BREAST CANCER IOeRT RATIONALE

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Seminars in
RADIATION
ONCOLOGY

Is Partial Breast Irradiation A Step Forward or Backward?

Thomas A. Buchholz, MD,* Henry M. Kuerer, MD, PhD,† and Eric A. Strom, MD*

Approximately 80% of the breast tumor recurrences origins at the site of the original disease. These data suggest that the majority of breast tumor recurrences result from residual foci of disease from the original index tumor that approximate the site of the original surgery.

Thus is clear that giving radiation only to a volume of 1-cm radius around the tumor site would also be an ineffective strategy.

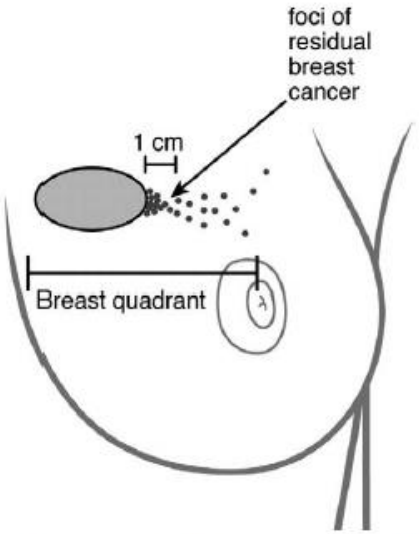
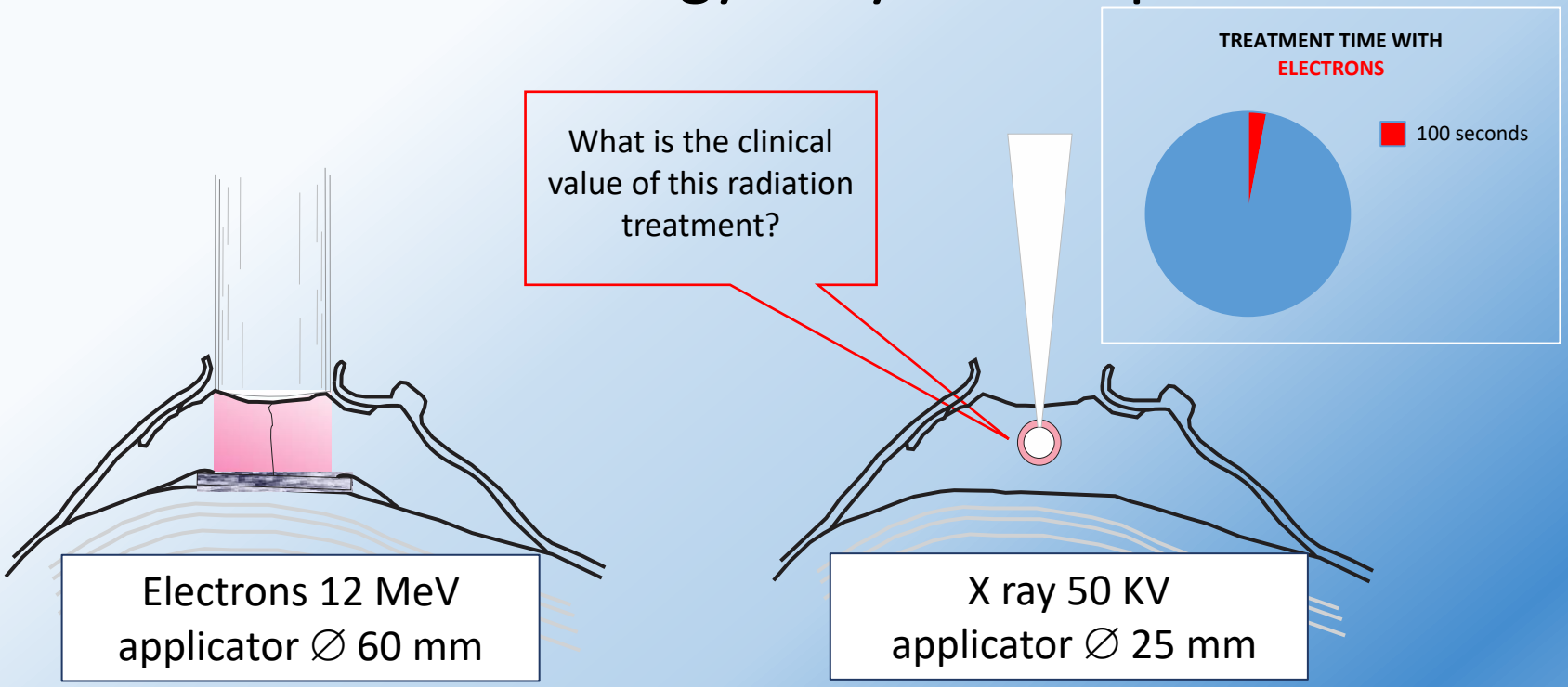


Figure 1 Illustration of a medial tumor bed with residual disease extending from the tumor bed into upper lateral quadrant. If no radiation was given in this situation, it is likely that the tumor would recur first at the tumor bed site. However, it is clear that giving radiation only to a volume of 1-cm radius around the tumor site would also be an ineffective strategy.

