Postmastectomy Radiotherapy in T1–2 Women Breast Cancer Patients with 1–3 Positive Axillary Lymph Nodes: A Propensity Score Matched SEER Analysis

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Research article

Keywords: Breast cancer, postmastectomy radiotherapy, SEER, propensity score matching.

Posted Date: December 7th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-121109/v1

Abstract

Purpose: The application of postmastectomy radiotherapy (PMRT) in T1–2 women breast cancer patients with 1–3 positive lymph nodes has been controversial. We sought to determine the survival benefits of PMRT in the patients with T1–2 and 1–3 positive nodes.

Methods: A retrospective study using the Surveillance, Epidemiology, and End Results (SEER) Regs Custom Data (with additional treatment fields) from 2001 to 2011 was performed. Patients who received PMRT were matched by the propensity score with patients who did not receive PMRT. The Overall survival (OS) and breast cancer-specific survival (BCSS) were analyzed.

Results: We identified 56,725 women breast cancer patients with T1–2 and 1–3 positive nodes, and 18,646 patients were included in the analysis. After propensity score matching (1:1), with a median follow-up of 116 months, PMRT showed an increase in the OS (P = 0.018) but had no effect on the BCSS. The 10-year OS rates were 76.8% and 74.4%, and the 10-year BCSS rates were 82.8% and 82.2% for the patients who received and who did not receive PMRT, respectively. Only patients with 3 positive nodes could gain the benefit of PMRT for BCSS.

Conclusion: PMRT for patients with T1–2 and 1–3 positive lymph nodes could increase the 10-year OS, and had no effect on the 10-year BCSS. Subgroup analysis indicated that only patients with 3 positive lymph nodes could benefit from PMRT for both the OS and BCSS.

Introduction

Breast cancer is the most commonly malignancy and the leading cause of cancer-related deaths in women worldwide, with about 2.1 million newly diagnosed cases in 2018 [1]. Postmastectomy radiotherapy (PMRT) plays an important role in the treatment of breast cancer who underwent mastectomy with the risk of local recurrence [2, 3]. The addition of RT to breast-conserved surgery decreased the 10-year risk of local recurrence by 15.7%, which translated into a 15-year risk reduction cancer death by 3.8% [4]. An Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis showed that PMRT reduced the locoregional recurrence (LRR), overall recurrence and breast cancer mortality in women with 1–3 positive axillary lymph nodes(n = 1314); systemic therapy (cyclophosphamide, methotrexate, and fluorouracil, or tamoxifen) was administered to 1,133 patients, and PMRT reduced LRR, overall recurrence, and breast cancer mortality [5].

There are some controversial issues in the application of PMRT. First, the studies enrolled in the meta-analysis were more than 50 years old, and systemic treatment was far from optimal. A previous report showed that PMRT decreased the 5-year LRR from 9.5–3.4% and the 15-year LRR rates from 14.5–6.1% before and after the year 2000 [6]. In the EBCTGG meta-analysis, the 5-year LRRs were 25.7% and 10.7% in the no RT and RT groups, respectively. Second, the T stage was not considered in the meta-analysis; another meta-analysis from 10 clinical studies (n = 3,432) showed that PMRT significantly decreased the relative risk (RR) of LRR, and the pooled RR for the overall survival (OS) was not significantly different between the PMRT and no-PMRT groups. Many retrospective studies showed that PMRT decreased LRR, but no significant benefit was observed in the OS of women breast cancer patients with T1–2 and 1–3 axillary positive nodes [7–10]. According to the reports mentioned above, PMRT is not essential for all patients with T1–2 and 1–3 positive nodes. Moreover, PMRT induces several toxicities, which affect patients' quality of life, such as chest wall symptoms, arm edema, and later cardiac toxicity [11–13]. We therefore aimed to investigate the role of PMRT in women breast cancer patients with T1–2 and 1–3 axillary positive nodes and to identify which patients could benefit from PMRT.

Materials And Methods

Data Source and Study population

We used data from the SEER 18 Regs Custom Data (with additional treatment fields) for the period 1975 to 2016 using SEER*Stat software (version 8.3.6.1; National Institutes of Health, Bethesda, MD, USA). For this study, the covariates included

age, race, sex, year of diagnosis, marital status, pathological grade, tumor laterality, ICD-O-3Hist/behave, malignant, AJCC 6th T, N, M, regional nodes examined, regional nodes positive, radiation sequence with surgery, radiation recode, chemotherapy recode, estrogen (ER) status, progesterone (PR) status, SEER cause-specific death, survival months, and vital status. The enrollment criteria were as follows: diagnosed year: 2001–2011, women, underwent mastectomy, infiltrating carcinoma (duct carcinoma or duct and lobular carcinoma), T1–2, examined lymph nodes ≥ 10, positive lymph nodes 1–3, with no distant metastasis, known death cause and survival time, and active follow-ups. Patients with missing data were excluded. We identified 18,646 patients who underwent mastectomy with or without PMRT in this study. Patients were divided by age: <40 years, 40–59 years, and > 60 years. Marital status was classified as unmarried (divorced, separated, single, and widowed) and married. Stage T was divided into T1 (T1mic, T1a, T1b, and T1c) and T2.

The primary objective of this study was to compare OS and BCSS in breast cancer patients with T1–2 and 1–3 positive nodes treated with or without PMRT. OS and BCSS were measured from the date of diagnosis to the date of death owing to any cause and breast cancer, respectively.

Statistical analysis

Propensity score matching (PSM, 1:1 ratio) by PMRT status was performed using SPSS, version 23 (SPSS Inc., Chicago, IL, USA). The following covariates were considered for the matching in patients with and without PMRT: age, race, marital status, pathological grade, laterality, Stage T, number of positive nodes, chemotherapy, ER, and PR. For good matching, we selected a caliper width equal to 0.01 of the standard deviations. The balance in the baseline covariates in the matched data was determined using standardized differences [14].

