Efficacy of post-mastectomy radiotherapy in patients with T1-2N1 breast cancer aged ≤35 years or with a positive HER-2 status

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Abstract. Post-mastectomy radiotherapy (PMRT) is highly recommended for patients with breast cancer with one to three positive nodes; however, there remains some controversy regarding its use. The present retrospective study aimed to explore which patients may be able to avoid PMRT and its associated side effects. A total of 728 patients with T1-2N1 breast cancer who were treated with or without PMRT were included in the present study. The results suggested that PMRT significantly decreased the locoregional recurrence rate (LRR) [hazard ratio (HR)=5.602, 95% confidence interval (CI)=3.139-9.998, P<0.01; 3-year LRR: 4 vs. 17%] and improved overall survival (OS) (HR=0.651, 95% CI=0.437-0.971, P=0.03; 3-year OS: 91 vs. 87%) for patients with T1-2N1 breast cancer. By contrast, PMRT had no significant effect on the distant metastasis (DM) rate (HR=0.691, 95% CI=0.468-1.019, P=0.06; 3-year DM: 10 vs. 15%). Further stratified analysis revealed that PMRT did not reduce the LRR and DM, or improve OS in patients aged ≤35 years or in those with a positive human epidermal growth factor receptor-2 (HER-2) status. The analysis of 438 patients treated with PMRT revealed that patients aged ≤35 years or those with a positive HER-2 status were more likely to experience local recurrence even following PMRT. Thus, the benefits of using PMRT in patients with T1-2N1 breast cancer who are aged ≤35 years or in those with a positive HER-2 status need to be carefully considered. Further studies are required to confirm whether this patient group may be exempted from PMRT.

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Introduction

The main treatment options for breast cancer include surgery, chemotherapy, radiotherapy, and endocrine and targeted therapies. Different patients may select one or more treatment methods based on their condition. Post-mastectomy radiotherapy (PMRT) is a critical and validated treatment modality for patients with breast cancer who have at least four positive nodes (1,2); however, the efficacy of PMRT in patients with one to three positive lymph nodes remains unclear (3). Several randomized clinical trials (4-6) and the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) (7) have outlined clear benefits for patients with one to three positive nodes (N1) undergoing PMRT. Furthermore, the American Society of Clinical Oncology has updated its recommendation of PMRT to the strong level for patients with tumors sized ≤5 cm (T1-2) and with one to three involved lymph nodes (8). However, these research studies (4-6) predominantly recruited patients in the 1970s and 1980s when systemic therapies differed from the modern adjuvant treatment, and they also did not take into account high-risk factors, including age, estrogen receptor (ER)/progesterone receptor (PR), human epidermal growth factor receptor-2 (HER-2) and Ki67. A retrospective study from the MD Anderson Cancer Center indicated that the locoregional recurrence rate (LRR) for patients with T1-2 breast cancer with one to three positive lymph nodes (T1-2N1) was highly dependent on the era of treatment (9). Thus, certain controversies remain regarding the use of PMRT for patients with one to three positive lymph nodes (10).

It is well recognized that the immediate and long-term side effects of PMRT, including radiation-induced cardiac disease, arm lymphedema, secondary cancer and further complications with reconstruction, are important (5). Therefore, the present retrospective study aimed to examine which patients may be able to avoid the use of PMRT and thus its related side effects.

Materials and methods

Patients. A retrospective consecutive analysis was conducted on patients with breast cancer who were treated between January 2011 and June 2020 at the Second Affiliated Hospital, Medical School of Xi'an Jiaotong University (Xi'an, China). Patient information was only collected after June 2020 and a

total of 728 patients were included in the present study. The inclusion criteria were as follows: i) Patients with clinical T1-2N1M0 stage; ii) patients who had undergone radical mastectomy; iii) patients who had undergone chemotherapy, endocrine and targeted therapy according to the National Comprehensive Cancer Network guidelines (11); iv) patients for which ER/PR, HER-2 and Ki67 had been detected; and v) patients who had completed a follow-up study period. Notably, male patients were excluded. The clinicopathological data of the patients were collected from the electronic medical records of the university. Among these, 438 patients received PMRT.

Definition of molecular markers. Immunohistochemical staining was used to detect the proportion of ER/PR-, HER-2- and Ki-67-positive tumor cells. The results of immunohistochemical analysis were obtained from the medical records. The percentage score was defined as the percentage of positive tumor cells in the total number of malignant cells evaluated. According to the experience of various pathologists, as well as the current national and international recommendations (12,13), the following definitions were used: i) ER/PR were categorized as negative (<1%) and positive (≥1%) according to the percentage of tumor cell nuclear staining; ii) a negative HER-2 status was defined when HER-2 expression was negative or '+' as detected by immunohistochemical staining, and a positive HER-2 status was defined when its expression was positive '+++'; its expression was further determined by *in situ* fluorescence hybridization when status was '++' (14); iii) Ki67 expression was divided into low (<14%) or high (≥14%) labeling indexes (15).

