



# Hypofractionation for postoperative breast cancer radiotherapy: is acute toxicity a limiting factor?

Marco Krengli<sup>1,2</sup>, Salvatore Terrazzino<sup>3</sup>, Letizia Deantonio<sup>1,2</sup>

<sup>1</sup>Department of Radiotherapy, University Hospital Maggiore della Carità, Novara, Italy; <sup>2</sup>Department of Translational Medicine, <sup>3</sup>Department of Pharmaceutical Sciences, University of “Piemonte Orientale”, Novara, Italy

*Correspondence to:* Marco Krengli, MD. Chair of Radiotherapy, University of “Piemonte Orientale”, Via Solaroli, 17-28100 Novara, Italy. Email: marco.krengli@med.uniupo.it.

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Whole-breast radiotherapy (RT) after conservative surgery in women with early breast cancer is the standard of care, providing a reduction of local recurrence and breast cancer mortality (1). In order to facilitate the access to RT centers, to optimize the allocation of RT resources, and to preserve the patient quality of life, the scientific community has investigated the efficacy and toxicity of abbreviated courses of postoperative breast RT by using a radiobiologically-equivalent total dose with hypofractionated schedules in randomized controlled trials as well as in several prospective and retrospective studies (2-5). These trials have demonstrated similar results in terms of tumor control, overall survival, and cosmetic outcome compared to the standard regimen. In particular, the two largest randomized trials, START A and B, testing different accelerated hypofractionated RT regimens demonstrated the efficacy and the safety of the RT schedule delivering 40 Gy in 15 fractions along three weeks that has become one of the most commonly used hypofractionated schedules (4). Additionally, alternative abbreviated RT schedules, including those in which RT is administered once a week, have been investigated. In this regard, the UK FAST trial tested two 5-fraction schedules delivering one fraction of 5.7 *vs.* 6.0 Gy per week to total doses of 28.5 *vs.* 30 Gy, respectively, in comparison with the standard regimen of 50 Gy in 25 fractions (6). At 3-year median follow-up, 28.5 Gy in 5 fractions resulted comparable to the standard regimen and developed even lower breast adverse effects than the schedule delivering 30 Gy in 5 fractions.

Recently, the FAST-Forward randomized, multicenter phase III trial, has been launched to test the hypothesis that

a 1-week course of RT is as effective and safe as a 3-week hypofractionated schedule (7). The study protocol plans to randomize 4,000 patients to 15 or 5 daily fractions to the whole breast or chest wall, followed by sequential tumor bed boost after lumpectomy. Each patient is allocated to one of the following dose levels: 40.05 Gy in 15 fractions of 2.67 Gy, 27.0 Gy in 5 fractions of 5.4 or 26.0 Gy in 5 fractions of 5.2 Gy. The primary endpoint is local tumor control and the secondary endpoint is the evaluation of acute and late adverse events in normal tissues, quality of life, as well as contralateral primary tumors, regional or distant metastases, and survival.

A preliminary assumption of this trial was that acute skin reactions would be less sensitive to fraction size than late effects in normal tissues and consequently the weekly fractionation schedules with higher dose per fraction and lower total dose are expected to produce an inferior severity and duration of acute effects, despite the shorter overall treatment time. In order to verify this hypothesis, the results on acute skin toxicity observed in two substudies undertaken during 2011 and 2013 in the first 353 patients enrolled in the FAST-Forward trial were recently published by Brunt *et al.* (7).

The authors justified the need for two cohorts treated with 1-week schedule in relation to the inadequacy of the scoring system used at the beginning of the trial. In the first study design, acute skin reactions in the treated breast were scored using the radiation therapy oncology group (RTOG) toxicity scale (8) that is not able to score separately moist desquamation and edema. Actually, moist desquamation was the main concern in the study and the

onset of edema represented a potential confounding factor when scoring with the RTOG scale. A second substudy was therefore undertaken using the standard CTCAE system (9) that is able to score different levels of skin desquamation, independently from edema.

Primary endpoint in the Brunt's study (7) was the proportion of patients within each treatment group with grade  $\geq 3$  toxicity detected with RTOG and CTCAE scale, respectively from the first RT fraction to 4 weeks after RT completion. Secondary endpoints were the evaluation of the worst grade of acute skin toxicity and the adherence to the acute toxicity assessments.

In the first substudy, the percentage of patients with grade 3 RTOG toxicity was slightly lower after the 1-week (10% in the 27 Gy/5 fraction group and 6% in the 26 Gy/5 fraction group) than after the 3-week schedule (14%). Moreover, no evidence of higher rate of grade 3 toxicity was observed in the subset of patients who received a tumor bed boost. In the second substudy, only one patient developed acute grade 3 CTCAE toxicity in the 27 Gy/5 fraction group while two patients developed grade 2 moderate edema in the 40 Gy/15 fraction group and one in the 26 Gy/5 fraction group. In this substudy, toxicity grade 2 was mainly due to "moderate to brisk erythema" that arose in 27–30% of the patients in the 1-week schedules and in 47% in the 3-week schedule.

The slightly higher incidence of grade 3 toxicity in the first substudy that used the RTOG scale could be related to the different definition of the grades of skin toxicity of the two scoring systems used the two substudies however no comparison was performed since statistics was not designed to detect differences across the treatment groups. Anyway, the results confirmed a low incidence rate of clinically relevant acute skin toxicity. Upon these findings, no concern for the 1-week regimens emerged in terms of more severe or longer acute skin reactions. It will be of interest at the study completion to see the definitive rate of acute skin toxicity and to analyze the potential prognostic factors such as breast volume, body mass index (BMI), patient comorbidities, and RT dosimetry.