Is Partial Breast Irradiation A Step Forward or Backword?, Buchholz T. A., Kuerer H., Strom E. A., Semin. Radiat. Oncol., pp. 69-75, 2005.

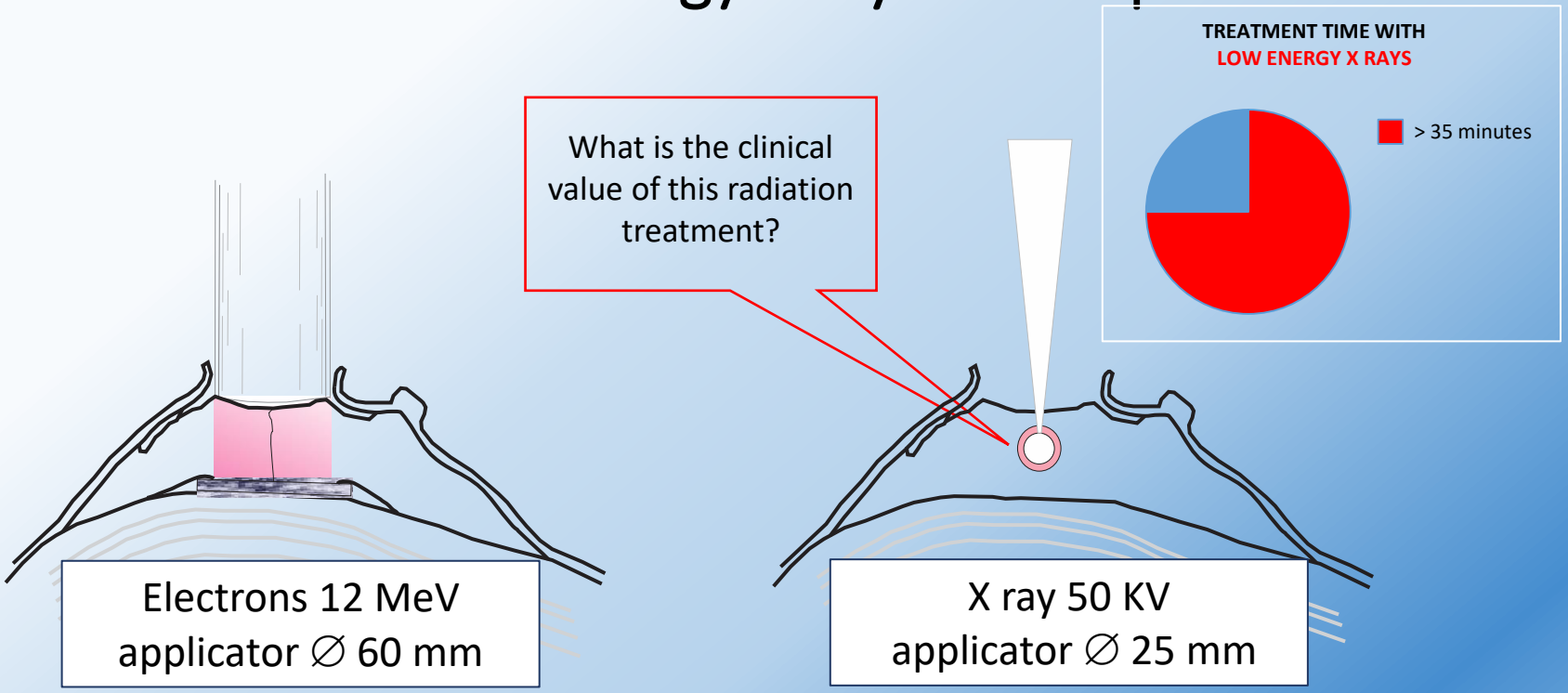
Electrons vs. low energy X rays: a comparison



Consider a patient, who has a 2 cm tumor removed along with a small margin and her incision is sutured in such a way the target to be irradiated is 3 cm thick.
For **LIAC HWL** the recommended settings would be 60 mm diameter applicator, 12 MeV energy and 21 Gy prescribed at 3 cm. The effective irradiated volume inside 90% isodose is a cylinder with a diameter about 50 mm and a depth of 32 mm, for a total volume of about 63 cm^3.