Pearson χ^2 or Fisher's exact test was used for assessing the associations between PMRT and patient demographics and clinical characteristics. The Kaplan Meier (K-M) survival curves were assessed using the log-rank test, and the univariate and multivariate analyses were conducted on all the variables using the Cox regression model. A value of $P = 0.05$ was considered statistically significant. All analyses were performed with IBM SPSS Statistics 23.0 (IBM, Armonk, NY, USA) and R version 4.0.1 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Propensity Score Matching and Patient Characteristics

Between 2001 and 2011, we identified 56,725 women breast cancer patients with T1–2, 1–3 positive nodes, and 18,646 patients were included in the analysis and segregated into 2 groups: PMRT (n = 4,934) and No-PMRT (n = 13,712). Baseline patient characteristics are listed in Table 1. Propensity score matching was performed with the consideration of unbalanced distribution between the 2 groups, and 4,916 patients from the PMRT group were matched with 4,736 patients in the No-PMRT group (Fig. 1). The distribution of baseline covariates was adequately balanced in the matched data set compared to the original data according to the standardized difference (Table 1)

Table 1
Demographic and clinical characteristics of patients with breast cancer with or without PMRT before and after PSM

	Before PSM (n = 18646)				After PSM (n = 9652)			
	No PMRT (%)	PMRT (%)	Sdiff	p value	No PMRT (%)	PMRT (%)	Sdiff	p value
Age								
< 40	1186(8.6)	771(15.6)	0.21		690(14.6)	768(15.6)	0.03	
40–59	6726(49.1)	2901(58.8)	0.19		2727(57.6)	2891(58.8)	0.02	
>=60	5800(42.3)	1262(25.6)	0.36	0.000	1319(27.9)	1257(25.6)	0.05	0.029
Race								
White	10966(80.0)	3787(76.8)	0.08		3846(81.2)	3773(76.7)	0.11	
Black	1460 (10.6)	601(12.2)	0.05		472(10.0)	600(12.2)	0.07	
Other	1286(9.4)	546(11.1)	0.06	0.000	418(8.8)	543(11.0)	0.07	0.000
Marital status								
Unmarried	4997(36.4)	1566(31.7)	0.10		1665(35.2)	1713(34.8)	0.01	
Married	8715(63.5)	3368(68.3)	0.09	0.000	3071(64.8)	3203(65.2)	0.01	0.765
Grade								
I	1728(12.6)	347(7.0)	0.19		363(7.7)	343(7.0)	0.03	
II	5927(43.2)	1912(38.8)	0.09		1857(39.2)	1905(38.8)	0.01	
III	5880(42.9)	2602(52.7)	0.20		2422(51.1)	2595(52.8)	0.03	
IV	177(1.3)	73(1.5)	0.02	0.000	94(2.0)	73(1.5)	0.04	0.092
Tumor laterality								
Left	6860(50.0)	2414(48.9)	0.02		2334(49.3)	2404(48.9)	0.01	
Right	6852(50.0)	2520(51.1)	0.02	0.184	2402(50.7)	2512(51.1)	0.01	0.714
Stage T								
T1	6330(46.2)	1635(33.1)	0.27		1608(34.0)	1629(33.1)	0.02	
T2	7382(53.8)	3299(66.9)	0.27	0.000	3128(66.0)	3287(67.9)	0.02	0.4
Positive nodes								
1	7548(57.2)	1868(37.9)	0.40		1771(37.4)	1858(37.8)	0.01	
2	4098(29.9)	1595(32.3)	0.05		1720(36.3)	1590(32.3)	0.08	
3	2066(15.1)	1471(29.8)	0.36	0.000	1245(26.3)	1468(29.9)	0.08	0.000
Chemotherapy								
No/Unkown	5072(37.0)	462(9.4)	0.69		472(10.0)	457(9.3)	0.02	
Yes	8640(63.0	4472(90.6)	0.69	0.000	4264(90.0)	4459(90.7)	0.02	0.265
ER								

PMRT: postmastectomy radiotherapy; PSM: propensity score-matching; Sdiff: standardized difference; ER: estrogen; PR: progesterone.

	Before PSM (n = 18646)				After PSM (n = 9652)			
Negative	3040(22.2)	1353(27.4)	0.12		1289(27.2)	1347(27.4)	0.00	
Positive	10672(77.8)	3581(72.6)	0.12	0.000	3447(72.8)	3569(72.6)	0.00	0.855
PR								
Negative	4488(32.7)	1849(37.5)	0.10		1826(38.6)	1843(37.5)	0.02	
Positive	9224(67.3)	3085 (62.5)	0.10	0.000	2910(61.4)	3073(62.5)	0.02	0.285

PMRT: postmastectomy radiotherapy; PSM: propensity score-matching; Sdiff: standardized difference; ER: estrogen; PR: progesterone.

Survival Analysis In Propensity Score-matched Data

The 5-year and 10-year OS rates were 87.4% and 75.5%, respectively, and the 5-year and 10-year BCSS were 90.2% and 82.4%, respectively, with a median follow-up duration of 116 months in the dataset after PSM. All baseline characteristics were included in the univariate and multivariate analyses in relation to both the OS and BCSS (Table 2). Univariate analysis showed that PMRT is beneficial for the OS (Hazard ratio [HR] 0.90, 95% confidence interval [CI] 0.83–0.98) but had no effects on the BCSS (HR 0.99, 95% CI 0.89–1.09), and a similar result was shown in the multivariate analysis with the OS (HR 0.91, 95% CI 0.84–0.99) and BCSS (HR 0.97, 95% CI 0.87–1.07). The survival curves of the OS and BCSS according to PMRT are shown in Fig. 2a and Fig. 2b. The 5- and 10-year OS were 87.9% and 76.8% in the PMRT group and 86.8% and 74.4% in the No-PMRT group, respectively. The 5- and 10-year BCSS were 90.3% and 82.8% in the PMRT group and 90.1% and 82.2% in the No-PMRT group, respectively. The results showed that PMRT increased the OS ($P = 0.018$) and had no effects on the BCSS in women breast cancer patients with T1–2 and 1–3 positive lymph node.

