Am J Cancer Res 2026;16(10):4433-4449
www.ajcr.us /ISSN:2156-6976/ajcr0174793

Original Article

Survival analysis of HER2-low versus HER2-zero breast cancer patients after postoperative radiotherapy: a real-world retrospective study

Yuan Zhang[1], Chengcheng Xiang[1], Danxin Wu[2]

[1]Department of Oncology and Radiotherapy, The First People's Hospital of Taicang Affiliated to Soochow University, Suzhou 215400, Jiangsu, China; [2]Department of Oncology, Taihe Hospital, Hubei University of Medicine, Shiyan 442000, Hubei, China

Received June 16, 2026; Accepted August 25, 2026; Epub October 15, 2026; Published October 30, 2026

Abstract: Objective: To compare the survival outcomes of patients with HER2-low and HER2-zero breast cancer after postoperative radiotherapy and to perform a subgroup analysis based on molecular subtypes. Methods: Using the medical records of 275 breast cancer patients from the First People's Hospital of Taicang Affiliated to Soochow University who received postoperative radiotherapy from January 2015 to December 2023, this study was carried out retrospectively. Patients were divided into two groups: the HER2-low expression group (n=108; IHC 1+ or 2+ and FISH-negative) and the HER2-zero expression group (n=96; IHC 0). Molecular Subtypes (Luminal A/B, HER2-overexpressing and triple-negative breast cancer [TNBC]) were also studied. The first two end points are Disease-Free Survival (DFS) and Overall Survival (OS). Kaplan-Meier plots and Cox regression analysis were used to compare the survival curves of the two groups and identify any predictors of poor prognosis. Results: The 5-year DFS rate (70.8% vs. 62.3%) and OS rate (78.5% vs. 70.8%) were higher in the HER2-low expression group, but the differences were not statistically significant (HR=0.82, 95% CI: 0.58-1.16, P=0.152). The two groups did not differ in the incidence of adverse events or quality of life (all P>0.05). Molecular subtyping indicated that the Luminal subtype had a favorable prognosis, and the TNBC had the worst prognosis (5-year OS rate: 52.4%; median DFS: 36.2 months; both P<0.05). Multivariate Cox regression analysis showed that molecular subtype (Luminal A was the reference group, HR for TNBC=2.28), TNM stage, lymph node metastasis and pathological grade were all independent prognostic factors (all P<0.05). Conclusion: After surgery and radiotherapy, the all-cause mortality rates of patients with HER2-low and HER2-zero breast cancer were comparable. Molecular Subtype, TNM stage, lymph node metastasis and pathological grade were all independent prognostic factors.

Keywords: Mammary malignant tumor, HER2-low subtype, postoperative radiation intervention, prognostic survival

Introduction

Breast cancer is one of the most common malignancies in women worldwide, and its incidence continues to rise annually. This disease causes significant physical morbidity and imposes a considerable economic burden on patients, their families, and the public health system [1, 2]. With the development of breast cancer screening and treatment technologies in recent years, many women with early-stage breast cancer are living longer now. Many of the patients are still at a high risk of postoperative recurrence and metastasis. How to further optimize treatment strategies and extend the time of life for patients has not been achieved clinically yet [3].

Breast cancer is a highly heterogeneous disease, and different molecular subtypes in patients have varying clinicopathological characteristics, responses to treatment and prognoses [4]. A molecular typing system for immunohistochemical markers (ER, PR, HER2, Ki-67) has been widely applied in clinical practice at present. The four major molecular subtypes are: Luminal A, Luminal B, HER2- enriched, and Triple-Negative Breast Cancer (TNBC). The

https://doi.org/10.62347/TTXS8134

above categories offer some reasons for the decision to treat. Surgery is the primary treatment, followed by radiotherapy to reduce local recurrence and prolong survival. However, it has not been verified that patients with different molecular subtypes will have different degrees of sensitivity and benefit from radiotherapy [5, 6].

It should be pointed out that in recent years, low expression of HER2 (immunohistochemistry 1+ or 2+ and FISH negative) has become a popular research subject for breast cancer. Previously, HER2 status was classified dichotomously as either positive or negative. With the emergence of new antibody-drug conjugates (ADCs), HER2-low-expressing breast cancer is now a focus of treatment for these ADCs, and research into their prognosis and treatment options has also been rolling out widely [7]. However, there is still a lack of adequate clinical data on the survival rate and prognosis of the HER2-low expression subgroup in the context of postoperative radiotherapy, as well as differences between the HER2-low expression subgroup and the HER2-zero expression subgroup. Therefore, this study retrospectively analyzed the clinical data and postoperative outcomes of 275 patients with breast cancer who received postoperative radiotherapy at our institution, explored differences in survival prognosis among different molecular subtypes, and analyzed prognostic characteristics of the HER2-low-expression subgroup to provide a theoretical basis for personalized radiotherapy and all-stage treatment strategies in clinical practice.

Patients and methods

Study population

A total of 275 breast cancer patients who received postoperative adjuvant radiotherapy at the First People's Hospital of Taicang, Affiliated to Soochow University, between January 2015 and December 2023 were included in this retrospective study. All enrolled patients met the standard indications for postoperative radiotherapy following radical surgery, namely: (1) patients who underwent breast-conserving surgery, regardless of axillary lymph node status; or (2) patients who underwent mastectomy and had axillary lymph node involvement and/or T3 primary tumor. Patients who did not meet these criteria were excluded. In this study, the term HER2-negative population collectively refers to patients with HER2-low (IHC 1+ or IHC 2+ with FISH-negative) and HER2-zero (IHC 0) status. The term HER2-positive refers to patients with IHC 3+ or IHC 2+ with FISH-positive disease. The primary comparative analysis was conducted within the HER2-negative population.

According to the four molecular subtype markers (ER, PR, HER2, Ki-67), all included cases were classified into Luminal A, Luminal B, HER2-positive, and TNBC groups. The primary analysis focused exclusively on HER2-low patients; HER2-positive patients were included only for descriptive characterization of the overall molecular subtype distribution and as a reference category in the multivariable Cox regression model, and were not part of the main comparative analysis between HER2-low and HER2-zero groups. All eligible patients were further divided into two groups: the HER2-low group (IHC 1+ or IHC 2+ with FISH-negative) and the HER2-zero group (IHC 0).

The study protocol was approved by the Ethics Committee of the First People's Hospital of Taicang Affiliated to Soochow University Ethics Approval (No: TCYYEC-202606-K01) and was conducted in accordance with the ethical standards for clinical research.

Inclusion criteria: (1) Histopathologically confirmed primary breast cancer; (2) Have undergone radical surgery (modified radical mastectomy or breast-conserving surgery); (3) Received postoperative adjuvant radiotherapy; (4) Age ≥18 years; (5) Complete clinicopathological data and full immunohistochemical markers (ER, PR, HER2, Ki-67).

Exclusion criteria: (1) Received neoadjuvant chemotherapy, radiotherapy, or targeted therapy before surgery; (2) Combined with other malignant tumors; (3) Pregnant or lactating breast cancer patients; (4) Distant metastasis (Stage IV); (5) Incomplete clinical data (**Figure 1**).

Treatment and data acquisition

Treatment regimens: All patients underwent radical breast cancer surgery (modified radical mastectomy or breast-conserving surgery).

