The Breast 60 (2021) 1–5

Contents lists available at ScienceDirect

The Breast

journal homepage: www.elsevier.com/brst

The effect of postmastectomy radiation therapy on high-risk patients with T1-2N0 breast cancer

Chuanxu Luo [a], Xiaorong Zhong [a], Yu Fan [a], Chengshi Wang [a], Yu Wang [a], Ting Luo [b, *]

[a] Laboratory of Molecular Diagnosis of Cancer & Breast Medical Oncology, Clinical Research Center for Breast, West China Hospital, Sichuan University, Chengdu, China
[b] Department of Head, Neck and Mammary Gland Oncology, Cancer Center, West China Hospital, Sichuan University, Chengdu, China

ARTICLE INFO

Article history:
Received 22 June 2021
Received in revised form
1 August 2021
Accepted 17 August 2021
Available online 20 August 2021

Keywords:
Breast cancer
High risk
Lymph node negative
Mastectomy
Radiation therapy

ABSTRACT

Background: The prognostic impact of postmastectomy radiation therapy (PMRT) on high-risk patients with T1-2N0 breast cancer is controversial. We aimed to investigate the effect of PMRT on high-risk patients with T1-2N0 breast cancer.

Methods: A total of 3439 patients diagnosed with T1-2N0 breast cancer who received mastectomy between 2000 and 2016 in our institute were retrospectively analyzed. Leveraging the Fine and Gray competing risks regression in unirradiated patients, risk factors of locoregional recurrence (LRR) were identified. All patients were stratified into high-risk (3 or 4 risk factors) and low-risk (no more than 2 risk factors) groups. The prognostic effect of PMRT was estimated in two subgroups. This subgroup analysis was also performed in patients with T2N0 breast cancer.

Results: The median follow-up was 89 months. The 5-year cumulative incidence of LRR was 2.2% in unirradiated patients. Tumor size, estrogen receptor (ER) status, histologic grade and lymphovascular invasion (LVI) were identified as independent risk factors of LRR. In the high-risk group, PMRT was correlated with a 8.3% risk reduction of 5-year LRR, 7.8% risk reduction of 5-year distant recurrence (DR), and 6.4% risk reduction of 5-year breast cancer mortality (BCM), whereas it was not correlated with LRR, DR, or BCM in low-risk group. In patients with T2N0 breast cancer, PMRT was associated with decreased LRR, DR and BCM in high-risk group, other than low-risk group.

Conclusions: PMRT presented heterogenous effect on patients with T1-2N0 breast cancer. Patients at high risk of LRR were more likely to benefit from PMRT.

1. Introduction

Patients with T1-2 node-negative breast cancer presented low risk of locoregional recurrence (LRR) and were not recommended for postmastectomy radiation therapy (PMRT). However, increasing evidence demonstrated that patients with T1-2N0 breast cancer and unfavorable biological profile were at high risk of LRR (2%–9%) [1–5], which was comparable to those of patients with one to three positive nodes [6–8], indicating a potential candidate for PMRT. Thus, in the latest NCCN guidelines, PMRT was considered for patients with T1-2N0 breast cancer who were at high risk of recurrence [9].

In the Early Breast Cancer Trialists Collaborative Group meta-analysis, PMRT did not improve the survival outcome of node-negative patients, in terms of LRR, overall recurrence and breast cancer mortality (BCM) [10]. In the EORTC 22922/10,925 trial, T1-2N0 breast cancer patients with high-risk features who received mastectomy constituted a minority of the trial cohort. The 15-year results of this trial demonstrated significant risk reduction of overall recurrence and BCM with the addition of internal mammary and medial supraclavicular irradiation to whole-breast radiation therapy [11]. The other studies focused on identifying risk factors of LRR and defining the high-risk patients by the number of risk factors [1–5,12]. However, whether patients with T1-2N0 breast cancer at high risk of LRR can benefit from PMRT was still controversial and rarely investigated.

In this study, we aimed to identify the risk factors of LRR and investigate the effect of PMRT on high-risk patients with T1-2N0 breast cancer.

