The role of postoperative radiation therapy in stage I–III male breast cancer: A population-based study from the surveillance, epidemiology, and End Results database

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ABSTRACT

Background: This study aimed to investigate the role of postoperative radiation therapy in a large population-based cohort of patients with stage I–III male breast cancer (MaBC).
Methods: Patients with stage I–III breast cancer treated with surgery were selected from the Surveillance, Epidemiology, and End Results cancer database from 2010 to 2015. Multivariate logistic regression identified the predictors of radiation therapy administration. Multivariate Cox regression model was used to evaluate the predictors of survival.
Results: We identified 1321 patients. Age, stage, positive regional nodes, surgical procedure, and HER2 status were strong predictors of radiation therapy administration. There was no difference between patients who received radiation therapy and those who did not (P = 0.46); however, after propensity score matching, it was associated with improved OS (P = 0.04). In the multivariate analysis of the unmatched cohort, the factors associated with better OS were administration of radiation therapy and chemotherapy. In the subset analysis of the unmatched cohort, postoperative radiation therapy was associated with improved OS in men undergoing breast-conserving surgery (BCS), with four or more node-positive or larger primary tumours (T3/T4). Furthermore, we found no benefit of radiation therapy, regardless of the type of axillary surgery in mastectomy (MS). In older MaBC patients with T1-2N1 who underwent MS, radiation therapy showed no significant effects, regardless of chemotherapy.
Conclusion: Postoperative radiation therapy could improve the survival of MaBC patients undergoing BCS, with four or more node-positive or larger primary tumours. Moreover, it should be carefully considered in patients undergoing MS and older T1-2N1 patients.

1. Introduction

Male breast cancer (MaBC) is a relatively rare disease, which accounts for less than 1% of all male cancers and approximately 1% of all breast tumours worldwide. According to epidemiological studies, approximately 2650 cases of MaBC were newly diagnosed and 530 men died of primary cancer in 2020 [1]. The incidence rate of MaBC has increased in recent years [2,3]. Owing to its rarity, few clinical trials have been conducted exclusively on MaBC, and most clinical trials have routinely excluded men [4]. Treatment strategies for MaBC are mainly

extrapolated from numerous retrospective studies and clinical guidelines or experiences in women [5]. However, there is considerable heterogeneity in the clinicopathological characteristics of MaBC in comparison to female breast cancer, such as older age at diagnosis, more advanced stage, more frequently oestrogen receptor (ER) and progesterone receptor (PR) positive, human epidermal growth factor receptor 2 (HER-2) negative, and more frequently associated with BRCA2 gene mutations [6–8]. Therefore, MaBC should be assessed and managed as a distinct group.

The largest series studies of MBC patients in a large country found

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mortality has significantly decreased over time, from 44.8% in 1990–1995 to 26.9% in 2006–2010. Highly ER+, highly PR+, and highly AR + are associated with better OS and RFS, whereas, grade, Ki67 and HER-2status were not [8]. Currently, prospective data and high-quality retrospective reviews on the benefits of postoperative radiation therapy in men are insufficient [9], only a few retrospective studies have shown that postoperative radiotherapy is associated with improved survival, especially in patients with node-positive [10–13]. However, the low rate of postoperative radiotherapy is a concern. Cardoso F et al. showed that 45% of patients treated with BCS, regardless of nodal status and 30.7% of patients with lymph node positive tumours undergoing mastectomy did not receive postoperative radiotherapy [8]. Therefore, further investigations are necessary to improve our understanding of radiotherapy in male breast cancer.

2. Materials and methods

2.1. Data resource

The SEER database is one of the world's largest open cancer databases, established by the National Cancer Institute of the United States, and accounts for approximately 28% of the US population [14]. The data we selected were obtained from the Incidence-SEER Research Plus Data, 18 Registries, Nov 2020 Sub (2000–2018), released April 2021, based on the November 2020 submission. Institutional review board approval and informed consent were not required for this study because our data were obtained from the SEER database, which is publicly available.

2.2. Patient cohort

Men aged ≥20 years diagnosed with breast cancer who underwent BCS or MS (surgery codes: BCS, 20–24; MS, 30, 40–75) from 2010 to 2015 were enrolled in this study. Patients were included based on the following criteria: (1) patients with primary cancer only, (2) patients with stages I–III (American Joint Committee on Cancer [AJCC] 7th edition), and (3) patients with ductal and/or lobular carcinoma (ICD 8500–8549). Patients were excluded based on the following criteria: (1) patients with unknown AJCC stage; (2) patients with follow-up type of autopsy or death certificate; (3) patients receiving radiation prior to surgery, radiation before and after surgery, and surgery before and after radiation or with unknown sequence; (4) patients who survived <1 month from the time of diagnosis (to minimize immortal time bias); and (5) patients with missing surgical records. Fig. 1 illustrates the selection process. A total of 1321 patients with MaBC were included in our cohort.

