

Research on the cutoff tumor size of omitting radiotherapy for BCSS after breast conserving surgery in women aged 65 years or older with low-risk invasive breast carcinoma: Results based on the SEER database

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ABSTRACT

Background: Radiotherapy after breast-conserving surgery (BCS) is not always necessary in older women staged T1N0M0 with low-risk invasive breast cancer, but few studies have concluded the detailed tumor size as a reference for avoiding radiotherapy. The study was conducted to explore and identify the optimal cutoff tumor size.

Methods: The study population was from the Surveillance, Epidemiology, and End Results (SEER) database in 2010–2016. Propensity score matching was used to balance the confounders between groups. Predictors associated with survival were analyzed by Kaplan–Meier, X-tile, Cox proportional hazards model and competing risk model.

Results: A total of 52049 women and 3846 deaths were included in the cohort with a median follow-up of 34 months. Based on the cutoff value determined by X-tile analysis, the study population were divided into small tumor group (≤ 14 mm in diameter) and large tumor group (> 14 mm in diameter). Small tumors and radiotherapy were correlated with better breast cancer-specific survival (BCSS). In subgroup analysis, the absolute benefit of BCSS in 6 years attributed to radiotherapy was only 0.90% (RT vs. non-RT: 98.77% vs. 97.87%) for patients with small tumors but up to 3.33% (RT vs. non-RT: 97.10% vs. 93.77%) for those with large tumors.

Conclusion: Small tumors and adjuvant radiotherapy were associated with improved long-term prognosis, and 14 mm in diameter was the cutoff tumor size of omitting radiotherapy for patients aged 65 or older with T1N0M0 stage, ER+ and HER2-breast carcinoma after BCS.

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1. Background

Adjuvant radiotherapy (RT) is a component of breast-conserving

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therapy (BCT) in order to obtain locoregional control for patients with early-stage breast cancer [1–3]. The administration of adjuvant RT could reduce both the risk of local relapse and 15-year breast cancer-specific death (BCSD) irrespective of age [1]. However, advancing age was associated with more favorable tumor biology and elderly patients with breast cancer generally were considered having distinctive biologic and clinical characteristics [4–7]. And no significant advantage was gained in overall survival (OS) or disease-free survival from adjuvant RT after breast-conserving surgery (BCS) by previous randomized controlled trials (CALGB 9343 and PRIME II), for elderly patients with T1-

T2N0M0 stage and estrogen receptor-positive (ER+) female breast cancer (FBC) [8,9]. Such results indicated that postoperative RT after BCS is not always necessary in selected elderly women staged T1N0M0 with ER + FBC. Moreover, as a relatively general term, stage T1 ranging from 1 mm to 20 mm in tumor size in the 7th edition of AJCC/TNM staging system for breast cancers, it was still unknown the detailed tumor size at which postoperative RT after BCS might be omitted without causing a significant reduction in both OS and breast cancer specific survival (BCSS).

A retrospective study based on the Surveillance, Epidemiology, and End Results (SEER) database showed that for elderly women with hormone receptor-positive and T1N0 stage breast cancer, postoperative RT after BCS could be omitted only in patients who meet both the criteria of a small tumor size (≤ 10 mm) and low tumor grade [10]. However, the study was simply grouped as 1–10 mm and 11–20 mm by tumor size. The detailed tumor size that defines the cutoff point by which omission of RT could be considered for patients staged T1N0M0 with low-risk (ER+ and HER2-) invasive breast cancer remains uncertain. The age of 65 was commonly used as the threshold of old age [11, 12,13,14] and the lower limit for assessing the effect of omitting whole-breast irradiation on local control (PRIME II) in the published study [9]. For this, we have to renew the interest in identifying patients age 65 years or older with indolent tumors who are unlikely to die of their tumors and could avoid RT [15].

To further explore and identify the detailed tumor size which could affect the prognosis OS and BCSS for patients aged 65 years or more with negative lymph nodes and ER-positive, T1 stage FBC, we conducted a large cohort of women with FBC from 2010 to 2016 from the population-based database SEER cancer registry program.

2. Methods

2.1. Data source

We used data from the national cancer institute's SEER program database, which includes population-based data from 18 cancer registries and represents approximately 28% of the U.S population from 1975 to 2016 (18). SEER*Stat Software version 8.3.6 (<https://seer.cancer.gov/seerstat/>) (Information Management Service, Inc. Calverton, MD, USA) was used to generate the case listing. All procedures were performed in accordance with approved guidelines. This study was approved by the Ethics Committee of the First Affiliated Hospital of Xi'an Jiaotong University. The SEER data erases the identity information of patients, so there is no need for informed consent from the patients.

2.2. Patient cohort

Female patients with pathologically confirmed breast cancer from 2010 to 2016 were enrolled in the study. Patients were included by following criteria: 1) primary breast cancer; 2) ER positive and HER2 negative; 3) underwent BCS; 4) TNM (Derived AJCC Stage Group, 7th ed (2010–2015), Derived SEER Cmb Stg Grp (2016+)) stages T1N0M0; 5) aged 65 years or more.