* Corresponding author. Department of Head, Neck and Mammary Gland Oncology, Cancer Center, West China Hospital, Sichuan University, 37 Guoxuexiang, Wuhou District, Chengdu, 610041, China.
E-mail address: tina621@163.com (T. Luo).

https://doi.org/10.1016/j.breast.2021.08.006

2. Materials and methods

2.1. Patients

Patients diagnosed with T1-2N0 breast cancer after mastectomy between January 2000 and December 2016 from our institutional database were retrospectively analyzed. We further excluded those with synchronous distant metastases or other malignancies, or those who had received neoadjuvant therapy. In total, 3439 patients were included into this study.

2.2. Treatment

All patients underwent mastectomy with negative surgical margin. Radiation therapy was administrated with modern computed tomography (CT)-based dose planning. The total dose of 46–50 Gy was separated into 23 to 25 fractions. The area of irradiation included ipsilateral chest wall, infraclavicular, and supraclavicular area. Internal mammary nodes were irradiated when tumors located medially. Chemotherapy regimen was determined on the basis of clinical characteristics and patient willingness. Adjuvant endocrine therapy for hormone receptor-positive tumor maintained for at least 5 years.

2.3. Follow-up

Frequency of patient follow-up was once every 4 months in the first 3 years after surgery, once every 6–12 months in the fourth and fifth years, and annually after 5 years. Methods of follow-up included office visit, telephone call, or postal contact. LRR was defined as tumor recurrence in the ipsilateral chest wall or regional lymph nodes as the first event. Distant recurrence (DR) was defined as disease recurrence at distant organs. All-cause death was considered as the competing risk event of LRR and DR. Other-cause mortality was deemed as the competing risk event of BCM. Time interval was counted from the date of surgery.

2.4. Statistical analysis

Correlations between variables and receipt of PMRT were evaluated using Chi-square test. The rates of LRR, DR, and BCM were calculated by cumulative incidence function and compared by Gray's test between groups. Based on Fine and Gray competing risks proportional hazards regression model, correlates of LRR were analyzed using univariate and multivariate analysis, with hazard ratio (HR) adjusted by age, year of diagnosis, tumor size, estrogen receptor (ER) status, progesterone receptor (PR) status, human epidermal growth factor receptor 2 (HER2) status, histologic grade, histologic type and lymphovascular invasion (LVI).

All unirradiated and irradiated patients were classified into high-risk (3 or 4 risk factors) and low-risk (no more than 2 risk factors) groups. In subgroup analysis, the prognostic impact of PMRT in two subgroups was examined using Fine and Gray regression model adjusted by age, year of diagnosis, ER status, HER2 status, PR status, histologic grade, histologic type, LVI, receipt of chemotherapy and receipt of endocrine therapy. This subgroup analysis was performed twice in patients with T1-2N0 breast cancer or patients with T2N0 breast cancer. All tests were two sided using R version 3.5.0 (R Foundation for Statistical Computing, Vienna, Austria). A P value less than 0.05 was deemed statistically significant.

3. Results

Of the 3439 patients identified, 162 of which (4.7%) received PMRT. Table 1 presented the baseline characteristics of patients stratified by receipt of PMRT. Patients diagnosed in the earlier period and those with younger age, larger tumors, ER-negative, or higher histologic grade disease were more likely to received PMRT. A total of 2068 (60.1%) patients received adjuvant chemotherapy, 91.9% (n = 1900) of which received anthracycline- or taxane-based regimens.

After a median follow-up period of 89 months (interquartile range, 58 to 122), 87 patients experienced LRR and 190 patients experienced DR. A total of 104 patients died from breast cancer. The 5-year cumulative incidence of LRR, DR, and BCM of the whole population was 2.2%, 4.4%, and 2.1%, respectively. In unirradiated patients, univariate and multivariate analysis demonstrated that four variables (tumor size, ER status, histologic grade and LVI) were significantly associated with LRR (Table 2). Most (92.0%) irradiated patients with T1-2N0 breast cancer have one or more risk factors.

For the whole population, PMRT was not significantly associated with LRR ($P = 0.094$), DR ($P = 0.400$) or BCM ($P = 0.160$; Table 3). Patients with 3 or 4 risk factors were classified into high-risk group (n = 668), with the others classified into low-risk group (n = 2771).

