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The survival benefit of postmastectomy radiotherapy for breast cancer patients with T1-2N1 disease according to molecular subtype

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ABSTRACT

Objective: To evaluate the significance of postmastectomy radiotherapy (PMRT) in female breast cancer patients with T1-2N1M0 disease according to molecular subtypes and other risk factors.
Method: We conducted a retrospective cohort-based study utilizing the Surveillance, Epidemiology, and End Results database. Patients who were diagnosed with T1-2N1M0 invasive breast cancer and received mastectomy between 2010 and 2014 were enrolled in our study. Overall survival (OS) was calculated with Kaplan-Meier method, and multivariant Cox hazard model was conducted to identify the impact of PMRT according to molecular subtypes and other risk factors. Propensity score matching (PSM) was applied to balance measurable confounders.
Results: Of all the 16,521 enrolled patients, 5775 (35.0%) cases received PMRT. The distribution of molecular subtype is 71.4% for Luminal A, 13.2% for Luminal B, 5.1% for HER2 enriched, and 10.3% for TNBC. The OS was significantly better for patients in PMRT group than the Non-PMRT group ($P < 0.0001$). Stratified by molecular subtype, PMRT significantly prolonged survival in Luminal A patients (HR: 0.759, 95% CI: 0.651−0.884, $P < 0.001$), Yet it brought no significant survival advantage in Luminal B, TNBC or HER2 enriched subtype ($P = 0.914$, $P = 0.124$, $P = 0.103$, respectively). Also, PMRT bore prognostic significance among those patients who were older than 56 years old, single, white, exempt from reconstruction and chemotherapy, and were with ductal, GradeIItumor (all $P < 0.05$). After PSM, the survival benefit of PRMT sustained in Luminal A patients with T1 tumor concomitant with one positive lymph node.
Conclusion: Our study demonstrates a beneficial impact for PMRT on overall survival among Luminal A subtype breast cancer patients with T1-2N1 disease. The selection of PMRT should be stratified by molecular subtype and other risk factors.

1. Introduction

Breast cancer is still the most common cancer based on the 2018 prediction of the European Cancer Information System, and the leading cause of cancer related death in female [1]. To worsen the scenario, breast cancer is also a heterogenous disease. According to the St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2011, it can be identified into four subtypes based on the immunohistochemical evaluation of hormone receptors (HR) including estrogen receptor (ER) and progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) [2]. These subtypes, namely Luminal A, Luminal B, HER2 enriched and triple negative breast cancer (TNBC), possess distinct risk factors, distinct clinicopathological characteristics and distinct responses to therapies, which warrant administration of individualized treatments [2].

Postmastectomy radiotherapy (PMRT), eliminating potential residual tumor microfoci, has been shown to reduce locoregional recurrence (LRR) as well as improve overall survival (OS) in women with locally advanced breast cancer in multiple randomized trails and meta-analyses [3]. The national comprehensive cancer network (NCCN) guidelines hold PMRT as a standard therapy for those breast cancer patients with more than 4 positive axillary nodes, and strongly recommend it for patients with 1–3 positive

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axillary nodes [4]. However, the application of PMRT in patients with T1-2N1 breast cancer is still controversy. The recommendation of PMRT in T1-2N1 patients by NCCN guidelines [4] and European Society for Medical Oncology Clinical Practice Guidelines [5] was mostly based on the meta-analysis published in 2014 by Early Breast Cancer Trialists' Collaborative Group (EBCTCG) [6]. The analysis of 1133 patients with 1–3 positive lymph nodes treated with axillary dissection showed significantly reduced LRR rate and breast cancer mortality. Yet, this work was often questioned by the neglect of tumor stage during analysis and the old-fashioned treatment modalities [7]. Besides, other recent meta-analyses and clinical research of PMRT in this specific group of breast cancer patients observed no significant effect or modest increase in OS [8–11].

As a heterogenous disease, T1-2N1 breast cancer harbors a broad range of risks for disease progression [12] and calls for more tailored treatment, especially in the era of precision medicine guided by molecular subtypes [3]. Thus, we performed this retrospective analysis of T1-2N1 breast cancer patients according to subtypes trying to identify those patients who would benefit from PMRT.

2. Materials and methods

We performed this retrospective analysis based on the SEER 18 registry database, which collected data on patient demographics, clinical and pathological characteristics, survival, and treatment modalities of cancer patients in the United States. Patients fitting the following criteria were included: female patients, diagnosed with pathologically confirmed invasive breast cancer between 2010 and 2014, tumor no larger than 5 cm, one to three lymph nodes invasion, no distant metastasis, mastectomy performed, and one primary carcinoma only. Patients who received radiotherapy before surgery were excluded from our analysis. Data included age at diagnosis, year of diagnosis, race (white, black, other and unknown), marital status(married, not married, and unknown), laterality, histology, grade (four-grade system), tumor size, number of positive lymph nodes, number of lymph nodes examined, subtypes (HR+/HER2-as Luminal A; HR+/HER2+ as Luminal B; HR-/HER2+ as HER2 enriched; HR-/HER2-as TNBC), reconstruction, chemotherapy (yes or no/unknown) and radiotherapy were extracted by SEER*Stat software version 8.3.6 based on the November 2018 data submission [13]. Since information pertaining to scope of regional lymph node surgery were not accessible, we redefined this variable based on the number of lymph node examined in the surgery, namely 1 to 3 lymph nodes classified as sentinel lymph node biopsy (SLNB), 4 to 9 as unknown, and more than 10 as axillary lymph node dissection (ALND).

The independent ethical committee/institutional review board of Fudan University Shanghai Cancer Center Ethical Committee declared our study exempt from approval.

3. Statistical analysis

Clinicopathological characteristics were compared using the Pearson's $\chi 2$ test. Overall survival (OS) and breast cancer-specific survival (BCSS) were defined as the time interval from diagnosis to death due to any cause or breast cancer. Kaplan-Meier analysis was performed to compare the survival between subgroups. Multivariate Cox regression models were built to assess the independent association with OS as well as BCSS and to estimate hazard ratios (HR) and their 95% confidence intervals (CI). Given the difference between patients with and without radiotherapy, propensity score matching (PSM) was applied to balance measurable confounders. Logistic regression was conducted to assess patient factors associated with survival, and patients were matched based on their estimated propensity using 1:1 matching via nearest method without replacement with a caliper of 0.05. Statistical analysis was performed using SPSS 22.0 (Chicago, IL, USA) and the R programming language (version 3.5.3; https://www.r-project.org/) in RStudio (version 0.99.902; https://www.rstudio.com/). Two-sided P values < 0.05 were considered statistically significant.