After the preliminary selection, patients were excluded by following criteria: (1) the follow-up time was not clear or 0 months; (2) unknown tumor size; (3) unknown progesterone-receptor (PR) status; (4) unknown laterality; (5) unknown RT status. The selecting procedure was shown in Fig. 1. A total of 52049 elderly female patients with early breast cancer (EBC) were selected.

2.3. End points

The primary endpoint was BCSS, defined as the length of time

from either the date of diagnosis or the start of treatment for breast cancer, to the date of death from it. Patients who die from causes unrelated to breast cancer are not counted in this measurement. The secondary outcome measurement was overall survival (OS), defined as the length of time from either the date of diagnosis or the start of treatment for breast cancer to the data of death from any causes.

2.4. Statistics analysis

X-tile program developed by Yale University School of Medicine was used to determine the cut-points of optimal tumor size through comparing the survival between two sides of each tumor size and product a minimum p-value [16]. The baseline characteristics of patients were described using summary statistics. One-to-one (1:1) propensity score matching (PSM) helped to balance baseline characteristics and potential prognostic confounders between the groups [17]. By using "MatchIt" R package, all variables in Table 1 were included in PSM analysis to reduce the difference of the clinicopathological features between RT and non-RT group and achieve optimal comparability.

Kaplan-Meier analysis and Cox proportional hazards model were used to compare OS and BCSS among different patients. Fine and Gray multivariable regression model was performed to identify factors associated with risk of death from breast cancer, which aimed to reduce bias caused by informative censoring. Furthermore, a competing risk analysis model was built to evaluate the impact of RT on BCSD after excluding the impact of other cause-specific death (OCSD). SPSS version 23.0 (IBM Corporation, Armonk, NY, USA) and R software (version 3.6.2, R Foundation for Statistical Computing, Vienna, Austria. <http://www.R-project.org/>) were used for calculations. A two-sided p value < 0.05 considered statistically significant.

3. Results

3.1. X-tile analysis based on BCSS and OS

To explore and identify the optimal cutoff of tumor size which could affect the BCSS and OS most significantly for patients, X-tile analysis was used. Based on the cutoff value of 14 mm determined by X-tile analysis, 38400 (73.8%) eligible patients were classified into small tumor group (≤ 14 mm in diameter), while 13649 (26.2%) patients were classified into large tumor (>14 mm in diameter) group. On the whole, large tumors were associated with poorer BCSS (RR = 2.56, $P < 0.001$) and OS (RR = 1.46, $P < 0.001$) in comparison with the small tumors, as shown in Fig. 2a and b, and poorer BCSS (RR = 2.48, $P < 0.001$) after the application of PSM (Supplemental Fig. 1a). Compared with small tumors, large tumors were also associated with worse OS (RR = 1.40, $P < 0.001$) as well as BCSS (RR = 2.58, $P < 0.001$) for patients with RT, and worse BCSS (RR = 2.61, $P < 0.001$) for patients without RT (Supplemental Fig. 1b, 1c and 1d). After PSM, similar results were archived.

3.2. Baseline characteristics of patients

Among the cohort of 52049 patients with a median follow-up of 34 months (range 1–83 months), 35026 (67.29%) patients received radiotherapy (RT group), while 17023 (32.71%) had no radiotherapy (non-RT group). By comparing RT and non-RT groups, significant differences ($P < 0.05$) were found in most variables. PSM was used to avoid potential prognostic confounders which could affect the accuracy of the analysis results. After PSM, there were still 28068 cases in the whole cohort, including 14034 patients in RT and non-RT groups respectively. And there were no significant differences in