The treatment time with electrons takes 100 seconds.

Electrons vs. low energy X rays: a comparison



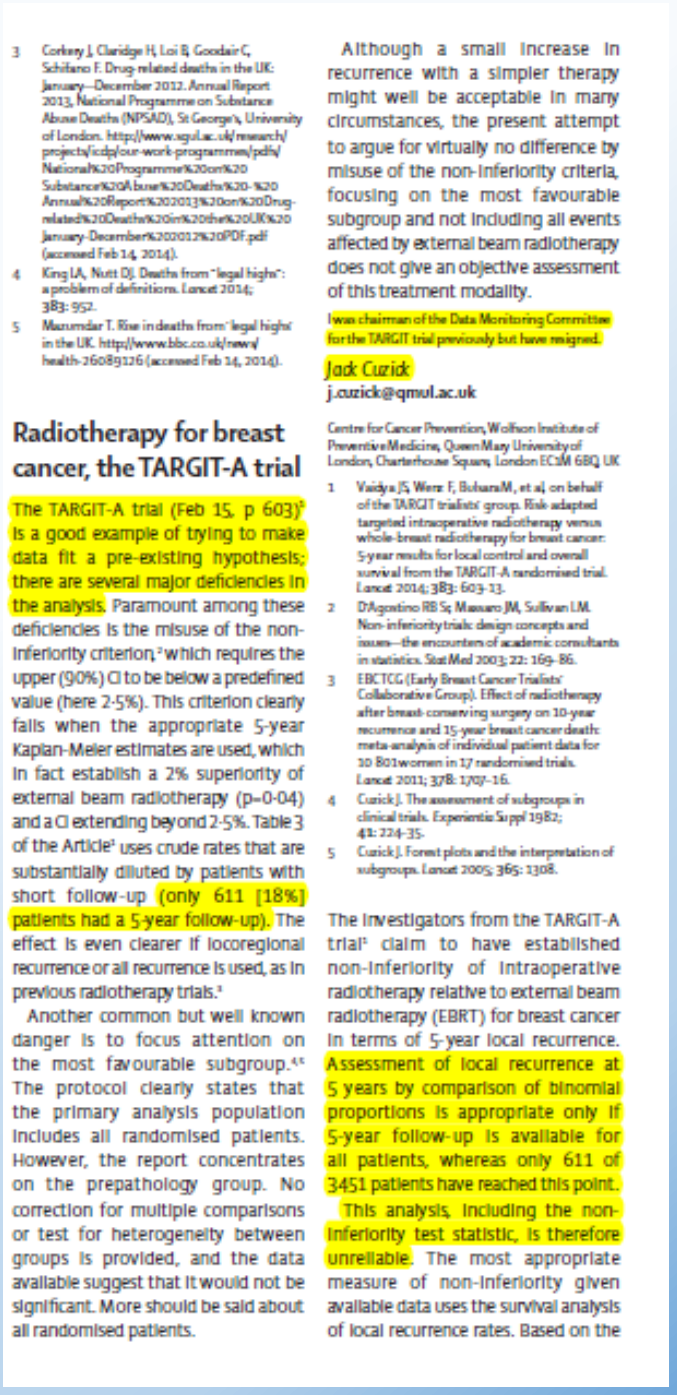
Consider a patient, who has a 2 cm tumor removed along with a small margin and her incision is sutured in such a way the target to be irradiated is 3 cm thick.
Intrabeam using a 25 mm applicator and 20 Gy at the surface of the applicator.
The volume treated within the 90% isodose is less about 2,1 cm^3.
The volume treated within the 50% isodose is less than 7,1 cm^3.

The low energy X rays treatment takes between 35 and 50 minutes.

TARGIT – A study : main criticisms

The TARGIT-A study has been criticized above all for :

- MEDIAN FOLLOW-UP
- STATISTICAL ANALYSIS
- PROTOCOL DEVIATIONS
- POST-PATHOLOGY STRATUM
- NON- BREAST CANCER DEATHS
- CONFLICT OF INTEREST
- RELATIVE BIOLOGICAL EFFECTIVENESS OF LOW-ENERGY PHOTONS



3 Corkery J, Claridge H, Loi B, Goodair C, Schifano F. Drug-related deaths in the UK: January—December 2012. Annual Report 2013, National Programme on Substance Abuse Deaths (NPSAD), St George's, University of London. http://www.sgul.ac.uk/research/projects/icdp/our-work-programmes/pdfs/National%20Programme%20on%20Substance%20Abuse%20Deaths%20-%20Annual%20Report%202013%20on%20Drug-related%20Deaths%20in%20the%20UK%20January-December%202012%20PDF.pdf (accessed Feb 14, 2014).

