Effect of Postoperative Radiotherapy In Women With Localized Pure Mucinous Breast Cancer After Lumpectomy: A Population-Based Study

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Abstract

Purpose

Pure mucinous breast cancer (PMBC) is a rare subtype of invasive breast cancer with favorable prognosis, in which the effect of postoperative radiotherapy remains unclear. We aimed to investigate the prognostic value of postoperative radiotherapy in women with localized PMBC after lumpectomy.

Methods

We conducted a retrospective cohort study to compare the effectiveness of postoperative radiotherapy (RT) and omitting postoperative radiotherapy (non-RT) in patients with first primary T1-2N0M0 (T ≤ 3cm) PMBC who underwent lumpectomy between 1998 and 2015 using the Surveillance, Epidemiology, and End Results (SEER) database. Breast cancer-specific survival (BCSS) was compared between RT and non-RT groups using Kaplan–Meier method and Cox proportional hazards regression model. Propensity score matching (PSM) was carried out to balance cohort baselines. In addition, an exploratory analysis was performed to verify the effectiveness of RT in subgroup patients.

Results

Overall, 5352(68.2%) and 2494(31.8%) eligible patients with tumor size ≤ 3cm localized PMBC received lumpectomy with postoperative RT and lumpectomy without postoperative RT respectively. The median follow-up duration was 92 months. The 15-year BCSS was 94.39% (95% CI, 93.08% to 95.35%) in the RT group versus 91.38% (95% CI, 88.86% to 93.35%) in the non-RT group ($P < 0.001$). The adjusted hazard ratio for BCSS was 0.64 (95%CI, 0.49 to 0.84; $P = 0.001$) for RT group versus non-RT group. After PSM, similar results were yielded. Adjuvant RT reduced the 15-year risk of breast cancer death from 7.92% to 6.15% ($P = 0.039$). The adjusted hazard ratio for BCSS were 0.66 (95%CI, 0.47 to 0.92; $P = 0.014$) for RT group versus non-RT group. The benefit of RT was well consistent across all subgroups.

Conclusion

Among women with T1-2N0M0 (tumor size ≤ 3cm) PMBC, the addition of RT after lumpectomy was significantly associated with a reduced incidence of breast cancer death compared with non-RT, and the magnitude of benefit may be modest. This suggests that postoperative RT is recommended in the treatment of localized PMBC.

Introduction

Mucinous breast carcinoma (MBC) accounting for approximately 1 to 6% of all breast cancer is divided into two pathological subtypes: pure mucinous breast cancer (PMBC) and mix mucinous breast carcinoma (MMBC) (1). PMBC exclusively consists of tumor tissue with extracellular mucin production over 90%, whereas MMBC usually mixes infiltrating ductal epithelial component with mucinous areas covering from 50–90%(2). The comparisons of biological features and clinical prognosis have been identified previously among PMBC, MMBC and invasive breast cancer of no special type (1, 3–13). PMBC usually occurs in elderly patients, especially in postmenopausal women(8). The tumor size of PMBC ranges from less than 1cm to more than 20cm, with an average of 3cm(14). On account of fewer genetic mutations, PMBC has a stabilized luminal A phenotype with higher expression of hormone receptor and a lower rate of positive human epidermal growth factors 2 (HER-2)(5, 15, 16). A mechanical barrier made of abundant pools of extracellular mucus around cellular island restricts carcinoma cell invasion, leading to less axillary lymph node or distant metastases. Axillary node involvement, although rare, appears to be the worst prognostic factor followed by tumor size, age, progesterone receptor(PR), HER-2 status and nuclear grade(3, 17–20). It has reported that the 5-year, 10-year disease-free survival (DFS) were up to 94%(1), 92%(9) for patients with node-negative PMBC, respectively. Hence, PMBC presents distinct clinicopathological characteristics with especially favorable prognosis.

At present, the recommendations of locoregional treatment for patients with operable PMBC from the latest National Comprehensive Cancer Network are the same as that for patients with typical breast cancer. However, it is difficult to evaluate the effect of local regional treatment on survival outcome in prospective cohort studies or randomized trials owing to the relatively low incidence rate and a limited follow-up prognosis of PMBC. Guidelines on radiotherapy of PMBC are extrapolated from evidence based on other common invasive breast cancer. Although scholars have done some retrospective studies, the effect of postoperative radiotherapy in patiens with PMBC is uncertain so far. Previous study showed that adjuvant radiotherapy was an independent protective factor for both overall survival(OS) and BCSS in patients with PMBC. However, this retrospective study was hetetogeneous in nature because inclusion criteria involved in advanced patients, and the surgical treatment before radiotherapy involved in mastectomy and lumpectomy. A recent SEER research presented that postoperative radiotherapy following lumpectomy improved the 10-year BCSS rates from 94.5–97.6% in patients aged ≥ 65 years diagnosed with T1–2N0 and hormone receptor-positive PMBC. Yet regrettably, patients aged < 65 years were not included in this study. Besides, patients with tumor size larger than 3cm were more likely to receive endocrine therapy, which may confuse results(21). Obviously, it is necessary to adequately assess individualized roles of postoperative RT in this special subtype of breast carcinoma. Hence, we proceeded to a large population-based study using SEER to investigate the effect of postoperative RT on BCSS in women undergoing lumpectomy with T1-2N0M0 (tumor size ≤ 3cm) stage PMBC.

Methods

Patients population

This retrospective study was performed utilizing the Surveillance, Epidemiology, and End Results (SEER) database (November 2018 submission) which released cancer data from 18 registries of national cancer institute and covered approximately 28% of the US population(22). A case-listing session was derived from SEER*Stat version 8.3.5.

