Ultra-targeted accelerated partial breast irradiation using TARGIT – a cautionary note

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One of the seven ongoing trials of accelerated partial breast irradiation (APBI) has concluded that single-dose intraoperative radiotherapy should be considered as an alternative to protracted whole-breast irradiation. With a median follow up of two years, such conclusions seem premature. Until the risk and pattern of recurrence is reported at longer follow up, APBI should remain experimental.

Accelerated partial breast irradiation (APBI) is an abbreviated radiotherapy course delivered to the tissue surrounding the excision cavity. It is under intense clinical investigation as a therapeutic approach for low-risk early-stage breast cancers.[1] Phase II studies of APBI using multicatheter brachytherapy or external-beam radiotherapy show high local-control rates at 7–12 years median follow up.[2–4] These studies highlight the long natural history of the low-risk early-stage breast cancers for which APBI is being proposed. It therefore seemed prudent to wait for the 5–10 year follow-up data on ~16,000 women enrolled in seven randomised controlled trials comparing APBI with whole-breast irradiation[2] to make definitive conclusions on the safety and efficacy of APBI and to establish the clinical, pathological or technical contexts where caution should be exercised with different APBI techniques.[2] However, the investigators of one of these trials, the TARGIT trial, thought otherwise.

In their report,[5] the TARGIT investigators state that their trial "provides robust and mature evidence... showing that targeted intraoperative radiotherapy is safe," and concluded that, "for

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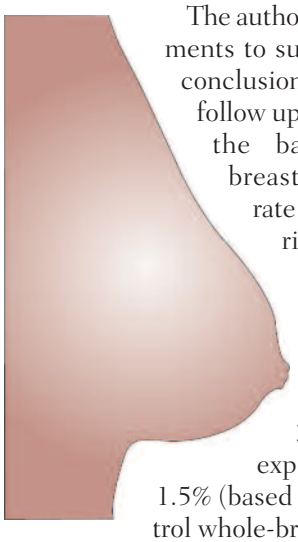
selected patients with early breast cancer, a single dose of radiotherapy delivered at the time of surgery by use of targeted intraoperative radiotherapy should be considered as an alternative to external beam radiotherapy delivered over several weeks." In the accompanying commentary, Azria and Bourgier[6] are convinced that, for elderly patients, "APBI is the new standard and TARGIT is an excellent approach." Furthermore, a lead TARGIT investigator has highlighted that the UK National Health Service wastes £4 million annually on homeopathy, which he argues could be used to provide TARGIT.[7] He goes on to question whether the introduction of TARGIT APBI will have to wait for financial approval while homeopathy continues to creep under the hurdle. Against this backdrop, they argue, the oncology community should take a stand on endorsing the wider use of TARGIT APBI as standard of care for women fulfilling the selection criteria of the TARGIT trial. While this view is endorsed by the TARGIT triallists and other reasearchers,[5–7] I would consider this premature because of issues highlighted in this article.



In the randomised, multicentre TARGIT trial, 2232 women aged ≥45 years with low-risk early-stage breast cancer received intraoperative TARGIT APBI or whole-breast irradiation for 5–7 weeks.[5] At its initiation in 2000, the trial aimed to publish the results in 2006 with median follow up of five years.[8] However, accrual was highly extended and two thirds of the patients were recruited in the last three years of the decade-long accrual. For the whole cohort of randomised patients, the minimum follow-up period is not specified and the median follow up is 25 months. Fewer than 20% of the enrolled patients were followed up beyond four years before publication of the data. The authors have, therefore, restricted the display of local recurrence rates to four years, which was not significantly different between the two arms – local recurrence rate of 1.2% with TARGIT and 0.95% with whole-breast irradiation (P=0.41). From this report, it is not clear if there were any incidences of local recurrence beyond the four-year period.

