

## Survival advantage of radiotherapy in triple-negative inflammatory breast cancer: A national cohort study

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### ABSTRACT

#### ► Original article

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**Background:** Inflammatory breast cancer (IBC) is an aggressive subtype of breast carcinoma for which radiotherapy (RT) is a recommended treatment. This retrospective analysis aimed to clarify the impact of RT on survival outcomes among patients with IBC, stratified by molecular subtype. **Materials and Methods:** Data concerning IBC patients diagnosed from 2010 through 2015 was based on the SEER (Surveillance, Epidemiology, and End Results) database. To evaluate survival differences among women with diverse molecular subtypes, comparisons were drawn between those treated with RT and those untreated, employing Cox proportional hazards modeling, Kaplan-Meier (KM) curves, and chi-square analysis. **Results:** The cohort included 532 female patients, of whom 263 (49.4%) received radiotherapy. Nodal involvement, metastatic status, and chemotherapy use were each significantly correlated with the likelihood of receiving RT (all  $P < 0.05$ ). Longer survival was exhibited in overall molecular subtypes who received RT ( $P < 0.001$ ). RT significantly improved outcomes in IBC cases of the hormone receptor (HR)-/human epidermal growth factor (HER2)- phenotype (OR, odds ratio = 0.525 [0.334–0.823],  $P = 0.005$ ), whereas those with HR+/HER2-, HR+/HER2+ or HR-/HER2+ subtypes had a comparable prognosis between the RT cohort and non-RT cohort. HR-/HER2- patients with pathologic stage N0-2M0 had longer survival with RT (OR=0.354 [0.178–0.704],  $P=0.003$ ), whereas those with N3M0 stage ( $P=0.880$ ) or M1 stage ( $P=0.443$ ) derived no benefit. **Conclusion:** Marked improvements in survival following RT were noted for HR-/HER2- IBC with pathologic N0–2M0 staging.

### INTRODUCTION

Associated with a poor prognosis, inflammatory breast cancer is an aggressive subtype of breast cancer that accounts for 1–5% of all cases<sup>(1)</sup>, with a 5-year overall survival (OS) of 34–47% and breast cancer-related mortality of 7–10%<sup>(2, 3)</sup>. IBC is linked to an elevated risk of death relative to non-IBC cases, driven by rapid progression, increased lymph node involvement, limited targeted treatment options, and a high rate of distant metastasis<sup>(4–7)</sup>. IBC is clinically characterized by diffuse erythema, edema, and peau d'orange of the breast in the absence of a palpable underlying mass<sup>(8)</sup>.

The treatment of IBC disease typically involves a multidisciplinary approach, including systemic chemotherapy, hormone therapy, Photodynamic therapy, mastectomy, and RT<sup>(9, 10)</sup>. The management and outcomes of breast cancer have markedly improved over the past two decades<sup>(11)</sup>. However, treatment of IBC is controversial, and survival with multimodal therapy is not high<sup>(7)</sup>. Mastectomy with dissection of axillary lymph node preceded by RT covering regional nodes and the chest wall is the most common therapeutic approach for IBC patients. RT combined with other therapy is recommended,

but the value of RT in the control of disease progression and survival is controversial. Due to the pathologic characteristics of IBC, it is usually refractory to conventional therapies, such as neoadjuvant systemic therapy, and has a lower median survival time and recurrence prevalence of  $\geq 50\%$  compared with those of other types of breast cancer<sup>(12, 13)</sup>. RT can improve locoregional control and OS in IBC<sup>(14)</sup>. However, different institutions have different standards on the dose and scope of RT, and multimodality therapy does not significantly improve the comparatively poor survival and prognosis seen in IBC versus other breast cancer subtypes<sup>(7)</sup>. IBC is a heterogeneous tumor, so different molecular subtypes need different treatment methods<sup>(15)</sup>. Research on the value of RT for the different molecular types of IBC is needed for precise RT options for patients.

We retrospectively analyzed data from the SEER database (2010–2015) to evaluate how survival varies across molecular subtypes of inflammatory breast cancer following radiotherapy. We aimed to guide the “personalized” and precise design of clinical -treatment plans through analyses of those results.

