

Clinical Investigation

De-intensifying Radiation Therapy in HER-2 Positive Breast Cancer: To Boost or Not to Boost?



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Purpose: Radiation therapy is fundamental in the management of breast cancer. After whole breast irradiation, an additional boost dose is often applied to the primary tumor bed. Here, we analyze the effect of radiation therapy boost on local control in patients with HER-2 positive breast cancer.

Methods and Materials: We studied 1082 patients with HER-2 positive breast cancer who were originally enrolled in the Herceptin Adjuvant Trial and treated with breast-conserving surgery, radiation therapy, and adjuvant chemotherapy with trastuzumab. The primary endpoint of the study was to determine the effect of a radiation boost on local recurrence. Kaplan-Meier curves were generated, and hazard ratios were estimated using Cox regression.

Results: Our analysis included 441 patients (40.8%) who received radiation therapy boost and 641 patients (59.2%) who did not, after completion of whole breast radiation. Patients from both groups had similar baseline characteristics in terms of age, nodal involvement, and grade. At a median follow-up of 11 years, local control was 93% (confidence interval, 90%-95%) in the radiation boost group compared with 91% (confidence interval, 89%-93%) in the no-boost group ($P = .33$). When analyzing patients by age, patients <40 years of age had a higher risk for local recurrence; however, this was not significantly lowered by the addition of boost. Furthermore, no local control benefit for boost was noted in both hormone receptor (HR) subtypes (HR+: $P = .11$; HR-: $P = .98$).

Conclusions: Patients with HER-2 positive breast cancer treated with breast-conserving surgery, whole breast radiation, and trastuzumab have excellent local control. Delivery of an additional radiation boost in this patient population was not shown to improve local control. Future studies are needed to identify subgroups of HER-2 positive patients who derive a clinically relevant benefit from radiation boost. © 2020 Elsevier Inc. All rights reserved.

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Joseph Abi Jaoude and Majd Kayali made equal contributions to this study.

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Introduction

Radiation therapy is an integral part of the management of breast cancer after breast-conserving surgery to reduce the risk of locoregional recurrence. Breast-conserving surgery, followed by whole-breast irradiation (WBI) and optionally a boost to the tumor bed, is a standard therapeutic option for early stage breast cancer. Previous studies have demonstrated that disease outcomes of breast-conserving surgery, in terms of locoregional control and overall survival, in early disease are similar to those of mastectomy.¹ Subsequent radiation therapy is aimed to decrease local recurrence (LR) and avoid mastectomy.

The benefit of postoperative radiation therapy was demonstrated in numerous studies, compiled in a meta-analysis by the Early Breast Cancer Trialists' Collaborative Group showing a 15.4% absolute reduction in 10-year recurrence (locoregional or distant) and a 3.8% absolute reduction in breast cancer death at 15 years of follow-up. In node-negative disease, these reductions were 15.4% and 3.3%, respectively; in node-positive disease, these reductions were 21.2% and 8.5%, respectively.²

WBI is typically administered over the entire breast whereas boost radiation targets the tumor vicinity specifically. The concept of tumor bed boost originated from the observation that the majority of ipsilateral breast cancer recurrences developed in close proximity to the original lesion. Thus, the rationale is elimination of any postsurgical microscopic tumor cells that may lead to LR in the future. This is shown to be of clinical importance in patient populations with several high-risk features for recurrence, including age, tumor size, use of hormone therapy, chemotherapy receipt, presence of ductal carcinoma in situ, and tumor grade.^{3,4} Boost radiation use is, however, challenged, mainly due to the increased treatment costs and a higher potential for adverse events. Short-term side effects related to boost include inconvenience, skin reactions, and breast edema. Long-term risks include breast fibrosis, rib fractures, and worse cosmetic outcomes.⁵ Advances in diagnostic tools, surgical and radiation techniques, and systemic therapies, coupled with increased knowledge of tumor biology, have led to improved local and systemic control of breast cancer. Targeted therapies, such as the human epidermal growth factor receptor 2 (HER-2) monoclonal antibody trastuzumab, markedly improve outcomes of HER-2 positive breast cancer. The Herceptin Adjuvant (HERA) Trial is an international multicenter trial, with 11-year median follow-up, that established the benefit of trastuzumab in HER-2 positive patients.^{6,7} In this analysis, we aim to analyze the effect of radiation boost in patients with HER-2 positive breast cancer treated with trastuzumab, based on a subgroup analysis of a nested cohort within the HERA trial.

