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THE TARGIT-A DEBATE

Letters Regarding the TARGIT-A Trial: The Editor's Introduction

Anthony Zietman, MD, FASTRO, *Editor-in-Chief*

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The first articles in the print edition of the *International Journal of Radiation Oncology, Biology, Physics* (the Red Journal) are usually its feature articles or editorials. It is unusual for us to choose to lead with correspondence. We have in this edition, however, broken with custom, and for good reason. All the correspondence we feature revolves around a single subject: the use of intraoperative radiation therapy in early-stage breast cancer. An early report from the TARGIT-A trial was published in *The Lancet* in 2014 and has, since that time, provoked vigorous debate (1). This debate was heightened by a recent exchange of editorials in this journal (2, 3). What we publish here are the unselected letters arising from that exchange. They come from senior investigators and breast cancer physicians from around the globe and are all passionately and articulately expressed. In the recent history of the Red Journal we have not seen such an exchange of polar opposite views, and we believe this results from the existential nature of the original TARGIT-A trial report. After decades of careful and progressive investigation into fractionated radiation therapy, women have been moved from a dark past of radical mastectomies into the modern era of breast conservation. TARGIT-A applauds that outcome but suggests there may be another way to achieve it. Many careers have been built around fractionated radiation therapy for breast cancer, and it comprises a substantial proportion of the practice of the average contemporary radiation oncologist. Depending on your perspective, intraoperative radiation therapy is thus either a very serious threat or a quantum leap forward. Data will ultimately resolve this debate as TARGIT-A matures and other studies are published, but for now it is, as you will read, "red hot."

The letters draw on 3 themes. The first is a scientific discussion of methodology that focuses on the advantages and pitfalls of noninferiority studies and the importance of mature follow-up. The second regards trial governance: how trials are organized, monitored, and overseen. The third is the interpretation of the data. It is in this latter category that the value, or otherwise, of intraoperative radiation therapy is in the eye of the beholder. There are some subjects for which the stakes are so high that scientific discourse can cross a line into irresolvable ideological or quasi-religious debate, and it is in this third category that we come closest to this. "My God is better than your God" is an irresolvable argument. In medicine, however, data and a common desire to benefit our patients should act as a compass to guide resolution. As you will read, both sides powerfully invoke the breast cancer patient to illuminate their case, and it will take a moral philosopher to separate them.

We have chosen to highlight this correspondence in a fashion unprecedented for the Red Journal, to show how difficult it can be to interpret data from randomized studies. Those of you who have taken a side on this issue may have your positions challenged. Those of you who have not considered this issue would do well to do so. It is one substantial aspect of our practice that may, or may not, change dramatically in the very near future. The discussion also casts a very revealing light on our own behaviors and attitudes as physicians and scientists.

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* Reprint requests to: Anthony Zietman, MD, FASTRO, Massachusetts General Hospital, Boston, MA 02114. E-mail: azietman@partners.org

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In Regard to Vaidya et al

To the Editor: The 2 publications of the TARGIT-A clinical trial have elicited robust criticism from a distinguished and multidisciplinary spectrum of international experts (1, 2). We will not attempt to restate the many detailed and profound critiques that have been so painstakingly presented elsewhere nor succumb to the temptation to indulge in a point-by-point rebuttal of the most recent comments by Vaidya et al (3). Sadly, the TARGIT-A trial investigators continue on a path of obfuscation and distraction when what is most needed is a forthright and thorough response to the many penetrating questions posed related to this controversial study.

Vaidya et al rationalize their premature publication of the TARGIT-A trial after less than 2.5 years of median follow-up by incorrectly claiming that breast recurrences peak in the second and third year after treatment and that external beam radiation therapy (EBRT) is ineffective in controlling local recurrence (LR) after 5 years. In support of this thesis, they cite 2 very early trials of breast conservation that used outmoded imaging, surgery, specimen processing, systemic therapy, and radiotherapeutic techniques. Actually, the incidence and time course of locoregional failures are influenced by multiple clinical and biological factors (4). For example, LR after excision alone rises at a nearly continuous rate out to 15 years in patients with hormone receptor−positive tumors who receive tamoxifen (5). The overwhelming preponderance of contemporary evidence as shown in meta-analyses (6) or individual randomized clinical trials (5) is that the benefit of EBRT continues to expand beyond 10 years of follow-up.

