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Original Article

Post-surgical radiation therapy for breast cancer patients with lymph vascular space invasion and 0-3 positive lymph nodes

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Abstract: Lymph vascular space invasion (LVSI) in breast cancer (BC) has reportedly been associated with shorter overall survival (OS) and disease-free survival (DFS). However, how LVSI affects optimal treatment, especially for BC patients with 0-3 positive lymph nodes, remains unclear. The current study investigated the roles of postmastectomy radiation therapy (PMRT) in patients with early-stage BC. This study selected 341 patients found to have LVSI with T1-T3, N0-N1, and M0 BC, after surgery, at the Tianjin Medical University Cancer Institute and Hospital. Effects of PMRT on 5-year OS and DFS were analyzed. For patients treated with and without PMRT, 5-year OS rates were 91.1% vs. 88.9% ($P = 0.51$), 5-year DFS rates were 87.1% vs. 73.7% ($P = 0.006$), and 5-year locoregional recurrence-free-survival (LRFS) rates were 97.6% vs. 84.3% ($P < 0.001$). According to stratification analysis, for PMRT-treated vs -untreated patients, 5-year OS rates (89.9% vs. 75.0%, $P = 0.035$), DFS rates (84.7% vs. 51.9%, $P < 0.001$), and LRFS rates (91.9% vs. 67.4%, $P < 0.001$) significantly favored treated patients. Results also showed that grade, T-stage, age, as well as status of human epidermal growth factor receptor-2, estrogen receptor, and progesterone receptor, did not significantly affect OS. Patients that have BC with LVSI, along with 0-3 positive lymph nodes, can benefit from PMRT.

Keywords: PMRT, breast cancer, OS, DFS, LRFS, LVSI

Introduction

Breast cancer (BC) is the most commonly diagnosed cancer in women. It accounts for ~15% of cancer deaths among women, worldwide [1-4]. Standard treatment for BC patients has evolved from surgery and radiation to refined surgery, followed by radiation and adjuvant systemic treatment, such as chemotherapy, hormone therapy, and targeted therapy [5]. Accumulating evidence has indicated that breast-conserving therapy (BCT), including breast-conserving surgery (BCS) and adjuvant radiotherapy, is the equivalent of a mastectomy in terms of survival outcomes and is superior in quality-of-life outcomes [6-10]. Multi-center clinical trials have shown that PMRT, combined with adjuvant chemotherapy, after mastectomy reduces locoregional recurrence and enhances survival rates in BC patients [11-15]. Although PMRT can substantially improve long-term survival for patients with BC, the optimal criteria for PMRT candidates remains unclear.

Evidence suggests that lymph vascular space invasion (LVSI), together with tumor size, pathological tumor grade, and expression of HER2, as well as estrogen receptor (ER) and/or progesterone receptor (PR), affects prognosis in BC patients [16, 17]. However, the suitability of radiotherapy for patients with different numbers of involved lymph nodes (LNs) and the relationship between PMRT and overall survival (OS) and disease-free survival (DFS) should be clarified [18]. PMRT is a routine treatment for BC patients with 4 or more positive LNs (LNs^+). Thus, its benefits for patients with LVSI should be assessed.

Table 1. Clinicopathological characteristics of breast cancer patients in this study

	PMRT		*P*-value
	Yes n = 124 (%)	No n = 217 (%)	
Age			
≤50	71 (57.3)	101 (46.5)	0.06
>50	53 (42.7)	116 (53.5)	
Lymph nodes stage			
N0	52 (41.9)	165 (76.0)	0.001
N1	72 (58.1)	52 (24.0)	
Tumor stage			
T1	43 (34.7)	51 (23.5)	0.001
T2	67 (54)	159 (73.3)	
T3	14 (11.3)	7 (3.2)	
Tumor grade			
I	2 (1.6)	5 (2.3)	0.78
II	110 (88.7)	195 (89.9)	
III	12 (9.7)	17 (7.8)	
Estrogen receptor			
Positive	91 (73.3)	172 (79.3)	0.16
Negative	34 (27.4)	45 (20.7)	
Progesterone receptor			
Positive	82 (66.1)	168 (77.4)	0.03
Negative	41 (33.1)	49 (22.6)	
HER2 status			
Positive	19 (15.3)	37 (17.1)	0.48
Equivocal by FISH	11 (8.9)	12 (5.5)	
Negative	94 (75.8)	168 (77.4)	
Histological subtype			
Invasive ductal	123 (99.2)	210 (97.2)	0.22
Invasive lobular	0 (0)	5 (2.3)	
All other types	1 (0.8)	1 (0.5)	
Molecular type			
HR (+) HER2 (-)	73 (58.9)	135 (62.2)	0.47
HR (+) HER2 (+)	18 (14.5)	37 (17.1)	
HR (-) HER2 (+)	12 (9.7)	12 (5.5)	
HR (-) HER2 (-)	21 (16.9)	33 (15.2)	
Type of surgery			
Mastectomy	110 (88.7)	217 (100)	0.001
Breast conserving	14 (11.3)	0 (0)	

FISH, fluorescence *in situ*; HER2, human epidermal growth factor receptor-2; HR, Hormone receptor; PMRT, Post-mastectomy radiation therapy. Lymph node stage represents both axillary dissections and sentinel node procedures.