In high-risk group, PMRT was significantly associated with lower LRR (5-year cumulative incidence 1.2% vs 9.5%; HR, 0.084; 95% CI, 0.010–0.692; $P = 0.021$), reduced DR (5-year cumulative incidence 2.6% vs 10.4%; HR, 0.187; 95% CI, 0.057–0.615; $P = 0.006$) and decreased BCM (5-year cumulative incidence 1.5% vs 7.9%; HR, 0.127; 95% CI, 0.034–0.481; $P = 0.002$; Table 3; Fig. 1). In contrast, PMRT was not correlated with LRR ($P = 0.470$), DR ($P = 0.260$) or BCM ($P = 0.480$; Table 3; Fig. 1) in low-risk group.

Of note, majority (75.3%) of irradiated patients in our study have

Table 1
Characteristics of patients by receipt of PMRT.

Characteristic	No-PMRT (n = 3277)	PMRT (n = 162)	P
Age (mean (SD))	50.17 (10.19)	46.23 (9.46)	<0.001
Year of diagnosis			<0.001
2000–2008	862 (26.3)	96 (59.3)	
2009–2016	2415 (73.7)	66 (40.7)	
Tumor size			<0.001
T1	1558 (47.5)	40 (24.7)	
T2	1719 (52.5)	122 (75.3)	
ER status			<0.001
Positive	2134 (65.1)	67 (41.4)	
Negative	1143 (34.9)	95 (58.6)	
PR status			0.932
Positive	2062 (62.9)	103 (63.6)	
Negative	1215 (37.1)	59 (36.4)	
HER2 status			0.743
Positive	602 (18.4)	33 (20.4)	
Negative	2264 (69.1)	111 (68.5)	
Unknown	411 (12.5)	18 (11.1)	
Histologic grade			<0.001
I-II	1596 (48.7)	38 (23.5)	
III	1681 (51.3)	124 (76.5)	
Histologic type			0.335
Ductal	2705 (82.5)	139 (85.8)	
Other	572 (17.5)	23 (14.2)	
LVI			0.329
Positive	353 (10.8)	13 (8.0)	
Negative	2924 (89.2)	149 (92.0)	
Adjuvant chemotherapy			0.612
Yes	1967 (60.0)	101 (62.3)	
No	1310 (40.0)	61 (37.7)	
Endocrine therapy			0.821
Yes	2166 (66.1)	109 (67.3)	
No	1111 (33.9)	53 (32.7)	

Abbreviations: PMRT, postmastectomy radiation therapy; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; LVI, lymphovascular invasion.

Table 2
Univariate and Multivariate[a] analysis for LRR in 3277 unirradiated patients.

Variable	Univariate analysis		Multivariate analysis	
	HR (95%CI)	*P*	HR (95%CI)	*P*
Age (continuous)	0.990 (0.970–1.011)	0.360		
Year of diagnosis				
2000–2008	Reference			
2009–2016	0.781 (0.482–1.267)	0.320		
Tumor size				
T2 vs. T1	3.817 (2.206–6.603)	<0.001	3.112 (1.783–5.430)	<0.001
ER status				
Positive vs. Negative	0.216 (0.134–0.348)	<0.001	0.325 (0.146–0.725)	0.006
PR status				
Positive vs. Negative	0.291 (0.185–0.458)	<0.001	0.853 (0.383–1.900)	0.700
HER2 status				
Negative	Reference			
Positive	1.508 (0.663–1.117)	0.263		
Unknown	0.895 (0.426–1.880)	0.770		
Histologic grade				
III vs.I-II	4.123 (2.388–7.119)	<0.001	2.547 (1.397–4.640)	0.002
Histologic type				
Other vs. ductal	2.024 (0.978–4.189)	0.057		
LVI				
Positive vs. Negative	4.641 (2.706–7.959)	<0.001	4.427 (2.542–7.710)	<0.001

Abbreviations: LRR, locoregional recurrence; HR, hazard ratio; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; LVI, lymphovascular invasion.
[a] The Fine-Gray model was adjusted by age, year of diagnosis, ER status, HER2 status, PR status, histologic grade, histologic type and LVI.

Table 3
Effect of PMRT on LRR, DR and BCM according to adjusted Fine-Gray model in different subgroups[a].

