The GEC-ESTRO breast brachytherapy trial: another important piece in the jigsaw picture of accelerated partial breast irradiation

Polgar et al present the results of the GEC-ESTRO accelerated partial breast irradiation (APBI) trial, whereby patients were randomised to whole breast irradiation (WBI) using 2Gy fractions for 6 weeks, or APBI using brachytherapy, typically delivered over 4 days. This study represents the largest reported APBI randomised trial (RCT) combined with the most comprehensive report on late normal tissue toxicity to date. Non-inferiority of the primary endpoint, ipsilateral breast local relapse rate, has already been proven in a previous publication[1]. These latest results demonstrate that APBI brachytherapy using the reported methods, show similar late toxicity profiles and cosmesis to WBI at 5 years following treatment. In addition, there was a statistically significant reduction in grade 2 or 3 late skin side-effects after APBI.

The trial team should be commended for their meticulous assessment and reporting of late toxicity with robust median follow-up of over 6 years. It is informative that both cumulative incidence of toxicity and prevalence at fixed time points has been reported; taking into account resolution of some side-effects over time. The authors acknowledge possible bias in unblinded assessment, but this tends to be unavoidable, especially for patient reported outcomes (PROs). However, they will also report on a planned photographic analysis, which will be blinded to assessors. In addition, further late toxicity assessment will be carried out at 10 years: this is particularly relevant for subcutaneous fibrosis, given that the natural history shows development of this side-effect after 5 years[2].

So how does this trial fit within the context of other reported APBI RCTs? The scientific rationale for APBI is that radiotherapy to the region around the tumour bed will decrease the late normal tissue side-effects by virtue of a smaller irradiated volume, whilst maintaining acceptably low local recurrence rates. So far, the hypothesis of reduced late toxicity with APBI has not been upheld. This is partly due to a paucity of side-effect reporting in the published APBI studies, but the available results have been drawn together within the recent Cochane systematic review[3]. This shows that APBI demonstrates no difference in late skin toxicity, but increases subcutaneous fibrosis and fat necrosis. However, it is premature to draw firm conclusions regarding both subcutaneous fibrosis and fat necrosis with APBI as these meta-analyses were dominated by the results of single trials, namely the interim report of RAPID (external beam radiotherapy - EBRT) and ELIOT (intraoperative radiotherapy) respectively. Clearly, a repeat of the systematic review will be required with the mature results of four other APBI RCTs involving more than 10,000 women (NSABP B-39 trial, IMPORT LOW, IRMA and SHARE)

So what are the key remaining questions with APBI? Interpretation of all these RCTs will present a major challenge: very different radiation techniques are used including EBRT, intraoperative and brachytherapy; total dose and overall treatment time vary widely within and between studies; and irradiated partial volume range from a small rim around the tumour bed (Targit) to one-third/half

the breast (IMPORT LOW). Reports of late toxicity with APBI using EBRT are conflicting. For example, the RAPID trial interim report using 38.5Gy in 10 fractions over 5 days showed significantly worse late side effects at 3 years with APBI compared with WBI[4]. This effect could be due to the higher biologically equivalent dose and incomplete repair with twice-daily treatment[5]. However, similar results were not found in the NSABP B-39 trial, using the same regimen[6]. A smaller treated volume in relation to whole breast size may mitigate this higher biological dose to some extent, but this "volume effect" is far from clear at present[7]. Careful reports of dosimetry and treated volume will add clarity in due course. It will be interesting to see the full publication of IMPORT LOW, which is the only RCT to investigate the effect of irradiated volume as the dose/fractionation and technique is constant across study arms, namely 40Gy in 15 fractions.

So what are the key messages for oncologists? This large RCT shows that APBI using these brachytherapy techniques and doses are an acceptable alternative to WBI using 2Gy fractions for 6 weeks. It remains to be seen whether this brachytherapy APBI technique becomes widely adopted, due to limitations in expertise and higher cost compared with hypofractionated EBRT. We need mature results of other RCTs, but this is a valuable piece in the emerging jigsaw picture of APBI. Finally, it emphasises the importance of high quality late toxicity data from breast radiotherapy trials, as these survivorship issues are vital in an era of excellent local control and survival.

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