4. Results

4.1. Patient characteristics by PMRT

A total of 16,521 female patients with T1-2N1 breast cancer were enrolled in our study. 5775 (35.0%) patients who received radiotherapy were classified as PMRT group, and the other 10,746 (65.0%) patients as Non-PMRT group. The demographic and clinicopathological characteristics of both groups were presented in Table 1. 6754 (40.9%) patients were diagnosed with T1 tumor and 9767(59.1%) patients with T2 tumor. The distribution of patients with one to three positive lymph nodes were 9826 (59.5%), 4364 (26.4%), and 2331 (14.1%) respectively. The number of patients presented with Luminal A, Luminal B, HER2 enriched, and TNBC breast cancer were 11,789 (71.4%), 2176 (13.2%), 849 (5.1%) and 1707 (10.3%), respectively. 5325 patients (32.2%) chose breast reconstruction, and 11,363 patients (68.8%) received chemotherapy. ALND were performed in 9167 patients (55.5%). The median follow-up time of our study was 48 months.

As shown in Table 1, patients in the PMRT group were significantly younger ($P < 0.001$), more likely to be black ($P = 0.006$) and married ($P < 0.001$). Also, compared with Non-PMRT group, tumors in the PMRT group were more aggressive, presenting with poorer differentiation, larger size, more lymph node invasion, and higher chance of being TNBC (all $P < 0.001$). Accordingly, higher portion of patients received chemotherapy ($P < 0.001$) in the PMRT group.

4.2. Survival by PRMT among different cohorts 特征重要性

The overall survival was significantly better for patients in PMRT group than the Non- PMRT group ($P < 0.0001$, Fig. 1). The 5-year OS rate in PMRT group and Non- PMRT group were 0.898 (95% CI:0.889–0.908) and 0.867 (95% CI:0.860–0.846), respectively. Stratified by subtype, patients with Luminal A, Luminal B, Her-2 enriched and TNBC tumors all obtained survival benefit from radiotherapy ($P < 0.0001$, $P = 0.0091$, $P = 0.0017$, and $P = 0.012$, respectively, Fig. 1). Similarly, compared with Non- PMRT group, favorable prognosis was observed in PMRT patients with one to three positive lymph nodes, T1 and T2 tumors ($P = 0.00038$, $P = 0.00013$, $P < 0.0001$, $P = 0.0011$, and $P < 0.0001$, respectively, Fig. 2). Yet, no BCSS difference by PMRT was observed in all the cohorts, except for patients with tumor larger than 2 cm ($P = 0.024$) or with 3 positive lymph nodes ($P = 0.015$, Supplementary Figs. 1 and 2).

4.3. Survival benefit of PMRT by subtype and other factors

Next, we performed multivariate Cox regression analysis in different cohorts according to different factors. As shown in Table 2, PMRT, together with tumor size, number of lymph nodes invasion, subtype, chemotherapy and reconstruction, were significantly independent prognostic predictors in the whole cohort (HR: 0.800, 95%CI: 0.714–0.897, $P < 0.001$). In order to identify those patients who would benefit from PMRT, we performed subgroup analysis according to subtype, tumor size, number of positive lymph nodes and other clinicopathological factors. PMRT significantly reduced the risk of dying in Luminal A patients (HR: 0.759, 95% CI:

Table 1
Patient characteristics by radiotherapy.

Characteristics	Radiotherapy				
	Yes		None		
	No.	%	No.	%	*P*
Age (years)					<0.001
≤46	1993	34.5	2436	22.7	
47-55	1533	26.5	2644	24.6	
56-65	1280	22.2	2608	24.3	
≥66	969	16.8	3058	28.5	
Year of diagnosis					<0.001
2010–2012	3323	57.5	6612	61.5	
2013–2014	2452	42.5	4134	38.5	
Race					0.006
White	4412	76.4	8395	78.1	
Black	736	12.7	1192	11.1	
Others	627	10.9	1159	10.8	
Marital status					<0.001
Single	1998	34.6	4091	38.1	
Married	3534	61.2	6100	56.8	
Unknown	243	4.2	555	5.2	
Histology					0.208
Ductal	4695	81.3	8654	80.5	
Lobular	529	9.2	973	9.1	
Others	551	9.5	1119	10.4	
Laterality					0.378
Right	2877	49.8	5275	49.1	
Left	2898	50.2	5471	50.9	
Grade					<0.001
I	567	9.8	1583	14.7	
II	2446	42.4	4989	46.4	
III-IV	2575	44.6	3892	36.2	
Unknown	187	3.2	282	2.6	
Tumor size (cm)					<0.001
≤2	1959	33.9	4795	44.6	
2 to 5	3816	66.1	5951	55.4	
No. of positive lymph nodes					<0.001
1	2793	48.4	7033	65.4	
2	1757	30.4	2607	24.3	
3	1225	21.2	1106	10.3	
Scope of regional lymph node surgery					0.002
SLNB	929	16.1	1963	18.3	
Unknown	1592	27.6	2870	26.7	
ALND	3254	56.3	5913	55	
Subtypes					<0.001
Luminal A	3910	67.7	7879	73.3	
Luminal B	856	14.8	1320	12.3	
HER2 enriched	300	5.2	549	5.1	
TNBC	709	12.3	998	9.3	
Reconstruction					0.001
None	3819	66.1	7377	68.6	
Yes	1956	33.9	3369	31.4	
Chemotherapy					<0.001
None	772	13.4	4386	40.8	
Yes	5003	86.6	6360	59.2	

0.651–0.884, $P < 0.001$), Yet it brought no significant survival advantage in Luminal B, TNBC or HER2 enriched subtype ($P = 0.914$, $P = 0.124$, $P = 0.103$, respectively, Fig. 3). After adjusting for other clinicopathological factors, PMRT was significantly correlated with prolonged survival in patients with one positive lymph node and three positive lymph nodes (HR: 0.838, 95% CI: 0.713–0.985, $P = 0.032$; HR: 0.637, 95% CI: 0.492–0.824, $P = 0.001$, respectively), but not in patients with two positive lymph nodes ($P = 0.162$, Fig. 3). Also, PMRT brought survival benefit in patients with T1 and T2 tumors (HR: 0.789, 95% CI: 0.623–0.998, $P = 0.048$; HR: 0.807, 95% CI: 0.709–0.920, $P = 0.001$, respectively, Fig. 3). Besides, radiotherapy bore prognostic significance among those patients who were older than 56 years old, single, white, spare from reconstruction and chemotherapy, and were with ductal, GradeIItumor (all $P < 0.05$, Fig. 3). As for BCSS, PMRT was ruled out as an independent prognostic factor in the whole population (HR: 0.901, 95% CI: 0.785–1.034, P = 0.137, Table 2), though it reduced cancer-specific death risk in patients who were older than 66 years old, did not receive chemotherapy or reconstruction, and presented with larger tumor and more lymph node invasion (Supplementary Fig. 3).

