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Influence of age as a continuous variable on the prognosis of patients with pT1-2N1 breast cancer

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ABSTRACT

Purpose: To assess the influence of age as a continuous variable on the prognosis of pT1-2N1 breast cancer and examine its decision-making value for postmastectomy radiotherapy (PMRT).

Methods: We retrospectively evaluated 5438 patients with pT1-2N1 breast cancer after mastectomy in 11 hospitals. A multivariable Cox proportional hazards regression model with penalized splines was used to examine the relationship between age and oncologic outcomes.

Results: The median follow-up was 67.0 months. After adjustments for confounding characteristics, nonsignificant downward trend in locoregional recurrence (LRR) risk was observed with increasing age (*P*-non-linear association = 0.640; *P*-linear association = 0.078). A significant non-linear association was found between age and disease-free survival (DFS) and overall survival (OS) (*P*-non-linear association <0.05; *P*-linear association >0.05, respectively). The DFS and OS exhibited U-shaped relationships, with the hazard ratios (HRs), reaching a nadir at 50 years old. A decreased risk of LRR with PMRT vs. no PMRT (HR = 0.304, 95% CI: 0.204–0.454) was maintained in all ages. The HR of PMRT vs. no PMRT for DFS and OS gradually increased with age. In patients ≤50 years old, PMRT was independently associated with favorable LRR, DFS, and OS, all $P < 0.05$). In patients >50 years old, PMRT was independently associated with reduced LRR ($P = 0.004$), but had no effect on DFS or OS.

Conclusions: Age was an independent prognostic factor for pT1-2N1 breast cancer; PMRT provided survival benefits for patients ≤50 years old, but not for patients >50 years old.

Abbreviations: PMRT, postmastectomy radiotherapy; LRR, locoregional recurrence; DFS, disease-free survival; OS, overall survival; HR, hazard ratios; P-splines, penalized splines; LVI, lymphovascular invasion; HER2, human epidermal growth factor receptor 2; RT, radiation therapy; Surveillance, Epidemiology; and End Results, SEER.

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1. Introduction

Breast cancer is the world's most common diagnosis of cancer [1], and many studies have examined the prognostic value of age at diagnosis in patients with breast cancer. Several large studies have concluded that a young age indicates an unfavorable prognosis and serves as an independent predictor for a higher risk of cancer recurrence and death [2–8]. However, the definition of "young age" and the different age cutoffs that have been proposed (younger than 35, 40, or 50 years of age) have been a source of controversy [2–5,7,9,10]. Previous studies that focused on age have examined outcomes of patients using crude age groupings, few studies have evaluated the effect of age as a continuous variable on the prognosis of breast cancer [5,6,8,11]. Currently, investigators adjust or match for age to negate the effect of age in statistical analyses, and few studies have focused on age as the primary exposure to observe its effects. Hence, clarification of the relationship between age and prognosis might provide insight into the biologic aspects of tumors.

Postmastectomy radiotherapy (PMRT) can significantly reduce the locoregional recurrence (LRR) and mortality rates of breast cancer in high-risk patients [12]. However, the role of PMRT in patients with pathologic T1-T2 breast cancer with 1–3 positive lymph nodes is controversial. The 2022 National Comprehensive Cancer Network guidelines (2nd edition) recommend that patients with 1–3 positive axillary lymph nodes strongly consider undergoing PMRT. The 2017 St. Gallen International Consensus Guidelines recommend PMRT in cases of 1–3 positive lymph nodes with adverse clinical features, including young age (≤40 years) or other adverse biological characteristics [13]. Until now, the independent effect of age as a continuous variable on the prognosis of pT1-2N1 breast cancer has not been well established. The extent to which PMRT influences this association and whether age influences the effect of PMRT are unknown [14,15].

In this study, we sought to examine the relationship between age and the prognosis of patients with pT1-2N1 breast cancer after mastectomy and determine its decision-making value for PMRT.

2. Materials and methods

2.1. Patients

The study protocol was approved (15–057/984) by the ethics review board of the Chinese Academy of Medical Sciences in Beijing, China. Data from patients with pathologically confirmed breast cancer who underwent mastectomy between September 1997 and January 2018 at 11 Chinese hospitals were analyzed retrospectively. The inclusion criteria were: (1) newly diagnosed breast cancer with a tumor size ≤5 cm and 1 to 3 positive lymph nodes (pT1-2N1 disease); (2) treatment with mastectomy and axillary lymph node dissection with negative margins; (3) no evidence of distant dissemination, supraclavicular or internal mammary nodal metastasis at diagnosis; and (4) no history of neoadjuvant therapy. We reviewed the data of 5537 patients, of whom, 99 were excluded either because of their unknown age at the time of diagnosis (n = 4), unknown adjuvant radiation therapy (n = 54), bilateral breast cancer (n = 2), unknown date of surgery (n = 2), or unknown date of the last follow-up (n = 37). A total of 5438 patients were included in the analyses.

