Using targeted intraoperative radiotherapy for early breast cancer reduces the incidence of late-onset lung cancer: 25-year update from the TARGIT-A randomised trial

Jayant S Vaidya*, Norman R Williams, Max Bulsara, Michael Baum, Chris-Brew Graves, Ingrid Potyka, Nicholas J Roberts, Julie Lindsay, Siobhan Laws, Sanjay Raj, Michael Douek, Mary Falzon, Gloria Petralia, Anu Malhotra, Sarah Needleman, Marcelle Bernstein, David Morgan, Jeffrey S Tobias.

Abstract

Background: With improvement in survival after breast cancer, the burden and longer-term side effects of treatment are increasingly relevant. Today, most patients can avoid a mastectomy, but having a breast conserving surgery has traditionally been followed by external beam whole breast radiotherapy (EBRT), which can be onerous and leads to inevitable and potentially carcinogenic irradiation of nearby vital organs such as the lungs.

Setting and **Method:** The results of the TARGIT-A randomised trial found that targeted intraoperative radiotherapy (TARGIT-IORT) during the initial lumpectomy is as effective as EBRT in controlling breast cancer, and has several benefits to the patient including reduced pain, improved cosmetic outcome and quality of life, and significantly fewer deaths from non-breast-cancer causes, leading to an overall survival benefit in patients with grade 1 or 2 cancers with a 12-year mortality reduction from 15% to 10.5%.

We collected long term data for health status and new diagnoses in the 714 UK patients who participated in the TARGIT-A randomised trial by using direct patient contact, and data from NHS records. For this paper, we analysed the comparative incidence of lung cancer as it has a well-established causal relationship with EBRT, to assess the magnitude of the difference between TARGIT-IORT and EBRT.

Results: Trial recruitment was from March 2000 to June 2012. The median follow up now is 12.4 years. There were significantly more new lung cancer diagnoses in the EBRT patients compared with TARGIT-IORT patients - HR 3.3 (95%CI 1.1-10.2), 16-year incidence: EBRT: 7.2% (95%CI 3.74 – 13.70) and TARGIT: 1.8% (95%CI 0.6-5.2), 5.38% excess lung cancers with EBRT (95%CI 0.3 -10.5), log rank p=0.0266.

An estimated 920,000 breast cancer patients worldwide are suitable for TARGIT-IORT annually. Using the 5.38% reduction in lung cancer risk that we have observed, if TARGIT-IORT were to be made accessible to these patients, then 49496 (95%CI 5500-134320) of these patients would be spared the diagnosis of a lung cancer during their follow up.

Discussion: These new data from very long-term follow up of a large, randomised trial show a substantial increase in incidence of lung cancer with EBRT compared with TARGIT-IORT. It is a tragedy when women who outlive breast cancer then succumb to this frequently lethal (EBRT) radiation-induced second cancer, the which is avoidable by using TARGIT-IORT during lumpectomy instead of EBRT.

These new data further mandate full discussion with patients about the benefits of TARGIT-IORT before their surgery, and enabling them to take it during their lumpectomy.

Short summary

In patients treated for early breast cancer in the TARGIT-A randomised trial, the long-term incidence of lung cancer was reduced by two thirds in patients randomised to targeted intraoperative radiotherapy (TARGIT-IORT) during lumpectomy, compared with post-operative whole breast radiotherapy. The use of TARGIT-IORT could prevent the development of many radiation-induced lung cancers.

Affiliations: University College London, (JSV, NRW, MBu, MBa, CBG, IP, NR)**,** Institute for Health Research, University of Notre Dame Australia (MB)**,** University College London Hospital (JST, MF, GP)**,** University of Oxford (MD), Oxford University Hospital (GP), Royal Free Hospital (SN), Royal Hampshire Hospital (SL, SR), Guy's and St Thomas' Hospital (AM, MD)**,** Ninewells Hospital (JL)**,** Nottingham University Hospitals (DM)
*Corresponding author: Prof Jayant S Vaidya, Professor of Surgery and Oncology, University College London, jayantvaidya@gmail.com, jayant.vaidya@ucl.ac.uk