Follow-up study and study endpoints. Follow-up data were obtained via medical records, and making telephone calls every 3 months for the first 2 years, every 6 months for years 3-5 and annually after 5 years. Therapeutic evaluation indicators included LRR, distant metastasis (DM) and overall survival (OS). LRR was defined as recurrent breast cancer in the ipsilateral chest wall, skin, axilla, internal mammary or supraclavicular lymph nodes. DM included all sites of recurrence, with the exception of locoregional recurrence, and contralateral breast cancer. OS was determined as the time from surgery until the date of mortality (from any cause) or was censored at the date of last follow-up. The follow-up deadline was December 2020.

Statistical analysis. The baseline characteristics of the patients were examined using the χ^2 test or Fisher's exact test for categorical variables assuming equal variance. LRR, DM and OS were assessed using Kaplan-Meier survival curves; group differences were compared using the log-rank test. P<0.05 was considered to indicate a statistically significant difference. All statistical calculations were conducted using SPSS Statistics 26.0 (IBM Corp.) The figures in the study were generated using SPSS Statistics 26.0 and GraphPad Prism 9 (Dotmatics).

Results

Baseline characteristics. Among the 728 patients with a T1-2N1 status following radical mastectomy, 438 patients (60.2%) received PMRT and 290 patients (39.8%) did not. All patients were considered to have negative surgical margins in the database following radical mastectomy, and received irradiation of the chest wall and regional lymph nodes.

The characteristics of the patients and tumors in the PMRT and non-PMRT subgroups are presented in Table I. The age of the patients ranged between 24 and 79 years, with a mean age at diagnosis of 59 years; 29 patients (4.0%) were ≤35 years at the time of diagnosis. In total, 26.5% of the patients had a positive HER-2 status, 70.5% had a positive ER/PR expression and 80.6% had a Ki67 expression status of ≥14%.

No benefit of PMRT in patients aged ≤35 years or those with a positive HER-2 status. The median follow-up time was 45 months (range, 6-108 months). At the cut-off date for this analysis, 66 patients (9.1%) had experienced local recurrence (3.0% in the PMRT group and 18.3% in the non-PMRT group); 103 patients (14.1%) had experienced DM (11.9 and 17.6%, respectively), and 97 patients (13.3%) had succumbed (10.5 and 17.6%, respectively).

PMRT significantly decreased the LRR [hazard ratio (HR)=5.602, 95% confidence interval (CI)=3.139-9.998, P<0.01; 3-year LRR: 4 vs. 17%] and improved OS (HR=0.651, 95% CI=0.437-0.971, P=0.03; 3-year OS: 91 vs. 87%); however, it had no significant effect on the DM rate (HR=0.691, 95% CI=0.468-1.019, P=0.06; 3-year DM: 10 vs. 15%), compared with the non-PMRT group (Fig. 1). Further stratified analysis revealed that PMRT did not reduce the LRR of patients aged ≤35 years, or in those with a positive HER-2 status or T1 stage (Fig. 2); it also did not improve the OS of patients aged ≤35 years, or in those who were had a positive ER/PR or HER-2 status, or T2, N+1 or N+2 stage (Fig. 3). Moreover, PMRT did not reduce the DM of patients, apart from those who had N+3 stage cancer (Fig. 4). These results suggested that there was no marked difference in the LRR, DM and OS of patients aged ≤35 years or in those with a positive HER-2 status between the PMRT and non-PMRT groups.

Patients aged ≤35 years or with a positive HER-2 status are more likely to experience local recurrence even following PMRT. Following the analysis of 438 patients with PMRT, it was found that patients aged ≤35 years were more likely to experience local recurrence compared with patients aged >35 years (P<0.01). Moreover, similar results were obtained for patients with a positive HER-2 status (P=0.03; Table II). Even following PMRT, the prognoses of patients with ER/PR^- (vs. ER/PR+, HR=0.483, 95% CI=0.278-0.839, P=0.01), $HER\text{-}2^+$ (vs. $HER\text{-}2^-$, HR=1.804, 95% CI=1.006-3.232, P=0.01) and T2 (vs. T1, HR=3.828, 95% CI=1.799-8.144, P<0.01) were poor (Fig. 5). These results indicated that patients aged ≤35 years or those with a positive HER-2 status are more likely to experience local recurrence even following PMRT.

A total of 29 patients aged ≤35 years were included in the present study, and 41.4% (12/29) of the patients experienced local recurrence (Fig. 6). Of these, patients with a positive HER-2 status accounted for 55.2% (16/29), and all 11 patients who received PMRT had a positive HER-2 status. However, 45.5% of the patients with a positive HER-2 status who received PMRT experienced local recurrence. These results suggested that patients aged ≤35 years and those with a positive HER-2 status have a higher rate of local recurrence.

Table I. Baseline characteristics of the study population (n=728).