Methods and Materials

Study population

The current study is a retrospective analysis of prospectively collected data. Clinical data were collected from the HERA trial, creating a nested cohort of 1082 patients treated with breast conservation. The Clinical Study Data Request team granted access to the HERA trial data.

The full description of the HERA trial is provided in the original publication.⁶ Briefly, the HERA (BIG 1- 01/ BO16348) trial is an international, intergroup, open-label, phase 3 randomized trial studying the efficacy and safety of trastuzumab in patients with HER-2 positive breast cancer. The trial originally enrolled 5099 female patients of all ages with HER-2 positive breast cancer between December 2001 and March 2005. Women with T4 tumors, supraclavicular nodes, or distant disease were excluded. Patients completed locoregional therapy using surgery with or without postoperative radiation therapy before study entry. For patients undergoing breast-conserving surgery, WBI followed. Most patients with involved axillary lymph nodes received additional nodal irradiation. Patients completed a minimum of 4 courses of chemotherapy. Patients were recruited and randomly assigned to either observation or 1 or 2 years of trastuzumab in a 1:1:1 ratio. Patients were followed up with a median follow-up of 11 years. The final analysis (after a median follow-up of 11 years) continued to show an improvement in disease-free survival, favoring trastuzumab over observation.^{6,7}

Figure 1 shows the flow diagram of the nested cohort in the present analysis. Eligible patients were women with HER-2 positive breast cancer after breast-conserving surgery who received 1 or 2 years of trastuzumab. Patients who were assigned to the observation arm, those who did not receive radiation therapy, and/or those who underwent mastectomy were not included. To study the effect of boost radiation therapy, patients were divided into 2 groups: boost (441 patients) and no boost (641 patients) (Table 1). Patient and tumor-related characteristics including age, tumor size, grade, estrogen receptor (ER)/progesterone receptor (PR) status, breast cancer laterality, number of positive lymph nodes, surgical margin positivity, and anthracycline/taxane therapy were recorded.

Outcomes

The primary endpoint of the present study was local control rate, defined as any LR after study entry. LR refers to recurrence of tumor (except lobular carcinoma in situ) within the conserved breast and required cytology or histology confirmation. Time-to-event endpoint definitions are in line with the DATECAN classification.⁸

Statistical analysis

Univariate analyses were conducted to describe the present cohort. Categorical variables are presented as frequencies and percentages. Differences in such variables between patients from the boost and no-boost groups were assessed with the likelihood ratio χ^2 . Multivariate regression was used to evaluate the association between boost and local control and overall survival. Survival data were analyzed using Kaplan-Meier curves. Cox proportional hazards regression was used to generate adjusted hazard ratios (HRs) with their corresponding 95% confidence interval (CIs). The reported HRs are for the comparison of boost versus no boost. Factors considered for inclusion in the multivariate analyses were dependent on statistical significance of the bivariate analyses, as well as clinical significance and implications. Nodal status, grade, and ER/PR expression were used for subgroup analyses. Statistical significance was set at an alpha of 5% for a 2-sided *P* value. All analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC).

Results

Population characteristics

Out of the 5099 patients originally enrolled in the HERA trial, 1082 patients (21.2%) met our inclusion criteria and were included in the current analysis (Fig. 1). Table 1