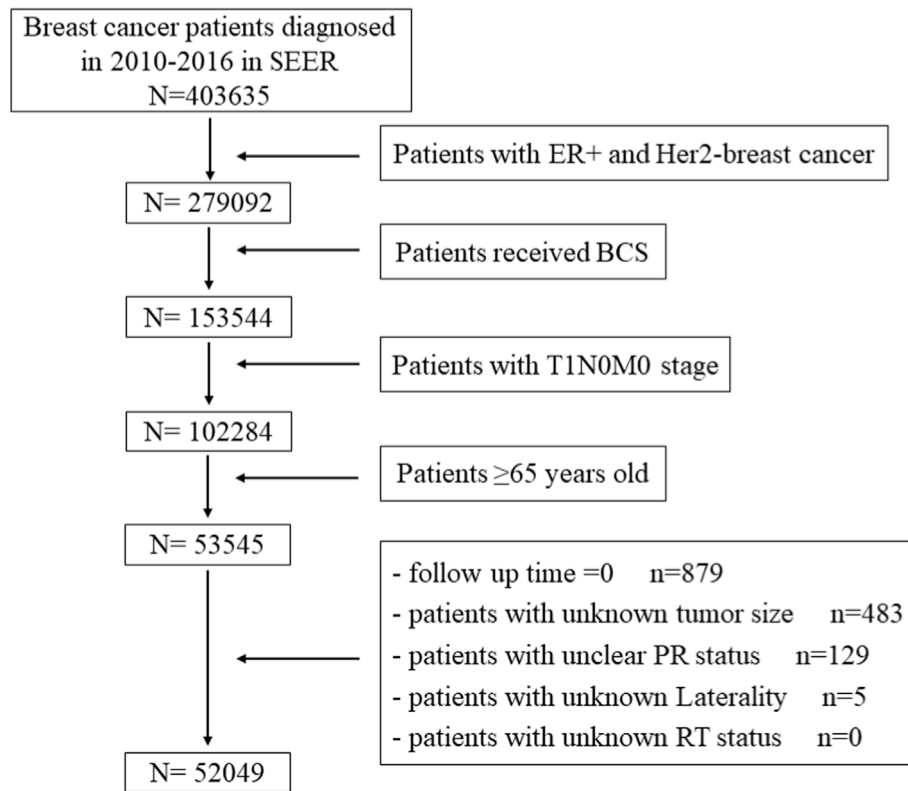


Fig. 1. Eligibility, inclusion, and exclusion criteria of study population.

clinicopathologic characteristics between RT and non-RT groups. The details were shown in Table 1.

3.3. BCSS and OS curve associated with radiotherapy using Kaplan-Meier analysis

Kaplan-Meier analysis were used to initially compare the effects of radiotherapy on survival in patients aged 65 or older with T1N0M0 stage, ER+ and HER2-small breast tumors after BCS. After 83 months of follow-up, a total of 3846 deaths occurred in the unmatched cohort, of which 11.93% (459/3846) of them were caused by breast cancer, and 88.07% (3387/3846) of them were from causes unrelated to breast cancer. After PSM, the BCSS at 6 years was 98.37% in RT group and 96.85% in non-RT group. Compared with the patients in non-RT group, the BCSS at 6 years for patients in RT group increased by 1.52% (Fig. 3a) while BCSS before PSM increased by 1.91% (98.49% vs. 96.58%) (Fig. 3b). The OS at 6 years was 84.41% for patients in RT group and 76.99% for patients in non-RT group after the application of PSM. The absolute value of improvement in OS, after and before PSM, were 7.42% (84.41% vs. 76.99%) and 15.01% (88.35% vs. 73.34%) for patients in RT group, separately, in comparison with those in non-RT group (Supplemental Figs. 2a and 2b).

3.4. Cox proportional hazards model of OS and BCSS

Based on the results of univariate analysis, age at diagnosis, race, marital status, histology, PR status, degree of differentiation, tumor size, chemotherapy, and radiotherapy were included in the multivariate analysis, as shown in Table 2. RT was associated with better BCSS (HR = 0.43, 95%CI: 0.33–0.55, $P < 0.001$) and OS (HR = 0.56, 95%CI: 0.52–0.61, $P < 0.001$) in comparison with no RT. And patients with large tumors was correlated with decreased BCSS

(HR = 2.16, 95%CI: 1.70–2.74, $P < 0.001$) and OS (HR = 1.37, 95%CI: 1.26–1.50, $P < 0.001$) and when compared with small tumors. Black race, unmarried status and poor-differentiation tumors were all adverse prognostic factors for both OS and BCSS ($P < 0.01$). In addition, when compared with duct carcinoma, lobular carcinoma seemed to be more beneficial to OS ($P < 0.001$) rather than BCSS ($P < 0.05$). Before PSM, similar results were archived. The results of univariate analysis are shown in Supplemental Table 1.

3.5. Multivariable fine and gray regression model analysis

According to the results of multivariate Cox regression analysis, several potential prognostic factors for survival in breast cancer patients were brought into the fine and gray multivariable regression model, including age at diagnosis, race, marital status, PR status, grade, tumor size, chemotherapy and radiotherapy (Table 3). The result showed that patients with large tumors had lower BCSS (HR = 2.02, 95%CI: 1.59–2.58, $P < 0.001$) than those with small tumors. Patients in RT group (HR = 0.46, 95%CI: 0.36–0.59, $P < 0.001$) had increased BCSS than those in non-RT group. The results before PSM also proved that patients with small tumors and RT were favorable prognostic factors. In addition, patients with highly differentiated grade I-II tumors or married tended to have significantly better BCSS than the corresponding subgroups ($P < 0.05$), regardless of before or after PSM.

3.6. Kaplan-Meier analysis in subgroups related to tumor size and radiotherapy

More detailed Kaplan-Meier analysis were performed to compare outcomes in four subgroups, including small tumor & RT group, large tumor & RT group, small tumor & non-RT group and large tumor & non-RT group. As shown in Fig. 4a, in the matched

Table 1
The clinical and pathological characteristics of patients before and after PSM.