Characteristic	Non-PMRT subgroup, n (%)	PMRT subgroup, n (%)	χ^2	P-value
Age, years			6.22	0.01
≤35	18 (6.21)	11 (2.51)		
>35	272 (93.79)	427 (97.49)		
ER/PR			0.19	0.66
Negative	83 (28.62)	132 (30.14)		
Positive	207 (71.38)	306 (69.86)		
HER-2			1.94	0.16
Negative	205 (70.69)	330 (75.34)		
Positive	85 (29.31)	108 (24.66)		
Ki67			0.17	0.68
<14%	54 (18.62)	87 (19.86)		
≥14%	236 (81.38)	351 (80.14)		
T stage			11.16	<0.01
T1	87 (30)	185 (42.24)		
T2	203 (70)	253 (57.76)		
Positive lymph nodes, n			4.60	0.10
1	155 (53.45)	204 (46.58)		
2	94 (32.41)	149 (34.02)		
3	41 (14.14)	85 (19.40)		

PMRT, post-mastectomy radiotherapy; ER, estrogen receptor; PR, progesterone receptor; HER-2, human epidermal growth factor receptor-2.

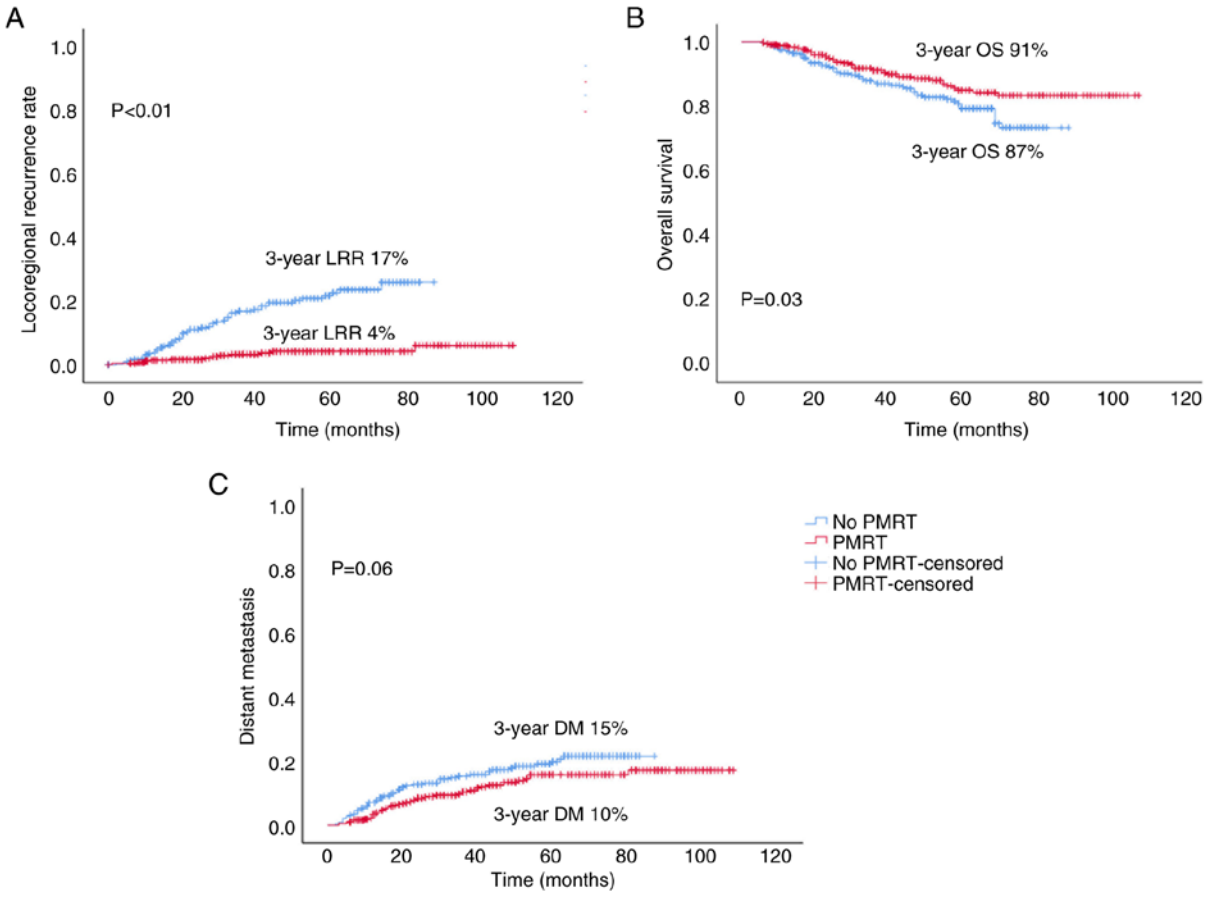

Figure 1. Effect of PMRT on LRR, DM and OS in patients with T1-2N1 breast cancer. Effect of PMRT on (A) LRR, (B) DM and (C) OS. PMRT, post-mastectomy radiotherapy; LRR, locoregional recurrence rate; DM, distant metastasis; OS, overall survival.