2.2. Follow-up and definitions of outcomes

Follow-up data were obtained from hospital records or through direct correspondence with the patients or their families. Patients were censored at last follow-up or death. Time to all events was calculated from the date of the mastectomy to the date of the event's occurrence or the last follow-up. The LRR was defined as tumor recurrences in the ipsilateral chest wall, the axillary, supra/infra-clavicular, or internal mammary lymph nodes; disease-free survival (DFS) events included any tumor recurrence or death; and overall survival (OS) events included death from any cause.

2.3. Statistics

Associations between the patients' characteristics and age groups were assessed using Pearson's Chi-square test for categorical variables. The LRR, DFS, and OS rates were estimated using the Kaplan-Meier method, and differences were compared using the log-rank test. A multivariable Cox proportional hazards regression model with penalized splines (P-splines) was used to examine the relationship between age and all outcomes [16]. The multivariable analyses was adjusted for potential confounders, including treatment era (1997–2007 vs. 2008–2018), tumor location (inner quadrant vs. others), pathological T stage (pT2 vs. pT1), tumor grade (G3 vs. G1-2), lymphovascular invasion (LVI) (yes vs. no), hormone receptors (negative vs. positive), positive lymph node ratio (≤10% vs. 10%–20% vs. > 20%), PMRT (yes vs. no), chemotherapy (yes vs. no), and human epidermal growth factor receptor 2 (HER2) status stratified by treatment (positive without trastuzumab vs. negative & positive with trastuzumab) [17–19]. The multivariable analysis was performed using Cox logistic regression, and the effect of PMRT vs. no PMRT in different ages was expressed using hazard ratio (HR) curves [20]. All *P* values were two-tailed, and a value of less than 0.05 was considered statistically significant. Statistical analyses were performed using SPSS Statistics v24.0 (IBM Corp., Armonk, NY, USA) and the rms, smoothHR, simPH, and survminer packages in R software v4.1.1 (http://www.r-project.org/).

3. Results

3.1. Patients' characteristics

This study's cohort consisted of 5438 patients. The distribution of patients by age group was as follows: 101 (1.9%) patients were ≤30 years old, 856 (15.7%) were 30–40, 2090 (38.4%) were 40–50, 1568 (28.8%) were 50–60, and 823 (15.1%) were >60 years old. The patient, tumor, and treatment characteristics are summarized in Table 1. The median number of axillary lymph nodes dissected was 16 (interquartile range [IQR] = 12–21), and the median number of positive lymph nodes was 1 (range = 1–3). Among the 5114 (94.0%) patients who underwent adjuvant chemotherapy, 4674 (91.4%) received anthracycline-based and/or taxane-based regimens. Among the 4150 (76.3%) patients with hormone receptor-positive tumors, 3452 (83.2%) underwent endocrine therapy. Among the 1043 (19.2%) patients with HER2-positive tumors, only 190 (18.2%) underwent anti-HER2 targeted therapy, because trastuzumab was not approved by the China Food and Drug Administration until September 2007.

A total of 1779 (32.7%) patients were treated with PMRT. The chest wall was irradiated in 1640 (92.2%) patients with a 0.5 cm-thick bolus being used for the first 2/5–3/5 RT courses, and the supra/infraclavicular region was irradiated in 1608 (90.4%) patients. Only 162 (9.1%) patients received internal mammary node irradiation, and 145 (8.2%) received axilla irradiation. Conventional fractionated radiation therapy (RT) was used for 1603 (90.1%) patients, and the dose was 45–50 Gy in 25 fractions over 5 weeks. Hypofractionated RT was used for 52 (2.9%) patients, with doses of 40–43.5 Gy in 15 fractions over 3 weeks. The dose fractionation of 124 (7.0%) patients was unknown.

3.2. Effect of age on the prognosis of the entire cohort

After a median follow-up of 67.0 months (IQR = 42.6–88.8 months), 395 (7.3%) patients developed LRR, 732 (13.5%) developed distant metastasis, and 496 (9.1%) died. The 5-year outcome rates of the entire cohort were LRR = 6.6%, DFS = 83.9%, and OS = 93.1%. In Fig. 1, the LRR (Fig. 1A), DFS (Fig. 1B), and OS (Fig. 1C) curves are summarized by the different age groups.

Table 1
Tumor and treatment characteristics of breast-cancer patients by age at diagnosis.

