Boost delivery in hypofractionated breast cancer radiotherapy: A registry-based analysis of treatment patterns and survival

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Abstract. Hypofractionated radiotherapy (RT) has become standard in breast cancer treatment; however, the factors guiding boost application and its impact on survival remain uncertain. In the present study, predictors of boost application and its association with survival were analyzed. A registry-based analysis of n=3,411 patients with breast cancer treated with hypofractionated RT, including 40 post-mastectomy cases, was conducted; n=1,366 patients received a boost. Predictors of boost administration were assessed using uni- and multivariate logistic regression, and overall survival (OS) was examined using Cox hazards models, including subgroup analyses stratified by boost RT, with missing data addressed using complete-case and multiple imputation approaches. The median age was 62 years (interquartile range, 54-70 years). Younger age [odds ratio (OR), 0.96 per year; 95% CI, 0.95-0.97], higher T-stage (T2; OR, 2.54; 95% CI, 1.86-3.48), positive HER2 status (OR, 1.85; 95% CI, 1.31-2.61) and RT target volume (whole-breast irradiation) predicted boost administration. Higher T-stage [T2: hazard ratio (HR), 1.72; 95% CI, 1.04-2.84; T3+: HR, 4.26; 95% CI, 1.55-11.7] and older age (HR, 1.06 per year; 95% CI, 1.04-1.09) were associated with worse OS, while positive progesterone receptor (PR) status predicted improved OS (HR, 0.46; 95% CI, 0.23-0.90). Boost administration exhibited no significant impact (HR, 0.98; 95% CI, 0.60-1.58). In this registry-based cohort, younger age, higher T-stage, positive HER2 status and RT target region independently predicted boost administration. While higher T-stage, older age and PR negativity were associated with worse OS, boost administration itself had no significant impact.

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Abbreviations: Boost, tumor-bed boost; BCS, breast-conserving surgery; DCIS, ductal carcinoma *in situ*; ECOG, Eastern Co-operative Oncology Group; ER, estrogen receptor; Gy, Gray; HR, hazard ratio; IQR, interquartile range; KM, Kaplan-Meier; LC, local control; LR, local recurrence; N-stage, nodal stage; OR, odds ratio; OS, overall survival; PR, progesterone receptor; PSM, propensity score matching; R-status, resection status; RT target region, radiation target region; RT target volume, radiation target volume; RT, radiotherapy; SMD, standardized mean difference; T-stage, tumor stage; WBI, whole-breast irradiation

Key words: breast neoplasm, hypofractionated radiotherapy, radiation boost, registry-based study, survival

Introduction

Breast cancer is the most common malignancy among women worldwide, accounting for nearly one quarter of all female cancers, with more than 2.2 million new diagnoses and approximately 685 000 deaths in 2020 (1). Advances in early detection and systemic therapy have substantially improved survival, which now exceeds 85% at five years in high-income regions, although breast cancer remains the leading cause of cancer-related mortality in women (2).

Long-term outcomes are primarily determined by tumour biology and patient characteristics. Hormone receptor positivity-particularly estrogen receptor (ER) expression-is associated with favorable prognosis and responsiveness to endocrine therapy (3). HER2 overexpression historically predicted poor survival, but HER2-targeted therapies such as trastuzumab have substantially reduced this negative prognostic impact (4,5). Tumour size, nodal involvement, histological grade, and patient age remain additional key prognostic factors that guide adjuvant treatment decisions. Large population-based analyses have demonstrated a clear association between tumour size, nodal status, and survival (6), while histological grade is an independent prognostic factor correlated with disease-free and OS (7). Patient age has also been shown to influence prognosis and treatment response (8).

Adjuvant RT after breast-conserving surgery (BCS) is a cornerstone of curative treatment. Meta-analyses have shown that RT halves the risk of local recurrence (LR) and provides a modest but significant improvement in breast cancer-specific

survival (8). Over the past two decades, hypofractionated WBI has become standard of care. Large randomized trials, including the Canadian and START A/B studies, demonstrated equivalent local control (LC), survival, and reduced toxicity compared with conventional fractionation (9,10). Accordingly, hypofractionated WBI is recommended by major international and national guidelines, including the German S3, DEGRO, and ESTRO/ASTRO recommendations (11,12).

The addition of a tumour-bed boost improves LC, particularly in younger women, but does not confer an OS benefit, as confirmed by the 20-year follow-up of the EORTC 22881/10882 trial (13). Randomized trials, however, are often limited by strict eligibility criteria and may not fully reflect clinical practice. International reviews and retrospective analyses suggest that clinical and patient-related risk factors influence the decision to apply a boost, highlighting its selective use in higher-risk populations (14,15).

Evidence from large-scale German registries on predictors of boost utilization and its impact on OS in modern hypofractionated regimens remains limited. The present study therefore aimed to (1) identify clinicopathological factors associated with tumour-bed boost administration and (2) evaluate whether boost irradiation influences OS in a contemporary, population-based cohort.

