Intraoperative radiotherapy for early breast cancer

Jayant Vaidya and colleagues (July 10, p 91)[1] suggest that a single dose of targeted intraoperative radiotherapy (TARGIT) should be considered as an alternative to external-beam radiotherapy delivered over several weeks for selected patients with breast cancer. We consider the results of this trial preliminary and immature since the follow-up is much too short to draw any conclusions about local recurrence rates.

The finding in this trial that most local recurrences occur in years 2 and 3 do not imply that local recurrences after this time will not occur. When using an orthovoltage technique with a very low-dose penetration to a depth of 1 cm,[2] the rate of in-breast recurrences has to be observed extremely carefully in the long term. The median time to true local recurrences is somewhere between 40 months[3] and 65 months,[4] and out-quadrant relapses occur later than that.[5]

Furthermore, the Kaplan-Meier plots in figure 4 show that, of 2232 patients at risk, only 420 (19%) completed 4-year follow-up (212 in the TARGIT group). Of these 212 patients, only 86% received intraoperative radiotherapy alone, meaning that about 14% received external-beam radiotherapy as well. 65% of patients also received endocrine treatment, which is known to be associated with a significant decrease or at least delay in the rate of local recurrences,[5] which become apparent after more than 5 years' follow-up.[4]

Another area of concern is the post-pathology stratum: 672 patients had a postpathology entry to the trial, meaning that about 336 patients allocated to TARGIT (most of the Danish and the Australian patients) were referred for a second surgical procedure. In those cases, targeted intraoperative radiotherapy was not an intraoperative treatment in the classic sense—a second surgical procedure had to be done for no reason other than the application of the radiation therapy.

Overall, we advise against the use of targeted intraoperative radiotherapy as a single shot outside a clinical trial until the long-term follow-up data for non-inferiority are available.

We declare that we have no conflicts of interest.

*Roland Reitsamer, Gerd Fastner, Michael Kopp, Christian Menzel, Felix Sedlmayer
r.reitsamer@salk.at

Breast Center, University Hospital Salzburg, 5020 Salzburg, Austria

1 Vaidya JS, Joseph DJ, Tobias JS, et al. Targeted intraoperative radiotherapy versus whole breast radiotherapy for breast cancer (TARGIT-A trial): an international, prospective, randomised, non-inferiority phase 3 trial. *Lancet* 2010; **376:** 91–102.
2 Nairz O, Deutschmann H, Kopp M, et al. A dosimetric comparison of IORT techniques in limited-stage breast cancer. *Strahlenther Onkol* 2006; **182:** 342–48.
3 Gujral DM, Sumo G, Owen JR, et al. Ipsilateral breast tumor relapse: local recurrence versus new primary tumor and the effect of whole-breast radiotherapy on the rate of new primaries. *Int J Radiat Oncol Biol Phys* 2010; published online May 13. DOI:10.1016/j.ijrobp.2009.10.074.
4 Brooks JP, Danforth DN, Albert P, et al. Early ipsilateral breast tumor recurrences after breast conservation affect survival: an analysis of the National Cancer Institute randomized trial. *Int J Radiat Oncol Biol Phys* 2005; **62:** 785–89.
5 Freedman GM, Anderson PR, Hanlon AL, et al. Pattern of local recurrence after conservative surgery and whole-breast irradiation. *Int J Radiat Oncol Biol Phys* 2005; **61:** 1328–36.

We congratulate Jayant Vaidya and colleagues[1] for their important contribution. Given their intriguing findings, we think it is important to highlight that the radiation doses used in TARGIT-A are substantially lower than historical standards.[2–4]

Standard doses of tumour-bed radiation in the postoperative setting are 50–66 Gy (in 2 Gy per fraction) when whole breast irradiation is used and 38·5 Gy in 10 fractions (equivalent to 49 Gy in 2 Gy per fraction) when accelerated partial breast irradiation is used.[4] Further, in nearly all of the published experience with breast brachytherapy,[5] the radiation dose has been reported as the minimum dose delivered to at least a 1 cm rim of tissue immediately adjacent to the lumpectomy cavity. If this standard nomenclature is applied to TARGIT-A, then the dose delivered in the experimental group is only 5–7 Gy in one fraction.

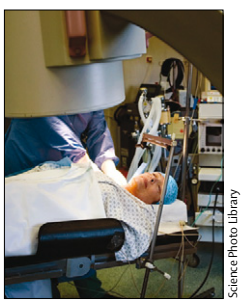
Even if we assumed the best-case scenario that the relative biological effectiveness for such low-energy photons is twice that of higher energy photons, the biologically equivalent dose used in TARGIT-A would still convert to only 24 Gy (in 2 Gy per fraction)—less than half the radiation dose used with accelerated partial or whole breast irradiation. We are therefore concerned that the radiation doses used in TARGIT-A might have been sufficient to delay, but not ultimately prevent, local recurrence and would urge extreme caution in adoption of the TARGIT-A approach until substantially longer follow-up data are accrued.

We declare that we have no conflicts of interest.

*Benjamin D Smith, Thomas A Buchholz, Henry M Kuerer
bsmith3@mdanderson.org

University of Texas MD Anderson Cancer Center, Houston, TX 77030, USA

1 Vaidya JS, Joseph DJ, Tobias JS, et al. Targeted intraoperative radiotherapy versus whole breast radiotherapy for breast cancer (TARGIT-A trial): an international, prospective, randomised, non-inferiority phase 3 trial. *Lancet* 2010; **376:** 91–102.
2 Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. *N Engl J Med* 2002; **347:** 1233–41.
3 Veronesi U, Cascinelli N, Mariani L, et al. Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. *N Engl J Med* 2002; **347:** 1227–32.
4 Clark RM, McCulloch PB, Levine MN, et al. Randomized clinical trial to assess the effectiveness of breast irradiation following lumpectomy and axillary dissection for node-negative breast cancer. *J Natl Cancer Inst* 1992; **84:** 683–89.
5 Smith BD, Arthur DW, Buchholz TA, et al. Accelerated partial breast irradiation consensus statement from the American Society for Radiation Oncology (ASTRO). *Int J Radiat Oncol Biol Phys* 2009; **74:** 987–1001.



Science Photo Library