Characteristics	Total (N = 5438), n (%)	≤50-year-old group (N = 3047), n (%)	>50-year-old group (N = 2391), n (%)	*P* value
Age (years)				
≤30	101 (1.9)			
30-40	856 (15.7)			
40-50	2090 (38.4)			
50-60	1568 (28.8)			
>60	823 (15.1)			
Age, Median (range)	49 (20–84)	43 (20–50)	58(51–84)	
Menopausal status				< 0.001
Premenopausal	2950 (54.2)	2682 (89.2)	268 (11.4)	
Menopausal	2241 (41.2)	222 (7.4)	2019 (86.1)	
Perimenopausal	159 (2.9)	102 (3.4)	57 (2.4)	
Unknown	88 (1.6)			
Treatment era				< 0.001
1997–2007	1910 (35.1)	1140 (37.4)	770 (32.2)	
2008–2018	3528 (64.9)	1907 (62.6)	1621 (67.8)	
Laterality				0.667
Left	2783 (51.2)	1567 (51.4)	1216 (50.9)	
Right	2654 (48.8)	1479 (48.6)	1175 (49.1)	
Unknown	1 (0.1)			
Tumor location				0.228
Inner quadrants	1142 (21.0)	658 (22.4)	484 (21.1)	
Other quadrants	4087 (75.2)	2273 (77.6)	1814 (78.9)	
Unknown	209 (3.8)			
Pathological type				0.968
Invasive ductal carcinoma	5086 (93.5)	2849 (93.5)	2237 (93.6)	
Others	351 (6.5)	197 (6.5)	154 (6.4)	
Unknown	1 (0.1)			
pT stage				0.055
pT1	2386 (43.9)	1302 (42.7)	1084 (45.3)	
pT2	3052 (56.1)	1745 (57.3)	1307 (54.7)	
Number of positive nodes				0.341
1	2723 (50.1)	1504 (49.4)	1219 (51.0)	
2	1673 (30.8)	940 (30.9)	733 (30.7)	
3	1042 (19.2)	603 (19.8)	439 (18.4)	
Number of nodes removed				0.224
<10	584 (10.7)	341 (11.2)	243 (10.2)	
≥10	4854 (89.3)	2706 (88.8)	2148 (89.8)	
Positive lymph node ratio				0.217
≤10%	2967 (54.6)	1635 (53.7)	1332 (55.7)	
10%–20%	1887 (34.7)	1069 (35.1)	818 (34.2)	
>20%	584 (10.7)	343 (11.3)	241 (10.1%)	
Tumor grade				0.610
I	131 (2.4)	66 (2.9)	65 (3.4)	
II	2938 (54.0)	1605 (70.1)	1333 (69.2)	
III	1145 (21.1)	618 (27.0)	527 (27.4)	
Unknown	1224 (22.5)			
Lymphovascular invasion				0.032
Yes	607 (11.2)	362 (12.7)	245 (10.8)	
No	4521 (83.1)	2488 (87.3)	2033 (89.2)	
Unknown	310 (5.7)			
Hormone receptors				0.082
Positive	4150 (76.3)	2343 (78.8)	1807 (76.8)	
Negative	1179 (21.7)	632 (21.2)	547 (23.2)	
Unknown	109 (2.0)			
HER2 status				0.526
Positive	1043 (19.2)	592 (22.9)	451 (22.2)	
Negative	3574 (65.7)	1989 (77.1)	1585 (77.8)	
Unknown	821 (15.1)			
Ki67 index				0.594
<14%	1698 (31.2)	941 (54.3)	757 (53.3)	
≥14%	1454 (26.7)	792 (45.7)	662 (46.7)	
Unknown	2286 (42.0)			
Molecular subtype				0.022
Luminal HER2-negative	2919 (53.7)	1616 (62.6)	1303 (64.0)	
Luminal HER2-positive	645 (11.9)	389 (15.1)	256 (12.6)	
HER2-overexpressing	398 (7.3)	203 (7.9)	195 (9.6)	
Triple-negative	653 (12.0)	372 (14.4)	281 (13.8)	
Unknown	823 (15.1)			
Endocrine therapy[a]				0.061
Yes	3452 (83.2)	1916 (87.2)	1536 (89.2)	
No	466 (11.2)	280 (12.8)	186 (10.8)	
Unknown	232 (5.6)			
Anti-HER2-targeted therapy[b]				0.005
Yes	190 (18.2)	125 (22.0)	65 (15.0)	
No	811 (77.8)	442 (78.0)	369 (85.0)	
Unknown	42 (4.0)			
Adjuvant chemotherapy				< 0.001
Yes	5114 (94.0)	2955 (97.8)	2159 (91.0)	
No	278 (5.1)	65 (2.2)	213 (9.0)	
Unknown	46 (0.8)			
Adjuvant radiotherapy				< 0.001
Yes	1779 (32.7)	1145 (37.6)	634 (26.5)	
No	3659 (67.3)	1902 (62.4)	1757 (73.5)	

Abbreviations: HER2 = human epidermal growth factor receptor 2.
[a] Only hormone-receptor positive patients were included.
[b] Only Her2 positive patients were included.

Fig. 2 shows the association of age as a continuous variable with LRR (Fig. 2A), DFS (Fig. 2B), and OS (Fig. 2C) after adjusting for confounders. The LRR risk generally showed a downward trend with increasing age, although the association did not reach significance (*P*-non-linear association = 0.640, *P*-linear association = 0.078). Significant non-linear associations of age with DFS and OS (*P*-non-linear association <0.05, P-linear association >0.05) were found. Age showed a similar U-shaped association with DFS and OS, suggesting 50 years being a reference age, with negative associations below and positive associations above that.