We used propensity score matching (PSM) to reduce the bias between the two groups, and the final cohort included 608 patients, with 304 each in the radiation and no radiation groups. The following covariates were matched: age, grade, stage, T classification, positive regional nodes, surgical procedure, chemotherapy, ER status, PR status, and HER-2 status. Univariate analyses were performed for both the whole cohort and matched cohort. Multivariate analyses and subgroup analysis were performed on the unmatched cohort. We selected the unmatched cohort instead of the matched cohort considering the act of matching may remove the matched covariates from its association with the outcome [10], and to avoid a decrease in effect size caused by a reduced sample size. The primary outcome of this study was overall survival (OS).

We further examined the patterns of nodal evaluation by defining
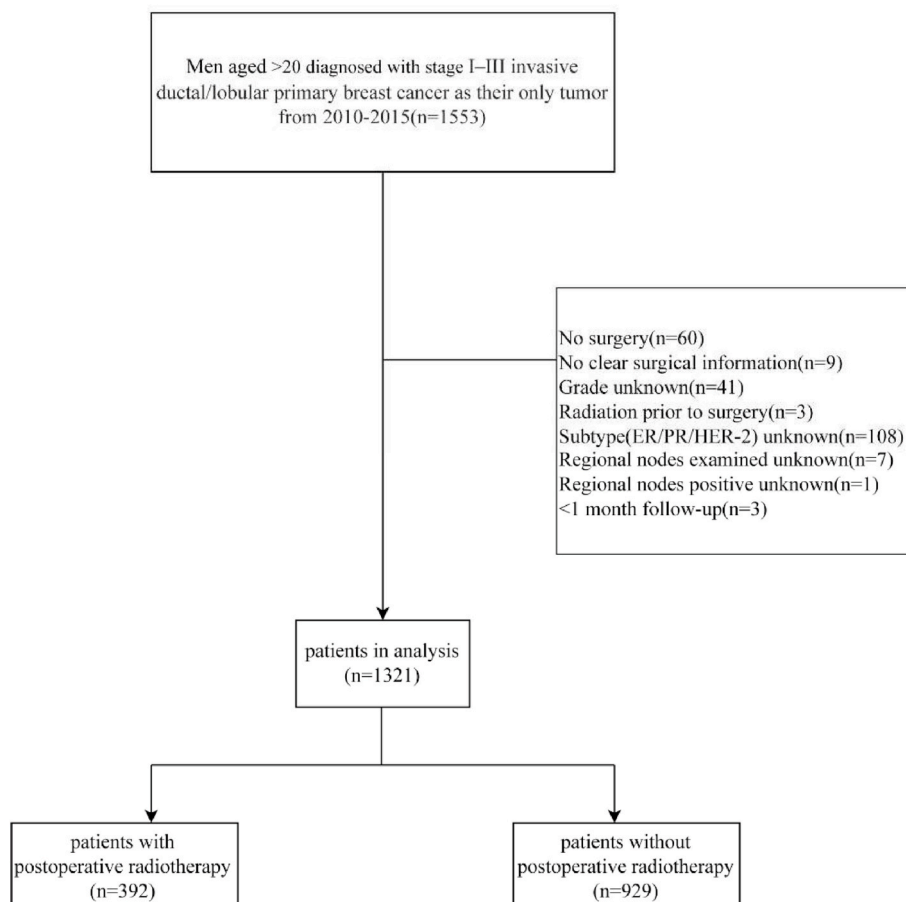

Fig. 1. Flowchart of the study cohort.

axillary surgery as sentinel lymph node biopsy (SLNB), axillary lymph node dissection (ALND), or no axillary surgery. The SEER database did not clear the type of axillary surgery. The 'number of regional lymph nodes examined' code was used to distinguish between SLNB and ALND. We defined patients who had 1–9 nodes resected as undergoing SLNB, and those who had 10 or more nodes resected as undergoing ALND [15–17].

2.3. Statistical analyses

All data were analyzed by statistical software packages R 3.3.2 (http://www.R-project.org, The R Foundation) and Free Statistics software version 1.4 [18]. The chi-squared test was used to compare categorical variables across the radiation therapy and no radiation therapy groups. OS was compared using Kaplan–Meier curves, and the log-rank test was used to determine significant differences before and after PSM. Multivariate Cox regression analysis was performed to identify the factors associated with survival. Subgroup analysis was performed using Kaplan–Meier curves. Statistical significance was set at $P \leq 0.05$.

3. Results

3.1. Baseline characteristics

A total of 1321 patients met the eligibility criteria and were analyzed (Table 1). The median age at diagnosis was 65 (range, 22–97) years. Of all patients, 53.7% of the patients were aged ≥65 years, and the majority were White (80.0%). Approximately 90% of the patients had grade II–III tumours. Most patients (42.0%) had centrally located tumours, and 74 (5.6%) had tumours located in the nipple. Only 29 (2.2%) tumours were ER-negative and 108 (8.2%) tumours were PR-negative. A total of 1165 (88.2%) tumours were HER-2 negative. Triple-negative breast cancer was observed in 18 (1.4%) patients. In total, 543 (41.1%) patients received chemotherapy. 1185 (89.7%) patients underwent MS, of whom 311 (26.2%) received postoperative radiation therapy, and 136 (10.3%) patients underwent BCS, of whom 81 (59.6%) received postoperative

Table 1
Patients demographic and clinical characteristics.