Variable	before PSM				after PSM			
	Total	non-RT	RT	P value*	Total	non-RT	RT	P value*
	N (%)	n (%)	n (%)		N (%)	n (%)	n (%)	
Total	52049	17023(32.7)	35026(67.3)		28068	14034(50.0)	14034(50.0)	
Age at diagnosis				< 0.001				0.895
Mean (SD)	73.80	77.37	72.07		75.39	75.40	75.38	
Year of diagnosis				< 0.001				0.514
2010–2013	27499(52.8)	8704(51.1)	18795(53.7)		14668(52.3)	7372(52.5)	7296(52.0)	
2014–2016	24550(47.2)	8319(48.9)	16231(46.3)		13400(47.7)	6662(47.5)	6738(48.0)	
Race				0.215				0.736
White	45455(87.3)	14906(87.6)	30549(87.2)		24465(87.2)	12245(87.3)	12220(87.1)	
Black	3240(6.2)	1066(6.3)	2174(6.2)		1810(6.4)	900(6.4)	910(6.5)	
Others ^a	3354(6.4)	1051(6.2)	2303(6.6)		1793(6.4)	889(6.4)	904(6.4)	
Marital status				< 0.001				0.835
Yes	25941(49.8)	7112(41.8)	18829(53.8)		12951(46.1)	6484(46.2)	6467(46.1)	
No ^b /Unknown	26108(50.2)	9911(58.2)	16197(46.2)		15117(53.9)	7550(53.8)	7567(53.9)	
Laterality				0.529				0.107
Right	25936(49.8)	8447(49.6)	17489(49.9)		13986(49.8)	7087(50.5)	6899(49.2)	
Left	26113(50.2)	8576(50.4)	17537(50.1)		14082(50.2)	6947(49.5)	7135(50.8)	
Primary site				< 0.001				0.987
Upper quadrant	26493(50.9)	8269(48.6)	18224(52.0)		13951(49.7)	6959(49.6)	6992(49.8)	
Lower quadrant	7564(14.5)	2437(14.3)	5127(14.6)		3992(14.2)	2023(14.4)	1969(14.0)	
Others ^c	17992(34.6)	6317(37.1)	11675(33.3)		10125(36.1)	5052(36.0)	5073(36.1)	
Histology				< 0.001				0.633
Duct carcinoma	41807(80.3)	13667(80.3)	28140(80.4)		22560(80.4)	11279(80.4)	11281(80.4)	
Lobular carcinoma	5048(9.7)	1497(8.8)	3551(10.1)		2611(9.3)	1267(9.0)	1344(9.6)	
Others	5194(10.0)	1859(10.9)	3335(9.5)		2897(10.3)	1488(10.6)	1409(10.0)	
PR status				0.042				0.788
Negative	5479(10.5)	1725(10.1)	3754(10.7)		2898(10.3)	1439(10.3)	1459(10.4)	
Positive	46570(89.5)	15298(89.9)	31272(89.3)		25170(89.7)	12595(89.7)	12575(89.6)	
Grade				< 0.001				0.661
I	22026(42.3)	7634(44.8)	14392(41.1)		12255(43.7)	6123(43.6)	6132(43.7)	
II	25366(48.7)	8025(47.1)	17341(49.5)		13432(47.8)	6692(47.7)	6740(48.0)	
III-IV	4657(8.9)	1364(8.0)	3293(9.4)		2381(8.5)	1219(8.7)	1162(8.3)	
Tumor size(mm)				< 0.001				0.320
Mean (SD)	10.81(4.66)	10.67(4.73)	10.88(4.62)		10.67(4.66)	10.64(4.74)	10.69(4.58)	
Tumor size(mm)				0.089				0.134
1-14	38400(73.8)	12639(74.2)	25761(73.5)		20975(74.7)	10433(74.3)	10542(75.1)	
15-20	13649(26.2)	4384(25.8)	9265(26.5)		7093(25.3)	3601(25.7)	3492(24.9)	
Chemotherapy				< 0.001				0.496
No	49988(96.0)	16602(97.5)	33386(95.3)		27222(97.0)	13623(97.1)	13599(96.9)	
Yes	2061(4.0)	421(2.5)	1640(4.7)		846(3.0)	411(2.9)	435(3.1)	

Abbreviations: RT, radiotherapy; PSM, propensity score matching; PR, progesterone receptor.

*p-value was assessed using the Pearson's χ^2 test.

^a Including Non-Hispanic American Indian/Alaska Native, Non-Hispanic Asian or Pacific Islander, Non-Hispanic Unknown Race.

^b Including divorced, separated, single (never married), and widowed.

^c Including C50.0-Nipple, C50.1-Central portion of breast, C50.6-Axillary tail of breast, C50.8-Overlapping lesion of breast, C50.9-Breast, NOS.