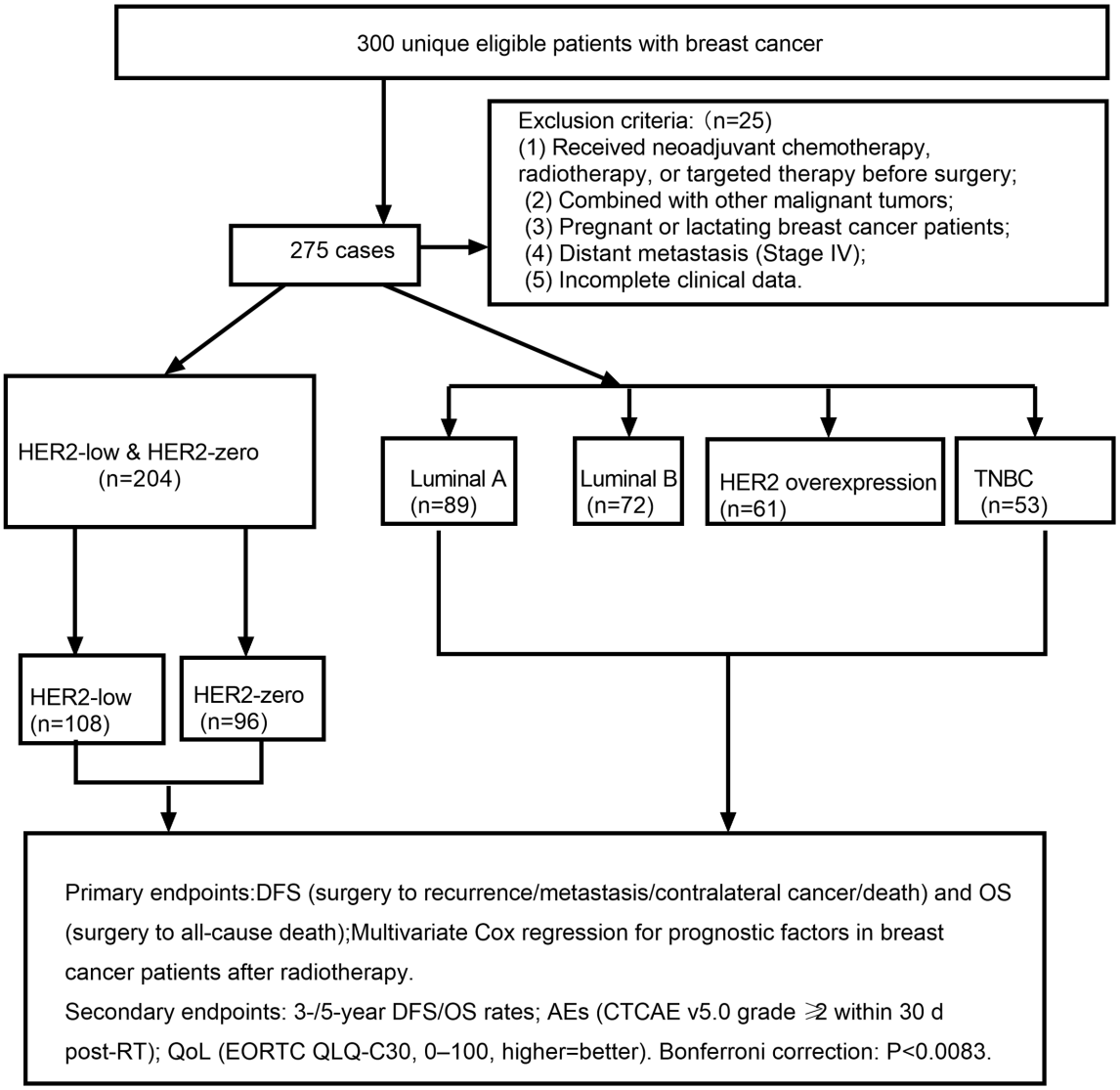


Figure 1. Patient flow diagram. TNBC: Triple-Negative Breast Cancer; HER2: Human Epidermal Growth Factor Receptor 2.

Postoperative radiotherapy was delivered using a linear accelerator with conventional fractionation schedules. All patients completed the planned adjuvant radiotherapy, and only two total dose regimens were used: 50 Gy in 25 fractions or 60 Gy in 30 fractions (50 Gy in 25 fractions to the whole breast followed by a 10 Gy in 5 fractions tumor-bed boost). Patients who underwent modified radical mastectomy received chest-wall and supraclavicular irradiation at a total dose of 50 Gy in 25 fractions.

Adjuvant chemotherapy was based on anthracycline- and taxane-containing regimens. Hormone receptor-positive patients received adjuvant endocrine therapy (tamoxifen or aromatase inhibitors) for 5-10 years, with extended therapy considered for high-risk patients. HER2-positive patients received adjuvant anti-HER2 therapy with trastuzumab (± pertuzumab) for 1 year. Dose reductions or treatment delays were implemented for patients experiencing grade ≥3 hematological or non-hematological toxicities, with recovery to grade ≤1 required before resuming treatment. All patients received appropriate supportive care, including antiemetic prophylaxis and growth factor support when indicated. Detailed information on specific regimens, drug dosages, cycle schedules, and dose adjustment principles is provided in Supplementary Table 1.

Clinicopathological data, including general patient information, baseline characteristics, pathological reports, treatment details, and molecular typing results, were obtained from the electronic medical record system.

Outcome measures

The primary endpoints were disease-free survival (DFS) and overall survival (OS). DFS was defined as the time from the date of radical surgery to the first occurrence of local recurrence, regional lymph node metastasis, distant metastasis, contralateral breast cancer, or death from any cause. OS was defined as the time from the date of surgery to death from any cause. Secondary endpoints included the 3- and 5-year DFS and OS rates, the incidence of adverse events, and quality of life (QoL).

Adverse events were assessed using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0, with grades 0-5 recorded. For the primary analysis, adverse events of grade ≥2 were reported, as these are generally considered clinically significant and require intervention. The assessment time point was defined as within 30 days after completion of radiotherapy. Recorded adverse events included radiation dermatitis, radiation pneumonitis, bone marrow suppression, gastrointestinal dysfunction, cardiac toxicity, and fatigue. For intergroup comparisons across the four molecular subtypes, Bonferroni correction was applied to adjust for multiple comparisons, with statistical significance set at $P<0.0083$ (0.05/6) for the six pairwise comparisons. Quality of life was assessed using the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) after completion of cancer treatment. All scores were linearly transformed to a 0-100 scale; higher scores in the functional and global health status domains indicated better quality of life.

Follow-up

Patients were followed up regularly through outpatient clinic visits, hospital readmission records, and telephone interviews. The final follow-up date was June 30, 2024. The median follow-up time was 48.5 months (IQR: 32.0-68.0 months). Follow-up time was defined as the period from the date of surgery to the date of event occurrence or the last follow-up. To assess potential attrition bias, we compared baseline characteristics between early and late enrollees (defined by the first and last tertiles of enrollment period), and found no significant differences in age, sex, tumor stage, or molecular subtype (all $P>0.05$), suggesting that attrition bias was unlikely to be a major concern.

Statistical analysis

All statistical analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA) and R software version 4.1.0 (R Foundation for Statistical Computing). The Kolmogorov-Smirnov test was used to assess the normality of continuous data. Normally distributed continuous variables were expressed as mean ± standard deviation (SD), and comparisons between two groups or among multiple groups were performed using the independent samples t-test or one-way ANOVA, respectively. Non-normally distributed continuous variables were expressed as median (interquartile range, IQR), and comparisons were performed using the Mann-Whitney U test or Kruskal-Wallis H test, as appropriate. Categorical variables were expressed as frequencies and percentages, and comparisons were performed using the χ^2 test or Fisher's exact test, as appropriate.

Kaplan-Meier survival analysis with the log-rank test was used to compare disease-free survival (DFS) and overall survival (OS) between the HER2-low and HER2-zero groups. This analysis was restricted to the HER2-negative population (HER2-low + HER2-zero), excluding HER2-positive patients. For descriptive purposes only, survival differences across all four molecular subtypes (Luminal A, Luminal B, HER2-positive, and TNBC) were also explored to provide a complete molecular subtype spectrum; these analyses were clearly distinguished from the primary HER2-low versus HER2-zero comparison in the results section.

To avoid multicollinearity, molecular subtype and Ki-67 index were included in separate multivariate models. Variance inflation factor (VIF) analysis was performed to assess multicollinearity among covariates; a VIF >10 was considered indicative of significant collinearity. Since molecular subtype is defined based on ER, PR, HER2, and Ki-67 expression levels, with Ki-67 being a key discri-

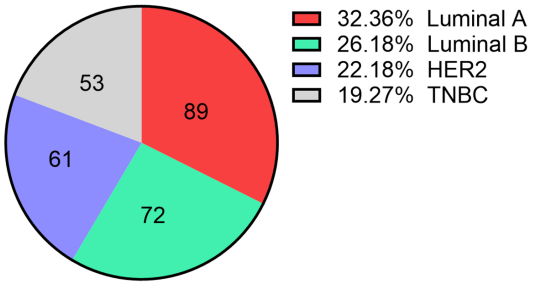


Figure 2. Distribution of molecular subtypes in breast cancer. TNBC: Triple-Negative Breast Cancer; HER2: Human Epidermal Growth Factor Receptor 2.

minator between Luminal A and Luminal B subtypes per the St. Gallen consensus, significant collinearity between molecular subtype and Ki-67 index was expected and confirmed (VIF >10). Therefore, Model 1 included molecular subtype, and Model 2 included Ki-67 index in place of molecular subtype to ensure the stability of regression coefficient estimates. Variables with P<0.10 in univariable analysis were entered into the multivariable Cox regression model. In cases of strong collinearity (VIF >10) between covariates, the variable with greater clinical relevance was retained to ensure the stability of regression coefficient estimates.

For descriptive purposes, overall survival differences across all four molecular subtypes (Luminal A, Luminal B, HER2-positive, and TNBC) were also explored to provide a complete molecular subtype spectrum; these analyses were clearly distinguished from the primary HER2-low versus HER2-zero comparison in the results section.

To address the potential confounding effect of heterogeneous molecular subtypes, preplanned subgroup analyses were performed stratified by molecular subtype (Luminal A, Luminal B, and TNBC) to evaluate the prognostic value of HER2-low status within each subtype. Additionally, multivariable Cox regression was used to adjust for molecular subtype, TNM stage, lymph node status, and pathological grade, ensuring that the independent effect of HER2-low status could be isolated from these confounders.