This is a pre-print deposited at University College London, London, 2 December 2025 @ The authors

Keywords: Breast cancer, radiotherapy, intraoperative radiotherapy, lumpectomy, wide local excision, breast conserving surgery, TARGIT-IORT, survival from breast cancer

Introduction

The survival from breast cancer has greatly improved over the past three decades, so for patients, the burden of treatment and its longer-term side effects have become increasingly relevant. Today, a large proportion of patients can have breast conserving surgery, avoiding a mastectomy. However, external beam whole breast radiotherapy (EBRT) has traditionally been part of the package of breast conservation to reduce local recurrence, and it is given over several days or weeks of daily treatments. Such a course of EBRT, even when it is shortened to five days is considered onerous by patients[1]. Furthermore, external beam radiotherapy inevitably leads to inadvertent irradiation of nearby vital organs such as the heart and lungs which can have fatal consequences[2].

Targeted intraoperative radiotherapy (TARGIT-IORT)[3-5] using INTRABEAM™ was developed at UCL and delivers radiation immediately after lumpectomy, under the same anaesthetic, and precisely to the tumour bed under direct vision. The rest of the breast and nearby vital organs (e.g., the heart and the lungs) are spared, and the treatment can be performed in a standard operating theatre. It is highly convenient to patients who prefer it even to the newer 5-day course of post-operative external beam radiotherapy[1]. It is also less expensive to the tax-payer[6] and significantly reduces the carbon footprint of cancer treatment[7].

The TARGIT-A international randomised trials recruited 3451 patients from 33 centres in 11 countries from March 2000 to June 2012. Randomisation for the TARGIT-A trial was stratified by country. The main trial (n=2298) compared immediate TARGIT-IORT given during the initial lumpectomy surgery vs. post-operative 3-6 weeks' course of whole breast radiotherapy (EBRT) and the latest results were published in 2020-2023[8-11]. The subsequently started parallel trial (n=1153) compared delayed TARGT-IORT given by re-opening the wound vs EBRT and the results were published in 2020[12]. The short- and long-term results found that TARGIT-IORT during the initial lumpectomy is as effective as EBRT in controlling breast cancer, and significantly fewer deaths from cardiovascular causes and lung problems and other cancers, leading to an overall survival benefit -12-year mortality reduction from 15% to 10.5%) in patients with grade 1 or 2 cancers, which form 78% of all cases[8-10 13-16]. Several studies have documented that TARGIT-IORT improves cosmetic outcome and quality of life, reduces pain[17-19], reduces travel (~730 miles per patient) and social burden; it is option for patients who have previously had whole breast radiotherapy, and is preferred by patients over mastectomy, external beam radiotherapy or 'no-radiotherapy'[1 6 18-32].

TARGIT-IORT has now been included in many international breast cancer guidelines, and adopted in over 35 countries around the world (https://targit.org.uk/targit-iort-in-guidelines). By 2019, over 45,000 patients had been treated in about 250 centres worldwide[33], and over 260 scientific papers from several countries have confirmed the original results[34]. In 2021, NIHR hailed the TARGIT research as "five amazing health breakthroughs"[35] alongside two COVID-19 treatments and the Oxford COVID-19 vaccine.

We aimed to collect data regarding UK patients from the TARGIT-A trial using a novel methodology (*methodology and its success are reported to the NIHR-HTA 14/49/13 project for publication in NIHR Journals Library*), with the objective of recording long-term outcomes including incidence of new cancers, the most common of which is lung cancer. In this short paper, we report the long-term incidence of lung cancer in the UK patients who participated in the TARGIT-A trials.

Funding: NIHR (HTA 14/49/13) for Extended follow up of the TARGIT-A trial, and University College London Hospitals (UCLH)/UCL Comprehensive Biomedical Research Centre, UCLH Charities, and Ninewells Cancer Campaign for the TARGIT-IORT research.

