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 Parmer 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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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 ischaemic heart disease in women after radiotherapy for breast cancer. *N Engl J Med* 2013; **368:** 987–98.

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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

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?