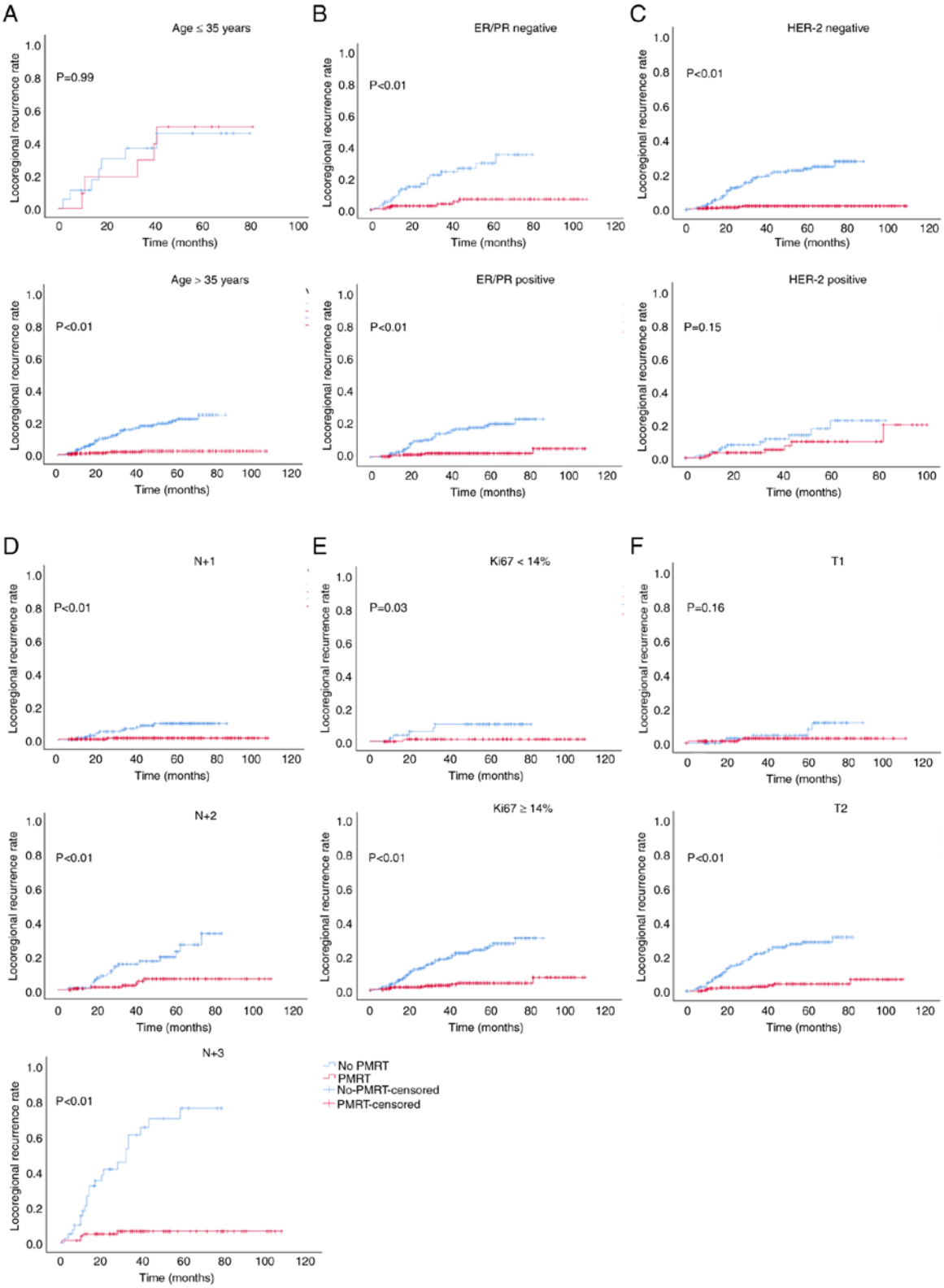

Figure 2. Subgroup analysis of the effects of post-mastectomy radiotherapy on LRR. Effect of (A) age, (B) ER/PR expression (C) HER-2 expression (D) number of positive lymph nodes, (E) Ki67 expression and (F) T stage on LRR. LRR, locoregional recurrence rate; ER, estrogen receptor; PR, progesterone receptor; HER-2, human epidermal growth factor receptor-2.

Discussion

Breast cancer is ranked second among the most common causes of cancer-related mortality in women worldwide (16). According to the results of the EBCTCG (7), PMRT is highly recommended for patients with one to three positive nodes. The aim of the present study was to determine whether the use of PMRT may be omitted in patients with one to three positive lymph nodes. The present study included 728 post-operative patients with T1-2N1 breast cancer at the Second Affiliated

Table II. Factors affecting the LRR of patients following post-mastectomy radiotherapy (n=438).

