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Editorial

The IMPORT LOW Trial: Collaborative Research Accelerates Practice Change in Breast Radiotherapy

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Developments in breast cancer detection, surgery, radiotherapy and systemic therapy have led to plummeting local relapse [1] and mortality rates [2], such that investigators, multidisciplinary teams and patients have been able to switch their focus for most patients to survivorship issues, including reducing long-term side-effects of treatments, optimising cosmetic outcomes and improving quality of life. In the field of radiotherapy for breast cancer, collaborations between investigators of multiple disciplines working across most of the UK's radiotherapy departments have led the way internationally in reducing long-term side-effects in breast tissue through hypofractionation studies (START A and B) [3,4] and through homogenisation of radiation dose across the breast (Breast Dosimetry Trial and Cambridge IMRT study) [5,6].

In the meantime, the pathological distribution of disease in mastectomy specimens and the clinical patterns of local tumour relapse after breast conservation surgery led to the hypothesis that the risk of local recurrence would be unaffected if radiation fields were to be reduced to cover only the tumour bed and surrounding breast tissue. IMPORT LOW [7] tested this hypothesis in women at low risk of breast cancer relapse (age $\geq$50 years, treated with breast conservation surgery to clear radial surgical excision margins of at least 2 mm, tumour size $\leq$30 mm, pN0-1), randomising them to standard whole-breast radiotherapy (40 Gy in 15 fractions) versus reduced-dose radiotherapy (40 Gy in 15 fractions to partial breast with 36 Gy in 15 fractions to the peripheries of breast tissue) versus radiotherapy only to the part of breast tissue at highest risk of relapse (again to a dose of 40 Gy in 15 fractions). The study used standard tangential external beam radiotherapy such that the partial breast radiotherapy was effectively standard tangents reduced in a superior to inferior direction.

The results of the IMPORT LOW trial showed that partial breast and reduced dose radiotherapy were non-inferior to whole-breast radiotherapy in terms of local control. At a median follow-up of 72 months, 5 year local relapse rates were 1.1% (95% confidence interval 0.5–2.3), 0.2% (0.02–1.2) and 0.5% (0.2–1.4) in the whole breast, reduced dose and partial breast groups, respectively. Extensive assessments of late normal tissue side-effects showed that the partial breast radiotherapy technique was associated with significantly lower rates of patient-reported change in breast appearance (15% at 5 years compared with 27% in the whole-breast radiotherapy group) and both the partial breast and reduced dose techniques were associated with significantly lower rates of patient-reported breast firmness and hardness than for whole-breast radiotherapy. Anticipated longer-term benefits of partial breast irradiation (PBI) include lower rates of late radiation-induced cardiac events, which could be assessed in a future meta-analysis of all PBI trials.

The IMPORT LOW results add to a growing body of literature on outcomes of PBI. Table 1 summarises the existing literature, highlighting the wide range of radiotherapy techniques and dose-fractionation schedules used. It is important to note that the trials showing non-inferiority of PBI are limited to those in which the irradiated margin of tissue around the tumour bed extends to centimetres rather than millimetres. In 2016, following publication of the GEC-ESTRO data [8] together with presentation of the IMPORT LOW data at the European Breast Cancer Conference, the UK RCR Breast Radiotherapy Consensus Meeting [11] concluded that PBI using either an external beam technique (as per IMPORT LOW) or an interstitial brachytherapy technique (as per GEC-ESTRO) to a dose of 40 Gy in 15 fractions can be considered in patients

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Table 1
Outcomes of phase III studies in partial breast irradiation

Trial	Partial breast irradiation technique	Volume irradiated	Dose-fractionation schedule	Target accrual	Median follow-up at time of reporting (years)	Cumulative IBTR rate at 5 years	
						Whole-breast irradiation	Partial breast irradiation
TARGIT-A [9]	Intraoperative 50 kV photon technique	Tumour bed plus 2 mm: 20 Gy/1 fractions at 2 mm from applicator surface. Attenuates to 5–7 Gy at 10 mm from applicator surface	WB 'as per standard schedules over several weeks' PB 20 Gy/1 fraction	3451	2.5	1.3%	3.3%
ELIOT [10]	Intraoperative 3–9 MeV electron technique	80% isodose at 24 mm depth (9 MeV)	WB 50 Gy/25 fractions PB 21 Gy/1 fraction	1305	5.8	0.4%	4.4%
GEC-ESTRO [8]	Interstitial brachytherapy	CTV = lumpectomy cavity plus 20 mm. 95% isodose covers CTV	WB 50 Gy/25 fractions PB 32 Gy/8 fractions/twice daily	1170	5.0	0.9%	1.4%
IMPORT Low [7]	External beam radiotherapy	Clip-defined tumour bed plus 15 mm to CTV plus 10 mm to PTV. 95% isodose covers PTV	WB 40 Gy/15 fractions Reduced dose 36 Gy/15 fractions and 40 Gy/15 fractions to PB PB 40 Gy/15 fractions	2015	6.0	1.1%	0.5%