Materials and methods

Study population and data source. We conducted a retrospective, registry-based analysis of female breast cancer patients treated with RT using anonymized data from the North Rhine-Westphalia cancer registry, Germany. The original cohort comprised n=23783 patients diagnosed between January 2016 and December 2022. Patients were excluded if they did not receive RT (n=13092) or if RT was not directed to the breast (n=3046), leaving n=7645 eligible for breast-targeted RT per predefined fractionation schemes.

Both invasive carcinomas and cases of ductal carcinoma *in situ* (DCIS) were included to comprehensively represent all breast-directed RT indications. DCIS cases were identified based on morphology codes and analyzed as a distinct subgroup within T-stage (labelled as 'carcinoma *in situ*') to preserve registry coding and ensure histopathological accuracy. While T0 typically indicates no detectable primary tumour, a small subset of patients had T0 coded despite histologically confirmed carcinoma *in situ*, which was therefore separately labelled to maintain data integrity.

Hypofractionated regimens without a boost delivered 2.6-2.7 Gy per fraction (total 36-42.56 Gy), whereas regimens with a boost used 2.5-2.67 Gy per fraction (total 48-55 Gy). Normofractionated regimens comprised 1.8 Gy per fraction (total 50.4-70.4 Gy), and ultra-hypofractionated regimens delivered 5-6 Gy per fraction (typical total 25-30 Gy; range 10-54 Gy). Patients undergoing BCS or mastectomy, including those receiving regional nodal irradiation, were included if fractionation criteria were met. After applying these criteria, n=3411 patients received hypofractionated RT, of whom n=1366 received an additional tumour-bed boost.

Extracted variables included patient demographics (age, sex and International Classification of Diseases-10 codes), tumour characteristics [T-stage (Tumour), N-stage (Nodal), grade, hormone receptor and HER2 status, morphology], and treatment details [surgery type, laterality, RT schedule and target region, Resection status (R-status), and systemic therapy]. Baseline characteristics of the hypofractionated cohort were summarized using descriptive statistics and stratified by boost status (Table I). Continuous variables are presented as median (interquartile range), and categorical variables as counts and percentages. Ethical approval was not required as only anonymized registry data were used. The study adhered to the Declaration of Helsinki.

Statistical analysis. Baseline characteristics were summarized descriptively. Predictors of boost administration were evaluated using uni- and multivariable logistic regression, including all clinically relevant variables (age, T-stage, N-stage, hormone receptor, HER2 status and histologic grade, laterality, and RT target region). Patients with unknown T/N-stage or bilateral disease were excluded to ensure model stability.

OS was analyzed from diagnosis to death or censoring at December 31, 2023, using Cox proportional hazards models. Boost status was included as a covariate in all survival models. Covariates included in the final Cox model were selected based on established prognostic relevance in early breast cancer and availability in the registry. The final model included age, N-stage (0, 1, micrometastases, N2+), T-stage (1, 2, T3+), PR-status (negative, positive), ER status (negative, positive), and R-status (R0, R1, Rx). Variables with rare categories or producing unstable estimates or not available (NA) values in model fitting (e.g., certain categories of RT target region) were excluded to improve model stability and interpretability. Results are reported as odds ratios (OR) or hazard ratios (HR) with 95% confidence intervals (CI); two-sided $p<0.05$ was considered significant. Median follow-up was estimated the reverse Kaplan-Meier method. The survival curves were presented descriptively and were not formally compared using a statistical test.

All analyses were performed in R (RStudio, version 2024.04.2 +764; R Foundation for Statistical Computing, Vienna, Austria) using the packages survival (16,17), survminer (18), and ggplot2 (19).

Handling of variables and missing data. Covariates were selected based on their established prognostic relevance in early breast cancer, as supported by patient-level meta-analyses, clinical boost studies, and international guideline recommendations, and included age, T-stage, N-status, hormone receptor status, and R-status (8,11,13). Variables with rare categories, extremely wide CIs, or unstable estimates were either combined or excluded to improve model stability and interpretability. Missing data were primarily handled by complete-case analysis, with sensitivity analyses using multiple imputation [mice package (20) five imputations, predictive mean matching]. An additional multivariable logistic regression model was fitted as a sensitivity analysis to identify predictors of missing boost data. P-values for this analysis were likewise derived using Wald tests. Logistic and Cox models were repeated across imputed datasets, with results pooled per Rubin's rules to confirm robustness. Eastern Co-operative Oncology Group (ECOG) performance status was recorded as 'unknown' for the majority of patients and

Table I. Patient characteristics by boost group.

