# Intraoperative radiotherapy for breast cancer: powerful evidence to change practice

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**The published article is available at https://rdcu.be/cep3x.**
**Supplementary detailed tables are at Supplementary information**

We believe that the recent News and Views article[1] (Sasieni, P. D. & Sawyer, E. J. Intraoperative radiotherapy for early breast cancer — insufficient evidence to change practice. Nature Reviews Clinical Oncology, https://doi.org/10.1038/s41571-020-00444-2 (2020)) about the TARGIT-A trial contains several factual and logical errors. It overlooks both the long-term positive findings[2] and the all-important patient perspective.

Risk-adapted single-dose targeted intraoperative radiotherapy during lumpectomy (TARGIT-IORT) is a method of partial breast irradiation (PBI) for early breast cancer. Most patients (80%) receiving TARGIT-IORT[2] during their lumpectomy complete their local treatment entirely during this single session, under the same anaesthetic. Supplemental whole breast external beam radiotherapy (WBRT) is only recommended for a minority of patients (20%) if unexpected prespecified tumour-related factors such as invasive lobular cancer and positive margins are found postoperatively. However, most patients with conventional 'high risk' features were treated without supplemental WBRT, including four-fifths of grade 3 or ER negative cases, and two-thirds of node positive cases. By contrast, traditional WBRT or other PBI approaches require up to 30 additional hospital visits - TARGIT-IORT involves far fewer clinic appointments[3]. Other benefits include fewer toxicities, less pain, better cosmetic results and better quality of life[2].

The TARGIT-A randomized trial compared risk-adapted TARGIT-IORT with WBRT. The long-term results[2] revealed no significant differences in local and distant control, breast preservation or breast cancer mortality. Local control was also comparable with that achieved with TARGIT-IORT alone[2]. A significant reduction in non-breast cancer mortality (from cardiovascular causes and other cancers) was also observed with TARGIT-IORT, from 9.85% to 4.41% at 12 years[2]. For patients, who sit on the more uncomfortable side of the consultation desk, these are most welcome results, particularly in the COVID-19 era.

The authors complain[1] that TARGIT-IORT was not compared with 'no radiotherapy'; however, we emphasize that the TARGIT-A cohort had a much higher proportion of high-risk patients than trials investigating this approach (Supplementary information). In fact, over three-quarters (1737/2298) of TARGIT-A trial patients would not have fulfilled the low-risk criteria for inclusion in a trial of 'no-radiotherapy' such as PRIME-II (inclusion criteria: age >65, size <=3cm, grade 1 or 2, node negative, ER positive). Despite this higher-risk cohort, local recurrence with TARGIT-IORT was 2–3 times lower than with 'no-radiotherapy' in those trials (Supplementary information). Crucially, for a more inclusive population such as this, which is more representative of clinical practice, a 'no-radiotherapy' arm would be unethical. We agree that "discriminating… those who can safely avoid radiotherapy altogether remains a fundamental challenge[1]", therefore, patients should not be recommended 'no radiotherapy necessary' without first discussing options such as TARGIT-IORT. We emphasize that with TARGIT-IORT completed during lumpectomy, 80% of patients do not need postoperative radiotherapy[2].

The proportion of high-risk patients in the TARGIT-A cohort (PBI versus WBRT) is remarkably similar to that of the Fast-Forward cohort (shorter-course WBRT versus 3-week daily WBRT) (Supplementary information), which the authors recommend[1]. The 5-year local recurrence with 3-week WBRT in Fast-Forward and TARGIT-IORT was virtually identical at 2.1%. If the authors[1] seriously question whether TARGIT-IORT is better than 'no radiotherapy'[1], should the same question not also apply to the Fast-Forward WBRT regimen? In any event, 'no radiotherapy' is not considered the standard of care for such patients, and therefore is not the correct comparator.