Furthermore, we analyzed the role of PMRT with a certain tumor size or number of positive lymph node within the four subtypes of breast cancer. As illustrated in Fig. 4, In Luminal A patients, PMRT was prognostic in T1, T2, one and three positive lymph nodes subgroups (HR: 0.616, 95% CI: 0.442–0.860, $P = 0.004$; HR: 0.801, 95% CI: 0.674–0.952, $P = 0.012$; HR: 0.767, 95% CI: 0.617–0.954, $P = 0.017$; HR: 0.607, 95% CI: 0.434–0.849, $P = 0.004$), but not in the two positive lymph nodes subgroup ($P > 0.05$). Quite differently, it was not associated with OS in all the subgroups of Luminal B, TNBC, and HER2 enriched patients. And PMRT only improved BCSS in Luminal A patients with 3 positive lymph nodes (HR: 0.586, 95% CI: 0.384–0.895, P = 0.013, Supplementary Fig. 4).

Based these results above, we further crossed tumor size with number of positive lymph nodes to classify patients into six subgroups in the whole cohort and Luminal A subtype. As demonstrated in Figs. 4 and 5 patients with T1 tumor concomitant with one positive lymph node, as well as patients with T2 tumor concomitant with three positive lymph node would benefit from PMRT (HR: 0.619, 95% CI: 0.431–0.889, $P = 0.009$; HR: 0.595, 95% CI: 0.444–0.799, $P = 0.001$, respectively). The findings were similar in the Luminal A subtype. In consistence with the findings of BCSS above, PMRT was associated with better survival in Luminal A patients with tumor larger than 2 cm concomitant with 3 positive lymph nodes (HR: 0.563, 95% CI: 0.386–0.821, P = 0.003, Supplementary Fig. 5).

There were 3312 patients diagnosed with T1 tumor concomitant with one positive lymph node in Luminal A subtype, and 680 out of them received PMRT. Kaplan-Meier analysis showed significant overall survival difference between patients with and without PMRT ($P < 0.0001$, Fig. 6A). Cox model also demonstrated that radiotherapy was an independently prognostic factor for this cohort (HR: 0.381, 95% CI: 0.214–0.676, $P = 0.001$, Supplementary Table 1). Since clinicopathological characteristic were not balanced between RT group and Non-RT group, as shown in Supplementary Table 2, we performed PSM to eliminate the influence of confounding factors. There were 1348 patients in the matched cohort. No significant difference was observed between the two groups in matched cohort (Supplementary Table 2), and standardized differences in observable characteristics were <5%. Survival benefit of RT group sustained in the matched group ($P = 0.026$, Fig. 6B). Besides, PMRT secured its prognostic role for this specific cohort of patients in multifactor regression analysis (HR: 0.416, 95%CI: 0.213–0.813, $P = 0.01$, Supplementary Table 1). BCSS showed no significant difference between patients with and without PMRT before and after PSM ($P = 0.069$, $P = 0.66$, respectively, Supplementary Fig. 6).

5. Discussion

This is so far the largest population-based study investigating the efficacy of PMRT in T1-2N1 breast cancer patients according to molecular subtypes. Our data showed that the survival benefit of PMRT varied among different subtypes and different number of positive lymph nodes. Our study provide evidence to administrate PMRT for those T1-2N1 patients according to their subtypes.

Presently, molecular subtype of breast cancer is not recommended to guide the indication of radiotherapy, however many literatures have followed on the prognosis depending on the

