Leukemia Group B 9343, which showed that locoregional recurrence continues to occur beyond 5 years (7). Furthermore, when compared with the initial results (5), the updated results of TARGIT-A (4) demonstrate a much higher increase in the rate of local recurrences for PBI (23 vs 6) compared with external beam radiotherapy group (11 vs 5). Further, we disagree with the authors (1) that this short-term follow-up can be used to report and conclude about the rates of secondary cancers (8). Finally, the authors claimed that the experimental arm had less cardiovascular toxicity (1), whereas the total number of patients in both groups was very low (2 vs 8), and because the data for left-sided cancers was not separately presented in any of the TARGIT-A–related publications, nor even the times of the cardiac deaths, their analysis of cardiovascular disease is misleading (4).

It seems that only "time" will resolve the "clash of the titans"—hopefully not at the expense of our patients. Until the publication of final long-term results, we recommend restraint before implementing this technique outside of clinical trials.

Orit Kaidar-Person, MD
Division of Oncology
Rambam Health Care Campus
Haifa, Israel

Marc Wygoda, MD
Sharett Institute of Oncology
Hadassah Hebrew University Medical Center
Jerusalem, Israel

Zvi Symon, MD
Department of Oncology
Chaim Sheba Medical Center
Ramat Gan, Israel

Benjamin W. Corn, MD
Department of Oncology
Tel Aviv Sourasky Medical Center
Tel Aviv, Israel

Abraham Kuten, MD
Oncology Service
Italian Hospital of Haifa
Haifa, Israel

http://dx.doi.org/10.1016/j.ijrobp.2015.05.028

References

1. Vaidya JS, Bulsara M, Wenz F, et al. Pride, prejudice, or science: Attitudes towards the results of the TARGIT-A Trial of targeted intraoperative radiation therapy for breast cancer. *Int J Radiat Oncol Biol Phys* 2015;92:491-497.
2. Hepel J, Wazer DE. A flawed study should not define a new standard of care. *Int J Radiat Oncol Biol Phys* 2015;1:255-257.
3. Silverstein MJ, Fastner G, Maluta S, et al. Intraoperative radiation therapy: A critical analysis of the ELIOT and TARGIT trials. Part 2—TARGIT. *Ann Surg Oncol* 2014;21:3793-3799.
4. Vaidya JS, Wenz F, Bulsara M, et al. Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial. *Lancet* 2014;383:603-613.
5. 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.
6. Shai A, Zur M, Leviov M, et al. Short term toxicity of intra-operative radiotherapy for patients with breast cancer treated at a single center [abstract]. In: Proceedings of the Thirty-Seventh Annual CTRC-AACR San Antonio Breast Cancer Symposium: Dec 9-13, 2014; San Antonio, TX. AACR. *Cancer Res* 2015;75(9 Suppl). abstract P1-15-13
7. Hughes KS, Schnaper LA, Bellon JR, et al. Lumpectomy plus tamoxifen with or without irradiation in women age 70 years or older with early breast cancer: Long-term follow-up of CALGB 9343. *J Clin Oncol* 2013;1:2382-2387.
8. Grantzau T, Overgaard J. Risk of second non-breast cancer after radiotherapy for breast cancer: A systematic review and meta-analysis of 762,468 patients. *Radiother Oncol* 2015;114:56-65.

In Regard to Vaidya et al

To the Editor: The TARGeted Intra-operative radioTherapy (TARGIT) trial investigated the noninferiority of low-energy 50-kV x-rays administered at surgery versus conventional external beam radiation therapy (EBRT). The authors concluded that the TARGIT treatment was noninferior to EBRT because a prespecified noninferiority boundary of 2.5% absolute difference in local recurrence was not exceeded.

This trial has several weaknesses impacting the reliability of the authors' conclusions that have been published earlier (1, 2). We wish to highlight a few of them. First, every center was allowed to restrict the inclusion criteria beyond the protocol and to stipulate local policy for EBRT. This could be a confounding element, especially considering that the protocol allowed EBRT for patients randomized to the TARGIT arm who had unfavorable features found either during surgery or subsequently in the pathological examination (about 14%). The authors maintained that in these cases, intraoperative radiation therapy given as a boost was to be considered equivalent to the EBRT arm, some of whose patients did not even receive a boost because of the center's local policy. If the EBRT policy varied between centers, it would be difficult to assess the equivalence between a 50-kV x-ray intraoperative radiation therapy boost and EBRT treatment, given the difference in boost dosages and the different centers' policies for EBRT.