The effectiveness of PBI approaches such as TARGIT-IORT has been repeatedly demonstrated (Supplementary information), yet the authors do not mention this important concept. Instead, they promote[1] the intensive 'Fast-Forward' whole-breast-radiotherapy approach, which we argue is an overtreatment for the majority of patients and comes with well-known hazards: The most important side effect of an increased irradiated volume and the associated scattered irradiation is the substantially increased cardiovascular[4,5] and cancer mortality[4,6], which is avoided by PBI techniques[7] such as TARGIT-IORT[2,8]. On the other hand, as expected with WBRT techniques, there is no mortality benefit with Fast-Forward. Fast-Forward also entails inevitable post-operative delay plus 7–15 hospital visits (for consultation and planning followed by daily WBRT with or without boost).

The authors criticize the TARGIT-A non-inferiority margin of 2.5%[2], and surprisingly claim[1] that no-radiotherapy (as used in PRIME-II, Supplemental information) is non-inferior to WBRT. We argue that the data disprove this claim — the actual difference in 5-year local recurrence in PRIME-II was 2.9%, with an upper confidence interval of 4.8% — both well above the 2.5% margin[2]. The 2.5% non-inferiority margin used in TARGIT-A[2] is one of the most stringent (in both absolute and relative terms) among trials involving PBI (Supplementary information). Nonetheless, the actual difference in 5-year local recurrence between the two treatment arms of TARGIT-A was just 1.16%.

The Kaplan-Meier model, which we used[2] to analyze local control, includes all relevant events[9,10] in addition to time of occurrence and length of follow-up monitoring, for every patient. This is not the case for a chi-square test, which was employed by the authors[1] to test for superiority, even though TARGIT-A was a noninferiority trial — a very

different concept: "Non-inferiority trials … test new treatments that have obvious non-oncological advantages… The non-inferiority statistical test … is not meant to check for superiority, but to assess if the difference is within an acceptable margin and the experimental treatment is not meaningfully worse than the control."[2]. The protocol-specified noninferior 5-year local recurrence associated with TARGIT-IORT was clearly confirmed in TARGIT-A.

Many countries across the world have enthusiastically embraced TARGIT-IORT, with >45,000 patients treated so far. TARGIT-IORT is now recommended in many international guidelines. Patient choice, informed by clearly presented evidence, is now recognised as being much more important than clinician preferences, a point powerfully underscored by the UK Supreme Court (Montgomery v Lanarkshire Health Board, 2015), the Royal College of Surgeons of England, and the UK General Medical Council.

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**Further information**

National and International Guidelines include TARGIT-IORT for breast cancer. https://www.targit.org.uk/targit-iort-in-guidelines
Consent: Supported Decision-Making https://www.rcseng.ac.uk/standards-and-research/standards-and-guidance/good-practice-guides/consent/
Decision making and consent https://www.gmc-uk.org/ethical-guidance/ethical-guidance-for-doctors/decision-making-and-consent

**References**

1 Sasieni, P. D. & Sawyer, E. J. Intraoperative radiotherapy for early breast cancer — insufficient evidence to change practice. *Nature Reviews Clinical Oncology*, doi:10.1038/s41571-020-00444-2 (2020).
2 Vaidya, J. S. *et al.* 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. *BMJ* **370**, m2836, doi:10.1001/jamaoncol.2020.0249 (2020).
3 Coombs, N. J. *et al.* Environmental and social benefits of the targeted intraoperative radiotherapy for breast cancer: data from UK TARGIT-A trial centres and two UK NHS hospitals offering TARGIT IORT. *BMJ open* **6**, e010703, doi:10.1136/bmjopen-2015-010703 (2016).

4 Taylor, C. *et al.* Estimating the Risks of Breast Cancer Radiotherapy: Evidence From Modern Radiation Doses to the Lungs and Heart and From Previous Randomized Trials. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* **35**, 1641-1649, doi:10.1200/JCO.2016.72.0722 (2017).

5 Darby, S. C. *et al.* Risk of Ischemic Heart Disease in Women after Radiotherapy for Breast Cancer. *New England Journal of Medicine* **368**, 987-998, doi:10.1056/NEJMoa1209825 (2013).