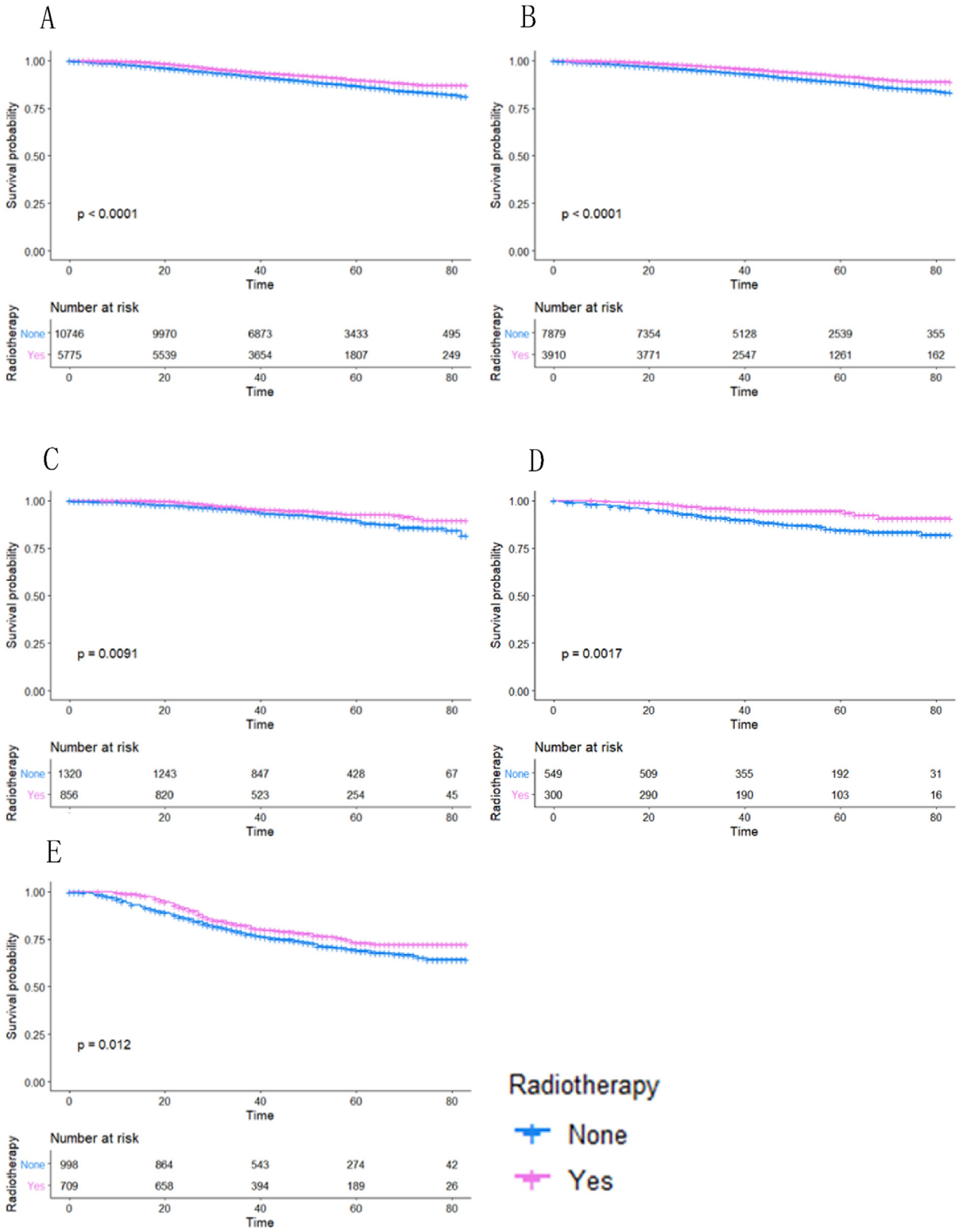

Fig. 1. Overall survival of breast cancer patients in the whole cohort (A), Luminal A subtype (B), Luminal B subtype (C), HER2 enriched subtype (D) and TNBC subtype (E).

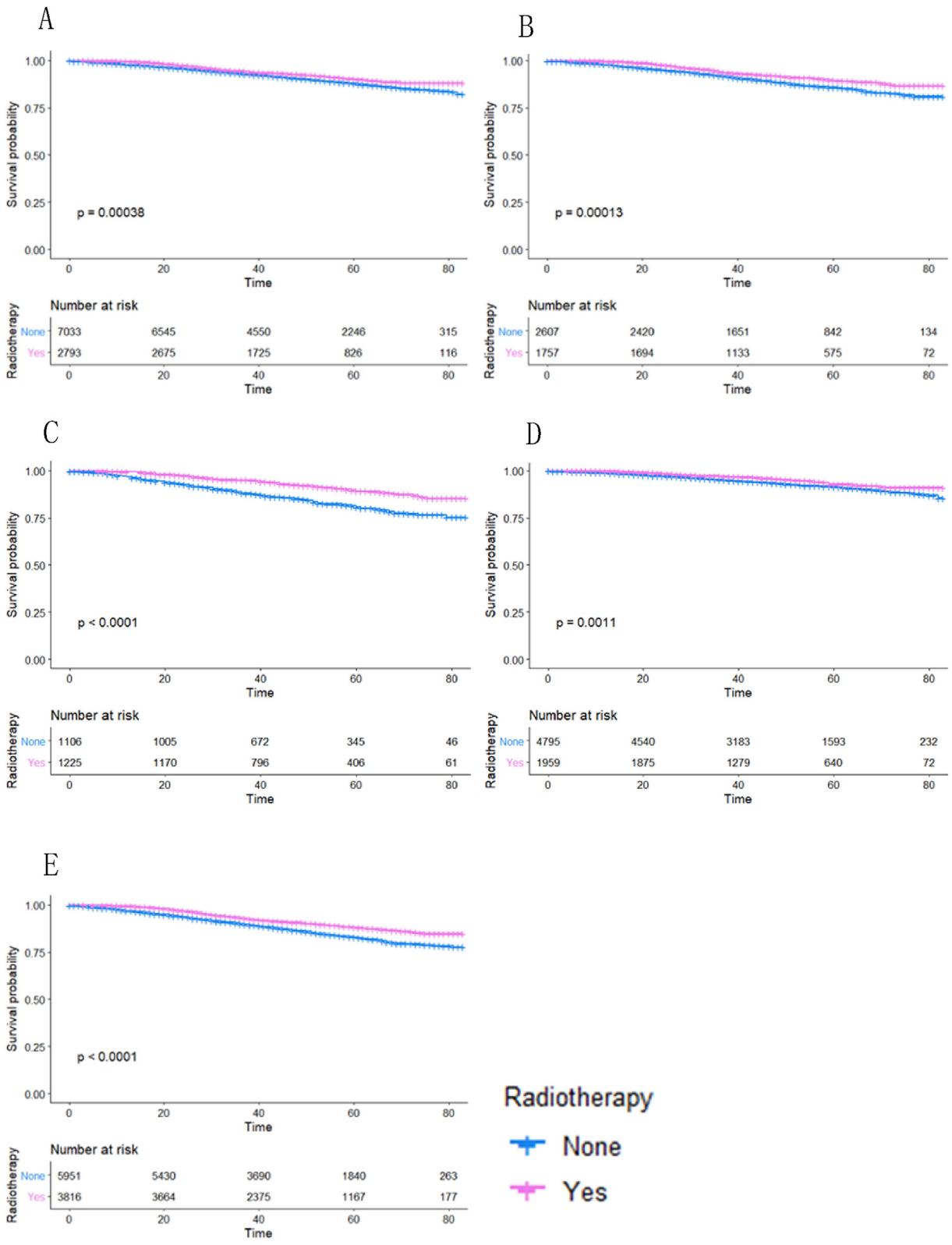

Fig. 2. Overall survival of breast cancer patients with one positive lymph node (A), two positive lymph nodes (B), three positive lymph nodes (C), T1 tumor (D) and T2 tumor (E).

Table 2
Multivariate Cox regression of overall survival in the whole cohort.