Table 2
Univariate and multivariate Cox model for overall survival and breast cancer specific survival in matched dataset

Characteristics	Univariate				Multivariate			
	OS		BCSS		OS		BCSS	
	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value
Age at diagnosis (< 40 as ref)								
40–59	0.99(0.86–1.13)	0.88	0.86(0.75–0.99)	0.04	1.01(0.89–1.16)	0.84	0.92(0.80–1.06)	0.26
>=60	2.18(1.91–2.50)	< 0.01	1.09(0.93–1.27)	0.29	2.07(1.80–2.37)	< 0.01	1.17(1.00-1.37)	0.05
Race (white as ref)								
Black	1.42(1.26–1.60)	< 0.01	1.61(1.41–1.85)	< 0.01	1.28(1.14–1.44)	< 0.01	1.36(1.18–1.56)	< 0.01
other	0.80(0.68–0.93)	< 0.01	0.95(0.80–1.13)	0.55	0.85(0.73–0.99)	0.04	0.96(0.80–1.14)	0.64
Marital status (single as ref)								
Married	0.68(0.63–0.74)	< 0.01	0.83(0.75–0.92)	< 0.01	0.79(0.73–0.86)	< 0.01	0.91(0.82–1.01)	0.08
Grade (I as ref)								
II	1.24(1.03–1.50)	0.023	2.22(1.61–3.07)	< 0.01	1.21(1.00-1.46)	0.05	1.96(1.42–2.71)	< 0.01
III	1.81(1.51–2.18)	< 0.01	4.20(3.07–5.76)	< 0.01	1.53(1.27–1.86)	< 0.01	2.90(2.10–4.01)	< 0.01
IV	1.39(0.97–1.98)	0.07	3.26(1.61–3.07)	< 0.01	1.10(0.77–1.58)	0.60	2.25(1.40–3.63)	< 0.01
Tumor location (left as ref)								
Right	1.03(0.95–1.12)	0.43	1.03(0.94–1.14)	0.51	1.04(0.96–1.13)	0.34	1.04(0.94–1.15)	0.42
Stage T (T1 as ref)								
T2	1.62(1.47–1.77)	< 0.01	1.87(1.66–2.11)	< 0.01	1.51(1.37–1.66)	< 0.01	1.66(1.47–1.87)	< 0.01
Positive lymph nodes (1 as ref)								
2	1.10(1.00-1.22)	0.04	1.14(1.02–1.29)	0.03	1.12(1.01–1.23)	0.03	1.13(1.00-1.28)	0.049
3	1.25(1.13–1.38)	< 0.01	1.34(1.19–1.52)	< 0.01	1.27(1.15–1.41)	< 0.01	1.31(1.16–1.48)	< 0.01
PMRT (not done as ref)								
Yes	0.91(0.83–0.98)	0.02	0.99(0.89–1.09)	0.81	0.91(0.84–0.99)	0.02	0.97(0.87–1.07)	0.48
Chemotherapy (no as ref)								

PMRT: postmastectomy radiotherapy; PSM: propensity score-matching; Sdiff: standardized difference; ER: estrogen; PR: progesterone.

Characteristics	Univariate				Multivariate			
Yes	0.51(0.46–0.57)	< 0.01	0.94(0.80–1.11)	0.49	0.57(0.51–0.64)	< 0.01	0.838(0.71-099)	0.04
ER (negative as ref)								
Positive	0.63(0.57–0.68)	< 0.01	0.49(0.44–0.54)	< 0.01	0.78(0.68–0.88)	< 0.01	0.78(0.67–0.90)	< 0.01
PR (negative as ref)								
Positive	0.63(0.58–0.68)	< 0.01	0.51(0.46–1.56)	< 0.01	0.83(0.73-.93)	< 0.01	0.74(0.64–0.85)	< 0.01

PMRT: postmastectomy radiotherapy; PSM: propensity score-matching; Sdiff: standardized difference; ER: estrogen; PR: progesterone.

Subgroup analysis evaluating the benefit of radiotherapy according to demographic and clinical characteristics

To detect subgroups of the patients that could benefit from PMRT, a subgroup analysis was performed, which included age, race, marital status, pathological grade, tumor laterality, T stage, number of positive nodes, chemotherapy, ER status, and PR status. PMRT increased the OS of the patients in the following subgroups: age ≥ 60 years, white race, pathology grade II, 3 positive nodes, ER positive and PR positive, and decreased the OS of the patients with black race (Fig. 3). Only the patients with 3 positive nodes had the benefit of PMRT for the BCSS (Fig. 4), and the patients with pathology grade IV and 1 positive node had worse BCSS in the PMRT group.

Discussion

Although the EBCTCG meta-analysis showed that PMRT reduced locoregional recurrence and mortality in women with 1–3 positive lymph nodes, and increased patients' radiotherapy session in recent years [15]. However, there are many controversial issues to identify, such as ages, T stage, treatment modality, and molecular subtypes [16-18].

In this study, we identified patients from 2001–2011 because the outcomes of treatment were different before and after 2000 [6], with sufficient time for follow-ups. In the dataset before matching, we found that majority of the patients (73.5%) did not undergo PMRT, and the data was also unbalanced between the PMRT and No-PMRT groups, so we used propensity scores for balancing the characteristic factors between the 2 groups.

Previous reports have reported several factors that are related to the prognosis of breast cancer, such as clinical stage, pathologic grade, tumor size, absolute positive lymph nodes, and molecular subtypes [19-21]. Since human epidermal growth factor receptor 2 status was recorded in the SEER database after 2010, different molecular subtypes have been reported as prognostic factors for breast cancer. With the consideration of enough follow-up time, we did not include the status of human epidermal growth factor receptor 2 in this study. In our study, the multivariate Cox model showed that older age, larger tumor size, and more positive nodes were related to the poor OS, and PMRT, chemotherapy, and hormone receptor positivity were related to the better prognosis. Higher pathological grade, large tumor size (T2), and more positive nodes were related to worse BCSS; chemotherapy and hormone receptor positivity are protective factors for BCSS.

