EDITORIAL

Pride, Prejudice, or Science: Attitudes Towards the Results of the TARGIT-A Trial of Targeted Intraoperative Radiation Therapy for Breast Cancer

CrossMark

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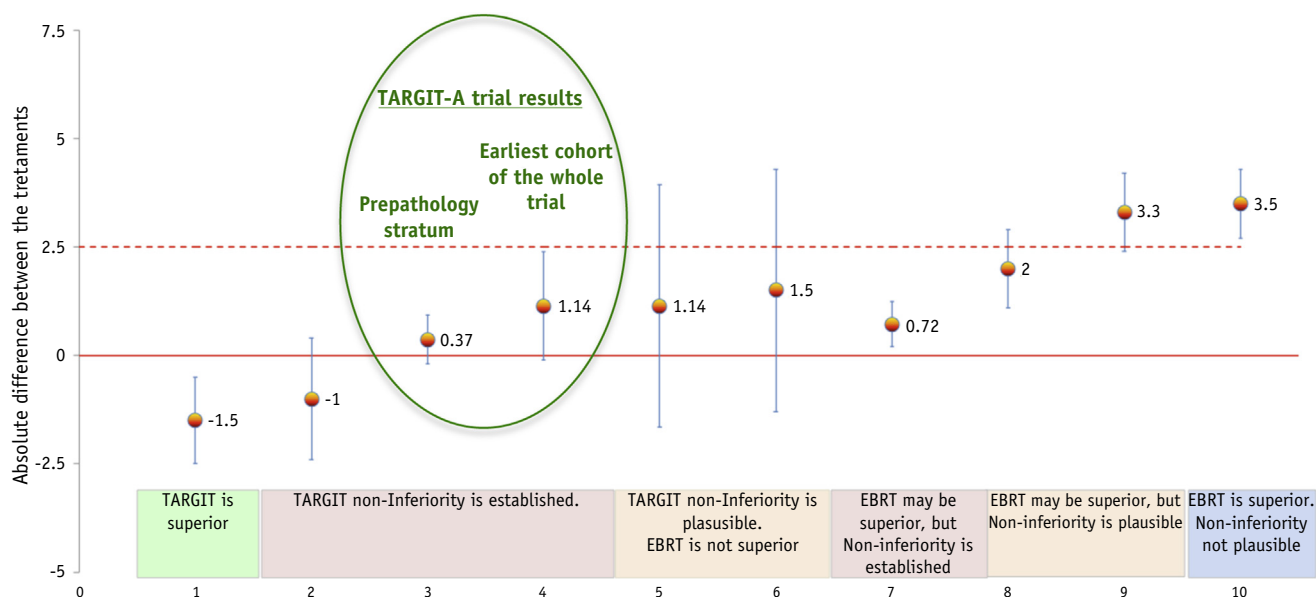
Fig. 1. The meaning of non-inferiority: 10 examples of different scenarios that might occur in a randomized trial testing noninferiority between 2 treatments. The dots represent the absolute difference; the lines represent the confidence intervals. The green circle includes 2 of the trial results: on the left is the targeted intraoperative radiation therapy (TARGIT) prepathology stratum (difference 0.37%), and on the right is the earliest cohort of the whole trial (n = 1222), which has the median follow-up time of 5 years (difference 1.14%) (see Table 3 of the main report) (1, 2).

Introduction

There has been a divergence of attitudes to the results of the targeted intraoperative radiation therapy (TARGIT)-A trial (1, 2). In Europe and Asia, TARGIT-IntraOperative RadioTherapy (IORT) is now being included in national guidelines and is available in over 250 centers worldwide. In the United States, too, it is available in more than 60 centers; yet, it has repeatedly been subjected to fierce criticism by the same set of individuals. A recent editorial in this journal by Hepel and Wazer (3) exemplifies the latter, and we believe it necessary to address their several conceptual, scientific, and factual inaccuracies.