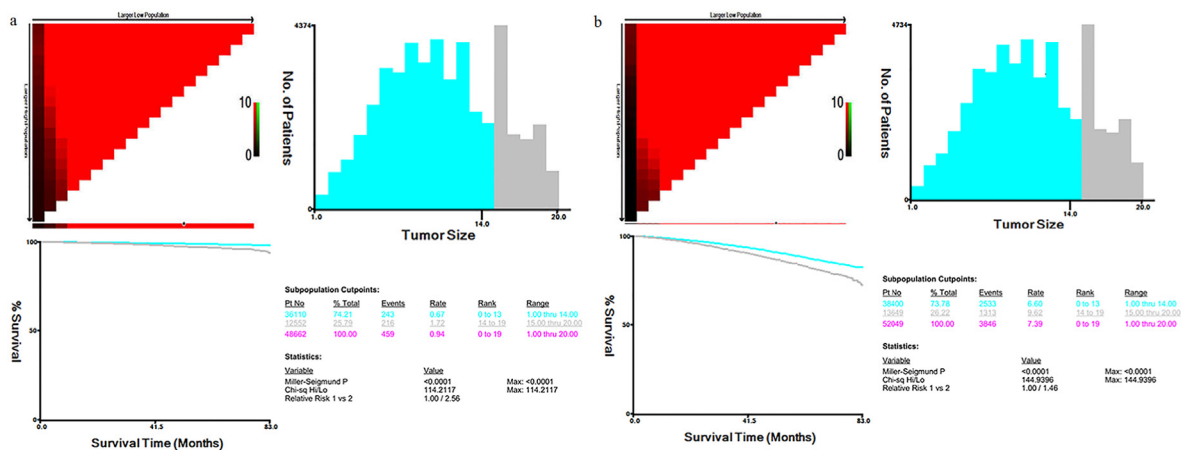


Fig. 2. X-tile analysis of survival data from the SEER registry. The optimal cutoff points of tumor size were obtained based on BCSS (a) and OS (b) of the whole population, before the application of PSM. Each graph contains the X-tile plot, a histogram, the K-M curve, and the data related to optimal cut-point.

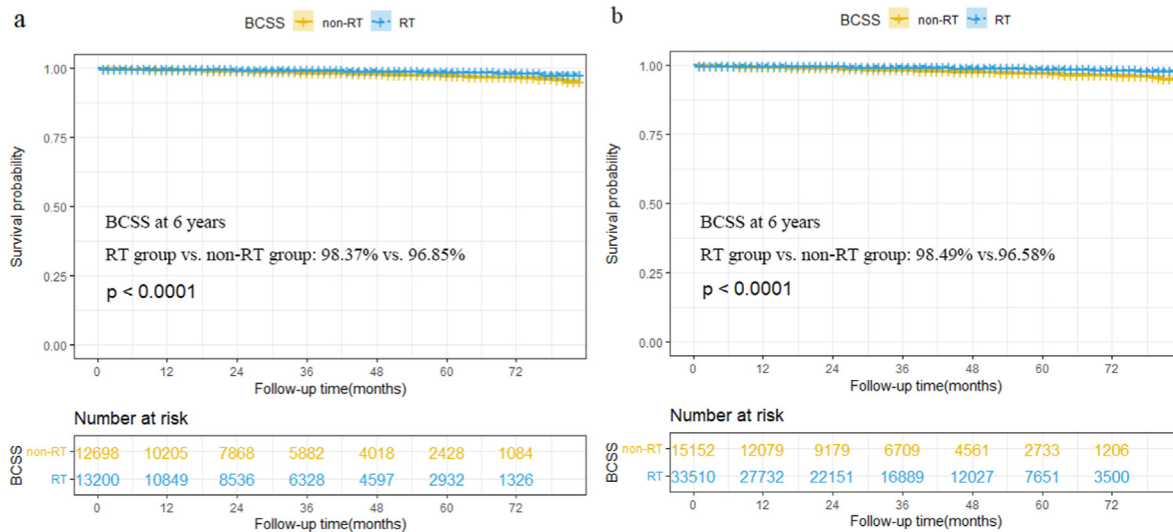


Fig. 3. BCSS associated with radiotherapy of the entire cohort displayed as Kaplan-Meier curve. a. BCSS curve of RT group vs. non-RT group after PSM. b. BCSS curve of RT group vs. non-RT group before PSM.

Table 2
Multivariate analyses of OS and BCSS for the EBC variable included in the study.

