

Moderately hypofractionated breast radiation therapy: is more evidence needed?

We applaud Shu-Lian Wang and colleagues¹ for the achievement of reporting the results of their trial investigating postmastectomy hypofractionated radiotherapy in *The Lancet Oncology*. In this well designed, randomised, non-inferiority, phase 3 trial, they randomly assigned patients to irradiation at a dose of 50 Gy in 25 fractions over 5 weeks (conventional fractionated radiotherapy) or 43.5 Gy in 15 fractions over 3 weeks (hypofractionated radiotherapy), directed to the chest wall and the supraclavicular and level III axillary nodal region in 820 patients with locally advanced breast cancer (at least four positive axillary lymph nodes). There were no significant differences in the 5-year cumulative incidence of locoregional relapse between the groups (8.3% [90% CI 5.8–10.7] hypofractionated radiotherapy vs 8.1% [5.4–10.6] conventional radiotherapy). Furthermore, the acute and late side-effects were similar in both groups, apart from the fact that fewer patients had grade 3 acute skin toxicity in the hypofractionated radiotherapy group than in the conventional fractionated radiotherapy group.

Although this trial has a high number of limitations (including use of outdated two-dimensional radiotherapy techniques, no internal mammary lymph node irradiation, an unconventional hypofractionated schedule, a high rate of locoregional recurrence, exclusion of patients with breast reconstruction, only 50% of patients with *HER2*-positive breast cancer receiving anti-*HER2* therapy, and the study being done at a single Chinese centre), we should

acknowledge that the results of this trial support further broadening of hypofractionated radiotherapy indications. Other groups are doing worldwide randomised clinical trials to robustly assess this issue, including in France (NCT03127995), the USA (NCT02700386, NCT02958774), Denmark (NCT02384733), and Egypt (NCT02690636). Over the coming years, results from these trials will produce data for another 4000 patients who have received hypofractionated radiotherapy in different clinical settings. Until these new data are available, the data from the START trials² and the trial by Wang and colleagues¹ suggest that moderately hypofractionated radiotherapy directed to the chest wall and part of the regional lymph nodes is similarly effective and safe compared with conventional radiotherapy, and should be considered as the standard treatment option for patients with breast cancer.

However, the question is to what extent is any further evidence still required? In the Netherlands, hypofractionation has been the standard treatment for nearly every indication regardless of patient-related, tumour-related, or treatment-related characteristics for several years now, based on the argument that with modern homogeneously delivered volume-based radiotherapy techniques the biological effects should be identical, independent of the target volumes.³ Similarly, do we need to question whether fractionation schedules for head and neck cancer are dependent on the anatomical subsite? Or is it actually due to reimbursement issues that hospital managers and doctors do not allow similar introduction of schedules with fewer fractions and a lower total dose? Reimbursement per radiotherapy fraction, and not for the treatment as a whole, is common in several countries and withholds broad application of hypofractionation because it reduces reimbursement or payment to the

hospital or doctor. This issue is even more important in low-income and middle-income countries—we should not wait until further evidence becomes available before making hypofractionated breast irradiation more widely accessible.

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