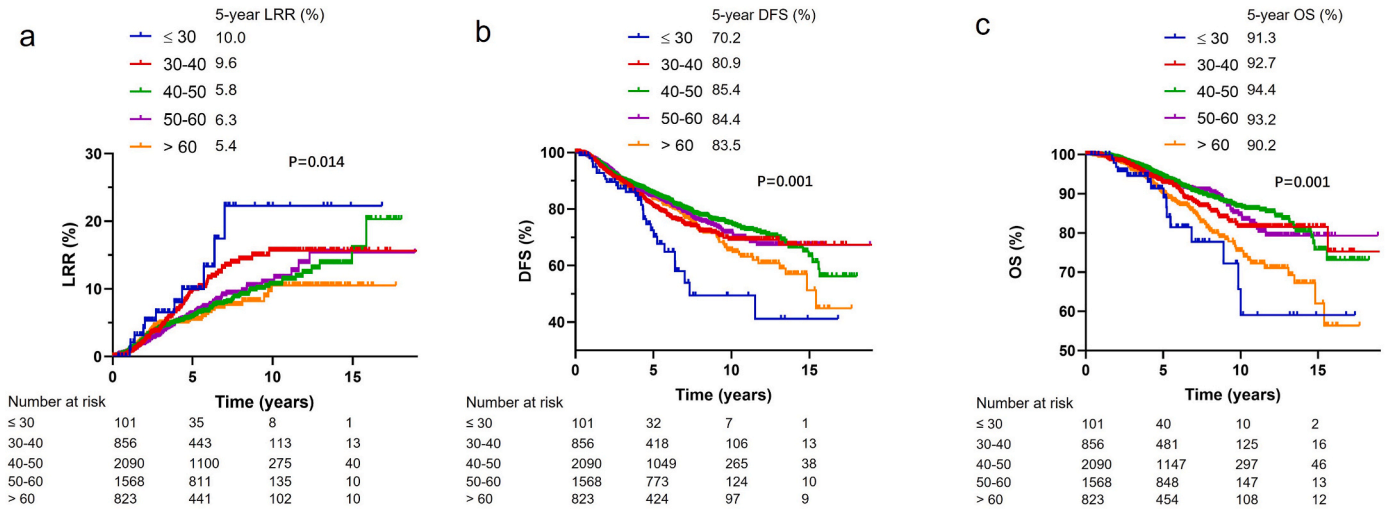

Fig. 1. Kaplan-Meier curves of LRR (A), DFS (B), and OS (C) in the entire cohort stratified by different age groups. *Abbreviations:* LRR = locoregional recurrence; DFS = disease-free survival; OS = overall survival.

3.3. Effect of age on the prognosis of patients with and without PMRT

Among the 3659 patients who did not receive PMRT, the effect of age, as a continuous variable, on their prognosis after adjusting for confounders, was similar to that observed in the entire cohort (Supplementary Fig. 1B and C).

Among the 1779 patients who received PMRT, no significant associations between age and any of the outcomes (LRR, DFS or OS) were found (*P*-non-linear association >0.05; *P*-linear association >0.05) (Supplementary Fig. 2A-C).

3.4. Treatment benefits of PMRT by age

The HRs for LRR, DFS, and OS by PMRT vs. no PMRT, after adjusting for confounders, were plotted when age was analyzed as a continuous variable in the entire cohort (Fig. 3). PMRT independently decreased LRR risk (HR: 0.304, 95% CI: 0.204–0.454), and the HR for the PMRT vs. no PMRT on LRR remained almost constant in patients of all ages (Fig. 3A). The HR for the DFS of patients who received PMRT vs. no PMRT (HR: 0.684, 95% CI: 0.552–0.846) gradually increased as their age increased, indicating that the older the age at diagnosis, the lower the likelihood of benefitting from PMRT for DFS (Fig. 3B); PMRT independently improved OS (Fig. 3C) (HR: 0.671, 95% CI: 0.484–0.929), and the trend was similar to that for DFS.

Given the significantly different trends in DFS and OS with increasing age between patients ≤50 and >50 years old, we stratified them into two age groups: ≤ 50 and >50 years old. The percentage of patients ≤50 years who were treated in the earlier era was higher than the percentage of patients >50 years. More patients in the ≤50-year-old group had LVI and triple-negative breast cancers, compared to those in the >50-year-old group. Compared to the patients in the >50-year-old group, those ≤50 years old were more likely to receive systemic therapy and PMRT. No significant differences in the other factors were found between the two groups (Table 1).

Among the 3047 patients ≤50 years old, the multivariable analysis showed that PMRT was independently associated with better LRR, DFS, and OS ($P < 0.01$; Table 2). Among the 2391 patients >50 years old, multivariable analysis showed that PMRT was independently associated with reduced LRR ($P = 0.004$), but had no effect on DFS or OS ($P > 0.05$; Table 3).

4. Discussion

In the present study, we examined the relationship between age at diagnosis and the prognosis of patients with pT1-2N1 breast cancer using a large multicenter cohort. While previous investigations have examined the effect of age in a dichotomous fashion using arbitrary classifications, we evaluated the associations between age and three outcomes on a continuous scale. After adjusting for confounders, we found a trend toward a decrease in LRR risk with an increase in age. Patients ≤50 and >50 years old differed in their associations with DFS and OS. Treatment with PMRT significantly decreased the risk of LRR in patients of all ages, and it independently provided a survival benefit for patients ≤50 years old, but not for those >50 years old.