Second, the authors of the TARGIT trial point out that the median follow-up of patients in their study (29 months, not 5 years as reported) covers the peak hazard of local recurrence that they maintain occurs between 2 and 3 years after

surgery (3). However, considering that the population included was dominated by patients with small, estrogen receptor−positive tumors, most of whom received endocrine therapy, the peak of recurrence will occur significantly later than 2 to 3 years (4). This is certainly the experience of every practicing breast clinician for such low-risk women. The TARGIT trialists' assertion of breast cancers peaking for this low-risk cohort of patients is simply not credible.

Moreover, these good-prognosis patients may not need radiation therapy at all when receiving endocrine therapy (5), even though adequate breast irradiation without 5 years of hormonal therapy will probably result in a similar recurrence risk with a much better quality of life.

We feel that even if the TARGIT treatment is very appealing as a time- and cost-saving technique (as are other approaches for partial breast delivery), more maturity in the data is needed to determine its efficacy and assert noninferiority versus EBRT, which remains the current standard of care.

Icro Meattini, MD
Department of Radiation Oncology
University of Florence
Florence, Italy

Liesbeth Boersma, MD, PhD
Department of Radiation Oncology (MAASTRO Clinic)
University Hospital Maastricht
The Netherlands

Lorenzo Livi, MD
Department of Radiation Oncology
University of Florence
Florence, Italy

Carine Kirkove, MD
Department of Radiation Oncology
Catholic University of Louvain
Brussels, Belgium

Dorota Gabryś, MD
Department of Radiation Oncology
Maria Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology
Gliwice, Poland

Navita Somaiah, MD, PhD
Division of Radiotherapy and Imaging
Institute of Cancer Research and The Royal Marsden
London, UK

Vincent Remouchamps, MD
Radiothérapie Oncologique
Clinique Ste Élisabeth Namur
Namur, Belgium

Paula H.M. Elkhuizen, MD, PhD
Department of Radiotherapy
The Netherlands Cancer Institute
Amsterdam, The Netherlands

Youlia Kirova, MD
Institut Curie
Paris, France

Sofia Rivera, MD
Department of Radiation Oncology
Gustave Roussy, France

http://dx.doi.org/10.1016/j.ijrobp.2015.05.030

References

1. Vaidya JS, Bulsara M, Wenz F, et al. Pride, prejudice, or science: Attitudes towards the results of the TARGIT-A trial of targeted intraoperative radiation therapy for breast cancer. *Int J Radiat Oncol Biol Phys* 2015;92:491-497.
2. Vaidya JS, Wenz F, Bulsara M, et al. Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial. *Lancet* 2014;383:603-613.
3. Retsky MW, Demicheli R, Hrushesky WJ, et al. Dormancy and surgery-driven escape from dormancy help explain some clinical features of breast cancer. *APMIS* 2008;116:730-741.
4. Hughes KS, Schnaper LA, Bellon JR, et al. Lumpectomy plus tamoxifen with or without irradiation in women age 70 years or older with early breast cancer: Long-term follow-up of CALGB 9343. *J Clin Oncol* 2013;31:2382-2387.
5. Kunkler IH, Williams LJ, Jack WJ, et al. Breast-conserving surgery with or without irradiation in women aged 65 years or older with early breast cancer (PRIME II): A randomised controlled trial. *Lancet Oncol* 2015;16:266-273.

In Regard to Hepel and Wazer

To the Editor: I read the Red Journal's editorial by Hepel and Wazer (1) with interest. I agree with many issues raised by the authors, yet the profound thoughts need further scrutiny.

If flawed studies (based on technique, randomization, statistics, and subgroup analyses, and others) should not be the basis of a future standard of care, then should conclusions of past trials, using what today would clearly be considered "flawed study," continue to be the basis of today's practice patterns? Also, if these issues (like dose, fractionation schedules, and others) were worth studying a few decades ago, then should they not be repeated with modern computer-based planning and technology, along with our current understanding of tumor biology and host-related factors?