Characteristic	n (%)	LRR		χ^2	P-value
		+ (n=13)	- (n=425)		
Age, years					<0.01
≤35	11 (2.51)	5	6	56.40	
>35	427 (97.49)	8	419		
ER/PR					0.33
Negative	132 (30.14)	6	126	0.94	
Positive	306 (69.86)	7	299		
HER-2					0.03
Negative	330 (75.34)	6	324	4.63	
Positive	108 (24.66)	7	101		
Ki67					0.45
≤14	87 (19.86)	1	86	0.58	
>14	351 (80.14)	12	339		
T stage					0.40
T1	185 (42.24)	4	181	0.72	
T2	253 (57.76)	9	244		
Positive lymph nodes, n					0.04
1	204 (46.57)	2	202	6.25	
2	149 (34.02)	6	143		
3	85 (19.41)	5	80		

LRR, locoregional recurrence; ER, estrogen receptor; PR, progesterone receptor; HER-2, human epidermal growth factor receptor-2.

Hospital, Medical School of Xi'an Jiaotong University. All factors were equally distributed in the PMRT and non-PMRT groups, apart from age and T stage.

The EBCTCG previously updated its PMRT meta-analysis and provided evidence recommending the use of PMRT for decreasing the 5-year LRR (PMRT, 2.8%; non-PMRT, 16.5%) among breast cancer patients with one to three involved nodes (7). The present study suggested that patients with T1-2N1 breast cancer benefited from PMRT, with a reduced 3-year LRR (PMRT, 4.0%; non-PMRT, 17%; P<0.01) and an improved 3-year OS (PMRT, 91%; non-PMRT, 87%; P=0.03); however, PMRT had no significant effect on DM. The LRR in the PMRT group in the present study was similar to that of a previous study (7), whereas it was higher in the non-PMRT group. This may be related to the fact that only 290 patients were included in the non-PMRT group. The data presented herein also suggested that patients with T1-2N1 breast cancer may benefit from PMRT.

The results of the present study demonstrated that PMRT did not reduce the LRR and DM, or improve OS in patients aged ≤35 years or in those with a positive HER-2 status. Thus, it is still necessary to explore and consider whether PMRT can be omitted, and whether systemic treatment methods may be used, for this group of patients. It was further revealed that patients aged ≤35 years or with a positive HER-2 status were more prone to local recurrence than patients aged >35 years or in those with a negative HER-2 status, even following PMRT. These results further suggested that PMRT had no significant effect on local control in this group of patients. Further studies are required to reduce the LRR in patients aged ≤35 years or in those with a positive HER-2 status by changing the scope of surgery, altering the conventional radiotherapy modality, scope or dosing.

Approximately one in 40 women diagnosed with early-stage breast cancer are very young (<35 years) and this age group has a worse prognosis (17,18); these patients deserve special attention as there are differences in the prognosis, histopathology, systemic and loco-regional treatment options, and outcomes in this specific age group. In a retrospective Danish cohort study, Kroman *et al* (19) concluded that women <35 years of age diagnosed with breast cancer should be regarded as high-risk according to age alone. In a large Korean study, the 5-year OS rate of women diagnosed at <35 years of age was 81.5% compared with 89.4% for women aged 35-50 years (P<0.0001) (20). Furthermore, breast cancer in very young women more frequently exhibits HER-2 upregulation compared with tumors in older women (18). The upregulation of HER-2 in breast cancer has been shown to be associated with a more aggressive tumor subtype, a poorer prognosis and a shorter OS rate (21). The very young patients (<35 years) with a positive HER-2 status in the present study accounted for 55.2% of the study population, and exhibited a high rate of local recurrence even following PMRT. However, the number of patients included in the present study was small and further studies are thus required to confirm the findings.

Hagio *et al* (22) recruited 13 women aged <35 years at diagnosis with early-stage breast cancer, and performed genomic DNA testing. This previous study detected