The much-hyped claim of fewer non−breast cancer deaths with TARGIT as a result of reduced early cardiac mortality has been rightly received with skepticism. Darby et al (7) clearly demonstrated that for mean doses to the heart of less than 3 Gy (readily achievable with contemporary EBRT), the increased absolute risk of death from ischemic heart disease over 30 years is less than 1%. Most tellingly, Vaidya et al steadfastly refuse to offer a lucid explanation for a particularly strange result in the TARGIT-A trial. An excess of non−breast cancer mortality with EBRT is not seen in the "postpathology" stratum but is confined exclusively to those patients in the "prepathology" stratum. Just as Vaidya et al overinterpret tiny differences in the number of events seen after prepathology and postpathology TARGIT, we assume they suppose that small changes in the timing of TARGIT are protective to the heart.

Vaidya et al proclaim superior local control with TARGIT as compared with that seen in trials in which patients received no EBRT based on an overtly misleading comparison of rates of in-breast−only recurrence in the TARGIT-A trial to breast plus regional nodal recurrence in trials of excision plus hormone therapy. Furthermore, they extol the alleged economic benefits to society of their self-defined "risk-adapted" strategy as being characteristic of the TARGIT technique. We think that Vaidya et al are missing an important point. Contemporary risk-adapted local therapy for early breast cancer is a complex and evolving paradigm with unquestioned evidence-based support for a range of options, including highly cost-effective hypofractionated EBRT (8) or, for selected low-risk patients, no radiation therapy at all (5, 9). The addition of an intraoperative radiation therapy of dubious benefit and undefined long-term toxicity to the management of patients who frequently go on to need additional EBRT or, worse yet, needed no radiation therapy whatsoever must be critically evaluated in the context of several other options.

The US Food and Drug Administration has recognized that the design and interpretation of noninferiority (NI) trials like the TARGIT-A study "is a formidable challenge" (10). As has been meticulously detailed by many prominent statisticians and clinical trial specialists (1), Vaidya et al have made basic errors in the justification of the margin of NI along with their method of analysis of the primary endpoint (10-12). Our strong suggestion is that Vaidya et al consider submitting the data from the TARGIT-A trial for an independent statistical review. This action would serve to address the valid concerns of many in the scientific community, silencing them if the original findings were upheld. Such a straightforward action will clarify the science and either silence the critics or prove them correct.

David E. Wazer, MD
Tufts University School of Medicine
Boston, Massachusetts

Jaroslaw T. Hepel, MD
Alpert Medical School of Brown University
Providence, Rhode Island

Adam I. Riker, MD
Advocate Cancer Institute at Advocate Christ Medical Center
Oak Lawn, Illinois
University of Illinois
Chicago, Illinois

Jay K. Harness, MD
St. Joseph Hospital Center for Cancer Prevention and Treatment
University of California
Irvine, Orange, California

Caroline Chung, MD
Princess Margaret Hospital
University of Toronto
Toronto, Ontario, Canada

Atif J. Khan, MD
Rutgers Cancer Institute of New Jersey
New Brunswick, New Jersey

Birgitte Vrou Offersen, MD, PhD
Aarhus University Hospital
Aarhus, Denmark

Philip Poortmans, MD, PhD
Radboud University Medical Center
Nijmegen, The Netherlands

Alphonse Taghian, MD
Massachusetts General Hospital
Harvard Medical School
Boston, Massachusetts

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In Regard to Hepel and Wazer

To the Editor: The initial editorial by Hepel and Wazer (1) contained several scientific, conceptual, and factual inaccuracies. In our own article, we had attempted to correct these and clarify the results of the trial. We find a striking absence of true scientific discourse in much of the content of the subsequent correspondence. Instead it seems we are now dealing with a clash of ideologies. In consequence, the objections to the trial seem to be theoretical or ad hominem attacks.

The correspondents are unable to fault any of our corrections, or the mathematics or the scientific analyses. They fault the very existence of the trial. It seems that they just do not like the results of a scientifically sound experiment.

Why such strong objection to the use of TARGIT intraoperative radiation therapy? The worst-case scenario is that the 1% difference in local recurrence that is currently nonsignificant could become statistically significant over time, yet without any detrimental effect on survival and with a significantly better patient experience.