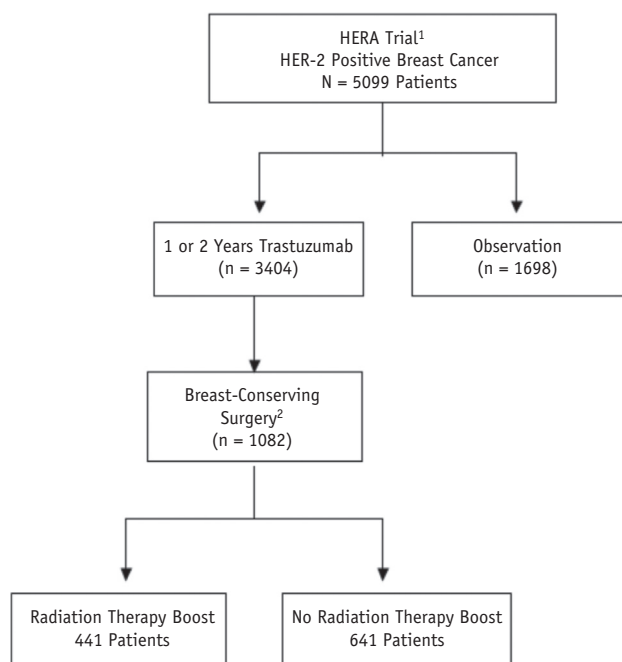


Fig. 1. Flow diagram of the study's nested cohort within the Herceptin Adjuvant Trial. ¹HERA Trial: Herceptin Adjuvant Trial. ²Breast-conserving surgery included lumpectomies, segmentectomies and quadrantectomies.

Table 1 Baseline characteristics of the patients, tumors, and treatments

Characteristic	Boost, n (%) n = 441	No boost, n (%) n = 641	<i>P</i> value
Age, y			.36
<35	27 (6.1)	49 (7.6)	
35-49	190 (43.1)	262 (40.9)	
50-59	134 (30.4)	217 (33.9)	
>59	90 (20.4)	113 (17.6)	
Menopausal status			.19
Premenopausal	64 (14.5)	104 (16.2)	
Postmenopausal	206 (46.7)	323 (50.4)	
Uncertain	171 (38.8)	214 (33.4)	
Nodal status			.08
0 Positive lymph nodes	195 (44.2)	260 (40.6)	
1-3 Positive lymph nodes	122 (27.7)	222 (34.6)	
≥4 Positive lymph nodes	92 (20.9)	125 (19.5)	
Tumor size			.94
0-2 cm	255 (64.3)	310 (63.6)	
2-5 cm	124 (35.4)	175 (35.9)	
>5 cm	1 (0.3)	2 (0.4)	
ER positive	230 (52.2)	295 (46.0)	.10
PR positive	191 (43.3)	235 (36.7)	.08
Hormone receptor status			.09
ER negative and PR negative	190 (43.1)	310 (48.4)	
ER positive and/or PR positive	251 (56.9)	331 (51.6)	
Histologic grade			.65
I (well differentiated)	142 (32.2)	219 (34.2)	
II (moderately differentiated)	276 (62.6)	398 (62.1)	
III (poorly differentiated)	12 (2.7)	13 (2.0)	
Not assessed	11 (2.5)	11 (1.7)	
Histology			.31
Ductal	415 (94.1)	612 (95.5)	
Other	26 (5.9)	29 (4.5)	
Anthracycline-taxane			.49
No anthracycline, no taxane	22 (5.0)	33 (5.2)	
Anthracycline and taxane	79 (17.9)	130 (20.3)	
Anthracycline, no taxane	339 (76.9)	478 (74.6)	
Taxane, no anthracycline	1 (0.2)	0 (0.0)	
Hormone therapy received	233 (52.8)	314 (49.0)	.21
Years on trastuzumab			.25
1	227 (51.5)	307 (47.9)	
2	214 (48.5)	334 (52.1)	
Median total radiation dose, Gy	60	50	
Primary breast cancer location			.04
Bilateral	0 (0.0)	6 (0.9)	
Left	205 (46.5)	325 (50.7)	
Right	236 (53.5)	310 (48.4)	
Negative margin	432 (98.0)	631 (98.4)	.55

Abbreviations: ER = estrogen receptor; PR = progesterone receptor.