Characteristic	Without boost (N=2,045)	With boost (N=1,366)
Age, years	64 (56, 71)	60 (52, 69)
T-stage		
0	5 (0.24)	0 (0.00)
1	1,301 (63.62)	809 (59.22)
2	369 (18.04)	417 (30.53)
3	23 (1.13)	20 (1.46)
4	16 (0.78)	7 (0.51)
Carcinoma *in situ*	33 (1.61)	16 (1.17)
Micrometastases	7 (0.34)	1 (0.07)
Unknown	291 (14.23)	96 (7.03)
N-stage		
0	1,488 (72.76)	1,115 (81.63)
1	159 (7.78)	109 (7.98)
2	16 (0.78)	17 (1.25)
3	9 (0.44)	3 (0.22)
Micrometastases	46 (2.25)	13 (0.95)
Unknown	327 (15.99)	109 (7.98)
Grading		
High	634 (31.00)	427 (31.26)
Intermediate	1,182 (57.80)	736 (53.88)
Low	228 (11.15)	191 (13.98)
Unknown	1 (0.05)	12 (0.88)
Her2neu status		
Negative	1,379 (67.43)	782 (57.25)
Positive	268 (13.11)	279 (20.42)
Unknown	398 (19.46)	305 (22.33)
Estrogen receptor status		
Negative	176 (8.61)	176 (12.88)
Positive	1,533 (74.96)	950 (69.55)
Unknown	336 (16.43)	240 (17.57)
Progesteron receptor status		
Negative	304 (14.87)	263 (19.25)
Positive	1,402 (68.56)	862 (63.10)
Unknown	339 (16.58)	241 (17.64)
Resection status		
R0	1,358 (66.41)	1,187 (86.90)
R1	27 (1.32)	31 (2.27)
R2	7 (0.34)	2 (0.15)
Rx	229 (11.20)	89 (6.52)
Unknown	424 (20.73)	57 (4.17)

Unknown includes missing data. Data are presented as the median (Q1, Q3) or n (%). Boost, tumor-bed boost.

was therefore considered insufficiently informative for inclusion in the primary multivariable models. Due to the limited interpretability and potential unreliability of imputing such a

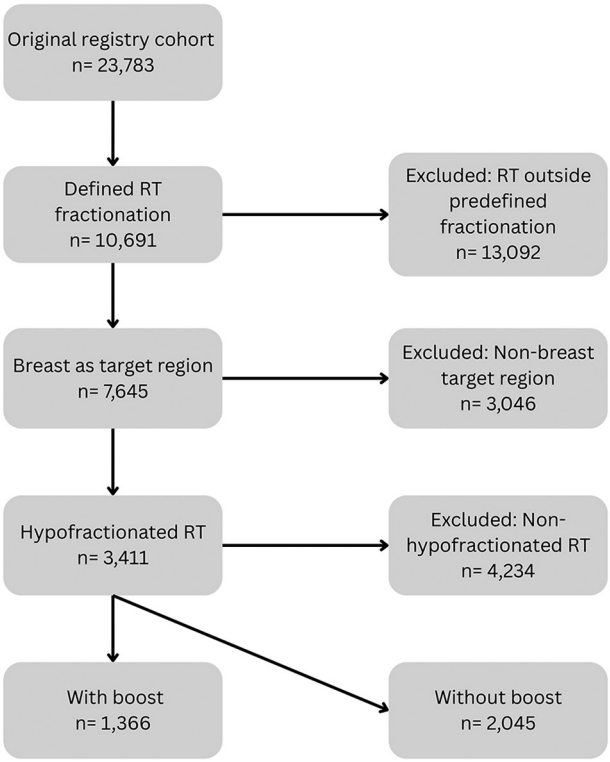

Figure 1. Case selection from original registry cohort. RT, radiotherapy.

variable, ECOG was not included in the primary multivariable analyses or the multiple imputation procedure. To assess the potential impact of performance status on the study findings, an additional sensitivity analysis including ECOG as a covariate was performed.

Propensity score matching analysis. To address potential indication bias due to the retrospective study design, a propensity score matching (PSM) analysis was performed as a sensitivity analysis. From the initial hypofractionated cohort of n=3411 patients, n=2527 patients with complete covariate and survival data were available for the primary survival analyses.

For the PSM analysis, patients were additionally restricted to those with complete data on all matching covariates, resulting in a matching cohort of n=2206 patients. A 1:1 nearest-neighbor matching without replacement was applied using a caliper width of 0.2 on the logit of the propensity score.

The propensity score model included age, T-stage, N-stage, grading, HER2 status, ER-status, and PR-status. Covariate balance before and after matching was assessed using standardized mean differences (SMDs) and visualized using Love plots, with values <0.1 considered indicative of adequate balance.

After matching, a total of n=900 patients in each group (boost vs. no boost) were included in the final matched cohort.

Results

Case selection. Restricting the eligible cohort to hypofractionated regimens yielded n=3411 patients, of whom n=1366 (40%) received a tumour-bed boost and n=2045 (60%) did not (Fig. 1). Median follow-up was 28 months overall [interquartile range