Methods

We recorded extended long-term follow up of UK patients from TARGIT-A trials (total 3451 patients) using two separate approaches: first by direct patient contact, and secondly by downloading routinely collected in the UK i.e., NHS data from the UK NHS Digital service. All 714 UK patients who had participated in the TARGIT-A trial were eligible. Those who had not died or withdrawn, were first contacted in collaboration with the recruiting site. One year after this consent was received by the UCL trials office, and annually thereafter, the trials office staff requested further follow-up information from each patient. We complemented these data with the data downloads from the UK NHS Digital service.

We used STATA (ver 18.0) for statistical analyses. We compared the incidence of lung cancer in each randomised arm using the Cox proportional hazard model and plotted the Kaplan-Meier graphs. We assessed the proportional hazards assumption using Schoenfeld residuals (stphtest) and graphical (stphplot) methods. Independent administrative censoring was assumed

We used Fine–Gray subdistribution hazard models to estimate the effect of death as a competing cause on the cumulative incidence function to ascertain whether any differences in number of deaths between the two arms influences the results.

Results

Patient characteristics and treatments received (other than the randomised allocation of radiotherapy) have been published previously and are well matched between the two randomised arms[8-10 13-16]. Age and Body Mass Index (BMI) which are risk factors for lung cancer were also well matched between the two trials (see supplementary tables 1 and 2 in our 2021 paper[9].

The median follow up was 12.4 years (IQR 7.9 to 14.5). The incidence of lung cancer was significantly higher in the EBRT patients compared with TARGIT-IORT patients, the difference staring to emerge after the first 9 years: (EBRT n=12/359 vs. TARGIT n=4/355); Hazard Ratio 3.3 (95%CI 1.1-10.2), p=0.0266.

The 16-year incidence was EBRT: 7.22% (95%CI 3.74 – 13.70) and TARGIT: 1.84% (95%CI 0.65 – 5.14). The excess incidence of lung cancer diagnosis in patients randomised to EBRT was 5.38% (95%CI 0.30% – 10.46%).

We found that the proportional hazards assumption was confirmed - there was no statistically significant change in hazards with time (global test rho = 0.25036 chi2= 1.01 p=0.3160). Visually, the lines did not cross (supplementary figure 1).

However, because of the visual appearance of loss of proportional hazards in the Kaplan-Meier curves, we also report time-stratified hazard ratios (e.g., 0–9 years vs ≥10 years) with death as a competing event, to provide a clear picture of the risk over time. We found that for period before 9 years HR 0.999 (95%CI 0.146 - 7.093) p=0.999 and sHR is 0.945 (95%CI 0.14 - 6.58), p=0.9544 and for the period after 9 years HR is 3.28 (95%CI 1.056 - 10.169), p= 0.0266 and sHR is 5.31 (95%CI 1.172 - 24.117) p=0.0303.

Analysis using the Fine-Gray competing risk model with death as the competing event did not change the results. We found that sHR was 3.11 (95%CI 1.002 – 9.665), p=0.0495. We have included this graph in the revised manuscript as the supplementary figure 2. Fine-Gray model.

We also confirmed that there is no evidence of bias in the length of follow up between the two arms of the trial. In fact, overall, the EBRT patients' follow up was slightly shorter (p=0.0399) (supplementary figure 3), so we may have missed some lung cancer cases amongst them. Therefore, any bias from shorter follow-up in the EBRT arm would tend to reduce the observed risk of lung cancer in EBRT rather than inflate it, so the real difference between the treatment arms might possibly have been even greater.