	PMRT	LRR		DR		BCM	
		HR (95%CI)	*P*	HR (95%CI)	*P*	HR (95%CI)	*P*
All patients	No (n = 3277)						
	Yes (n = 162)	0.305 (0.076–1.224)	0.094	0.743 (0.372–1.483)	0.400	0.544 (0.233–1.272)	0.160
Low-risk	No (n = 2696)						
	Yes (n = 75)	1.837 (0.356–9.466)	0.470	1.585 (0.711–3.535)	0.260	1.428 (0.527–3.867)	0.480
High-risk	No (n = 581)						
	Yes (n = 87)	0.084 (0.010–0.692)	0.021	0.187 (0.057–0.615)	0.006	0.127 (0.034–0.481)	0.002

Abbreviations: PMRT, postmastectomy radiation therapy; LRR, locoregional recurrence; DR, distant recurrence; BCM, breast cancer mortality; HR, hazard ratio.
[a] The Fine-Gray model was adjusted by age, year of diagnosis, ER status, HER2 status, PR status, histologic grade, histologic type, LVI, receipt of chemotherapy and receipt of endocrine therapy.

tumors 2–5 cm in size. Therefore, we further analyzed the effect of PMRT in patients with T2N0 breast cancer. As depicted in the forest plot (Fig. 2), PMRT was associated with decreased LRR (HR, 0.052; 95% CI, 0.006–0.477; $P = 0.009$), DR (HR, 0.184; 95% CI, 0.056–0.609; $P = 0.006$) and BCM (HR, 0.125; 95% CI, 0.033–0.482; $P = 0.003$) in high-risk group. In contrast, no correlation of PMRT with survival outcome was observed in low-risk group.

4. Discussion

The prognostic effect of PMRT in high-risk patients with T1-2 node-negative breast cancer is contentious. In this large population-based study, for patients at high risk of LRR, PMRT was associated with a 8.3% risk reduction in 5-year cumulative incidence of LRR, 7.8% risk reduction in 5-year cumulative incidence of DR and 6.4% risk reduction in 5-year cumulative incidence of BCM.

In the no-PMRT group of this study, 60.1% of patients received adjuvant chemotherapy, 91.9% (n = 1900) of which received anthracycline- or taxane-based regimens. This contemporary practice might account for the relative low rate of LRR in unirradiated patients (5-year cumulative incidence 2.2%). Consistently, previous studies also demonstrated low rate of LRR (2.1%–3.1%) in unirradiated patients with T1-2N0 breast cancer who mostly received chemotherapy [3–5]. In contrast, studies with minority of unirradiated patients receiving chemotherapy demonstrated higher rates of LRR (5.2%–9.2%) [2,12]. As the modern systemic therapy improved the outcome of breast cancer patients [13], effect of PMRT on patients with T1-2N0 breast cancer needs to be clarified with caution.

Several retrospective studies focused on identifying patients with T1-2N0 disease at high risk of LRR. In a study including 1136 unirradiated patients who were diagnosed between 1980 and 2004, larger tumor size (>2 cm), close or positive margin, younger age and LVI were found to be associated with increased LRR. The 10-year cumulative incidence of LRR for patients with three or more risk factors was 19.7%, while the rate for patients without risk factors was 2.0% [2]. In a cohort of 672 unirradiated patients treated between 2006 and 2011, increasing tumor size (>2 cm) was found as a correlate of LRR. Patients with four or more high-risk features exhibited a rate of 9.4% for 5-year LRR, whereas those with one