Characteristics	Before PSM				After PSM			
	Total (n = 1321)	0 (n = 929)	1(n = 392)	P-value	Total (n = 608)	0 (n = 304)	1 (n = 304)	P-value
Marital status				0.122				0.555
Married	875 (66.2)	628 (67.6)	247 (63.0)		388 (63.8)	190(62.5)	198 (65.1)	
Single/Unknown	446 (33.8)	301 (32.4)	145 (37.0)		220(36.2)	114 (37.5)	106 (34.9)	
Race				0.195				0.760
White	1057 (80.0)	751 (80.8)	306 (78.1)		484 (79.6)	244 (80.3)	240 (78.9)	
Black	185 (14.0)	120 (12.9)	65 (16.6)		92 (15.1)	43 (14.1)	49 (16.1)	
Other	79 (6.0)	58 (6.2)	21 (5.4)		32 (5.3)	17 (5.6)	15 (4.9)	
Age				0.003				0.626
<65 years	611 (46.3)	405 (43.6)	206 (52.6)		295 (48.5)	144 (47.4)	151 (49.7)	
≥65 years	710 (53.7)	524 (56.4)	186 (47.4)		313 (51.5)	160 (52.6)	153 (50.3)	
Grade				0.225				0.784
I	142 (10.7)	98 (10.5)	44 (11.2)		63 (10.4)	30 (9.9)	33 (10.9)	
II	698 (52.8)	505 (54.4)	193 (49.2)		299 (49.2)	147 (48.4)	152 (50.0)	
III	481 (36.4)	326 (35.1)	155 (39.5)		246 (40.5)	127 (41.8)	119 (39.1)	
Laterality				0.017				0.072
Left	717 (54.3)	484 (52.1)	233 (59.4)		343 (56.4)	160 (52.6)	183 (60.2)	
Right	604 (45.7)	445 (47.9)	159 (40.6)		265 (43.6)	144 (47.4)	121 (39.8)	
TNM stage				<0.001				0.160
I	464 (35.1)	389 (41.9)	75 (19.1)		129 (21.2)	55 (18.1)	74 (24.3)	
II	609 (46.1)	442 (47.6)	167 (42.6)		313 (51.5)	161 (53.0)	152 (50.0)	
III	248 (18.8)	98 (10.5)	150 (38.3)		166 (27.3)	88 (28.9)	78 (25.7)	
T stage				<0.001				0.495
T1	616 (46.6)	466 (50.2)	150 (38.3)		242 (39.8)	114 (37.5)	128 (42.1)	
T2	587 (44.4)	413 (44.5)	174 (44.4)		289 (47.5)	151 (49.7)	138 (45.4)	
T3/T4	118 (8.9)	50 (5.4)	68 (17.3)		77 (12.7)	39 (12.8)	38 (12.5)	
Positive Nodes				<0.001				0.142
0	758 (57.4)	637 (68.6)	121 (30.9)		219 (36.0)	98 (32.2)	121 (39.8)	
1–3	385 (29.1)	227 (24.4)	158 (40.3)		275 (45.2)	144 (47.4)	131 (43.1)	
4+	178 (13.5)	65 (7.0)	113 (28.8)		114 (18.8)	62 (20.4)	52 (17.1)	
Surgery				<0.001				0.071
BCS	136 (10.3)	55 (5.9)	81 (20.7)		125 (20.6)	53 (17.4)	72 (23.7)	
Mastectomy	1185 (89.7)	874 (94.1)	311 (79.3)		483 (79.4)	251 (82.6)	232 (76.3)	
Chemotherapy				<0.001				1.000
No	778 (58.9)	637 (68.6)	141 (36.0)		273 (44.9)	136 (44.7)	137 (45.1)	
Yes	543 (41.1)	292 (31.4)	251 (64.0)		335 (55.1)	168 (55.3)	167 (54.9)	
Subtype				0.365				0.936
HR+/HER2-	1147 (86.8)	804 (86.5)	343 (87.5)		534 (87.8)	269 (88.5)	265 (87.2)	
HR+/HER2+	147 (11.1)	109 (11.7)	38 (9.7)		60 (9.9)	29 (9.5)	31 (10.2)	
HR-/HER2+	9 (0.7)	6 (0.6)	3 (0.8)		6 (1.0)	3 (1.0)	3 (1.0)	
HR-/HER2-	18 (1.4)	10 (1.1)	8 (2.0)		8 (1.3)	3 (1.0)	5 (1.6)	
ER status				0.109				0.601
Negative	29 (2.2)	16 (1.7)	13 (3.3)		15 (2.5)	6 (2)	9 (3)	
Positive	1292 (97.8)	913 (98.3)	379 (96.7)		593 (97.5)	298 (98)	295 (97)	
PR status				0.101				1.000
Negative	108 (8.2)	68 (7.3)	40 (10.2)		60 (9.9)	30 (9.9)	30 (9.9)	
Positive	1213 (91.8)	861 (92.7)	352 (89.8)		548 (90.1)	274 (90.1)	274 (90.1)	
HER2 status				0.371				0.896
Negative	1165 (88.2)	814 (87.6)	351 (89.5)		542 (89.1)	272 (89.5)	270 (88.8)	
Positive	156 (11.8)	115 (12.4)	41 (10.5)		66 (10.9)	32 (10.5)	34 (11.2)	

Abbreviations: PSM:propensity score matching; BCS:breast-conserving surgery.

radiation therapy.

