Conventional versus hypofractionated postmastectomy proton radiotherapy in the USA (MC1631): a randomised phase 2 trial

Robert W Mutter, Sharmila Giri, Briant F Fruth, Nicholas B Remmes, Judy C Boughey, Christin A Harless, Kathryn J Ruddy, Lisa A McGee, Arslan Afzal, Robert W Gao, Dean A Shumway, Tamara Z Vern-Gross, Hector R Villarraga, Stephanie L Kenison, Yixiu Kang, William W Wong, Bradley J Stish, Kenneth W Merrell, Elizabeth S Yan, Sean S Park, Kimberly S Corbin, Carlos E Vargas

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Abstract

Background: Proton therapy is under investigation in breast cancer as a strategy to reduce radiation exposure to the heart and lungs. So far, studies investigating proton postmastectomy radiotherapy (PMRT) have used conventional fractionation over 25-28 days, but whether hypofractionated proton PMRT is feasible is unclear. We aimed to compare conventional fractionation and hypofractionation in patients with indications for PMRT, including those with immediate breast reconstruction.

Methods: We did a randomised phase 2 trial (MC1631) at Mayo Clinic in Rochester (MN, USA) and Mayo Clinic in Arizona (Phoenix, AZ, USA) comparing conventional fractionated (50 Gy in 25 fractions of 2 Gy [relative biological effectiveness of 1·1]) and hypofractionated (40·05 Gy in 15 fractions of 2·67 Gy [relative biological effectiveness of 1·1]) proton PMRT. All patients were treated with pencil-beam scanning. Eligibility criteria included age 18 years or older, an Eastern Cooperative Oncology Group performance status of 0-2, and breast cancer resected by mastectomy with or without immediate reconstruction with indications for PMRT. Patients were randomly assigned (1:1) to either conventional fractionation or hypofractionation, with presence of immediate reconstruction (yes vs no) as a stratification factor, using a biased-coin minimisation algorithm. Any patient who received at least one fraction of protocol treatment was evaluable for the primary endpoint and safety analyses. The primary endpoint was 24-month complication rate from the date of first radiotherapy, defined as grade 3 or worse adverse events occurring from 90 days after last radiotherapy or unplanned surgical interventions in patients with immediate reconstruction. The inferiority of hypofractionation would not be ruled out if the upper bound of the one-sided 95% CI for the difference in 24-month complication rate between the two groups was greater than 10%. This trial is registered with ClinicalTrials.gov, NCT02783690, and is closed to accrual.

Findings: Between June 2, 2016, and Aug 23, 2018, 88 patients were randomly assigned (44 to each group), of whom 82 received protocol treatment (41 in the conventional fractionation group and 41 in the hypofractionation group; median age of 52 years [IQR 44-64], 79 [96%] patients were White, two [2%] were Black or African American, one [1%] was Asian, and 79 [96%] were not of Hispanic ethnicity). As of data cutoff (Jan 30, 2023), the median follow-up was 39·3 months (IQR 37·5-61·2). The median mean heart dose was 0·54 Gy (IQR 0·30-0·72) for the conventional fractionation group and 0·49 Gy (0·25-0·64) for the hypofractionation group. Within 24 months of first radiotherapy, 14 protocol-defined

complications occurred in six (15%) patients in the conventional fractionation group and in eight (20%) patients in the hypofractionation group (absolute difference 4·9% [one-sided 95% CI 18·5], p=0·27). The complications in the conventionally fractionated group were contracture (five [12%] of 41 patients]) and fat necrosis (one [2%] patient) requiring surgical intervention. All eight protocol-defined complications in the hypofractionation group were due to infections, three of which were acute infections that required surgical intervention, and five were late infections, four of which required surgical intervention. All 14 complications were in patients with immediate expander or implant-based reconstruction.

Interpretation: After a median follow-up of 39·3 months, non-inferiority of the hypofractionation group could not be established. However, given similar tolerability, hypofractionated proton PMRT appears to be worthy of further study in patients with and without immediate reconstruction.