Noninferiority

We concluded (1, 2) that TARGIT-IORT was noninferior to external beam radiation therapy (EBRT). Yet, the authors allege that we claimed that the 2 treatments were equivalent, suggesting that they may not fully understand the basis of the trial design. In a noninferiority trial, if the difference between the treatments being tested (and its upper confidence limit) is less than a preset noninferiority margin, the treatments are considered noninferior even if the difference is "statistically significant" according to a log-rank test (Fig. 1). Furthermore, we recommended that TARGIT should be used during the initial lumpectomy, as in the prepathology stratum (not subgroup), where the difference between the 2 treatments was undoubtedly not statistically significant (P = .31). Finally, survival without local

recurrence, where deaths are not censored, in line with recommendations by the FDA and elsewhere (4, 5), is not statistically different between the 2 arms (Fig. 2).
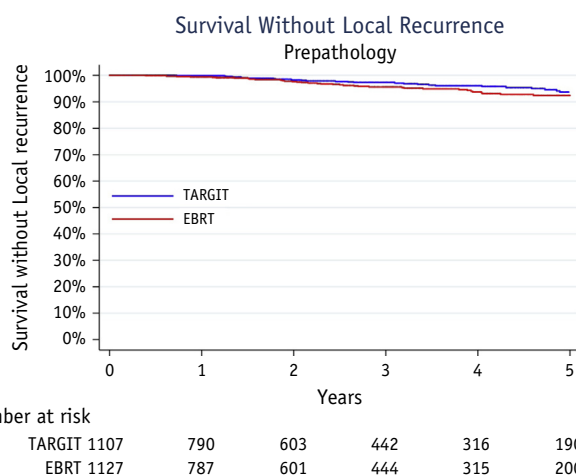
Fig. 2. Survival without local recurrence. This Kaplan-Meier plot is the true representation of how patients with breast cancer would fare in the first 5 years of their life after treatment with targeted intraoperative radiation therapy (TARGIT) during lumpectomy or external beam radiation therapy (EBRT) with respect to local control. Censoring is done at the point of last follow-up or withdrawal. For any patient, her chance of being alive without local recurrence can be read from this plot. The 5-year survival without local recurrence: TARGIT: 93.9% (95% CI 90.9-95.9); EBRT: 92.5% (95% CI 89.7-94.6), P = .35.

Table 1   Results of randomised trials comparing radiation therapy with no radiation therapy

Characteristic	CALGB	BASO 2	PRIME II	TARGIT-A prepathology
Number	636	1135	1326	1625
Age (y)	≥70	≥65	≥65	≥45
T size	≤2 cm	≤2 cm	≤2 cm	Small T2, preferably ≤3.5 cm
Grade		Grade 1	Grade 1 or Grade 2	No restriction
Nodes	Negative	Negative	Negative	No restriction
LV invasion		Negative	Negative	No restriction
ER status	Positive	Positive	Positive	No restriction
5-year LR	4% vs 1% Stat Sig.	6% vs 2% Stat Sig.	4.1% vs 1.3% Stat Sig.	2.1% vs 1.1% overall 1.4% vs 1.1% if ER Positive Both Not Statistically Significant
5-year LR in experimental arm	1 in 25	1 in 17	1 in 25	1 in 48 overall 1 in 71 if ER positive

Abbreviations: BASO = British Association of Surgical Oncology; CALGB = Cancer And Leukemia Group B (CALGB); ER = estrogen receptor; LR = local recurrence; LV = Lympho-Vascular; PRIME = Post-operative Radiotherapy In Minimum-risk Elderly; TARGIT = TARGeted Intra-operative radioTherapy.

Bearing in mind the caveats of comparisons between trials, these data suggest that despite having worse prognosis cancers in the TARGIT-A trial, local control with TARGIT during lumpectomy was excellent and clearly better than "no radiation therapy."

