**A Randomized Trial of Hypofractionated Post-Mastectomy Radiation Therapy (PMRT) in Women with Breast Reconstruction (RT CHARM, Alliance A221505)**

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**Purpose/Objective(s):** A 5-week course of conventionally fractionated radiation after mastectomy remains standard of care for women with intermediate- and high-risk breast cancer (BC), despite widespread adoption of shorter schedules in other BC patients (pts). To fill the evidence gap of shorter PMRT schedules, we conducted a non-inferiority, multi-institutional, prospective randomized trial of hypofractionated radiation after mastectomy in pts with completed or in-progress breast reconstruction, comparing 25 vs 16 fractions (fx) of daily radiation. Primary outcome was composite reconstruction complication (wound healing, readmission, capsular contracture, unplanned re-operation, reconstruction failure).

**Materials/Methods:** Women enrolled with unilateral invasive BC, pT0-2 pN1-2 or pT3N0, or clinically staged before neoadjuvant chemotherapy (NAC), who were planning delayed or immediate breast reconstruction and PMRT. Pts were randomized 1:1 to 50.0 Gy in 25 fx or 42.56 Gy in 16 fx, delivered 5 days/week using photon techniques. The study was designed to test non-inferiority of hypofractionated to conventional PMRT with non-inferiority margin of 10%, assuming a complication rate of 25% in the conventional arm. Accounting for 10% ineligibility, a sample size of 880 pts provided 90% power at one-sided type I error of 0.025 with 1 interim analysis. Randomization was stratified by planned immediate vs delayed and autologous vs implant-only reconstruction.

**Results:** From 2018 to 2021, 898 pts enrolled from 209 centers in United States and Canada; median follow-up was 4.5 years. Seventy-three women came off study before the primary event could be analyzed. Pt characteristics were well balanced with median age 49 years, 14% known genetic predisposition gene, 6% diabetes, and 67% with body mass index > 25. Tumor characteristics were well balanced. 51% of pts received NAC; 37% received adjuvant chemotherapy. Among 572 pts who completed reconstruction, 45% had immediate and 55% delayed (average 265-day delay), 57% had implant alone and 43% autologous +/- implant. The 24-month month incidence of reconstruction complications was 14% (59/422) with hypofractionation vs 11.7% (47/403) with conventional PMRT, estimated difference 2.3%, 95% CI = 2.2% to 6.9%, P = 0.0005. Complication rate was decreased (regardless of arm) with autologous vs implant only reconstruction, odds ratio 0.504, P = 0.0059. Acute and late toxicity rates were not statistically different between arms. Thirty-six month local or regional recurrences occurred in 1.5%, 95% CI = (0.7-3.3% of hypofractionated and 2.3%, 95% CI = 1.1-4.6% of conventional pts.

**Conclusion:** A 16-fraction course of hypofractionated PMRT appears safe and effective for pts undergoing breast reconstruction and is non-inferior to traditional 25-fraction course of PMRT. (NCT03414970)