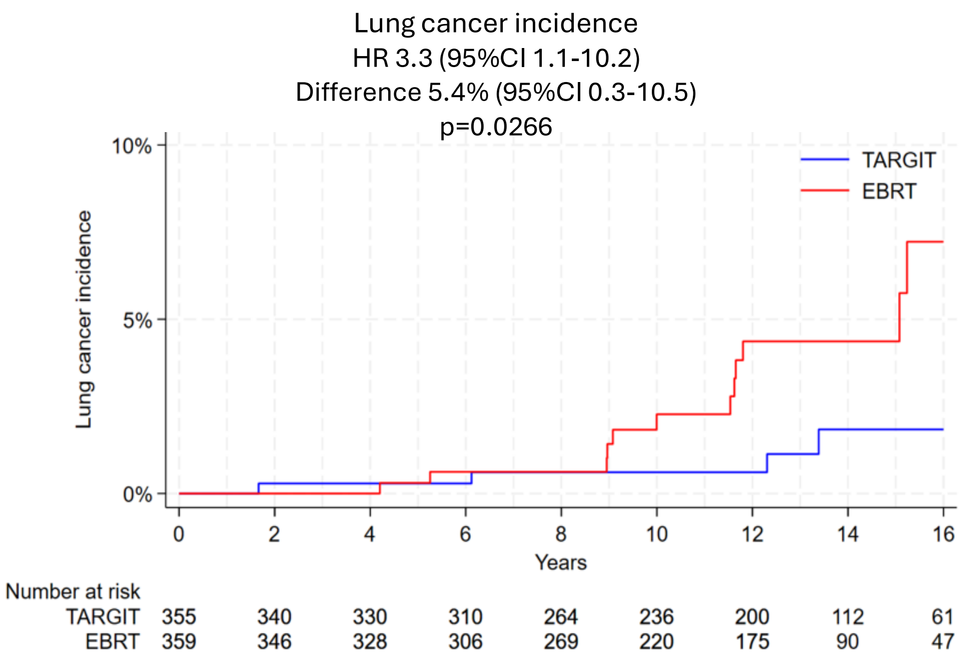

Figure 1. Long-term lung cancer incidence each arm of the randomised TARGIT-A trial. The 16-year incidence was EBRT: 7.22% (95%CI 3.74 – 13.70) and TARGIT: 1.84% (95%CI 0.65 – 5.14). The excess incidence of lung cancer diagnosis in patients randomised to EBRT was 5.38% (95%CI 0.30% – 10.46%).

Discussion

In the 714 UK patients from the TARGIT-A randomised trial, there was a substantial increase in lung cancer diagnosis in the EBRT arm, over three times higher compared with TARGIT-IORT, HR 3.3 (95%CI 1.1-10.2), p=0.0266, 16-year incidence EBRT 7.2% vs. TARGIT 1.8%).

Details of lung cancer histology or side is not available but as this is a RCT and the events are small – it is only the total number that is valuable here, and these data should be shared with patients, along with the caveats.

Patients in the TARGIT-IORT arm received a highly focussed dose of radiotherapy during surgery, sparing the lungs, whereas lungs of patients in the EBRT arm were exposed to scattered irradiation. Novel approaches of reducing damage to nearby vital organs at risk such as deep inspirational breath holding (DIBH) [36] during EBRT has been shown to reduce the radiation dose to the anterior descending coronary artery, but it can increase the volume of lung irradiated, and its benefit from potentially reducing lung mass dose or lung cancer risk remains to be proven [37-39]

Most (85%) lung cancers in the UK are caused by smoking[40 41]. From population incidence data, we can expect that only about 20% of patients in the TARGIT-A trial were smokers[42] and also, that smoking-induced lung cancers should be equally distributed in each of the randomised arms. Therefore, the observed difference – the excess (5.38%) in the EBRT arm – can reasonably be attributed to the difference between two treatments, and driven by EBRT-induced lung carcinogenesis.

The strength of this paper is the very long follow up duration in both arms of the trial and collection of data from NHS records as well as directly from patients. A weakness is that we could not assess the side (left or right) of lung cancer. However, as the comparison is between two randomised treatments, it is scientifically attributable to the difference in treatments, especially as it is biologically plausible and become apparent in the second decade (typical time taken for carcinogenesis), and consistent with previous data.

Our finding is plausible because it accords with a number of previous studies. In a meta-analysis of thirteen cohort studies comprising 762,468 breast cancer patients, EBRT given for breast cancer was found to be associated with the risk of new primary lung cancers. This risk was the highest 15 or more years after breast cancer diagnosis RR 1.66 (95% CI 1.36–2.01)[43]. In the meta-analysis of recent randomised trials that began by the year 2000[2], comparing radiotherapy vs no radiotherapy, lung cancer incidence rose mainly after 10 years following the treatment (RR, 2.10; 95% CI, 1.48 to 2.98; P < .001[2]). Their estimate is close to, (and falls within the 95%CI of) the hazard ratio that we found for the UK patients in the TARGIT-A trial, and so is the expected timeline as seen in figure 1, namely that the incidence starts rising about nine years after randomisation.