We could again answer each factual error point by point, but we would prefer to refer the reader back to our previous publications (2-4) in which we discuss these issues in detail.

The TARGIT-A trial questioned the prevailing dogma by designing and completing a proper scientific experiment. The results that support the clinical effectiveness of precisely delivered targeted radiation therapy to the area within the breast at greatest risk of recurrence clearly challenge some of the fundamental beliefs about adjuvant breast radiation therapy. These new data should refine such theories. It is the theories that should be questioned rather than the data.

We have published what we found in the most transparent manner; whether our data are "attractive and appropriate" depends on individual clinicians and their patients, not the vociferous minority defending a conceptual model based on a false premise. The widespread adoption of TARGIT intraoperative radiation therapy in more than 260 major breast cancer centers worldwide speaks for itself.

Jayant S. Vaidya, MBBS, MS, DNB, FRCS, PhD
Clinical Trials Group
Division of Surgery and Interventional Science
University College London
London, UK
Department of Surgery
Royal Free Hospital
Whittington Health
London, UK

Department of Surgery
Whittington Health
London, UK

Max Bulsara, PhD
Department of Biostatistics
University of Notre Dame
Fremantle

Frederik Wenz, MD
Department of Radiation Oncology
University Medical Centre Mannheim
University of Heidelberg
Heidelberg, Germany

David Joseph, MD, FRCR
Department of Radiation Oncology
Sir Charles Gairdner Hospital
Perth, WA, Australia

Christobel Saunders, FRCS
Department of Surgery
Sir Charles Gairdner Hospital
Perth, WA, Australia
School of Surgery
University of Western Australia
Perth, WA, Australia

Samuele Massarut, MD
Department of Surgery
Centro di Riferimento Oncologia
Aviano, Italy

Henrik Flyger, MD
Department of Breast Surgery
University of Copenhagen
Copenhagen, Denmark

Wolfgang Eiermann, MD
Department of Gynecology and Obstetrics
Red Cross Hospital
Munich, Germany

Michael Alvarado, MD
Laura Esserman, MD, MBA
Department of Surgery
University of California
San Francisco, California

Mary Falzon, FRCPath
Department of Pathology
University College London Hospitals
Whittington Health
London, UK

Chris Brew-Graves, MSc
Ingrid Potyka, PhD
Clinical Trials Group
Division of Surgery and Interventional Science
University College London
London, UK

Jeffrey S. Tobias, MD, FRCR
Department of Clinical Oncology
University College London Hospitals
Whittington Health
London, UK

Michael Baum, MBBS, MD, FRCS
Clinical Trials Group
Division of Surgery and Interventional Science
University College London
London, UK
on behalf of the TARGIT trialists' group

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In Regard to Vaidya et al

To the Editor: In Vaidya's response to Hepel and Wazer (1), Fig 1 illustrates how the upper confidence limit for the difference between treatment outcomes allows assessment of noninferiority in a trial (2). This follows US Food and Drug Administration guidelines (3). It is imperative, however, that the underlying statistical analysis method and associated confidence limit are appropriate to the event of interest and the completeness of data. It is disappointing, therefore, that the TARGeted Intra-operative radioTherapy (TARGIT) trialists persist in using a noninferiority test statistic based on binomial proportions. Binomial analysis simply divides the number of recurrences by the total number of patients; thus, subjects with 1 month or 5 years' follow-up contribute the same to the denominator. Moreover, subjects with very short follow-up are counted as *not* having had a local recurrence (LR). This is flawed, as shown by a simple example. Assume 2 groups of 30 patients with long follow-up and 10 and 20 failures, respectively: a statistically significant ($P = .01$) difference of 33% in failure rates is observed. Adding 200 cases with very short follow-up to each group (contributing no additional failures), the difference in failure rates is now only 4% and

no longer significant. In TARGIT-A, fewer than 700 patients have at least 5 years' follow-up or an observed LR—that is, have the full information required for a binomial analysis. In contrast, survival analysis methods use all available data, account for varying follow-up and timing of events, and incorporate censoring (a subject without an event at the time of last contact has a risk of failing in the future). The TARGIT trialists argue that their assessment is better because it uses all recorded events, in contrast to the "single snapshot point estimates of 5-year recurrence rates" obtained from Kaplan-Meier analysis—revealing a fundamental misunderstanding of survival analysis.