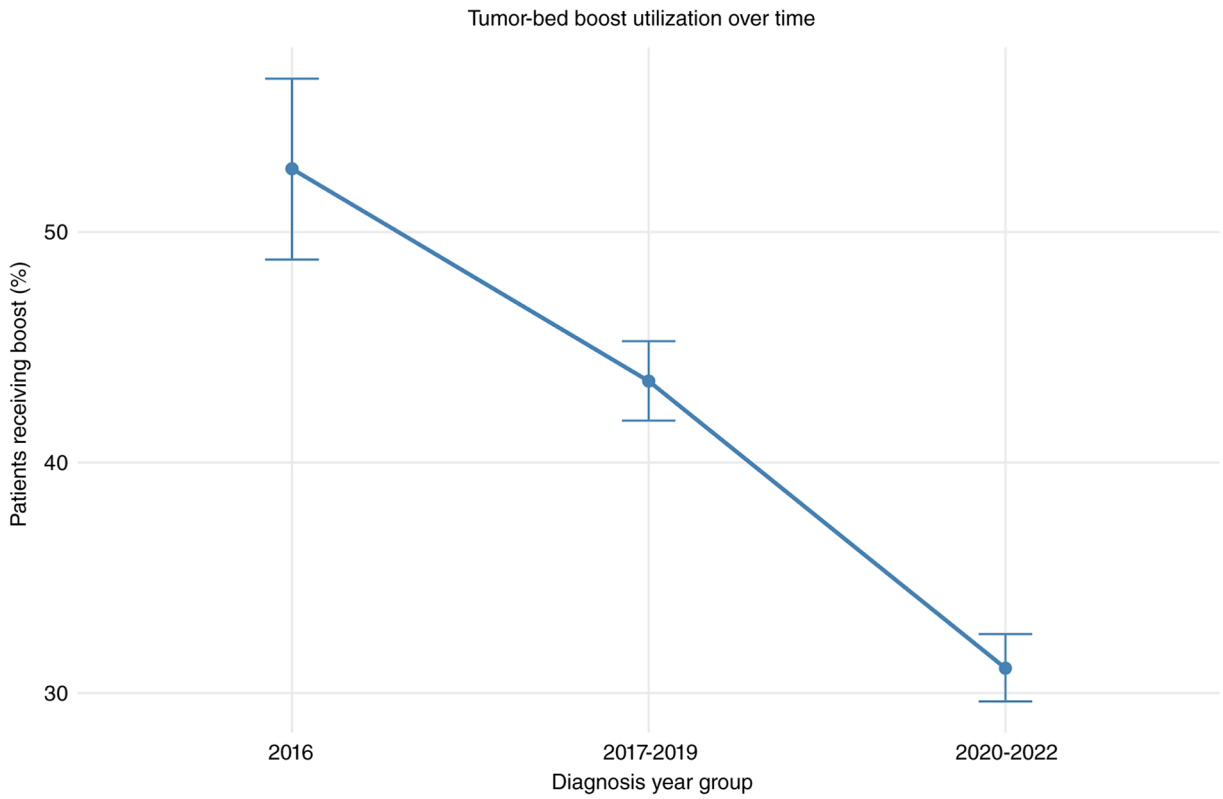

Figure 2. Trends in tumor-bed boost utilization over time.

(IQR): 17-47], 37 months in the boost group (IQR: 23-53), and 23 months without boost (IQR: 15-44).

Patient characteristics. Baseline demographics and tumour characteristics of the hypofractionated cohort stratified by boost administration are summarized in Table I. Patients receiving a boost were younger than those treated without a boost [median age 60 years (IQR 52-69) vs. 64 years (IQR 56-71)]. Most tumors were classified as T1 or T2 stage, although T2 tumors were more frequent among boost-treated patients (31% vs. 18%). Node-negative disease predominated in both groups and was more common in the boost group (82% vs. 73%). Histologic grade was comparable between groups, with approximately one-third of tumors being high grade. HER2-positive tumors were more frequent among patients receiving a boost (20% vs. 13%), while hormone receptor positivity was common in both groups. Final R0 resection status was achieved in 87% of boost-treated patients compared with 66% of patients without boost irradiation. Missing values were primarily observed for registry-derived variables, including T-stage, N-stage, receptor status, and R-status.

Predictors of boost administration. In univariable analyses, younger age was linked to higher odds of receiving a boost (OR 0.96 per year, 95% CI 0.95-0.97, P<0.001). Patients undergoing postoperative or multimodal treatment (systemic therapy + radiotherapy ± surgery) were significantly more likely to receive a boost compared to those treated with radiotherapy alone (all P≤0.001). Higher T-stage (T2 vs. T1; OR 2.38, 95% CI 1.85-3.05, P<0.001) and positive N-status (N1: OR 1.52, P=0.025; N2: OR 3.48, P=0.012) were also associated with increased odds of boost administration. HER2-positive tumors showed higher odds of boost (OR 3.04, 95% CI 2.28-4.05, P<0.001), whereas hormone receptor positivity was inversely associated, with lower odds in both PR-positive (OR 0.67, P=0.012) and ER-positive tumors (OR 0.47, P<0.001). Regarding the RT target region, WBI was associated with higher boost rates, while partial-breast irradiation without nodal coverage was linked to markedly reduced odds (OR 0.13, 95% CI 0.05-0.26, P<0.001).

Multivariable logistic regression confirmed that younger age (OR 0.96 per year, 95% CI 0.95-0.97), higher T-stage (T2 vs. T1: OR 2.54, 95% CI 1.85-3.48), HER2 positivity (OR 1.85, 95% CI 1.31-2.60), and WBI (OR 1.62, 95% CI 1.16-2.28) were independent predictors. Partial-breast irradiation without nodal coverage remained negatively associated (OR 0.21, 95% CI 0.08-0.45). Low tumour grade was also significantly associated with boost allocation (OR 1.57, 95% CI 1.00-2.43). N-stage, PR/ER status, and final R-status were not significant after adjustment (Table II).