3.2. Predictors of postoperative radiation therapy use

Of the 1321 patients, 929 (70.3%) did not receive postoperative radiation therapy. Age, stage, positive regional nodes, surgical procedure, and HER-2 status were strong predictors of radiation administration in multivariate logistic regression analysis (Table 2). Compared with men aged <65 years, older patients with MaBC were 27% less likely to receive postoperative radiation therapy. Patients with more advanced disease (stages II and III), more positive lymph nodes involved (N1–3 and N4+), HER-2 negativity, and patients undergoing BCS were more likely to receive postoperative radiation therapy.

3.3. Survival analysis for all patients with stage I–III cancer

In our study, the median follow-up period was 68 (range, 1–107) months. The 5- and 8-year OS rates were 81.0% and 69.4%, respectively. In the total cohort, there was no significant difference in OS between patients who received postoperative radiation therapy and those who did not (P = 0.46, Fig. 2A). However, it was associated with an improved OS after PSM (P = 0.04, Fig. 2B).

Multivariate analysis of the unmatched cohort showed independent predictors for improved OS were administration of postoperative radiation therapy (hazard ratio [HR] 0.73; 95% confidence interval [CI], 0.54–0.99) and chemotherapy (HR, 0.48; 95% CI, 0.36–0.64). Predictors of worse OS were high grade III tumour (HR, 1.88; 95% CI, 1.19–2.97), larger tumour size T2 (HR, 1.57; 95% CI, 1.20–2.06) T3/T4 (HR, 2.96;

Table 2
Predictors of Receipt of Radiation therapy Using Multivariable Analysis.

Characteristic	OR	95%CI	*P*-value
Age			
<65 years	Reference		
≥65 years	0.73	0.55–0.97	**0.027**
Race			
White	Reference		
Black	1.08	0.73–1.60	0.708
Other	0.82	0.44–1.51	0.526
Grade			
I	Reference		
II	0.86	0.54–1.39	0.546
III	0.92	0.55–1.52	0.731
Laterality			
Left	Reference		
Right	0.80	0.60–1.05	0.111
TNM stage			
I	Reference		
II	2.12	1.24–3.62	**0.006**
III	3.11	1.19–8.14	**0.021**
T stage			
T1	Reference		
T2	0.77	0.51–1.15	0.203
T3/T4	1.94	0.90–4.22	0.093
Positive Nodes			
0	Reference		
1–3	4.50	3.08–6.56	**<0.001**
4+	8.01	3.5–18.33	**<0.001**
Surgery			
BCS	Reference		
Mastectomy	0.08	0.05–0.13	**<0.001**
ER status			
Negative	Reference		
Positive	0.75	0.28–2.05	0.577
PR status			
Negative	Reference		
Positive	0.83	0.48–1.44	0.511
HER2 status			
Negative	Reference		
Positive	0.54	0.34–0.85	**0.008**

Abbreviations: BCS: breast-conserving surgery.

95% CI, 2.00–4.37), more positive nodes involved N1–3 (HR, 1.41; 95% CI, 1.06–1.87), N4+ (HR, 2.52; 95% CI, 1.76–3.60), Black race (HR, 1.39; 95% CI, 1.03–1.88), and older age ≥65 years (HR, 1.90; 95% CI, 1.46–2.47). Patients with PR positivity and HER-2 negativity seemed to have a trend of better survival. ER status was not an independent predictor of OS (Table 3).

3.4. Survival analysis stratified by clinical characteristics

A subgroup analysis was performed on the unmatched cohort (Fig. 3). Radiation therapy was predictive of better OS in patients undergoing BCS (P = 0.001). Interestingly, different effects of postoperative radiation therapy on the prognosis of different surgical approaches were observed on OS, and it appears to be a protective factor in patients undergoing BCS and an unfavourable prognostic factor for MS. Because the majority of patients in our cohort underwent MS, we further analyzed the patterns of axillary evaluation. Overall, 94.5% of the patients underwent axillary surgery. In BCS, the median number of lymph nodes examined was 3, and the mean number of positive lymph nodes was 0.8. Moreover, 106 (77.9%) patients underwent axillary surgery, with 92 (67.6%) and 14 (10.3%) undergoing SLNB and ALND, respectively. In MS, the median number of lymph nodes examined was 5, and the mean number of positive lymph nodes was 1.8. Furthermore, 1143 (96.5%) patients underwent axillary surgery, with 724 (61.1%) and 419 (35.4%) undergoing SLNB and ALND, respectively. We found no benefit of postoperative radiation therapy, regardless of the type of axillary surgery in MS (Fig. 4). Similarly, postoperative radiation therapy had a positive prognostic value for OS in patients with four or more positive nodes (P = 0.001) and larger primary tumours (T3/T4) (P = 0.009). We further analyzed the prognostic value of radiation therapy in patients with T3N0 disease and found a substantial trend towards a benefit of postoperative radiation therapy (P = 0.09, Fig. 5A).