Few studies have evaluated the effect of age as a continuous variable on the prognosis of breast cancer [5,6,8,11]. A 1993 study analyzed the association between age and the risk of recurrence in 3771 premenopausal breast-cancer patients, and found a 4% decrease in recurrence for each yearly increase in age [6]. Another early study from Korea, which included 9885 breast cancer patients ≤50 years old, also reported a negative correlation between age and the HR for death [5]. These findings are consistent with our results that younger age is associated with a worse prognosis among patients ≤50 years old. A Surveillance, Epidemiology, and End Results (SEER) database analysis including 206, 332 breast cancer women showed that adjusted risk of breast cancer-specific mortality decreases from 18 to 45 years and then increases thereafter [11]. A study conducted in Singapore evaluated the influence of age as a continuous variable on the outcomes of 2492 breast-cancer patients treated with breast-conserving therapy [8]. In that study, a U-shaped association of age with OS was observed, with the minimum HR at approximately 45 years old, and the HR of LRR decreased linearly with increasing age, which is similar to our results. Unlike our observations, the Singapore study found an L-shaped relationship between age and DFS. Different populations and treatment modalities may explain the discrepancies between their results and ours. All the patients in their study received breast-conserving therapy followed by adjuvant radiotherapy, and 73.7% of them had N0 disease. Different treatment modalities and tumor burdens may change the relationship between age and prognosis.

Our data showed that young age was associated with poor prognosis. Among the patients ≤50 years old, the risks for all outcomes increased rapidly with decreasing age. The results of previous studies have

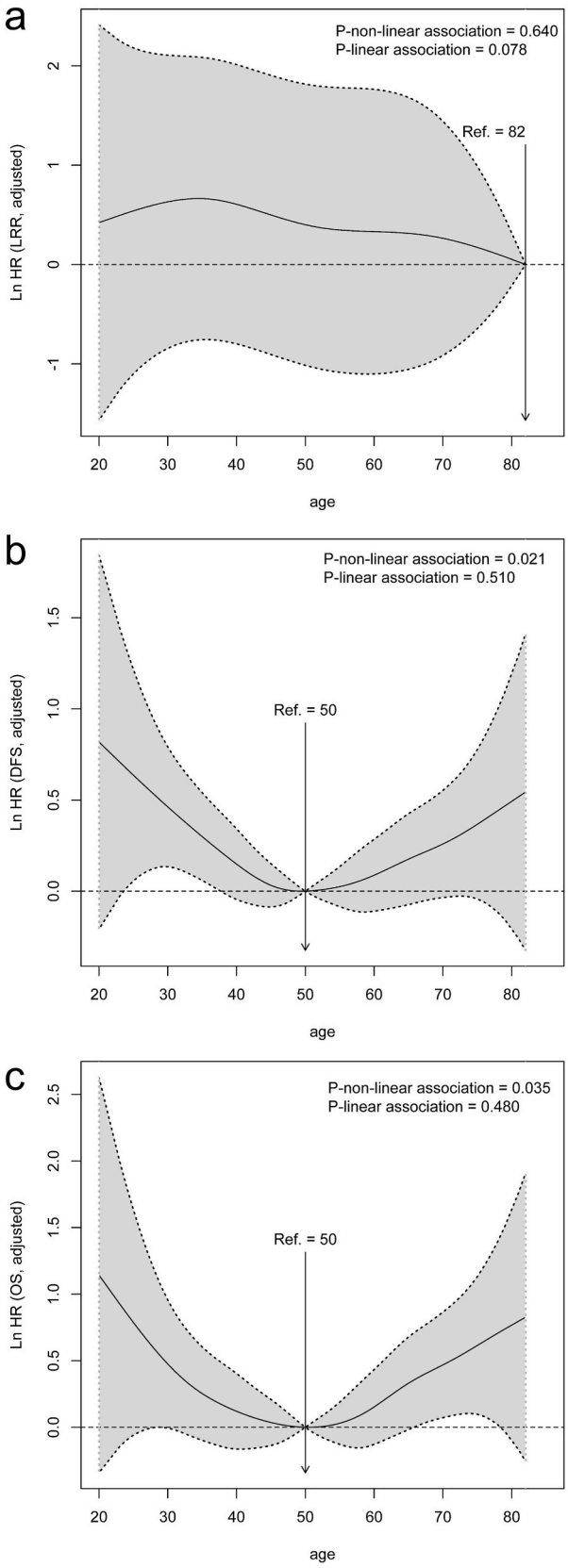

Fig. 2. The estimated natural logarithms of the hazard ratios (HRs) with 95% confidence intervals (CIs) for the associations of age with LRR (A), DFS (B), and OS (C) in the entire cohort. Solid black lines are multivariable adjusted natural logarithms of the HRs, and the shaded gray areas show the 95% CIs. All results were adjusted for treatment era (1997–2007 vs. 2008–2018), tumor location (inner quadrants vs. others), pathological T stage (pT2 vs. pT1), tumor grade (G3 vs. G1-2), lymphovascular invasion (yes vs. no), hormone receptors (negative vs. positive), positive lymph node ratio (≤10% vs. 10%–20% vs. > 20%), PMRT (yes vs. no), chemotherapy (yes vs. no), and human epidermal growth factor receptor 2 (HER2) status, stratified by treatment (positive without trastuzumab vs. negative & positive with trastuzumab). *Abbreviations:* Ln HR = natural logarithm of the hazard ratio; LRR = locoregional recurrence; DFS = disease-free survival; OS = overall survival.