Temporal trends in boost administration are illustrated in Fig. 2. The proportion of patients receiving a tumor-bed boost was highest in 2016 (>50%) and subsequently declined, with rates exceeding 40% in 2017-2019 and 30% in 2020-2022. CIs are shown to illustrate the precision of these estimates. Missing values for boost allocation were rare, ranging from 0.2 to 0.9% across the study years (2016: 0.5%, 2017-2019: 0.2%, 2020-2022: 0.9%) (Table SI). Additional details on temporal trends and data completeness are provided in Data S1.

Survival analyses. In univariable Cox models, increasing age, higher T-stage, and higher N-stage were associated with worse

Table II. Univariate and multivariate logistic regression analyses for predictors of tumor-bed boost administration.

	Univariate analysis				Multivariate analysis			
Characteristic	N	OR	95% CI	P-value	N	OR	95% CI	P-value
Age	1,917	0.96	0.95, 0.97	<0.001	1,649	0.96	0.95, 0.97	<0.001
Treatment								
Radiotherapy alone	177	-	-		41	-	-	
Postoperative radiotherapy	900	3.18	1.83, 5.99	<0.001	848	0.86	0.40, 1.97	0.699
Systemictherapy + radiotherapy	57	1.77	0.63, 4.56	0.251	19	0.44	0.11, 1.70	0.240
Systemictherapy + radiotherapy + surgery	783	2.65	1.52, 5.03	0.001	741	0.49	0.22, 1.14	0.086
Breast laterality								
Left	987	-	-		838	-	-	
Right	930	0.98	0.77, 1.24	0.858	811	0.96	0.73, 1.25	0.741
T-stage								
1	1,418	-	-		1,225	-	-	
2	473	2.38	1.85, 3.05	<0.001	400	2.54	1.86, 3.48	<0.001
Carcinoma *in situ*	26	0.24	0.01, 1.15	0.164	24	0.23	0.01, 1.25	0.169
N-stage								
0	1,671	-	-		1,435	-	-	
1	179	1.52	1.04, 2.18	0.025	151	0.99	0.61, 1.60	0.969
2	17	3.48	1.25, 9.13	0.012	16	1.13	0.31, 4.02	0.852
Micrometastases	50	0.95	0.41, 1.93	0.888	47	0.78	0.32, 1.72	0.560
HER2 status								
Negative	1,309	-	-		1,127	-	-	
Positive	296	3.04	2.28, 4.05	<0.001	281	1.85	1.31, 2.61	<0.001
Unknown	312	1.11	0.78, 1.55	0.546	241	1.90	0.96, 3.69	0.060
Progesteron receptor status								
Negative	258	-	-		220	-	-	
Positive	1,410	0.67	0.49, 0.92	0.012	1,231	1.05	0.61, 1.87	0.858
Unknown	249	0.53	0.33, 0.83	0.006	198	1.93	0.14, 21.40	0.589
Estrogen receptor status								
Negative	146	-	-		128	-	-	
Positive	1,526	0.47	0.33, 0.70	<0.001	1,325	0.56	0.28, 1.09	0.089
Unknown	245	0.37	0.22, 0.62	<0.001	196	0.11	0.01, 1.55	0.075
Radiation target region								
Partial breast	342	-	-		331	-	-	
Partial breast with lymph node region	52	2.76	1.51, 5.01	<0.001	49	2.04	0.99, 4.21	0.052
Partial breast without lymph node region	171	0.13	0.05, 0.26	<0.001	112	0.21	0.08, 0.45	<0.001
Whole breast	677	1.15	0.86, 1.56	0.347	620	1.62	1.16, 2.27	0.005
Whole breast with lymph node region	30	1.49	0.65, 3.24	0.328	25	2.11	0.81, 5.35	0.115
Whole breast without lymph node region	645	0.10	0.06, 0.16	<0.001	512	0.15	0.09, 0.26	<0.001
Final resection status								
R0	1,405	-	-		1,405	-	-	
R1/Rx	244	0.79	0.55, 1.12	0.200	244	1.21	0.79, 1.84	0.487

Table II. Continued.

	Univariate analysis				Multivariate analysis			
Characteristic	N	OR	95% CI	P-value	N	OR	95% CI	P-value
Histologic grade								
High	592	-	-		509	-	-	
Intermediate	1,095	1.16	0.88, 1.52	0.295	936	1.15	0.85, 1.58	0.359
Low	230	1.49	1.01, 2.18	0.041	204	1.57	1.00, 2.43	0.047

OR, odds ratio.

Table III. Uni- and multivariate Cox regression analyses for overall survival.

