

# Review of: "Acute toxicity and health-related quality of life after accelerated whole breast irradiation in 5 fractions with simultaneous integrated boost"

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With the advent of the FAST trials [1,2], there has been a growing interest in the use of ultra-hypofractionation for the adjuvant treatment of breast cancers. Nevertheless, in daily clinical practice, there are still some concerns about its use. Your study is perfect timing, as it will empower evidence in the use of ultra-hypofractionation. Indeed, the YO-HAI5 trial will generate a level one evidence [3] by randomizing an experimental arm VS control arm which is considered the standard of care.

The present paper is the interim analysis of the YO-HAI5 trial, made to analyze physicians 'assessed acute toxicity and patient-related outcomes for Quality of Life reported in the first 200 randomized patients. In this commentary we are going to analyze this study from a clinical and methodological point of view following the PICO criteria [4].

Population is the first aspect to be checked. Eligible patients were women > 18 years old, who underwent breast conservative surgery without any nodal or distant metastases and every case was discussed in a multidisciplinary tumor board.

Indeed, selection is well done and this sample of patients does represent the population that is encountered daily and, therefore, this study will be easily translated in clinical practice.

Intervention and Comparison are the next steps. The experimental arm is an ultra-hypofractionated treatment made of 28.5 Gy delivered in 5 fractions (5.7 Gy per fraction) to the whole breast every other day. The control arm is an hypofractionated schedule, as for START B trial [5], of 40.05 Gy delivered in 15 fractions (2.67 Gy per fraction) to the whole breast, daily.

From a methodological point of view, the procedure is correct as an experimental arm is compared to the standard one (as suggested by ASTRO guidelines [6]),

Furthermore, from a radiobiological point of view, using the Fowler formula for BED [7] the two treatments are equivalent. Using an alpha/beta parameter of 4.6 as suggested by the trial, indeed,  $BED_{4.6}$  of the experimental arm is 63.82 Gy and  $BED_{4.6}$  of the standard arm is 63.30 Gy. Using an alpha/beta parameter of 3.7 as used for the FAST-forward trial,  $BED_{3.7}$  was 72.41 Gy and 68.95 Gy respectively.

Also, the patients 'setup and the centring computed tomography were done as per standard of care.

Nevertheless, it is not described if treatments are delivered with a 3D conformal technique or with an Intensity Modulated technique.

Moreover, this study has the merit of clarifying one of the most controversial themes about the FAST-Forward trial: the use of the boost. The experimental arm prescribed 31 Gy in 5 fractions (6.2 Gy per fraction; BED<sub>4,6</sub> 72.78 Gy) to the tumor bed with a simultaneous integrated boost technique. The standard arm used the same technique to prescribe 46,8 Gy in 15 fractions (3.12 Gy per fraction; BED<sub>4,6</sub> 78.54 Gy) to the tumor bed. Therefore, while in the FAST-Forward trial a boost of at least 4 fractions nearly doubled the overall treatment time (and this was one of the most important criticism of this trial), in the YO-HAI5 a simultaneous integrated boost does not prolong the duration of therapy.

At last, treatment delivery in prone position could be criticized as it is not yet considered the standard of care. The most important concern involves interfraction changes that imply the use of daily CBCT to correct for rotational variations that occur in 20% of treatments as stated by Xiao et al [8].

Outcomes are the last point. The primary endpoint of the trial is breast retraction 2 years after RT. Secondary endpoints are acute breast toxicity, late toxicities other than breast retraction, fatigue, cosmesis, Quality of Life, cost effectiveness, locoregional and distant tumor control and dose/volume parameters of target and organs at risk.

The primary endpoint, so, is a late toxicity outcome. In the era of ultra-hypofractionation, toxicity is one of the biggest concerns for every radiation oncologist. This study will prove if these fears are founded or not. Nevertheless, 2 years for the late toxicity are few. The experience from previous trials [1,2,5, 9-11] shows that differences in toxicities between standard arms and experimental arms will occur in at least 5 years. Indeed, if no statistical differences will be detected between the two arms, it could be because of the insufficient time of follow-up.

Conversely, it is very interesting the analyses of the secondary endpoints as the focus is not only on the clinical or toxic outcomes but also on cost-effectiveness valuations and patients' perspective of their life after the treatment. Indeed, both physician-assessed toxicity and patient-reported outcome are evaluated, and the most common scales or questionnaire of evaluation were used to define these results.

Nevertheless, these endpoints were not prespecified for the statistical analyses. This means that, even if a statistically significant difference will be noticed between the two arms ( $p < 0.005$ ) this could be clinically irrelevant. Therefore, evidence generated on the secondary outcomes, will be weak.

At last, neither patients nor doctors are blinded, thus generating a detection and a performance bias.

Talking about this interim analysis of 200 patients, the results are strongly in favor of the experimental arm. Nonetheless this paper evaluates only the acute toxicities in terms of quality of life and cosmetic outcomes. This advantage is well predicted as the BED<sub>10</sub> (for the acute toxicity) of the experimental arm is of 44.75 Gy VS BED<sub>10</sub> of the standard arm of 50.74 Gy, i.e., less acutely toxic.

Therefore, the most important value of this interim analysis are the subjective outcomes that are shown to

be significantly better for the experimental arms. Indeed, the fact that patients feel better about a shorter course of radiation therapy is predictable but not taken for sure.

In conclusion, as a radiation oncologist will approach this paper, he will read some expected results as well as the important patients' perspective. The completeness of the YO-HAI5 trial will give important information about the use of ultra-hypofractionated regimens in the adjuvant treatment of early breast cancer even if there are some limitations.

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