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.

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References

1. Early Breast Cancer Trialists' Collaborative Group (EBCTCG)., Darby S, McGale P, et al. Effects of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. Lancet 2011;378:1707-16.
2. Cante D, Petrucci E, Sciacero P, et al. Ten-year results of accelerated hypofractionated adjuvant whole-breast radiation with concomitant boost to the lumpectomy cavity after conserving surgery for early breast cancer. Med Oncol 2017;34:152.
3. Franco P, Cante D, Sciacero P,et al. Tumor bed boost integration during whole breast radiotherapy:a review of the current evidence. Breast Care (Basel) 2015;10:44-9.
4. Harnett A. Fewer fractions of adjuvant external beam radiotherapy for early breast cancer are safe and effective and can now be the standard of care. Why the UK's NICE accepts fewer fractions as the standard of care for adjuvant radiotherapy in early breast cancer. Breast 2010;19:159-62.
5. Cante D, Rosa La Porta M, Casanova-Borca V, et al. Accelerated hypofractionated adjuvant radiotherapy with concomitant photon boost after conserving surgery for early stage breast cancer:a prospective evaluation on 463 patients. Breast J 2011;17:586-93.
6. Arcadipane F, Franco P, De Colle C, et al. Hypofractionation with no boost after breast conservation in early-stage breast cancer patients. Med Oncol 2016;33:108.
7. Franco P, Iorio GC, Bartoncini S, et al. De-escalation of breast radiotherapy after conserving surgery in low-risk early breast cancer patients. Med Oncol 2018;35:62.
8. Shaitelman SF, Schlembach PJ, Arzu I, et al. Acute and Short-term Toxic Effects of Conventionally Fractionated vs Hypofractionated Whole-Breast Irradiation: A Randomized Clinical Trial. JAMA Oncol 2015;1:931-41.
9. Jagsi R, Griffith KA, Boike TP, et al. Differences in

the Acute Toxic Effects of Breast Radiotherapy by Fractionation Schedule: Comparative Analysis of Physician-Assessed and Patient-Reported Outcomes in a Large Multicenter Cohort. JAMA Oncol 2015;1:918-30.
10. Rovea P, Fozza A, Franco P, et al. Once-Weekly Hypofractionated Whole-Breast Radiotherapy After Breast-Conserving Surgery in Older Patients: A Potential Alternative Treatment Schedule to Daily 3-Week Hypofractionation. Clin Breast Cancer 2015;15:270-6.
11. Lievens Y. Hypofractionated breast radiotherapy: Financial and economic consequences. Breast 2010;19:192-7.
12. Patel AK, Ling DC, Richman AH, et al. Hypofractionated Whole-Breast Irradiation in Large-Breasted Women-Is There a Dosimetric Predictor for Acute Skin Toxicities? Int J Radiat Oncol Biol Phys 2019;1:71-7.
13. Fernando IN, Ford HT, Powles TJ, et al. Factors affecting acute skin toxicity in patients having breast irradiation after conservative surgery: a prospective study of treatment practice at the Royal Marsden Hospital. Clin Oncol (R Coll Radiol) 1996;8:226-33.
14. Cante D, Franco P, Sciacero P, et al. Five-year results of a prospective case series of accelerated hypofractionated whole breast radiation with concomitant boost to the surgical bed after conserving surgery for early breast cancer. Med Oncol 2013;30:518.
15. Pignol JP, Truong P, Rakovitch E, et al. Ten years results of the Canadian breast intensity modulated radiation therapy (IMRT) randomized controlled trial. Radiother Oncol 2016;121:414-9.
16. Mukesh MB, Barnett GC, Wilkinson JS, et al. Randomized controlled trial of intensity-modulated radiotherapy for early breast cancer: 5-year results confirm superior overall cosmesis. J Clin Oncol 2013;31:4488-95.
17. Borca VC, Franco P, Catuzzo P, et al. Does TomoDirect 3DCRT represent a suitable option for post-operative whole breast irradiation? A hypothesis-generating pilot study. Radiat Oncol 2012;7:211.
18. Franco P, Zeverino M, Migliaccio F, et al. Intensity-modulated adjuvant whole breast radiation delivered with static angle tomotherapy (TomoDirect): a prospective case series. J Cancer Res Clin Oncol 2013;139:1927-36.
19. Iorio GC, Franco P, Gallio E, et al. Volumetric modulated arc therapy (VMAT) to deliver nodal irradiation in breast cancer patients. Med Oncol 2017;35:1.

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