This study uniquely analyzes survival outcomes of inflammatory breast cancer patients across different

molecular subtypes following radiotherapy, using a large population-based database. By highlighting subtype-specific responses, it provides important evidence to support more personalized and precise radiotherapy strategies for IBC patients, addressing a current gap in clinical practice.

## MATERIALS AND METHODS

### Patient selection

The data of 532 female patients from 2010 to 2015 were identified from the SEER database of the National Cancer Institute (<https://seer.cancer.gov/>). Our criteria for study inclusion are women with primary IBC: who had received beam radiation<sup>(16)</sup> for whom data on demographic and clinical characteristics were available. Patients with previous cancer or those diagnosed through autopsy or death certificate were excluded. Patients with previous cancer or those diagnosed through autopsy or death certificate were excluded. Given the rarity of male inflammatory breast cancer cases<sup>(17)</sup>, our study focused exclusively on female patients to ensure sufficient statistical power and data consistency.

The SEER database uses the seventh edition of the staging manual set by the American Joint Committee on Cancer for the classification of IBC disease. According to those guidelines, IBC was defined as T4d disease<sup>(18)</sup>. We collected the demographic and clinical characteristics of patients (age, ethnicity, tumor grade, nodal and metastasis status, molecular subtype, chemotherapy status). HR-positive (HR+) disease express estrogen receptor (ER) and/or progesterone receptor (PR), while HR-negative (HR-) disease lacks both ER and PR expression. The molecular type was classified as HR+/HER2-, HR+/HER2+, HR-/HER2+, and HR-/HER2- according to biomarker expression. Triple-negative breast cancer (TNBC) corresponds to tumors negative for hormone receptors (HR) and HER2<sup>(19)</sup>.

### Radiotherapy information extraction

Radiotherapy information was extracted from SEER treatment records; however, specific radiotherapy modalities including stereotactic body radiotherapy (SBRT) or intensity-modulated radiotherapy (IMRT) were not distinguishable due to unavailable or nonspecific coding. Therefore, patients were categorized simply as having received radiotherapy or not.

### Definition of endpoint

BCSS (Breast cancer-specific survival) was measured from diagnosis until death caused specifically by breast cancer. Deaths due to reasons unrelated to breast cancer and survivors at the end of follow-up were censored at the last contact date. Survival duration, recorded in months, was obtained from the SEER database.

### Statistical analyses

Chi-square test was performed to assess patients' demographic and clinical variables. The association of each variable with RT was examined using univariate analysis. To investigate the associations between patient demographic factors, tumor characteristics, and treatment variables with the administration of radiotherapy, patients were stratified into two groups based on whether they received radiotherapy or not. Comparative analyses between these groups were then performed to identify factors correlated with radiotherapy utilization. Kaplan-Meier curves illustrated BCSS in RT and non-RT groups, with differences assessed by the log-rank test. Multivariate Cox proportional hazards modeling was performed to evaluate how patient characteristics influenced BCSS. Statistical analyses were conducted using SPSS version 26.0 (IBM Corp., Armonk, NY, USA). A two-sided P value less than 0.05 was considered statistically significant.

## RESULTS

### Clinical characteristics of patients

Retrospective data was examined for 532 women who had a confirmed diagnosis of IBC (table 1). These patients had a median age of 56. From 0 to 83 months, the total study cohort had a median BCSS of 31.9 months. The median survival period among the persons evaluated was 36.4 months, and 263 patients (49.4%) underwent radiation treatment. In contrast, the median survival time for the 269 patients (50.6%) who did not receive radiation therapy was only 27.6 months. Factors such as year of diagnosis, patient age, ethnicity, and tumor grade showed no significant correlation with the use of RT. Among all participants, the largest group was composed of those diagnosed with nodal stage 1 disease (47.0%). Interestingly, nodal stage 0 was significantly more common among patients who did not receive RT ( $P = 0.047$ ). Moreover, patients without distant metastasis demonstrated a higher likelihood of receiving RT, while metastatic patients showed significantly lower RT utilization rates ( $P < 0.001$ ). The proportion of patients receiving RT did not significantly differ across molecular subtypes. Nevertheless, chemotherapy administration correlated significantly with increased radiotherapy utilization ( $P < 0.001$ ).