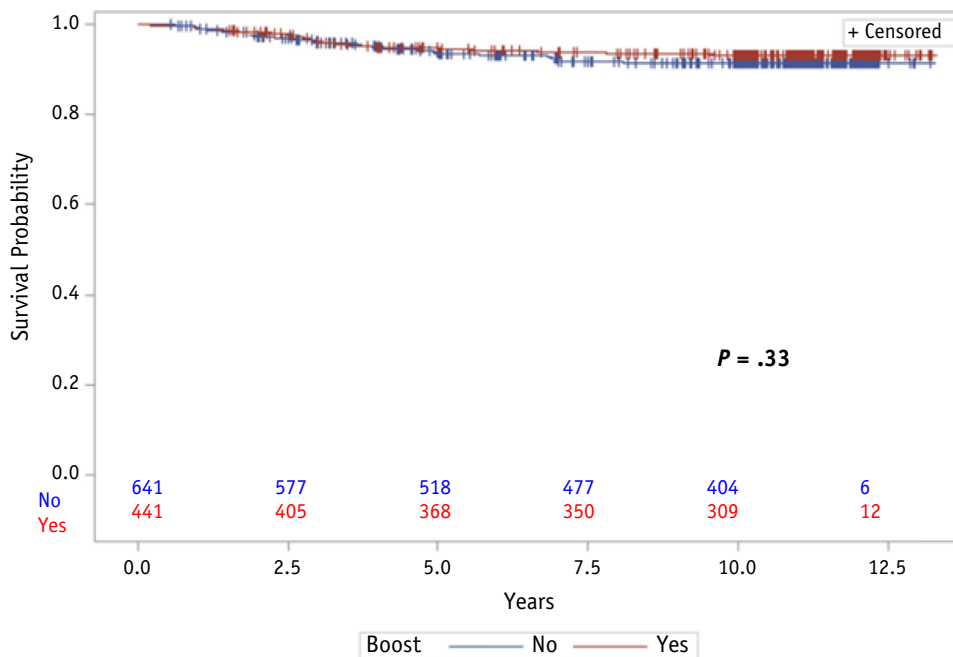


Fig. 2. Kaplan-Meier curve showing local recurrence-free survival in patients treated with trastuzumab receiving radiation therapy boost (red) or no boost (blue). (A color version of this figure is available at <https://doi.org/10.1016/j.ijrobp.2020.06.078>.)

presents the baseline characteristics of the patients, tumors, and treatments received. In our cohort, 441 patients (40.8%) received radiation therapy boost to the primary tumor bed, and 641 patients (59.2%) received whole-breast radiation therapy without radiation boost. The median whole-breast radiation dose was 50 Gy (range, 50-50.4 Gy), and the median radiation boost dose was 10 Gy (range, 10-15 Gy). Both groups of patients had a similar age distribution, with most patients being between 35 and 60 years of age (boost group: 73.5% vs no boost group: 74.8%). Similar nodal involvement was present in both groups, and around half of patients had N0 disease (boost group: 44.2% vs no boost group: 40.6%). The majority of patients had grade 2, moderately differentiated (62.3%) ductal carcinoma (94.9%). The boost group had slightly more patients with ER or PR positive tumors (56.9% vs no boost: 51.6%). Patients treated with radiation therapy boost had more right-sided cancers (53.5% vs 46.5% left breast cancer). Anthracycline, taxane, hormone therapy, and trastuzumab receipt were similar between the boost and no boost groups.

Local recurrence

In total, 78 LR events were recorded in the 1082 patients analyzed (7.2%) (Fig. 2). Of these, 28 happened in the boost group (6.3% of patients receiving radiation therapy boost) and 50 in the no-boost group (7.8% of patients with no boost), yielding a 1.4% absolute reduction in LR rates. At a median follow-up of 11 years, no significant LR benefit was noted in patients receiving boost compared with

those who did not receive radiation therapy boost ($P = 0.33$) (Fig 2).

In parallel, we analyzed LR in 687 patients from the observation arm of the HERA trial (no adjuvant trastuzumab). At a median follow-up of 11 years, 48 LRs (8.9%) were detected, with no significant differences between boost and no-boost subgroups ($P = 0.51$) (Fig 3). Our results were also validated in a multivariate regression model (Table 2). Patient age strongly correlated with recurrence (HR: 0.97; $P = .006$) whereas the addition of radiation boost did not ($P = .35$).

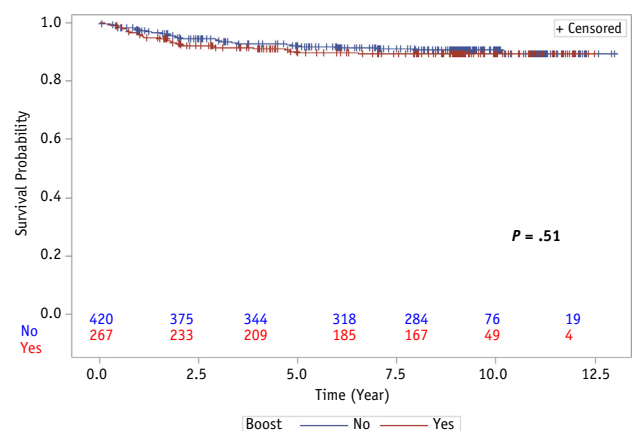


Fig. 3. Kaplan-Meier curves showing local recurrence-free survival in patients not treated with trastuzumab receiving radiation therapy boost (red) or no boost (blue). (A color version of this figure is available at <https://doi.org/10.1016/j.ijrobp.2020.06.078>.)