The present study evaluated the value of PMRT in clinical subgroups by retrospectively analyzing clinical data of 341 patients with stage T1T3 disease and 0-3 positive axillary LNs that had received mastectomies.

Materials and methods

Case selection

Researchers collected the data of all 3,815 female patients that underwent surgery for BC at the Tianjin Medical University Cancer Institute and Hospital, between January and December 2012. Criteria for inclusion were (a) Primary breast cancer; (b) Available pathology results after surgery; (c) Clear TNM staging, 0-3 LNs^+; (d) LVSI-positive; (e) Hormone receptor $(HR)^+$ patients that received endocrine therapy after surgery; and (f) All $HER2^+$ patients received anti-HER2 treatment after operation. Patients with (a) Metastatic breast cancer; (b) Other primary cancers; (c) Incomplete clinical data; and (d) Patients lost to follow-up were excluded. A total of 341 women meeting these criteria were identified.

Pathological and immunohistochemical criteria

Presence of LVSI was determined mainly by hematoxylin-eosin-stained (HE) slides [18, 19]. A specimen was considered $LVSI^+$ when found outside of the tumor border, plus two of the following conditions: (a) Variance between the shape of the tumor embolus and surrounding blood vessels; (b) Emergence of a vessel near the suspected LVSI loci; and (c) An endothelial lining along the suspected lymph vessel. When retraction artifacts surrounded the primary tumor, they were not considered LVSI foci.

PR and ER status was considered positive when more than 1% of neoplastic cells showed positive immunohistochemical (IHC) nuclear staining [20]. Specimens were considered $HER2^+$ based on an IHC score of 3 (range: 0-3) or a score of 2 followed by a positive fluorescence *in situ* hybridization (FISH) result [21, 22]. Specimens with IHC scores of 0 or 1, or negative FISH results, were considered $HER2^-$.

Treatment

Patients underwent modified radical mastectomies or BCS. Chemotherapy regimens were based on either (1) Anthracycline; (2) Taxane; (3) Anthracycline + taxane; or (4) Taxane + platinum. Of the 341 patients, 329 (94.7%) received