The prespecified noninferiority boundary of 2.5% absolute difference in local recurrence is very conservative and is validated in patient preference studies (6-8). It is much smaller than the 7.5% margin of the ELectron IntraOperative radioTherapy (ELIOT) trial and lower than the difference considered "acceptable" by the Cancer And Leukemia Group B (CALGB) (5% difference) and Post-operative Radiotherapy In Minimum-risk Elderly PRIME II studies (3% difference). At this boundary, TARGIT is noninferior to EBRT ($P_{noninferiority} < .00001$). Within the trial of 3451 patients, the first 1222 patients have a median follow-up time of 5-years; the safety, efficacy, and non-inferiority results in these 1222 patients were similar to those seen in all patients, as shown in Table 3 of Vaidya et al (1). The Appendix gives details of other arithmetic and factual errors of Hepel and Wazer, including those of Haviland et al (9), whom they cite.

Pragmatic

TARGIT-A is a pragmatic randomized controlled trial: it seeks to address the question "what is the efficacy and safety of the TARGIT technique if used in clinical practice." TARGIT is meant to be used within a risk-adapted approach designed to enable the addition of conventional EBRT if additional risk factors come to light postoperatively. This approach reflects the real-world scenario and avoids the "one size fits all" ideology. Thus, within the trial, patients randomized to TARGIT who were given additional EBRT were not "protocol deviations" or "crossovers" but were being treated correctly, as per protocol.

TARGIT alone was effective as well

The authors suggest that the additional EBRT obscured any difference between TARGIT and EBRT. e-Table 2 in

Vaidya et al (2) shows how patients who received only TARGIT in the prepathology stratum had relatively poor prognosis cancers but had excellent local control (97.3%), which was not dissimilar to the whole TARGIT arm (97.9%).

Stratification

The authors wrongly state that the prepathology (TARGIT simultaneous with lumpectomy) and postpathology (delayed TARGIT) strata were subgroups. They were not. The protocol (10) (http://www.nets.nihr.ac.uk/projects/hta/076049) specified stratification before randomization to accommodate different practices in the participating sites. Direct comparison between the 2 strata is not valid because patients were not randomly allocated between the 2 strata (2).

Only as good as "no radiation therapy"?