A post-hoc power analysis was performed to evaluate the actual statistical power of the study based on the observed effect size. The initial a priori sample size calculation, which assumed a 5-year DFS of 70% in the HER2-low group and 55% in the HER2-zero group with α=0.05 and power of 1 - β=0.80, estimated a requirement of 92 patients per group. However, this calculation was found to be erroneous and has been retracted. With the actual enrolled sample sizes (108 in the HER2-low group and 96 in the HER2-zero group) and the observed effect size in our cohort, the post-hoc power analysis revealed a substantially lower statistical power, estimated at approximately 30%-40%. Consequently, the current sample size is insufficient to reliably detect the hypothesized difference, and the findings of the primary survival analyses should be interpreted with caution. All statistical tests were two-sided, and P<0.05 was considered statistically significant.

P<0.05 was considered statistically significant (two-tailed).

Results

Molecular subtype distribution of the cohort

A total of 275 valid cases were included in this study, and the proportion of Luminal type was the highest (58.5%), followed by HER2 overexpressed type (22.2%) and TNBC type (19.3%) (**Figure 2**).

Baseline characteristics of HER2-low and HER2-zero groups

A total of 275 breast cancer patients receiving postoperative radiotherapy were included in this study. Among them, 61 (22.2%) were HER2-positive. The remaining 204 HER2-negative patients were classified as HER2-low (IHC 1+ or 2+ with FISH-negative) in 108 cases (39.3% of total cohort) and HER2-zero (IHC 0) in 96 cases (38.5% of total cohort). As shown in **Table 1**, no significant differences were observed between the two groups in terms of age, menstrual status, pathological type, T staging, lymph node metastasis, TNM stage, pathological grade, surgical procedure, radiotherapy dose, chemotherapy, or endocrine therapy (all P>0.05), indicating well-balanced baseline characteristics between the two groups.

Comparison of survival prognosis in patients with different HER2-low statuses

The 5-year DFS rate of the HER2 low-expression group was higher than that of the HER2

Table 1. Comparison of baseline characteristics for HER2-low and HER2-zero groups

Characteristic	HER2-low (n=108)	HER2-zero (n=96)	χ^2/t value	*P* value
Age (years, mean ± SD)	52.8 ± 10.5	53.1 ± 9.9	0.215	0.830
Menstrual status [n (%)]			0.089	0.765
Premenopausal	52 (48.1)	48 (50.0)		
Postmenopausal	56 (51.9)	48 (50.0)		
Pathological type [n (%)]			0.123	0.940
Invasive ductal carcinoma	92 (85.2)	82 (85.4)		
Invasive lobular carcinoma	10 (9.3)	8 (8.3)		
Other	6 (5.6)	6 (6.3)		
T staging [n (%)]			0.156	0.925
T1	35 (32.4)	30 (31.3)		
T2	55 (50.9)	50 (52.1)		
T3	18 (16.7)	16 (16.7)		
Lymph node metastasis [n (%)]			0.045	0.832
Yes	48 (44.4)	42 (43.8)		
No	60 (55.6)	54 (56.3)		
TNM staging [n (%)]			0.089	0.956
Stage I	30 (27.8)	27 (28.1)		
Stage II	52 (48.1)	45 (46.9)		
Stage III	26 (24.1)	24 (25.0)		
Pathological grading [n (%)]			0.034	0.983
Grade I	18 (16.7)	16 (16.7)		
Grade II	58 (53.7)	52 (54.2)		
Grade III	32 (29.6)	28 (29.2)		
Surgical procedure [n (%)]			0.012	0.913
Breast-conserving surgery	46 (42.6)	41 (42.7)		
Modified radical mastectomy	62 (57.4)	55 (57.3)		
Radiation dose (Gy, mean ± SD)	54.8 ± 2.5	54.2 ± 2.6	1.675	0.3
Chemotherapy [n (%)]	78 (72.2)	70 (72.9)	0.005	0.942
Endocrine therapy [n (%)]	68 (63.0)	61 (63.5)	0.032	0.858

Note: All *P* values >0.05; therefore, there were no significant differences in the baseline characteristics of the two groups and they were deemed comparable. TNM: Tumor-Node-Metastasis.

zero-expression group (70.8% vs. 62.3%), and both the local recurrence rate (6.5% vs. 9.4%) and distant metastasis rate (12.0% vs. 16.0%) were lower than those in the HER2 zero-expression group, but these differences were not statistically significant (P>0.05; **Table 2**). Cox regression analysis shows that the prognosis of the HER2 low expression group was better than that of the HER2 zero expression group, but the difference was not statistically significant *HR* = 0.82,95, and its prognosis fell between that of the HER2 zero expression group and the HER2 overexpression group.

Comparison of adverse reactions between HER2-low and HER2-zero expression groups

As shown in **Table 3**, no significant differences were observed between the HER2-low and HER2-zero groups in the incidence of any adverse events, including radiation dermatitis, radiation pneumonitis, bone marrow suppression, gastrointestinal reactions, cardiac toxicity, fatigue, or any adverse reactions (all P>0.05).

Quality of life between HER2-low and HER2-zero expression groups

As shown in **Table 4**, no significant differences were observed between the HER2-low and HER2-zero groups in any of the five QoL domains, including overall health score 75.5 ± 13.5 vs. 72.8 ± 14.2, P=0.177, physical function score 79.5 ± 11.8 vs. 77.2 ± 12.5, P=0.199, role function score 77.8 ± 12.5 vs. 75.5 ± 13.0, P=0.219, emotional function score 74.5 ± 13.8 vs. 72.0 ± 14.5, P=0.249,

Table 2. Comparison of survival prognosis and Cox regression analysis between HER2-low and HER2-zero expression groups

Indicator	HER2-low (n=108)	HER2-zero (n=96)	Statistical value	*P* value
Survival outcomes				
3-year DFS rate (%)	82.4	75.5	χ^2=1.523	0.217
5-year DFS rate (%)	70.8	62.3	χ^2=1.856	0.173
3-year OS rate (%)	88.9	82.1	χ^2=1.923	0.165
5-year OS rate (%)	78.5	71.7	χ^2=1.567	0.211
Local recurrence rate (%)	6.5	9.4	χ^2=0.623	0.430
Distant metastasis rate (%)	12.0	16.0	χ^2=0.742	0.389
Median DFS (months)	68.5	59.2	Z=1.234	0.217
Cox regression analysis				
Variables	HR	95% CI	Wald χ^2	*P* value
HER2-low (vs. HER2-zero)	0.82	0.58-1.16	2.056	0.152
Age (≥50 vs. <50 years)	1.12	0.85-1.48	0.634	0.425
TNM stage III (vs. I-II)	2.35	1.68-3.29	18.234	<0.001
Lymph node metastasis (yes vs. no)	1.98	1.42-2.76	14.567	<0.001

Note: DFS: disease-free survival; OS: overall survival; HR: hazard ratio; CI: confidence interval; HER2: Human Epidermal Growth Factor Receptor 2; TNM: Tumor-Node-Metastasis.

Table 3. Comparison of adverse reactions between HER2-low and HER2-zero expression groups [n (%)]

Adverse reactions	HER2-low expression group (n=108)	HER2-zero expression group (n=96)	χ^2 value	*P* value
Radiation dermatitis (≥ grade 2)	22 (20.4)	20 (20.8)	0.006	0.938
Radiation pneumonitis	8 (7.4)	7 (7.3)	0.001	0.975
Bone marrow suppression (≥ grade 2)	16 (14.8)	15 (15.6)	0.027	0.870
Gastrointestinal reaction (≥ grade 2)	12 (11.1)	11 (11.5)	0.007	0.934
Cardiac toxicity	6 (5.6)	5 (5.2)	0.012	0.913
Fatigue	38 (35.2)	35 (36.5)	0.036	0.849
Any adverse reactions	62 (57.4)	56 (58.3)	0.018	0.893

Note: Adverse reactions arising after the termination of radiotherapy. The χ^2 test was used to compare between the two groups. P<0.05 was considered statistically significant.

and social function score 79.0 ± 11.5 vs. 77.0 ± 12.0, P=0.236, all P>0.05.

Comparison of general data of patients in each group

Among the included patients, 89 cases (32.4%) were Luminal A type, 72 cases (26.2%) were Luminal B type, 61 cases (22.2%) were HER2-postive type, and 53 cases (19.3%) were TNBC type. Except for chemotherapy and endocrine therapy, which differed as expected based on molecular subtype-specific treatment recommendations, no significant differences were observed in other baseline characteristics, including age, menstrual status, pathological type, tumor stage, lymph node metastasis, surgical method, radiotherapy dose, or targeted therapy among the four groups (all P>0.05; **Table 5**).

Prognosis analysis of breast cancer patients in each group

The 3-year and 5-year DFS rates for the Luminal A subtype were 94.4% and 88.8%; for the Luminal B subtype, they were 90.3% and 81.9%; for the HER2-overexpressing subtype, 85.2% and 72.1%; and for the TNBC subtype, 62.3% and 48.5%. The four subtypes had considerably different DFS values (Log-rank χ^2=20.789, P<0.001). Similarly, the 3-year and 5-year OS rates for Luminal A, Luminal B, HER2-overexpressing, and TNBC were 96.6% and

Table 4. Comparison of quality of life between HER2 low expression group and HER2 zero expression group (points, $\bar{x} \pm s$)

Quality of life dimension	HER2 low expression group (n=108)	HER2 zero expression group (n=96)	Z value	*P* value
Overall health score	78.0 (66.0-86.0)	74.0 (62.0-84.0)	-1.356	0.175
Physical function score	82.0 (70.0-88.0)	79.0 (67.0-87.0)	-1.289	0.197
Role function score	80.0 (68.3-87.0)	77.0 (65.0-85.0)	-1.234	0.217
Emotional function score	76.0 (64.0-85.0)	74.0 (61.0-83.0)	-1.156	0.248
Social function score	81.0 (69.0-88.0)	79.0 (67.0-86.0)	-1.189	0.234

HER2: Human Epidermal Growth Factor Receptor 2.