6 Grantzau, T. & Overgaard, J. Risk of second non-breast cancer after radiotherapy for breast cancer: a systematic review and meta-analysis of 762,468 patients. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology* **114**, 56-65, doi:10.1016/j.radonc.2014.10.004 (2015).

7 Vaidya, J. S. *et al.* Reduced Mortality With Partial-Breast Irradiation for Early Breast Cancer: A Meta-Analysis of Randomized Trials. *International journal of radiation oncology, biology, physics* **96**, 259-265, doi:10.1016/j.ijrobp.2016.05.008 (2016).

8 Aziz, M. H. *et al.* Can the risk of secondary cancer induction after breast conserving therapy be reduced using intraoperative radiotherapy (IORT) with low-energy x-rays? *Radiat Oncol* **6**, 174, doi:10.1186/1748-717X-6-174 (2011).

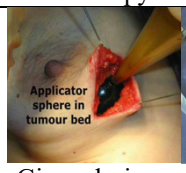
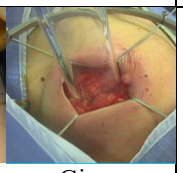
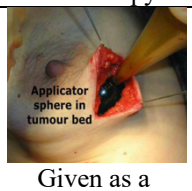
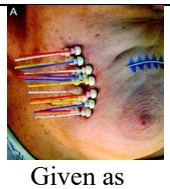
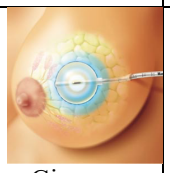
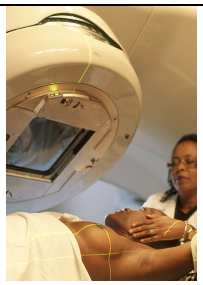
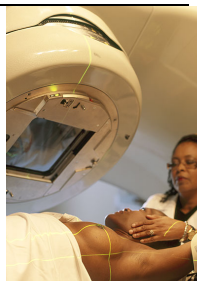
9 Gourgou-Bourgade, S. *et al.* Guidelines for time-to-event end point definitions in breast cancer trials: results of the DATECAN initiative (Definition for the Assessment of Time-to-event Endpoints in CANcer trials)dagger. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO* **26**, 873-879, doi:10.1093/annonc/mdv106 (2015).

10 Hudis, C. A. *et al.* Proposal for standardized definitions for efficacy end points in adjuvant breast cancer trials: the STEEP system. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* **25**, 2127-2132, doi:10.1200/JCO.2006.10.3523 (2007).