Table 1 gives results of randomized trials testing the effect of completely omitting radiation therapy (11-13). One in every 17 to 25 of even the most stringently selected low-risk patients would have a local recurrence if radiation therapy were omitted (10-12). By contrast, when TARGIT is given during lumpectomy, local recurrence is rare: 1 in 48, and a reduction to 1 in 71 (ie, 1.4%) when just a single selection criterion (estrogen receptor positivity) is applied. This is despite the fact that TARGIT-A trial eligibility was not limited to "good prognosis" cases, as detailed in the Appendix. Would clinicians and patients really wish to completely omit radiation therapy in anyone who would have been eligible for the TARGIT-A trial (ie, ≥45 years old with a unifocal invasive ductal carcinoma ≤3.5 cm in size)? Surely not.
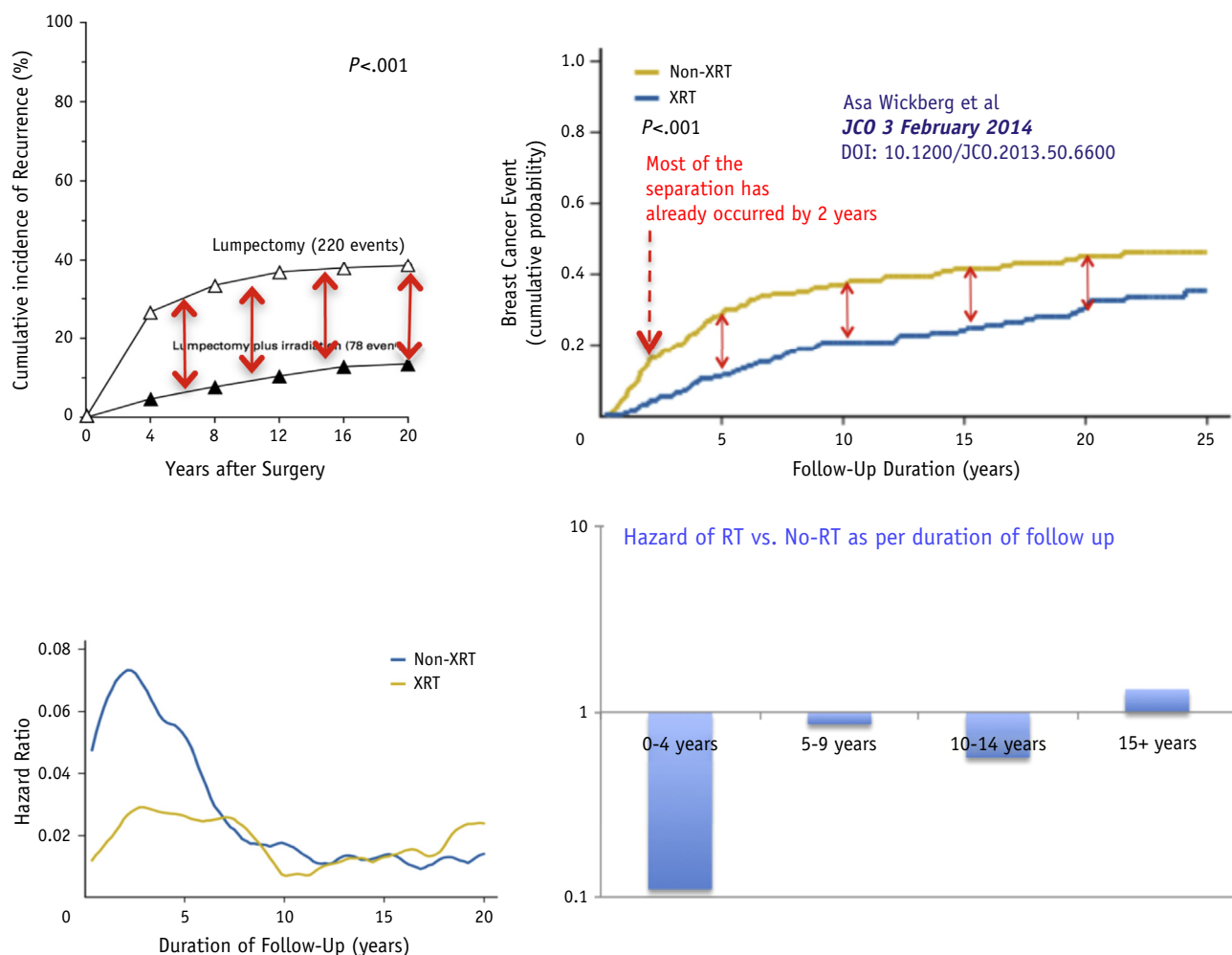
Fig. 3. Demonstration of how the reduction in local recurrence by radiation therapy occurs only in the first 5 years, most of the effect being already seen in the first 2 to 3 years. The top 2 figures are Kaplan-Meier plots from the landmark National Surgical Adjuvant Breast and Bowel Project (NSABP) B06 (17) (left) and the Swedish trial (right) of radiation therapy (XRT) versus no radiation therapy after lumpectomy (18). The bottom half shows the data from the Swedish trial expressed as hazard of local recurrence of radiation therapy versus no radiation therapy from the same Swedish trial. On the left are the smoothened hazard plots and on the right the absolute values of hazard ratios taken from Wickberg et al (19), again showing that almost all the reduction in recurrence by radiation therapy is in the first 5 years.

Follow-up

The peak hazard of recurrence of breast cancer is in the first 2 to 3 years. Vitally, the effect of radiation therapy on local recurrence is limited to the first 5 years, with most of the radiation therapy effect already seen in the first 2 to 3 years (14, 15) (Fig. 3). Thus, local recurrence between 5 and 25 years is no more frequent even in nonirradiated patients compared with those who have received radiation therapy (14-16). The TARGIT-A trial includes 3451 patients with a median follow-up time of 2.5 years and 1222 patients with a median follow-up time of 5 years; therefore, the available follow-up time amply covers the period of risk and also the benefit from radiation therapy. It thus gives complete confidence for the use of TARGIT in clinical practice.