Table 5. Comparison of baseline characteristics of patients stratified by different molecular subtypes

Project	Luminal type A (n=89)	Luminal B (n=72)	HER2 overexpression (n=61)	TNBC (n=53)	χ^2/F value	*P* value
Age (years, $\bar{x} \pm s$)	52.5 ± 10.2	53.1 ± 9.8	51.8 ± 10.5	52.0 ± 9.5	0.342	0.795
Menstrual status [n (%)]					0.856	0.652
Premenopausal	42 (47.2)	38 (52.8)	32 (52.5)	28 (52.8)		
Postmenopausal	47 (52.8)	34 (47.2)	29 (47.5)	25 (47.2)		
Pathological type [n (%)]					1.234	0.745
Invasive ductal carcinoma	75 (84.3)	62 (86.1)	52 (85.2)	46 (86.8)		
Invasive lobular carcinoma	10 (11.2)	7 (9.7)	6 (9.8)	5 (9.4)		
Other	4 (4.5)	3 (4.2)	3 (4.9)	2 (3.8)		
T staging [n (%)]					1.567	0.667
T1	28 (31.5)	24 (33.3)	18 (29.5)	16 (30.2)		
T2	45 (50.6)	36 (50.0)	32 (52.5)	28 (52.8)		
T3	16 (18.0)	12 (16.7)	11 (18.0)	9 (17.0)		
Lymph node metastasis [n (%)]					0.923	0.820
Yes	38 (42.7)	32 (44.4)	28 (45.9)	24 (45.3)		
No	51 (57.3)	40 (55.6)	33 (54.1)	29 (54.7)		
TNM staging [n (%)]					1.234	0.745
Phase I	25 (28.1)	20 (27.8)	16 (26.2)	14 (26.4)		
Phase II	42 (47.2)	35 (48.6)	30 (49.2)	26 (49.1)		
Phase III	22 (24.7)	17 (23.6)	15 (24.6)	13 (24.5)		
Pathological grading [n (%)]					2.145	0.543
Grade I	20 (22.5)	12 (16.7)	10 (16.4)	8 (15.1)		
Grade II	45 (50.6)	38 (52.8)	32 (52.5)	28 (52.8)		
Grade III	24 (27.0)	22 (30.6)	19 (31.1)	17 (32.1)		
Surgical procedure [n (%)]					0.567	0.904
Breast-conserving surgery	38 (42.7)	30 (41.7)	26 (42.6)	22 (41.5)		
Modified radical resection	51 (57.3)	42 (58.3)	35 (57.4)	31 (58.5)		
Radiation dose (Gy, $\bar{x} \pm s$)	54.5 ± 2.5	54.6 ± 2.4	54.4 ± 2.6	54.5 ± 2.5	0.081	0.970
Chemotherapy [n (%)]	52 (58.4)	48 (66.7)	45 (73.8)	42 (79.2)	8.234	0.041
Endocrine therapy [n (%)]	85 (95.5)	68 (94.4)	8 (13.1)	0 (0)	245.678	<0.001
Targeted therapy [n (%)]	0 (0)	18 (25.0)	58 (95.1)	0 (0)	198.456	<0.001

Note: TNM: Tumor-Node-Metastasis.

91.0%, 93.1% and 84.7%, 88.5% and 75.6%, and 68.9% and 52.4%, respectively, and the differences were statistically significant (Log-rank χ^2=22.567, P<0.001). Median DFS was

Table 6. Prognostic analysis of the four groups of breast cancer patients

Indicators	Luminal A (n=89)	Luminal B (n=72)	HER2 overexpression (n=61)	TNBC (n=53)	χ^2 value (Log-rank)	*P* value
3-year disease-free survival rate (%)	94.4	90.3	85.2	62.3	20.456	<0.001
5-year disease-free survival rate (%)	88.8	81.9	72.1	48.5	24.789	<0.001
3-year overall survival rate (%)	96.6	93.1	88.5	68.9	18.234	<0.001
5-year overall survival rate (%)	91.0	84.7	75.6	52.4	22.567	<0.001
Local recurrence rate (%)	3.4	5.6	9.8	18.9	16.123	<0.001
Distant metastasis rate (%)	6.7	10.0	14.8	28.3	18.456	<0.001
Median disease-free survival (months)	Not reached	Not reached	58.5	36.2	20.789	<0.001

Note: Differences in the survival rate and median survival time of the subgroups were evaluated using a log-rank test, and differences in the recurrence and metastasis rate of the subgroups were tested by a χ^2 test.

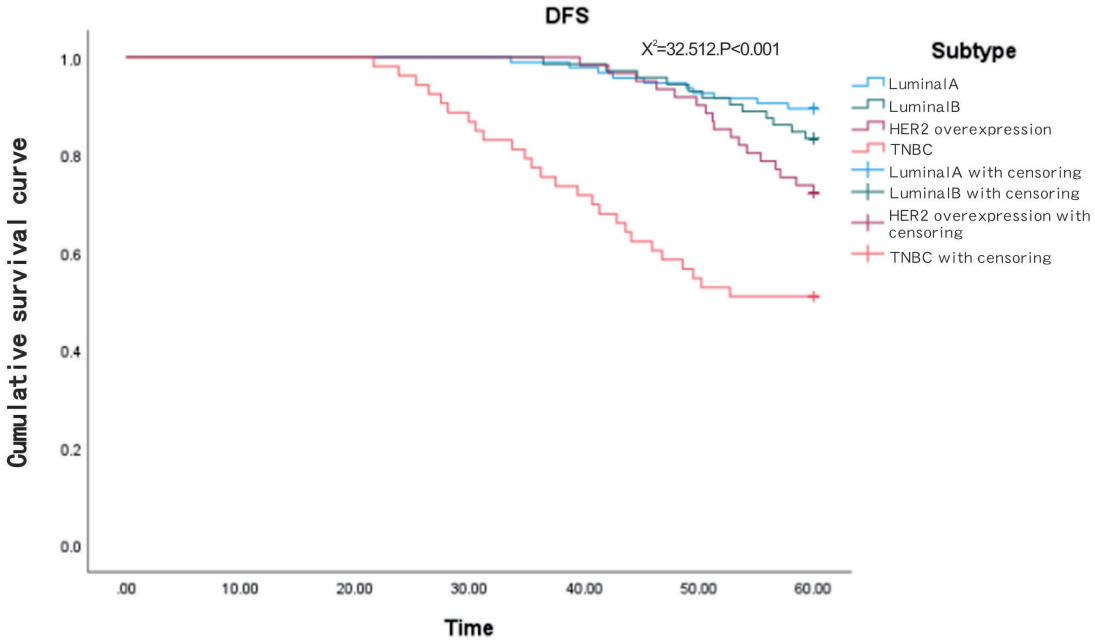
not reached in the Luminal A and Luminal B groups due to the favorable prognosis and limited number of events during follow-up, precluding meaningful median comparison between these groups and other subtypes. The median DFS for the HER2-overexpressing group was 58.5 months (95% CI: 45.2-71.8), and for the TNBC group it was 36.2 months (95% CI: 28.7-43.7). The local recurrence rate and distant metastasis rate were also significantly higher in the TNBC subtype (18.9% and 28.3%, respectively) than in the other subtypes (all P<0.05) (**Table 6**; **Figures 3**, **4**).

