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EDITORIAL

# A Flawed Study Should Not Define a New Standard of Care

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Targeted intraoperative radiation therapy (TARGIT) puts forward the tantalizing prospect of marked simplification of breast radiation therapy to a single treatment delivered with an easily shielded low-energy (50-kV) x-ray device at the time of breast surgery. Based upon the results of the TARGIT-A trial, on July 25, 2014, the National Institute of Health and Care Excellence (NICE) in the United Kingdom gave preliminary recommendation for the use of TARGIT within the UK National Health Service (1). This endorsement and the growth in the use of this modality appear to be occurring without the full knowledge and recognition of the methodologic flaws of the TARGIT-A trial. These flaws are sufficiently profound as to undermine confidence in both the efficacy and the safety of TARGIT and should provide pause to any clinician considering its application.

The prospective TARGIT-A trial used a noninferiority design to randomly assign patients to TARGIT or whole breast external beam radiation therapy (EBRT). For 67% of the study participants, the randomization and treatment occurred at the lumpectomy (classified as "pre-pathology"). The patients with high-risk features went on to receive EBRT after TARGIT. These features were defined as margin <1 mm, extensive ductal carcinoma in situ, invasive lobular carcinoma, or "individual centers could specify more than these core factors" (2) at their discretion. For 33% of the study participants, the definitive pathology was already available from a prior lumpectomy. This "post-pathology" stratum of patients was predetermined as being at low risk and, if randomized to TARGIT, was returned for reopening of the lumpectomy wound specifically for intraoperative irradiation.

Vaidya et al (2) reported the TARGIT-A trial with a median follow-up time of 2.4 years. Of the entire cohort (including "pre- and post-pathology"), EBRT was given to 15% of patients in the TARGIT arm. The results would seem to indicate a clear failure of TARGIT, given that the 5-year actuarial local failure (LF) rate was higher than with EBRT (3.3% vs 1.3%, respectively; $P = .042$). However, the authors concluded that the predetermined 2.5% noninferiority threshold was met, and, as such, TARGIT successfully proved itself as equivalent to EBRT.

Subgroup analysis revealed a 5-year LF for "pre-pathology" of 2.5% with TARGIT versus 1.7% with EBRT ($P = .31$). In "post-pathology," the 5-year LF was 5.4% with TARGIT versus 1.7% with EBRT ($P = .069$). The investigators concluded that TARGIT is more effective "pre-pathology" than "post-pathology."

The articles that report the TARGIT-A trial often leave readers pondering some direct questions. Has a radically new paradigm been defined that upends our understanding of the pathologic anatomy of early breast cancer, the physical laws that define the dosimetry of a 50-kV x-ray source, and the well-established biological principles that underpin the therapeutic effect of radiation therapy? Or is something amiss in how the TARGIT-A trial was designed, executed, and analyzed? A critical review of the methods and data would suggest the latter.

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In a statement that pointedly encapsulates the shortcomings associated with the TARGIT-A trial, the internationally renowned statistician Professor Jack Cuzick wrote, "The TARGIT-A trial is a good example of trying to make data fit a preexisting hypothesis; there are several major deficiencies in the analysis" (3). The force of his words is underscored by the fact that he served as the initial chair of the Data Monitoring Committee for the TARGIT-A trial. A cogent critique of the TARGIT-A trial by Professor Cuzick appears alongside those of other distinguished experts in an extraordinary series of letters published recently in *The Lancet* (3-7). We will briefly summarize the points raised by these authors and discuss additional questions that surround the TARGIT technique.

The fundamental design and statistical analysis of the TARGIT-A trial has been challenged: "Paramount among these is the misuse of noninferiority criterion" (3). This requires the upper 90% confidence interval be below the predetermined threshold of 2.5%. Contrary to the conclusions of Vaidya et al (2), this criterion was *not* met. When the appropriate 5-year LF rates are used, there was a significant 2% *superiority* of EBRT and a confidence interval that extended beyond 2.5% (3, 4). Haviland et al (4) stated that the noninferiority test statistic is unreliable because its appropriate application requires that 5-year follow-up data be available for all patients. Such data were available for fewer than 20% of the TARGIT-A cohort. Professor Cuzick concludes that "the present attempt to argue for virtually no difference by misuse of the noninferiority criterion….does not give an objective assessment of this treatment modality."