**Table 1a:** Modern trials of no-radiotherapy, short course whole breast radiotherapy and the TARGIT-A trial

| | **CALGB No RT vs WBRT**[1,2] | **BASO 2 No RT vs WBRT** [3] | **PRIME 2 No RT vs WBRT**[4] | **FAST-FORWARD WBRT vs Shorter WBRT** [5] | **TARGIT-A trial Risk-adapted single-dose TARGIT-IORT vs WBRT**[6] |
|---|---|---|---|---|---|
| **Number for comparison** | 636 | 1135 | 1326 | 2562 | 2298 |
| **Number at 6 yrs follow up** | <500 | N/A | <600 | 1025 | 1967 |
| **Age limits** | >=70<br>0%<70 | >=65<br>0% < 65 | >=65<br>0% < 65 | >18<br>84% < 70 | >=45<br>60% < 65<br>85% < 70 |
| **T Size limits** | <=2cm | <=2cm | <=3cm | T1-T3 | <=3.5cm |
| **Grade limits** | No info. | Grade 1 | Grade 1 or 2, only 2% grade 3 | No restriction<br>28% grade 3 | No restriction<br>20% grade 3 |
| **Nodes limits** | Negative | Negative | Negative | N0-N1<br>19% node positive | No restriction<br>22% node positive |
| **LV invasion** | No info. | Negative | Neg if Gr 3 | No restriction | No restriction |
| **ER status** | Positive | Positive | Positive | No restriction | No restriction |
| **Additional hospital visits** | 1 | 1 | 1 | 7 to 15 | None in 80% of cases; WBRT recommended in 20% |
| **5-year local recurrence rates** | 4% vs 1% | 6% vs 2% | 4.1% vs 1.3%<br>Difference 2.9% (upper 95%CI 4.8%) | 2.1% vs 1.4% (including 7% post-mastectomy radiotherapy)<br>No difference | 2.11% vs. 0.95%<br>Non-inferiority confirmed with complete 5-year follow up<br>Difference 1.16% Upper 90%CI 1.99% |
| **Long term outcomes, more than 5years** | 10-yr OS 67% vs 66%;<br>LR 8% vs 2%;<br>10-yr LRFS ~53% vs ~61% | 10-yr LRFS ~89% vs ~97% | Not available | Not available | At median follow up of 9 years (max 19 years):<br>No difference in local/distant control/breast preservation/breast cancer mortality<br>Significantly fewer deaths from other causes<br>(5.41% vs 9.85% at 12 years) |
| **Significant scatter radiation to vital organs?** | No | No | No | Yes | No |
| **Mortality** | No difference | No difference | No difference | No difference | Significantly reduced non-BC mortality with TARGIT-IORT<br>No difference in BC mortality |
| **Toxicity in experimental arm** | Not reported | Not reported | Not reported | Higher (e.g. breast induration/hardness) | Reduced |
| **Quality of life with experimental treatment** | Not reported | Not reported | Higher insomnia<br>No improvement in QOL | Not reported | Improved breast related QOL<br>Improved cosmetic outcome<br>Reduced pain |

**Table 1b:** Modern trials of partial breast irradiation compared with whole breast radiotherapy

| | **Intraoperative** | | **Post-operative 2nd procedure interstitial** | | | **Post-operative external beam** | |
|---|---|---|---|---|---|---|---|
| | **TARGIT-A Risk-adapted TARGIT-IORT during lumpectomy[6]** | **Electron IORT during lumpectomy ELIOT[7]** | **TARGIT-A Delayed second-procedure TARGIT-IORT[8,9]** | **Interstitial wires x 5 days GEC-ESTRO[10]** | **NSAPB-B039 Balloon[11] (6% of exp. arm)** | **NSAPB-B39[11]/ RAPID[12] /Florence[13] 3DCRT /IMRT** | **IMRT IMPORT-Low[14]** |
| **Patients** | | | | | | | |
| Total | 2298 | 1305 | 1153 | 1184 | 811 | 2193/ 1754/ 520 | 1343 |
| At 6-yr FU | **1967** | **676** | **1068** | **784** | **708** | **1915/ 1548/ 503** | **661** |
| **KM curves to** | 12 years | 9 years | 12 years | 6.5 years | 10 years | 10/9/10.5 yrs | 7 years |
| **Tumours** | Medium risk | Medium risk | Low risk | Low risk | Low risk | Low risk | Low risk |
| **Grade 3 (%)** | 20% | 20% | 6% | 9% | 1% | 1%/15%/11% | 9% |
| **Pos. nodes (%)** | 22% | 26% | 6.5% | 0% | 10% | 10%/1%/ 10% | 3% |
| **5-year Local recurrence** | 2.11% vs. 0.95% | 4.4% vs. 0.4% | 3.96% vs. 1.05% | 1.44% vs.0.92% | 2.8% vs. 2.1% | 2.8/2.3/2.5% vs 2.1/1.7/1.3% | 0.5% vs. 1.1% |
| **Non-inferiority Margin and whether achieved?** | 2.5% (bkgr 6%) Non-inferior | Equivalence margin 4.5% (bkgr 3%) (4.4% v 0.4%) | 2.5% (bkgr 6%) No. Non-inferior in HR+HER-, ET | 3% (bkgr 4%) Non-inferior | NA Not equivalent | NA/ 2.75% (bkgr 4%)/ 2% (bkgr 3%) Not equivalent/Non-inferior/Non-inferior | 2.5% (bkgr 2.5%) Non-inferior |
| **Breast cancer control similar to WBRT?** | Yes | No | Yes | Yes | No | No/Yes/Yes | Yes |
| **Toxicity/ QOL less or more than WBRT?** | Less toxicity, better QOL | Not reported | Less toxicity, better QOL | Less toxicity, but wire-entry scarring not reported | More toxicity, QOL not reported | Generally more toxicity, QOL not reported | No major difference |
| **Deaths from other causes different?** | Sig. reduced (HR0.59); by 4.4% at 12y | No significant difference | No significant difference | No significant difference | No significant difference | No significant difference | No significant difference |
| **Significant scatter radiation to vital organs?** | No | Possibly, if lead shield is not properly used | No | Yes | Yes | Yes | Yes |
| **Additional hospital visits and time?** | **No additional visits for 80%**; 20% had supplemental WBRT (~16 half days) | **No additional visits** | Additional surgical procedure for 1 dose single dose **1 full day** | Additional procedure 10# over 5 days, 2# /day as inpatient **5 full days** | Additional procedure 10 # over 8 days 2#/ day **5 full days** | 10# twice per day over 5-8 days or 5# over 2 weeks **5.5 full days or 6 half days over 2wks** | 16 hospital visits **16 half-days** |
| **Where is it done?** | Standard OR like c-arm fluoroscopy | Lead-lined walls | Standard OR like c-arm fluoroscopy | Lead-lined walls | Lead-lined walls | Lead lined bunker | Lead lined bunker |
| **How it is done?** |   Given during lumpectomy surgery |  Given during lumpectomy surgery. Needs extensive dissection + deep lead shield |   Given as a second-procedure by re-opening the lumpectomy wound |  Given as second-procedure and radioactive wires remain in place for 4 days (in-patient) |  Given as second procedure and the baloon remains in place for 8 days (in-patient) |  Given as twice daily treatments over 8 days or 5 non-consecutive days over 2 weeks |  Given as daily doses for 15 days over 3 weeks |