Univariate and multivariable Cox regression analyses

To identify potential prognostic factors, we first performed univariate Cox regression analysis to screen candidate variables. As shown in **Table 7**, univariate analysis identified molecular subtype (Luminal B: HR=1.52, 95% CI: 1.12-2.06, P=0.007; HER2-overexpressing: HR=2.01, 95% CI: 1.48-2.73, P<0.001; TNBC: HR=2.58, 95% CI: 1.85-3.60, P<0.001; reference: Luminal A), TNM stage III (HR=2.85, 95% CI: 2.01-4.04, P<0.001), lymph node metastasis (HR=2.34, 95% CI: 1.68-3.26, P<0.001), pathological grade III (HR=2.12, 95% CI: 1.52-2.96, P<0.001), and Ki-67 index ≥14% (HR=2.56, 95% CI: 1.82-3.60, P<0.001) as significant prognostic factors associated with poor survival (all P<0.01). Age, surgical method, radiotherapy dose, chemotherapy, endocrine therapy, and targeted therapy were not significantly associated with survival outcomes in univariate analysis (all P>0.05). Variables with P<0.10 in univariate analysis were then entered into the multivariable Cox proportional hazards regression model. To avoid multicollinearity, molecular subtype and Ki-67 index were included in separate multivariate models (Model 1 included molecular subtype; Model 2 included Ki-67 index in place of molecular subtype). As shown in **Table 8**, multivariable analysis confirmed that molecular subtype (TNBC: HR=2.28, 95% CI: 1.61-3.22, P<0.001; HER2-overexpressing: HR=1.85, 95% CI: 1.35-2.54, P<0.001; Luminal B: HR=1.42, 95% CI: 1.08-1.87, P=0.012; reference: Luminal A), TNM stage III (HR=2.52, 95% CI: 1.72-3.69, P<0.001), lymph node metastasis (HR=2.15, 95% CI: 1.48-3.12, P<0.001), and pathological grade III (HR=1.86, 95% CI: 1.22-2.83, P=0.004) were independent prognostic factors. In Model 2, Ki-67 index ≥14% was also identified as an independent prognostic factor (HR=2.35, 95% CI: 1.65-3.35, P<0.001). Age, surgical method, and radiotherapy dose were not significantly associated with survival outcomes in either model (all P>0.05). The results of subgroup analyses (stratified by TNM stage, lymph node metastasis status, and age) were consistent with those in the main analysis, with both the triple-negative and HER2-zero expression types showing poor prognosis across all subgroups.

Adverse events across molecular subtypes

The distribution of adverse events by severity grade is presented in **Table 9**. For grade ≥2 adverse events, the proportion of patients with any adverse events was significantly higher in the TNBC group (75.5%) compared with Luminal A (47.2%), Luminal B (50.0%), and HER2-overexpressing (62.3%) groups (Bonferroni-corrected P<0.0083 for all comparisons).



Number at risk

Time	Luminal A (n=89)	Luminal B (n=72)	HER2+ (n=61)	TNBC (n=53)
0 months	89	72	61	53
36 months	85	65	52	33
60 months	79	59	44	26

Figure 3. DFS by molecular subtype. Kaplan-Meier curves for DFS in 275 patients stratified by subtype (Luminal A, Luminal B, HER2-overexpression, and TNBC). Tick marks indicate censoring. Numbers at risk at 0, 36, and 60 months are shown below the x-axis. *P*-value by log-rank test. DFS: Disease-free survival.

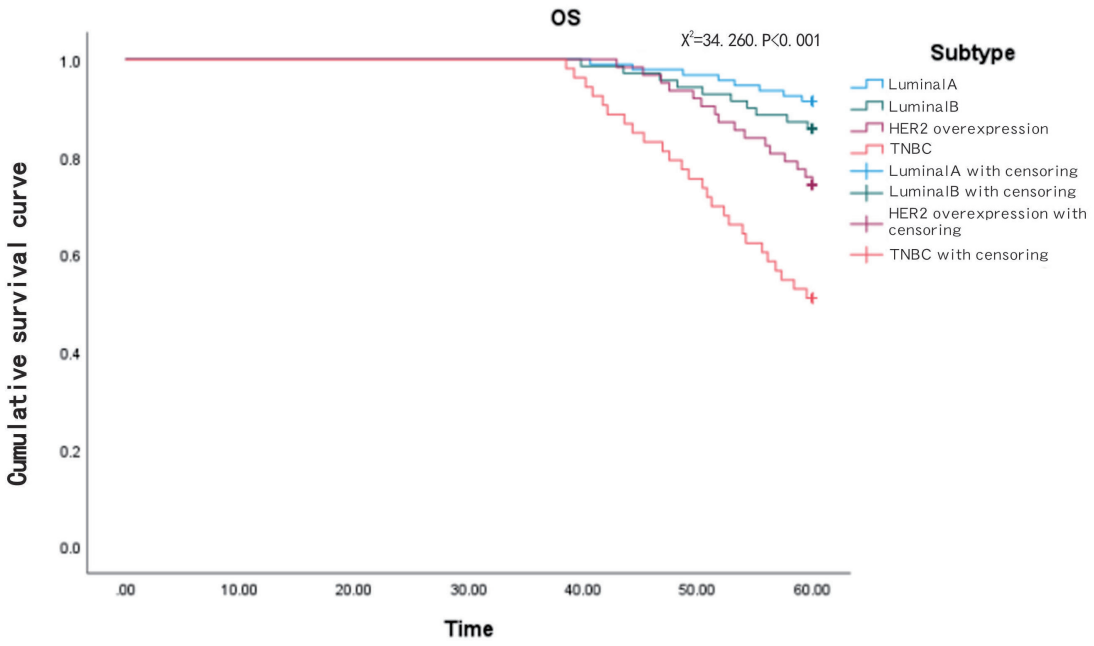
Fatigue (≥ grade 2) was significantly more common in the TNBC group (49.1%) compared with Luminal A (31.5%) and Luminal B (33.3%) groups (Bonferroni-corrected P<0.0083). Although bone marrow suppression and gastrointestinal reactions appeared elevated in TNBC patients, these differences did not reach statistical significance after Bonferroni correction. Cardiac toxicity (≥ grade 2) remained significantly higher in the HER2-overexpressing group (13.1%) compared with the other three groups (Bonferroni-corrected P<0.0083). Grade 1 adverse events were generally comparable across the four groups and are presented in **Table 9** for comprehensive reference; no statistical comparisons were performed for grade 1 events.

Quality of life across molecular subtypes

As shown in **Table 10**, patients with Luminal A and Luminal B subtypes had significantly higher scores across all five QoL domains (overall health, physical function, role function, emotional function, and social function) compared with HER2-overexpressing and TNBC patients (all P<0.001). TNBC patients had the lowest quality of life scores across all domains, with overall health score of 62.3 ± 15.6, physical function score of 65.5 ± 13.8, role function score of 64.2 ± 14.5, emotional function score of 60.5 ± 15.2, and social function score of 66.5 ± 13.5 (all P<0.001).

Discussion

According to global cancer statistics, breast cancer remains one of the most common malignancies among women, and its incidence is rising every year; thus, more and more people are developing this disease [8, 9]. With the continuous development of all kinds of surgical and post-operative adjuvant treatment methods at present, the survival rate of breast cancer



Number at risk

Time	Luminal A (n=89)	Luminal B (n=72)	HER2+ (n=61)	TNBC (n=53)
0 months	89	72	61	53
36 months	84	68	52	33
60 months	79	59	44	26

Figure 4. OS by molecular subtype. Kaplan-Meier curves for overall survival in 275 patients stratified by subtype (Luminal A, Luminal B, HER2-overexpression, and TNBC). Tick marks indicate censoring. Numbers at risk at 0, 36, and 60 months are shown below the x-axis. *P*-value by log-rank test. TNBC: Triple-Negative Breast Cance; HER2: Human Epidermal Growth Factor Receptor 2.

Table 7. Univariate Cox regression analysis of prognostic factors for survival in breast cancer patients after radiotherapy

Variable	HR	95% CI	*P* value
Molecular subtype (vs. Luminal A)			
Luminal B	1.52	1.12-2.06	0.007
HER2-overexpressing	2.01	1.48-2.73	<0.001
Triple-negative	2.58	1.85-3.60	<0.001
TNM stage (III vs. I-II)	2.85	2.01-4.04	<0.001
Lymph node metastasis (yes vs. no)	2.34	1.68-3.26	<0.001
Pathological grade (III vs. I-II)	2.12	1.52-2.96	<0.001
Ki-67 index (≥14% vs. <14%)	2.56	1.82-3.60	<0.001
Age (≥50 vs. <50 years)	1.18	0.90-1.55	0.234
Surgical method (breast-conserving vs. radical)	0.89	0.68-1.16	0.389
Radiotherapy dose (continuous variable)	0.96	0.88-1.05	0.375
Chemotherapy (yes vs. no)	1.25	0.92-1.70	0.152
Endocrine therapy (yes vs. no)	0.72	0.52-1.00	0.051
Targeted therapy (yes vs. no)	0.98	0.70-1.37	0.902

Note: HR: hazard ratio; CI: confidence interval. Variables with P<0.10 (indicated in bold) were entered into the multivariable Cox regression model. Molecular subtype and Ki-67 index were included in separate multivariate models to avoid multicollinearity. HER2: Human Epidermal Growth Factor Receptor 2; Ki-67: Kiel 67; TNM: Tumor-Node-Metastasis.