	OS			BCSS		
Characteristics	HR	95% CI	*P*	HR	95% CI	*P*
Age(years)						
≤46	Reference			Reference		
47-55	0.936	0.786–1.114	0.456	0.957	0.793–1.154	0.644
56-65	1.207	1.025–1.421	0.024	0.989	0.820–1.193	0.908
≥66	2.138	1.834–2.492	<0.001	1.387	1.156–1.666	<0.001
Race						
White	Reference			Reference		
Black	1.069	0.932–1.225	0.341	1.115	0.941–1.320	0.208
Others	0.632	0.520–0.768	<0.001	0.590	0.458–0.759	<0.001
Marital status						
Single	Reference			Reference		
Married	0.627	0.565–0.695	<0.001	0.737	0.647–0.839	<0.001
Unknown	0.747	0.595–0.938	0.012	0.797	0.594–1.070	0.131
Histology						
Ductal	Reference			Reference		
Lobular	0.787	0.650–0.953	0.014	0.743	0.562–0.983	0.038
Others	0.797	0.667–0.952	0.012	0.791	0.626–1.000	0.050
Grade						
I	Reference			Reference		
II	1.258	1.045–1.514	0.015	1.807	1.313–2.487	<0.001
III-IV	1.869	1.540–2.268	<0.001	3.620	2.624–4.994	<0.001
Unknown	1.335	0.945–1.887	0.101	2.585	1.616–4.135	<0.001
Tumor size (cm)						
≤2	Reference			Reference		
2 to 5	1.766	1.581–1.972	<0.001	2.086	1.799–2.420	<0.001
No. of positive lymph nodes						
1	Reference			Reference		
2	1.185	1.056–1.330	0.004	1.138	0.982–1.319	0.086
3	1.466	1.275–1.687	<0.001	1.455	1.222–1.733	<0.001
Scope of regional lymph node surgery						
SLNB	Reference			Reference		
Unknown	0.802	0.693–0.927	0.003	0.775	0.640–0.938	0.009
ALND	0.706	0.616–0.808	<0.001	0.696	0.583–0.830	<0.001
Subtypes						
Luminal A	Reference			Reference		
Luminal B	0.926	0.780–1.098	0.377	0.758	0.603–0.952	0.017
HER2 enriched	1.140	0.909–1.431	0.256	1.172	0.894–1.536	0.249
TNBC	2.939	2.583–3.345	<0.001	3.310	2.837–3.861	<0.001
Reconstruction						
None	Reference			Reference		
Yes	0.558	0.483–0.644	<0.001	0.670	0.570–0.787	<0.001
Chemotherapy						
None	Reference			Reference		
Yes	0.544	0.485–0.610	<0.001	0.661	0.568–0.769	<0.001
Radiation						
None	Reference			Reference		
Yes	0.800	0.714–0.897	<0.001	0.901	0.785–1.034	0.137

subtypes of breast cancer receiving radiotherapy in different clinical settings [14–20]. Few studies focused on the different role of PMRT for T1-2N1 patients according to subtypes. Our study found that Luminal A subtype breast cancer could gain significant overall survival benefit from PMRT. The additional advantage for TNBC patients was marginal (HR: 0.839, 95%CI: 0.679–1.04, $P = 0.103$), while HER2 positive patients (including Luminal B and HER2 enriched subtype) received no merits of survival. This finding was in line with a review by He et al. [3], who concluded that a significantly prolonged OS was observed in Luminal A and TNBC patients treated with breast conserving surgery and conventional whole-breast irradiation. Chen et al. [21] conducted a retrospective analysis of TNBC patients from one single institution and found PMRT was associated with lengthened disease-free survival (DFS) in patients with T1-2N1 disease. A study of 1369 patients published in 2015 discussed the role of PMRT in T1-2N1 breast cancer patients according to subtype [18]. In this research, PMRT reduced LRR rate in HER2 enriched subtype and TNBC, but showed no effect on OS irrespective of subtypes. This work, though shed some light on the research of PMRT within the scope of molecular subtype, was blighted by small cohort and uncommon distribution of the four subtypes (33.0%, 42.9%, 11.9% and 12.2% for Luminal A, Luminal B, HER2 enriched and TNBC subtype respectively). The intrinsic mechanisms of radiosensitivity in Luminal A breast cancer were documented to be related with the ER signal pathway [22], epidermal growth factor receptor and its downstream signals [3,23]. The reasons for the radioresistance of HER2 positive breast tumors were associated with a loop-like HER2-NF-κB-HER2 pathway[24] and epithelial-to-mesenchymal transition [25]. In our analysis, we also found that PMRT increased OS in Luminal A subtype patients with T1 tumor concomitant with one positive lymph node. This may partly be explained by the fact that only half of the patients (1689/3312) in this subgroup received chemotherapy. Thus, the omission of PMRT for Luminal A patients warrants further