*bkgr = expected background risk in the control arm. ET = Endocrine therapy. For NSABP-39 overall LR used for balloon. External beam days includes half a day for planning. QOL= quality of life. The very old or small trials with less than 500 patients or those with less than 5-year follow up - from Leeds (EBRT over 28 days, n=174, published 2005)[15] and Christie (EBRT 10 days, n=708, published 1995)[16] both with worse outcome for PBI, Budapest

(interstitial wires twice a day over 7 days, n=258, published 2013) with similar outcome for PBI[17] and trials with no published cancer outcome data[18] are not included in this table. Numbers are for patients with invasive breast cancer. References are listed in the supplement.

**References cited in the Supplemental information**


1 Hughes, K. S. *et al.* Lumpectomy plus tamoxifen with or without irradiation in women 70 years of age or older with early breast cancer. *The New England journal of medicine* **351**, 971-977, doi:10.1056/NEJMoa040587 (2004).

2 Hughes, K. S. *et al.* Lumpectomy Plus Tamoxifen With or Without Irradiation in Women Age 70 Years or Older With Early Breast Cancer: Long-Term Follow-Up of CALGB 9343. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology* **31**, 2382-2387, doi:10.1200/JCO.2012.45.2615 (2013).

3 Blamey, R. W. *et al.* Radiotherapy or tamoxifen after conserving surgery for breast cancers of excellent prognosis: British Association of Surgical Oncology (BASO) II trial. *Eur J Cancer* **49**, 2294-2302, doi:10.1016/j.ejca.2013.02.031 (2013).

4 Kunkler, I. H. *et al.* Breast-conserving surgery with or without irradiation in women aged 65 years or older with early breast cancer (PRIME II): a randomised controlled trial. *The lancet oncology* **16**, 266-273, doi:10.1016/S1470-2045(14)71221-5 (2015).

5 Murray Brunt, A. *et al.* Hypofractionated breast radiotherapy for 1 week versus 3 weeks (FAST-Forward): 5-year efficacy and late normal tissue effects results from a multicentre, non-inferiority, randomised, phase 3 trial. *Lancet* **395**, 1613-1626, doi:10.1016/S0140-6736(20)30932-6 (2020).