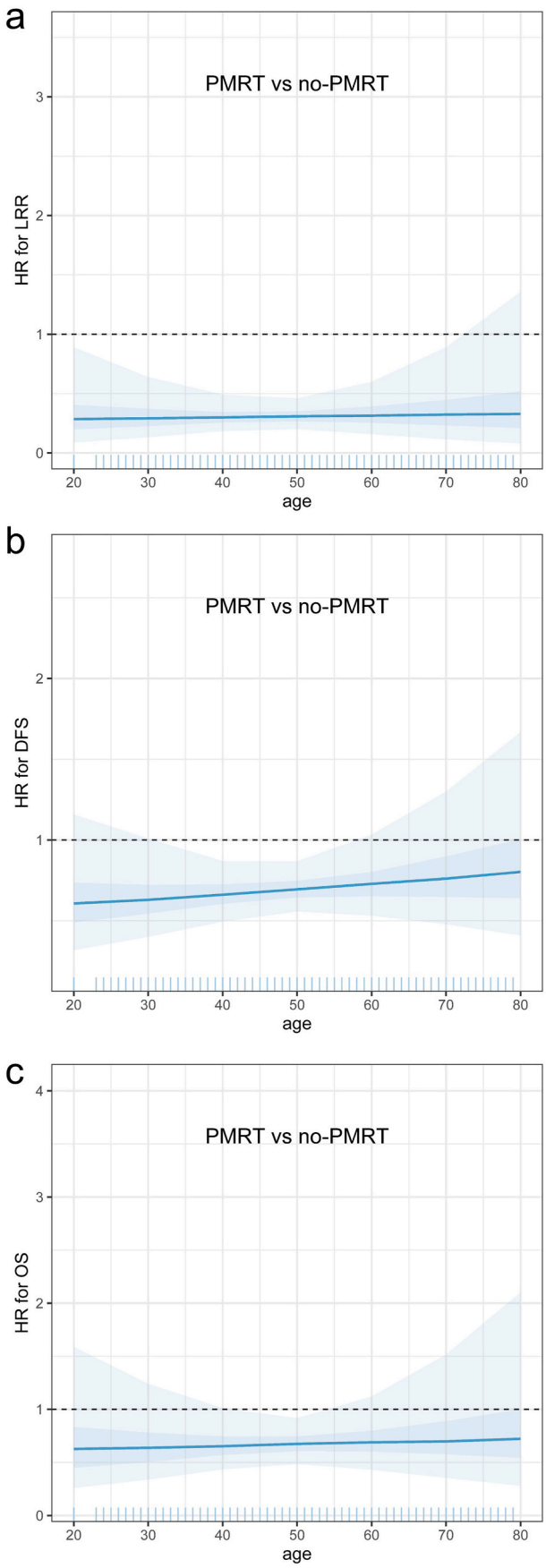

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Fig. 3. The impact of PMRT on LRR (A), DFS (B), and OS (C) outcomes of patients of various ages. Hazard ratios (HRs) are presented as PMRT vs. no PMRT. The solid blue line represents the HR estimate, and the shaded areas show the 95% confidence intervals (CIs). All results were adjusted for treatment era (1997–2007 vs. 2008–2018), tumor location (inner quadrants vs. others), pathological T stage (pT2 vs. pT1), tumor grade (G3 vs. G1-2), lymphovascular invasion (yes vs. no), hormone receptors (negative vs. positive), positive lymph node ratio (≤10% vs. 10%–20% vs. > 20%), PMRT (yes vs. no), chemotherapy (yes vs. no), and HER2 status, stratified by treatment (positive without trastuzumab vs. negative & positive with trastuzumab). *Abbreviations:* HR = hazard ratio; PMRT = postmastectomy radiotherapy; LRR = locoregional recurrence; DFS = disease-free survival; OS = overall survival. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

indicated that breast cancer in young women is more aggressive and more likely to have a worse prognosis [2–8,21]. It is probable that the breast-cancer tumors in young women behave more aggressively than those in older women do [2,3,7]. Younger patients tend to have tumors with grade 3 histology, LVI, and negative hormone receptors, unlike older patients [7,22]. In our study, the proportion of patients with LVI and triple-negative disease was higher among those ≤50 years old than their older counterparts >50 years old (Table 1). It is possible that age-related differences reside at the molecular level or by gene expression [23]. A recent study based on breast cancer genomic datasets revealed a dysregulation of age-associated cancer-relevant gene sets in both cancer and normal breast tissues, and sub-sets of which adversely affect the survival in young women with breast cancer [24]. Further studies are warranted to identify a biological or molecular explanation for the higher relapse rate of breast cancer in younger patients.