### Survival and prognostic factors analysis

Univariate analysis demonstrated that neither the year of diagnosis nor patient age showed a statistically significant association with BCSS. In contrast, several clinical and pathological factors were found to have a significant impact on BCSS. These included ethnicity, tumor grade, nodal stage, presence of distant metastasis, molecular subtype, and receipt of chemotherapy, all of which exhibited

statistically significant correlations (all  $P < 0.05$ ). Notably, RT emerged as a strong predictive factor positively associated with improved BCSS, with a robust statistical significance of  $P$ -value less than 0.001 (table 2). These findings suggest that while

demographic factors such as age and diagnosis year may not independently influence survival outcomes, tumor biology and treatment modalities play crucial roles in determining patient prognosis.

Predictors identified as correlated with BCSS in

**Table 1.** Baseline clinical features of IBC patients according to radiotherapy receipt in the SEER database.

Characteristic	N (%)	Radiotherapy (%)	Non-radiotherapy (%)	P-value
Total	532 (100)	263 (49.4)	269 (50.6)	
Median age (years)	56 (22-95)	53.9 (24-91)	58.2 (22-95)	
BCSS (months)	31.9 (0-83)	36.4 (0-83)	27.6 (0-83)	
Year of diagnosis				0.110
2010	96 (18.0)	51 (19.4)	45 (16.7)	
2011	85 (16.0)	49 (18.6)	36 (13.4)	
2012	103 (19.4)	57 (21.7)	46 (17.1)	
2013	87 (16.4)	36 (13.7)	51 (19.0)	
2014	72 (13.5)	30 (11.4)	42 (15.6)	
2015	89 (16.7)	40 (15.2)	49 (18.2)	
Age (years)				0.066
<50	178 (32.4)	98 (37.3)	80 (29.7)	
≥50	372 (67.6)	165 (62.7)	189 (70.3)	
Ethnicity				0.416
White	419 (78.8)	211 (80.2)	208 (77.3)	
Black	68 (12.8)	34 (12.9)	34 (12.6)	
Others	45 (8.5)	18 (6.8)	27 (10.0)	
Tumor grade				0.528
I	10 (1.9)	5 (1.9)	5 (1.9)	
II	157 (29.5)	85 (32.3)	72 (26.8)	
III	352 (66.2)	166 (63.1)	186 (69.1)	
IV	13 (2.4)	7 (2.7)	6 (2.2)	
Nodal stage				0.047
0	73 (13.7)	31 (11.8)	42 (15.6)	
1	250 (47.0)	115 (43.7)	135 (50.2)	
2	95 (17.9)	58 (22.1)	37 (13.8)	
3	114 (21.4)	59 (22.4)	55 (20.4)	
Metastasis stage				<0.001
No	355 (66.7)	195 (74.1)	160 (59.5)	
Yes	177 (33.3)	68 (25.9)	109 (40.5)	
Molecular subtype				0.782
HR+/HER2-	195 (36.7)	93 (35.4)	102 (37.9)	
HR+/HER2+	109 (20.5)	56 (21.3)	53 (19.7)	
HR-/HER2+	96 (18.0)	51 (19.4)	45 (16.7)	
HR-/HER2-	132 (24.8)	63 (24.0)	69 (25.7)	
Chemotherapy				<0.001
No	65 (12.2)	14 (5.3)	51 (19.0)	
Yes	467 (87.8)	249 (94.7)	218 (81.0)	

Grade: I, Well-differentiated; II, moderately differentiated; III, poorly differentiated; IV, undifferentiated, anaplastic.

univariate analyses were subsequently evaluated using multivariate analyses. According to multivariate results, the prognosis for black patients was poorer compared to those from other ethnic groups (OR=1.632 [1.160-2.295],  $P=0.005$ ). The tumor grade did not appear to significantly influence BCSS outcomes. Compared to nodal stage 0, each increasing nodal stage displayed a trend towards reduced BCSS, though this was not statistically conclusive ( $P=0.052$ ). Additionally, metastasis presence was associated with substantially decreased BCSS (OR=3.607 [2.745-4.738],  $P < 0.001$ ). Among different molecular subtypes, the HR-/HER2- group exhibited the poorest BCSS (OR = 2.601 [1.882-3.595],  $P < 0.001$ ). Conversely, chemotherapy administration significantly improved patient

prognosis (OR=0.392 [0.279-0.551],  $P<0.001$ ).