Several retrospective studies have shown that PMRT decreases LRR but has no effect on the OS and BCSS in women breast cancer patients with T1–2 and 1–3 positive nodes. In our study, we found that PMRT increased the OS of the patients but had no effect on the BCSS in the patients with T1–2 and 1–3 positive lymph nodes. In our study, we found that PMRT increased the OS of the patients but had no effect on the BCSS in the patients with T1–2 and 1–3 positive lymph nodes. The reason could be that the patients in the No-PMRT group might be associated with other diseases, which was not included in the SEER database, and this could have caused data bias.

Several studies have reported that not all the patients will benefit from PMRT [6-8, 10, 15,18, 22, 23]. Some researchers integrated the factors related to the benefit from PMRT and powered nomograms for predicting the LRR and OS, thereby assisting in the clinical decision of PMRT [24, 25]. In the present study, a study based on SEER database also showed that PMRT had no effect on breast cancer-specific survival (BCSS), and the median follow-up time was 76 months, which was not enough for evaluating the 10-year OS or BCSS [15]. In our study, we found that only patients with 3 positive nodes will benefit from PMRT for both the OS and BCSS. Histopathological grade is an important prognostic factor in N1 breast cancer patients; higher grade tumors had more LRR and worse OS than lower grade tumors and was independent of other risk factors [26, 27]. We found that the BCSS was worse when PMRT was administered to patients with histopathological grade IV breast cancer, which could be owing to the following reasons: first, the sample size was small (n = 167) compared with the sample size of patients having grades I, II, and III breast cancer (n = 706, 3762, and 5017, respectively). The data deviation was relatively large; second, systemic therapy including endocrine therapy, target therapy, and chemotherapy is unclear. Therefore, a further study is required; the result of an ongoing prospective randomized controlled trial SUPREMO is very much expected [28].

In conclusion, PMRT increased the OS and had no effect on the BCSS in the patients with T1–2 and 1–3 positive nodes. Subgroup analysis showed that only patients with 3 positive nodes could gain the benefit of PMRT for BCSS.

Abbreviations

PMRT	postmastectomy radiotherapy
SEER	Surveillance, Epidemiology, and End Results
OS	Overall survival
BCSS	Breast cancer-specific survival
EBCTCG	Early Breast Cancer Trialists' Collaborative Group
LRR	locoregional recurrence
RR	relative risk
ER	estrogen
PR	progesterone
PSM	Propensity score matching
HR	Hazard ratio
CI	confidence interval

Declarations

Funding This study was funded by Henan health commission (Grant No. LHCJ 20190630)

Conflicts of interest All the authors declare that there are no conflicts of interest.

Ethics approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the Helsinki declaration.

Consent to participate For this type of study formal consent is not required.

Consent for publication Not applicable.

Availability of data and material All data was available in the SEER database.

Code availability Not applicable.

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Figures

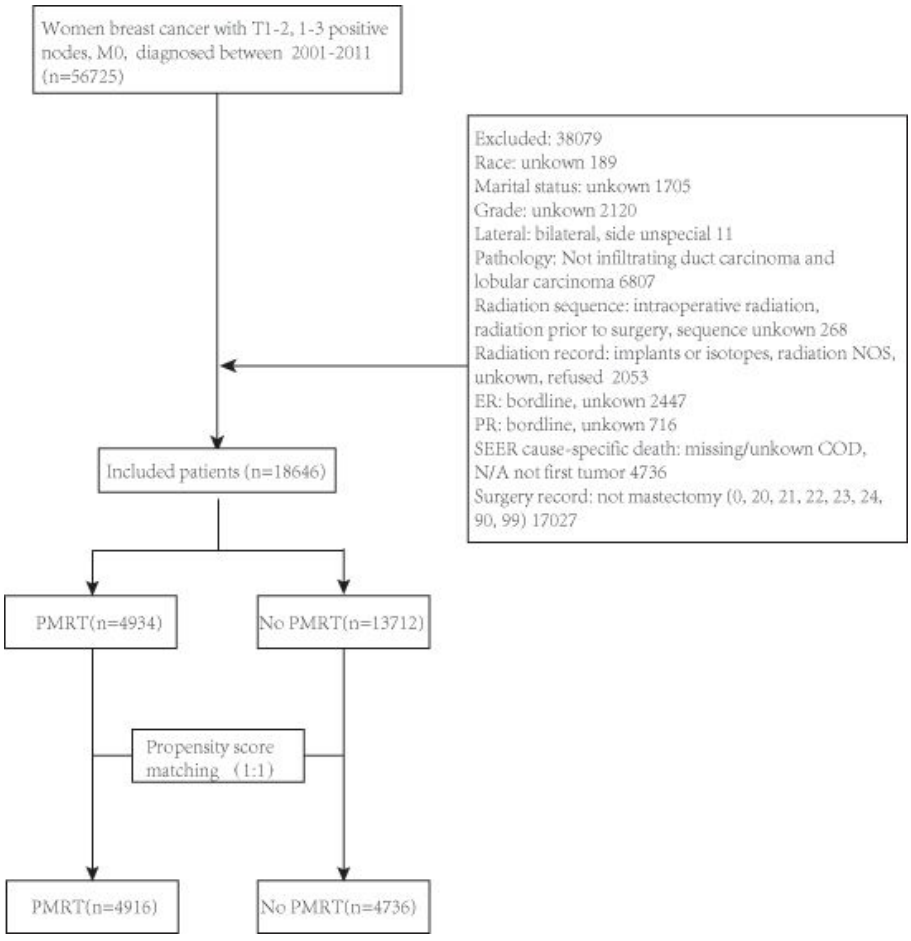
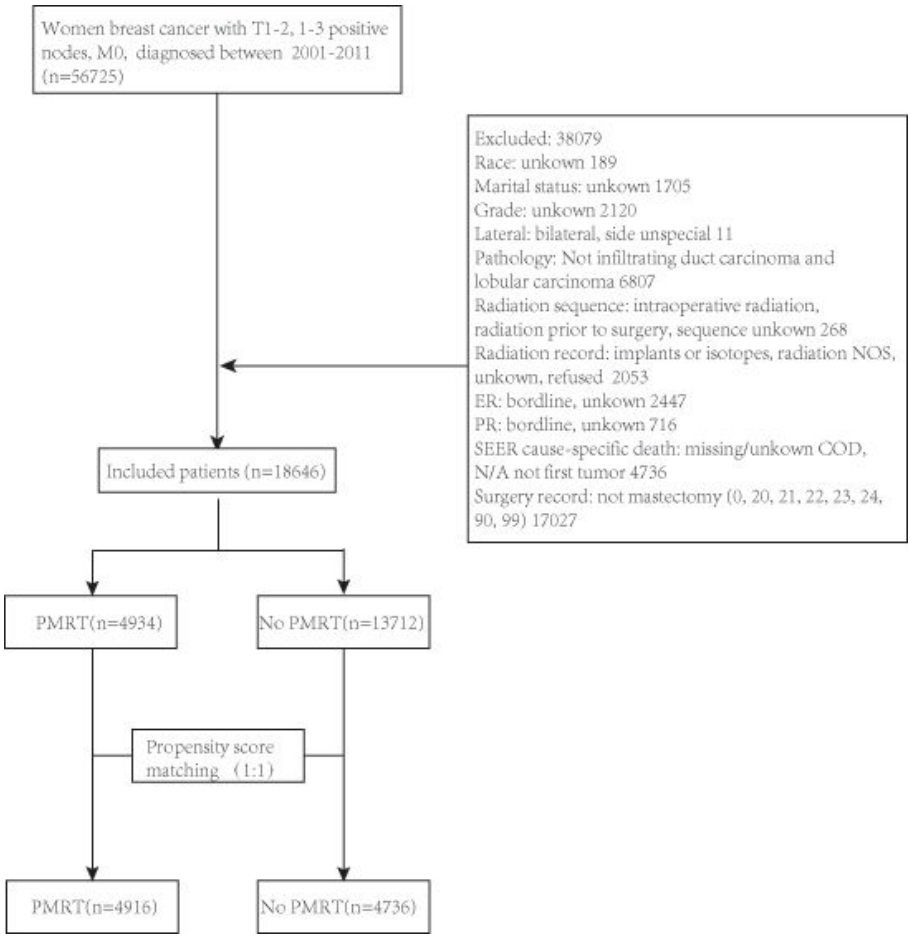