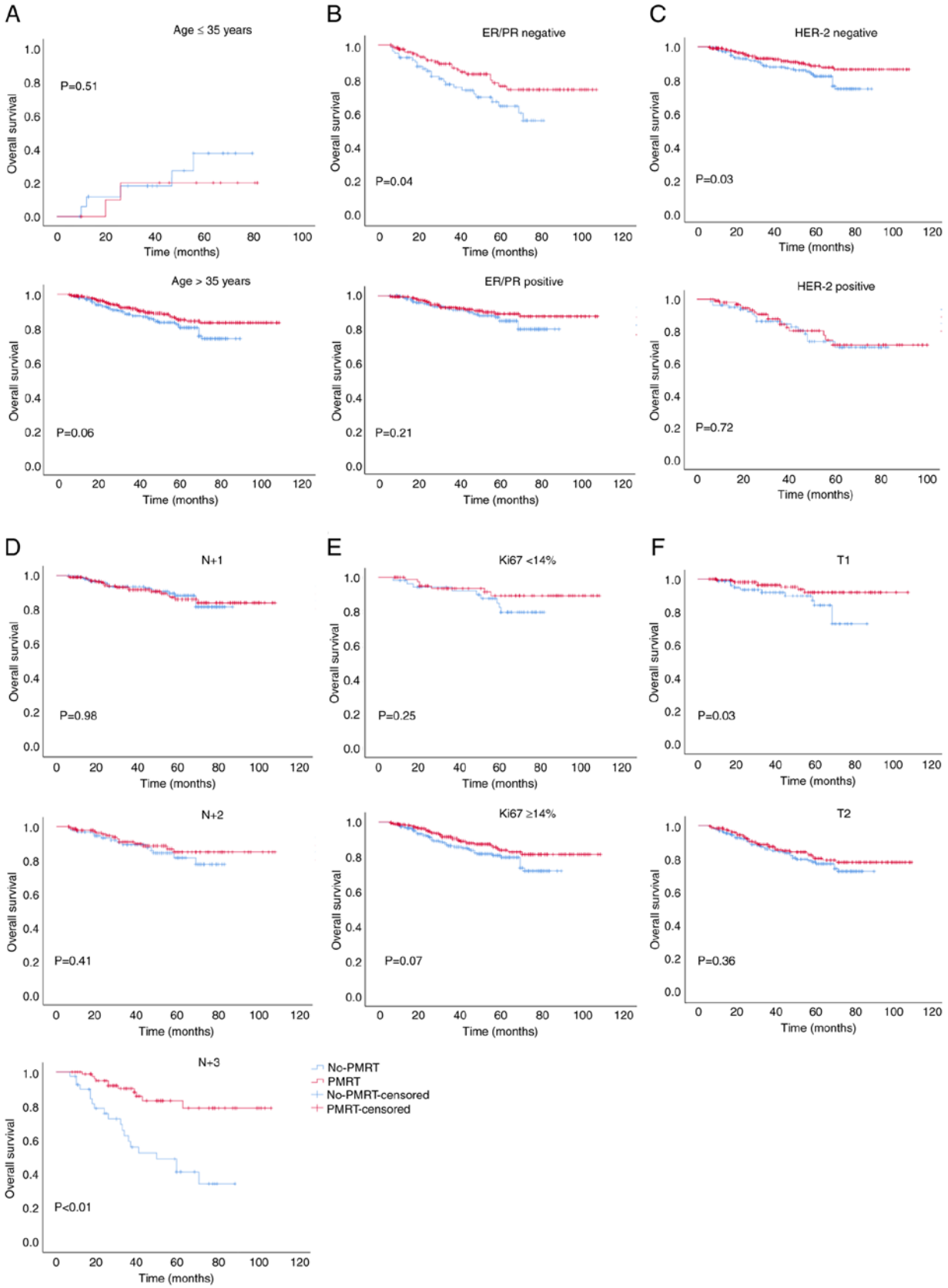

Figure 3. Subgroup analysis of the effects of post-mastectomy radiotherapy on DM. Effect of (A) age, (B) ER/PR expression (C) HER-2 expression (D) number of positive lymph nodes, (E) Ki67 expression and (F) T stage on DM. DM, distant metastasis; ER, estrogen receptor; PR, progesterone receptor; HER-2, human epidermal growth factor receptor-2.

germline gene alterations in all patients, with the exception of one (22). This finding suggests the need for genetic testing in younger patients with breast cancer in order to develop more personalized treatments. In addition, the fear of cancer