#### Survival among patients with different molecular subtypes of IBC

In all, 238 individuals (44.7%) succumbed to BC (Breast Cancer) or complications stemming from BC. Statistically, patients in the RT group had a longer BCSS. Among patients with the HR+/HER2-, HR+/HER2+, and HR-/HER2+ subtypes, RT considerably extended survival time in the univariate analysis (all  $P<0.05$ ). Statistical significance was not achieved ( $P = 0.681$ ) in the HR-/HER2+ subtype when comparing survival rates between the RT-treated and untreated groups. Figure 1 shows KM survival plots, which graphically depict these interactions.

To further elucidate the impact of RT on BCSS

**Table 2.** Overall BCSS between patients who received radiotherapy and those who did not.

Characteristic	Univariate			Multivariate		
	OR	95% CI	P	OR	95% CI	P <sup>a</sup>
Year of diagnosis			0.174			
2010	1					
2011	1.338	0.892-2.006	0.161			
2012	1.198	0.796-1.803	0.390			
2013	1.127	0.723-1.758	0.490			
2014	1.831	1.154-2.904	0.012			
2015	1.171	0.676-2.028	0.722			
Age (years)			0.149			
<50	1					
≥50	1.227	0.929-1.619	0.149			
Ethnicity			<0.001			0.016
White	1			1		
Black	2.132	1.537-2.958	<0.001	1.632	1.160-2.295	0.005
Others	0.966	0.607-1.537	0.884	0.955	0.595-1.531	0.848
Tumor grade			0.031			0.136
I	1			1		
II	2.108	0.515-8.636	0.300	1.544	0.375-6.366	0.548
III	2.990	0.741-12.068	0.124	2.031	0.499-8.259	0.322
IV	1.296	0.216-7.770	0.777	0.866	0.143-5.232	0.875
Nodal stage			0.009			0.052
0	1			1		
1	1.602	1.022-2.512	0.040	1.752	1.111-2.762	0.016
2	1.651	0.993-2.746	0.053	1.689	1.010-2.825	0.046
3	2.245	1.390-3.626	0.001	1.980	1.216-3.225	0.006
Metastasis status			<0.001			<0.001
No	1			1		
Yes	3.245	2.495-4.221	<0.001	3.607	2.745-4.738	<0.001
Molecular subtype			<0.001			<0.001
HR+/HER2-	1			1		
HR+/HER2+	0.493	0.318-0.766	0.002	0.572	0.364-0.899	0.015
HR-/HER2+	1.060	0.730-1.540	0.759	1.216	0.823-1.796	0.327
HR-/HER2-	1.945	1.439-2.629	<0.001	2.601	1.882-3.595	<0.001
Chemotherapy			<0.001			<0.001
No	1			1		
Yes	0.451	0.320-0.636	<0.001	0.435	0.303-0.625	<0.001
Radiotherapy			<0.001			0.012
No	1			1		
Yes	0.581	0.449-0.751	<0.001	0.710	0.543-0.929	0.012

OR, odds ratio; CI, confidence interval; Grade: I, well-differentiated; II, moderately differentiated; III, poorly differentiated; IV, undifferentiated, anaplastic; Pa was obtained through a Cox proportional hazard regression model incorporating ethnicity, tumor grade, nodal stage, metastasis status, chemotherapy status, molecular subtype, and RT.

