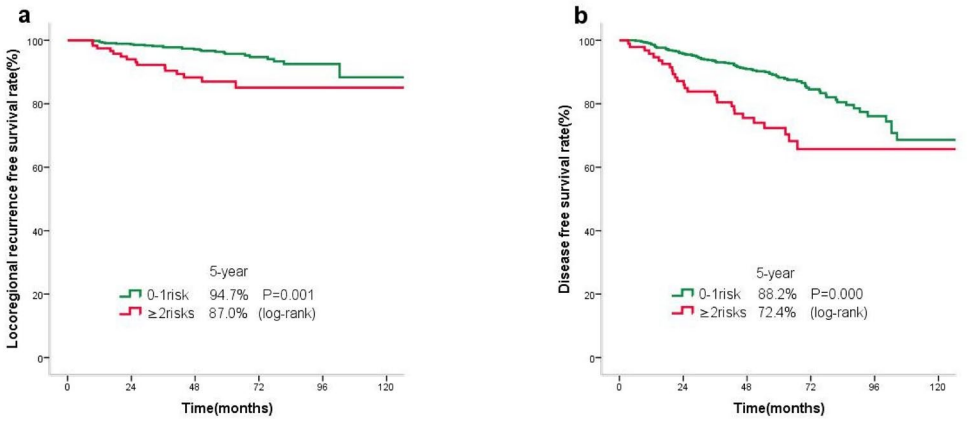

Fig. 1 Locoregional recurrence-free survival (**a**, $n=672$) and disease-free survival (**b**, $n=696$) of the risk subgroups after adjusting treatment characteristics with PSM

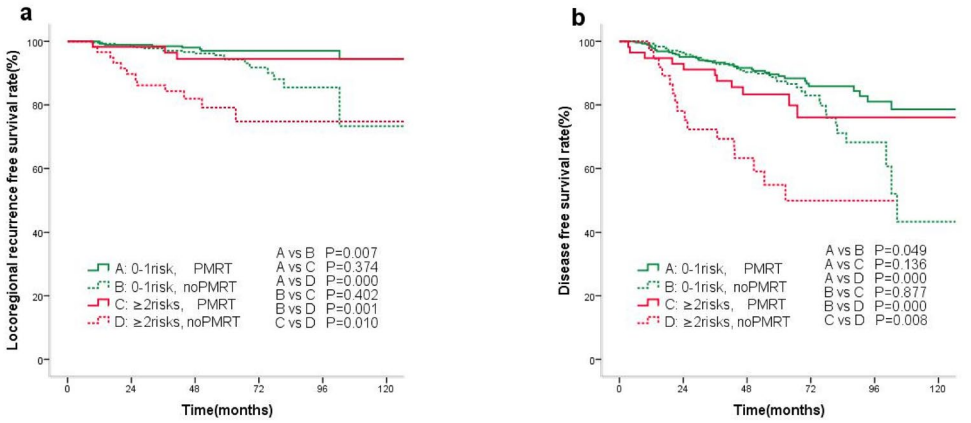

Fig. 2 Subgroup analysis of locoregional recurrence-free survival (**a**, $n=672$) and disease-free survival (**b**, $n=696$) of the risk subgroups after adjusting treatment characteristics with PSM

values of various inflammatory parameters used in different studies and the lack of a standard method for determining the optimal cutoff values. This study conducted statistical analysis on the study population in our center, and used X-tile software to determine the optimal cutoff values of the inflammatory markers for assessing LRR. Although the methods for determining the optimal cutoff values were different, our results were similar to many studies with similar patients [29–32].

We combined the preoperative inflammatory parameters in peripheral blood samples with the patients' clinicopathological factors, and multivariate analysis found that that tumor size ≥ 4 cm, ER- and PR-negative tumor, high NLR and low NMR can be prognostic factors for breast cancer patients with T1-2 tumors and 1 to 3 positive lymph nodes. Although in the low-risk patients group, there was a statistically significant difference in 5-year LRRFS and DFS between patients who received PMRT and those who without PMRT (97.0 vs. 94.3%, $P=0.007$; 89.1 vs.87.4%, $P=0.049$), the clinical outcomes of low-risk patients without PMRT were not bad actually [33]. In the high-risk patients group, patients who received PMRT had similar 5-year rates of LRRFS and DFS than low-risk patients without PMRT (94.5 vs. 94.3%, $P=0.402$; 83.4 vs.87.4%, $P=0.877$, respectively); it shows that the PMRT can help to increase locoregional control in those patients significantly. Therefor, the omission of PMRT should be decided selectively and carefully.

There are limitations to this study. First, pathological results such as HER2 and Ki67 expression levels were not re-evaluated. Second, although we excluded the preoperative samples showing abnormal white blood cells in the peripheral blood, the inflammatory parameters we studied might have been affected by other causes, including infection, strenuous exercise, malnutrition, and menstruation. In addition, at present, a consensus on determining the optimal cutoff value of NLR and NMR is lacking.

The advantage to this study included our combining clinicopathological factors with inflammatory parameters to evaluate LRR and DM. After adjusting for factors associated with systemic treatment, we compared the differences between the survival outcomes of patients with and without PMRT. Our findings demonstrated that some subgroups of breast cancer patients with 1–3 positive LNs could derive benefit from PMRT even in the era of modern treatment. However, determination of the optimal NLR and NMR

cutoff values and independent validation of our findings are warranted. Our optimal cutoff values of the inflammatory markers in this study may provide references for others.

Conclusions

In conclusion, tumor size, tumor ER/PR status, and preoperative NLR and NMR were effective indices for predicting the risk of recurrence of breast cancer patients with T1–2 tumors and 1–3 positive lymph nodes. Different risk subgroups showed different outcomes. PMRT could improve locoregional control even in low-risk subgroup of breast cancer patients significantly. Considering the toxicity and potential survival benefits, PMRT should be given selectively and carefully.

Funding This study was funded by the Science and Technology Plan Project of Shenyang(19–112-4–083), Science and Technology Plan Project of Liaoning Province of China (201602452, 20180540129, and 20180530095), Key Laboratory of Tumor Radiosensitization and Normal Tissue Radioprotection Project of Liaoning Province (No. 2018225102), and the Personnel Training Project of Liaoning Cancer Hospital & Institute of China (201703).

Data availability The datasets during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Compliance with ethical standards

Ethical approval For this type of study formal consent is not required.

Informed consent Formal consent was not required for this type of study.

Conflict of interest The authors declare that they have no conflict of interest.

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