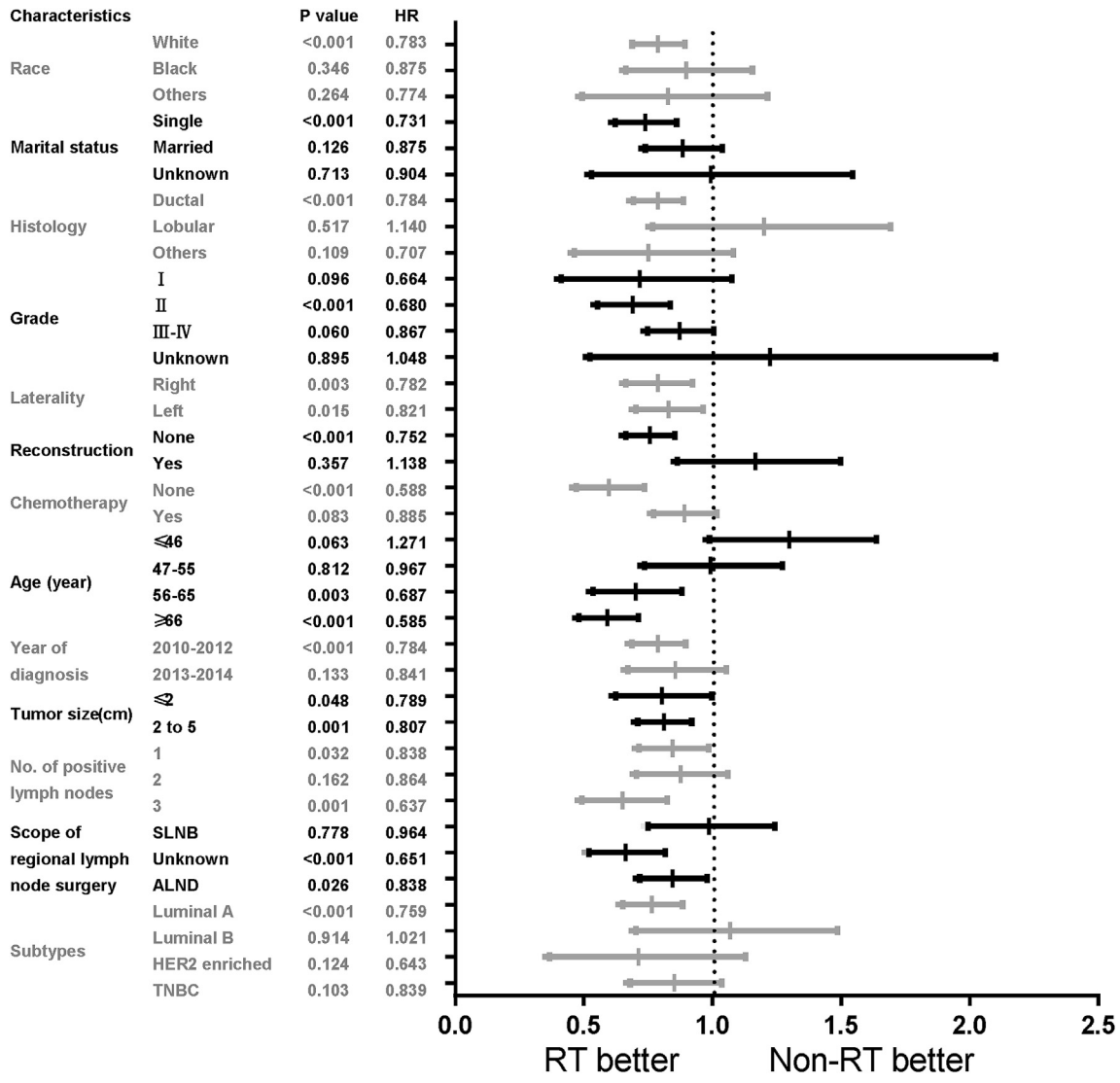

Fig. 3. Hazard ratio and 95% confidence interval for overall survival stratified by clinicopathological characteristics according to radiotherapy.

exploration and verification. Given the lack of treatment modality for TNBC patients, PMRT, though with limited survival gain, still stands as an indispensable option.

11,363 patients (68.8%) in our study received chemotherapy, and we noticed that PMRT provided neither overall survival benefits (HR: 0.885, 95%CI: 0.772–1.02, P = 0.083) nor cancer-specific survival benefits for these patients (HR: 0.988, 95%CI: 0.846–1.155, P = 0.883). Our finding was consistent with other literatures. A multicenter analysis of 714 patients who were treated with modified radical mastectomy and adjuvant taxane-based chemotherapy in 12 hospitals between January 2006 and December 2010 found that PMRT had no significant impact on DFS, or OS in pT1-2N1 patients after a median follow-up duration of 69 months [26]. A research published by Zeidan et al. [27] in 2018 analyzed patients with T1-2N1 disease enrolled on the Breast International Group (BIG) 02–98 trial. 684 patients who received adjuvant anthracycline with or without taxane chemotherapy were included in this study, of whom 337 (49%) had additional PMRT. No benefit difference was noted in breast cancer-specific survival (84.3% vs 83.9%) nor OS (81.7% vs 78.3%) according to receipt of PMRT, though patients randomized to receive chemotherapy with no taxane showed lower LRR after PMRT (10-year LRR: 3.4% vs 9.1%; P = 0.02). Likewise, Abdel-Rahman[28] found that PMRT brought no OS advantage in T1-2 N1 breast cancer patients enrolled in 3 prospective phase III chemotherapy trials including the BIG 02–98, the Breast Cancer International Research Group (BCIRG) 001 and the BCIRG 005 trials. Herein, in the era of anthracycline and taxane-based adjuvant chemotherapy, for patients with pT1-2N1 disease who did receive chemotherapy, PMRT may be dispensable, though prospective studies are needed.

There are certain limitations to this study. First, the follow-up time is relatively short due to the fact that HER2 status in SEER database only becomes available since 2010. Thus, in order to balance between study cohort and follow-up time, we confine our study patients to those diagnosed from 2010 to 2014. Even so, PSM was only done in Luminal A subgroup patients. Second, we cannot obtain data on recurrent and/or metastasis rates or pattern, the analysis of LRR was not performed in our study. We believe that OS is a qualified endpoint as it takes PMRT-induced toxicities of mortality [29] into consideration. Besides, other factors with certain

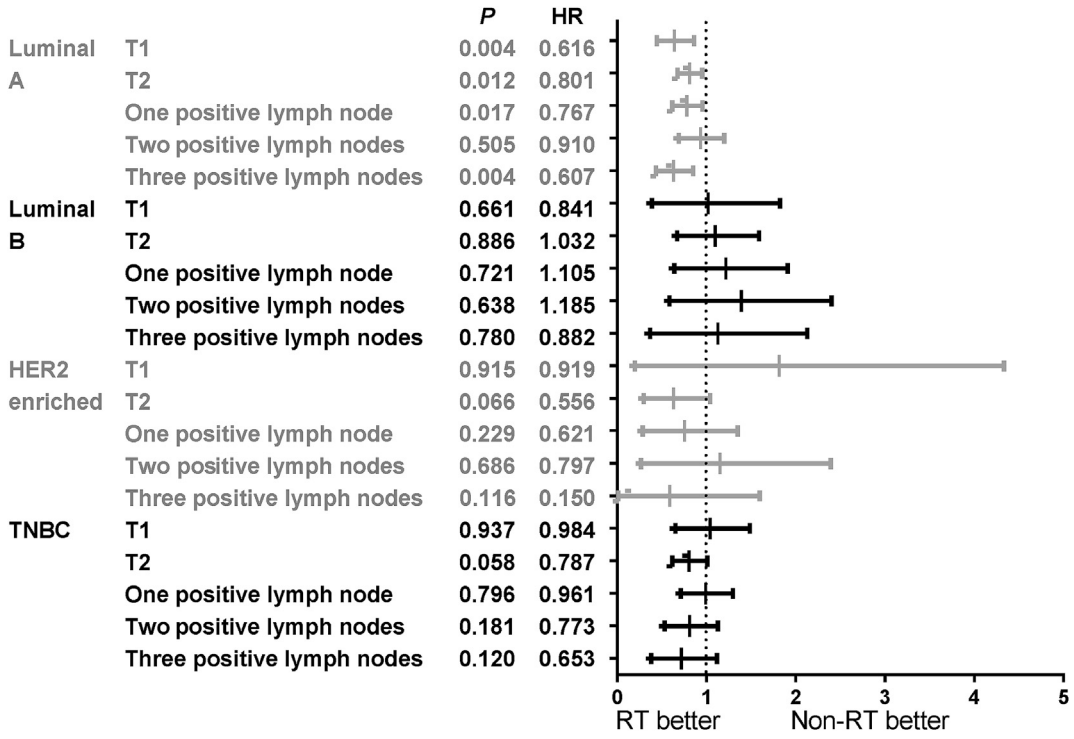

Fig. 4. Hazard ratio and 95% confidence interval for overall survival stratified by tumor size and number of positive lymph nodes in different subtypes of breast cancer patients according to radiotherapy.