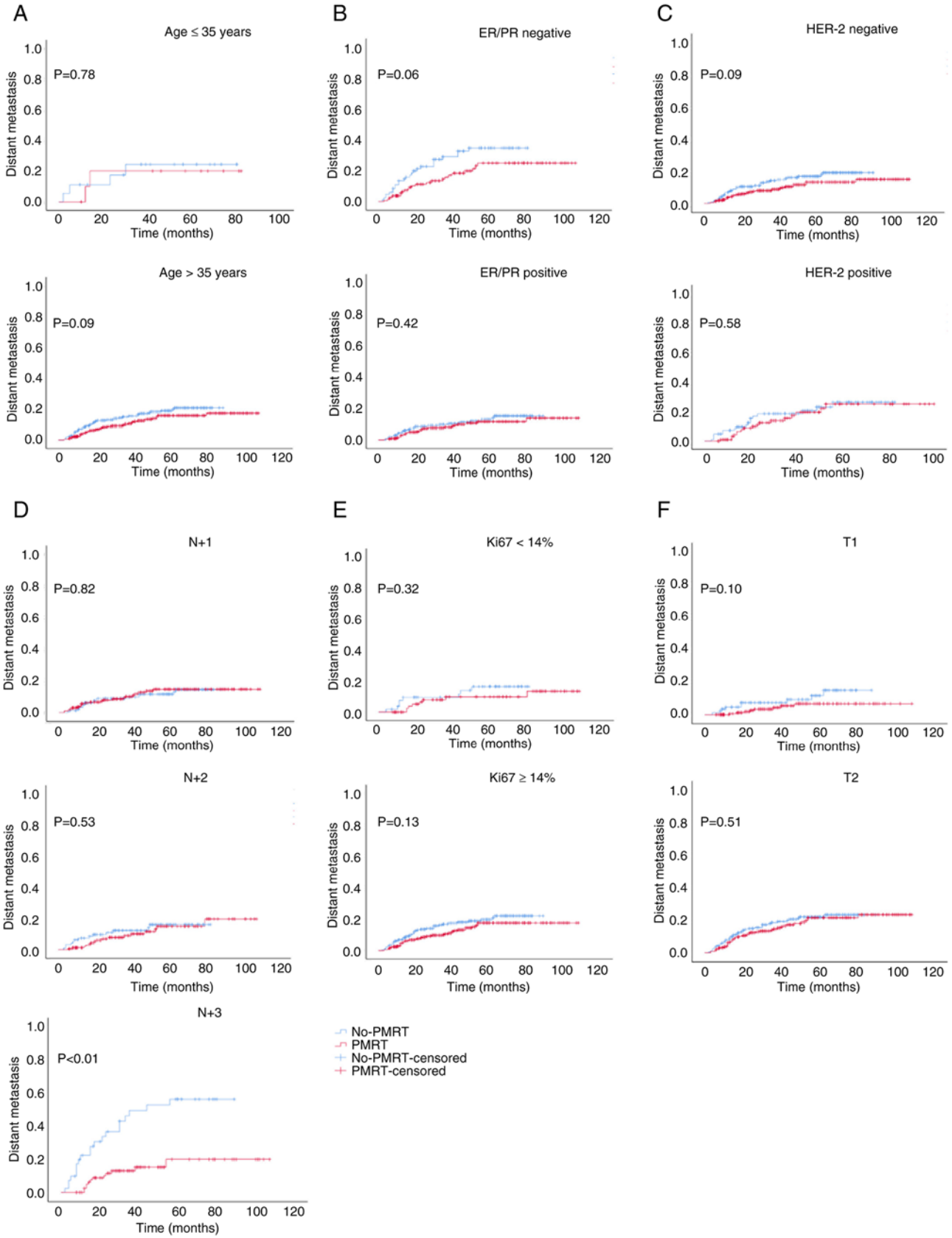

Figure 4. Subgroup analysis of the effects of post-mastectomy radiotherapy on OS. Effect of (A) age, (B) ER/PR expression (C) HER-2 expression (D) number of positive lymph nodes, (E) Ki67 expression and (F) T stage on OS. OS, overall survival; ER, estrogen receptor; PR, progesterone receptor; HER-2, human epidermal growth factor receptor-2.

recurrence is more intense in younger women and they may require targeted mental health intervention (23). Attention to appropriate psychosocial support is critical due to the potential for distress and reduced compliance with therapy