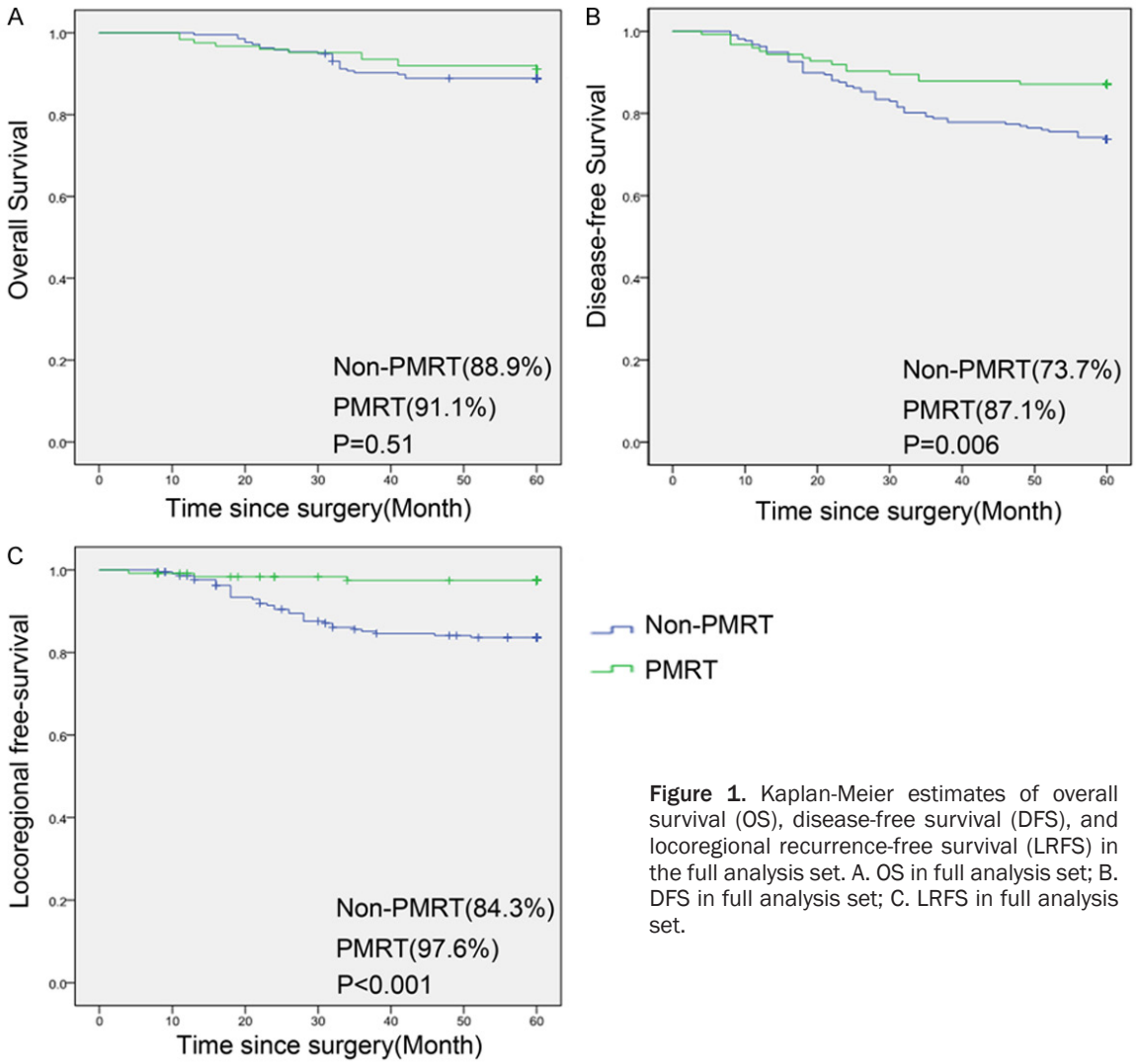


Figure 1. Kaplan-Meier estimates of overall survival (OS), disease-free survival (DFS), and locoregional recurrence-free survival (LRFS) in the full analysis set. A. OS in full analysis set; B. DFS in full analysis set; C. LRFS in full analysis set.

4-8 cycles of one of these regimens. A total of 217 (63.6%) received PMRT within 1 year after surgery, while 124 (36.4%) did not receive PMRT. Radiation therapy (RT) generally included the ipsilateral chest wall and supraclavicular area. The chest wall was irradiated with electron ray (36-60 Gy). The supraclavicular area was irradiated with 6 MV X-ray or X-ray + electron line (20-50 Gy). BCS was followed by RT (50 Gy in 2-Gy fractions to the whole breast, followed by a 14-Gy boost to the lumpectomy cavity, regardless of margin status).

Statistical analysis

Locoregional recurrence-free survival (LRFS) is defined as the time from the first surgical to the ipsilateral chest wall, supraclavicular area, ipsilateral axillary, or internal mammary LN region until recurrence. DFS is the time from surgery to first relapse, development of a second primary cancer, death, or last follow-up. OS is the time from diagnosed date to last contact or death from BC. All statistical analyses were performed with SPSS (version 20.0, IBM). Survival data were evaluated by the Kaplan-Meier method with log-rank test. Cox proportional hazards regression model was applied to prognostic indicators for survival. $P < 0.05$ indicates statistical significance.

Results

Patient characteristics and follow-up

Relevant clinicopathological parameters are listed in **Table 1**. Of the 341 patients, 124 patients underwent PMRT and 217 did not. The follow-up time was 60 months. The average age at diagnosis was 48.5 years (range: 28-78