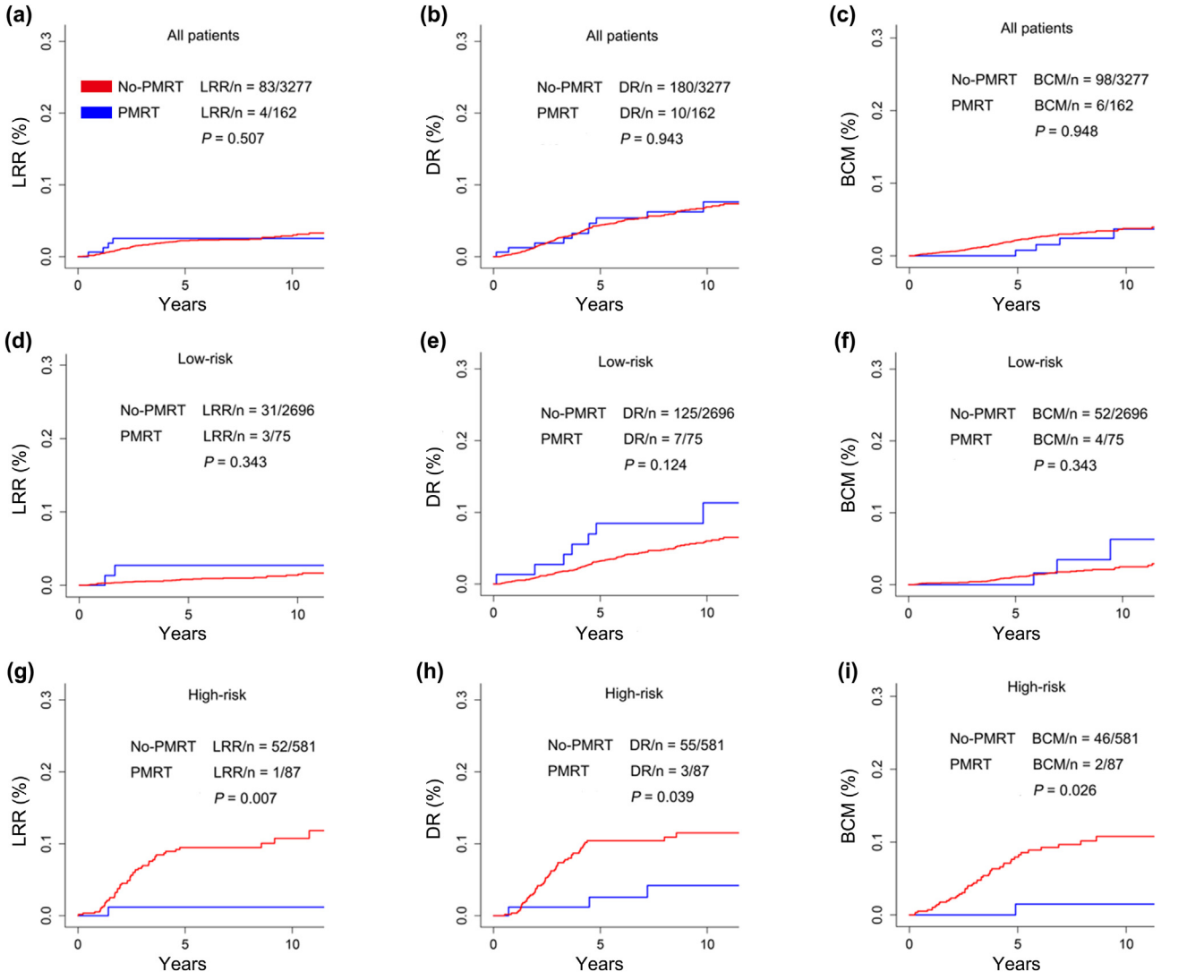

Fig. 1. Cumulative incidence of LRR, DR and BCM by PMRT in all patients with T1-2N0 breast cancer (**a**–**c**), low-risk group (**d**–**f**) and high-risk group (**g**–**i**). Abbreviations: LRR, locoregional recurrence; DR, distant recurrence; BCM, breast cancer mortality; PMRT, postmastectomy radiation therapy.

high-risk feature presented a rate of 3.8% [1]. In a study of 1505 unirradiated patients treated between 1989 and 1999, Truong et al. [4] demonstrated that larger tumor size (>2 cm), higher tumor grade and LVI were predictive of LRR. Patients with two or more risk factors presented a 10-year LRR risk of 20%, while those without risk factors exhibited a rate of 5.5%. In the present study, we identified tumor size, ER status, histologic grade and LVI as the risk factors of LRR. The 5-year rate of LRR for unirradiated patients with 3 or 4 risk factors was 9.5%, while the rate for low-risk patients was 0.8%, which is comparable to the above-mentioned rates. Although studies concentrated on identifying risk factors of LRR, the results were varied. Thus, the patient selection criteria for PMRT in patients with T1-2N0 breast cancer was still uncertain.