Age interaction refers to situations in which breast-cancer risk factors, tumor characteristics, or treatment outcomes differ across age groups [15]. Age may reflect many fundamental and incompletely understood biological processes. The analysis of age-specific effects may be a fundamental way to fill the gap in our understanding of tumor biology, and to optimize treatment for breast cancer [15]. Our results showed that decreasing age was associated with increasing LRR risk, and the HR of PMRT vs. no PMRT for LRR remained almost constant in all ages (Fig. 3A). Thus, as the LRR risk decreased with increasing age, the absolute benefits of PMRT for LRR decreased. Among the younger patients (≤50 years old) in our cohort, PMRT was independently associated with better LRR, DFS, and OS outcomes. This observation is consistent with the results of a previous study, which found that radiotherapy not only affected the locoregional control of breast cancer, but was also related to differences in distant metastasis and OS [25]. We further investigated whether PMRT influenced the association between age and prognosis, and found that age was not a prognostic factor for any of the three outcomes among the patients who received PMRT. The different effects of PMRT among patients of different ages may explain these findings. The relapse risk among younger patients with a worse prognosis was significantly reduced by PMRT, but it did not influence the outcomes of older patients with a better prognosis. As a result, discrepancies in the prognosis among patients of different ages were diminished after PMRT.

Patients with pT1-2N1 breast cancer are heterogeneous, and the role of PMRT is controversial. A meta-analysis by the Early Breast Cancer Trialists' Collaborative Group revealed that PMRT significantly reduced LRR and breast cancer mortality in pT1-2N1 breast cancer [12]. However, most trials included in that meta-analysis were conducted 15–20 years ago; thus, the conclusion is limited by the outdated therapies used in the trials. The St. Gallen International Expert Consensus suggested that omitting PMRT could be considered in patients with pT1-2N1 breast cancer with favorable biological profiles [13]. Several retrospective studies focusing on this question have recommended a risk-adapted strategy. Multi-factor models or nomogram models have been developed to predict the prognosis for these intermediate-risk patients in previous studies. Young age, histology grade 3, hormone receptor negativity, LVI, a large number of positive lymph nodes, and a large tumor size have been identified as adverse prognostic factors [18,26–34]. All studies evaluated the effect of age using crude age groupings, and most of them demonstrated that age was an independent prognostic factor. Most studies have reported that PMRT can provide benefits for younger patients. However, all of these studies defined "young patients" using crude age groupings, and different cutoff values were used arbitrarily or empirically, including 35 [29], 40 [18,26,27,33], 45 [34], and 50 [31] years of age. Further analyzing the prognostic value of age as a continuous variable will help increase the knowledge of tumor characteristics and determine the optimal cutoff of age in these patients. In the present study, we explored the effect of age as a continuous variable on prognosis, and found different trends in DFS and OS with increasing age between patients ≤ and >50 years old. Patients ≤50 years old were recipients of a survival benefit of PMRT, unlike those >50 years old. Differences in the magnitude of the benefit provided by PMRT in the different subgroups revealed an age interaction. The large-scale population-based studies using SEER database reported several observations. High-risk tumors were more common in younger women (<50 years old), low-risk tumors were more common in older adults (≥50 years old), and after 50 years of age, the incidence of high-risk tumors declined, while the incidence of low-risk tumors continued to increase [9]. These age interactions are a further testament

Table 2
Multivariate analyses of the variables associated with the prognosis of 3047 patients ≤50 years-old.

Variable	LRR	*P* value	DFS	*P* value	OS	*P* value
	HR (95%CI)		HR (95%CI)		HR (95%CI)	
Treatment era (1997–2007 vs. 2008–2018)	1.06 (0.73–1.55)	0.748	1.09 (0.85–1.39)	0.518	1.13 (0.78–1.64)	0.504
Tumor location (Inner quadrants vs. others)	1.50 (1.02–2.20)	0.037	1.47 (1.14–1.88)	0.003	1.36 (0.94–1.98)	0.107
pT stage (pT2 vs. pT1)	1.77 (1.21–2.58)	0.003	1.57 (1.24–2.00)	< 0.001	1.56 (1.09–2.22)	0.015
Tumor grade (G3 vs. G1-2)	1.54 (1.05–2.24)	0.026	0.98 (0.76–1.27)	0.905	0.91 (0.63–1.33)	0.639
LVI (yes vs. no)	1.36 (0.85–2.18)	0.203	1.02 (0.73–1.44)	0.898	1.10 (0.66–1.82)	0.714
Hormone receptors (negative vs. positive)	2.08 (1.41–3.09)	< 0.001	2.24 (1.73–2.90)	< 0.001	3.69 (2.58–5.28)	< 0.001
LNR						
≤10%	Referent		Referent		Referent	
10%–20%	1.86 (1.27–2.72)	0.001	1.38 (1.08–1.77)	0.011	1.49 (1.04–2.15)	0.032
>20%	3.15 (1.73–5.74)	< 0.001	1.85 (1.23–2.78)	0.003	1.82 (0.99–3.36)	0.054
Radiotherapy (no vs. yes)	3.73 (2.24–6.20)	< 0.001	1.69 (1.28–2.23)	< 0.001	2.00 (1.30–3.08)	0.002
Chemotherapy (yes vs. no)	3.38 (0.47–24.28)	0.227	1.32 (0.54–3.21)	0.543	1.01 (0.32–3.23)	0.983
HER2 status[a]	1.16 (0.75–1.80)	0.494	1.15 (0.86–1.53)	0.349	1.42 (0.96–2.11)	0.078

Abbreviations: LRR = locoregional recurrence; DFS = disease-free survival; OS = overall survival; LVI = lymphovascular invasion; LNR = positive lymph-node ratio; HER2 = human epidermal growth factor receptor 2.