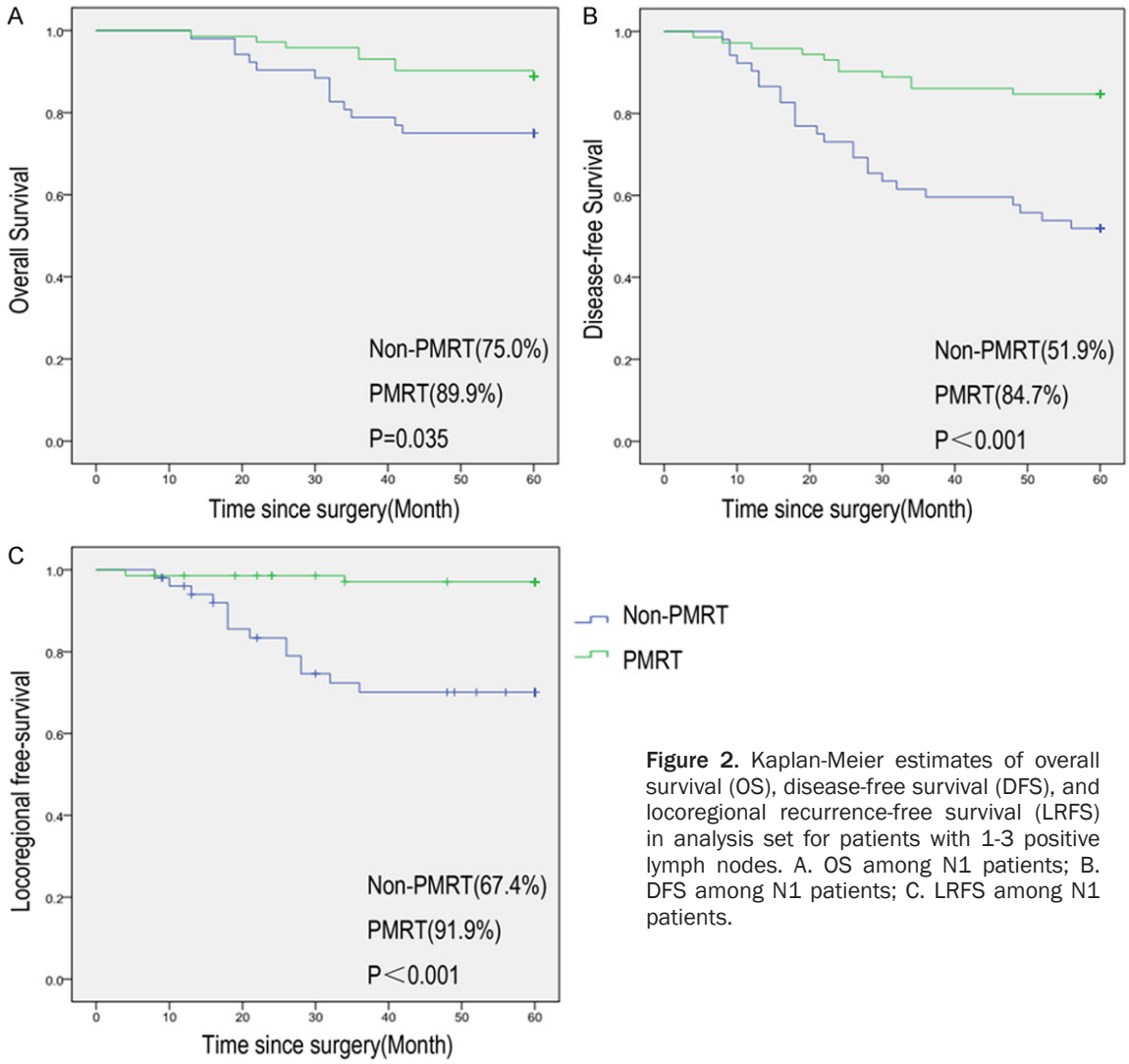


Figure 2. Kaplan-Meier estimates of overall survival (OS), disease-free survival (DFS), and locoregional recurrence-free survival (LRFS) in analysis set for patients with 1-3 positive lymph nodes. A. OS among N1 patients; B. DFS among N1 patients; C. LRFS among N1 patients.

years). Main pathological type was invasive ductal carcinoma (*n* = 336, 98.5%). Pathological tumor grades were grade 1-2: *n* = 312 (91.5%) and grade 3: *n* = 29 (8.5%). Moreover, 217 patients (63.6%) had 1-3 LN metastases, while 124 patients had no LN metastases (36.4%). Because of the heterogeneity of KI-67, molecular typing was based only on HER2, ER, and PR expression. The distribution was $HR^+/HER2^+$: *n* = 56, $HR^+/HER2^-$: *n* = 20, $HR^-/HER2^+$: *n* = 27, and $HR^-/HER2^-$: *n* = 53.

Analysis of the survival and prognostic factors

All 341 BC patients were followed-up for 60 months. Five-year survival rates were LRFS: 79.1%, DFS: 78.6%, and OS: 89.7%. Five-year OS rates were similar in PMRT and no-PMRT groups (91.1% vs. 88.9%, *P* = 0.51; **Figure 1A**), but 5-year DFS rates were higher in the PMRT group (87.1% vs. 73.7%, *P* = 0.006; **Figure 1B**) and 5-year LRFS was higher in the PMRT group (97.6% vs. 84.3%; *P* < 0.001; **Figure 1C**). Further stratification analysis showed that, of the 217 patients with 1-3 LNs^+ (N1M0), 5-year OS rates in PMRT and no-PMRT groups were 89.9% versus 75.0%, respectively (*P* = 0.035, **Figure 2A**), 5-year DFS rates were 84.7% and 51.9%, respectively (*P* < 0.001, **Figure 2B**), and 5-year LRFS rates were 91.9% and 67.4% respectively (*P* < 0.001, **Figure 2C**). All differences are statistically significant.

Of patients with 0 LN metastases (N0M0; *n* = 124), between PMRT and no-PMRT groups, 5-year OS rates (94.2% and 93.3%, respectively; *P* = 0.852, **Figure 3A**) and 5-year DFS rates (90.4% and 80.6%, respectively; *P* = 0.132, **Figure 3B**) did not significantly differ. However, 5-year LRFS rates favored the PMRT group