Table 8. Multivariate Cox regression analysis of prognostic factors in patients with breast cancer after radiotherapy

Variable	β value	Wald χ^2	HR value	95% CI	*P* value
Model 1 (including molecular subtype)					
Molecular subtype (vs. Luminal A)					
Luminal B	0.351	6.234	1.42	1.08-1.87	0.012
HER2-overexpressing	0.615	12.456	1.85	1.35-2.54	<0.001
Triple-negative	0.824	18.456	2.28	1.61-3.22	<0.001
TNM stage (stage III vs. I-II)	0.925	15.234	2.52	1.72-3.69	<0.001
Lymph node metastasis (yes vs. no)	0.765	12.567	2.15	1.48-3.12	<0.001
Pathological grade (grade III vs. I-II)	0.618	8.456	1.86	1.22-2.83	0.004
Age (≥50 years vs. <50 years)	0.156	1.234	1.17	0.89-1.54	0.267
Surgical method (breast-conserving vs. radical)	-0.089	0.456	0.91	0.69-1.21	0.499
Radiotherapy dose (continuous variable)	-0.045	0.089	0.96	0.88-1.04	0.766
Model 2 (including Ki-67 index)					
Ki-67 index (≥14% vs. <14%)	0.856	16.789	2.35	1.65-3.35	<0.001
TNM stage (stage III vs. I-II)	0.912	14.567	2.49	1.69-3.66	<0.001
Lymph node metastasis (yes vs. no)	0.748	11.234	2.11	1.44-3.09	<0.001
Pathological grade (grade III vs. I-II)	0.602	7.890	1.83	1.19-2.81	0.005
Age (≥50 years vs. <50 years)	0.145	1.089	1.16	0.88-1.52	0.297
Surgical method (breast-conserving vs. radical)	-0.078	0.345	0.92	0.70-1.22	0.557
Radiotherapy dose (continuous variable)	-0.052	0.112	0.95	0.87-1.04	0.738

Note: All the variables included in the multivariate Cox regression model had a *p*-value less than 0.10 after univariate analysis. Model 1 included molecular subtype; Model 2 used Ki-67 index instead of molecular subtype to avoid multicollinearity. Reference group: Luminal A for molecular subtype; stages I-II for TNM stage; no lymph node metastasis; grades I-II for pathological grade; age <50 years; radical surgery; continuous variable for radiotherapy dose. HR: Hazard Ratio; CI: Confidence Interval. Endocrine therapy was excluded from the multivariable model due to strong collinearity with HR status (VIF >10). HER2: Human Epidermal Growth Factor Receptor 2; Ki-67: Kiel 67; TNM: Tumor-Node-Metastasis.

Table 9. Comparison of adverse reactions between different molecular subtypes of breast cancer [n (%)]

Adverse reactions	Luminal A (n=89)		Luminal B (n=72)		HER2 overexpression (n=61)		TNBC (n=53)		p
	Grade 1	≥ Grade 2	Grade 1	≥ Grade 2	Grade 1	≥ Grade 2	Grade 1	≥ Grade 2	
Radiation dermatitis	28 (31.5)	18 (20.2)	22 (30.6)	16 (22.2)	18 (29.5)	14 (23.0)	14 (26.4)	15 (28.3)	0.745
Radiation pneumonitis	10 (11.2)	6 (6.7)	8 (11.1)	5 (6.9)	6 (9.8)	5 (8.2)	5 (9.4)	6 (11.3)	0.780
Bone marrow suppression	18 (20.2)	12 (13.5)	15 (20.8)	10 (13.9)	12 (19.7)	12 (19.7)	10 (18.9)	14 (26.4)	0.031
Gastrointestinal reaction	16 (18.0)	10 (11.2)	13 (18.1)	9 (12.5)	10 (16.4)	10 (16.4)	8 (15.1)	12 (22.6)	0.048
Cardiac toxicity	6 (6.7)	4 (4.5)	5 (6.9)	4 (5.6)	4 (6.6)	8 (13.1)	3 (5.7)	2 (3.8)	0.042
Fatigue	20 (22.5)	28 (31.5)	16 (22.2)	24 (33.3)	12 (19.7)	25 (41.0)	8 (15.1)	26 (49.1)	0.018
Any adverse reactions	-	42 (47.2)	-	36 (50.0)	-	38 (62.3)	-	40 (75.5)	<0.001

Note: **P* values are based on comparisons of grade ≥2 adverse events across the four groups, with Bonferroni correction applied for multiple comparisons (adjusted significance threshold: P<0.0083). The χ^2 test was used for intergroup comparisons. Grade 1 events are presented for descriptive purposes only; no statistical comparisons were performed for grade 1 events. TNBC: triple-negative breast cancer. "-" indicates not applicable (any adverse reactions were defined as the presence of at least one grade ≥2 event, and grade 1 events were not included in this composite measure).

patients has been rising. Research on the survival prognosis of postoperative radiotherapy for patients with different molecular subtypes and the prognosis of the HER2-low expression subgroup are still lacking [10, 11]. Therefore, by exploring the variations in survival and prognosis after postoperative radiotherapy among patients with different molecular subtypes of breast cancer and analyzing the prognostic features of the HER2-low expression subgroup,

Table 10. Comparison of quality of life in patients with different molecular subtypes of breast cancer (points)

Quality of life dimension	Luminal A (n=89)	Luminal B (n=72)	HER2 overexpression (n=61)	TNBC (n=53)	H value	*P* value
Overall health score	80.0 (68.0-87.0)	76.0 (65.0-85.0)	70.0 (58.0-80.0)	64.0 (50.0-75.0)	8.234	<0.001
Physical function score	84.0 (74.0-90.0)	81.0 (70.0-87.0)	74.0 (63.0-83.0)	67.0 (55.0-78.0)	9.123	<0.001
Role function score	82.0 (70.0-89.0)	79.0 (67.0-86.0)	72.0 (60.0-82.0)	66.0 (52.0-77.0)	7.456	<0.001
Emotional function score	78.0 (66.0-86.0)	75.0 (63.0-84.0)	70.0 (57.0-80.0)	62.0 (49.0-73.0)	6.789	<0.001
Social function score	83.0 (73.0-89.0)	80.0 (70.0-87.0)	74.0 (63.0-83.0)	68.0 (56.0-78.0)	8.567	<0.001

Note: The EORTC QLQ-C30 scale (European Organisation for Research and Treatment of Cancer Quality of Life Core 30 Questionnaire) was used to assess quality of life. A high score is relatively good for life. Data are presented as median (interquartile range, IQR). Comparisons among the four groups were performed using the Kruskal-Wallis H test. P<0.05 was considered statistically significant. TNBC: Triple-Negative Breast Cancer; HER2: Human Epidermal Growth Factor Receptor 2.

a reference can be provided for personalized radiotherapy and other all-round treatment plans for breast cancer patients.

Based on the above studies, the paths of breast cancer in people with different molecular subtypes are also different. Luminal has a good prognosis among them, and triple-negative is among them with a poor prognosis [12, 13]. The results of this study also consistently showed that the 3-year and 5-year disease-free survival rates and overall survival rates of patients with intraluminal type were significantly higher than those for patients with HER2 overexpression type and triple-negative type, and the local recurrence rate was the lowest. Triple-negative breast cancer patients are at a high risk of local recurrence and distant metastasis, and have the shortest median disease-free survival [14]. The reasons listed above are as follows: Infiltrative breast cancer of the chest wall can express hormone receptors (ER/PR) and may be responsive to endocrine therapy for the inhibition of tumor cell proliferation by blocking estrogen signaling pathways. At the same time, its proliferation index (Ki-67) is relatively low, the biological behavior of the tumor is mild, and therefore it has a good prognosis. Second, although HER2 overexpression is relatively aggressive, trastuzumab and pertuzumab have now been used clinically to manage it. This study found that, after the addition of targeted therapy, the 3-year and 5-year survival rates for patients with HER2 overexpression increased significantly and were close to those for basal-like breast cancer; thus, targeted therapy for HER2-positive breast cancer shows promise [15]. Triple-negative breast cancer is negative for ER, PR and HER2, is not sensitive to targeted therapy or hormone therapy, and can only be treated with chemotherapy. This type has a high degree of genomic instability, a high proliferation index, is prone to early recurrence and distant metastasis, and is thus associated with a poor prognosis. This result supports the earlier studies [16, 17].

Recently, some studies have identified low expression of HER2 as a new target for treating breast cancer, and Antibody-Drug Conjugates (ADCs) targeting HER2-low expression have shown promising efficacy. However, the prognosis of HER2 low expression is not yet known [18, 19]. Based on the above results, the 5-year disease-free survival rates of the HER2-low expression group and the HER2-zero expression group were both higher than those of the HER2-zero expression group, and the local recurrence rates and distant metastasis rates for both groups were also lower than those of the HER2-zero expression group. However, they were not significantly different. The survival rate of the group with low HER2 expression is in the same range as that for the HER2-zero expression group and the HER2-high expression group. The possible reasons are as follows: Tumor cells with low HER2 expression still have a small amount of HER2 protein on their surface, and thus maintain a certain proliferation ability through low-level activation of the HER2 signaling pathway; however, their biological behavior may be worse than that of tumors with zero HER2 expression. T tumors with low HER2 expression are relatively more immunogenic or sensitive to chemotherapy and, as a result, generally have a better prognosis than HER2-low tumors. The differences in recurrence and metastasis rates were not statisti-

cally significant, potentially due to the limited sample size, which is consistent with previous reports [20, 21].