	Univariate Cox analysis				Multivariate Cox analysis			
Characteristic	N	HR	95% CI	P-value	N	HR	95% CI	P-value
Boost	2,464	0.88	0.56, 1.37	0.566	2,181	0.98	0.60, 1.58	0.919
Age	2,464	1.07	1.04, 1.09	<0.001	2,181	1.06	1.04, 1.09	<0.001
N-stage								
0	2,114	-	-		1,905	-	-	
1	216	1.93	0.99, 3.76	0.054	190	1.08	0.50, 2.34	0.843
Micrometastases	52	1.37	0.34, 5.62	0.658	49	1.37	0.33, 5.69	0.666
N2+	40	7.42	2.67, 20.60	<0.001	37	2.64	0.81, 8.58	0.105
T-stage								
1	1,729	-	-		1,562	-	-	
2	630	2.05	1.28, 3.29	0.003	570	1.72	1.04, 2.84	0.036
T3+	55	10.90	5.05, 23.30	<0.001	49	4.26	1.55, 11.70	0.005
Progesteron receptor status								
Negative	440	-	-		384	-	-	
Positive	2,024	0.56	0.34, 0.91	0.019	1,797	0.46	0.23, 0.90	0.023
Estrogen receptor status								
Negative	275	-	-		241	-	-	
Positive	2,189	0.59	0.32, 1.06	0.079	1,940	1.15	0.49, 2.71	0.752
Final resection status								
R0	1,958	-	-		1,915	-	-	
R1	45	0.76	0.11, 5.46	0.783	45	0.71	0.10, 5.30	0.738
Rx	227	1.63	0.84, 3.17	0.152	221	1.73	0.84, 3.53	0.134

Boost, tumor-bed boost; HR, hazard ratio.

OS, while positive PR-status predicted improved survival; ER-status, final R-status, and tumour-bed boost showed no significant association (Table III). KM curves for OS stratified by boost status are shown in Fig. 3. Multivariable Cox regression confirmed that age (HR 1.06 per year, 95% CI 1.04-1.09), higher T-stage (T2: HR 1.72, 95% CI 1.04-2.84; T3+: HR 4.26, 95% CI 1.55-11.7), and positive PR-status (HR 0.46, 95% CI 0.23-0.90) were independent predictors of OS. No significant associations were observed for N-stage, ER-status, final R-status, or tumour-bed boost (HR 0.98, 95% CI 0.60-1.58). Median OS was not reached during follow-up. Given the relatively short median follow-up of 28 months, estimated short-term OS rates were additionally assessed. The 2-year OS rate was 98.1% (95% CI 97.3-98.9) in the non-boost group and 98.2% (95% CI 97.3-99.0) in the boost group. Corresponding 3-year OS rates were 97.0% (95% CI 95.8-98.1) and 96.8% (95% CI 95.6-98.1), respectively.

Sensitivity analyses. Sensitivity analyses using multiple imputation for missing covariates confirmed the robustness of our findings (Tables SII and SIII). Logistic regression assessing predictors of boost allocation identified age,