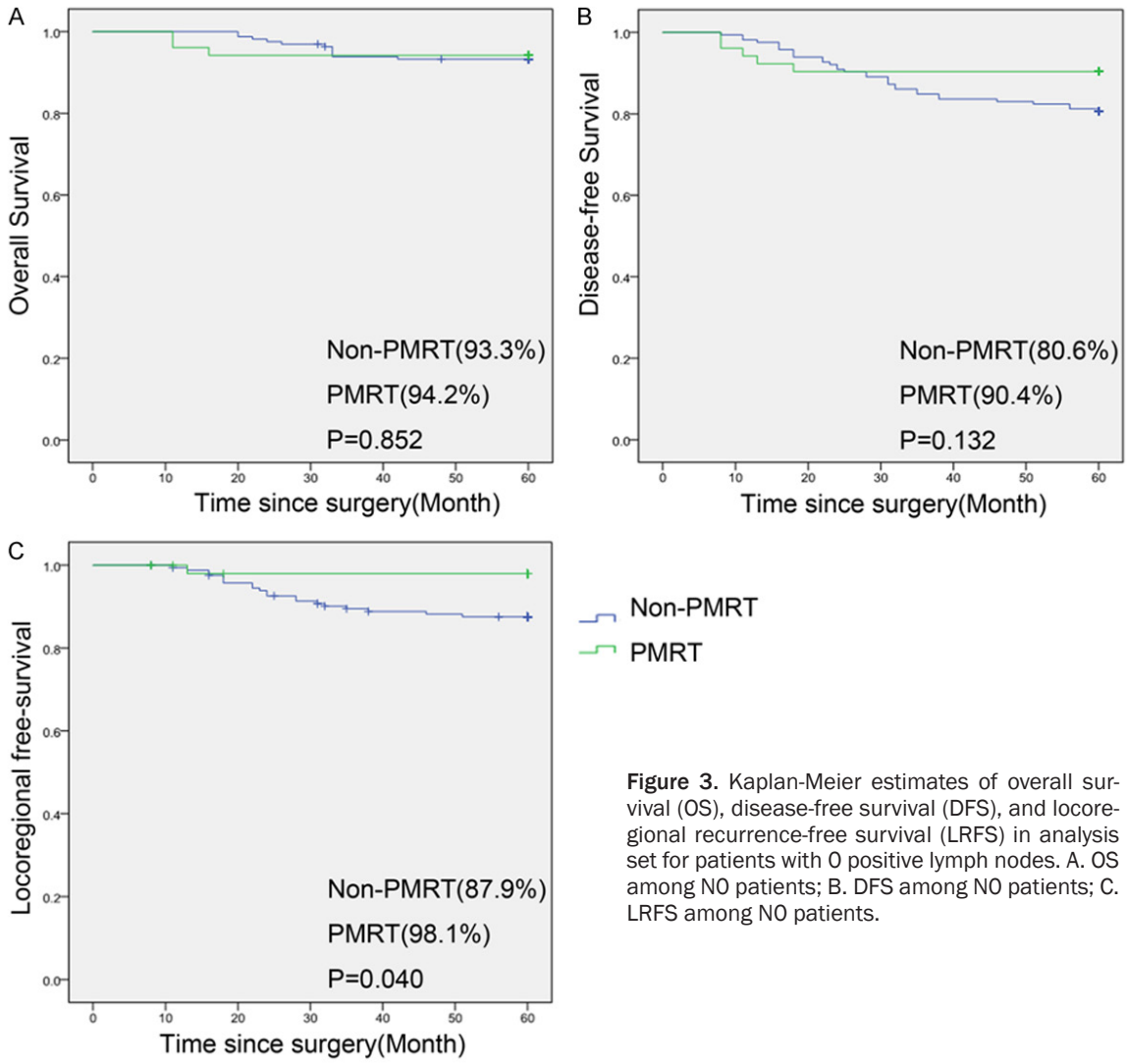


Figure 3. Kaplan-Meier estimates of overall survival (OS), disease-free survival (DFS), and locoregional recurrence-free survival (LRFS) in analysis set for patients with 0 positive lymph nodes. A. OS among N0 patients; B. DFS among N0 patients; C. LRFS among N0 patients.

(98.1% and 87.9%, respectively; *P* = 0.040, **Figure 3C**).