Figure 1

CONSORT diagram. PMRT: postmastectomy radiotherapy; ER: estrogen; PR: progesterone.



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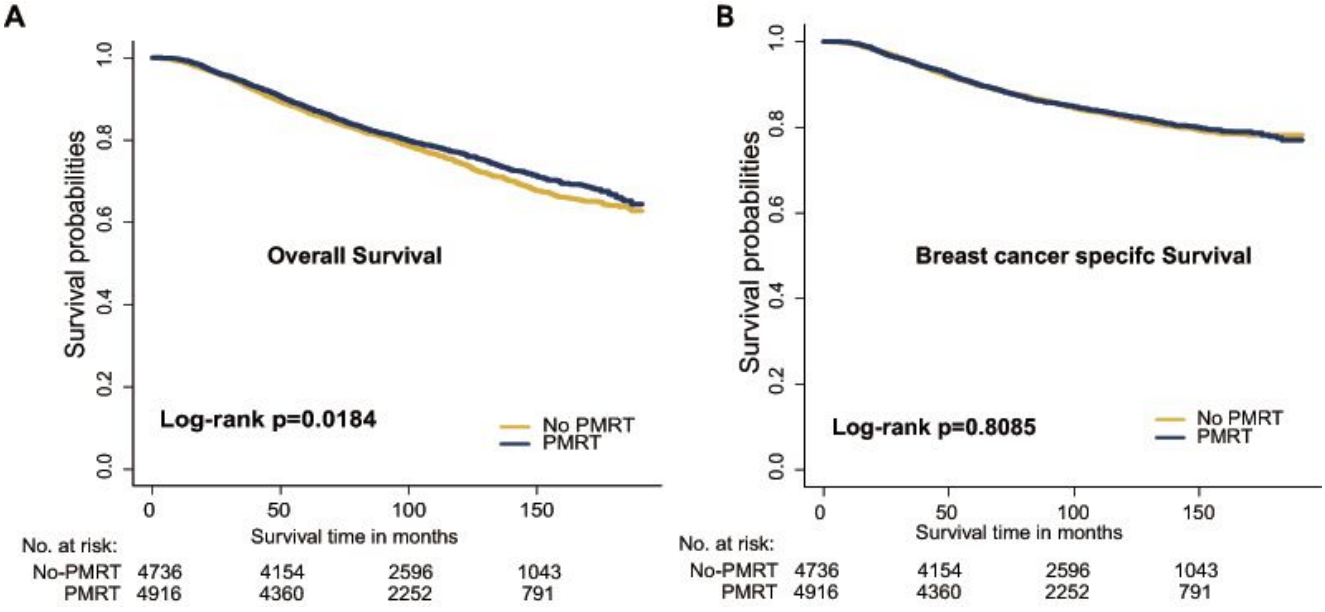
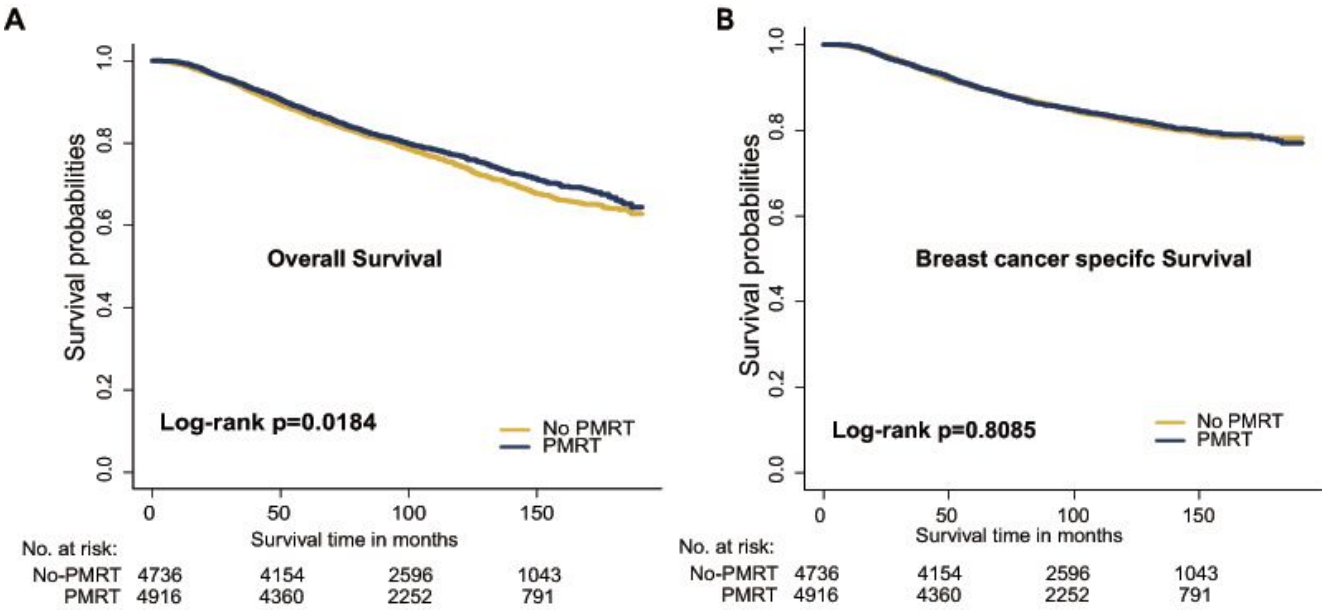