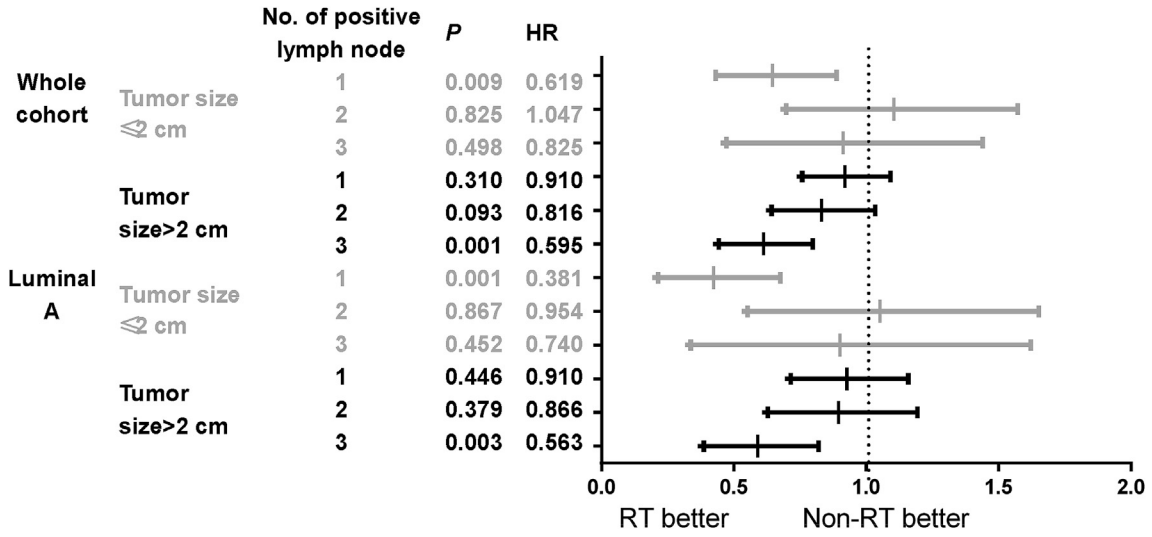

Fig. 5. Hazard ratio and 95% confidence interval for overall survival stratified by tumor size and number of positive lymph nodes in the whole cohort and Luminal A patients according to radiotherapy.

guidance indication, such as the presence of lympho-vascular invasion, extranodal tumor extension, surgical margin status, the extent of irradiation and molecular medicine administration [7] were not available from SEER database. Also, the chemotherapy regimen and administration of hormonal therapy were beyond our accessibility. The discrepancy between OS and BCSS may be attributable to this lack of information. Third, our study, as a retrospective research, might suffer from selection bias. The result of a prospective randomized controlled trial SUPREMO will be reported in 2023 [30,31]. This trial randomized female breast cancer patients with T1-2N1, T3N0 or T2N0 disease to receive or not PMRT after mastectomy.

In conclusion, the current analysis demonstrates a beneficial impact for PMRT on overall survival among Luminal A subtype, not HER2 positive subtype, breast cancer patients with T1-2N1 disease. In this heterogenous arbitrarily defined subgroup, the option of PRMT should be stratified upon risks factors.

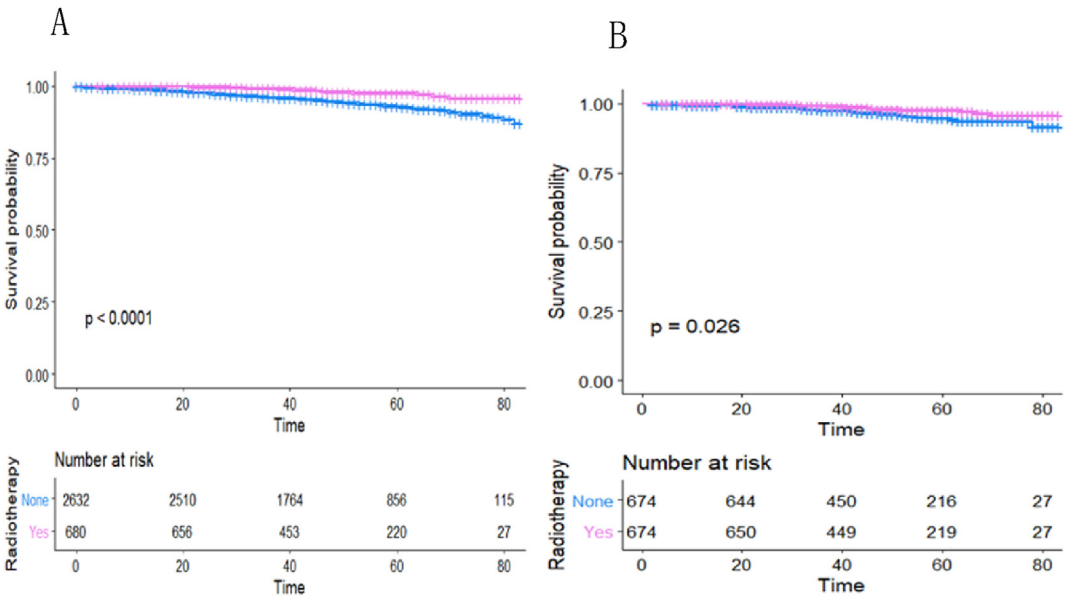

Fig. 6. Overall survival of Luminal A breast cancer patients with T1 tumor and one positive lymph node before (A) and after (B) propensity score matching.

Declarations

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Not applicable.

Declaration of competing interest

The authors declare no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.breast.2020.03.003.