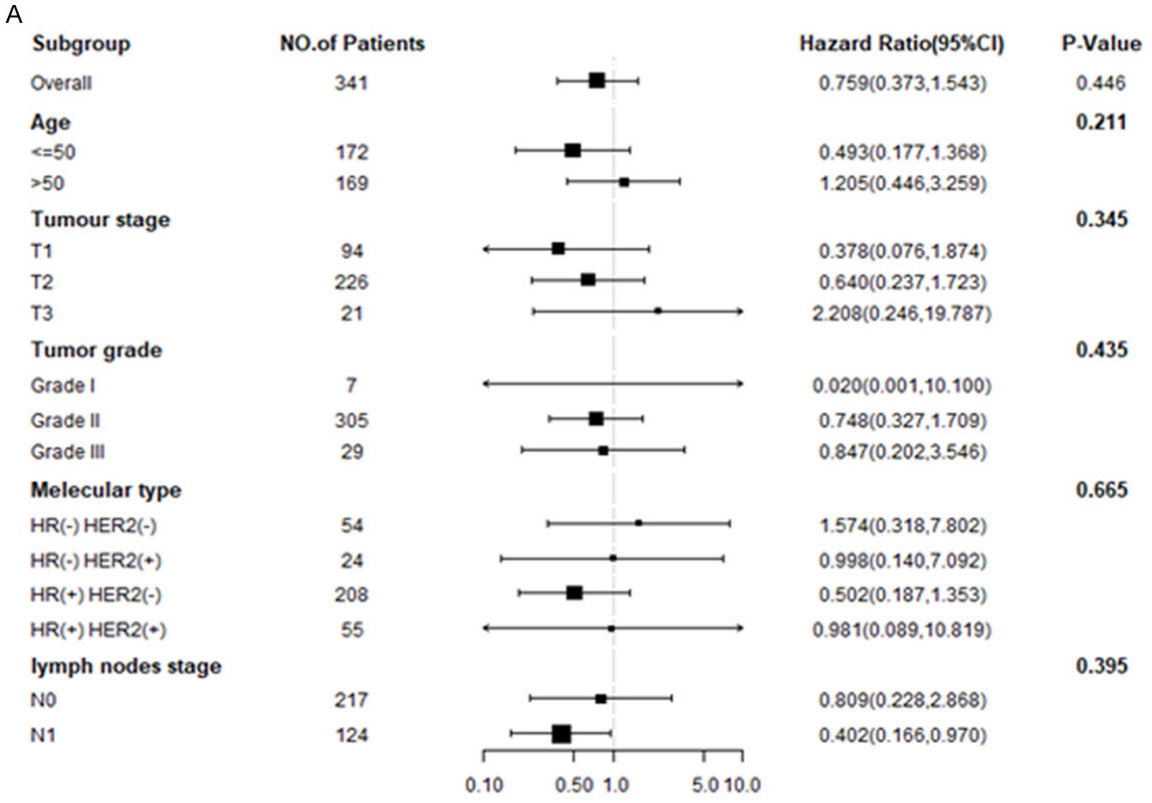
Subgroup analyses of PMRT and no-PMRT groups showed that grade, T-stage, age, ER, PR, and HER2 did not significantly affect OS (**Figure 4A**), but N1 showed significant effects (P = 0.043, HR = 0.402, 95% CI: 0.116-0.970). Subgroup analyses also indicated that age < 50 years, T1, T2, HR^+, $HER2^-$, and N1 significantly affected DFS (**Figure 4B**) and LRFS (**Figure 4C**).

Discussion

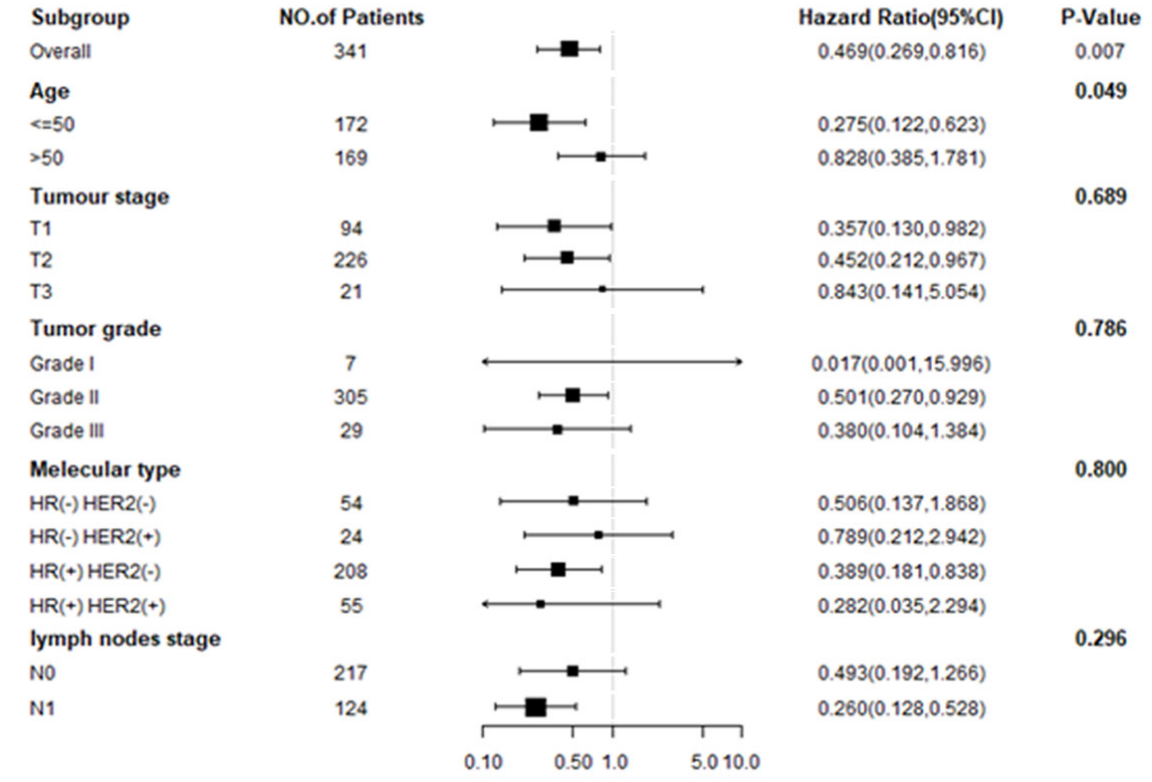
Although PMRT is a standard adjuvant therapy for BC patients with more than 4 LNs^+, its benefits for patients with 0-3 LNs^+ remain unclear [14, 23-25]. The purpose of this study was to clearly define the subset of women with N0-N1 BC that may benefit from radiation. This study assessed different possible influential factors over a 5-year follow-up period. To reduce deviation in this study, all patients were treated during the 2012 calendar year, all HR^+ patients received endocrine therapy after operation, and all $HER2^+$ patients received anti-HER2 treatment after surgery.