Table 2 Percentage increase in the rate of major coronary events per Gray, according to time since radiation therapy

Time since radiation therapy (y)	No. of case patients	No. of control individuals	Increase in rate of major coronary events: % increase/Gy (95% CI)
0-4	206	328	16.3 (3.0-64.3)
5-9	216	296	15.5 (2.5-63.3)
10-19	323	388	1.2 (−2.2 to 8.5)
≥20	218	193	8.2 (0.4-26.6)

Abbreviation: CI = confidence interval. Data taken from Darby et al, Risk of ischemic heart disease in women after radiation therapy for breast cancer (*N Engl J Med* 2013; 368:987-998).
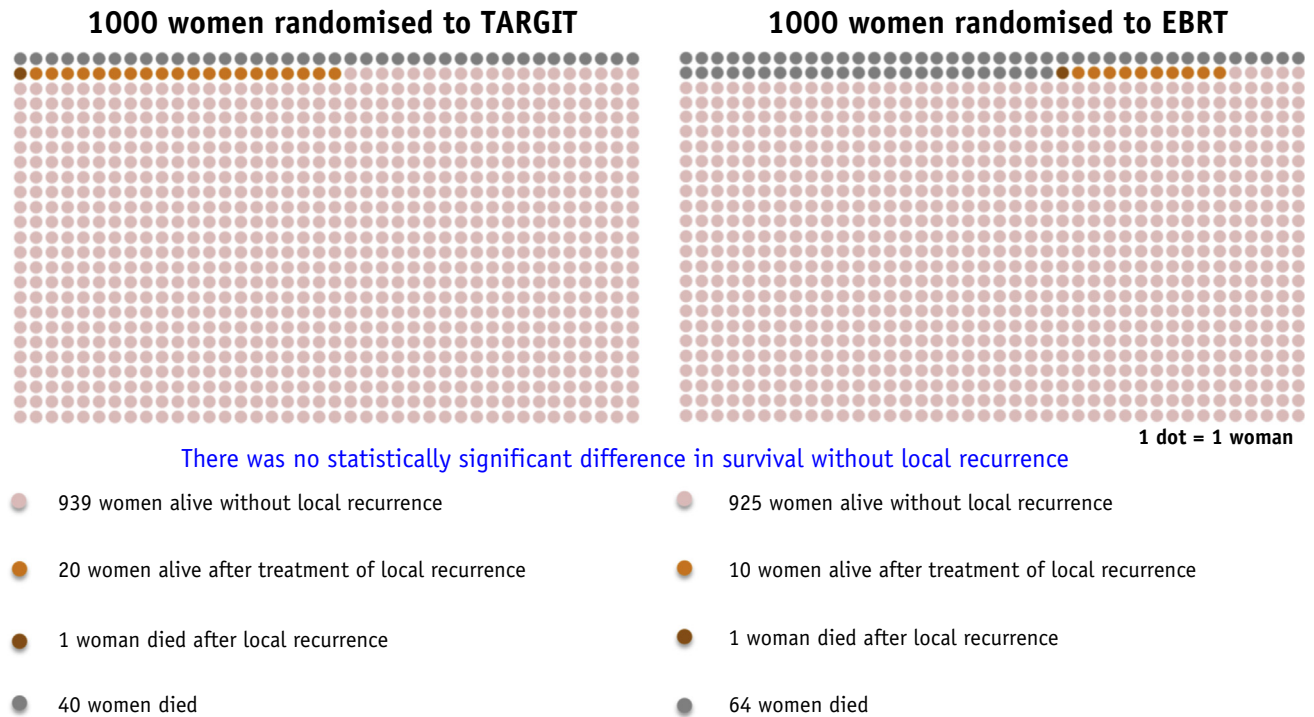
Non—breast cancer deaths

TARGIT-IORT with Intrabeam delivers almost no dose to the heart (17). As it happens, the finding of reduced non—breast cancer mortality with TARGIT (18) is

What happened to women with early breast cancer, treated with TARGIT during lumpectomy compared with those treated with EBRT, over the first 5 years?