There is limited evidence to directly investigate the effect of PMRT on patients with T1-2N0 breast cancer. The Early Breast Cancer Trialists Collaborative Group meta-analysis demonstrated no benefit form PMRT for node-negative patients, in terms of LRR, overall recurrence and BCM. Consistently, we found no correlation between PMRT and outcomes of interest in all patients with T1-2N0 breast cancer in the present study. For patients with T1-2N0 breast cancer and high-risk features, the favorable findings from the EORTC 22,922/10,925 trial support the addition of nodal irradiation to whole-breast radiation therapy [11]. In the present study, for patients with 3 or 4 risk factors of LRR, PMRT was significantly associated with reduced LRR, DR and BCM, suggesting a heterogeneous effect of PMRT on patients with T1-2N0 breast cancer. PMRT might be beneficial for patients at high risk of LRR by eradicating the remaining tumor foci after surgery. On the contrary, despite the advances in radiation technology [14], the risk of detrimental effect of PMRT might outweigh its benefit for patients at low risk of LRR. The benefit-risk evaluation of PMRT in patients with T1-2N0 breast cancer should be taken into consideration in clinical practice.

Since majority of irradiated patients in our study have tumors 2–5 cm in size, we further analyzed the effect of PMRT in patients with T2N0 breast cancer. PMRT was found to be correlated with decreased LRR, DR and BCM in high-risk group, other than low-risk group. These results were consistent with the former findings in patients with T1-2N0 breast cancer, confirming the hypothesis that patients with higher risk of LRR might benefit from PMRT.

The limitation to this study is the retrospective nature, which might subject to selection bias.

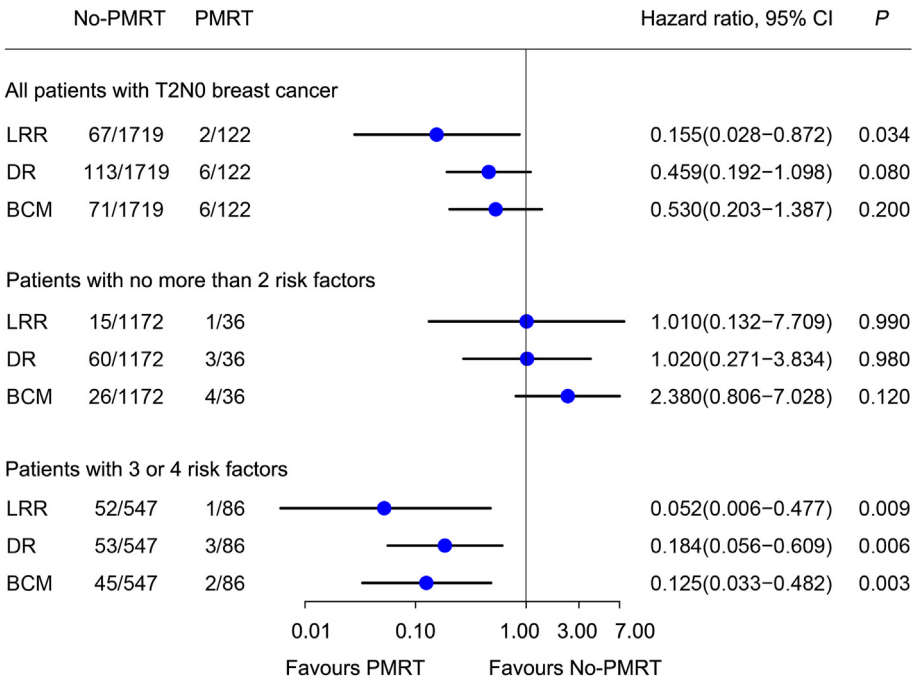

Fig. 2. The effect of PMRT on patient subgroups with T2N0 breast cancer. Abbreviations: PMRT, postmastectomy radiation therapy; LRR, locoregional recurrence; DR, distant recurrence; BCM, breast cancer mortality.

5. Conclusions

In this large sample sized study, we identified tumor size, ER status, histologic grade and LVI as the risk factors of LRR in patients with T1-2N0 breast cancer. Patients with 3 or 4 risk factors were more likely to benefit from PMRT. Our findings need to be validated by further studies.