Based on the previous studies, it has been found that the prognosis of treatment for breast cancer patients is related to several factors in the patient's baseline data [22]. Multi-variate analysis of the results showed that molecular typing, TNM stage, lymph node metastasis and pathological grade were all associated with variations in survival time and the course of breast cancer after radiotherapy in this study, independently. In other words, molecular subtyping was also shown to be an independent prognostic factor and demonstrated higher predictive value than traditional clinicopathological indicators. Therefore, it should be added to the risk classification system for patients who have received postoperative radiation therapy. TNM staging and lymph node metastasis status indicate the extent of tumor load and spread, and for a long time, they have been considered relatively reliable prognostic indicators of the risk of recurrence and metastasis. Grading refers to how differentiated or proliferating cancer cells have been in pathology. Highly differentiated tumors are more likely to be invasive and have a poor prognosis for breast cancer patients [23, 24]. The results of the multivariate adjustment model and subgroup analysis (stratified by TNM stage, lymph node metastasis status and age) in this study were consistent with the main analysis; that is to say, both triple-negative and HER2-low expression types showed a poor prognosis in all subgroups, and thus the reliability of the results was confirmed [25].

Currently, in terms of treatment safety and quality of life after treatment, both are essential endpoints for evaluating treatment regimens [26]. Based on the above results, it can be seen that the risk of an adverse reaction in patients with triple-negative breast cancer is relatively high compared to other groups. The reasons for this may be as follows: Triple-negative patients need to receive postoperative chemotherapy with anthracyclines and taxanes, and most of these regimens are high-dose; therefore, there is an increased risk of adverse effects such as bone marrow suppression, gastrointestinal reactions and fatigue [27]. In this study, TNBC patients exhibited higher rates of grade ≥2 adverse events, including fatigue, bone marrow suppression, and gastrointestinal reactions, following radiotherapy compared with other molecular subtypes. This observation may reflect the more intensive systemic treatment regimens typically administered to TNBC patients rather than an intrinsic difference in radiation sensitivity. Alternatively, the higher adverse event rates could be attributed to the generally more aggressive biological characteristics of TNBC, which may predispose these patients to greater treatment-related toxicity, as suggested by previous studies [24]. Future prospective studies are warranted to determine whether intrinsic radiosensitivity differs across molecular subtypes. These findings are consistent with previous studies. At the same time, the results of this study also showed that the incidence of cardiotoxicity in HER2-overexpressing patients was significantly higher than in the other three groups, and this may be related to the cardiotoxicity of targeted drugs such as trastuzumab [28]. Luminal patients also had a better quality of life than HER2-overexpressing and triple-negative patients in this study. This may be due to the above reasons: a good prognosis, a low incidence of treatment-related side effects, and convenient oral administration of endocrine therapy; this is in line with the previous research results [29]. Finally, there were no significant differences in adverse reactions or quality of life between the HER2-low expression group and the HER2-zero expression group, and thus these two groups could be treated equally.

Several limitations of this study should be acknowledged. First, this was a single-center retrospective study. Although the overall sample size was 275 patients, a post-hoc power analysis based on the observed effect size revealed that the actual statistical power was only approximately 30%-40%, indicating that the sample size was insufficient to reliably detect the hypothesized survival differences. This limitation is particularly pronounced in the HER2-low and triple-negative subgroups, where the small case numbers further compromised statistical precision. Consequently, the conclusions of this study should be regarded as exploratory and hypothesis-generating rather than confirmatory, and all significant findings require validation in larger, independent cohorts. Second, the median follow-up time was

48.5 months, which is relatively short for assessing long-term survival outcomes; extended follow-up is needed to collect more comprehensive data on post-treatment survival in breast cancer patients. Third, although all enrolled patients met the standard indications for postoperative radiotherapy, the inclusion of Luminal A patients with early-stage disease - who generally have favorable prognosis - may have introduced heterogeneity in baseline risk. This heterogeneity was addressed by adjustment for molecular subtype, TNM stage, lymph node status, and pathological grade in the multivariable Cox regression model. Fourth, the heterogeneity of systemic treatment regimens (including chemotherapy, endocrine therapy, and anti-HER2 therapy) across different molecular subtypes may have introduced residual confounding that could not be fully adjusted for in the multivariable model. Fifth, this study spanned approximately nine years (2015-2023), during which systemic treatment protocols for breast cancer evolved over time. Although radiotherapy regimens remained relatively stable throughout the study period and we adjusted for treatment variables in the multivariable Cox regression model, the retrospective nature of the study precluded a formal era-based subgroup analysis due to the lack of precise temporal records for treatment protocol changes and the limited adoption of newer agents (e.g., CDK4/6 inhibitors, PARP inhibitors) during the study period. The potential impact of treatment era on outcomes should therefore be interpreted with caution. Sixth, for Luminal A and Luminal B subgroups in which median survival was not reached, conventional median-based survival comparison was not feasible, which limited the comprehensiveness of survival analysis across molecular subtypes. The restricted mean survival time (RMST) method, which does not rely on the proportional hazards assumption and can provide a more comprehensive summary of survival differences even when medians are not estimable, has been increasingly recommended in such settings. However, due to the retrospective design and the limited follow-up duration, we were unable to perform RMST analysis in the current study. Future prospective studies with extended follow-up and larger sample sizes are warranted to apply RMST analysis for more robust comparisons across molecular subtypes. Seventh, quality of life (QoL) was assessed only at a single time point at the end of radiotherapy without baseline measurements, which precludes any causal inference regarding the impact of molecular subtype on QoL changes. Additionally, the QoL analysis was not adjusted for potential confounders. Therefore, the QoL findings should be considered exploratory and descriptive only, and should be interpreted with caution. Future prospective studies with longitudinal QoL assessments and appropriate adjustment for confounders are needed to evaluate the dynamic changes in QoL across molecular subtypes. Therefore, large-scale, multicenter prospective studies with standardized treatment protocols and longer follow-up are warranted to validate and extend our findings.

In conclusion, survival outcomes after radiotherapy vary considerably among different molecular subtypes of breast cancer. Among them, Luminal breast cancer patients have a good prognosis; triple-negative breast cancer patients are at high risk of recurrence and metastasis and have the lowest 5-year survival rate. At the same time, there is an increased risk of treatment-related adverse effects, and the quality of life for triple-negative breast cancer patients is significantly lower than that of the other two types.

Disclosure of conflict of interest

None.

Address correspondence to: Danxin Wu, Department of Oncology, Taihe Hospital, Hubei University of Medicine, No. 32 Renmin South Road, Maojian District, Shiyan 442000, Hubei, China. Tel: +86-15897878583; E-mail: wudanxin.hbmu@vip.163.com

References

[1] Katsura C, Ogunmwonyi I, Kankam HK and Saha S. Breast cancer: presentation, investigation and management. Br J Hosp Med (Lond) 2022; 83: 1-7.

[2] Michaels E, Worthington RO and Rusiecki J. Breast cancer: risk assessment, screening, and primary prevention. Med Clin North Am 2023; 107: 271-284.

[3] Ben-Dror J, Shalamov M and Sonnenblick A. The history of early breast cancer treatment. Genes (Basel) 2022; 13: 960.

[4] Jiang J, Li L, Yin G, Luo H and Li J. A molecular typing method for invasive breast cancer by se-