1000 women randomised to TARGIT   **1000 women randomised to EBRT**

1 dot = 1 woman

There was no statistically significant difference in survival without local recurrence

939 women alive without local recurrence   925 women alive without local recurrence

20 women alive after treatment of local recurrence   10 women alive after treatment of local recurrence

1 woman died after local recurrence   1 woman died after local recurrence

40 women died   64 women died

TARGIT-A international multi-centre trial included 3451 women randomised to receive TARGIT or EBRT. These figures are created by applying 5-year Kaplan-Meier estimates of survival without local recurrence to 1000 women having breast conserving therapy in the two trial arms. Distant or regional disease not shown: there was no difference seen between TARGIT and EBRT.

Fig. 4.   Pictogram to help patients and doctors make a shared, well-informed decision. EBRT = external beam radiation therapy; TARGIT = targeted intraoperative radiation therapy.

consistent with the observation that EBRT raises the risk of mortality from other cancers (19) and cardiovascular disease (20). Contrary to the popular notion, the increased incidence of major coronary events (myocardial infarction, coronary revascularization, or death of ischemic heart disease) becomes evident in the first 5 years after radiation therapy (Table 2) (20). Hepel and Wazer claim that the difference in non—breast cancer deaths (TARGIT 17 vs EBRT 35) (1) will disappear with longer follow-up times because in their view, it has arisen from a baseline imbalance: allegedly more women with premorbid cardiac conditions were inadvertently randomized to the EBRT arm. But this is surely perverse: to equalize the deaths with longer follow-up times, the next 52 deaths would need to be in the ratio of TARGIT 35 versus EBRT 17, which is highly improbable if women in the TARGIT arm are presumed to have had a lower baseline risk of non—breast cancer deaths!

A more plausible explanation is the following: about a third of the 2.1% absolute difference in non—breast cancer mortality (0·6%) was from cardiac causes. This small increase in non—breast cancer mortality might have been

uncovered early because of the otherwise excellent outcome from breast cancer (5-year mortality 2.2%). In older trials, such a small but lethal effect might have been masked until the high breast cancer mortality—eg, 30% at 5 years in the CRC1 trial (21)—diminished in later years.

Small detrimental effects of treatments have become much more important today, when mortality from the disease for many women diagnosed now is relatively low, so the potential hazards of overtreatment become ever more important.

The study is not flawed

The TARGIT-A trial passed a rigorous peer review including statistical assessment before it was published in *The Lancet* on 2 separate occasions (2010 and 2014). The authors state that Professor Jack Cuzick was the "initial" chair of the Data Monitoring Committee (DMC). The fact is that he was the first and only chair. The DMC were privy to all the unblinded data and approved the formal Statistical

Analysis Plan and all the analyses. Their remit ended when the trial concluded in June 2012. The DMC were thanked and dissolved, nearly a year later. Professor Jack Cuzick did not resign (22), and no letter of resignation was received.

Adoption and financial implications

A decision analytic framework based on the consequences of early adoption if the results do not hold, and the opportunity cost of late adoption if the results do hold (23), strongly supports adoption of TARGIT (23). TARGIT has better health care value: noninferior results and higher patient value, requiring less time, fewer out-of-pocket expenses, and fewer resources overall (estimated savings of at least $1.2 billion in the United States alone over 5 years). The fact that TARGIT saves money within the health care system (24, 25) should be taken as a bonus rather than a threat in the modern era of increasing health care costs.