Appropriate assessment of noninferiority in the TARGIT-A trial would employ survival analysis to estimate the absolute difference in 5-year recurrence rates (protocol-specified primary endpoint), with a confidence interval (CI). The upper confidence limit would indicate whether or not the prespecified threshold for noninferiority had been crossed. Survival analysis provides a hazard ratio (HR) calculated using all reported events, which can be applied to any time-specific rate to obtain an estimate of the difference in event rates between treatment groups (with CI) (4). As the relevant figures were not presented in the TARGIT-A *Lancet* 2014 paper (5), it was previously necessary to estimate them indirectly from the information provided to establish an estimate that accounted for the variability in both treatment groups and not just TARGIT (6, 7). The TARGIT trialists can and should provide a proper analysis of LR rates at 5 years (with CI) to enable an unequivocal assessment of noninferiority.

Vaidya's citation of Cuzick (8) reflects a fundamental misunderstanding of 1-sided versus 2-sided CIs as calculation of the upper limit of a 2-sided 90% CI provides the same limit as of a 1-sided 95% CI. Vaidya confirms that the significance level set for the primary outcome changed from 5% in the protocol to 1% for the final analyses; therefore, should assessment of noninferiority not be based on the higher 1-sided 99% CI?

Another major misunderstanding is to state that predefined strata are not subgroups. *P* values are designed for a single predefined hypothesis and should not be applied to separate subgroups/strata without a Bonferroni correction. The TARGIT protocol clearly states that the main analysis will include all randomized patients and the focus on the prepathology subgroup was clearly post hoc after seeing the results. The dangers of restricting results to subgroups are well known (9).

Joanne S. Haviland, MSc
Faculty of Health Sciences
University of Southampton
Southampton, United Kingdom

Judith M. Bliss, MSc
ICR-CTSU
Division of Clinical Studies
The Institute of Cancer Research
London, United Kingdom

Søren M. Bentzen, PhD, DMSc
Division of Biostatistics & Medical Informatics
Department of Epidemiology & Public Health
University of Maryland School of Medicine
Baltimore, Maryland

Jack Cuzick, PhD
Centre for Cancer Prevention
Wolfson Institute of Preventive Medicine
Queen Mary University of London
London, United Kingdom

http://dx.doi.org/10.1016/j.ijrobp.2015.05.026

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In Regard to Hepel and Wazer

To the Editor: The efficacy and safety of low photon energy intraoperative radiation therapy (IORT) during breast-conserving surgery (BCS) was evaluated in the TARGIT-A trial (1), which provides robust level 1 evidence for acceptance of IORT as an alternative to whole-breast radiation (WB-EBRT) for selected patients. Several recent articles (2-6) have criticized IORT on the basis of misinterpretation or misrepresentation of TARGIT-A.

Patient selection is the foremost factor when considering any breast cancer therapy. The TARGIT-A outcome data

confirm that IORT in the prepathology strata is noninferior, not absolutely equivalent to WB-EBRT, and therefore a suitable option for selected women. The trial mandated the addition of WB-EBRT to patients with higher-risk features on final pathology. This potential need for additional radiation therapy is routinely addressed in the informed consent process. This approach is consistent with other widespread community practice standards of modifying the treatment plan according to surgical pathology and patient preferences.

One criticism of the TARGIT-A trial references short median follow-up on the whole cohort, although substantial numbers have minimum 5-year follow-up reported. The TARGIT-A dataset indicates that IORT administered in the prepathology setting will likely remain noninferior to WB-EBRT with longer follow-up. Expected patterns of local recurrence may be extrapolated from landmark breast-conserving therapy trials. In the Oxford Overview (7) meta-analysis of randomized trials comparing BCS alone with BCS plus WB-EBRT for women with node-negative invasive breast cancer, more than two-thirds of 10-year local recurrences had occurred by the fifth year of follow-up. If long-term randomized data are absolutely required for the adoption of new modalities, then we must abandon all forms of interstitial, intracavitary, and 3-dimensional conformal accelerated partial-breast irradiation until such long-term data emerge.