Considering that the majority of patients in this study were aged ≥65 years, we performed a more detailed analysis. Most of these patients had stage I–II cancer (83.0%), 89.9% underwent MS, 26.2% received postoperative radiation therapy, 29.9% received chemotherapy, 98.6% were HR-positive, and 90.7% were HER-2-negative. Postoperative radiation therapy had no significant benefit in older men with HR-positive breast cancer (P = 0.43). Among the 168 elderly male patients with T1-2N1 breast cancer who underwent MS, 56.2% had grade II tumours, 32.0% received postoperative radiation therapy, 40.8% received chemotherapy, 98.8% were HR-positive, and 91.1% were HER-2-negative. We found no survival benefit from postoperative radiation, regardless of chemotherapy (Fig. 5B, C, D).

4. Discussion

Because of the rarity of MaBC, there is a lack of clinical trials and treatment guidelines specifically focused on this disease, particularly regarding radiation therapy. Evidence has been provided for endocrine and targeted therapies in male patients; however, the effect of radiation therapy remains unclear [19]. Several retrospective studies on MaBC have demonstrated improvements in local control and survival after postoperative radiation therapy [12,20], and some have identified benefits of postoperative radiation therapy have been observed for early and locally advanced stages with positive nodes involved or stage III disease [10,12,13,21]. Conversely, postoperative radiation therapy is often underused in MaBC patients [22–24].

In our analysis, the median age of men was 65 years, several years older than that of women [25,26]. The vast majority of male patients underwent primary MS (89.7%), and modified or simple MS was more common than BCS, mainly due to the comparative scarcity of breast tissue in men, more advanced stage at diagnosis, and higher rates of chest wall and post-areolar infiltration [27,28]. We found that postoperative radiation therapy improved OS in MaBC patients, particularly for those with larger tumours (T3/T4) and more positive lymph nodes
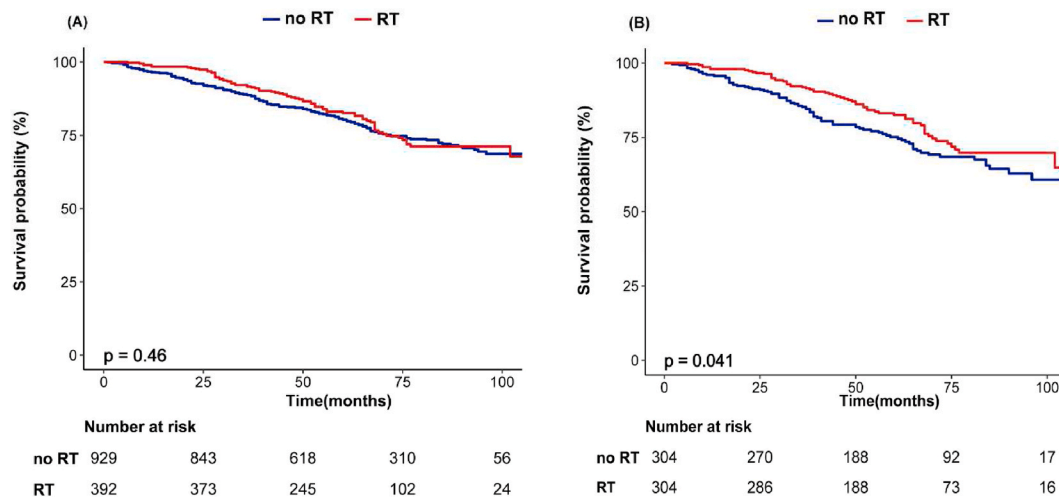
Fig. 2. Kaplan–Meier curves for all patients with and without postoperative radiation therapy:**(A)** before PSM;**(B)** after PSM.

Table 3
Multivariate Cox regression model analysis of MBC patients.