We selected all female cases of histological diagnosed first primary PMBC with the International Classification of Diseases for Oncology, 3rd Revision (ICD-O-3) code 8480/3 from January 1998 through December 2015. Patients with T1-2N0M0 (tumor size less than 3 centimeters) stage who received lumpectomy with or without beam postoperative RT were included in the cohort. The exclusion criteria were listed as follows: diagnosed from death certificate or autopsy only; no active or complete follow-up data; unknown T, N, M stage; with nodal positive disease or metastases disease at diagnosis; without operation or unknown surgery; unknown RT; non-beam RT; non-postoperative radiotherapy; bilateral cancer or unknown laterality; unknown tumor size. The flowchart for patient selection was shown in Fig. 1.

Study Covariates

According to administrations of lumpectomy and postoperative RT, a total of 7846 eligible patients under the inclusion criteria were stratified into RT group and non-RT group. We subsequently reviewed variable information of each case on patient baseline demographics, such as age at diagnoses, year of diagnoses, race, marital status at diagnoses. Then, tumor clinicopathological characteristics, including tumor laterality, tumor grade, T stage, tumor size, estrogen receptor (ER) and progesterone receptor (PR) status, were extracted. Among them, the T stage was adjusted by the 6th American Joint Committee on Cancer (AJCC) TNM Staging System. Tumor grade was categorized into four levels on the biasis of the degree of differentiation: grade I, well differentiated; grade II, moderately differentiated; grade III, poorly differentiated; grade IV, undifferentiated or anaplastic. Borderline ER/PR status defined as having 1–10% positivity by immunohistochemistry were merged into positive ER/PR status(23, 24). In this study, we did not evaluate HER-2 status because of lacking data before 2010.

Statistical Analysis

Categoric variables were compared across treatment groups using the Pearson chi-squared test, and continuous variables were analyzed by two independent sample t-tests or Wilcoxon rank sum test. The primary endpoint of this study was breast cancer-specific survival (BCSS). BCSS was defined as an interval from the data of PMBC diagnosis to death as a result of breast cancer. Using Kaplan–Meier survival analysis, BCSS were estimated with log-rank tests in unmatched groups and matched groups. Hazard Ratio (HR) and 95% confidence interval (95%CI) were calculated by Cox proportional hazards model to estimate the effect of RT. The multivariable Cox proportional hazards regression analysis incorporated variables that were significant or approximately significant in univariate analyses. The proportional-hazards assumption was checked based on Schoenfeld residuals after fitting a Cox model. And all of the Cox models obeyed the proportional risk hypothesis. PMS method was used to control confounding bias in the retrospective study. Propensity scores of being receipt of RT were calculated by using a multivariable logistic regression model. The independent variables are being those that were statistically significant for correlation with treatment modality. Patients treated with RT were matched 1:1 to patients managed without RT on propensity scores by using nearest neighbor matching algorithm. The threshold value of Caliper matching was set to 0.2. A standardized difference of less than 0.1 was considered an indifferent imbalance between comparison groups. Further, exploratory analysis and tests of interaction were undertaken to evaluate the effect of adjuvant RT among subgroups according to patient and tumor characteristics.

Statistical analyses were performed with SPSS, version 24.0 (SPSS Inc., Chicago, IL, USA) and STATA, version 15 (Stata Corp., College Station, TX, USA). Two-tailed $P < 0.05$ was considered statistically significant.

Results

1. Patient demographics and tumor characteristics

Comparisons of patient demographics and tumor characteristics between RT and non-RT group were summarized in Table 1. A total of 7846 eligible patients with PMBC were identified in the cohort (mean [SD] age, 67.1 [13.3] years), of whom 5352 (68.2%) received lumpectomy and postoperative RT, 2494 (31.8%) were treated with lumpectomy without RT. Among patients underwent lumpectomy, those who received RT were on average 9 years younger than those who did not ($P < 0.001$). The proportion of patients receiving radiotherapy fluctuated around 70% each year (Fig. 2). The main pathological feature of patients was hormone receptor positive and well differentiated. As such, the majority of patients (92.3%) did not receive chemotherapy. There was no significant difference between treatment groups in tumor size ($P = 0.433$). In order to eliminate the imbalance between groups that may affect results, PMS was subsequently conducted. After PMS between the RT group and non-RT group, 2149 pairs were generated. The distribution of covariates was well balanced between propensity-matched groups (Table 2).

Table 1. Demographic and tumor characteristics among all patients with pure mucinous breast cancer.

	RT		Non-RT		
Characteristics	No.	%	No.	%	*P**
Patients	5352	68.2	2494	31.8	
Age of diagnosis, years					
Mean (SD)	64.4(12.5)		72.8(13.3)		<0.001
Median (IQR)	66.0(56.0-74.0)		76.0(65.0-83.0)		<0.001
<50	749	14.1	197	7.9	<0.001
50-59	1008	18.8	234	9.4	
60-69	1495	27.9	388	15.6	
≥70	2100	39.2	1675	67.1	
Era of diagnosis					
1998-2004	2027	37.9	847	34.0	0.002
2005-2009	1515	28.3	777	31.1	
2010-2015	1810	33.8	870	34.9	
Race					
White	4292	80.2	2089	83.8	<.001
Black	453	8.5	226	9.1	
Other[a]	602	11.3	179	7.2	
Marital status					
Married	2892	54.0	989	39.6	<0.001
Non-married[b]	680	12.7	262	10.5	
DSW[c]	1680	30	1109	44.5	
Unknown	172	3.2	134	5.4	
Laterality					
Left	2782	52.0	1321	53.0	0.415
Right	2570	48.0	1173	47.0	
Tumor size (T stage), cm					
Mean (SD)	1.4(0.7)		1.4(0.7)		0.092
Median (IQR)	1.3(0.9-1.8)		1.3(0.9-1.8)		0.139