The median follow-up time for the TARGIT-A cohort of just over 2 years is inadequate to enable conclusions to be drawn regarding risk of LF or normal tissue toxicity. For LF, the distorting effect of short follow-up is particularly applicable to the high proportion of low-risk patients with small, estrogen receptor (ER) positive tumors. For such a population, LF will mostly occur after 5 years (8). TARGIT patients with high-risk features also received EBRT (22% of patients in the "pre-pathology" stratum), obscuring any difference in outcome between TARGIT alone and EBRT. For normal tissue toxicity associated with high-dose focal breast irradiation, the brachytherapy-based accelerated partial breast irradiation experience has shown that the evolution of late effects requires at least 5 years of follow-up to be accurately characterized (9).

In subgroup analysis, the 5-year LF rate for "pre-pathology" TARGIT (2.5%) was higher than that of "post-pathology" (5.4%) and was not statistically different from EBRT (1.7%). On the basis of this observation, the trial authors concluded that the timing of TARGIT in relationship to lumpectomy was an important variable. Professor Cuzick has succinctly described that for any subgroup inquiry, to prevent spurious statistical results, correction for multiple comparisons and tests for heterogeneity between subgroups (eg final margin status) should be performed (3). The results of such analyses were not provided in the TARGIT-A trial.

The TARGIT-A investigators claim that non−breast cancer deaths were increased almost immediately after treatment in the EBRT arm secondary to a greater incidence of lethal cardiovascular events and rapidly fatal radiation-induced malignancies. Antiquated EBRT techniques can cause a very small rise in non−breast cancer (mostly cardiac) mortality (10, 11). Death secondary to radiation-induced morbidity is usually not discernible until a minimum latency of 10 years (10, 11). By contrast, the TARGIT-A trial observed virtually no latency in that a mortality difference was apparent after only 2 years of follow-up. This finding strains credibility because it asserts a heretofore unreported rapidity by which contemporary EBRT allegedly causes not only injury but nearly immediate lethal consequences. The TARGIT-A investigators further claim that some of the deaths due to EBRT included stroke and bowel ischemia.

In the TARGIT-A trial, the toxic effect of EBRT appeared to be related to whether randomization occurred before or after clinicians had access to the definitive pathology results. On subgroup analysis, "pre-pathology" TARGIT resulted in a lower rate of non−breast cancer deaths, whereas for "post-pathology" TARGIT, non−breast cancer mortality was no different than that for EBRT. The most direct explanation, and one that cuts to the core of the structural design of the TARGIT-A trial and the integrity of its enrollment and randomization process, is that patients were not appropriately assessed and stratified for preexisting comorbidities. The predictable end product of such a grievous design flaw would be unbalanced allocation to the treatment arms and resultant regimen-associated mortality statistics that defy common sense.

A common question when highly favorable results are presented for partial breast irradiation is whether any breast radiation was truly necessary. Most patients enrolled in TARGIT-A were postmenopausal and had tumors that were grade 1 to 2, ER positive, Her2 negative, size $<2$ cm, node negative, and treated with systemic therapy. Any patient randomized to TARGIT alone who had high-risk features went on to receive EBRT. As such, only the most favorable patients were treated exclusively with TARGIT. What is the expected risk of LF if they were to receive no radiation at all? Several clinical trials have evaluated the utility of EBRT in low-risk women with small, node negative, ER positive tumors treated with endocrine therapy. These trials (8, 12, 13) reported 4% to 8% 5-year rates of ipsilateral breast plus regional nodal recurrence after lumpectomy and hormonal therapy *without* radiation therapy. These results compare favorably with the 5-year 3.3% in-breast only recurrence rate reported in the TARGIT-A trial. This suggests unnecessary irradiation of many patients who might have been best served with hormonal therapy alone.

The seductive power of a large randomized trial to influence clinical practice cannot be dismissed. However, robust accrual, prominent publication, and aggressive promotion cannot substitute for critically objective

evaluation of the methods and data that have been advanced in support of the TARGIT technique. The TARGIT-A trial has many methodologic and analytic flaws that deeply undermine the scientific validity of its claims. In the interest of all women with early breast cancer, clinicians and policy makers must carefully assess the actual state of our current knowledge associated with this modality and recognize that many more questions need to be addressed before we can declare that we have arrived at a new standard of care.

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