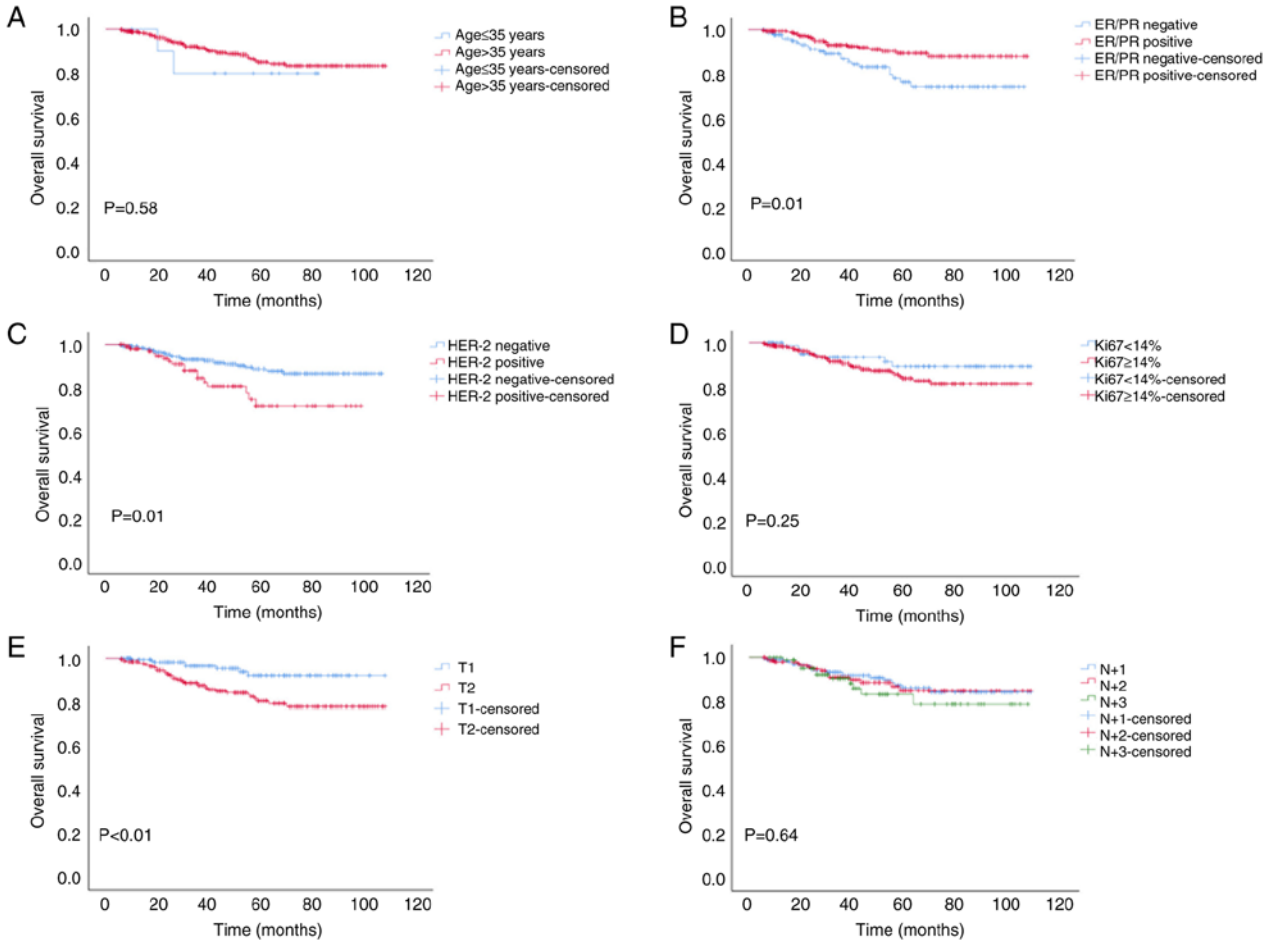

Figure 5. Factors affecting the OS of patients treated with post-mastectomy radiotherapy. Effect of (A) age, (B) ER/PR expression, (C) HER-2 expression, (D) Ki67 expression, (E) T stage and (F) number of positive lymph nodes on OS. OS, overall survival; ER, estrogen receptor; PR, progesterone receptor; HER-2, human epidermal growth factor receptor-2.

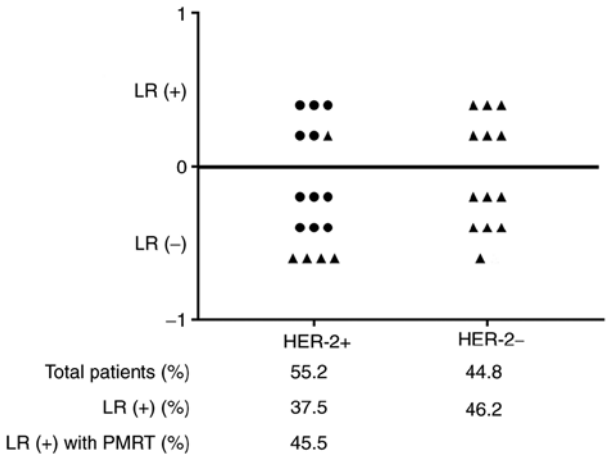

Figure 6. LR of patients aged ≤35 years. Triangles indicate patients that did not receive PMRT and circles indicate patients that received PMRT. PMRT, post-mastectomy radiotherapy; HER-2, human epidermal growth factor receptor-2; LR, local recurrence.

in very young patients diagnosed with early-stage breast cancer (24). A more comprehensive evaluation and a more individualized treatment plan is required for young patients with breast cancer.

In conclusion, the findings of the present retrospective study suggested that further studies are required to confirm the need for the stratification of patients with T1-2N1 breast cancer in order to determine whether they should undergo PMRT. It is hoped that further studies will be conducted to perform more in-depth analyses and allow patients to avoid non-essential treatments, and thus reduce the side effects of treatments and improve the quality of life of patients.

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Availability of data and materials

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

Authors' contributions

MW and ZW confirm the authenticity of all the raw data, made substantial contributions to conception and design, and wrote the main manuscript text. YW was responsible for the statistical analysis. FX was responsible for table and figure generation, and analyzed data. HR and JC were responsible for collecting patient information, conducting follow-up visits and acquisition of data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study followed The Declaration of Helsinki and was approved by the Second Affiliated Hospital of Xi'an Jiaotong University Medical Ethics Committee (approval no. 2022258). All subjects included in this study orally agreed to participate. All methods were carried out in accordance with relevant guidelines and regulations.

Patient consent for publication

The publication of the research received oral consent from all subjects. All forms of personally identifiable data, including biomedical, clinical and biometric data, are not included in the manuscript.

Competing interests

The authors declare that they have no competing interests.

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