≤1.0 (T1)	2034	38.0	910	36.5	0.433
1.1-2.0 (T1)	2456	45.9	1174	47.1	
2.1-3.0 (T2)	862	16.1	410	16.4	
Tumor grade					
I	2977	55.6	1376	55.2	0.002
II	1478	27.6	629	25.2	
III	135	2.5	52	2.1	
IV	8	0.2	4	0.2	
unknown	754	14.1	433	17.4	
ER status					
Positive	5002	93.5	2187	87.7	<0.001
Negative	88	1.6	31	1.2	
Unknown	262	4.9	276	11.1	
PR status					
Positive	4503	84.1	1964	78.7	<0.001
Negative	510	9.5	207	8.3	
Unknown	339	6.4	323	13.0	
Chemotherapy					
No/Unknown	4854	90.7	2385	95.6	<0.001
Yes	498	9.3	109	4.4	
*Categoric variables were analyzed by the Pearson x^2 test, and continuous variables (age, tumor size) were analyzed by the t tests or Mann-Whitney tests.					
[a]Including Asian or Pacific Islander, American Indian, Alaska Native and unknown race.					
[b]Including unmarried or domestic partner, single (never married).					
[c]Including divorced, separated and widowed.					
Abbreviation: RT, radiotherapy; SD, standard deviation; IQR, interquartile range; DSW, divorced, separated and widowed.					

Table 2. Demographic and tumor characteristics among propensity-matched population with pure mucinous breast cancer.

	RT		Non-RT		standardized difference
Characteristics	No.	%	No.	%	
Patients	2149	50.0	2149	50.0	
Age of diagnosis, years					
Mean (SD)	70(11.9)		71(12.9)		0.081
<50	163	7.6	194	9.0	0.050
50-59	233	10.8	232	10.8	0.000
60-69	463	21.5	380	17.7	0.096
≥70	1290	60.0	1343	62.5	0.051
Era of diagnosis					
1998-2004	792	36.9	731	34.0	0.061
2005-2009	585	27.2	673	31.3	0.090
2010-2015	772	35.9	745	35.3	0.011
Race					
White	1769	82.3	1782	82.9	0.015
Black	186	8.7	202	9.4	0.026
Other	194	9.0	165	7.7	0.047
Marital status					
Married	932	43.3	956	44.5	0.022
Non-married	215	10.0	227	10.6	0.020
DSW	902	42.0	880	40.9	0.022
Unknown	100	4.7	86	4.0	0.033
Laterality					
Left	1124	52.3	1139	53.0	0.014
Right	1025	47.7	1010	47.0	0.014
Tumor size (T stage), cm					
Mean (SD)	1.4(0.7)		1.4(0.7)		0.000
≤1.0 (T1)	817	38.0	822	38.3	0.006
1.1-2.0 (T1)	985	45.8	1009	47.0	0.024

2.1-3.0 (T2)	347	16.1	318	14.8	0.036
Tumor grade					
I	1164	54.2	1212	56.4	0.044
II	566	26.3	558	26.0	0.007
III	45	2.1	46	2.1	0.000
IV	4	0.2	4	0.2	0.000
unknown	370	17.2	329	15.3	0.052
ER status					
Positive	1912	89.0	1952	90.8	0.060
Negative	34	1.6	30	1.4	0.012
Unknown	203	9.4	167	7.8	0.058
PR status					
Positive	1732	80.6	1754	81.6	0.027
Negative	182	8.5	186	8.7	0.005
Unknown	235	10.9	209	9.7	0.039
Chemotherapy					
No/Unknown	2019	94.0	2040	94.9	0.039
Yes	130	6.0	109	5.1	0.039
Abbreviation: RT, radiotherapy; SD, standard deviation; DSW, divorced, separated and widowed.					

2. Survival analyses of BCSS

Overall, the median follow-up time was 92 months (rang, 0-227 months), and 239 breast cancer-special deaths were observed. The Kaplan–Meier survival estimate showed that 5-year, 10-year, 15-year BCSS rates were 99.01% (95% CI, 98.68–99.26%), 96.95% (95% CI, 96.29–97.49%), 94.39% (95% CI, 93.08–95.35%) for patients treated with RT respectively, whereas the corresponding were 97.31%(95% CI, 96.48–97.94%), 94.43% (95% CI, 93–95.56%), 91.38%(95% CI, 88.86–93.35%) for non-RT respectively. The difference between RT and non-RT curve was statistically significant (log-rank test, $P < 0.001$; Fig. 3A). The univariate Cox proportional hazards regression model showed the HR of BCSS for RT versus non-RT was 0.52 (95% CI, 0.40 to 0.67; $P < 0.001$). For the purpose of controlling the potential confounding factors in adjuvant RT effectiveness, the multivariable Cox proportional hazards regression analysis was further applied. After the prognostic analysis was adjusted for the following clinicopathological parameters: tumor size, tumor grade, PR status, age at diagnosis, race and married status, we observed postoperative RT was independently associated with better BCSS benefit (adjusted HR, 0.64; 95%CI, 0.49 to 0.84; *P* = 0.001). Moreover, the results also indicated that larger tumor size, age ≥ 70 years, negative PR expression and DSW (divorced, separated, widowed) marital status were risk predictors which independently associated with BCSS(Table 3).