4 King LA, Nutt DJ. Deaths from "legal highs": a problem of definitions. Lancet 2014; 383: 952.

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Radiotherapy for breast cancer, the TARGIT-A trial

The TARGIT-A trial (Feb 15, p 603)[1] is a good example of trying to make data fit a pre-existing hypothesis; there are several major deficiencies in the analysis. Paramount among these deficiencies is the misuse of the non-inferiority criterion,[2] which requires the upper (90%) CI to be below a predefined value (here 2·5%). This criterion clearly fails when the appropriate 5-year Kaplan-Meier estimates are used, which in fact establish a 2% superiority of external beam radiotherapy (p=0·04) and a CI extending beyond 2·5%. Table 3 of the Article[1] uses crude rates that are substantially diluted by patients with short follow-up (only 611 [18%] patients had a 5-year follow-up). The effect is even clearer if locoregional recurrence or all recurrence is used, as in previous radiotherapy trials.[3]

Another common but well known danger is to focus attention on the most favourable subgroup.[4,5] The protocol clearly states that the primary analysis population includes all randomised patients. However, the report concentrates on the prepathology group. No correction for multiple comparisons or test for heterogeneity between groups is provided, and the data available suggest that it would not be significant. More should be said about all randomised patients.

Although a small increase in recurrence with a simpler therapy might well be acceptable in many circumstances, the present attempt to argue for virtually no difference by misuse of the non-inferiority criteria, focusing on the most favourable subgroup and not including all events affected by external beam radiotherapy does not give an objective assessment of this treatment modality.

I was chairman of the Data Monitoring Committee for the TARGIT trial previously but have resigned.

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1 Vaidya JS, Wenz F, Bulsara M, et al, on behalf of the TARGIT trialists' group. 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: 603-13.

2 D'Agostino RB Sr, Massaro JM, Sullivan LM. Non-inferiority trials: design concepts and issues—the encounters of academic consultants in statistics. Stat Med 2003; 22: 169-86.

3 EBCTCG (Early Breast Cancer Trialists' Collaborative Group). Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10 801 women in 17 randomised trials. Lancet 2011; 378: 1707-16.

4 Cuzick J. The assessment of subgroups in clinical trials. Experientia Suppl 1982; 41: 224-35.

5 Cuzick J. Forest plots and the interpretation of subgroups. Lancet 2005; 365: 1308.

The investigators from the TARGIT-A trial[1] claim to have established non-inferiority of intraoperative radiotherapy relative to external beam radiotherapy (EBRT) for breast cancer in terms of 5-year local recurrence. Assessment of local recurrence at 5 years by comparison of binomial proportions is appropriate only if 5-year follow-up is available for all patients, whereas only 611 of 3451 patients have reached this point.

This analysis, including the non-inferiority test statistic, is therefore unreliable. The most appropriate measure of non-inferiority given available data uses the survival analysis of local recurrence rates. Based on the

TARGIT-A STUDY DEBATE: MEDIAN FOLLOW-UP AND STATISTICAL ANALYSIS

Prof. Cuzick, who wrote these cogent words, was the Chairman of Data Monitoring Committee for the TARGIT-A trial previously but he have resigned.

The protocol clearly states that primary analysis population includes all randomised patients. The study focuses on the most favorable subgroup defined prepathology group; but more should be said about all randomised trial: the investigators from TARGIT-A trial claim to have established non-inferiority of IORT relative to EBRT for breast cancer in terms of 5-year local recurrence.