Figure 2

OS (A) and BCSS (B) in T1–2 women breast cancer patients with 1–3 positive axillary lymph nodes after PSM. OS: overall survival; BCSS: breast cancer specific survival; PSM: propensity score matching.



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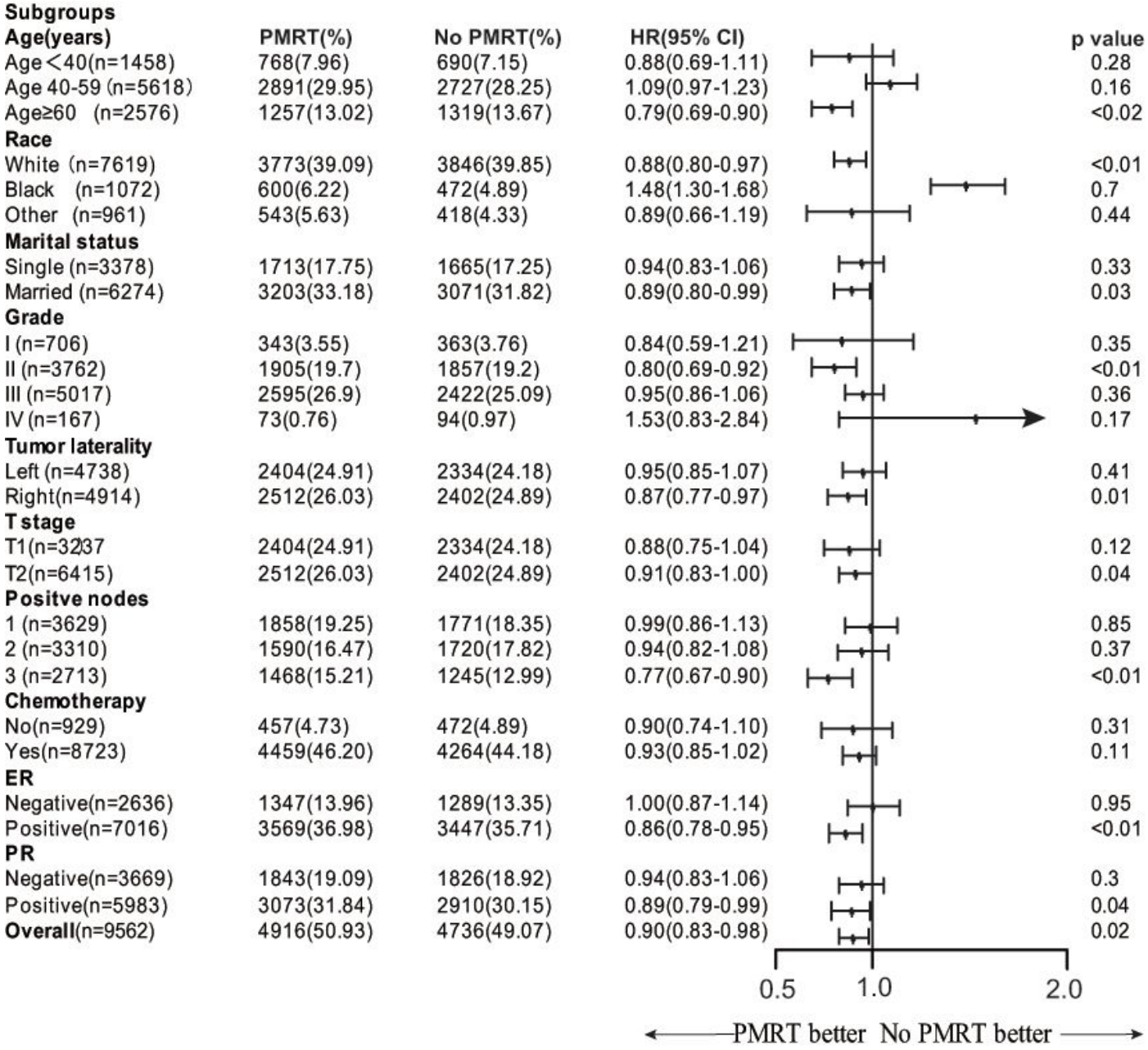
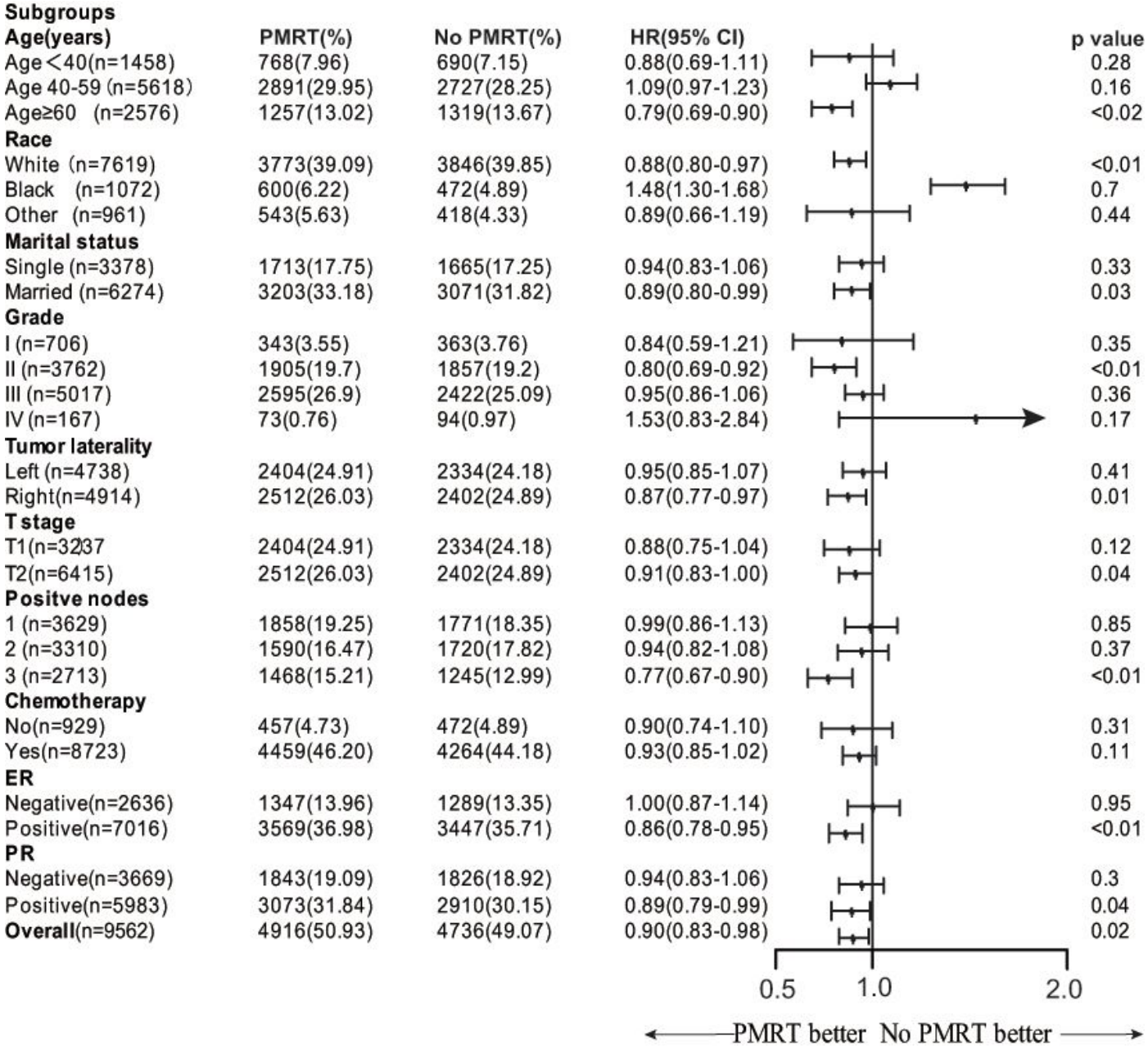