Variable	before PSM				after PSM			
	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	1.08(1.07–1.09)	<0.001	1.06(1.05–1.08)	<0.001	1.08(1.07–1.09)	<0.001	1.07(1.05–1.09)	<0.001
Race (white as ref.)								
Black	1.21(1.06–1.36)	<0.01	1.40(1.01–1.94)	0.04	1.18(1.01–1.38)	0.04	1.54(1.03–2.30)	0.035
Others	0.71(0.60–0.83)	<0.001	0.94(0.63–1.42)	0.78	0.58(0.47–0.73)	<0.001	0.92(0.55–1.56)	0.77
Marital status (married as ref.)								
Single/Unknown	1.29(1.21–1.38)	<0.001	1.41(1.16–1.72)	<0.001	1.27(1.16–1.38)	<0.001	1.41(1.10–1.81)	<0.01
Histology (duct carcinoma as ref.)								
Lobular carcinoma	0.81(0.72–0.91)	<0.001	0.89(0.65–1.23)	0.48	0.78(0.67–0.90)	<0.001	0.89(0.60–1.34)	0.59
Others	0.88(0.79–0.98)	0.02	0.72(0.51–1.01)	0.06	0.85(0.74–0.97)	0.01	0.77(0.51–1.17)	0.22
PR status (negative as ref.)								
Positive	0.89(0.81–0.98)	0.01	0.74(0.57–0.95)	0.02	0.89(0.79–0.99)	0.048	0.74(0.54–1.02)	0.07
Grade (G1 as ref.)								
G2	1.07(1.00–1.15)	0.04	1.54(1.24–1.92)	<0.001	1.08(0.99–1.18)	0.07	1.31(0.99–1.71)	0.052
G3–G4	1.23(1.10–1.37)	<0.001	2.75(2.07–3.65)	<0.001	1.22(1.06–1.40)	0.005	2.16(1.50–3.10)	<0.001
Tumor size (1–14 mm as ref.)								
15–20 mm	1.40(1.31–1.50)	<0.001	2.23(1.84–2.69)	<0.001	1.37(1.26–1.50)	<0.001	2.16(1.70–2.74)	<0.001
Chemotherapy (no/unknown as ref.)								
Yes	0.99(0.80–1.21)	0.90	1.68(1.14–2.47)	<0.01			1.70(0.98–2.97)	0.06
Radiotherapy (no as ref.)								
Yes	0.55(0.51–0.59)	<0.001	0.47(0.38–0.57)	<0.001	0.56(0.52–0.61)	<0.001	0.43(0.33–0.55)	<0.001

Abbreviations: OS, overall survival; BCSS, breast cancer specific survival; EBC, early breast cancer; PSM, propensity score matching; HR, hazard ratio; PR, progesterone receptor.

cohort, the absolute benefit of BCSS in 6 years attributed to RT was only 0.90% (RT vs. non-RT: 98.77% vs. 97.87%) for patients with small tumors but up to 3.33% (RT vs. non-RT: 97.10% vs. 93.77%) for those with large tumors. There was no significant improvement of BCSS in large tumor & RT (HR = 1.10, 95%CI: 0.76–1.59, P = 0.61) subgroup when compared with small tumor & non-RT subgroup, which was similar to the result before PSM (Fig. 4b). The improvement of OS in 6 years resulted from RT were 6.35% (RT vs. non-RT: 85.75% vs. 79.40%) in patients with small tumors and 10.06% (RT vs. non-RT: 80.26% vs. 70.20%) in patients with large tumors (Supplemental Fig. 3a). The result before PSM was shown in Supplemental Fig. 3b. These that the importance of RT in the treatment of breast cancer cannot be omitted for patients with large tumors. These findings suggested that RT should not be

omitted as it could significantly prolong survival in old patients with low-risk breast cancer after BCS.

4. Discussion

Survival of cancer patients, especially cancer specific survival (CSS), as a reliable, objective and easily accessible indicator, has been widely used in the evaluation and analysis of long-term prognosis of breast cancer patients. In our study, based on analysis of a large cohort of 52049 patients in SEER database from 2010 to 2016, the absolute value of improvement in BCSS was only 1.52% after PSM. Such result was consistent with the retrospective study reported previously [10]. And our finding demonstrated that, to some older patients with early-stage, low-risk breast cancer, the

Table 3
Fine and Gray Multivariable Regression Model Analysis in patients aged 65 or older with T1N0M0 stage and ER+, HER2-breast cancer after BCS.

Variable	before PSM		after PSM	
	HR (95%CI)	P value	HR 95%CI	P value
Age at diagnosis	1.05(1.03–1.06)	<0.001	1.06(1.04–1.08)	<0.001
Race (white as ref.)				
Black	1.34(0.96–1.86)	0.082	1.52(1.02–2.27)	0.042
Others	0.98(0.66–1.47)	0.920	1.01(0.60–1.70)	0.980
Marital status (married as ref.)				
No/Unknown	1.35(1.10–1.65)	0.003	1.34(1.04–1.73)	0.025
PR status (negative as ref.)				
Positive	0.75(0.58–0.97)	0.025	0.76(0.55–1.04)	0.088
Grade (G1 as ref.)				
II	1.55(1.24–1.93)	<0.001	1.30(0.99–1.70)	0.058
III-IV	2.72(2.04–3.62)	<0.001	2.17(1.49–3.16)	<0.001
Tumor size (1–14 mm as ref.)				
15–20 mm	2.09(1.73–2.53)	<0.001	2.02(1.59–2.58)	<0.001
Chemotherapy (no/unknown as ref.)				
Yes	1.73(1.16–2.57)	0.007	1.80(1.01–3.21)	0.048
Radiotherapy (no as ref.)				
Yes	0.50(0.41–0.61)	<0.001	0.46(0.36–0.59)	<0.001

Abbreviations: BCS, breast-conserving surgery; PSM, propensity score matching; HR, hazard ratio; CI, confidence interval; PR, progesterone receptor.

efficacy of radiotherapy may be omitted. Tumor size is closely related to the effect of radiotherapy after BCS for patients with breast cancer [18]. Subjects with T2-stage tumors (21–50 mm) after BCS tended to have a bigger absolute benefit in 10-year risk of a locoregional or distant recurrence than those with T1-stage tumors (1–20 mm) [1]. The result suggested that participants with smaller tumors were likely to have less advantage of long-term survival through postoperative RT and could be exempted for some patient after BCS. For example, postoperative RT was proven not to be necessary in elderly patients (65 years and older) with T1-stage tumors after BCS, due to no significant benefit in OS or disease-free survival from adjuvant RT by previous studies (CALGB 9343 and PRIME II).

