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Reaffirming Radiation's Role After NRG-BR008: Real-World Survival Benefit in Early-Stage HER2-Positive Breast Cancer

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Abstract
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Abstract

Purpose: The role of adjuvant radiation therapy (RT) in early-stage HER2-positive breast cancer treated with breast-conserving surgery (BCS) and systemic therapy remains an area of clinical uncertainty, particularly considering modern HER2-targeted regimens. This study evaluates the survival impact of RT in patients aligned with the HERO trial (NRG-BR008), using real-world data across both adjuvant and neoadjuvant treatment sequences.

Methods: Using the National Cancer Database (2004–2021), we identified patients with HER2-positive invasive breast carcinoma treated with BCS and systemic therapy, stratified into two cohorts aligned with the HERO trial design: Arm 1 (adjuvant systemic therapy cohort) for patients with tumors ⩽2 cm who received systemic therapy after surgery, and Arm 2 (neoadjuvant systemic therapy cohort) for patients with tumors ⩽3 cm who received systemic therapy prior to surgery and subsequently achieved pathologic complete response (ypT0N0). Patients were grouped by RT receipt status (RT vs no RT), and propensity score matching was performed for each cohort using demographic and clinical covariates with exact matching on NRG-BR008 trial stratification variables: patient age (1 cm), and estrogen receptor status (positive; negative). Survival time was left-truncated at 6 months and evaluated using Kaplan-Meier estimates, Cox proportional hazards regression, and restricted mean survival time (RMST).

Results: After matching, Arm 1 (adjuvant cohort) included 894 patients (447 RT, 447 No RT) with 104 deaths, and Arm 2 (neoadjuvant cohort) included 190 patients (95 RT, 95 No RT) with 13 deaths. In Arm 1, 5-year OS was 97.7% with RT vs 87.4% without RT; 10-year OS was 86.6% vs 68.6% (log-rank P<.001). Stratified Cox regression showed a significantly increased mortality risk in the no RT group (HR, 5.44; 95% CI, 3.26–9.09; P<.001). RMST analysis demonstrated survival benefit in favor of RT of +3.03 months at 5 years and +14.28 months at 10 years (both P<.001).

In Arm 2, 5-year OS was 97.8% with RT vs 90.7% without RT; 107-month OS was 91.7% vs 89.1% (log-rank P=.08). Cox modeling showed omission of RT was associated with a nonsignificant 147% increase in the hazard of death (HR, 2.47; 95% CI, 0.77–7.93; P=.13), although RMST demonstrated significant survival benefit of RT (+1.8 months at 5 years, P=.006; +4.6 months at 107 months, P=.008).

Conclusion: In a national cohort of patients with early-stage HER2-positive breast cancer aligned with the HERO trial design treated with BCS and adjuvant systemic therapy, RT was associated with clinically and statistically significant improvements in long-term survival. In the neoadjuvant systemic therapy cohort, RT was associated with modest survival benefit, although the results were nonsignificant and underpowered. These findings provide timely real-world evidence supporting the continued role of RT in early-stage HER2-positive breast cancer pending prospective trial results.