within different molecular classifications, a multivariate analysis incorporating pathologic nodal staging, presence or absence of distant metastasis, and chemotherapy administration status was performed. Patients with the HR-/HER2- molecular subtype had a significantly improved BCSS after RT treatment, according to the multivariate analysis (OR = 0.525 [95% CI: 0.334-0.823], P=0.005). Nonetheless, for the HR+/HER2-, HR+/HER2+, and HR-/HER2+ subtypes, there was no statistically significant change in BCSS between the RT-treated

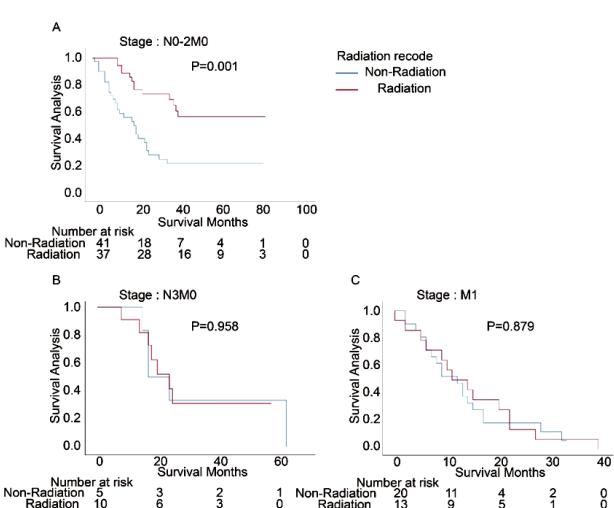
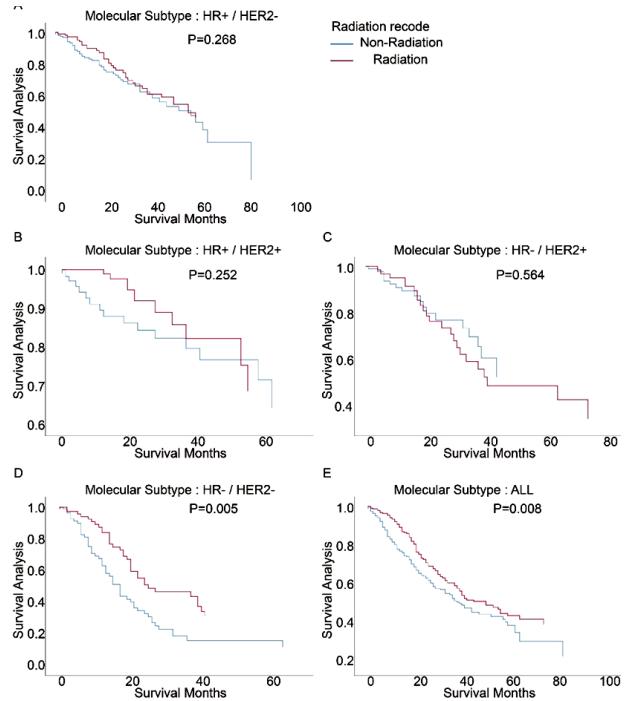
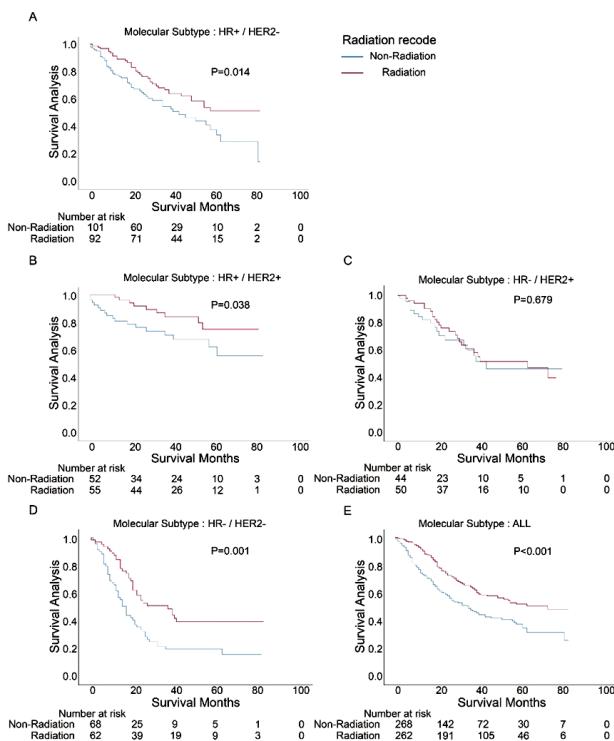
and untreated groups (all P>0.05) (table 3, figure 2).

