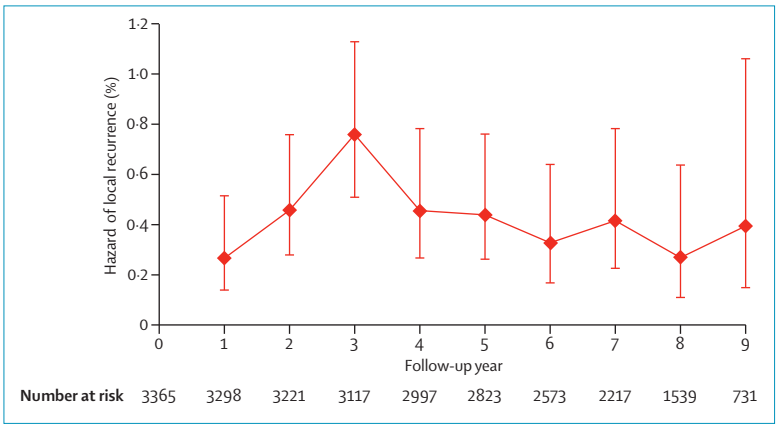

Figure: **Annual hazard of local recurrence from the START trials for patients aged 45 years or older with tumour size less than 3·5 cm, after wide local excision**
Error bars indicate 95% CIs.

Jayant Vaidya and colleagues[1] report early findings from TARGIT-A. We note that only 11 local recurrences have been recorded so far and their figure 4 indicates that median follow-up in trial patients is 2 years. Treatment effect is estimated at 4 years, a time-point which only 420 patients have reached. In this context, the citing of numbers of patients in subgroups with a given median follow-up (eg, 4 years) is uninformative.

Although Vaidya and colleagues might be correct that the peak incidence of local recurrence occurs at 2–3 years after surgery, long-term data from the START (Standardisation of Breast Radiotherapy) trials[2,3] in a similar group of patients show that local recurrences continue to occur for many years (figure). It is premature to conclude that TARGIT-A follow-up is sufficiently mature.

The low incidence of local recurrence reported is consistent with other trials. However, we question whether the non-inferiority margin of 2·5% remains appropriate. Comparing rates of 1·5% with 4·0% translates to a risk ratio of 2·7, a figure which is the same order of magnitude as that for radiotherapy versus no radiotherapy after wide local excision for early breast cancer.[4]

Intraoperative radiotherapy has the potential to affect practice worldwide. Although we support quality research into its application, we caution against early confidence in the assessment of therapeutic equivalence with the standard whole-breast radiotherapy.

We declare that we have no conflicts of interest.

*Joanne S Haviland, Roger A'Hern, Judith M Bliss
jo.haviland@icr.ac.uk

Institute of Cancer Research—Clinical Trials and Statistics Unit (ICR-CTSU), Institute of Cancer Research, Sutton SM2 5NG, UK

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 The START Trialists' Group. The UK Standardisation of Breast Radiotherapy (START) Trial A of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. *Lancet Oncol* 2008; **9:** 331–41.
3 The START Trialists' Group. The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. *Lancet* 2008; **371:** 1098–107.
4 Early Breast Cancer Trialists' Collaborative Group (EBCTCG). Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. *Lancet* 2005; **366:** 2087–106.

We disagree with the conclusion of Jayant Vaidya and colleagues that the TARGIT-A trial,[1] in which external-beam and intraoperative tumour-bed radiotherapy were compared in low-risk operable breast cancer, provides "robust and mature evidence… that targeted intraoperative radiotherapy is safe".

We are concerned that publication based on 11 recurrences in 2232 randomised patients is premature. Audit of the Edinburgh breast conserving series of more than 1800 patients shows a constant annual rate of ipsilateral breast recurrence over more than 20 years. To mirror the TARGIT-A patient population, we considered a subset of 901 patients older than 50 years with low-risk or medium-risk breast cancer: 86% had tumours that were strongly oestrogen-receptor positive, 82% were grade 1 or 2, 84% were node negative, and 86% pT1 (primary tumour diameter <10 mm). There have been 56 local ipsilateral recurrences with actuarial rates of 1·6% at 4 years, 4·3% at 10 years, and 10·3% at 20 years. Thus, although the 4-year rate was similar to that of TARGIT-A, it was sixfold greater at 20 years with a confidence interval of ±3·5%, greater than the absolute difference to be excluded by TARGIT-A.

In TARGIT-A, the efficacy of intraoperative radiotherapy alone on local control is uncertain because 66 patients in that group received external-beam radiotherapy, which might have prevented some local recurrences in the intraoperative group of the trial.

We support the ASTRO consensus statement on partial breast irradiation[2] that "women…should be informed of the much longer track record of safety and efficacy of postoperative whole breast irradiation". Mature outcome data are needed from TARGIT-A before it can be regarded as safe.

We declare that we have no conflicts of interest.

*David Cameron, Ian Kunkler, Mike Dixon, Wilma Jack, Jeremy Thomas, Gill Kerr
d.cameron@ed.ac.uk

Edinburgh University (DC, IK, MD, WJ), Edinburgh Breast Unit (DC, IK, MD, WJ, JT, GK), Department of Oncology (DC, IK, MD, WJ, GK), and Department of Pathology (JT), Western General Hospital, Edinburgh EH4 2XU, UK

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 Smith BD, Arthur DW, Buchholz TA, et al. Accelerated partial breast irradiation consensus statement from the American Society for Radiation Oncology (ASTRO). *Int J Rad Oncol Biol Phys* 2009; **74:** 987–1001.