under-reporting of non-breast cancer deaths in the test group.

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 Baum M. A revolution in breast cancer therapy. London: *The Telegraph*, Nov 10, 2013.

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.

4 Deutsch M, Land SR, Begovic M, Wieand HS, Wolmark N, Fisher B. The incidence of lung carcinoma after surgery for breast carcinoma with and without postoperative radiotherapy. Results of national surgical adjuvant breast and bowel project (NSABP) clinical trials B-04 and B-06. *Cancer* 2003. **98:** 1362–68.

Jayant Vaidya and colleagues[1] claim that TARGIT treatment results in increased survival since the number of non-breast cancer deaths are higher in the external beam radiotherapy (EBRT) cohort. The investigators cite higher incidences of cardiac toxic effects and deaths from non-breast cancers in the EBRT group as the major cause for the difference in overall survival, even though the TARGIT group currently has a higher, although not significantly breast cancer death rate (2·6% *vs* 1·9%, p=0·56).

The data, with a 29-month median follow-up, show a total of 37 deaths in the TARGIT group, from all causes, and 51 deaths in the EBRT group, from all causes. The authors included deaths from stroke and ischaemic bowel disease as cardiac toxic effects. However, these diseases are caused by narrowing of the arteries (arteriosclerosis) or clot formation, which are unlikely to result from any purported radiation damage to cardiac vessels or valves caused by the EBRT breast treatment. Moreover, deaths from other cancers are not credible to attribute to the breast EBRT treatment. The latency period for induced cancers from breast treatment is well established to be at least 15–20 years. Even after developing a radiation-induced cancer, treatments should prolong survival for several further years, even if cure is not affected. Thus, it is impossible for the 12-year old TARGIT-A study[1] to affect other cancer deaths. If you include only cardiac deaths and breast cancer deaths, the difference between TARGIT and EBRT is only two patients, and is thus hardly significant.

The authors state that although cardiac deaths from radiotherapy typically do not manifest until 7–10 years after treatment (well outside the median follow-up of this study), a recent study[2] that included patients treated as late as 2001 shows that significant cardiac toxic effects are apparent within the first 4 years. Since 35% of the trial patients (1222 patients) had a median follow-up of 5 years, they claim that the study[2] supports the increased toxic effects with EBRT noted in the TARGIT trial.[1] This statement is supported neither by the science nor by any evidence the investigators present.

Darby's study[2] began in 1958 and ended in 2001, so most of their patients were treated with outdated radiotherapy techniques and equipment, and before the era when cardiac toxic effects from breast irradiation were fully appreciated. Furthermore, 76% of the patients in Darby's study[2] had radiation after mastectomy, which is known to result in higher doses to the heart, especially for left breast irradiation. The consensus is that modern radiation techniques should limit the cardiac dose to less than 2 Gy for left-breasted tumours, and to less than 1 Gy for right-breasted tumours. These small doses 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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Authors' reply

Regarding the follow-up, it is tempting to speculate that in the future a difference in local recurrence will become apparent and that the trend in lower overall mortality will disappear, but neither our data[1] nor previous trial results support this speculation. Statistically, to use median follow-up on its own without taking into account the absolute number of patients is inappropriate. Biologically, the temporal distribution of local recurrence shows that the first 2–3 year period covers the peak hazard of local recurrence after surgery (see figure 2 in Cheng and colleagues' paper[2]). Importantly, results from various clinical trials have shown that the effect of local therapy such as surgery or radiation is mainly seen in the first 5 years, with the peak of the hazard by the first 2–3 years. The lines representing local recurrence between radiotherapy and no radiotherapy in Kaplan-Meier plots remain almost parallel after 5 years in the NSABP B06, NSABP B04, and the Oxford Overview. The conclusion of the 25-year follow-up of the Swedish trial[3] of radiotherapy versus no radiotherapy was explicit: "Radiotherapy protects against recurrences during the first 5 years of follow-up." Whatever difference was going to be noted at 25 years was already seen at 5 years, with most of the difference already seen by 2–3 years (as seen figure 2A in Wickberg and colleagues' paper[3]). The TARGIT-A trial[1] has a substantial number of patients (n=1222) with a median follow-up of 5 years, and 2232 patients had a median follow-up of nearly 4 years.

Regarding non-breast cancer deaths, we found that in the 52 deaths we have recorded so far, the ratio of TARGIT:EBRT was 17:35; such a notable baseline imbalance in cardiac morbidity favouring TARGIT seems unlikely in a randomised trial of this size. We noted a significant difference in non-breast cancer mortality with a high degree of confidence (p=0·0086), which seems to lead to a trend in reduced overall mortality with TARGIT.[1]

Our data are consistent with the recent analysis of Darby and colleagues.[4] They reported that the risk is highest in the first 10 years—during this period, the risk of cardiac mortality is increased by 16·3% (95% CI 3·0–64·3)—ie, a risk ratio of 1·163 (1·03–1·643) per Gy.[4] Presence of ischaemic heart disease (equally balanced between cases and controls) has a multiplicative effect and the risk ratio rises to 13·4% (95% CI 7·65–23·58) per Gy. As the risk increases linearly with dose, for a typical patient with an exposure of 3 Gy, the risk would be three-times higher with a relatively wide upper confidence limit. These estimates are consistent with the TARGIT-A trial results.[1]

One might expect irradiation for left-sided cancers to result in higher cardiac toxic effects. However, the ratio of cardiac risk of left:right sided cancers is small (1·34 as per Darby and colleagues).[4] Furthermore, Darby and colleagues[4] recorded no significant effect of laterality on cardiac toxic effects per Gy. With modern radiotherapy designed to reduce cardiac dose, the absolute difference between sides is likely to be even lower and undetectable with few events. So an absence of a difference between the left and right sides should not be interpreted as an absence of cardiac toxicity.


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In the TARGIT-A trial,[1] the 5-year risk of non-breast cancer mortality was 1·4% (TARGIT) versus 3·5% (EBRT). The absolute difference in non-breast-cancer mortality was 2·1%, about a third of which (0·6%) was from cardiac causes. This small increase in non-breast cancer mortality might have been uncovered early in the TARGIT-A trial because of the otherwise excellent outcome from breast cancer (5-year mortality 2·2%). In older trials, this small but lethal effect might have been masked until the early high breast cancer mortality (eg, 30% at 5 years in the CRC1 trial) diminished in later years.

Furthermore, intraoperative irradiation of a fresh tumour bed has been shown to abrogate the stimulatory and inflammatory effects of surgical wounding.[5] Could this possibly have systemic beneficial effects that contribute to the reduction in non-breast-cancer mortality? This bold conjecture is supported by the observation of a significant reduction in non-breast cancer mortality when patients receive TARGIT plus EBRT compared with EBRT alone.[6] The hypothesis can be fortuitously tested in the TARGIT-B superiority trial in higher risk women (TARGIT boost plus EBRT *vs* EBRT boost plus EBRT).

Although non-inferiority trials are becoming more common, especially when cure rates are high and a reduction in treatment toxicity without a loss of efficacy is desirable, the concept of non-inferiority can be difficult to grasp. The TARGIT-A trial was such a non-inferiority trial, which means that