6 Vaidya, J. S. *et al.* 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. *BMJ* **370**, m2836, doi:10.1136/bmj.m2836 (2020).

7 Veronesi, U. *et al.* Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomised controlled equivalence trial. *The lancet oncology* **14**, 1269-1277, doi:10.1016/s1470-2045(13)70497-2 (2013).

8 Vaidya, J. S. *et al.* Effect of Delayed Targeted Intraoperative Radiotherapy vs Whole-Breast Radiotherapy on Local Recurrence and Survival: Long-term Results From the TARGIT-A Randomized Clinical Trial in Early Breast Cancer. *JAMA Oncol* **6**, e200249, doi:10.1001/jamaoncol.2020.0249 (2020).

9 Vaidya, J. S., Bulsara, M. & Baum, M. Targeted Intraoperative Radiotherapy for Early Breast Cancer-Reply. *JAMA Oncol*, doi:10.1001/jamaoncol.2020.2730 (2020).

10 Strnad, V. *et al.* 5-year results of accelerated partial breast irradiation using sole interstitial multicatheter brachytherapy versus whole-breast irradiation with boost after breast-conserving surgery for low-risk invasive and in-situ carcinoma of the female breast: a randomised, phase 3, non-inferiority trial. *Lancet* **387**, 229-238, doi:10.1016/S0140-6736(15)00471-7 (2016).

11 Vicini, F. A. *et al.* Long-term primary results of accelerated partial breast irradiation after breast-conserving surgery for early-stage breast cancer: a randomised, phase 3, equivalence trial. *The Lancet* **394**, 2155-2164, doi:10.1016/s0140-6736(19)32514-0 (2019).

12 Whelan, T. J. *et al.* External beam accelerated partial breast irradiation versus whole breast irradiation after breast conserving surgery in women with ductal carcinoma in situ and node-negative breast cancer (RAPID): a randomised controlled trial. *The Lancet* **394**, 2165-2172, doi:10.1016/s0140-6736(19)32515-2 (2019).

13 Meattini, I. *et al.* Accelerated Partial-Breast Irradiation Compared With Whole-Breast Irradiation for Early Breast Cancer: Long-Term Results of the Randomized Phase III APBI-IMRT-Florence Trial. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*, JCO2000650, doi:10.1200/JCO.20.00650 (2020).

14 Coles, C. E. *et al.* Partial-breast radiotherapy after breast conservation surgery for patients with early breast cancer (UK IMPORT LOW trial): 5-year results from a multicentre, randomised, controlled, phase 3, non-inferiority trial. *Lancet* **390**, 1048-1060, doi:10.1016/S0140-6736(17)31145-5 (2017).

15 Dodwell, D. J. *et al.* A Randomised Study of Whole-breast vs Tumour-bed Irradiation After Local Excision and Axillary Dissection for Early Breast Cancer. *Clinical oncology* **17**, 618-622, doi:10.1016/j.clon.2005.07.018 (2005).

16 Ribeiro, G. G., Magee, B., Swindell, R., Harris, M. & Banerjee, S. S. The Christie Hospital breast conservation trial: an update at 8 years from inception. *Clin.Oncol.(R.Coll.Radiol).* **5**, 278-283 (1993).

17 Polgar, C., Fodor, J., Major, T., Sulyok, Z. & Kasler, M. Breast-conserving therapy with partial or whole breast irradiation: ten-year results of the Budapest randomized trial. *Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology* **108**, 197-202, doi:10.1016/j.radonc.2013.05.008 (2013).

18 Yadav, B. S., Loganathan, S., Sharma, S. C., Singh, R. & Dahiya, D. Comparison of Toxicity and Cosmetic Outcomes After Accelerated Partial Breast Irradiation or Whole Breast Irradiation Using 3-Dimensional Conformal External Beam Radiation Therapy. *Adv Radiat Oncol* **5**, 171-179, doi:10.1016/j.adro.2019.09.005 (2020).