Editorial Commentary

Do hypofraction and large breast size reciprocally fit in breast cancer radiotherapy?

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At present, postoperative whole breast irradiation (WBI) is standard of care for early-stage breast cancer patients (EBC) after breast conserving surgery (BCS), leading to a reduction in terms of both 'any breast cancer recurrence' and 'breast-cancer mortality' (1,2). With respect to fractionation, hypofractionated WBI has been tested within 4 prospective randomised controlled trials, reporting robust and reliable long-term local control and survival, toxicity profile and cosmetic outcome (3). This prompted clinicians to adopt hypofractionated schedules to deliver WBI after breast conservation in daily clinical practice and, nowadays, this approach is considered good clinical practice in this setting (4). Hypofractionation implies the delivery of a daily dose per fraction >2 Gy, employing fewer fractions over a shorter overall treatment time, usually with a slight reduction in the total nominal dose (5). This strategy is based on the assumption, relying on radiobiological findings, that breast cancer cells have similar sensitivity to the dose per fraction compared to surrounding normal tissues, allowing for a mild increase in daily dose with no detrimental effect on the therapeutic window (6). In general, hypofractionated schedules are designed to be milder in terms of biologically effective dose compared to conventionally fractionated WBI up to 50 Gy, with a gentler effect on normal tissue (7). This is mirrored by clinical data, as in the MD Anderson Cancer Center randomised study, where hypofractionation lead to a lower rate of acute toxicity (dermatitis, pruritus, breast pain, hyperpigmentation and fatigue), which was reflected also by quality of life and patient's reported outcome measures with less lack of energy and lower incidence of issues in meeting family needs (8). This data was recently confirmed by the study of the Michigan Radiation Oncology Consortium, in which patients treated with hypofractionation had lower rates of physician-rated moist desquamation, > G2 dermatitis, self-reported moderate to severe pain, frequent burning/stinging bother, hurting and swelling bother and fatigue (9). At the same time, hypofractionation is a cost-effective approach for both patient and healthcare providers, allowing for an optimal allocation of financial and human resources (10,11). On average, hypofractionated radiotherapy is underutilized in breast cancer patients having large-sized breast. This is mainly due to the concerns of clinicians regarding the likelihood to obtain dose homogeneity within the breast for this type of patients and the lack of robust consensus on dose parameters to decrease dose heterogeneity (12). Large breast size and excessive radiation dose within the breast (>10% of the prescribed dose) have been identified as risk factors for radiation-induced acute skin toxicity (13). The presence of the so called 'hot spots', areas receiving unintended excessive dose, is particularly related to the occurrence of moist desquamation and it is critical whenever hypofractionated schedules are employed because of the 'double trouble' issue (14). In classical

radiobiology, this is described as the phenomenon in which over-irradiated areas, while employing hypofractionation, do not only receive a higher total nominal dose (for example: 110% of the prescribed dose), but also a higher biologically equivalent dose, due to the higher dose per fraction delivered (for example: 2.67+0.267 Gy =2.937 Gy for each fraction). Reduction of dose heterogeneity is hence crucial, particularly for hypofractionated schedules, and therefore the study by Patel *et al.* provides useful insights on this specific topic (12). The authors investigated their cohort of 502 patients, having whole breast clinical target volume (CTV) >1,000 cm^3, treated with hypofractionated WBI (42.56 Gy/16 fractions). In the whole series, the rate of Grade 3 dermatitis (rated according to the CTCAE v 4.0 scale), was as low as 3.4%. By limiting the whole-breast CTV V_{105} to <10%, the same rate dropped down to <2% (12). On multivariate analysis, age >64 years, whole breast CTV >1,500 cm^3, body max index ≥34 and whole-breast CTV V_{105} ≥10% were found to be predictors of Grade 3 dermatitis (12). Interestingly, patients with all 4 of these factors had a 40% risk of grade 3 skin toxicity, compared to a <5% risk for patients with 0–2 of these factors (12). The aforementioned data, even if biased by the retrospective nature of the study and the subjective nature of the toxicity scoring together with the applicability of the results to patients treated in supine position only, stress the importance of achieving homogeneous dose distribution within the breast minimizing 'hot spots' within and outside the breast, in order to robustly implement the use of hypofractionated schedules in large-sized breast cancer patients submitted to BCS and post-operative WBI, decreasing the likelihood for the patient to experience major acute skin toxicity, and thus, minimizing the rate of consequential late effects, as shown with the long-term data of the Canadian IMRT trial, together with a significant effect on cosmetic outcomes (15,16). This can be achieved through different approaches such as 'field-in-field' 3D conformal radiation, forward planned IMRT, simple inverse planned IMRT, or complex volumetric IMRT strategies (15-19). Modern radiotherapy provides versatile tools and techniques to adapt to patient's anatomy and specific clinical needs, enabling radiation oncologists to deliver personalized treatments able to increase the therapeutic index.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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