rum Raman spectroscopy. Clin Breast Cancer 2024; 24: 376-383.
[5] Xiang DL and Yue X. Research progress of molecular typing and targeted therapy for triple-negative breast cancer. Front Oncol 2025; 15: 1666126.
[6] Ugiagbe EE and Owolabi DO. Molecular subtypes of breast cancer in a Tertiary Centre in Edo State: south-south Nigeria. West Afr J Med 2024; 41: 767-774.
[7] Yoon J and Oh DY. HER2-targeted therapies beyond breast cancer - an update. Nat Rev Clin Oncol 2024; 21: 675-700.
[8] Modi S, Jacot W, Yamashita T, Sohn J, Vidal M, Tokunaga E, Tsurutani J, Ueno NT, Prat A, Chae YS, Lee KS, Niikura N, Park YH, Xu B, Wang X, Gil-Gil M, Li W, Pierga JY, Im SA, Moore HCF, Rugo HS, Yerushalmi R, Zagouri F, Gombos A, Kim SB, Liu Q, Luo T, Saura C, Schmid P, Sun T, Gambhire D, Yung L, Wang Y, Singh J, Vitazka P, Meinhardt G, Harbeck N and Cameron DA; DESTINY-Breast04 Trial Investigators. Trastuzumab deruxtecan in previously treated HER2-low advanced breast cancer. N Engl J Med 2022; 387: 9-20.
[9] Bardia A, Hurvitz SA, Tolaney SM, Loirat D, Punie K, Oliveira M, Brufsky A, Sardesai SD, Kalinsky K, Zelnak AB, Weaver R, Traina T, Dalenc F, Aftimos P, Lynce F, Diab S, Cortés J, O'Shaughnessy J, Diéras V, Ferrario C, Schmid P, Carey LA, Gianni L, Piccart MJ, Loibl S, Goldenberg DM, Hong Q, Olivo MS, Itri LM and Rugo HS; ASCENT Clinical Trial Investigators. Sacituzumab Govitecan in metastatic triple-negative breast cancer. N Engl J Med 2021; 384: 1529-1541.
[10] Intriago-Baldeón DP, Pérez-Coral ES, Armas Samaniego MI, Romero VI, Pozo Palacios JC and Bigoni-Ordóñez GD. Decoding breast cancer: emerging molecular biomarkers and novel therapeutic targets for precision medicine. Int J Mol Sci 2025; 27: 138.
[11] Schmid P, Adams S, Rugo HS, Schneeweiss A, Barrios CH, Iwata H, Diéras V, Hegg R, Im SA, Shaw Wright G, Henschel V, Molinero L, Chui SY, Funke R, Husain A, Winer EP, Loi S and Emens LA; IMpassion130 Trial Investigators. Atezolizumab and Nab-paclitaxel in advanced triple-negative breast cancer. N Engl J Med 2018; 379: 2108-2121.
[12] Montazeri Aliabadi H. Molecular targets for breast cancer therapy. Biomolecules 2024; 14: 1219.
[13] von Minckwitz G, Huang CS, Mano MS, Loibl S, Mamounas EP, Untch M, Wolmark N, Rastogi P, Schneeweiss A, Redondo A, Fischer HH, Jacot W, Conlin AK, Arce-Salinas C, Wapnir IL, Jackisch C, DiGiovanna MP, Fasching PA, Crown JP, Wülfing P, Shao Z, Rota Caremoli E, Wu H, Lam LH, Tesarowski D, Smitt M, Douthwaite H, Singel SM and Geyer CE Jr; KATHERINE Investigators. Trastuzumab emtansine for residual invasive HER2-positive breast cancer. N Engl J Med 2019; 380: 617-628.
[14] Harbeck N, Rastogi P, Martin M, Tolaney SM, Shao ZM, Fasching PA, Huang CS, Jaliffe GG, Tryakin A, Goetz MP, Rugo HS, Senkus E, Testa L, Andersson M, Tamura K, Del Mastro L, Steger GG, Kreipe H, Hegg R, Sohn J, Guarneri V, Cortés J, Hamilton E, André V, Wei R, Barriga S, Sherwood S, Forrester T, Munoz M, Shahir A, San Antonio B, Nabinger SC, Toi M, Johnston SRD and O'Shaughnessy J; monarchE Committee Members. Adjuvant abemaciclib combined with endocrine therapy for high-risk early breast cancer: updated efficacy and Ki-67 analysis from the monarchE study. Ann Oncol 2021; 32: 1571-1581.
[15] Yoshitake R, Mori H, Ha D, Wu X, Wang J, Wang X, Saeki K, Chang G, Shim HJ, Chan Y and Chen S. Molecular features of luminal breast cancer defined through spatial and single-cell transcriptomics. Clin Transl Med 2024; 14: e1548.
[16] Ma D, Dai LJ, Wu XR, Liu CL, Zhao S, Zhang H, Chen L, Xiao Y, Li M, Zhao YZ, Yang L, Zhou T, Li JJ, Yang WT, Jiang YZ and Shao ZM. Spatial determinants of antibody-drug conjugate SHR-A1811 efficacy in neoadjuvant treatment for HER2-positive breast cancer. Cancer Cell 2025; 43: 1061-1075, e7.
[17] Cai YW, Liu CC, Zhang YW, Liu YM, Chen L, Xiong X, Shao ZM and Yu KD. MAP3K1 mutations confer tumor immune heterogeneity in hormone receptor-positive HER2-negative breast cancer. J Clin Invest 2024; 135: e183656.
[18] Huppert LA, Gumusay O, Idossa D and Rugo HS. Systemic therapy for hormone receptor-positive/human epidermal growth factor receptor 2-negative early stage and metastatic breast cancer. CA Cancer J Clin 2023; 73: 480-515.
[19] Chen N, Freeman JQ, Yarlagadda S, Atmakuri A, Kalinsky K, Pusztai L, Sparano JA, Huo D, Nanda R and Howard FM. Impact of anthracyclines in genomic high-risk, node-negative, HR-positive/HER2-negative breast cancer. Ann Oncol 2025; 36: 1356-1365.
[20] Ahuja S, Khan AA and Zaheer S. Understanding the spectrum of HER2 status in breast cancer: from HER2-positive to ultra-low HER2. Pathol Res Pract 2024; 262: 155550.
[21] Bischoff H, Espié M and Petit T. Neoadjuvant therapy: current landscape and future horizons for ER-positive/HER2-negative and triple-negative early breast cancer. Curr Treat Options Oncol 2024; 25: 1210-1224.

[22] Gabrielson M, Hammarström M, Bergqvist J, Lång K, Rosendahl AH, Borgquist S, Hellgren R, Czene K and Hall P. Baseline breast tissue characteristics determine the effect of tamoxifen on mammographic density change. Int J Cancer 2024; 155: 339-351.

[23] Benitez Fuentes JD, Morgan E, de Luna Aguilar A, Mafra A, Shah R, Giusti F, Vignat J, Znaor A, Musetti C, Yip CH, Van Eycken L, Jedy-Agba E, Piñeros M and Soerjomataram I. Global stage distribution of breast cancer at diagnosis: a systematic review and meta-analysis. JAMA Oncol 2024; 10: 71-78.

[24] Teichgraeber DC, Guirguis MS and Whitman GJ. Breast cancer staging: updates in the *AJCC cancer staging manual*, 8th edition, and current challenges for radiologists, from the *AJR* special series on cancer staging. AJR Am J Roentgenol 2021; 217: 278-290.

[25] Gkekos L, Gunnarsdóttir KÁ, Humphreys K, Fredriksson I and Johansson ALV. Age-specific breast cancer incidence by subtype, TNM stage and screening status in Sweden 2008-2019 estimated with multiple imputation. Int J Cancer 2026; 159: 101-110.

[26] Lu Y, Hui B, Yang D, Li Y, Li B, Zhou L, Xu L, Tang F, Wang W, Chen R and Zhao D. Efficacy and safety analysis of hypofractionated and conventional fractionated radiotherapy in postoperative breast cancer patients. BMC Cancer 2024; 24: 181.

[27] Di Nardo P, Lisanti C, Garutti M, Buriolla S, Alberti M, Mazzeo R and Puglisi F. Chemotherapy in patients with early breast cancer: clinical overview and management of long-term side effects. Expert Opin Drug Saf 2022; 21: 1341-1355.

[28] Franzoi MA, Agostinetto E, Perachino M, Del Mastro L, de Azambuja E, Vaz-Luis I, Partridge AH and Lambertini M. Evidence-based approaches for the management of side-effects of adjuvant endocrine therapy in patients with breast cancer. Lancet Oncol 2021; 22: e303-e313.

[29] Abdo J, Ortman H, Rodriguez N, Tillman R, Riordan EO and Seydel A. Quality of life issues following breast cancer treatment. Surg Clin North Am 2023; 103: 155-167.

Supplementary Table 1. Detailed systemic therapy regimens

Treatment modality	Regimen	Drug and dosage	Cycle	Dose adjustment principles
Chemotherapy	AC → Paclitaxel	Doxorubicin 60 mg/m^2 IV + Cyclophosphamide 600 mg/m^2 IV, followed by Paclitaxel 80 mg/m^2 IV weekly	AC: 4 cycles (q2-3w); Paclitaxel: 12 weeks	For grade ≥3 hematologic (ANC <1.0×10^9/L, PLT <50×10^9/L) or non-hematologic toxicity, delay until recovery to ≤ grade 1; reduce subsequent doses by 15-25% per institutional guidelines
	AC → Docetaxel	Doxorubicin 60 mg/m^2 IV + Cyclophosphamide 600 mg/m^2 IV, followed by Docetaxel 75-100 mg/m^2 IV	AC: 4 cycles (q2-3w); Docetaxel: 4 cycles (q3w)	Same as above; docetaxel reduced to 75 mg/m^2 for grade ≥3 toxicity
	TC (low cardiac risk)	Docetaxel 75 mg/m^2 IV + Cyclophosphamide 600 mg/m^2 IV	4 cycles (q3w)	Same as above
Endocrine therapy	Tamoxifen	Tamoxifen 20 mg PO daily	5-10 years (extend to 10 years for high-risk)	-
	Aromatase inhibitor	Letrozole 2.5 mg, Anastrozole 1 mg, or Exemestane 25 mg PO daily	5-10 years (extend to 10 years for high-risk)	-
Anti-HER2 therapy	Trastuzumab (3-weekly)	Loading 8 mg/kg IV, then 6 mg/kg IV q3w	17 cycles (1 year)	For LVEF decline ≥15% or to <50%, withhold and reassess in 3 weeks; resume if recovered
	Trastuzumab (weekly)	Loading 4 mg/kg IV, then 2 mg/kg IV weekly	52 weeks (1 year)	Same as above
	Trastuzumab + Pertuzumab	Trastuzumab (as above) + Pertuzumab loading 840 mg IV, then 420 mg IV q3w	17 cycles (1 year)	Same as above; pertuzumab dose modification not required for toxicity

Abbreviations: AC, doxorubicin + cyclophosphamide; TC, docetaxel + cyclophosphamide; IV, intravenous; PO, per os (orally); q2-3w, every 2-3 weeks; q3w, every 3 weeks; ANC, absolute neutrophil count; PLT, platelet; LVEF, left ventricular ejection fraction.