[a] HER2 status stratified by treatment (positive without trastuzumab vs. negative & positive with trastuzumab).

Table 3
Multivariate analyses of the variables associated with the prognosis of 2391 patients >50 years-old.

Variable	LRR	*P* value	DFS	*P* value	OS	*P* value
	HR (95%CI)		HR (95%CI)		HR (95%CI)	
Treatment era (1997–2007 vs. 2008–2018)	0.93 (0.59–1.47)	0.769	1.31 (1.00–1.71)	0.051	1.85 (1.27–2.69)	0.001
Tumor location (Inner quadrants vs. others)	2.00 (1.31–3.06)	0.001	1.14 (0.86–1.51)	0.354	1.10 (0.74–1.63)	0.644
pT stage (pT2 vs. pT1)	2.15 (1.38–3.35)	0.001	1.76 (1.36–2.27)	< 0.001	1.87 (1.30–2.70)	0.001
Tumor grade (G3 vs. G1-2)	1.44 (0.95–2.19)	0.088	1.35 (1.05–1.75)	0.021	1.55 (1.09–2.22)	0.016
LVI (yes vs. no)	1.73 (1.03–2.91)	0.040	1.53 (1.09–2.15)	0.014	1.30 (0.78–2.18)	0.313
Hormone receptors (negative vs. positive)	1.83 (1.17–2.86)	0.009	1.78 (1.35–2.35)	< 0.001	1.79 (1.22–2.64)	0.003
LNR						
≤10%	Referent		Referent		Referent	
10%–20%	1.72 (1.12–2.63)	0.013	1.08 (0.83–1.40)	0.582	1.05 (0.73–1.54)	0.783
>20%	1.54 (0.72–3.29)	0.268	1.10 (0.70–1.72)	0.679	1.32 (0.73–2.39)	0.351
Radiotherapy (no vs. yes)	2.56 (1.35–4.88)	0.004	1.18 (0.85–1.64)	0.336	1.09 (0.67–1.78)	0.735
Chemotherapy (yes vs. no)	1.79 (0.72–4.43)	0.209	0.61 (0.42–0.88)	0.009	0.35 (0.23–0.54)	< 0.001
HER2 status[a]	1.28 (0.80–2.04)	0.300	1.09 (0.81–1.47)	0.585	1.11 (0.73–1.71)	0.624

Abbreviations: LRR = locoregional recurrence; DFS = disease-free survival; OS = overall survival; LVI = lymphovascular invasion; LNR = lymph-node ratio; HER2 = human epidermal growth factor receptor 2.

[a] HER2 status was stratified by treatment (positive without trastuzumab vs. negative & positive with trastuzumab).

to the heterogeneity of breast cancer, indicating that the hypothesis that early-onset/high-risk and late-onset/low-risk cancers may be derived from different pathways [14].

This study has two main strengths. First, it consisted of a large number of patients from different centers. Second, it is the first study to evaluate the interaction between age as a continuous variable and the effect of PMRT in patients with pT1-2N1 breast cancer, to the best of our knowledge.

This study has several limitations. First, it is a retrospective study, with a selection bias towards patients undergoing PMRT. The recent prospective or randomized trials have showed the benefit of comprehensive regional nodal irradiation [35–37], however, only a small portion of our patients received internal mammary nodal irradiation which might underestimate the benefit of current PMRT. Second, the median follow-up time of 67.0 months may be limited, especially for patients with ER-positive tumors. Third, the time span of the patients' enrollment was as long as 20 years, and advances in diagnoses and treatment during this period may have affected their prognoses. Given recent changes in treatment paradigms, including omission of chemotherapy in post-menopausal women with 1–3 positive nodes who have low oncotype scores [38], and now omission of ALND in cN0 patients with 1–2 positive sentinel lymph nodes [39,40], the findings of our study need to be interpreted with caution, particularly in patients >50 years old. It is possible that contemporary de-escalation of both chemotherapy and axillary surgery could augment the DFS and OS benefits of PMRT. Therefore, our findings need to be validated in patients who have been diagnosed and treated in contemporary era.

5. Conclusion

Age as a continuous variable was an independent prognostic factor among patients with pT1-2N1 breast cancer. Treatment with PMRT significantly decreased the risk of LRR in patients of all ages, and it independently provided a survival benefit for patients ≤50 years old, but not for those >50 years old. Thus, age has an independent prognostic value in decision-making for PMRT in patients with pT1-2N1 breast cancer.

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Declaration of competing interest

All listed authors declare that they have no conflict of interests.

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Appendix A. Supplementary data

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