Table 2 Multivariate Cox regression for local recurrence

Variables	HR (95% CI)	P value
Boost	0.80 (0.50-1.28)	.35
Age	0.97 (0.95-0.99)	.006
Tumor size	0.98 (0.96-1.01)	.17
Trastuzumab	0.91 (0.58-1.43)	.70
Anthracycline	1.79 (0.43-7.38)	.42
Taxane	0.98 (0.55-1.74)	.94
LN	1.14 (0.65-2.01)	.65
Grade	1.19 (0.78-1.80)	.42

Abbreviations: 95% CI = 95% confidence interval; HR = hazard ratio; LN = lymph nodes.

Comparison groups: No boost, younger age, smaller tumor size, no trastuzumab, no anthracycline, no taxane, 3 or fewer LN, lower tumor grade.

When analyzing results by age, patients <40 years old who received a boost had an LR rate of 8.9% versus 11.1% in the no-boost group; however, the difference did not reach statistical significance ($P = .92$) (Table 3). Patients older than 40 years had a lower LR absolute risk reduction of 1.3% (boost: LR, 5.7% vs no boost: LR, 7.0%; $P = .29$). Moreover, no significant difference in LR rate was present among patients regardless of hormone receptor status. Patients with ER and PR negative disease had an LR rate of 9.0% with boost and 8.1% without boost ($P = .980$). Patients with ER and/or PR positive disease had an LR rate of 4.4% with boost and 7.6% without boost (LR absolute reduction: 3.2%, $P = .11$) (Table 3). Furthermore, we identified 19 patients with positive surgical margins (9 boost and 10 no boost). Two recurrences occurred in this subgroup, and both were in the no-boost cohort.

Discussion

Radiation therapy is an essential component of the complex management of breast cancer. Particularly, patients

Table 3 Multivariate Cox regression analysis for the development of local recurrence

Subgroups	Boost LR (%)	No boost LR (%)	aHR (95% CI)	P value
All patients	6.35	7.80	0.8 (0.5-1.3)	.30
Age <50 y	7.53	10.42	0.7 (0.4-1.3)	.30
Age >50 y	4.95	4.92	1.0 (0.4-2.2)	.94
Age <40 y	8.89	11.11	1.0 (0.4-2.3)	.92
Age >40 y	5.70	6.99	0.7 (0.4-1.3)	.29
ER and/or PR positive	4.38	7.55	0.6 (0.3-1.1)	.11
ER and PR negative	8.95	8.06	1.0 (0.5-1.9)	.98

Abbreviations: 95% CI = 95% confidence interval; aHR = adjusted hazard ratio; ER = estrogen receptor; LR = local recurrence; PR = progesterone receptor.

undergoing breast-conserving surgery are commonly treated with subsequent breast radiation therapy. This population of patients commonly receives an additional radiation therapy boost, in the hope of further improving clinical outcomes. Recommendations by the American Society for Radiation Oncology suggest the use of a radiation boost in patients under the age of 50 years, patients aged 51 to 70 with high-grade tumors, and patients with positive surgical margins.⁹ In this study, we examine the impact of additional radiation therapy boost after conventional whole-breast radiation therapy in patients with HER-2 positive breast cancer treated with breast-conserving surgery and adjuvant trastuzumab. Our results show that the addition of a radiation boost does not significantly improve local control in this population.

The role of radiation therapy boost was initially studied in the Lyon trial in the late 1980s.¹⁰ The study showed improved 5-year local control in patients treated with additional boost, but no overall survival benefit.¹⁰ Later, a large phase 3 randomized trial ran by the European Organization for Research and Treatment on Cancer group analyzed the role of radiation therapy boost in patients with breast cancer who have undergone breast-conserving surgery.¹¹⁻¹⁴ With long-term follow-up of 20 years, the trial consistently showed improved local control in patients who received radiation therapy boost.¹⁴ Furthermore, improved local control was noted in all age groups, with the largest absolute benefit (9.3%) in patients under the age of 40 years (HR = 0.56; $P = .003$).

