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# Long-term data confirms that single dose radiotherapy during surgery for breast cancer (TARGIT-IORT) is as effective as whole breast radiotherapy

***A commentary on: Long term survival and local control outcomes from single dose targeted intraoperative radiotherapy during lumpectomy (TARGIT-IORT) for early breast cancer: TARGIT-A randomised clinical trial.***

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**Summary**

While planning treatment with patients with early breast cancer eligible for breast conservation, the option of risk adapted single-dose TARGIT-IORT during lumpectomy under the same anaesthetic should be discussed. The long-term results of the TARGIT-A trial has shown TARGIT-IORT to be as effective as conventional long course of post-operative whole breast radiotherapy, and leads to fewer deaths from non-breast cancer causes.

In 1996[1], it was proposed that smaller cancer foci away from the primary tumour in the breast may not be clinically relevant because of local recurrence after breast conservation occurs mainly at the site of primary tumour. To test this hypothesis, the TARGIT-A randomised trial[2] was set up, and compared risk-adapted targeted intraoperative radiotherapy (TARGIT-IORT) given during lumpectomy vs conventional whole breast external beam radiotherapy (EBRT). The trial recruited from March 2000 to June 2012 and the latest results were recently published in the British Medical Journal[3] (https://www.bmj.com/content/370/bmj.m2836.full.pdf https://youtu.be/5Xby04NBanY. More information at http://targit.org.uk )

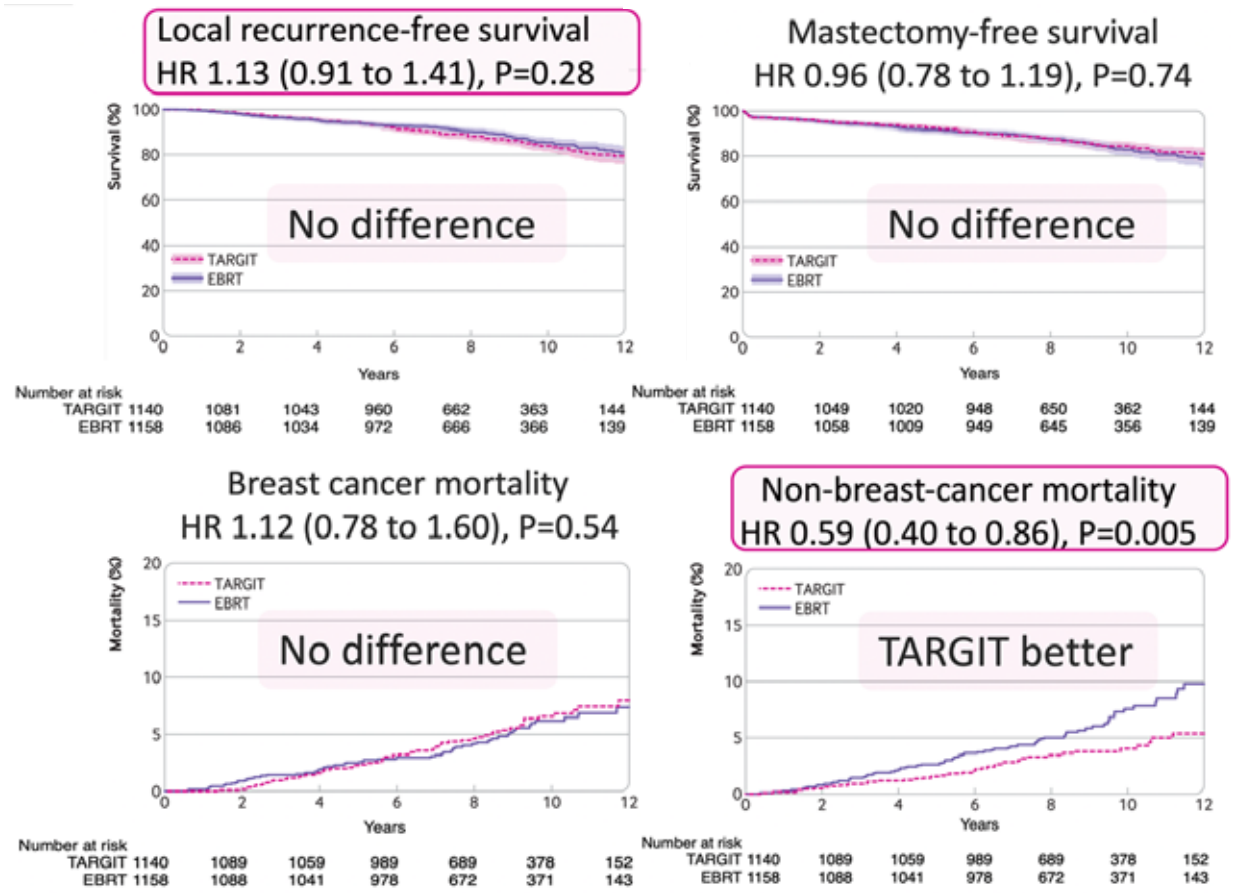
The risk-adapted approach in the experimental arm of the trial meant that some patients (15-20%) who had received TARGIT-IORT during lumpectomy were recommended, as per protocol, to receive whole breast radiotherapy (TARGIT-IORT was considered as a boost in those cases). These cases would be selected on the basis of criteria that placed them at an unacceptable risk of local recurrence. For example, involved margins and certain relatively rare criteria such as unexpected findings, or invasive lobular cancers coming to light at the post-operative MDT, it was felt it would be safer to give such patients whole breast radiotherapy. Consequently, the majority of patients the well-known 'high-risk' groups did not receive supplemental EBRT after TARGIT-IORT as part of the risk-adapted approach.