The EBCTCG meta-analysis[44] of randomised trials found a significant increase in lung cancer mortality among women treated with radiotherapy (rate ratio of 1.78 (95% CI: 1.22–2.59; P=0.0004)[44]. Previously published TARGIT-A trial results have also shown that TARGIT-IORT significantly reduces deaths from other causes including deaths from other cancers[8 9 14-16 45]. This results in an overall survival benefit in patients with the grade 1 or 2 cancers which together comprise 78% of all cases (12-year mortality reduction from 15% to 10.5%, HR 0.72 (95%CI 0.53-0.98), p=0.0361)[9].

Modern radiotherapy to the left breast now involves deep inspiratory breath hold techniques to reduce greatly the radiation dose to the heart. Theoretically this could reduce the chance of death from ischaemic heart disease, 10 - 30 years after radiotherapy. However, there is also a significantly raised risk of death from lung cancer (even higher than deaths from ischaemic heart disease), especially in smokers who have had EBRT [2]. Deep inspiratory breath hold during radiotherapy reduces the dose to the heart, but there is debate whether it also reduces the degree of lung toxicity. Therefore, our report is now even more relevant for long-term breast cancer survivors, who now represent the large majority. As opposed to omitting radiotherapy altogether, TARGIT-IORT reduces the risk of radiation-induced lung cancer without detriment to long-term local control of the breast cancer.

Of the 2.3 million new cases of breast cancer diagnosed worldwide[46], an estimated 920,000 patients worldwide may be suitable for TARGIT-IORT annually [7]. Using the 5.38% reduction in lung cancer risk that we have observed, if TARGIT-IORT were to be made accessible to these patients, the number of patients who would be spared the diagnosis of a lung cancer during their follow up could be very substantial (the calculated estimate is 49,496 (95%CI 5500-134,320)).

Lung cancer is likely to have a substantially higher mortality than breast cancer, and it is a tragedy when women who outlive breast cancer then succumb to this frequently lethal radiation-induced second cancer.

These new data further strengthen our initial conclusions, first published in 2010[13] that for suitable patients with breast cancer, targeted intraoperative radiotherapy (TARGIT-IORT) should be offered as an alternative to external beam whole breast radiotherapy. Given both the UK General Medical Council's guidance[47] and the UK law[48], it follows that good clinical practice should mandate full discussion about TARGIT-IORT with patients before their surgery, including reduction in lung cancer risk, and enabling them to take it during their lumpectomy.

Acknowledgements
We thank the Independent Steering Committee for providing trial oversight. The members were appointed by the Health Technology Assessment programme of the National Institute of Health Research, Department of Health and Social Care, UK. Independent members were: Freddie Hamdy (Nuffield Department of Surgical Sciences, University of Oxford), Ian Fentiman (Guy's and St Thomas' Hospital, London), Mangesh Thorat (Centre for Cancer Prevention, Wolfson Institute of Preventive Medicine, Queen Mary University of London), Carolyn Murphy (King's Clinical Trials Unit, Kings College London), Ann Millman (Oxford), Martin Bland (Department of Health Sciences, University of York), David Dommett (Southend University Hospital NHS Foundation Trust), David Morgan (Nottingham), Rishikesh Parmeshwar (University Hospitals of Morecambe Bay, Lancaster), Sankaran Narayanan (University Hospitals of North Midlands NHS Trust and at Keele University). We thank all the patients and their families who kindly participated in the trial and continued to provide follow up information. Manuscript preparation was helped by the trial operations staff and their respective families

Patient and Public Involvement
A patient was involved as a member of the Trial Steering Committee and another patient is an author on the paper. They contributed by giving a patient's perspective throughout the study and in writing the manuscript.