Breast IORT is associated with other important potential advantages, including significantly lower incidence of grade 3 or 4 treatment-related complications compared with whole-breast irradiation (8), increased rates of breast conservation for women who live far from radiation treatment facilities (9), excellent cosmetic results compared with WB-EBRT (10), and possibly lower non−breast cancer related mortality (1). Intraoperative radiation therapy is associated with improvements in breast-specific quality of life compared with whole-breast irradiation (11), and costs associated with IORT are lower compared with other forms of adjuvant radiation therapy (12).

Another criticism often stated is that 50-kV IORT provides inadequate doses, ignoring phase 3 local recurrence data. Low-energy photons have long been known to have a higher relative biological effectiveness as compared with standard-energy photon beams. This higher relative biological effectiveness has led to modeling of a sphere of equivalent control to standard external beam radiation that accounts for the relative lower absorbed dose at depth (13). Treating at the time of surgery may also have a significant biological advantage (14).

Breast IORT is associated with higher-level evidence than any other form of partial-breast irradiation currently in clinical use. In reference specifically to the TARGIT-A results, international governmental regulatory bodies acknowledge the rigor of the existing data sufficiently to have endorsed this treatment modality as an acceptable option in the treatment of low-risk breast cancer (15, 16). The data are the data. More time will not change the facts.

We are conducting the TARGIT-US Registry Trial to further study, in a scientifically robust setting, the efficacy and toxicity of breast IORT. We are motivated to facilitate US institutions' ability to provide access to this promising treatment modality. Intraoperative radiation therapy, which is supported by level 1 evidence, should be offered to appropriately selected patients, with eligibility defined by published guidelines and predefined selection criteria. We hypothesize that our study will provide confirmatory information to the results of the TARGIT-A study in a US population.

Eleanor Elizabeth Harris, MD
Department of Radiation Oncology
East Carolina University
Greenville, North Carolina

William Small, Jr, MD
Department of Radiation Oncology
Cardinal Bernardin Cancer Center
Stritch School of Medicine
Loyola University Chicago
Chicago, Illinois

Dennis Holmes, MD, FACS
Los Angeles Center for Women's Health
California Hospital Medical Center
Los Angeles, California

Stephen Grobmyer, MD, FACS
Breast Services Department
Cleveland Clinic
Cleveland, Ohio

Daniel Pavord, MS
Department of Radiation Oncology
Health Quest
Poughkeepsie, New York

Janis Scanlon Rice, MPH
Michael Alvarado, MD
Department of Surgery
University of California
San Francisco
San Francisco, California

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In Regard to Vaidya et al

To the Editor: The manner in which results of the TARGeted Intra-operative radioTherapy (TARGIT)-A trial (1) have been presented has precipitated a strong response from the international community of doctors and scientists working in breast cancer treatment (2-6). The patient community has had little input to date, but their interest has been provoked by Figure 4 from the TARGIT-A co-investigators' recent manuscript (7). This figure is potentially misleading to women trying to make decisions regarding their breast cancer treatment. It presents data from a single study as "proven fact" with no reference to 95% confidence intervals. In reality, the number of events and length of follow-up in TARGIT-A is too short to be able to draw firm conclusions about the causation of non-breast cancer deaths (5). The excess of non-breast cancer deaths in the external beam radiotherapy (EBRT) arm is highly unlikely to be due to the use of EBRT (5), as is suggested by Figure 4. Indeed, assuming mean heart doses of around 3 Gy in the EBRT arm of TARGIT-A, and assuming that the risk of major cardiac events increases by 7.4% per Gy mean heart dose (8), the use of EBRT could account for, at most, 1 cardiac death in the EBRT arm (4). With use of heart-sparing EBRT techniques, mean heart doses of <1 Gy are achievable (9) such that the risk of death from radiation-induced heart disease is almost negligible from modern EBRT.

In Jane Austen's *Pride and Prejudice* (10), Mr Darcy states that "My good opinion once lost is lost forever." So it is for patients and their families. To maintain our current and future patients' trust, we must ensure that we present as balanced a view of the existing data as is possible. It is our recommendation that Figure 4 from the recent manuscript should not be used in clinical practice.