That aside, the patients in the TARGIT-A trial were in fact representative of the usual patients we see in our clinics. Any patient with invasive ductal carcinoma suitable for breast conservation (preferably <=3.5cm in size) was eligible. Consequently, 83% were younger than 70, 19% had ER/PgR negative tumours, 20% had grade 3 cancers, 22% had involved nodes – each of these groups had more than 400 patients in the trial. Furthermore, TARGIT-IORT was the only treatment given to 78% of Grade 3, 82% of ER negative and 67% of node positive patients. So TARGIT-A trial cohort was not a 'low-risk population' as some have suggested.

## What are the results and their implications?

The long-term results (median follow up 9 years, maximum 19 years) have confirmed comparable long-term effectiveness of risk-adapted TARGIT-IORT and EBRT, in terms of local and distant control, breast preservation and breast cancer survival. Deaths from causes other than breast cancer were significantly fewer in the TARGIT-IORT arm HR 0.59 (0.40 to 0.86) p=0.005, with at 4.45% difference at 12- (5.41% vs 9.85%). Notably, the Kaplan-Meier curve for overall survival for TARGIT-IORT always remains above EBRT, with the curves continuing to separate well beyond 10 years (figure). With regard to follow up TARGIT-A trial is larger and more comprehensive than any other trial of partial breast irradiation for invasive breast cancer.

The observation of fewer non-breast cancer deaths with TARGIT-IORT is not an anomaly. Other studies including those from the Oxford group have shown how modern radiotherapy still leads to significant scatter radiation and increases cardiac and lung cancer mortality[4-8]. Overall partial breast irradiation with whole breast irradiation reduces non-breast-cancer as well as overall mortality as seen in two meta-analyses[9,10]. Data from the TARGIT-A trial suggests another possibility – that intraoperative radiotherapy during lumpectomy may have a beneficial abscopal effect[11] contributing to the reduced mortality. This possibility is explored in a separate paper, currently under review.




These results should be considered in the context of the eligibility for other trials of partial breast irradiation such as IMPORT-Low, as well as from the trials of no-radiotherapy such as PRIME-II or CALGB[12-14]. For eligibility for such trials, patients needed to be much older (eg >65 years), node negative, and with low grade, good prognosis cancers. Despite this, the 5-year local recurrence rates with 'no-radiotherapy' were 2 to 3 times higher than those seen with TARGIT-IORT.

Therefore TARGIT-IORT is suitable for most patients planned for breast conservation. By contrast, a large proportion of such patients would be ineligible to receive other forms of partial breast irradiation. By having TARGIT-IORT during their lumpectomy, under the same anaesthetic, such patients have their radiotherapy without even realising it, saving repeated visits to the radiotherapy department, and avoiding the consequent toxicity. They can have their cake and eat it too.

**Conclusions**

TARGIT-IORT is equally effective as whole breast radiotherapy while avoiding in 8 out of 10 patients the inconvenience[15], pain[16] and toxicity[17], of whole breast radiotherapy. It also reduces non-breast cancer mortality, breast pain, and the overall burden of treatment[15], whilst improving quality of life along with a cosmetically superior outcome[18,19].

Clinicians and patients in 38 countries (260 centres) have already adopted TARGIT-IORT, and over 45,000 patients have been treated so far. We believe that the long-term data presented in this paper, taken together with so many benefits for the patient, provide compelling evidence for a wider adoption. All doctors in the UK are now obliged to follow the new GMC guidelines underlining the essential nature of adequate patient information (i.e., what they can reasonably expect to be told) in order to provide valid consent (https://www.gmc-uk.org/ethical-guidance/ethical-guidance-for-doctors/consent). and in the guidelines of the Royal College of Surgeons (https://www.rcseng.ac.uk/standards-and-research/standards-and-guidance/good-practice-guides/consent/). In the UK, this powerful principle is now fully enshrined in law (Montgomery v Lanarkshire Health Board, 2015).

Potential conflict of interest of the authors and references are in the paper (https://www.bmj.com/content/370/bmj.m2836.full.pdf)

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