Furthermore, the relationship between RT and pathologic nodal and metastasis stages was analyzed among patients diagnosed with HR-/HER2- category of IBC (table 4, figures 3, 4). Patients with pathologic stage N0-2M0 demonstrated significantly better BCSS with RT (OR=0.354 [0.178-0.704], P=0.003). In contrast, patients with stage N3M0 (P=0.880) or M1 (P=0.443) disease showed no significant difference in BCSS.

**Table 3.** Value of radiotherapy in IBC patients with different subtypes.

Characteristic	Univariate			Multivariate		
	OR	95% CI	P	OR	95% CI	P <sup>a</sup>
Overall	0.581	0.449-0.751	<0.001	0.698	0.535-0.912	0.008
HR+/HER2-	0.587	0.380-0.905	0.016	0.772	0.489-1.220	0.268
HR+/HER2+	0.436	0.194-0.978	0.044	0.612	0.265-1.416	0.252
HR-/HER2+	0.878	0.473-1.630	0.681	1.230	0.609-2.484	0.564
HR-/HER2-	0.482	0.312-0.745	0.001	0.525	0.334-0.823	0.005

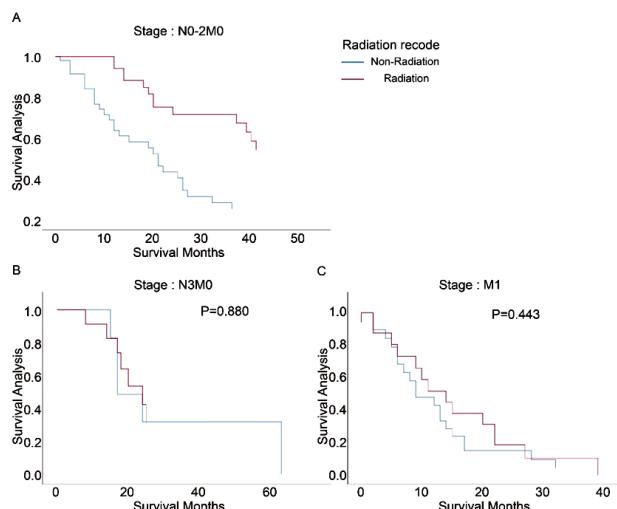
OR, odds ratio; CI, confidence interval; Pa was adjusted by a multivariate Cox proportional hazard regression model including nodal stage, metastasis status, chemotherapy status, molecular subtype, and radiotherapy.



**Table 4.** Survival analysis in different nodal and metastasis stages in IBC patients with HR-/HER2- subtype.

Characteristic	Univariate			Multivariate		
	OR	95% CI	P	OR	95% CI	P <sup>a</sup>
N0-2M0	0.310	0.160-0.601	0.001	0.354	0.178-0.704	0.003
N3M0	0.967	0.283-3.310	0.958	0.907	0.256-3.220	0.880
M1	0.946	0.466-1.924	0.879	0.731	0.328-1.629	0.443

OR, odds ratio; CI, confidence interval; Pa was adjusted by a multivariate Cox proportional hazard regression model including chemotherapy status and radiotherapy.



**Figure 4.** The multivariate analyzed survival curves in different pathological nodal and metastasis stages in HR-/HER2- IBC patients between the RT and the non-RT cohorts. **A-C:** the overall BCSS of IBC patients with N0-2M0, N3-4M0, and M1 stage disease.