Although those studies present valuable insight into the management of patients with breast cancer, it remains unclear how to apply the results to the various molecular subtypes. HER-2 positive breast tumors are particularly underrepresented in studies assessing the clinical utility of molecular phenotype.¹⁵ Therefore, it is prudent to question the applicability of older studies to patients treated with modern therapies.¹⁶⁻¹⁸ Specifically, patients with HER-2 positive breast cancer have markedly improved clinical outcomes, including disease-free and overall survival, with the use of the modern anti-HER-2 targeted agents, such as trastuzumab.^{6,7} The impact of anti-HER-2 therapies on locoregional control resulted in an overall reduction in the absolute benefit of radiation therapy.¹⁹

Given the improved clinical outcomes of patients with HER-2 positive breast cancer with novel treatments, it is important to understand the impact of radiation therapy boost after breast-conserving surgery in this population. At a median follow-up of 11 years, our data show no significant increment in local control with the addition of radiation therapy boost ($P = .70$). Notably, although previous data highlight an increased benefit in younger patients, our results show 2.2% absolute benefit in local control in the population <40 years of age. However, this difference in local control did not reach significance ($P = .92$), probably due to the low number of young patients (206). In previous randomized controlled trials with long follow-up, the magnitude of local control benefit for boost was around

4.0%.¹⁴ With the addition of trastuzumab and chemotherapy, it is conceivable that the magnitude of the benefit is even lower (2.0% in the current study). With such a low absolute benefit, more study patients would be required to reach statistical significance.

Breast cancer subtype is an essential predictor of radiation therapy response. For instance, ER signaling confers increased radiosensitivity through accelerating the G1/S phase transition and diminishing DNA repair.^{20,21} Lower locoregional control benefits after radiation therapy were reported in patients who lack hormone receptor expression compared with patients with ER and/or PR positive disease.^{19,22} On the other hand, HER-2 expression confers a radioresistant phenotype.²³ This is attributed to activation of the focal adhesion kinase pathway. Conversely, inhibition of HER-2 signaling has been associated with increased radiosensitivity.²⁴⁻²⁶ In our analysis, the addition of radiation boost had similar outcomes regardless of hormone receptor status. This could be related to the enhanced radiosensitivity conferred by trastuzumab, thereby eliminating the need for a radiation boost after whole-breast radiation in some patients. Future utilization of individual radiosensitivity scores will be key for selecting patients for treatment escalation or de-escalation.²⁷

Optimal treatment for HER-2 positive breast cancer continues to evolve. Our results are applicable to patients receiving at least 1 year of adjuvant trastuzumab. As the medical oncology community is currently reconsidering the optimal duration of trastuzumab therapy, it remains unclear whether our results hold in the setting of shorter targeted therapies.^{28,29} On the other hand, further escalation in targeted systemic therapy, particularly with dual anti HER-2 therapy, may offer improved disease control in patients with early HER-2 breast cancer. The APHINITY trial showed improved rates of invasive-disease-free survival in patients receiving adjuvant pertuzumab in addition to trastuzumab.³⁰ Therefore, it is prudent for radiation oncologists to keep track of the evolving landscape of HER-2 targeted therapies to tailor treatments to individual patient risks.

The current analysis carries some limitations that are worth noting. First, our study is an unplanned, retrospective subgroup analysis based on prospectively collected data from the HERA trial. As such, radiation therapy boost was not randomized. Furthermore, radiation therapy delivery was based on institutional preferences and thus was not standardized across all patients. Second, data on lymphovascular invasion and extracapsular extension were not collected in the HERA trial and therefore were not analyzed in our study. Finally, our results do not apply to patients with HER-2 positive breast cancer receiving neoadjuvant systemic therapy, which is a question that still needs to be addressed by modern trials. Despite these limitations, our study remains the largest to date to examine the effect of radiation therapy boost after breast-conserving surgery in patients with HER-2 positive breast cancer treated with modern therapy and follow-up over a median of 11 years.

Conclusions

In this secondary analysis of the HERA trial studying women with HER-2 positive breast cancer treated with breast-conserving therapy and adjuvant breast radiation therapy, the benefit of an additional radiation boost appeared minimal. Therefore, the risk/benefit ratio of additional tumor bed boost needs to be carefully considered in this patient population. Our findings warrant further validation to select HER-2 positive patients for treatment escalation or de-escalation. Future studies, including the analysis of real-life data, are still needed to better assess the role of radiation therapy boost in patients with HER-2 positive breast cancer.

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