The 5-year follow-up is not available for all patients because **only 611 (18%) of 3451** have reached this point; it means that **this analysis,** including the non-inferiority test statistic, **is therefore UNRELIABLE.**

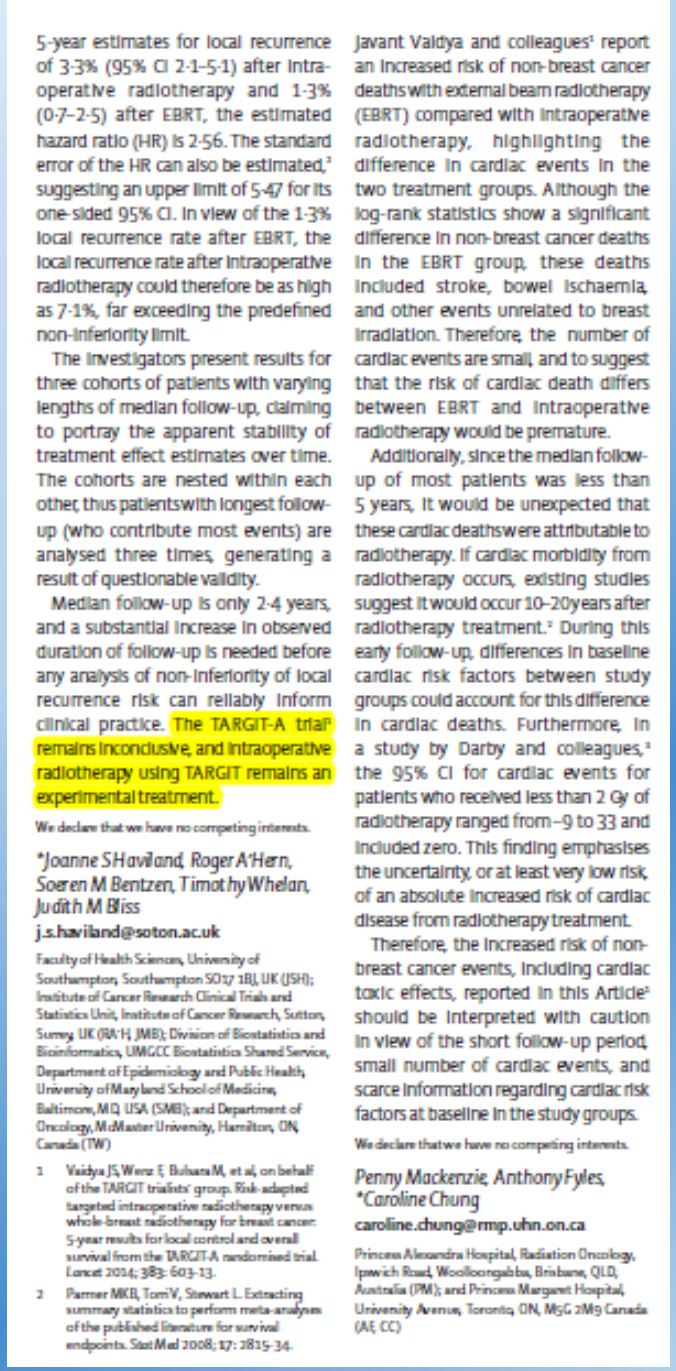
Radiotherapy for breast cancer, The TARGIT-A trial, Cuzick J., Wazer D. E. et al., Lancet, Vol. 383, pp. 1716-1719, 2014.

TARGIT-A STUDY DEBATE: MEDIAN FOLLOW-UP

The length of median follow-up for three cohorts of patients is different and considering that the cohorts are nested within each other, the patients with longest follow-up are analyzed three times generating a result of questionable validity.

The median follow-up is **only 29 months** and an increase duration of follow-up is necessary before any analysis of non-inferiority for the clinical practice.

Haviland et al. conclude this letter with the following words: ***The TARGIT-A trial remains inconclusive, and intraoperative radiotherapy using TARGIT remains an experimental treatment.***



5-year estimates for local recurrence of 3·3% (95% CI 2·1–5·1) after intraoperative radiotherapy and 1·3% (0·7–2·5) after EBRT, the estimated hazard ratio (HR) is 2·56. The standard error of the HR can also be estimated,[2] suggesting an upper limit of 5·47 for its one-sided 95% CI. In view of the 1·3% local recurrence rate after EBRT, the local recurrence rate after intraoperative radiotherapy could therefore be as high as 7·1%, far exceeding the predefined non-inferiority limit.

The investigators present results for three cohorts of patients with varying lengths of median follow-up, claiming to portray the apparent stability of treatment effect estimates over time. The cohorts are nested within each other, thus patients with longest follow-up (who contribute most events) are analysed three times, generating a result of questionable validity.

Median follow-up is only 2·4 years, and a substantial increase in observed duration of follow-up is needed before any analysis of non-inferiority of local recurrence risk can reliably inform clinical practice. The TARGIT-A trial[1] remains inconclusive, and intraoperative radiotherapy using TARGIT remains an experimental treatment.

We declare that we have no competing interests.

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1 Vaidya JS, Wenz F, Bulsara M, et al, on behalf of the TARGIT trialists' group. 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: 603–13.