## DISCUSSION

This population-based investigation provides critical insights into how RT influences BCSS in patients diagnosed with triple-negative inflammatory breast cancer (TN-IBC), stratified by molecular subtype and pathologic stage. The analysis demonstrated that RT led to increased BCSS, notably in patients with the HR-/HER2- subtype at pathologic N0-2M0 stage. In contrast, cohort members with HR-/HER2- subtype at N3M0 or M1

stage, and those with other molecular subtypes, showed limited or no benefit from RT.

These findings align with several previous studies reporting that RT improves prognosis in IBC patients (15, 20). However, some researchers have suggested that rapid tumor repopulation in IBC may reduce the effectiveness of standard RT regimens (21). Several investigations have investigated the contribution of RT in patients with IBC, but the results have varied (22, 23), highlighting the importance of developing individualized radiotherapy strategies based on biological subtypes and disease stage.

It is noteworthy that TNBC, representing close to one-third of IBC cases (24), was consistently observed to demonstrate worse prognosis and lower response to RT (25). Treatment interruptions or delays in radiotherapy have been linked to diminished OS among individuals diagnosed with TNBC (26, 27), which may partially explain why survival benefits were primarily observed in early-stage TNBC patients. Fayanju *et al.* also demonstrated prolonged OS with RT in IBC patients with N1-2 stage and no metastases (28), consistent with our observations.

In contrast, we observed limited RT benefit in HER2-positive IBC. This may be due to radioresistance mediated by HER2-driven pathways such as Ras/Raf signaling and NF- $\kappa$ B activation, which inhibit radiation-induced apoptosis (29, 30). Given the effectiveness of targeted therapies like trastuzumab, systemic treatment remains the cornerstone of HER2+ IBC management (31, 32), and RT may not be necessary as first-line local therapy in all cases.

For HR+/HER2- IBC patients, our results showed no significant difference in BCSS with or without RT. This may reflect the strong survival advantage conferred by endocrine therapy in this subtype (33, 34). These patients may benefit more from systemic hormone therapy than from aggressive locoregional interventions.

However, this study also has important limitations. As a retrospective, observational analysis, it is subject to inherent selection bias. Another important aspect is, the SEER database is deficient in detailed information on RT techniques (e.g., SBRT vs. IMRT), total dose, fractionation schedules, radiation fields, chemotherapy regimens, and recurrence data. As such, we could not evaluate how different RT protocols may influence outcomes. We assumed standard systemic therapy was used across patients, though actual regimens likely varied.

To our knowledge, our findings first highlight the subtype-specific survival benefits of RT in IBC, and suggest that RT should be applied selectively based on molecular and clinical characteristics. Molecular and clinical markers should be embedded in protocol design, care strategies, and efficacy evaluation to verify these conclusions in a prospective manner.

## CONCLUSION

We analyzed the role of RT in IBC patients with different molecular subtypes. RT could improve the BCSS of IBC patients significantly, especially those with TNBC and pathological N0-2M0 stage. However, there is no clear evidence that RT was beneficial to the survival of patients with other molecular subtypes of IBC, pathologic N3M0, or M1 stage TNBC. Further prospective clinical trials are needed to verify our results.

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**Conflict of Interest:** The authors declare there was no conflict of interest with any companies, whose products or services may be related to the subject matter of the article.

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**Ethical consideration:** This study was conducted using publicly available, de-identified data from the Surveillance, Epidemiology, and End Results (SEER) database. As per SEER guidelines, the use of this data is exempt from institutional review board (IRB) approval and ethical committee registration. The study complies with the Declaration of Helsinki.

**Authors' contributions:** Z.Z.: Conceptualization, methodology, software, investigation, formal analysis, writing - original draft; Y-Y.L.: Data curation, software, writing - original draft, visualization; Z.H.: (Corresponding Author): Conceptualization, funding acquisition, resources, supervision, writing - review & Editing. Z-H.Z. and Y-Y.L. contributed equally to this work.

**Possible AI usage:** The authors confirm that artificial intelligence tools were used solely to assist in language polishing and grammar correction of the manuscript. All intellectual content, data interpretation, and conclusions were independently developed by the authors without AI involvement.

**Availability of supporting data:** All datasets generated and analyzed in this study are available in the SEER database (<https://seer.cancer.gov/>).

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