Anna Kirby, MD(Res)
Royal Marsden & Institute of Cancer Research
London, UK

Gerard Hanna, PhD
Department of Clinical Oncology
Centre for Cancer Research and Cell Biology
Queen's University of Belfast, UK

Maggie Wilcox
Mairead MacKenzie
Independent Cancer Patients' Voice
London, UK

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In Regard to Hepel and Wazer

To the Editor: We read with great interest the recent editorial by Hepel and Wazer (1) on the TARGIT-A trial (2), a study that has generated a tremendous amount of scientific debate (3-6). Although we firmly believe that scientific debate is essential, the authors' main argument against Intrabeam therapy is based on a flawed premise.

Our main disagreement lies with the authors' (mistaken) belief—apparent in the editorial's title—that Intrabeam has been proposed as the new standard of care. These authors seem to have misinterpreted the conclusions of the TARGIT-A study, which clearly state that "within a risk-adapted approach, [TARGET] should be considered an option for [carefully selected] eligible patients . . . as an alternative to postoperative EBRT." Vaidya and colleagues (7) in no way suggest that Intrabeam is, or should be, the new standard of care, yet Hepel and Wazer use this alleged proposal to create a straw man argument. Although Intrabeam may one day be considered a standard treatment option, no one is making that claim at present.

Because of space limitations, we cannot discuss the many other debatable points raised in the editorial; however, we would like to address one particular criticism: the suggestion that "only the most favorable patients were treated exclusively with Intrabeam." Hepel and Wazer cite several studies in which the 5-year recurrence rate in unirradiated patients ranges from 4% to 8%, suggesting that these rates compare favorably with the TARGIT-A trial. However, the recurrence rate in the prepathology TARGIT-A group was much lower (only 2.1%), a finding that supports the use of Intrabeam, even in patients with favorable characteristics.

The underlying rationale for Intrabeam is sound, outcomes are good, and the technique offers numerous advantages over competing therapies (cost and time savings, reduced patient stress and radiation exposure) (8). More importantly, in patients with at least 5 years' follow-up, there are no differences in 5-year recurrence rates between Intrabeam and standard external beam radiation therapy.

At this early juncture, we believe that it is premature to rule out any of the competing treatments (accelerated partial-breast irradiation, external beam radiation therapy, Intrabeam) that have proven effective in treating breast cancer. In the future, it seems likely that breast cancer patients will be offered a wide array of treatments—in various combinations—according to their particular characteristics, as is currently done in prostate cancer. For the moment, the available data suggest that Intrabeam may be an excellent option for patients with good prognosis, mobility difficulties, or who reside far from a treatment center.

Ferran Guedea, MD, PhD
Arantxa Eraso, MD
Department of Radiation Oncology
Catalan Institute of Oncology
L'Hospitalet de Llobregat Barcelona, Spain

David Azria, MD, PhD
Département de Cancérologie Radiothérapie
CRLC Val d'Aurelle-Paul Lamarque
Montpellier, France

Pedro Lara, MD, PhD
Department of Radiation Oncology
Dr. Negrín University Hospital
Las Palmas, Spain

Françoise Izar, MD
Department of Radiation Oncology
Institut Universitaire du Cancer de Toulouse
Toulouse, France

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In Regard to Vaidya et al

To the Editor: With regard to Vaidya et al (1), the scientific shortcomings of the TARGIT trial can be partly attributed to weak regulatory oversight. Human research in the United States is federally regulated by rules from the Department

of Health and Human Services and the Office for Human Research Protections, (2). In the UK, the National Institute of Health Research (NIHR) lists the legal responsibilities that trial sponsors must fulfill, in accordance with 2004 Clinical Trials Regulations (3). These include responsibilities, often delegated to a Chief Investigator (Principal Investigator in the US), to appoint a Trial Steering Committee (TSC) that operates on behalf of the trial sponsor, here University College London (UCL), to ensure adherence to good clinical practice (GCP). UK Medical Research Council 1998 Guidance on GCP explains how TSC membership should be limited to an independent chair, at least 2 other independent members, 1 or 2 principal investigators, and, where possible, a consumer representative (4). Trial coordinators, trial statistician, and others are invited to attend as requested by the chair. The TARGIT-A International Steering Committee (TISC) listed on the NIHR website names 24 individuals, all closely linked to the trial. They include a chair (Baum) drawing monthly fees over an undisclosed number of years from Zeiss (the manufacturer of the device tested in the TARGIT-A trial) while holding this position and 4 senior employees of the Zeiss corporation, including Rospert, Vice-President of Sales. While the TARGIT-A trial may not have been in breach of formal legal requirements at the time it was initiated in 2000, the MRC guidelines had already been adopted. This construct, rectified as recently as 2014, clearly represents a vulnerability.