Table 3. Univariate and multivariate prognostic analyses of BCSS in all patients.

Characteristics		Univariate			ultivariate	
	HR	95%CI	*P*	aHR	95%CI	*P*
Treatment groups						
Non-RT	1.00			1.00		
RT	0.52	0.40-0.67	<0.001	0.64	0.49-0.83	0.001
Age of diagnosis, years						
<50	1.00			1.00		
50-59	1.08	0.58-2.03	0.803	1.11	0.62-2.20	0.746
60-69	1.46	0.83-2.57	0.192	1.51	0.91-2.88	0.166
≥70	3.51	2.12-5.80	<0.001	3.05	2.06-5.73	<0.001
Era of diagnosis						
1998-2004	1.00					
2005-2009	1.04	0.77-1.41	0.789			
2010-2015	0.88	0.55-1.41	0.606			
Race						
White	1.00			1.00		
Black	1.49	1.00-2.18	0.047	1.44	0.95-2.12	0.076
Other	0.52	0.30-0.91	0.022	0.70	0.38-1.20	0.213
Marital status						
Married	1.00			1.00		
Non-married	0.92	0.56-1.51	0.736	0.98	0.59-1.61	0.931
DSW	2.25	1.71-2.96	<.001	1.56	1.17-2.08	0.002
Unknown	1.90	1.02-3.54	0.045	1.36	0.72-2.56	0.339
Laterality						
Left	1.00					
Right	0.95	0.74-1.23	0.690			
Tumor size (T stage), cm						
≤1.0 (T1)	1.00			1.00		
1.1-2.0 (T1)	1.85	1.35-2.53	<0.001	1.92	1.40-2.63	<.001

2.1-3.0 (T2)	2.95	2.05-4.24	<0.001	3.02	2.09-4.36	<.001
Tumor grade						
I	1.00			1.00		
II	1.35	1.00-1.82	0.049	1.31	0.97-1.77	0.079
III/IV	1.95	1.05-3.63	0.034	1.91	1.02-3.59	0.043
unknown	1.20	0.85-1.68	0.305	1.16	0.83-1.64	0.390
ER status						
Positive	1.00					
Negative	1.65	0.78-3.53	0.120			
Unknown	1.24	0.83-1.85	0.300			
PR status						
Positive	1.00			1.00		
Negative	1.56	1.08-2.26	0.020	1.47	1.01-2.13	0.045
Unknown	1.37	0.95-1.98	0.100	1.47	0.82-1.72	0.368
Chemotherapy						
No/Unknown	1.00					
Yes	0.75	0.46-1.21	0.460			
Abbreviation: HR,hazard ration; aHR,adjust hazard raion;CI,confidence interval.						

In the propensity-matched cohort, the survival analysis of BCSS also showed a significant difference between the two groups (log-rank test, *P* = 0.039; Fig. 3B). The BCSS rate for RT group was marginally better than non-RT group. The 5-year BCSS was 98.85% (95%CI,98.24–99.25%)in RT group and 94.93% (95%CI, 93.46–96.08%) in non-RT group. The 10-year BCSS was 95.96% (95%CI, 94.66–96.95%) in RT group and 94.93% (95%CI, 0.93.46–96.08%) in non-RT group.The 15-year BCSS rate was 93.82% (95%CI, 91.75–95.38%) in RT group and 92.02% (95%CI, 89.39–94.03%) in non-RT group. The univariate analyses also confirmed that the RT group indicated a significantly favorable prognosis (HR, 0.71; 95%CI, 0.51 to 0.99; *P* = 0.041). After adjusted age, race, marital status and tumor size, the result of multivariable Cox analysis did not change substantially (adjusted HR, 0.66; 95%CI, 0.47 to 0.92; *P* = 0.014).

The salutary effect of adjuvant RT on BCSS was further assessed in different subgroups among the matched population who underwent lumpectomy, and the HR interactions were tested(Fig. 4). The benefit of RT seemed to be significant in some patients. The HR was 0.64 (95%CI, 0.43 to 0.95) for patients aged 70 years and older, 0.44 (95%CI, 0.24 to 0.81) for married women, 0.44 (95%CI, 0.27 to 0.71) for patients with 1.1-2.0cm tumor size, 0.63 (95%CI, 0.44 to 0.91) for patients with positive ER disease, 0.60 (95%CI, 0.40 to 0.90) for patients with positive PR tumor, 0.31 (95%CI, 0.10 to 0.96) for patients diagnosed during 2010–2015. However, as we can see from the Fig. 4, there were no statistically significance in global test for interaction ($P > 0.05$).

Discussion

Among women with early-stage breast cancer receiving lumpectomy, the addition of RT is a standardized treatment based not only on its benefit in reducing ipsilateral breast cancer recurrence, but also on its ability to significantly improve BCSS(25, 26). Nevertheless, the magnitude of the effect of adjuvant RT in PMBC patients has not been clearly quantified because of its relatively favorable behaviors and prognosis. In this large population-based study, by using matched approach among patients who received lumpectomy with T1-2N0M0 (T ≤ 3cm) PMBC, our result clearly indicated that adjuvant irradiation following lumpectomy was significantly associated with BCSS benefit.