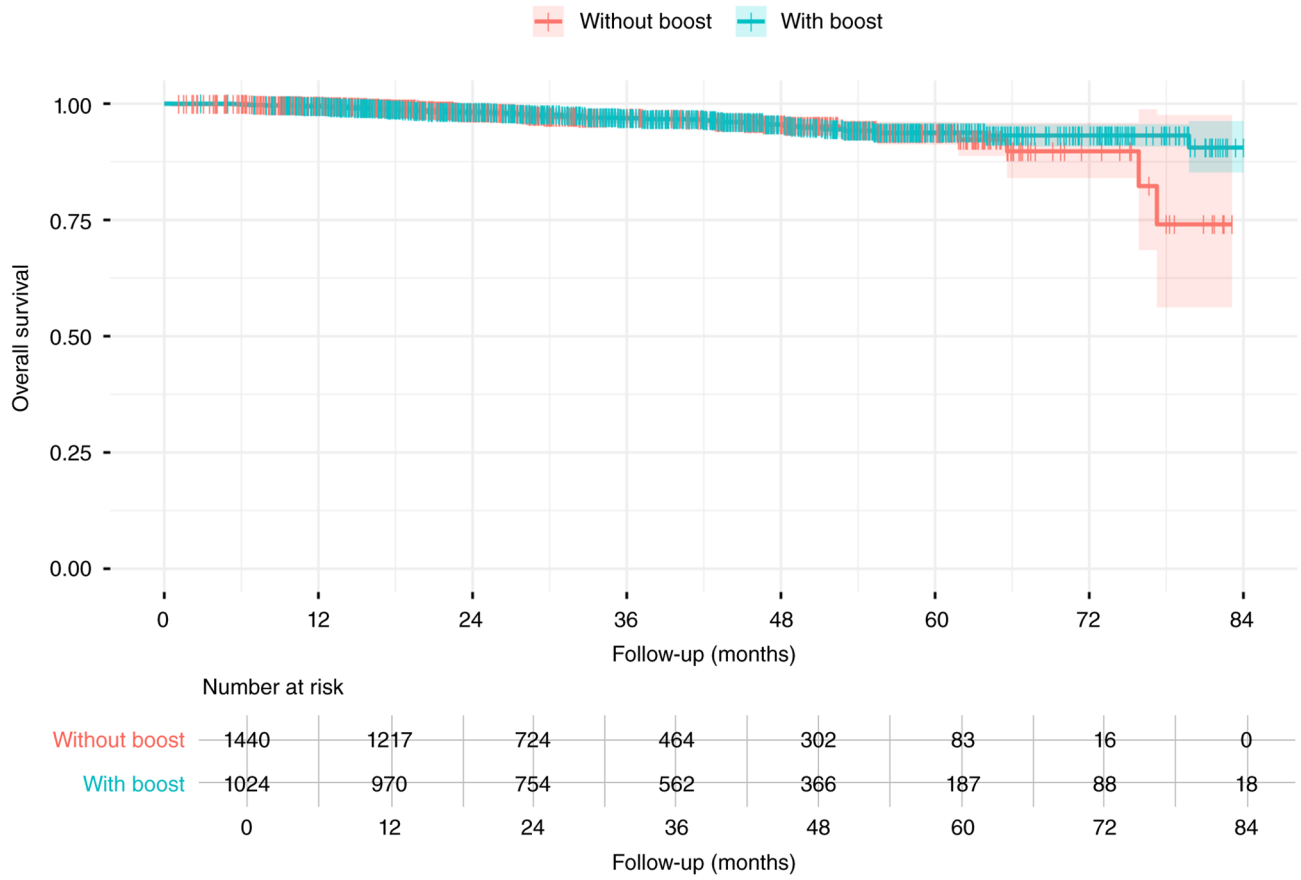

Figure 3. Kaplan-Meier curve (boost vs. no boost). Boost, tumor-bed boost.

higher T-stage, and radiation target volume (RT target volume) and lower grading as significant factors. An additional analysis of missing boost documentation across all n=7549 patients showed that older age slightly decreased, while certain treatment patterns-such as partial breast irradiation with lymph node coverage-increased the likelihood of missing data (OR 0.99 and OR 2.26, respectively) (Table SIV). Overall, missing boost information was rare (<1%) (Table SI). Boost irradiation was not associated with OS (HR 1.01, 95% CI 0.63-1.63), and PR positivity showed a non-significant trend toward improved survival. Further methodological details and additional analyses are provided in Data S1.

In an additional sensitivity analysis including ECOG performance status, the results remained largely unchanged. Boost irradiation was not associated with OS (HR 1.01, 95% CI 0.62-1.64, P=0.97). Age, T-stage, and PR-status remained significant prognostic factors. Higher ECOG categories (ECOG ≥2) were associated with worse OS (HR 14.43, 95% CI 3.67-56.81, P<0.001), although estimates should be interpreted cautiously because of the small number of patients in these categories (Table SV).

PSM was performed as an additional sensitivity analysis to reduce potential indication bias. After 1:1 nearest-neighbor matching, n=900 patients receiving a boost were matched to n=900 patients without boost irradiation. Covariate balance was substantially improved after matching, with all SMDs below 0.1 (Fig. S1; Table SVI). In the matched cohort, boost irradiation remained not significantly associated with OS (HR 0.87, 95% CI 0.50-1.49, P=0.60). In an additional sensitivity analysis including ECOG performance status (Table SVII), the results remained largely unchanged. Boost irradiation was not associated with OS (HR 1.01, 95% CI 0.62-1.64, P=0.97). Age, T-stage, PR-status and ECOG performance status were independently associated with OS.

Discussion

In this large, registry-based cohort of patients treated with hypofractionated breast RT, boost irradiation was not associated with improved OS. Instead, age, tumour stage, and PR status were the dominant prognostic factors. These results are consistent with previous registry analyses and long-term randomized trials, including the EORTC 22881/10882 study with 20-year follow-up, which demonstrated improved LC but no OS benefit with boost therapy (13).

In the multivariable analysis, older age and advanced T-stage were confirmed as adverse prognostic factors, whereas PR positivity was associated with improved OS. This observation aligns with previous multivariable analyses identifying PR positivity as an independent prognostic factor for improved OS, particularly in hormone receptor-positive breast cancer (21). Boost application was not associated with a significant improvement in OS (HR 0.98, 95% CI 0.60-1.58). This finding is consistent with long-term evidence indicating that survival outcomes in early-stage breast cancer are

primarily determined by tumour biology and systemic disease control, whereas escalation of local treatment mainly affects local recurrence risk rather than OS (13).

Boost allocation patterns reflected risk-adapted clinical practice. International guidelines recommend boost irradiation primarily for patients at higher risk of LR, such as younger women or those with higher tumour burden. Independent predictors considered in these recommendations include age, T-stage, HER2 status, and the RT target volume (11,12,22,23). Temporal trends further illustrated a decline in boost utilization over time, with rates exceeding 40% in 2017-2019 and 30% in 2020-2022, indicating adaptation to evolving evidence and guideline recommendations. This decline likely reflects the increasing establishment of hypofractionated regimens as the therapeutic standard and the more selective use of boost irradiation-consistent with an individualized, guideline-concordant approach to treatment planning (11,12,23).

Furthermore, long-term studies have shown that while a boost improves LC, it is associated with increased toxicity and cosmetic deterioration (13). Registry and cohort analyses likewise suggest that boost application is becoming increasingly selective, supporting an individualized, risk-adapted approach to RT (24).