WB, whole breast; PB, partial breast; CTV, clinical target volume; PTV, planning target volume; IBTR, ipsilateral breast tumour recurrence.

of 50 years or older, with grade 1–2 disease, tumour size ≤30 mm, oestrogen receptor positive and human epidermal growth factor receptor negative. These inclusion criteria reflect the clinicopathological characteristics of most women entered into the GEC-ESTRO and IMPORT LOW trials. Implementation of PBI in the UK has yet to be assessed but, although changes to the radiotherapy workflow are likely to be a slowing factor in many centres, no capital investment is required to be able to deliver PBI according to the IMPORT LOW protocol, such that it is anticipated that a change in practice will be relatively swiftly implemented across the UK.

The impact of the IMPORT trials has, however, been much broader than the de-escalation of irradiated breast volume precipitated by the results of IMPORT LOW. First, the radiotherapy quality assurance aspects of IMPORT LOW and its partner trial for high-risk patients, IMPORT HIGH, meant that centres needed to implement three-dimensional field-in-field intensity-modulated radiotherapy in order to participate. This had a beneficial impact outside of the trials, accelerating the implementation of three-dimensional field-in-field intensity-modulated radiotherapy [12,13] and thus reducing the incidence of early moist desquamation and late firmness and shrinkage across the population of patients undergoing breast radiotherapy. A second legacy of the trial is the practice of marking the margins of the resection cavity with titanium clips. Under the leadership of the surgeons on the Trial Management Group (TMG) and with the support of the Association of Breast Surgery, participation in the IMPORT trials led to widespread adoption of this practice by the surgical community, thereby increasing the accuracy of PBI for women in the IMPORT LOW trial and the accuracy of boost dose delivery for women being treated outside the study [14]. Third, the IMPORT trials have extended the use of patient-reported outcome measures (PROMs) under the guidance of patient advocate members of the TMG (including MW, a co-author on the IMPORT LOW *Lancet* publication) who have worked across the series of UK breast radiotherapy trials to ensure PROMs capture side-effects of greatest relevance to patients.

Where next for UK breast radiotherapy research? The collaborations established over the years from the previous breast radiotherapy trials continue to expand and strengthen in ongoing trials of dose modulation for high-risk patients (IMPORT-High [15]), 5 day hypofractionation (FAST-Forward [16]) and omission of radiotherapy in patients at very low risk of recurrence (PRIMETIME [17]). For all of these trials, the aim is to reduce side-effects while maintaining local tumour control. The challenge for the future is how best to design such trials in the era of very low recurrence rates. Alternatives to the traditional large-scale phase III randomised controlled trial need to be considered, utilising novel methodologies and validating early

surrogate biomarkers. The PRIMETIME trial, for example, is a non-randomised study that selects patients for inclusion on the basis of biomarkers. A further challenge for breast radiotherapy trials is how best to collect data on late normal tissue effects long after patients would usually have been discharged from routine hospital follow-up. Increased emphasis on the collection of PROMs may be a solution; the START trials showed that the PROMs were sensitive to small differences in dose between the randomised schedules [18] and, in IMPORT LOW, PROMs identified differences in rates of side-effects between the groups [7].

Finally, in order for the culture of collaboration to continue to grow we must work hard to attract, build and retain a next generation of bright, innovative and collaborative researchers in radiotherapy. In the UK, the Cancer Research UK Clinical Trials Unit-based Fellowship Programme places trainees within active trials units where they learn first-hand about collaborative working within trial teams and gain the knowledge and skills (including learning the importance of good patient-public involvement) required for working in clinical trials. Within the UK breast radiotherapy research community a further initiative has been to include early career investigators on TMGs in active roles, such as that of Chief Clinical Co-ordinator, through which those investigators can act as 'apprentice' to the Chief Investigator and TMG, learning the ropes in order to be able to lead effectively on subsequent trials. Breast radiotherapy research has come a long way; we need to ensure that it continues to adapt and grow in line with new challenges, to ensure that patients reap the maximum benefits.

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References

[1] Mannino M, Yarnold JR. Local relapse rates are falling after breast conserving surgery and systemic therapy for early breast cancer: can radiotherapy ever be safely withheld? *Radiother Oncol* 2009;90(1):14–22.