In the cohort, the cumulative 15-year BCSS rate was 94.39% for women with PMBC received adjuvant RT after lumpectomy, and 91.38% for patients treated with lumpectomy alone (HR = 0.52; 95% CI, 0.40 to 0.67; $P < 0.001$; Table 2). After adjustment for potential confounding factors, it was translated that the relative reduction of breast cancer-special death was 34%, and the absolute risk reduction at 15 years was 1.8%. On average, 55 women would need to be treated with RT to save 1 life. In addition, heterogeneity tests of the interaction term were not significant among the matched population, suggesting that the protective prognostic value of adjuvant RT were consistent across different populations.

Our research has several potential strengths. To our best knowledge, this is a large cohort used to evaluate the effect on postoperative RT following lumpectomy among patients with early-stage PMBC. Our study only aims to patient with tumor size less than 3cm, which minimizes the impact of endocrine therapy on results. PSM was generated to eliminate the confounding factors, leading to the baseline was comparable between treatment groups. In addition, the heterogeneity of RT effect was tested in subgroup interaction, which further verified the benefit of BCSS was attributable to radiotherapy rather than a baseline imbalance in clinicopathologic features.

Only a few studies have assessed the role of postoperative RT in this special type of breast cancer. Histological types of breast cancer, as prognostic risk factors, have rarely been evaluated in randomized trials related to radiation therapy(27). Single-center experiences did not demonstrate that adjuvant RT increased recurrence/metastasis-free survival (RFS) among patient with PMBC(11). In several retrospective studies, they were also failed to show that receiving adjuvant RT could improve the OS or DFS in PMBC(1, 3, 6, 11, 19, 28, 29). A previous SEER analysis including 11422 patients with PMBC between 1973 and 2002, with a mean follow-up period of 84 months, showed that the addition of radiotherapy was not significantly asscosiated with prognosis using multivariable Cox regression analysis(3). Here, we assessed BCSS benefit of adjuvant RT following lumpectomy compared with lumpectomy alone in T1-2N0M0(tumor size ≤ 3cm) PMBC by using PSM method and multivariable Cox regression analysis (adjust HR = 0.66; 95% CI, 0.47 to 0.92; P = 0.014; Table 4). Combined with the above, we believe that adjuvant RT is a value option for patients underwent lumpectomy with PMBC, even in those with low-risk factors.

Table 4.Univariate and multivariate prognostic analyses of BCSS after PSM.

Characteristics		Univariate			multivariate	
	HR	95%CI	*P*	aHR	95%CI	*P*
Treatment groups						
Non-RT	1.00			1.00		
RT	0.71	0.51-0.98	0.039	0.66	0.47-0.92	0.014
Age of diagnosis, years						
<50	1.00			1.00		
50-59	0.81	0.30-2.17	0.678	0.91	0.34-2.45	0.919
60-69	1.52	0.68-3.39	0.311	1.71	0.75-3.88	0.152
≥70	2.73	1.32-5.62	0.006	2.83	1.32-6.05	0.002
Era of diagnosis						
1998-2004	1.00					
2005-2009	1.02	0.70-1.50	0.902			
2010-2015	0.87	0.48-1.57	0.649			
Race						
White	1.00			1.00		
Black	1.60	0.99-2.61	0.055	1.67	1.02-2.74	0.042
Other	0.55	0.26-1.19	0.130	0.68	0.31-1.47	0.325
Marital status						
Married	1.00			1.00		
Non-married	1.18	0.62-2.22	0.614	1.18	0.62-2.25	0.620
DSW	2.14	1.48-3.08	<.001	1.60	1.10-2.35	0.015
Unknown	1.99	0.94-4.22	0.072	1.66	0.78- 3.52	0.189
Laterality						
Left	1.00					
Right	1.03	0.74-1.42	0.879			
Tumor size (T stage), cm						
≤1.0 (T1)	1.00			1.00		
1.1-2.0 (T1)	2.09	1.38-3.18	0.001	2.19	1.44-3.33	<.001

2.1-3.0 (T2)	3.46	2.15-5.59	<.001	3.58	2.21-5.79	<.001
Tumor grade						
I	1.00					
II	1.12	0.76-1.67	0.550			
III/IV	1.80	0.78-4.13	0.168			
unknown	0.87	0.57-1.38	0.594			
ER status						
Positive	1.00					
Negative	1.84	0.68-5.00	0.228			
Unknown	1.19	0.71-1.82	0.598			
PR status						
Positive	1.00					
Negative	1.22	0.72-2.07	0.452			
Unknown	1.19	0.77-1.85	0.421			
Chemotherapy						
No/Unknown	1.00					
Yes	0.56	0.25-1.27	0.169			
Abbreviation: HR,hazard ration; aHR,adjust hazard raion;CI,confidence interval.						

In the cohort, the risk prediction stratified score basing on clinical features and molecular biomarkers is low among patients with PMBC, which might explain why absolute reductions in 15-year risk of breast cancer death tend to be modest. Besides, we believe patterns of intrinsic tumorigenesis of PMBC may contribute to the result. This special type of breast cancer is distinct from other ER-positive/HER2-negative form of breast cance in terms of the tumorigenicity of mutated genes (5, 16), suggesting that the genomic profiling of unusual variants of breast cancer should be taken into account in developing suitable personalized management for patients. Meanwhile, it is doubtful whether the modest benefit is worth tolerating radiation treatment-indued adverse events. Late toxicity for normal tissues impaired quality of life. Potential radiation-related cardiac toxicity and an additional second cancer risk threaten to roll back life expectancy(30–33). In the future, for those with specific types of breast cancer, it is required to further study the prediction of clinical benefit from radiation therapy, and the identification of low-risk patients in whom radiation can be safely omitted.