Funding

Supported by the 135 project for disciplines of excellence, West China Hospital, Sichuan University (grant number: ZYGD18012).

Ethics statement

Institutional review board approval was acquired from the Clinical Test and Biomedical Ethics Committee of our institution.

Declaration of competing interest

The authors have no conflicts of interest to disclose.

References

[1] Mamtani A, Patil S, Stempel MM, et al. Are there patients with T1 to T2, lymph node-negative breast cancer who are "high-risk" for locoregional disease recurrence? Cancer 2017;123(14):2626–33.
[2] Abi-Raad R, Boutrus R, Wang R, et al. Patterns and risk factors of locoregional recurrence in T1-T2 node negative breast cancer patients treated with mastectomy: implications for postmastectomy radiotherapy. Int J Radiat Oncol Biol Phys 2011;81(3):e151–7.
[3] Sharma R, Bedrosian I, Lucci A, et al. Present-day locoregional control in patients with t1 or t2 breast cancer with 0 and 1 to 3 positive lymph nodes after mastectomy without radiotherapy. Ann Surg Oncol 2010;17(11):2899–908.
[4] Truong PT, Lesperance M, Culhaci A, et al. Patient subsets with T1-T2, node-negative breast cancer at high locoregional recurrence risk after mastectomy. Int J Radiat Oncol Biol Phys 2005;62(1):175–82.
[5] Yildirim E, Berberoglu U. J International journal of radiation oncology, biology, physics. Can a subgroup of node-negative breast carcinoma patients with T1-2 tumor who may benefit from postmastectomy radiotherapy be identified? Int J Radiat Oncol Biol Phys 2007;68(4):1024–9.
[6] Luo C, Zhong X, Deng L, et al. Nomogram predicting locoregional recurrence to assist decision-making of postmastectomy radiation therapy in patients with T1-2N1 breast cancer. Int J Radiat Oncol Biol Phys 2019;103(4):905–12.
[7] Taghian A, Jeong JH, Mamounas E, et al. Patterns of locoregional failure in patients with operable breast cancer treated by mastectomy and adjuvant chemotherapy with or without tamoxifen and without radiotherapy: results from five National Surgical Adjuvant Breast and Bowel Project randomized clinical trials. J Clin Oncol 2004;22(21):4247–54.
[8] Matsunuma R, Oguchi M, Fujikane T, et al. Influence of lymphatic invasion on locoregional recurrence following mastectomy: indication for post-mastectomy radiotherapy for breast cancer patients with one to three positive nodes. Int J Radiat Oncol Biol Phys 2012;83(3):845–52.
[9] National Comprehensive Cancer Network (NCCN). NCCN Clinical Practice Guidelines in Oncology. Breast Cancer Version 3.2021. 2021 March 29; National Comprehensive Cancer Network. https://www.nccn.org/professionals/physician_gls/pdf/breast.pdf.
[10] McGale P, Taylor C, Correa C, et al. Effect of radiotherapy after mastectomy and axillary surgery on 10-year recurrence and 20-year breast cancer mortality: meta-analysis of individual patient data for 8135 women in 22 randomised trials. Lancet 2014;383(9935):2127–35.
[11] Poortmans PM, Weltens C, Fortpied C, et al. Internal mammary and medial supraclavicular lymph node chain irradiation in stage I-III breast cancer (EORTC 22922/10925): 15-year results of a randomised, phase 3 trial. Lancet Oncol 2020;21(12):1602–10.
[12] Wallgren A, Bonetti M, Gelber RD, et al. Risk factors for locoregional recurrence among breast cancer patients: results from International Breast Cancer Study Group Trials I through VII. J Clin Oncol 2003;21(7):1205–13.
[13] Peto R, Davies C, Godwin J, et al. Comparisons between different polychemotherapy regimens for early breast cancer: meta-analyses of long-term outcome among 100,000 women in 123 randomised trials. Lancet 2012;379(9814):432–44.
[14] Giordano SH, Kuo YF, Freeman JL, et al. Risk of cardiac death after adjuvant radiotherapy for breast cancer. J Natl Cancer Inst 2005;97(6):419–24.