References

[1] Dafni U, Tsourti Z, Alatsathianos I. Breast cancer statistics in the European union: incidence and survival across European countries. Breast Care 2019;14:344–53.
[2] Goldhirsch A, Wood WC, Coates AS, et al. Strategies for subtypes–dealing with the diversity of breast cancer: highlights of the St. Gallen international Expert Consensus on the primary therapy of early breast cancer 2011. Ann Oncol 2011;22:1736–47.
[3] He L, Lv Y, Song Y, et al. The prognosis comparison of different molecular subtypes of breast tumors after radiotherapy and the intrinsic reasons for their distinct radiosensitivity. Canc Manag Res 2019;11:5765–75.
[4] The National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology breast cancer. NCCNOrg; 2019 2018. Version 4.[J].
[5] Senkus E, Kyriakides S, Ohno S, et al. Primary breast cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2015;26(Suppl 5):8–30.
[6] Ebctcg, McGale P, Taylor 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;383:2127–35.
[7] Kassak F, Rossier C, Picardi C, et al. Postmastectomy radiotherapy in T1-2 patients with one to three positive lymph nodes - past, present and future. Breast 2019;48:73–81.
[8] Poortmans PM, Collette S, Kirkove C, et al. Internal mammary and medial supraclavicular irradiation in breast cancer. N Engl J Med 2015;373:317–27.
[9] Whelan TJ, Olivotto IA, Levine MN. Regional nodal irradiation in early-stage breast cancer. N Engl J Med 2015;373:1878–9.
[10] Headon H, Kasem A, Almukbel R, et al. Improvement of survival with post-mastectomy radiotherapy in patients with 1-3 positive axillary lymph nodes: a systematic review and meta-analysis of the current literature. Mol Clin Oncol 2016;5:429–36.
[11] Li Y, Moran MS, Huo Q, et al. Post-mastectomy radiotherapy for breast cancer patients with t1-t2 and 1-3 positive lymph nodes: a meta-analysis. PloS One 2013;8:e81765.
[12] Bazan JG, Majithia L, Quick AM, et al. Heterogeneity in outcomes of pathologic T1-2N1 breast cancer after mastectomy: looking beyond locoregional failure rates. Ann Surg Oncol 2018;25:2288–95.
[13] National Cancer Institute. Surveillance, Epidemiology, and End results program. Turning cancer data into discovery. http://seer.cancer.gov/seerstat/. [Accessed 30 November 2018].
[14] Garvin S, Vikhe Patil E, Arnesson LG, et al. Differences in intra-tumoral macrophage infiltration and radiotherapy response among intrinsic subtypes in pT1-T2 breast cancers treated with breast-conserving surgery. Virchows Arch 2019;475:151–62.
[15] Mao JH, Diest PJV, Perez-Losada J, et al. Revisiting the impact of age and molecular subtype on overall survival after radiotherapy in breast cancer patients. Sci Rep 2017;7:12587.
[16] Sjostrom M, Lundstedt D, Hartman L, et al. Response to radiotherapy after breast-conserving surgery in different breast cancer subtypes in the Swedish breast cancer group 91 radiotherapy randomized clinical trial. J Clin Oncol 2017;35:3222–9.
[17] Liu QQ, Sun HF, Yang XL, et al. Survival following radiotherapy in young women with localized early-stage breast cancer according to molecular subtypes. Cancer Med 2019;8:2840–57.
[18] Shen H, Zhao L, Wang L, et al. Postmastectomy radiotherapy benefit in Chinese breast cancer patients with T1-T2 tumor and 1-3 positive axillary lymph nodes by molecular subtypes: an analysis of 1369 cases. Tumour Biol 2016;37:6465–75.
[19] Tramm T, Mohammed H, Myhre S, et al. Development and validation of a gene profile predicting benefit of postmastectomy radiotherapy in patients with high-risk breast cancer: a study of gene expression in the DBCG82bc cohort. Clin Canc Res 2014;20:5272–80.
[20] Wadasadawala T, Kannan S, Gudi S, et al. Predicting loco-regional recurrence risk in T1, T2 breast cancer with 1-3 positive axillary nodes postmastectomy: development of a predictive nomogram. Indian J Canc 2017;54:352–7.
[21] Chen X, Yu X, Chen J, et al. Radiotherapy can improve the disease-free survival rate in triple-negative breast cancer patients with T1-T2 disease and one to three positive lymph nodes after mastectomy. Oncol 2013;18:141–7.
[22] Chen X, Ma N, Zhou Z, et al. Estrogen receptor mediates the radiosensitivity of triple-negative breast cancer cells. Med Sci Mon Int Med J Exp Clin Res 2017;23:2674–83.
[23] Qu YY, Hu SL, Xu XY, et al. Nimotuzumab enhances the radiosensitivity of cancer cells in vitro by inhibiting radiation-induced DNA damage repair. PloS

One 2013;8:e70727.
[24] Cao N, Li S, Wang Z, et al. NF-kappaB-mediated HER2 overexpression in radiation-adaptive resistance. Radiat Res 2009;171:9–21.
[25] Duru N, Fan M, Candas D, et al. HER2-associated radioresistance of breast cancer stem cells isolated from HER2-negative breast cancer cells. Clin Canc Res 2012;18:6634–47.
[26] Kim YJ, Park W, Ha B, et al. Postmastectomy radiotherapy in patients with pT1-2N1 breast cancer treated with taxane-based chemotherapy: a retrospective multicenter analysis (KROG 1418). Canc Res Treat 2017;49:927–36.
[27] Zeidan YH, Habib JG, Ameye L, et al. Postmastectomy radiation therapy in women with T1-T2 tumors and 1 to 3 positive lymph nodes: analysis of the breast international group 02-98 trial. Int J Radiat Oncol Biol Phys 2018;101:316–24.
[28] Abdel-Rahman O. Impact of postmastectomy radiotherapy on the outcomes of breast cancer patients with T1-2 N1 disease : an individual patient data analysis of three clinical trials. Strahlenther Onkol 2019;195:297–305.
[29] Duma MN, Molls M, Trott KR. From heart to heart for breast cancer patients - cardiovascular toxicities in breast cancer radiotherapy. Strahlenther Onkol 2014;190:5–7.
[30] Velikova G, Williams LJ, Willis S, et al. Quality of life after postmastectomy radiotherapy in patients with intermediate-risk breast cancer (SUPREMO): 2-year follow-up results of a randomised controlled trial. Lancet Oncol 2018;19:1516–29.
[31] Kunkler IH, Canney P, van Tienhoven G, et al. Elucidating the role of chest wall irradiation in 'intermediate-risk' breast cancer: the MRC/EORTC SUPREMO trial. Clin Oncol 2008;20:31–4.