The results from the Brunt's study (7) are substantially consistent with those of randomized as well as prospective and retrospective literature studies showing that acute toxicity rate is similar or even milder compared to that of standard fractionation. In the randomized START trials, 1.5% of the patients who received conventional fractionation experienced acute dermatitis grade  $>3$  compared to only 0.3% of patients who received hypofractionated RT (4). Similarly, retrospective studies on hypofractionation reported a very low incidence of acute

grade  $>3$  skin toxicity, ranging between 1% and 5% (10-12).

Nowadays, one of the main issues of highly hypofractionated RT still remains the patient selection criteria. The majority of the patients included in the literature studies is of old age and affected by early-stage invasive breast cancer with relatively low-risk, i.e., with positive hormonal receptor status and histological low proliferative grade. As a matter of fact, this favorable subset of patients could be eligible also for other alternative treatments, such as partial-breast irradiation (PBI), including intraoperative radiotherapy (IORT), or even hormonal therapy alone for elderly patients. In this regard, the American Society of Therapeutic Radiology and Oncology (ASTRO) guidelines report that whole breast RT with a hypofractionated schedule is appropriate in patients of  $\geq 50$  years, with pathological stage T1–T2 N0 disease treated with breast conserving surgery, without indication to chemotherapy, and with a dose inhomogeneity on RT plan  $<7\%$  (13). In such a scenario, where a satisfactory local control rate can be achieved with different approaches, the lowest risk of toxicity and the best patient quality of life could be the real endpoints for treatment decision making. In terms of selection criteria, the Brunt's study (7) included patients who underwent post-lumpectomy RT but also post-mastectomy irradiation of the thoracic wall, of the axillary lymph nodes, and of the tumor bed with a boost dose. The latter patient population represents a subset at higher risk compared to that of other clinical trials investigating hypofractionated regimens. Long-term outcome on the total estimated accrual of 4,000 patients will further clarify the suitability of the hypofractionated RT approach in such a patient sub-population.

As far as the radiation technique is concerned, the FAST-Forward trial applied a 3-dimensional computed tomography (CT)-based planning in supine position with a conventional RT delivery by two megavoltage tangential beams and using dose constraints as recommended by ICRU documents (14). Nowadays, more sophisticated techniques are available such as those with prone patient setup, intensity-modulated RT, breathing-hold modality, and even particle therapy that could improve dose homogeneity and reduce the irradiation of healthy tissues (15-18). These technical aspects were not considered in the FAST-Forward trial but actually they can be more easily implemented in a monoinstitutional pilot study rather than in a multicenter trial. Moreover, a relatively simple technique like that adopted in the FAST-Forward trial represents quite well what can be done in common daily practice and be applied in most of the centers worldwide.

From literature data, the severity of acute as well as late skin reactions has been attributed to several factors not only related to radiation technical aspects, but also to patient characteristics, such as breast size, patient age, BMI, and smoking and alcohol habits (1,3-5,12). These factors however are not sufficient to fully explain the inter-individual variability for the occurrence of skin reactions, suggesting that other factors including genetic predisposition may play a relevant role in the individual response. Several lines of evidence support a genetic basis for normal tissue radiosensitivity, however the specific genetic determinants and the underlying molecular mechanisms are only partly understood. Single nucleotide polymorphisms (SNPs) in candidate genes related to genomic DNA and mitochondrial DNA have been hypothesized to confer an increased risk or to have a protective role for the development of acute and late toxicity after breast RT (19-22). Unfortunately these results suffer from the lack of large prospective population groups, and of a second cohort of breast cancer patients to validate the data. With the recent advances of high throughput genotyping in the context of multicenter collaborations, the genome wide approach is expected to provide an important step forward in understanding the genetic architecture of normal tissue radiosensitivity of the breast (21). In light of these developments, it could be of interest if these large ongoing randomized trials, such as FAST-Forward, would consider also the analysis of genetic assessment.

Another interesting aspect to be discussed is the possible relation between the occurrence of acute and late effects in the irradiated skin. Few studies on hypofractionation analyzed this possible association and did not find that the grade of acute toxicity could be related to and consequently predict the risk of late fibrosis (5,23). As far as late effects are concerned, considering an  $\alpha/\beta$  ratio of 3 Gy for late skin effects in the radiobiological linear-quadratic model, we could expect more severe effects in the 1-week hypofractionated groups of patients of the FAST-Forward trial, however the possible increase of late effects should be analyzed and discussed after the completion of the study. Moreover, it will be of great interest to assess other possible late effects in terms of pulmonary and cardiac toxicity in order to clarify the impact of the 1-week hypofractionation schedules on the morphology and functionality of these organs.

In conclusion, looking at the study design and at the preliminary data of the FAST-Forward trial published by Brunt *et al.* (7), we can argue that acute toxicity should not be a limiting factor for highly hypofractionated RT. However other issues should be carefully taken into account when using

highly hypofractionated regimens, first of all the risk of late effects not only at the level of the skin but also of the other irradiated healthy tissues and organs like lung and heart.

The optimal modality for treating breast cancer is still a challenge despite the several studies conducted in the last decades. In particular, the best adjuvant radiation treatment is still an open issue in the era of customization of cancer therapy. We expect that the FAST-Forward trial will substantially contribute to the understanding of the role of highly hypofractionated regimens not only aiming at obtaining an optimal disease control but also at preserving the patient quality of life.

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