Nevertheless, we must acknowledge several limitations of this study. There are inherent biases in retrospective study inevitably. The SEER database at present cannot provide the code on surgical margins, lymphovascular invasion, Ki-67 and hormone therapy. Data are missing in some cases for fundamental variables such as tumor size, grade, TNM stage, hormone receptor status. Fortunately, missing data in TNM stage and tumor size did not have an impact on the study. It was reported that the utilization of radiotherapy was under reported in SEER database(34). The radiotherapy treatment was not assigned at random. Although the propensity score matching method is efficient for reducing the confounding bias, a significant proportion of samples are censored in the paired matching process.

Conclusion

In patients with localized PMBC receiving lumpectomy, our results indicated that the management with adjuvant RT slightly improved BCSS compared with its omission. The adjvuant radiotherapy is an appropriate therapeutic option for patients received lumpectomy with localized PMBC.

Abbreviations

Pure mucinous breast cancer (PMBC); postoperative radiotherapy (RT); the Surveillance, Epidemiology, and End Results database (SEER); Breast cancer-specific survival (BCSS); Propensity score matching (PSM); Mucinous breast carcinoma (MBC); mix mucinous breast carcinoma (MMBC); progesterone receptor(PR); estrogen receptor(ER); human epidermal growth factors 2 (HER-2); disease-free survival (DFS);overall survival(OS);American Joint Committee on Cancer (AJCC);Hazard Ratio (HR); 95% confidence interval (95%CI).

Declarations

Ethical Approval and Consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of supporting data

Any request of supporting data may be sent to the corresponding author.

Conflict of interest statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Author contribution statement

MQP contributed to study conception and design, data collection and analysis, manuscript writing. WYZ wrote and edited the manuscript. SJL,WXC reviewed the manuscript.WXC acquired the funding. All authors contributed to the submitted version. MQP, WYZ and SJL have contributed equally to this work and share first authorship.

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Figures

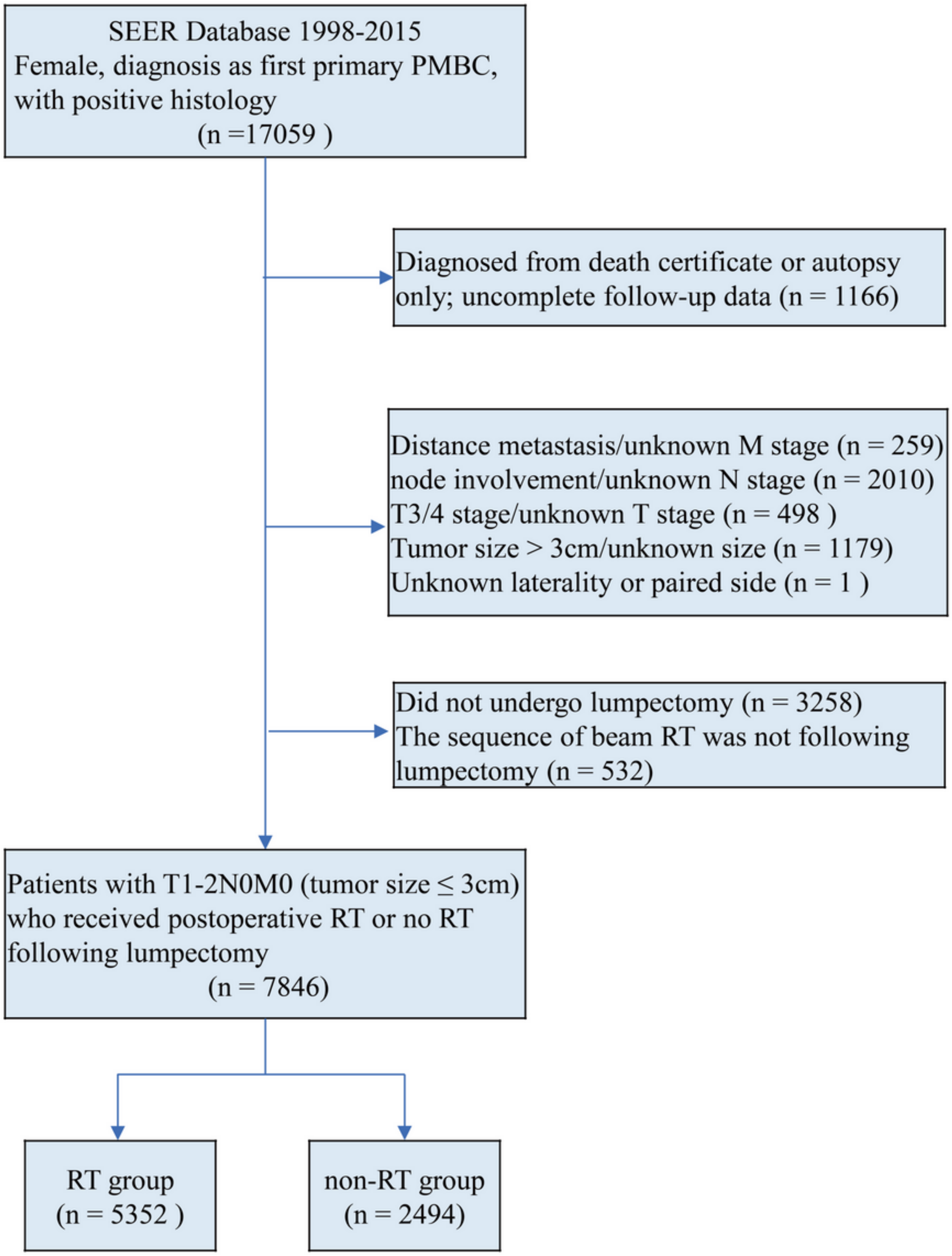

Figure 1

Patient selection diagram.