There are other worrisome aspects that have implications for the UK trial sponsor, UCL, in addition to the acrimony over the circumstances under which the independent monitoring committee was disbanded (5). The chair of the TISC (Baum) has long been head of the Clinical Trials Group that collects and analyses TARGIT-A trial data. This alone is a risky arrangement, but the Clinical Trials Group is located in the Division of Surgery where the CI (Vaidya) is employed. The 2014 TARGIT-A *Lancet* publication states that Vaidya was 1 of 2 members responsible for the statistical analysis (6). No doubt well-meaning, but Vaidya, Baum, and Tobias are experienced enough to know that these arrangements are perceived as real conflicts of interest. The TARGIT-A trial needs to mature in better shape.

John Yarnold, MD
Division of Radiotherapy and Imaging
Institute of Cancer Research and Royal Marsden NHS Foundation Trust
London, UK

Søren M. Bentzen, PhD, DMSc
Division of Biostatistics and Medical Informatics
Department of Epidemiology and Public Health
University of Maryland School of Medicine
Baltimore, Maryland

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In Regard to Vaidya et al

To the Editor: Intrabeam (Carl Zeiss Meditec AG, Germany) is 1 of the few technologies to have been the subject of dispute between world experts in the most prestigious of scientific journals (1, 2). Such public debate mandates that readers have more than average understanding of statistical methods, radiotherapeutic technique (kV-x rays, electrons, MV) and familiarity with current data regarding this unique subgroup of low-risk breast cancer (BC) patients (1-3). Low-risk BC has become a prevalent disease thanks to early detection, and from a public standpoint, we cannot afford to lessen the level of "skepticism and criticism" of any new treatment because mistakes or hasty decisions might constitute a heavy burden on public health in the long term. A few major concerns come to mind when reviewing the publications regarding the TARGeted Intra-operative radioTherapy (TARGIT)-A study (1, 2). The role of partial breast irradiation (PBI) in low-risk BC patients, by various techniques, is currently being evaluated in several large-scale clinical trials. The dosimetric requirements for covering the planning target volume in these trials are far more stringent than the dose delivered in the TARGIT-A trial. Thus, whether kV-x-ray radiotherapy (TARGIT-A) is sufficient for PBI remains a major concern. Using this intraoperative technique, the applicator surface dose is 20 Gy, but only 5 to 7 Gy reaches the depth of 1 cm (3-5). It should also be kept in mind that this technique may lead to significant rates of postoperative complications (6). Currently PBI can be considered in selected BC patients who fulfill rigorous international criteria. The TARGIT-A study entry criteria were broader; however, the majority of the recruited population had low-risk BC (4, 5). The short-term follow-up, especially in this low-risk population, is not sufficient for determining treatment efficacy. This is demonstrated by the extended follow-up from Cancer and

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

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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

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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?

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

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Should a panel lay down the currently accepted minimum significant major and minor prognostic factors related to tumor, host, and therapy that need to be factored into the design of trials? Or do we wait for another series of editorials a decade from now to refute current trials based on well-accepted deficiencies? More importantly, such criteria will prevent the theoretical trial goals from being diluted by including patients who clearly would not and do not benefit from the new treatment approach. A "prostate model" using high-risk, intermediate-risk, and low-risk cancer should be developed for most cancers. This would help design trials and applications of their results in clinical practice.

Another editorial issue is the reported marginal improvement. Unfortunately "incremental benefit" is today considered an acceptable benchmark of research, yet small incremental improvement, albeit statistically significant, ipso facto, demonstrates that the new approach did not benefit most of the patients in the trial, while subjecting all subjects to the toxicity of the treatment, including cost, "financial toxicity."

Switching treatment patterns (new or additional drugs or techniques) can be based on reduced toxicities, including reduced "financial toxicity." Hence if a trial is based on a noninferiority design (as is happening with increasing frequency), authors should expend efforts to do a cost analysis of the new technology and minimum patient volume needed to make this technology worth its cost in resources and time (including professional time).

Gilbert A. Lawrence, MD, DMRT, FRCR
Radiation Oncology
Faxton Hospital
Regional Cancer Center
Utica, New York

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