Editorial

Hypofractionated radiation therapy for early breast cancer and regional nodal irradiation—the jury is still out

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A recent study on the shoulder-arm morbidity of the breast cancer UK START trials in axillary node positive women argues that hypofractionated lymph node radiation therapy is safe, as the long-term complications rates such as arm edema and shoulder stiffness remained low at 10-year follow-up (1). Can the authors' conclusions apply to all patients with breast cancer who require lymph nodes irradiation after lumpectomy or mastectomy? Is hypofractionation really safe?

First, let us take a look at the context of the study in question. There was concern before START A and B trials were conducted that the cost-effectiveness of hypofractionation for breast cancer may be hampered by its complication, mainly brachial plexopathy. The Editorials raised the fear of radiotherapy-induced brachial plexopathy (RIBP) in both patients and clinicians at the time as, even though rare with conventional fractionation, its severity may lead to significant deterioration of patient quality of life because of pain and arm paralysis (2). Indeed, the risk of brachial plexopathy was real and increased over time following treatment. Bajrovic *et al.* (3) reported that the risk of brachial plexopathy increased from 3.9% at 5 years to 46% at 19 years after treatment with hypofractionation. The risk was correlated to the dose to the brachial plexus which received 2.6 Gy/fraction at 3 cm depth with a daily fraction of 3 Gy. The onset of RIBP may also be delayed. The median onset of neurologic symptoms in 48 patients who developed RIBP was 27 months after breast cancer treatment (4). Delayed onset of RIBP was also corroborated in another study where 3 out of 31 patients (10%) developed neurologic complications 27 to 35 months after treatment (5). Late onset of brachial plexopathy and increased rates of neurologic complications with longer follow-up may be postulated secondary to scarring after surgery and radiotherapy which induced nerve ischemia (6). The extent of axillary dissection after hypofractionated chest wall irradiation may also be a factor in RIBP. Sixty-seven out of 216 (31%) who underwent mastectomy and axillary lymph nodes dissection developed RIBP following hypofractionated radiotherapy to the chest wall (7). Taken together, RIBP is a late event that increases with time following treatment for breast cancer. Patients most vulnerable to RIBP had mastectomy and axillary nodes dissection.

Second, if we look in depth at the three UK START trials, only 202 out of 864 patients (23%) had positive axillary lymph nodes suggesting that the remaining 77% did not have axillary lymph nodes dissection, thus, not at risk for RIBP as the axillary lymph node would not have been irradiated. In addition, only 547 out of 864 patients (63%) had total mastectomy. As a result, only a small proportion of patients in the studies were at risk for RIBP. Pain, numbness, and weakness of the arms are the hallmark of RIBP, but clinicians only graded the severity

of arms edema and shoulder stiffness. Using the latter measures as a diagnosis of RIBP, the incidence at 5 years is low. Delayed onset of neurologic symptoms at 5 and 10 years were not assessed or not reported. The conclusion that hypofractionated radiotherapy is safe for breast cancer patients who have undergone axillary lymph nodes dissection is, in our opinion, premature.

Third, there are several disquieting aspects in the study. The 10-year follow-up differs only by 0.1 year from the 9.9 years follow-up previously reported 5 years ago (8). The study performs subgroup analyses of subgroups that were not designed in the trials. Missing data are mentioned regarding patients' characteristics. But, the increasingly missing data in the response assessments, when they are the most critical to appreciate the long-term reliability, are glossed over. In the patient-assessed shoulder arm symptoms at 5 years, 21% (67/318) assessments were missing from the START-A cohort, and 39% (63/161) were missing from the START-B cohort. In the physician-assessed arm oedema and shoulder stiffness, the total available assessments dropped from 77% (298/385), to 46% (176/385) at 5 years, to 25% (96/385) at 10 years in the START-pilot, dropped from 96% (304/318), to 64% (204/318) at 5 years, to 28% (88/318) at 10 years in the START-A, and dropped from 96% (154/161), to 67% (108/161), to 29% (47/161) in the START-B cohort. That is, there were huge losses to follow-up, exceeding one third of the cohorts at 5 years, exceeding two-thirds at 10 years.

The START trials' physician assessment were not based on standardized measurement procedures but used subjective scoring. In a non-blinded study context, the subjective assessment compounds the potential of bias. In the Belgian TomoBreast randomized clinical trial of hypofractionated radiation therapy for early breast cancer for which methodical limb measurements were performed, and in which the assessors were blinded to treatment allocation, the post-radiation increase in limb volume and the impairment of shoulder arm mobility have been shown to be in the range of 28% incidence of grade 1 or more limb volume increase, and 15–25% grade 1 or more loss of mobility (9). By systematic serial assessment to avoid confounding due to contralateral arm impairment (for not yet elucidated mechanisms, the contralateral arm can also be affected), 25% of the patients had at least one of volume or abduction impairment of the ipsilateral limb, and 18% had at least a volume or abduction impairment of the contralateral limb (9). Interestingly, the crude incidence of patient-assessed shoulder-arm symptoms in the START study averaged 19%, more in keeping with the TomoBreast measurements, whereas the physician-assessed crude incidence averaged 11.5%, lower than expected.

Subset analyses reduce the number of available patients, which is further reduced with the follow-up attrition rate, and the number of events is further reduced by the lack of precise measurements. The combined effect of subsetting, of cohorts disappearing to follow-up, of imprecision and non-blinded assessment can only lead to fuzzy non-significant results. No inference can be made from these data about the safety of hypofractionated nodal irradiation regarding shoulder-arm morbidity or regarding RIBP. The START authors appropriately recognized that limitation.

Hypofractionation might be unavoidable when treatment facilities are few, have long waiting times, in geographical areas where distances are considerable without easy access such as the Caribbean, the Middle East and many other countries. In that perspective, the START and other hypofractionation trials are important.

Beyond the populations' need, are there patients who may benefit from hypofractionated radiotherapy to the axilla following lumpectomy or mastectomy for locally advanced breast cancer (large tumor size and/or positive lymph nodes)? Common sense dictates that elderly cancer patients with multiple co-morbidity factors or frail patients with a short life expectancy would benefit the most from this fractionation. Those patients already had difficulty with their daily life activity because of their medical conditions (10).

Reducing the need for daily transportation from 6 to 3 weeks or even less may improve their quality of life. However, as elderly breast cancer patients are frequently excluded from clinical trials, the benefit of hypofractionated radiotherapy need to be assessed in future clinical trials.

It is our opinion that future prospective trials with long-term follow up are required to demonstrate the safety of hypofractionated radiotherapy in patients who require axillary radiotherapy after breast cancer surgery. Until that time, the jury is still out. Such trials should carefully include documented radiotherapy dose to the brachial plexus, heart, and lungs. Modern radiotherapy techniques such as intensity modulated radiotherapy, gating, and image-guided radiotherapy may be employed to reduce excessive radiation to the normal organs for reduction of late complication (11). Comorbidity factors such as diabetes, high blood pressure which may influence the rates of complication should be recorded. Finally, chronological age should not be a reason to exclude the patients from clinical trials.

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