Recent prospective studies of hypofractionated WBI with a simultaneous integrated boost have demonstrated excellent LC and low toxicity, confirming the safety of modern hypofractionated regimens (25,26). While such trials enrolled selected populations, this registry analysis represents real-world practice, including older and comorbid patients who are often under-represented in randomized controlled trials. These findings further reinforce the concept that long-term outcomes in early breast cancer are predominantly driven by tumour biology and systemic disease characteristics, while the contribution of local treatment intensification to OS remains limited. This interpretation is consistent with the EBCTCG meta-analysis, which demonstrated that radiotherapy primarily reduces local recurrence, whereas its effect on long-term breast cancer mortality is comparatively modest (13,27).

Beyond established clinicopathological factors, genomic assays such as Oncotype DX and MammaPrint have become important tools for recurrence risk stratification. Emerging evidence suggests that genomic signatures may also correlate with LR patterns and could therefore contribute to more individualized decisions regarding treatment intensification, including boost irradiation (28). Future integration of molecular biomarkers with RT outcomes may further refine personalized local treatment strategies.

The median follow-up of 28 months limits conclusions regarding long-term survival outcomes. The excellent 2-year and 3-year OS rates exceeding 96% in both groups reflect the low number of events and favorable short-term prognosis of this cohort. Longer follow-up will be required to determine whether differences in long-term outcomes emerge over time.

Key strengths include the large, population-based datasets reflecting real-world treatment patterns and adjustment for multiple clinicopathological factors. Restricting analyses to hypofractionated regimens ensures relevance to current practice. In addition, comprehensive sensitivity analyses, including multiple imputation, PSM, and adjustment for ECOG performance status, confirmed the robustness of the primary findings.

This study also has several limitations inherent to its retrospective and registry-based design. Boost delivery was not randomized but based on clinical judgement, leading to potential confounding by indication. Patients receiving a boost typically had less favorable baseline characteristics, which may bias crude outcome comparisons. However, comprehensive multivariable adjustment for relevant clinicopathologic factors and sensitivity analyses using multiple imputation support the robustness of our findings (Tables SII and SIII).

Additional limitations include reliance on a single regional cancer registry and missing data for several covariates, particularly T-stage, N-stage, receptor status, HER2 status, and ECOG performance status, which may have reduced the precision of subgroup analyses. Because the majority of ECOG values were recorded as unknown, this variable was not included in the primary multivariable analyses or the multiple imputation procedure. Nevertheless, an additional sensitivity analysis incorporating ECOG yielded results that were consistent with the main findings, suggesting that omission of this variable did not materially influence the observed association between boost irradiation and OS. The absence of LC, treatment-related toxicity, cosmetic outcome, and patient-reported quality-of-life data limits direct conclusions regarding treatment-related benefits and burdens. Consequently, the present analysis was restricted to oncologic outcomes and cannot address potential differences in tolerability or quality of life associated with boost irradiation. Nonetheless, OS represents a clinically meaningful and unbiased endpoint in this context. The median follow-up of 28 months further limits interpretation of long-term outcomes, and longer follow-up is required to assess potential late survival differences. Incomplete documentation of systemic therapy may also have introduced residual bias, although this variable was included in adjusted models where available.

Despite these limitations, this study represents one large real-world analyses of boost utilization in hypofractionated breast RT. It complements randomized evidence by illustrating that, in everyday clinical practice, boost allocation follows guideline-based, risk-adapted principles and that survival outcomes are primarily determined by tumour and patient characteristics rather than by boost delivery itself. Future studies integrating molecular biomarkers, patient-reported outcomes, and health-economic aspects may further refine individualized radiotherapy strategies and optimize treatment escalation for patients most likely to benefit.

In this large, registry-based cohort of patients receiving hypofractionated breast RT, tumour-bed boost was not associated with improved OS. Instead, established prognostic factors-older age, higher tumour stage, and PR status-were the principal determinants of outcome, while age, T-stage, HER2 positivity, and RT target volume independently predicted boost allocation. These findings align with current guideline recommendations, underscoring that boost therapy should be individualized according to patient- and tumour-related risk factors rather than applied routinely with the expectation of survival benefit (11,12,23).

Despite limitations-including the lack of LC and toxicity data, incomplete therapy documentation, and relatively short

follow-up-this study provides robust real-world evidence supporting the selective use of boost in modern hypofractionated breast RT. Future work should integrate registry-based and prospective data, extend follow-up, and include endpoints beyond survival to better define the role of boost therapy in contemporary breast cancer management.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

KEH, DV, DM and JAM contributed to the study conception and design. Material preparation, data collection and analysis were performed by KEH, DV, DM and JAM. The first draft of the manuscript was written by KEH and all authors commented on previous versions of the manuscript. DM and JAM confirm the authenticity of all the raw data. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study is based exclusively on pseudonymized data provided by the Cancer Registry of North Rhine-Westphalia (Landeskrebsregister Nordrhein-Westfalen). According to the North Rhine-Westphalia State Cancer Registry Act (Landeskrebsregistergesetz Nordrhein-Westfalen), the use of pseudonymized cancer registry data for scientific research does not require individual informed consent or approval by an ethics committee. Because the study involved only pseudonymized registry data and no identifiable patient information, the Ethics Committee of the Medical Faculty of Martin Luther University Halle-Wittenberg (Halle/Saale, Germany) was not required to review the study and did not issue an approval or waiver.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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