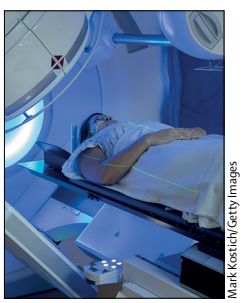
1-week hypofractionated adjuvant whole-breast radiotherapy: towards a new standard?

Hypofractionated radiotherapy delivers a higher dose (>2 Gy) per fraction than conventional radiotherapy, reducing overall treatment duration and associated costs. In women with early stage breast cancer, moderate hypofractionated (eg, 40–42·5 Gy per 15–16 fractions in 3–3·2 weeks) adjuvant whole-breast radiotherapy was shown to be non-inferior in terms of long-term tumour control and toxicities than the conventional schedule (50 Gy in 2 Gy daily fractions over 5 weeks).[1,2] Subsequently, moderate hypofractionation has become the preferred dose-fractionation scheme for many patients.[1–3]

In *The Lancet*, Adrian Murray Brunt and colleagues[3] report the 5-year results of a three-arm, multicentre, randomised controlled, phase 3, non-inferiority trial (FAST-Forward) in which 4096 patients with invasive carcinoma of the breast were randomly assigned to treatment with 40 Gy in 15 fractions over 3 weeks (n=1361), or moderate hypofractionated radiotherapy with 27 Gy in five fractions of 5·4 Gy over 1 week (n=1367) or 26 Gy in five fractions of 5·2 Gy over 1 week (n=1368). The primary endpoint was ipsilateral breast tumour relapse, and normal tissue effects were assessed by clinicians, patients, and photographs. The population mainly comprised lower-risk patients (2551 [62·3%] of 4096, aged ≥50 years, and grade 1 or 2 breast cancer). Both five-fraction schedules were not inferior to 40 Gy in 15 fractions (5-year cumulative incidence of ipsilateral breast tumour relapse was 1·7% [95% CI 1·2–2·6] for the 27 Gy group, 1·4% [0·9–2·2] for the 26 Gy group, and 2·1% [1·4–3·1] for the 40 Gy group). Of those with at least one annual clinical assessment of normal tissue effects available (3975 [97%] of 4096), any moderate or marked clinician-assessed normal tissue effects in the breast or chest wall at 5 years were reported for 155 (15·4%) of 1005 participants in the 27 Gy group, 121 (11·9%) of 1020 in the 26 Gy group, and 98 (9·9%) of 986 in the 40 Gy group, with a significant difference between 40 Gy and 27 Gy (p<0·0001) but not between 40 Gy and 26 Gy (p=0·20). Incidence of locoregional relapse, distant relapse, disease-free survival, and overall survival was not different.[3]

Hence, should 26 Gy in five fractions be considered an effective and safe alternative to moderate hypofractionated whole-breast radiotherapy? These findings provide robust evidence that limits of hypofractionated radiotherapy in the breast were not reached by previous trials, and that longer-term follow-up is needed because both recurrence and radiotherapy toxicity might occur late. After 5 years of adjuvant endocrine treatment (3649 [89·1%] of patients in the present trial),[3] the risk of distant recurrence generally lasts for at least the subsequent 15 years.[4] Increased risk of long-term side-effects might be noticed with increased doses per fraction, by contrast with data from the present study. The mean dose to the heart linearly increases the risk of a major coronary event (7·4% [95% CI 2·9–14·5] per Gy) and this risk continues for at least 20 years.[5] Modern radiotherapy techniques (eg, intensity-modulated radiotherapy and breath hold) could restrict the dose delivered to the heart, but such techniques were not reported in the present study.[3] Breast size was also not described in this study and different normal tissue effects could be observed in patients with larger breasts.[3,6]

The results of Murray Brunt and colleagues might not be applicable in some biological subtypes of breast cancer and high-risk patients, particularly with larger tumours and positive nodes. A substudy of patients in FAST-Forward comparing 40 Gy in 15 fractions and 26 Gy in five fractions for patients requiring regional radiotherapy is ongoing.[3] A 2019 trial suggested non-inferiority of post-mastectomy moderate hypofractionated radiotherapy compared with conventional fractionation.[7] Further trials comparing moderate hypofractionated to conventional lymph node radiotherapy are ongoing (NCT03127995, NCT02690636, NCT03829553, NCT04025164, NCT02912312, and NCT04228991). A boost of radiotherapy to the tumour bed is intended to decrease locoregional recurrence, but its benefit in patients who have received hypofractionated radiotherapy is less clear. In the present study, 1011 (24·7%) patients had a boost, which was delivered in conventional fractions (10 Gy in five fractions or 16 Gy in eight fractions).[3] This choice of boost dose per fraction is difficult to understand because the boost is doubling the treatment time, and as such, the authors



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could have provided a rational for a hypofractionated boost schedule.

In summary, we concur with the authors that 26 Gy in five fractions over 1 week might be changing practice for low-risk patients with breast cancer who have had surgery, but long-term disease outcomes and subset analyses are eagerly awaited. During the coronavirus disease 2019 (COVID-19) pandemic, hypofractionation could restrict the exposure of health-care professionals and patients to COVID-19. In this context, a schedule of 26 Gy in five fractions has been endorsed by an international panel of experts.[8] Different shorter fractionation schedules will hopefully also be compared to determine the restrictions of hypofractionation. The FAST-Forward schedule could challenge accelerated-partial breast radiotherapy as the preferred therapy in similar populations, but expected long-term outcomes and subanalyses of accelerated-partial breast radiotherapy trials (IMPORT-LOW, NSABP-B39, and RAPID) will help in positioning these options. Ultrahypofractionation with stereotactic body radiotherapy has been tested as an alternative therapy in women with early breast cancer who have had surgery, have been carefully selected, and do not need nodal radiotherapy (NCT03643861, NCT01290835, NCT02685332, and NCT01162200). In the future, patients' selection for adjuvant radiotherapy will ideally integrate tumour[9] and healthy tissue biology.[10,11]

We declare no competing interests.

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