Characteristic	HR	95%CI	P-value
Age			
<65 years	Reference		
≥65 years	1.90	1.46–2.47	**<0.001**
Race			
White	Reference		
Black	1.39	1.03–1.88	**0.033**
Other	0.37	0.16–0.83	**0.016**
Grade			
I	Reference		
II	1.18	0.75–1.85	0.468
III	1.88	1.19–2.97	**0.007**
T stage			
T1	Reference		
T2	1.57	1.20–2.06	**0.001**
T3/T4	2.96	2.00–4.37	**<0.001**
Positive Nodes			
0	Reference		
1–3	1.41	1.06–1.87	**0.019**
4+	2.52	1.76–3.60	**<0.001**
Surgery			
BCS	Reference		
Mastectomy	0.84	0.53–1.32	0.447
Chemotherapy			
No	Reference		
Yes	0.48	0.36–0.64	**<0.001**
Radiation therapy			
No	Reference		
Yes	0.73	0.54–0.99	**0.040**
ER status			
Negative	Reference		
Positive	1.11	0.43–2.89	0.831
PR status			
Negative	Reference		
Positive	0.69	0.45–1.05	0.083
HER2 status			
Negative	Reference		
Positive	1.37	0.97–1.93	0.076

Abbreviations:BCS:breast-conserving surgery.

Fig. 3. The forest plots of sub-group analysis.

and undergoing BCS. We found a higher proportion of patients with grade 3 tumours (35.1%–41.8%) than the 20% identified in a large cohort study by Cardoso F et al. [8]. However, that study showed that no association between grade and outcome, as was observed in the second largest international series of studies [29].

Overall, our results are consistent with several prior analyses of National Cancer Data Base (NCDB) and SEER that showed a survival benefit for postoperative radiation therapy in these patients. An analysis

of 1337 patients from SEER showed that post-MS radiation therapy (PMRT) was associated with improved OS in stage I, and there was a trend towards improved survival in stages II and III [13]. Another analysis of 1933 patients from SEER with localized or regional non-metastatic disease showed an improved 5-year OS in the PMRT group (83% vs. 54%). PMRT was also associated with better 5-year OS both in men with 1–3 positive nodes and those with 4+ positive nodes in a subgroup analysis [10]. Notably, these two studies did not obtain chemotherapy information and HER-2 status since both of these variables are significant prognostic factors for breast cancer. In addition, our cohort selected from 2010 to 2015 was modern compared with these cohorts (1983–2002 and 1998–2013). Two NCDB analyses from similar time periods also showed that radiation therapy was associated with
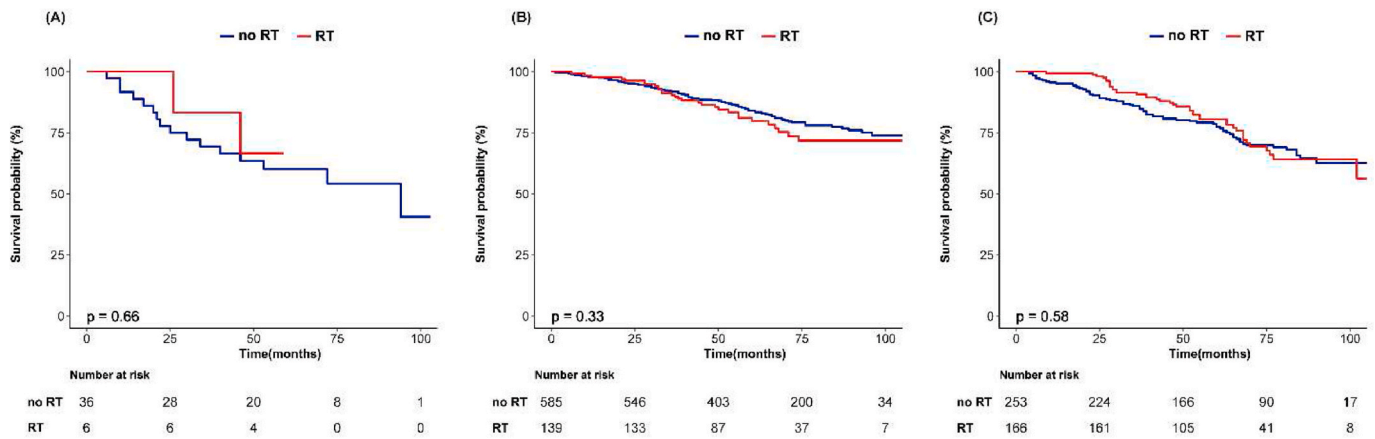
Fig. 4. Kaplan–Meier curves of overall survival stratified by different patterns of axillary evaluation in patients with mastectomy: **(A)** no axillary surgery;**(B)** sentinel lymph node biopsy (SLNB);**(C)** axillary lymph node dissection (ALND).
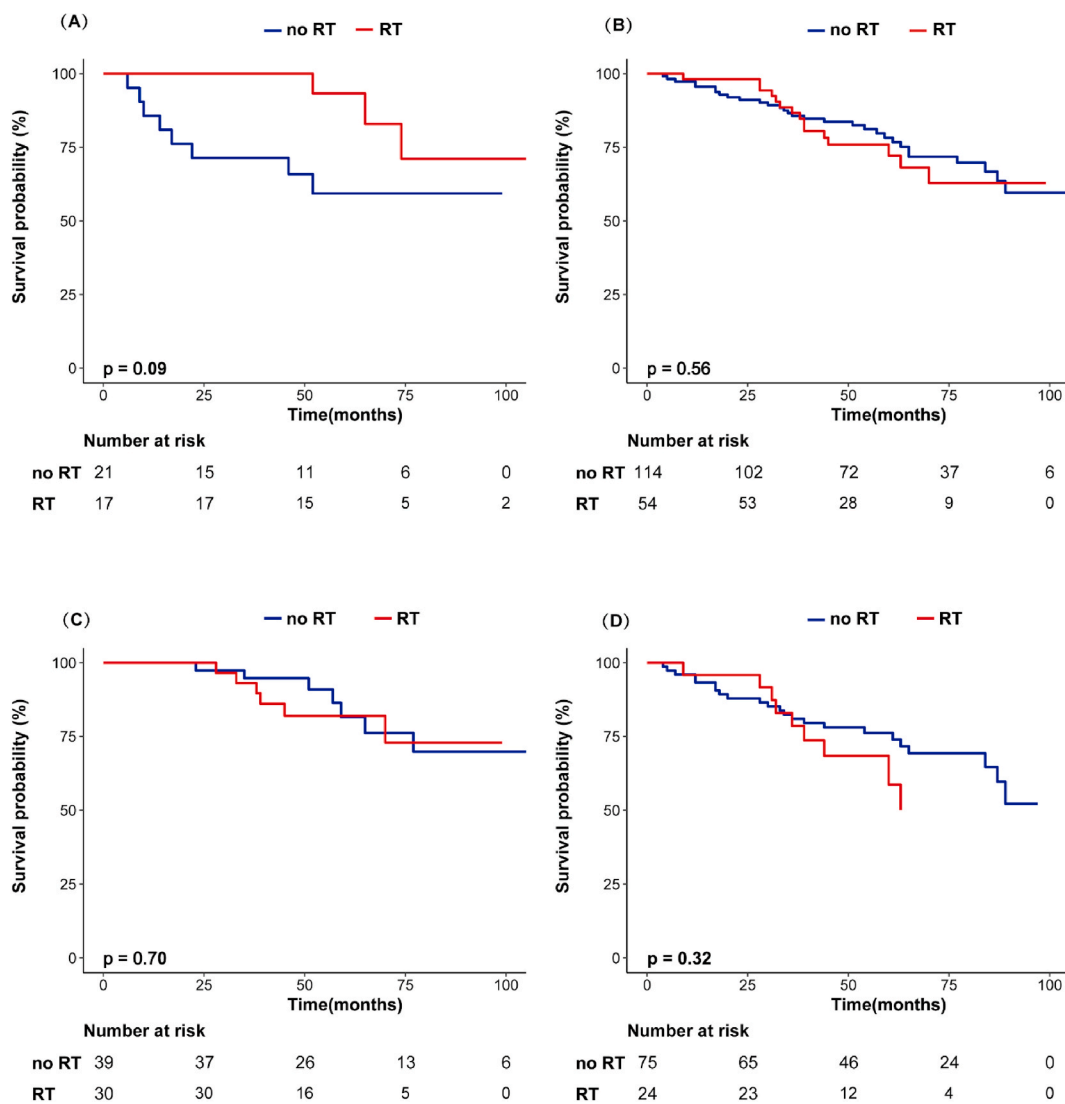
Fig. 5. Kaplan–Meier curves of overall survival in different groups: **(A)** patients with T3N0 breast cancer underwent mastectomy;**(B)** older age patients with T1-2N1 breast cancer underwent mastectomy;**(C)** older age patients with T1-2N1 breast cancer underwent mastectomy with chemotherapy;**(D)** older age patients with T1-2N1 breast cancer underwent mastectomy without chemotherapy.