As early as 2005, the St Gallen Conference put forward a proposal for relapse risk stratification, in which LVSI was classified as an independent risk factor for recurrence [26]. The proposal was based on three studies by Hasebe, Kato, Pinder, and their colleagues [27-29]. In two retrospective studies of patients with node-negative BC that had undergone mastectomies, LVSI was confirmed as an independent

A


Subgroup
NO.of Patients
Hazard Ratio(95%CI)
P-Value
Overall 341 0.759(0.373,1.543) 0.446
Age 0.211
<=50 172 0.493(0.177,1.368)
>50 169 1.205(0.446,3.259)
Tumour stage 0.345
T1 94 0.378(0.076,1.874)
T2 226 0.640(0.237,1.723)
T3 21 2.208(0.246,19.787)
Tumor grade 0.435
Grade I 7 0.020(0.001,10.100)
Grade II 305 0.748(0.327,1.709)
Grade III 29 0.847(0.202,3.546)
Melecular type 0.665
HR(-) HER2(-) 54 1.574(0.318,7.802)
HR(-) HER2(+) 24 0.998(0.140,7.092)
HR(+) HER2(-) 208 0.502(0.187,1.353)
HR(+) HER2(+) 55 0.981(0.089,10.819)
lymph nodes stage 0.395
N0 217 0.809(0.228,2.868)
N1 124 0.402(0.166,0.970)
0.10 0.50 1.0 5.0 10.0

B


Subgroup
NO.of Patients
Hazard Ratio(95%CI)
P-Value
Overall 341 0.469(0.269,0.816) 0.007
Age 0.049
<=50 172 0.275(0.122,0.623)
>50 169 0.828(0.385,1.781)
Tumour stage 0.689
T1 94 0.357(0.130,0.982)
T2 226 0.452(0.212,0.967)
T3 21 0.843(0.141,5.054)
Tumor grade 0.786
Grade I 7 0.017(0.001,15.996)
Grade II 305 0.501(0.270,0.929)
Grade III 29 0.380(0.104,1.384)
Melecular type 0.800
HR(-) HER2(-) 54 0.506(0.137,1.868)
HR(-) HER2(+) 24 0.789(0.212,2.942)
HR(+) HER2(-) 208 0.389(0.181,0.838)
HR(+) HER2(+) 55 0.282(0.035,2.294)
lymph nodes stage 0.296
N0 217 0.493(0.192,1.266)
N1 124 0.260(0.128,0.528)
0.10 0.50 1.0 5.0 10.0