2 Parmar MKB, Torri V, Stewart L. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. Stat Med 2008; 17: 2815–34.

Javant Vaidya and colleagues[1] report an increased risk of non-breast cancer deaths with external beam radiotherapy (EBRT) compared with intraoperative radiotherapy, highlighting the difference in cardiac events in the two treatment groups. Although the log-rank statistics show a significant difference in non-breast cancer deaths in the EBRT group, these deaths included stroke, bowel ischaemia, and other events unrelated to breast irradiation. Therefore, the number of cardiac events are small, and to suggest that the risk of cardiac death differs between EBRT and intraoperative radiotherapy would be premature.

Additionally, since the median follow-up of most patients was less than 5 years, it would be unexpected that these cardiac deaths were attributable to radiotherapy. If cardiac morbidity from radiotherapy occurs, existing studies suggest it would occur 10–20 years after radiotherapy treatment.[2] During this early follow-up, differences in baseline cardiac risk factors between study groups could account for this difference in cardiac deaths. Furthermore, in a study by Darby and colleagues,[3] the 95% CI for cardiac events for patients who received less than 2 Gy of radiotherapy ranged from −9 to 33 and included zero. This finding emphasises the uncertainty, or at least very low risk, of an absolute increased risk of cardiac disease from radiotherapy treatment.

Therefore, the increased risk of non-breast cancer events, including cardiac toxic effects, reported in this Article[1] should be interpreted with caution in view of the short follow-up period, small number of cardiac events, and scarce information regarding cardiac risk factors at baseline in the study groups.

We declare that we have no competing interests.

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Radiotherapy for breast cancer, The TARGIT-A trial, Cuzick J., Wazer D. E. et al., Lancet, Vol. 383, pp. 1716-1719, 2014.

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1 Vaidya JS, Wenz F, Bulsara M, et al, on behalf of the TARGIT trialists' group. 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: 603–13.

2 Gagliardi G, Constine LS, Moiseenko V, et al. Radiation dose-volume effects in the heart. *Int J Radiat Oncol Biol Phys* 2010; 76: S77–85.

3 Darby SC, Ewertz M, McGale P, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. *N Engl J Med* 2013; 368: 987–98.

In reporting the testing of intraoperative radiotherapy against standard whole breast radiotherapy (WBRT), the investigators of the TARGIT trial[1] claim an excess of non-breast cancer deaths are "almost certainly" due to the adverse effects of WBRT.[2]

We argue that causation is very unlikely. The risk of a major cardiac event increases by 7% per Gy of mean heart dose.[3] Based on expected mean heart doses in the WBRT group of 1–5 Gy, radiotherapy cannot explain more than one of the 11 cardiovascular deaths. This is the case even if all eight cardiac deaths occurred in patients with left-sided cancers. Neither is it credible to attribute an excess of eight other, non-breast, cancer deaths in the WBRT group to radiotherapy. The NSABP B-04 trial[4] followed 1665 patients for a median of 21·4 years after randomisation with or without locoregional radiotherapy after mastectomy, confirming a small excess (n=6) of primary lung cancer that took more than 10 years to emerge. The excess was attributed to large anterior axillary radiotherapy beams. No excess of lung cancers was noted in 1261 patients in the B-06 trial[4] at a median of 19 years after randomisation with or without WBRT after lumpectomy. Lung cancer is the most common cause of death from other cancers in this context, but the TARGIT[1] investigators provide no information about tumour site in relation to randomisation.

The difference in non-breast cancer deaths between randomised groups in the TARGIT trial is explained either by imbalances in risk factors or by

TARGIT-A STUDY DEBATE: NON-BREAST CANCER DEATHS

Javant Vaidya and colleagues report an increased risk of non-breast cancer deaths with external beam radiotherapy (EBRT) compared with intraoperative radiotherapy, highlighting the difference in cardiac events in the two treatment groups.

The number is small and considering the short follow-up period would be premature taking into account that **existing studies suggest it would occur at least 10-20 years after radiotherapy treatment.**

Radiotherapy for breast cancer, The TARGIT-A trial, Cuzick J., Wazer D. E. et al., Lancet, Vol. 383, pp. 1716-1719, 2014.

result in very low cardiac toxic effects. In Darby's study,[2] the median heart dose for a cardiac event was 4-9 Gy, with heart doses as high as 25 Gy. The risk of cardiac toxic effects rose with increasing dose. All modern radiation treatment planning systems have constraints that limit the cardiac dose, so it is unlikely that any centre participating in the study would deliver high cardiac doses, and any EBRT breast radiation study should surely include the requirement to limit the dose to the heart for EBRT radiation. Furthermore, even with data from Darby's study, for doses limited to 3 Gy, the increased risk of death from ischaemic heart disease over 30 years is less than 1%—data that hardly support the TARGIT investigators' assertions. Although the authors state that data for comorbidities were not collected at the time of randomisation, the exclusion criteria listed on ClinicalTrials.gov excludes "Patients with any severe concomitant disease that may limit their life expectancy." It should have been the responsibility of the participating centre to undertake such screening.