[2] Maddams J, Moller H, Devane C. *Cancer prevalence in the UK*. Thames Cancer Registry and Macmillan Cancer Support; 2008.

[3] Bentzen SM, Agrawal RK, Aird EG, Barrett JM, Barrett-Lee PJ, Bliss JM, *et al*. 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(4):331–341.

[4] Bentzen SM, Agrawal RK, Aird EG, Barrett JM, Barrett-Lee PJ, Bliss JM, *et al*. The UK Standardisation of Breast Radiotherapy (START) Trial B of radiotherapy hypofractionation for treatment of early breast cancer: a randomised trial. *Lancet* 2008;371(9618):1098–1107.

[5] Donovan E, Bleakley N, Denholm E, Evans P, Gothard L, Hanson J, *et al*. Randomised trial of standard 2D radiotherapy (RT) versus intensity modulated radiotherapy (IMRT) in patients prescribed breast radiotherapy. *Radiother Oncol* 2007;82(3):254–264.

[6] Mukesh MB, Barnett GC, Wilkinson JS, Moody AM, Wilson C, Dorling L, *et al*. Randomized controlled trial of intensity-modulated radiotherapy for early breast cancer: 5-year results confirm superior overall cosmesis. *J Clin Oncol* 2013;31(36):4488–4495.

[7] Coles CE, Griffin CL, Kirby AM, Titley J, Agrawal RK, Alhasso A, *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* 2017;390(10099):1048–1060.

[8] Strnad V, Ott OJ, Hildebrandt G, Kauer-Dorner D, Knauerhase H, Major T, *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* 2016;387(10015):229–238.

[9] Vaidya JS, Wenz F, Bulsara M, Tobias JS, Joseph DJ, Keshtgar M, *et al*. Risk-adapted targeted intraoperative radiotherapy versus whole-breast radiotherapy for breast cancer: 5-year results for local control and overall survival from the TARGIT-A randomised trial. *Lancet* 2014;383(9917):603–613.

[10] Veronesi U, Orecchia R, Maisonneuve P, Viale G, Rotmensz N, Sangalli C, *et al*. Intraoperative radiotherapy versus external radiotherapy for early breast cancer (ELIOT): a randomised controlled equivalence trial. *Lancet Oncol* 2013;14(13):1269–1277.

[11] https://www.rcr.ac.uk/publication/postoperative-radiotherapy-breast-cancer-uk-consensus-statements; 2016.

[12] Tsang Y, Ciurlionis L, Kirby AM, Locke I, Venables K, Yarnold JR, *et al*. Clinical impact of IMPORT HIGH trial (CRUK/06/003) on breast radiotherapy practices in the United Kingdom. *Br J Radiol* 2015;88(1056). 20150453.

[13] Venables K, Tsang Y, Ciurlionis L, Coles CE, Yarnold JR. Does participation in clinical trials influence the implementation of new techniques? A look at changing techniques in breast radiotherapy in the UK. *Clin Oncol* 2012;24(8). e100–5.

[14] Coles CE, Wilson CB, Cumming J, Benson JR, Forouhi P, Wilkinson JS, *et al*. Titanium clip placement to allow accurate tumour bed localisation following breast conserving surgery: audit on behalf of the IMPORT Trial Management Group. *Eur J Surg Oncol* 2009;35(6):578–582.

[15] Donovan EM, Harris EJ, Mukesh MB, Haviland JS, Titley J, Griffin C, *et al*. The IMPORT HIGH image-guided radiotherapy study: a model for assessing image-guided radiotherapy. *Clin Oncol* 2015;27(1):3–5.

[16] Brunt AM, Wheatley D, Yarnold J, Somaiah N, Kelly S, Harnett A, *et al*. Acute skin toxicity associated with a 1-week schedule of whole breast radiotherapy compared with a standard 3-week regimen delivered in the UK FAST-Forward Trial. *Radiother Oncol* 2016;120(1):114–118.

[17] Kirwan CC, Coles CE, Bliss J. It's PRIMETIME. Postoperative avoidance of radiotherapy: biomarker selection of women at

very low risk of local recurrence. *Clin Oncol* 2016;28(9):594–596.

[18] Hopwood P, Haviland JS, Sumo G, Mills J, Bliss JM, Yarnold JR, *et al*. Comparison of patient-reported breast, arm, and shoulder symptoms and body image after radiotherapy for early breast cancer: 5-year follow-up in the randomised Standardisation of Breast Radiotherapy (START) trials. *Lancet Oncol* 2010;11(3):231–240.