**Primary Outcome Analysis for Shortening Adjuvant Photon Irradiation to Reduce Edema (SAPHIRE): A Randomized, Phase III Trial of Hypo- vs. Conventionally Fractionated Regional Nodal Irradiation (RNI)**

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**Purpose/Objective(s):** Although RNI improves breast cancer survival, it increases risk of upper extremity lymphedema. We hypothesized that hypofractionated RNI may reduce lymphedema risk.

**Materials/Methods:** Patients with a recommendation for RNI for cT0-T3, N0-N2a, N3a invasive breast cancer were randomized between standard RNI (STD-RNI: 50 Gy to breast/chest wall and 45 Gy to RN) or shorter RNI (SH-RNI: 40.05 Gy to breast/chest wall and 37.5 Gy to RN). Patients were stratified by receipt of chemotherapy, body mass index (BMI), type of axillary surgery, and difference in arm volume prior to RNI. RN targets included the internal mammary, infraclavicular, and supraclavicular nodal basins; the level I and II axilla was treated if axillary lymph node dissection was not performed. Boost to the tumor bed or chest wall was permitted. Lymphedema was assessed via standard toxicity grading by the treating physician and by serial perometry measurement prior to surgery, postoperatively and then 6, 12, 18, and 24 months after radiation. The primary outcome was defined as a ≥ 10% relative difference in arm volume on at least one post-radiation perometry assessment, normalized by the pre-operative perometry measurement. Secondary outcomes included comparison of physician-reported toxicities using the NCI CTCAE version 4.0 scale graded weekly during RT, at 6 months, and then annually. Fisher’s exact tests compared groups. Local-regional recurrence (LRR) was calculated using the Kaplan-Meier method and compared using the log-rank test.

**Results:** There were three hundred twenty-four patients across 5 treatment centers were enrolled and randomized from 2017 to 2022 with median follow up of 4.75 years. Clinical-pathologic covariates were well-balanced by treatment arm. Median age was 54 years, 64% were non-Hispanic White, and 39% had body mass index (BMI) > 30. 57% underwent mastectomy with or without reconstruction and 42% underwent segmental mastectomy. Sixty-eight percent underwent axillary lymph node dissection and 90% received chemotherapy. Perometry-assessed lymphedema, the primary outcome, was less common after SH-RNI (29%) than STD-RNI (36%), but the difference was not statistically significant (P = 0.24). In contrast, physicianassessed lymphedema was significantly less common with SH-RNI than STD-RNI (15% vs. 27%, P = 0.009). Patients randomized to SH-RNI were less likely to experience any grade ≥ 2 toxicity (52% vs. 78%, P < 0.001).

Pneumonitis was uncommon and similar between groups (3% vs 2%, P = 0.46). There were no brachial plexopathy events. Five-year LRR risk was 3% with SH-RNI and 2% with STD-RNI (P = 0.48).

**Conclusion:** In this primary outcome analysis of a multisite phase III randomized clinical trial, SH-RNI did not lower risk of perometry-assessed lymphedema. However, SH-RNI conferred a low risk of LRR and reduced the risk of physician-reported lymphedema and grade 2 or higher toxicity when compared to STD-RNI.