Figure 3

Forest plot depicting hazard ratios and 95% confidence intervals for OS between non-PMRT and PMRT cohorts in different subgroups after PSM. OS: overall survival; PMRT: postmastectomy radiotherapy; PSM: propensity score matching.



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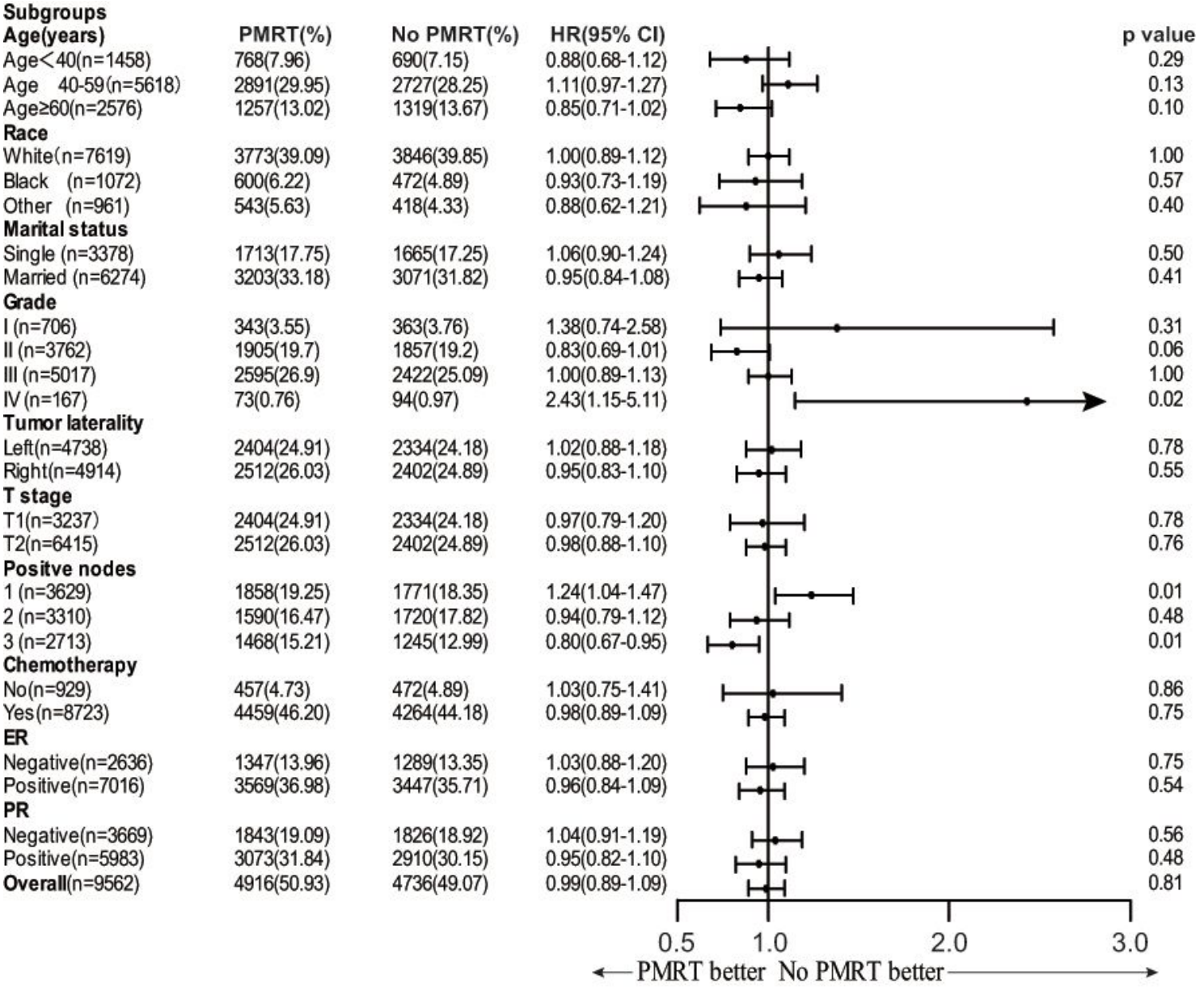
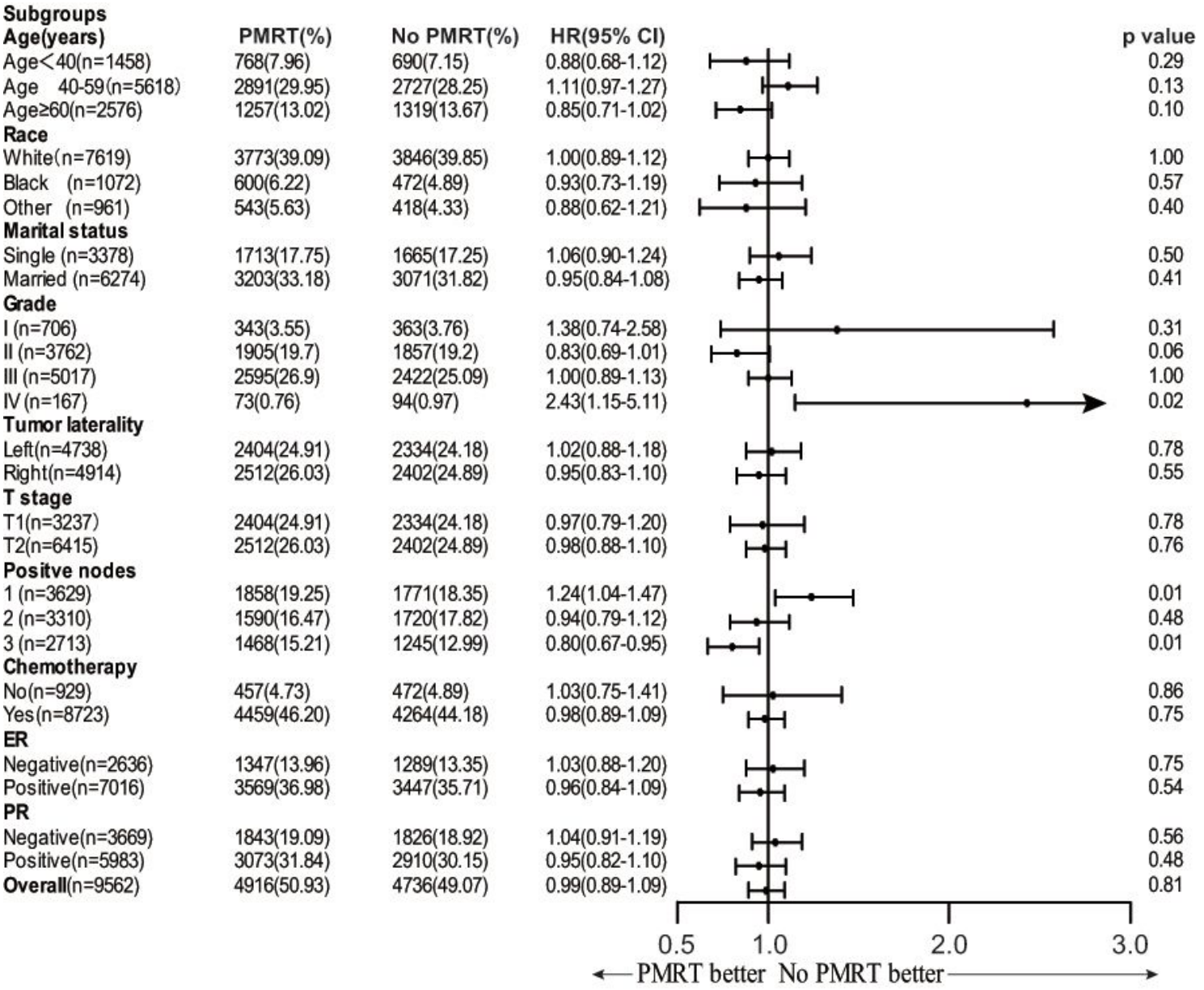


Figure 4

Forest plot depicting hazard ratios and 95% confidence intervals for BCSS between non-PMRT and PMRT cohorts in different subgroups after PSM. OS: overall survival; PMRT: postmastectomy radiotherapy; PSM: propensity score matching.



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Forest plot depicting hazard ratios and 95% confidence intervals for BCSS between non-PMRT and PMRT cohorts in different subgroups after PSM. OS: overall survival; PMRT: postmastectomy radiotherapy; PSM: propensity score matching.