To prove their contention of reduced cardiac toxic effects with TARGIT, the authors should have taken four things into account. First, they should have calculated the heart dose for those patients who had a cardiac event. (There are only a total of eight EBRT patients so this would not be too burdensome). Second, they should have identified and presented in the paper whether the left or right breast was irradiated in those patients that died from cardiac toxic effects. Third, the authors should have identified the time after the completion of EBRT that the cardiac events occurred. Finally, they should have indicated whether deaths occurred in those who actually received the prescribed treatment since they used the intention-to-treat population to establish non-breast cancer deaths. 26 patients assigned to EBRT actually received TARGIT; were any of the eight deaths in the EBRT group in these 26 patients?

Clinicians, on the basis of the existing immature TARGIT-A data, would be well advised not to suggest that TARGIT treatment can result in improved non-breast cancer survival.

JKH has received honoraria from IntraOp Medical for proctoring sessions at new institutions using a Mobetron. MJS sometimes speaks at satellite symposia on behalf of Xoft IORT balloon devices. AIR and DEW declare that they have no competing interests.

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TARGIT –A STUDY DEBATE: NON-BREAST CANCER DEATHS

On the basis of the previous critique (an increased risk of non-breast cancer deaths with EBRT), Wazer et al. wrote that the TARGIT-A authors should have indicated the 4 following things :

1. the heart dose for those patients who had a cardiac event;
2. if was the left or right breast irradiated in every specific case ;
3. the time after the completion of EBRT where the cardiac events occurred;
4. whether deaths occurred in those patients who actually received the prescribed treatment since they used the intention-to-treat population to establish non-breast cancer deaths.

No one of the listed things were reported. In fact, this critique ends as ***«Clinicians, on the basis of the existing immature TARGIT-A data, would be well advised not to suggest that TARGIT treatment can result in improved non-breast cancer survival.»***

Radiotherapy for breast cancer, The TARGIT-A trial, Cuzick J., Wazer D. E. et al., Lancet, Vol. 383, pp. 1716-1719, 2014.

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.

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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 Naim 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.

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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

TARGIT-A STUDY DEBATE: NON INFERIORITY OF POSTPATHOLOGY STRATUM

An other point to pay attention is about the **POSTPATHOLOGY STRATUM**: **the patients that received a second surgical procedure for no reason other than the application of the radiation therapy.**

Reitsamer R., Fastner G., Sedlmayer F. , Kopp M., Intraoperative radiotherapy for early breast cancer, Lancet, Vol. 376 , 2010.

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TARGIT-A STUDY DEBATE: SHORT MEDIAN FOLLOW-UP

The follow-up of the TARGIT-A trial, defined as preliminary and immature, is much too short to draw any conclusions about local recurrence rates.

1. Anyway the TARGIT –A authors adfirm that the most local recurrences occur in years 2 and 3, but this do not imply that local recurrences after this time will not occur.
2. For a very low-dose penetration to a depth of 1 cm, 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 and 65 months but out-quadrant relapses occur later than that.

THUS, IT'S CLEAR AND EVIDENT TO AVOID THE USE OF INTRAOPERATIVE RADIOTHERAPY AS A SINGLE SHOT OUTSIDE A CLINICAL TRIAL UNTIL THE LONG-TERM FOLLOW-UP DATA FOR NON-INFERIORITY WILL BE AVAILABLE.

Such conclusion published in 2010 has led to the ASTRO udpated reccomendations (september 2016) on IORT with low energy X rays.

Reitsamer R., Fastner G., Sedlmayer F. , Kopp M., Intraoperative radiotherapy for early breast cancer, Lancet, Vol. 376 , 2010.

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.

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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.
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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.[2–5]

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.

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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.
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TARGIT-A STUDY DEBATE: RELATIVE BIOLOGICAL EFFECTIVENESS OF LOW-ENERGY PHOTONS

This correspondence begins: *«We congratulate Jayant Vaidya and colleagues for their important contribution….the radiation doses uses in TARGIT-A are substantially lower than historical standards»*

The standard dose with EBRT for the treatment of breast cancer is 50-66 Gy. In the TARGIT-A study they adfirmed that the dose delivered in the experimental group is only 5-7 Gy at 1 cm depth.

