
Supplementary information

Intraoperative radiotherapy for breast cancer: powerful evidence to change practice

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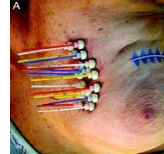



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Table 1a: Modern trials of no-radiotherapy, short course whole breast radiotherapy and the TARGIT-A trial

	CALGB No RT vs WBRT^{1,2}	BASO 2 No RT vs WBRT³	PRIME 2 No RT vs WBRT⁴	FAST-FORWARD WBRT vs Shorter WBRT⁵	TARGIT-A trial Risk-adapted single-dose TARGIT-IORT vs WBRT⁶
Number for comparison	636	1135	1326	2562	2298
Number at 6 yrs follow up	<500	N/A	<600	1025	1967
Age limits	>=70 0% <70	>=65 0% < 65	>=65 0% < 65	>18 84% < 70	>=45 60% < 65 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 28% grade 3	No restriction 20% grade 3
Nodes limits	Negative	Negative	Negative	N0-N1 19% node positive	No restriction 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% Difference 2.9% (upper 95%CI 4.8%)	2.1% vs 1.4% (including 7% post-mastectomy radiotherapy) No difference	2.11% vs. 0.95% Non-inferiority confirmed with complete 5-year follow up Difference 1.16% Upper 90%CI 1.99%
Long term outcomes, more than 5years	10-yr OS 67% vs 66%; LR 8% vs 2%; 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): No difference in local/distant control/breast preservation/breast cancer mortality Significantly fewer deaths from other causes (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 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 No improvement in QOL	Not reported	Improved breast related QOL Improved cosmetic outcome 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 lumpectomy⁶	Electron IORT during lumpectomy ELIOT⁷	TARGIT-A Delayed second-procedure TARGIT-IORT^{8,9}	Interstitial wires x 5 days GEC-ESTRO¹⁰	NSABP-B039 Balloon¹¹ (6% of exp. arm)	NSABP-B39¹¹/RAPID¹²/Florence¹³ 3DCRT /IMRT	IMRT IMPORT-Low¹⁴
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 balloon 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 PBI¹⁷ and trials with no published cancer outcome data¹⁸ 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).