Competing interests: For the TARGIT-A trial in the UK: support from University College London Hospitals (UCLH)/UCL Comprehensive Biomedical Research Centre, UCLH Charities, National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme, Ninewells Cancer Campaign; JSV, JST, NRW, MBu, IP, CBG, and NR receive funding from HTA, NIHR, Department of Health and Social Care for some activities related to the TARGIT trials. JSV has received a research grant from Photoelectron Corp (1996-99) and from Carl Zeiss for supporting data management at the University of Dundee (Dundee, UK, 2004-2008), and has received honorariums. MBa was briefly on the scientific advisory board of Carl Zeiss and was paid consultancy fees before 2010. Carl Zeiss sponsors some of the travel and accommodation for meetings, when necessary, where targeted intraoperative radiotherapy is being discussed for all authors apart from JL, SL, SR, MD, MF, GP, AM, SN and DM. JSV and MD are Vice-President and President of British Association of Surgical Oncology-Association of Cancer Surgeons.

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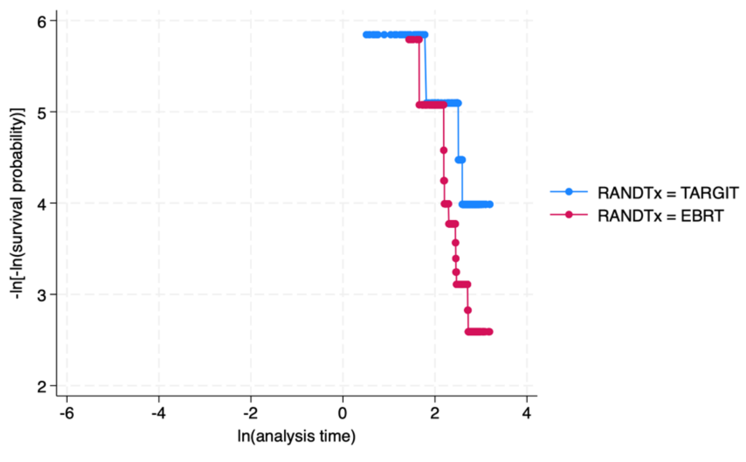
Supplementary Figures

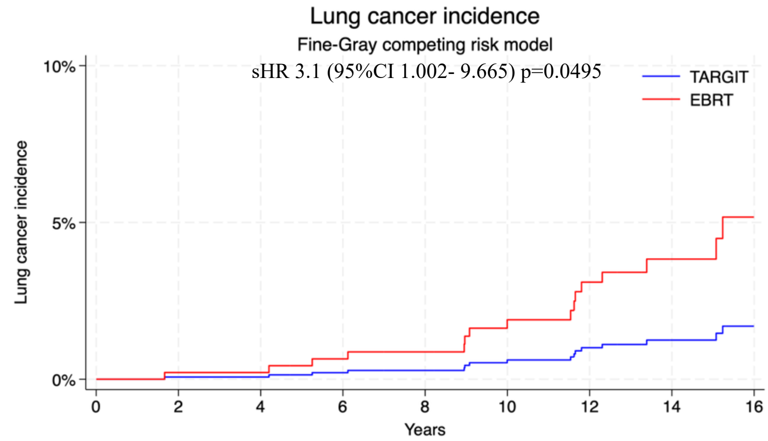
Supplementary figure 1

Test of proportional hazards assumption: The proportional hazards assumption assessed using Schoenfeld residuals (stphtest) and graphical (stphplot) methods. The proportional hazards assumption did not fail (rho = 0.25036 chi2= 1.01 p=0.3160), and visually, the lines did not cross as below



Supplementary figure 2

Competing risk model: The cumulative incidence functions (CIFs) for lung cancer with death as a competing event, using the Fine–Gray sub distribution hazards model to estimate hazard ratios (sHRs). The sHR is similar to HR we originally found 3.11 (95%CI 1.002 – 9.665), p=0.0495.



Supplementary figure 3:

Follow up duration of UK patients in the two arms of the TARGIT-A trial: The patients in the EBRT arm had slightly shorter follow up than the EBRT arm. Therefore, any bias from shorter follow-up in the EBRT arm, would tend to reduce the observed risk of lung cancer in EBRT rather than inflate it, so the real difference between the treatment arms might have been even greater.