If it assumes 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: LESS THAN HALF THE RADIATION DOSES USED WITH ACCELERATED PARTIAL OR WHOLE BREAST IRRADIATION.

IT MEANS THAT THE RADIATION DOSE USED IN TARGIT-A MIGHT HAVE SUFFICIENT TO DELAY, NOT PREVENT LOCAL RECURRENCES.

Buchholz T.A., Smith B.D., Kuerer H.M., Intraoperative radiotherapy for early breast cancer, Lancet, Vol. 376 , 2010.

TARGIT –A STUDY DEBATE: PROTOCOL DEVIATIONS

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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*

Received May 26, 2015. Accepted for publication May 27, 2015.

As written by Cuzick et al., TARGIT trialists used a non inferiority test statistic based on binomial proportions; each subject with 1 month or 5 years follow-up contributed the same to the denominator. In particular, the subjects with very short follow-up are counted as not having a local recurrence.

Haviland et al. concluded this comment *«The TARGIT trialists can and should provide a proper analysis of LR rates at 5 years (with CI) to enable an unequivocal assessment of non inferirority».* They reported that the TARGIT protocol would have included all randomized patients and **FOCUSING ON THE PREPATHOLOGY SUBGROUP WAS CLEARLY POST HOC AFTER SEEING THE RESULTS. THE DANGERS OF RESTRICTING RESULTS TO SUBGROUPS ARE WELL KNOWN.**

(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).

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Letters Regarding the TARGIT-A Trial: The Editor's Introduction, Red Journal, Vol. 92, No. 5, pp. 951- 962, 2015.

TARGIT –A STUDY DEBATE: CONFLICT OF INTEREST

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THE TARGIT-A DEBATE

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

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Received May 26, 2015. Accepted for publication May 27, 2015.

As reported by Haviland et al., the TARGIT-A International Steering Committe is composed for the majority by professionals who cooperate and cooperated with Zeiss.

In fact, they reported that ***"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."***

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.

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http://dx.doi.org/10.1016/j.ijrobp.2015.05.033

Letters Regarding the TARGIT-A Trial: The Editor's Introduction, Red Journal, Vol. 92, No. 5, pp. 951- 962, 2015.

TARGIT STUDY: A FLAWED STUDY

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EDITORIAL

A Flawed Study Should Not Define a New Standard of Care

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Received Sep 9, 2014, and in revised form Sep 13, 2014. Accepted for publication Sep 13, 2014.

Volume 91 • Number 2 • 2015

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.

The final judgment on the TARGIT –A study is , thus, that expressed by Wazer et al. :

"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."

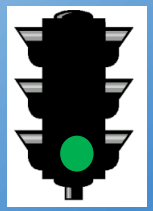
A Flawed Study Not Define a New Standard of Care, Hepel J., Wazer D. E., Int. J. Radiation Oncol. Bio. Phys., Vol. 91, No. 2, pp. 255-257, 2015.

All these criticisms have lead to the ASTRO 2016 APBI guidelines update

ASTRO GUIDELINES UPDATE

On the basis of the published evidence and the mature results obtained thanks to the **5.8 years follow-up** of the **ELIOT trial**, it has been recognized the efficacy of performing the IORT with electrons compared to the **29 months follow up** of the **TARGIT- A trial** (the reference study of IORT with low energy x-rays).

The ASTRO society stated the following recommendations [1]:



- **IORT with electrons (IOeRT) can be used in the clinical practice outside of a clinical trial for the suitable group of patient;**

- **IORT with low energy x-rays can never be used outside of a clinical trial.**

As ASTRO commented on web site [2] : *"Low-energy X-ray IORT should be used only in the context of a prospective registry or clinical trial and restricted to women with invasive cancer who are considered otherwise suitable for partial breast irradiation.*
This recommendation reflects the short, 2.4-year median follow-up of existing trial data".

1. *Accelerated Partial Breast Irradiation: Executive Summary for the Update of an ASTRO Evidence-Based Consensus Statement,* Correa C., Harris E.E., Leonardi M.C. et al., Practical Radiation Oncology, 2016, doi: 10.1016/j.prro.2016.09.007
2. https://www.astro.org/News-and-Publications/News-and-Media-Center/News-Releases/2016/Updated-ASTRO-guideline-expands-pool-of-suitable-candidates-for-accelerated-partial-breast-irradiation/).