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Breast

Increasing the value of radiotherapy in breast cancer

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Comment on:

Intraoperative irradiation for early breast cancer (ELIOT): long-term recurrence and survival outcomes from a single-centre, randomised, phase 3 equivalence trial. Roberto Orecchia et al: Lancet Oncol. 2021 May;22(5):597-608.

Radiotherapy plays an important role in breast cancer management. After breast-conserving surgery, radiotherapy reduces the probability of recurrence and improves overall survival. Adjuvant whole-breast irradiation (WBI) was previously delivered in daily treatments, given over five–six weeks. These treatments, coupled with other multidisciplinary advances such as increasing the use of systemic therapy, yielded outstanding outcomes.

With these excellent outcomes, attention turned towards increasing the value, defined as achieving the best outcome at the lowest possible cost, of radiotherapy treatments by decreasing treatment toxicity, improving convenience, and reducing cost. A strategy to produce greater value of treatment is hypofractionation, which reduces the number of treatments and shortens the treatment course. Hypofractionation can be done with WBI or newer partial breast irradiation techniques that also decrease the volume of tissue treated. Both WBI and partial breast irradiation hypofractionation strategies have proven beneficial. Initial trials of WBI hypofractionation showed that three-week treatments yielded the same high tumour control rates as five-week treatments, and also reduced toxicity compared with five-week treatments. The FAST-Forward trial showed that five days of treatment with WBI was equivalent to a three-week regimen of WBI with respect to tumour control and avoidance of toxicity.

Partial breast irradiation radiotherapy trials have also used hypofractionation but focused the distribution of radiation to the breast volume immediately adjacent to the tumour bed. Various methods exist for delivering partial breast irradiation. A common method conformally shapes radiation doses around a tumour bed volume with the use of beams, such as those used in WBI. A second type of partial breast irradiation is brachytherapy, which inserts radioactive sources around the tumour bed to achieve conformal radiation dose distributions. Finally, partial breast irradiation can also be delivered with intraoperative radiotherapy, in which a single fraction treatment is given during the lumpectomy surgery.

In The Lancet Oncology, the long-term results of an intraoperative radiotherapy partial breast irradiation randomised trial by Roberto Orecchia and colleagues are reported. In this well-designed trial, patients were randomly assigned to a single fraction of radiotherapy delivered during their surgery versus five weeks of WBI. Unfortunately, the primary endpoint of the study was not met, with the ipsilateral breast recurrence rate being four-times higher in the intraoperative group than in the five-week WBI treatment group (15-year rates of 12.6% in the intraoperative group vs 2.4% in the WBI group). One takeaway of the study is the remarkably low 15-year recurrence rate in both groups, and an exceptionally low rate with WBI treatment. The authors also report that patients with well-differentiated, luminal A molecular subtype disease with a tumour measuring less than 1.0 cm had the lowest recurrence rates, and that there was no difference in recurrence by treatment in this low-risk cohort. However, this was an unplanned subgroup analysis that represented only 10.8% of the study population, so this finding must be interpreted with caution.

Given the myriad of trial data emerging for both hypofractionated WBI and partial breast irradiation, there are various strategies available to radiation oncologists. Ultimately, weighing the value of each approach should drive the decision of which radiotherapy strategy to use, where the value of each strategy is considered as outcome versus cost. The largest prospective randomised trial that found equivalence or improvement in outcomes with a partial breast irradiation approach versus a WBI approach was the IMPORT LOW trial done in the UK. This trial used an identical three-week hypofractionation dose schedule for both the WBI and partial breast irradiation groups. The two groups only differed with respect to the irradiated volume. The results showed very low recurrence in both groups and less treatment toxicity in the partial breast irradiation group than in the WBI group. As noted earlier, in the FAST-Forward trial, many of these same investigators subsequently showed that the even shorter one-week WBI treatment (five fractions) had equivalent outcomes to the three-week WBI treatment course. Accordingly, it is logical to hypothesise that this

same 1-week dose fractionation schedule should also prove equivalent if used for partial breast irradiation volumes as defined in the IMPORT LOW trial. This hypothesis is further supported by a trial published by investigators from Florence, Italy, who also used a one-week dose fractionation schedule.

There are many potential advantages for considering a partial breast irradiation approach that uses a conformal external beam on a once-per-day schedule, with the use of simple treatment-planning techniques. Unlike intraoperative approaches, the final pathology is known at the time of treatment and the treatment volume can be customised according to the operative pathology. Unlike brachytherapy approaches, no foreign materials such as catheters are introduced into the breast, most likely improving the patient's treatment and decreasing the risk of breast infection. Furthermore, this approach substantially reduces the total cost of radiotherapy compared with previous standards.

The value of radiotherapy in breast conservation has truly increased during the past few decades. In oncology, it is uncommon to define new paths that achieve important improved outcomes while simultaneously reducing the cost of care.