The authors have used two arguments to support their definitive conclusions, despite such short follow up. First they argue that the background five-year breast cancer recurrence rate in their cohort of low-risk breast cancer patients, which they had projected 10 years ago to be 6% and formed the basis of recruiting 2232 women, is now expected to be around 1.5% (based on data from the control whole-breast irradiation group in the study) and, therefore, only 585 cases are sufficient to prove non-inferiority. In contrast, other prospective APBI studies, such as the MammoSite study,[9] that have discussed results of a subset of their patients having a longer follow up than the whole cohort, have showed the characteristics and treatment variables of this subset, and have refrained from drawing practice-changing conclusions. With a decade-long accrual in the TARGIT trial,[5] the characteristics of patients, disease and treatment may have changed during the trial period and it should be seen how representative they are of the entire enrolled population of 2232 women. Vaidya et al.[5] argue that a quarter of the 2232 enrolled patients are sufficient to draw conclusions on noninferiority; however, no mention is made about the international steering committee of the TARGIT trial increasing the sample size from 2232 to 3432 women in March 2010.[10] The second argument is that the short follow-up period covers the peak hazard of local recurrence that occurs between two and three years after surgery, allowing them to draw cautious yet reasonable conclusions about efficacy. Yet prospective studies on similar low-risk patients treated with quality-assured APBI have shown that actual breast cancer recurrence rates increase with time. For example, the German–Austrian ESTRO phase II trial[4] that assessed 273 patients with a median 63 months follow up showed that a negligible four-year breast cancer-recurrence rate, similar to the present TARGIT report, equated to a recurrence rate of 2.3% at five years and 5% at eight years. Moreover, in women with a nonhomogeneous dose of radiation, the eight-year recurrence rate was 7.5%. If the TARGIT trial with just 212 women at risk at four years after intraoperative APBI can draw reasonable conclusions on efficacy, many other ongoing or recently concluded randomised trials of APBI would be better placed to draw similar conclusions without any further wait.

When mature data are presented from the TARGIT study, interpretation should acknowledge that 234 out of 1113 women (21%) in the TARGIT APBI cohort received treatment in the form of mastectomy or whole-breast radiotherapy either because of protocol violation or adverse pathology.[5] The primary analysis has been performed on an intention-to-treat basis, as recommended by the CONSORT guidelines. However, with one in five women

in the TARGIT arm undergoing standard treatment, the effect of TARGIT APBI may have been overestimated. It would be important to know the median follow up in the women who received TARGIT APBI without whole-breast radiotherapy and the number and site of breast cancer recurrences in this cohort at clinically appropriate time points.

Based on radiobiological modelling, Vaidya et al.[5] suggest that the biological dose from TARGIT 50 kV X-rays will be 20%–30% higher than the physical dose. Assuming this is true, it means that at 1 cm from the excision cavity the physical dose equivalent is only 7 Gy. If the long-term results of TARGIT show that a single dose of 20 Gy at the surface and 5–7 Gy at a depth of 1 cm is able to control breast cancer, it would imply that either the volume of tissue that needs full-dose irradiation is a few millimetres or that the low dose of radiation at 1 cm, which we otherwise consider subtherapeutic, is sufficient to control cancer. Such findings would have far-reaching implications for cancer treatment with adjuvant radiotherapy. If the low physical dose of 5 Gy at 1 cm with TARGIT is radiobiologically a much higher dose and sufficient to control cancer then it can also be expected to correlate with late toxic effects, especially in the 142 women who received full-dose conventional whole-breast irradiation following full-dose TARGIT. The absence of reported incidences of fat necrosis in the Vaidya et al.[5] study is unusual for an APBI series. Without knowing the compliance with annual mammography during follow up, site of recurrence and its distance from the lumpectomy site, the possibility of under-reporting of breast cancer recurrence cannot be ruled out. Imaging of another spherical device placed intraoperatively in the excision cavity has shown that in some instances there could be a significant gap between the surface of the applicator and the breast tissue.[1] As TARGIT is an ultra-targeted form of radiotherapy with very sharp fall off of the radiation dose and is delivered in a single sitting, placement precision and its verification is crucial. Even a few millimetres of fluid between the applicator surface and excision cavity wall would seriously compromise the absorbed dose with 50 kV X-ray.

Trials evaluating new adjuvant therapy in early-stage breast cancer refrain from reporting results at very short median follow up, without clearly indicating them as interim results, and do not make practice-changing conclusions at these interim time points. Leading publications with definitive therapeutic recommendations based on selective discussion on a subgroup of less than 20% of patients with a four-year follow up is a new phenomenon in early-stage breast cancer. This requires all triallists, reviewers and editors to take a clear stand. I fear that the premature report[5] with definitive conclusions, accompanying supportive commentary[6] and correspondence in a leading medical journal, and associated media coverage, may trigger a race to report the remaining six APBI trials prematurely.

Most of these trials already have much longer median follow up than the TARGIT trial and if the statistical rationale proposed for early reporting and drawing definitive conclusions are accepted for the TARGIT trial, they will be applicable to almost all the remaining trials.

There is no doubt that APBI is approaching a very exciting phase and has real potential to offer safe, convenient and cost-effective breast conservation in the coming decade. But when dealing with a low-risk disease with long natural history, premature conclusions can sometimes be counterproductive.

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