lower mortality in all stages for patients who underwent BCS [11,12], whereas a significant benefit of radiation therapy for patients with MS was not observed [12], or was observed only in patients with stage III disease [11]. This is in line with our results that postoperative radiation therapy was associated with improved OS in the entire cohort, particularly in patients with BCS; however, only a few benefits were observed in patients undergoing MS.

Multiple retrospective studies also further support our results. Yu et al. evaluated 81 MaBCs from 1997 to 2006 and showed a lower risk of locoregional recurrence (LRR) in patients with MaBC treated with PMRT (4% vs. 24%, P < 0.001), suggesting that PMRT can be considered in patients with high-risk factors, including positive nodes involved, stage III disease, and insufficient margins [30]. Similarly, a multi-institutional study between 2003 and 2019 found a lower risk of relapse after postoperative radiation therapy (19% vs. 32%, P = 0.05), and no in-field relapse after postoperative radiation therapy (0%) versus 10% in patients not receiving radiation therapy [20]. A third study cohort of 664 patients with a median follow-up period of 26.2 years showed that PMRT was associated with longer OS in men with stage III breast cancer (HR, 0.60; P = 0.008) [21]. In a systematic review evaluating radiation therapy for MaBC, 29 retrospective series of studies published between 1984 and 2017 were included, and the use of postoperative radiation therapy in MaBC varied between 3% and 100% (mean, 54%). The review showed that radiation therapy improved locoregional control in six, OS in three, and distant metastasis-free survival in one series [31].