C

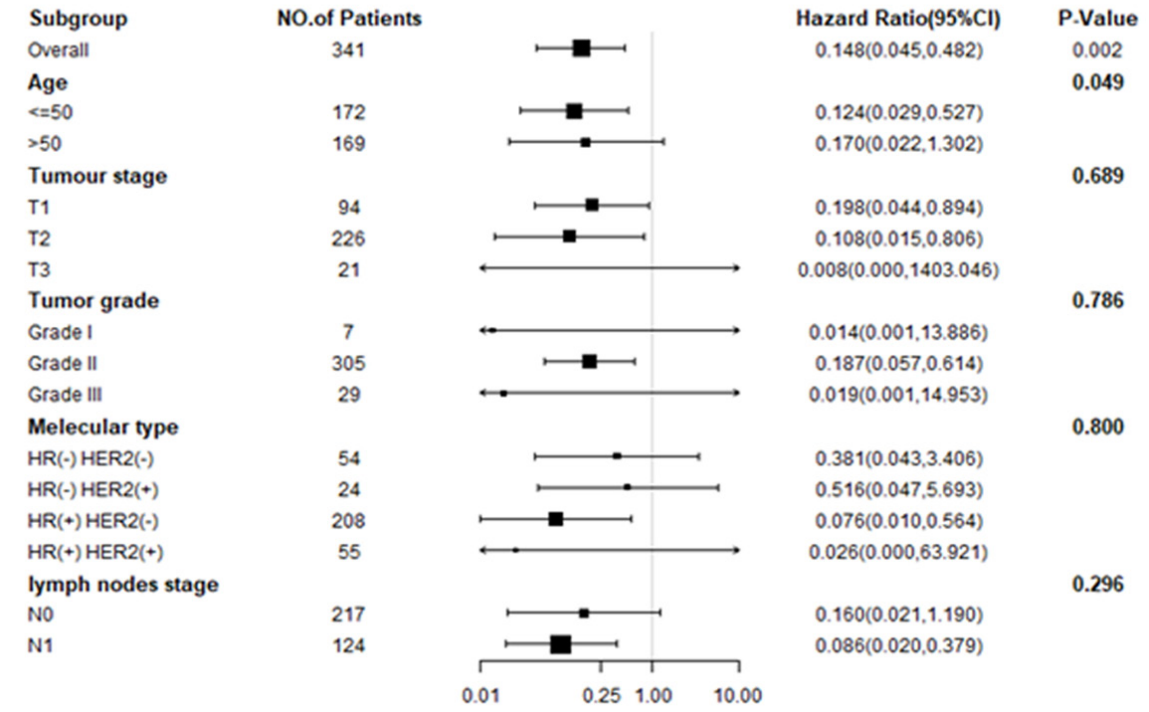


Figure 4. Subgroup analysis of overall survival (OS), disease-free survival (DFS), and locoregional recurrence-free survival (LRFS) in analysis set for patients with 0 positive lymph nodes. Subgroup analyses of OS (A), DFS (B), LRFS (C), using the full analysis set. Subgroup analyses for background or prognostic factors were designed to investigate hazard ratios (HR) with 95% CI and to evaluate relationships among subgroups (two-sided *P* values, based on the Cox model).

risk indicator for local recurrence risk (LRR). However, the effects of PMRT on LVSI+ BC patients have not been widely reported. A retrospective analysis by Frandsen et al. of 219 patients, aged ≤ 40 years, that underwent radical mastectomies for LN- T1-T2 BC, found that patients without LVSI gained a good prognosis, even though they did not receive PMRT, regardless of other recurrence risks (margin of the tumor near the tumor margin, tumor size larger than 2 cm, or missing of systematic therapy). Although LVSI significantly increases LRR, PMRT can diminish this risk [30]. Katz et al. reviewed 224 cases of axillary sentinel LNs+ not treated with neoadjuvant chemotherapy, finding that patients with ≥ 4 axillary LNs+ received more benefits from modified tangential-field radiation than comprehensive nodal radiation, especially without LVSI [31]. In the current study, 5-year DFS and LRFS rates for the PMRT group were significantly higher than those for the no-PMRT group (DFS: 87.1% vs. 73.7%, $P = 0.006$; LRFS: 97.6% vs. 84.3%, $P < 0.001$), indicating that PMRT can significantly improve 5-year LRFS and DFS rates in this setting.

The present study showed that PMRT improved LRFS and DFS rates among select patients. Reportedly, adding lymphatic drainage area radiation plus whole-breast PMRT after BCS can increase 10-year DFS rates by 5% ($P = 0.01$) [32], which may reflect reduced regional LN recurrence. Poortmans et al. [33] showed that, after BCS or modified radical mastectomies, PMRT could improve 10-year rates for non-local recurrence, metastasis-free survival ($P = 0.02$), and DFS ($P = 0.04$). In the current study, 5-year OS rates were: entire cohort 89.7%, no-PMRT group 88.9%, and PMRT group 91.1%. Results suggest a slight, but not significant, improvement. However, as 5-year LRFS and DFS rates were significantly better, the benefits of PMRT for 0-3 LN+/LVSI+ BC cannot be completely denied.

Separate analysis of the N1 group showed that 5-year OS was significantly higher in the PMRT subgroup than the no-PMRT subgroup

(89.9% and 75.0%, $P = 0.035$). Five-year DFS and LRFS rates were also significantly higher in the PMRT subgroup (DFS: 84.7% and 51.9%, $P < 0.001$; LRFS: 91.9% and 67.4%, $P < 0.001$). In the N0 subgroup, LRFS, but not OS and DFS, significantly differed between PMRT and no-PMRT patients. Continued stratification of OS-related factors analyses showed that OS was not related to age, histology, and tumor size. Katz et al. [31] suggested that patients with ≥ 4 sentinel LN^+ and LVSI should be treated with supraclavicular fossa/axillary apex PMRT. It has been suggested that LVSI may benefit more from PMRT with some special factors [34-37]. Present findings imply that PMRT improves 5-year OS for patients with $LVSI^+$/1-3 LN^+ BC.

The current study had some limitations, however. It was a retrospective and single-institution study. Some data between the two groups were not uniform, which may have biased results. For example, postoperative chemotherapy regimens varied and relative high proportion of patients were in tumor grades I and II. Relatively few subjects were in single centers. This study also had a short follow-up time that could not reflect longer-term effects (over 10 years). A larger and longer-term study, based in several institutions, is necessary to confirm present results.

In conclusion, PMRT is effective for BC patients LVSI and 0-3 positive LNs. Current study results suggest that PMRT prolonged DFS and OS for these patients.

Disclosure of conflict of interest

None.

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