However, little evidence exists for the appropriate cut-points of tumor size at which postoperative RT after BCS played a minor role in elderly patients (65 years or older) with T1-stage tumors after BCS because many trials, historically, excluded patients older than age 65 years. And, there is no global way to visualize the best cut-points for creating such divisions. Studies typically use quartiles or medians to group tumors, which may not accurately reflect the

biology of tumor size. X-tile analysis tool, a bio-informatics tool for biomarker assessment developed by the Yale team, is characterized by the determination in an optimal cut-point occurred by comparing differences in outcome events between any possible subpopulations of biomarkers [15]. Through X-tile analysis, the result in our study demonstrated that tumor size of 14 mm was the optimal cutoff for predicting BCSS and OS for patients aged 65 years or older after BCS with ER-positive, HER2-negative and clinical negative lymph nodes FBC. Small tumors (≤ 14 mm) were associated with better OS and BCSS for patients with radiotherapy as well as better BCSS for patients with no radiotherapy in comparison with large tumors (>14 mm) through X-tile analysis. To our knowledge, this was the first and largest population-based study to assess the impact of tumor size with a cutoff as 14 mm on BCSS and OS using propensity score matching analysis, X-tile analysis, survival variables, demographic and pathological factors.

Multivariate Cox proportional hazards model were performed to analyze OS and BCSS under the premise of considering confounders. The results showed that patients with small tumors or receiving radiotherapy had better OS and BCSS. To eliminate the estimation bias and further investigate the efficacy of tumor size on BCSD or other causes of death for FBC, Fine and Gray multivariable regression model analysis was performed. In our study, the patients with small tumors had better BCSS than those with large tumors. To minimize the selection bias resulting from baseline variables inherent in retrospective studies, PSM analysis was performed since PSM could eliminate a greater proportion of baseline differences between any two treatment groups than stratification or covariates adjustment. After PSM analysis, the tumor size 14 mm was still shown to be the optimal cutoff for predicting BCSS. Patients with small tumors still had better BCSS than those with large tumors. These results suggested that small ER+, HER2-, and T1N0M0 tumors should be an independent indicator for patients aged ≥ 65 years.

To further analyze and assess the efficacy of radiotherapy in patients with small or large tumors, a subgroup analysis was performed. In our study, after BCS, the application of radiotherapy could reduce the 6-year cumulative incidence rate of BCSD by 2.47% in patients with large tumors but only 0.72% in patients with small tumors (Supplemental Fig. 4). And the benefit of radiotherapy in patients with large tumors showed a steady increase with the extension of follow-up time. Meanwhile, the introduction of radiotherapy could improve the 6-year OS by 6.35% in patients with small tumors and 10.06% in patients with large tumors. The

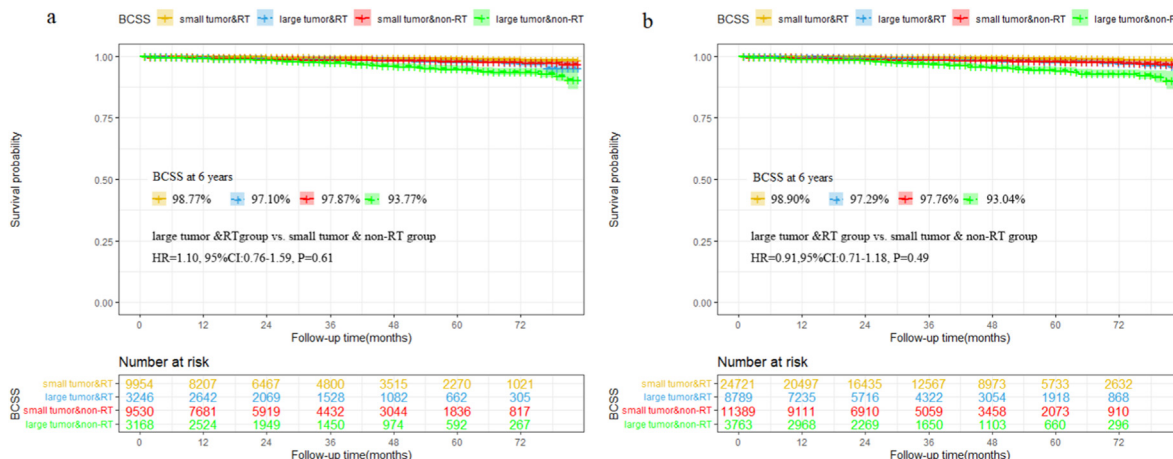


Fig. 4. BCSS in four subgroups related to tumor size and radiotherapy, including small tumor & RT subgroup, large tumor & RT subgroup, small tumor & non-RT subgroup, and large tumor & non-RT subgroup, displayed as Kaplan-Meier curve. (a) BCSS curve of four subgroups after PSM. (b) BCSS curve of four subgroups before PSM.