We also performed exploratory subgroup analyses for node-negative men with tumours >5 cm after MS, as the use of PMRT remains controversial owing to the absence of prospective trials addressing specifically among this subset of patients. Nearly half of them received PMRT, whereas the other half received systemic therapy or observation only in the United States [32]. An NCDB analysis cohort with 13901 patients with female breast cancer showed that PMRT improved OS in patients with pT3N0 disease (7-year OS 74% vs. 65%, P < 0.001), but the benefit was limited to those who did not receive postoperative chemotherapy. PMRT did not improve OS in patients with cT3N0 disease who received preoperative chemotherapy(P = 0.29); however, there might be a benefit in patients with a poor response to chemotherapy [33]. A retrospective review identified 162 such patients in the MDACC that reported a lower rate of LRR with the addition of PMRT (4% vs. 24%, P < 0.001) [34]. Similarly, our results showed a significant trend toward a survival benefit from radiation therapy in MaBC (P = 0.09), although no statistical differences were detected due to the limited sample size. These studies will help guide management decisions for patients with T3N0 disease while awaiting the clinical results of the above-mentioned SUPREMO trial [35].

For patients with T1–2N1 disease, the indication for PMRT is uncertain [36–38]. A pooled analysis of 1053 patients with breast cancer referred for postoperative therapy in three clinical trials (BIG 02/98, BCIRG001, and BCIRG005) showed no beneficial effect of PMRT on overall or relapse-free survival among patients with T1–T2 N1 disease who received standard postoperative systemic therapy [39]. The survival effect of PMRT in patients with T1-2N1 disease will also be addressed by the SUPREMO trial (NCT00966888) [35]. Considering the comorbidities, performance status, and life expectancy, older patients are more likely to receive de-intensified treatment concordant with guideline; however, few studies have been conducted on PMRT in older patients with T1-2N1 breast cancer. The results of the two SEER studies were inconsistent. An analysis indicated that PMRT did not show a survival benefit in older patients with breast cancer with T1-2N1 diagnosed between 1992 and 1999 [40]. Another recent study of similar patients between 2004 and 2015 found that the effect of post-MS radiation therapy remains heterogeneous. There was an absolute 10.7% risk reduction associated with PMRT in older patients with high-risk disease, including 3 positive lymph nodes and 2–5 cm of tumours who did not be administered chemotherapy, whereas no significant correlation was found in patients who received chemotherapy [41]. Modern systemic

therapies have decreased the possibility of local recurrence of patients with breast cancer, Thus PMRT might have less benefit and should be interpreted with caution. Even though the EBCTCG meta-analyses have shown PMRT to be beneficial for T1-2N1 patients who received systemic therapy, patients in this pooled analysis were treated between 1964 and 1986, where postoperative systemic therapy protocols were not standardised. Moreover, patients in the pooled EBCTCG analysis had T1–4 disease [42]. Our exploratory subgroup analyses specifically for older patients with MaBC with T1-2N1 diseases showed that postoperative radiation therapy did not appear to provide a survival benefit, regardless of chemotherapy.

The study is limited by the retrospective design, as well as the potential selection biases inherent in such studies. Important prognostic factors, such as family history, margin status, lymphovascular invasion, targeted therapy, and endocrine use, were not available in the SEER database. Furthermore, irradiation dose and fractionation may have an influence on the outcome; however, SEER does not capture these data. Nevertheless, this study was highly reliable. First, we included as many variables as possible from SEER database, including ER, PR, and HER-2 status and details of lymph node surgery, since these characteristics are significant prognostic factors in breast cancer, and established strict criteria to select the target population to ensure that our study is reliable. Additionally, we stratified the patients according to clinical characteristics (surgical procedure, T classification, number of positive nodes involved), which were proven to be strong predictors of radiation therapy administration in clinical practice. Moreover, we performed a subgroup analysis of patients who remained controversial in radiation therapy management. Unfortunately, due to the limited sample size, we did not adjust for subgroup analysis; hence, the true benefits of postoperative radiation therapy may be masked by imbalances in the group, as observed in our study. Consequently, a prospective randomised trial investigating radiation therapy for MaBC is urgently required. A suitable alternative may be to include these rare patients in prospective trials of female breast cancer as a separate group, as historically they have been largely excluded.

5. Conclusion

In summary, our study suggests that postoperative radiation therapy is associated with improved survival, especially after BCS, more positive node involvement, and larger tumours. Moreover, it should be carefully considered in patients undergoing MS and older T1-2N1 patients.

Author contributions

PW, DH, and SZ are the lead authors who participated in data analysis and drafting of the manuscript. HC and QW generated the tables and figures. QS revised the manuscript. GL was responsible for the design and study supervision. All authors have read and approved the final manuscript.

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Data availability statement

Publicly available datasets were analyzed in this study. These data are available at www.seer.cancer.gov./

Declaration of competing interest

None.

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