Conclusions

The data from this large randomized international clinical trial do indeed challenge the current paradigm of whole breast radiation therapy for the majority of breast cancer patients. That clearly adds to the discomfiture of our critics. Yet, we remain concerned about the adoption of new techniques such as balloon brachytherapy that are untested by the rigors of a randomized controlled trial (including those promoted by the authors [26] http://www.accuboost. com).

The level 1 randomized evidence produced by the TARGIT-A trial shows that TARGIT-IORT with Intrabeam during lumpectomy, which is very convenient for the patient, is effective and has fewer side effects than the conventional alternative of whole breast radiation therapy. Hepel and Wazer clearly accept that "5-year LF (local failure) rate for prepathology TARGIT is not statistically different from EBRT" (3), in which case they should not object to TARGIT, bearing in mind the much greater convenience for patients completing their entire local treatment during surgery rather than the significantly more onerous and expensive postoperative treatment or procedures. Patients have every right to be offered an informed choice, and Figure 4 may be used to facilitate a shared decision.

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Appendix

Arithmetic errors of critics such as Hepel and Wazer

Hepel and Wazer cite Haviland et al (6), who disregard that noninferiority is not tested for the single snapshot point estimates of "5-year recurrence rate"; these do not represent actual events but only estimates, and using these values as if they are simple proportions leads to erroneous calculations. Noninferiority is tested using the actual number of recurrences that occur in the follow up period.

Haviland and colleagues state that "Based on the 5-year estimates for local recurrence of 3.3% (95% CI 2.1-5.1) after intra operative radiation therapy 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 1-sided 95% CI. In view of the 1.3% local recurrence rate after EBRT, the local recurrence rate after intraoperative radiation therapy could therefore be as high as 7.1%, far exceeding the predefined noninferiority limit." This calculation by Haviland and colleagues that the upper 95% CI using point estimates is 7.1%, when the raw data−driven real value is 5.1%, is obviously inaccurate and demonstrates the flaws of using multiple nested assumptions. Read their paragraph carefully: the real 95% CI based on raw data is given in the first sentence, and then they derive a hazard ratio and estimate it again and believe the latter rather than the original, wrongly influenced by their own estimates.

Finally, for noninferiority testing, the convention is to use 90% CI rather than 95% as suggested by Professor Jack Cuzick in his letter (22) and elsewhere (27-29).

Three examples of factually incorrect statements by Hepel and Wazer

1. Hepel and Wazer allege that there was no difference in non−breast cancer mortality in the postpathology stratum. This is not strictly true. Although there were fewer total deaths, the ratio was still in favor of TARGIT (TARGIT 5; EBRT 8).

2. They wrongly state that "the 5-year LF rate for 'prepathology' TARGIT (2.5%) was higher [sic] than that of 'postpathology' (5.4%)." First, this is obviously erroneous (2.5% is not higher than 5.4%). Second, the 2 strata were not formally compared, so there is no basis for such a statement anyway. Third, the actual numbers are also wrong: in reality, the prepathology TARGIT recurrence rate is 2.1%, not 2.5%, and it is not statistically different from EBRT (1.1%).

3. They claim that TARGIT failed because the LF rate of TARGIT was higher than that of EBRT. However, as explained in *The Lancet* (2), the difference between TARGIT and EBRT ($P = .042$) is in fact statistically not significant because we prespecified $P < .01$ as the cutoff for statistical significance because of our initial α spend in 2010.

TARGIT-A trial eligibility was not limited to "good prognosis" cases

In the TARGIT-A trial, 85% of patients were younger than 70 years, and a large number had adverse prognostic factors: node positive (n = 502), ER or PgR negative (n = 554), grade 3 (n = 459), or >2 cm (n = 397). Only hormone receptor status made any difference to the outcome (30). More than 60% of cases in the TARGIT-A trial would be considered "unsuitable" or "cautionary" by the ASTRO criteria (31). Only 17.5% of patients in the TARGIT-A trial prepathology stratum would have been eligible for the PRIME2 trial; all others (82.5%) had "worse" prognosis cancers.