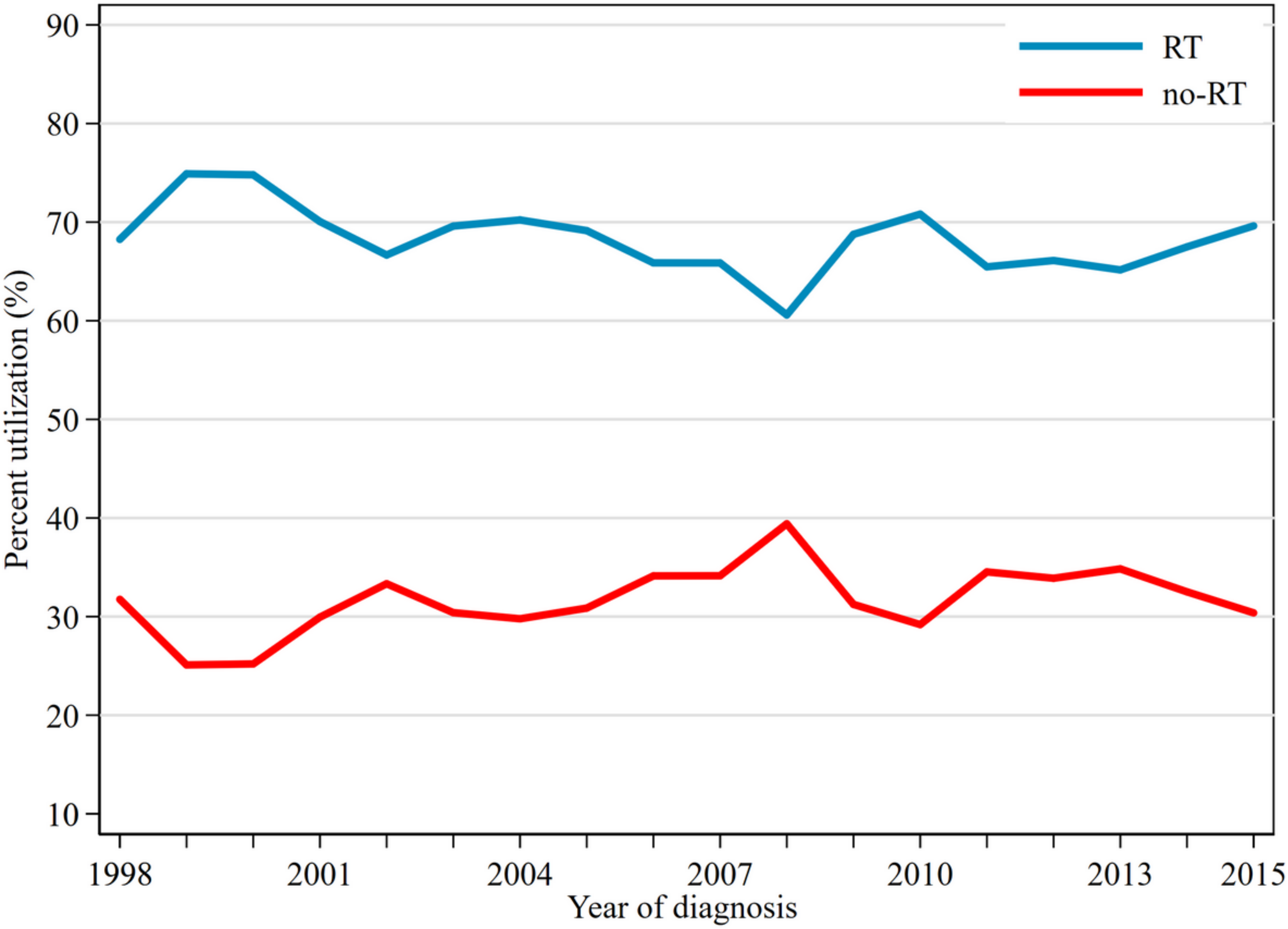

Figure 2

Utilization of postoperative radiotherapy versus omission over time in patients with T1-2N0M0(tumor size ≤ 3cm) PMBC from SEER Database, 1998-2015.

