Breast cancer is the most common type of malignant tumor and the main cause of cancer mortality in women worldwide. In general, a multidisciplinary therapeutic approach comprising surgical, medical, and radiation oncology is needed for the optimal management of breast cancer; this combination is correlated with improved overall survival rates. After breast-conserving surgery or mastectomy, post-operative radiation therapy decreases cancer mortality and loco-regional relapse rates in most breast cancer patients.

Historically, conventionally-used radiation doses ranged from 50 to 50.4 Gy in fractions of 1.8 to 2.0 Gy over the course of 25 to 28 days. This dose was empirically confirmed based on the hypothesis this schedule was safe and effective. This idea was enhanced by studies that assessed early skills of the moderately hypofractionated whole breast irradiation practice; however, these reports used obsolete and incorrect radiobiological models and outmoded devices of treatment delivery and calculation, hence exhibiting unacceptably high rates of side effects.

Nonetheless, other groups posteriorly provided assessments of normal-tissue damage and fraction size in breast tumors developing the current protocols of moderately hypofractionated whole-breast irradiation which involved fraction ranges up to nearby 3 Gy pooled with an abridged total dose delivered over a shorter period of time (e.g., three weeks). This schedule attained radiobiological equivalence to the conventional radiation doses. Long term follow-up in large clinical trials sustained the efficacy and safety of the moderately hypofractionated whole breast irradiation practices.

In fact, the all-purpose engagement of hypofractionation can serve to reduce the therapeutic period, decreasing the total number of fractions, and offering a more convenient treatment schedule for patients. Moreover, hypofractionation can also increase patients’ access to oncology centers (particular importance for countries with limited resources with restricted radiation therapy assets), decrease indirect costs associated with work breaks and travel to the medical care center, and reduce treatment costs.

Now, the first tumor-results associated endpoint assessment from the FAST Forward trial was published, which offers a treatment extreme hypofractionated schedule of just five fractions in five consecutive days for patients with early breast cancer. In this timely, multicenter, non-inferiority, prospective phase 3 randomised trial, 4,096 patients (pT1–3, pN0–1, M0) were randomly allocated into three groups to receive moderated hypofractionated RT (15x2.67 Gy; over three weeks) or two schedules of ultra-hypofractionated RT over one week (5x5.2 Gy – 26 Gy or 5x5.4 Gy – 27 Gy) directed to the whole breast or chest wall. No statistically significant difference in the 5-year cumulative incidence of breast tumor relapse among the groups was found (2.3% in moderated hypofractionated RT versus 2.0% in 27 Gy versus 1.5% in 26 Gy). Likewise, the acute and late adverse events were similar in the groups, apart from a higher late normal tissue effect in the 27 Gy RT arm. We would therefore certainly not consider the highlighted results for 26 Gy versus 40 Gy for breast distortion and breast/chest wall oedema clinically relevant. The other highlighted result, the one for breast induration outside the tumor bed, is statistically significant at p<0.0001; however, it is hard to maintain for clinical significance with the demonstrated 5-year moderate/marked events rates only 0.1% in 40 Gy and 1.9% in 26 Gy. In fact, the side effects are properly low across all of the endpoints, regardless the treatment schedule. Hence, it should be recognized that the clinical outcomes of this trial could support the adoption of 26 Gy in 5 consecutive daily fractions as a treatment option for most of early breast cancer patients in the near future.
Despite patients with ductal carcinoma in situ (DCIS) were not a formal inclusion criterion in the FAST Forward trial, extreme hypofractionated ones can also be considered, as there is no radiobiological concern regarding why five fractions are expected to be less effective in the DCIS setting. This is coherent with a previous policy which adopted moderately hypofractionated irradiation for DCIS once the results of clinical trials that assessed patients with invasive breast cancer have been extrapolated to the context of in situ disease.

Along the same reasoning lines, extreme hypofractionated can be considered in patients who received both implant and autologous reconstructions as acute and late normal tissue site effects overall were similar in five fractions (26 Gy group) and 15 fractions in the FAST Forward trial, although numbers of reconstructions were small. In other words, the results of the FAST Forward trial showed that most normal tissue adverse events that are frequently associated with radiation-related toxicities in implant and autologous breast reconstructions (e.g., fibrosis, skin retraction, and breast shrinkage) were similar in patients who underwent five fractions (26 Gy group) or 15 fractions. Additionally, no randomized phase III trial has yet validated the use of a conventional or moderately hypofractionated radiation doses after breast reconstruction. Historically, in empirical studies, the conventional dose has been used whenever breast-reconstruction techniques were described. In recent decades, in clinical practice, once a treatment has been performed with conventional doses, there has been a simple incorporation of reconstructive surgeries.

When indicated, sequential boost can be added to 26 Gy in five fractions whole breast RT. In the FAST Forward trial, 25% of patients received a sequential boost of five to eight fractions of 2 Gy and were well tolerated. More will emerge with the FAST Forward nodal sub-study which is yet to report and where all patients are node-positive by definition. The adoption of an extreme hypofractionated schedule for higher risk breast cancer patients still need to be evaluated.

Since the majority of patients in the FAST Forward trial are relatively low risk cases, we should be very careful when changing guidelines based on one clinical trial in particular for use in the higher risk patients. This is the reason why the UK group has a call-out for treatment de-escalation studies FAST Forward trial HIGH focusing on patients with high-risk disease, including those requiring internal mammary lymph nodes treatment.

Finally, the economic issues behind new ways of delivering radiation therapy need to be discussed. How to deal with the possible financial loss on reimbursement due to adopting extreme-hypofractionated radiation therapy schedules? While in countries like The Netherlands, Italy, and the UK (where reimbursement is largely independent from the number of fractions), moderate hypofractionated breast irradiation practice is used by the majority of centers, in the more reimbursement-driven models with payment-per-fraction countries, including Germany, France, Portugal and the USA, a lot of reluctance exists towards applying moderate hypofractionation in daily practice. The possible financial loss induced by the reduction in per-patient income due to fractionation-based reimbursement could be compensated by an evolution of the reimbursement model from a fee-for-service system to a bundled payment system based on quality parameters. It is important to encourage payers to abandon payment per fraction as the use of moderate radiation therapy and extreme-hypofractionation for breast cancer patients is a concrete reality.

REFERENCES