absolute benefit of BCSS attributed to radiotherapy was only 0.90% in patients with small tumors and as high as 3.33% in those with large tumors. There was no significant difference in BCSS between patients with large tumors who received radiotherapy and patients with small tumors who did not receive radiotherapy. Such results showed, for patients aged ≥ 65 years with ER+, HER2-, and T1N0M0 tumors after BCS, small tumors were associated with favorable prognosis, which suggested that radiotherapy could be abandoned with caution for that omitting radiotherapy did not decrease the BCSS rate of patients with a tumor size ≤ 14 mm significantly.

The result of our study indicated that, patients with smaller tumors were likely to have less advantage of long-term survival through postoperative RT. The most basic reason for this was that radiotherapy following BCS could control the microscopic tumor foci and reduce the risk of recurrence in the ipsilateral breast [15,19]. Another reason we recommend that patients with small breast tumors avoid radiation was the adverse effects caused by radiotherapy [20], such as the radiation injury of skin [21], radiation-induced heart disease [22] and radiation pneumonia and the risk of contralateral breast cancer [23]. What's more, the contribution of radiation therapy to BCSS remained hypothetical. In prognostic nomograms like the often used "PREDICT V2.0", radiation therapy had not been included as a variable. Therefore, to some extent, the slightest survival benefit of radiotherapy in patients after BCS with small tumors could be counterbalanced by the adverse effects after radiotherapy. Simultaneously, in our study, the results support the hypothesis that radiation treatment plays a role in survival in breast cancer patients aged 65 or older with T1N0M0 stage, ER+ and HER2-large tumors.

In addition, married patients with highly-differentiation level, and PR positive tumors tended to have better prognostic indicators with BCSS than the corresponding subgroups. These results, which consistent with the previous reports, indicated that clinicopathological features, such as tumor differentiation level, TNM stage, PR status, marital status and income level are objective and reliable prognostic indicators in patients with breast carcinoma [24–26]. Moreover, patients receiving chemotherapy had worse BCSS. The underlying reason maybe that the local therapeutic effect of adjuvant chemotherapy on EBC patients cannot offset the systemic damage and long-term side effects [27].

4.1. Limitations

There are still some possible limitations in this study. Firstly, this retrospective cohort study was conducted using data from the national cancer institute's SEER program database, and the integrity and authenticity of the records were uncertain, which directly affected the reliability of the results and lead to uncontrolled confounding factors and selection bias. Secondly, the administration of PSM could only balance and control observable confounders rather than missing data. When the important confounders are missing, the results obtained by PSM analysis may be deviated from the real situation. Thirdly, we were unable to avoid the possibility that the observed risk reductions might exclude the influence of potential confounders, such as family history, insurance coverage, patient anxiety, detailed regimens of endocrine therapy, frailty or comorbid conditions known to be related to receipt of specific treatments, and so on. These data greatly impacted the clinical decisions and even breast cancer prognosis [28–30]. Nevertheless, these factors were not available in the SEER database. Prospective cohort studies, which might remedy this deficiency, need to be further performed, but this requires considerable time. In addition, there was a lack of information about local recurrence, adverse effects of normal tissue after radiotherapy, which were essential to guide the optimization of treatment options. Finally, but most

importantly, the SEER database registered HER2 subtype of breast cancer patients from 2010. Even we have used the most complete data available, the media follow-up in this study was merely 34 months. Longer follow-up times may be necessary for an accurate assessment of prognostic factors for patients with T1N0M0 FBC.

5. Conclusions

Our study demonstrated that small tumors (≤ 14 mm in diameter) and adjuvant radiotherapy were associated with improved survival, and both the BCSS and OS were slightly affected by radiotherapy in breast cancer patients aged 65 or older with T1N0M0 stage, ER+ and HER2-small tumors. As a consequence, 14 mm in diameter was the cutoff tumor size of omitting RT for BCS patients aged 65 or older with low-risk invasive breast carcinoma. Randomly controlled clinical trials or multi-center, prospective case-control study is needed to further verify the role of the cutoff tumor size of 14 mm in diameter for patients aged 65 or older with low-risk breast carcinoma after BCS.

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Ethics

This study was approved by the Ethics Committee of the First Affiliated Hospital of Xi'an Jiaotong University. The SEER data erases the identity information of patients, so there is no need for informed consent from the patients.

Declaration of competing interest

No conflict of interest.

Acknowledgements

Not applicable.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.breast.2021.11.015>.

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