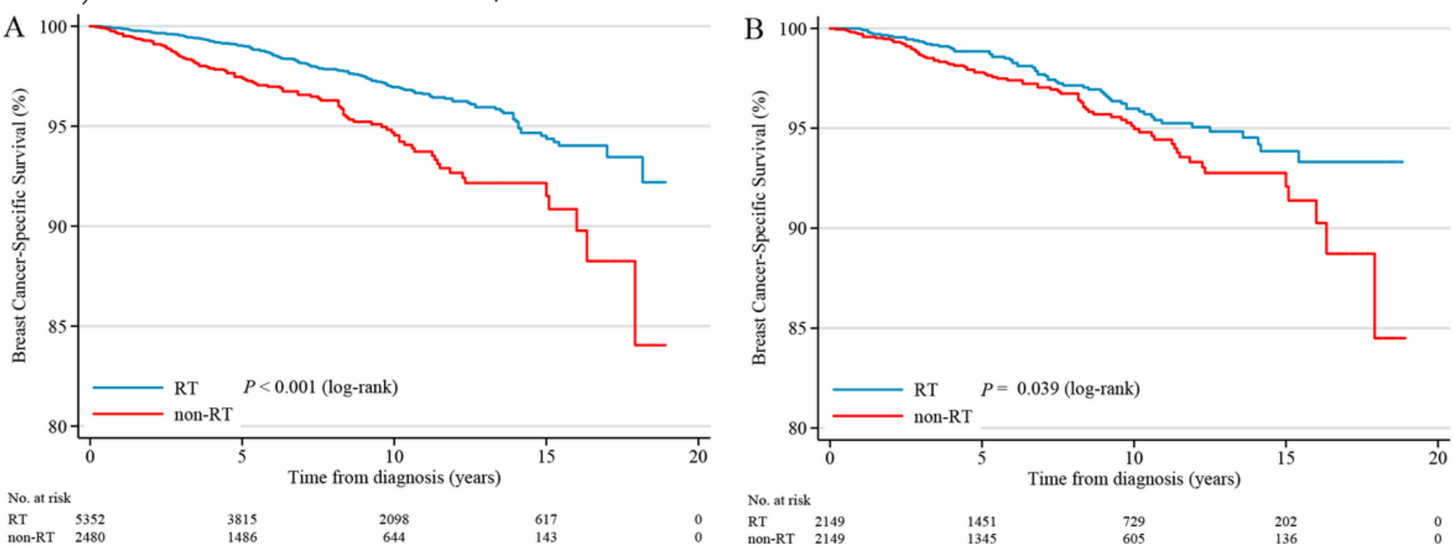

Figure 3

Kaplan-Meier curves comparing BCSS between treatment groups for A) all patients; B) propensity-matched patients.

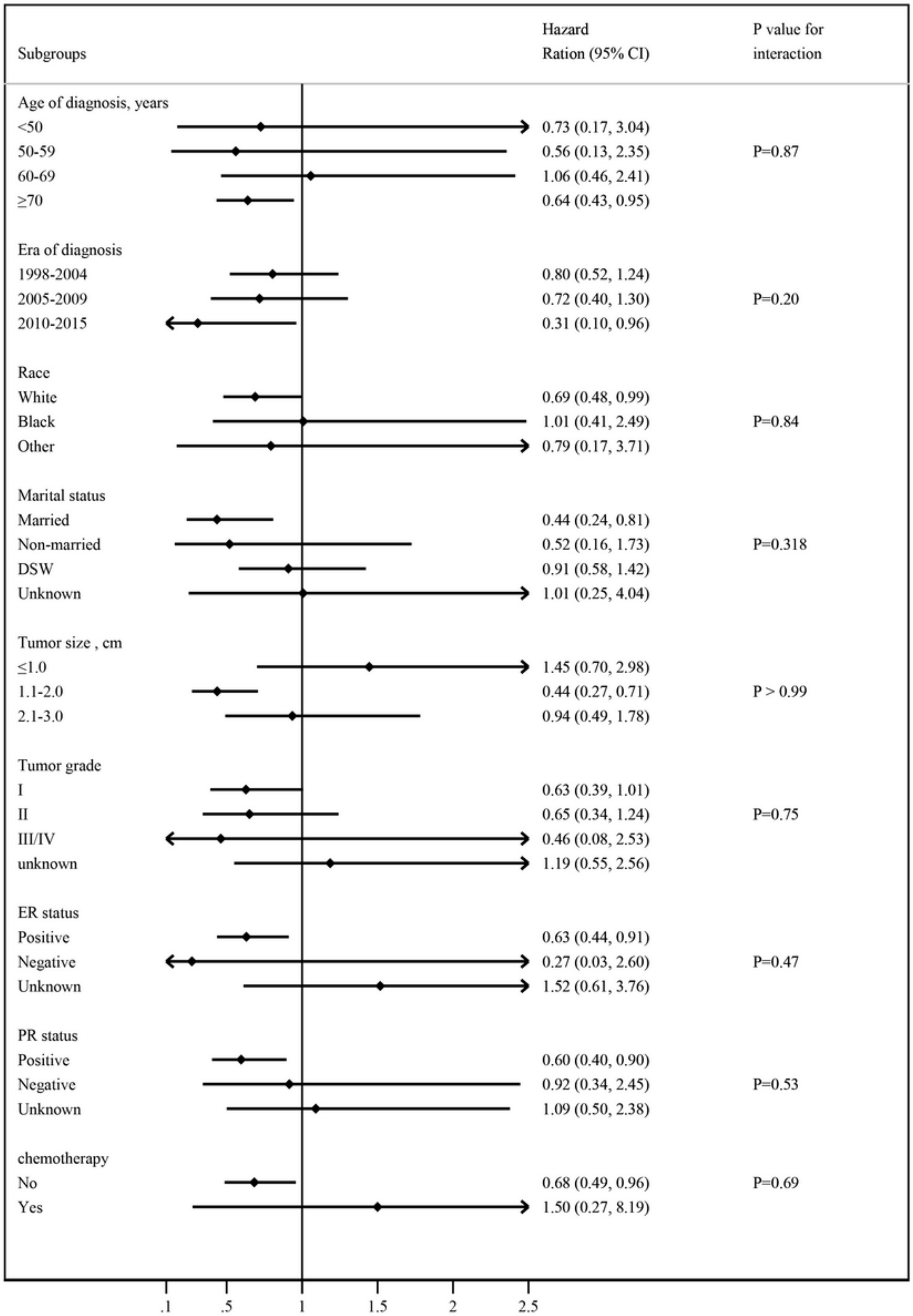

Figure 4

Forest plot depicting hazard ratios of adjuvant radiotherapy following lumpectomy versus lumpectomy alone for early-stage PMBC in the propensity-matched population.