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Editorial

International Guidelines on Radiation Therapy for Breast Cancer During the COVID-19 Pandemic



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There is an urgent need to share expertise and offer emergency guidance for breast radiation therapy (RT) during the COVID-19 (Coronavirus) pandemic. As per the World Health Organisation (WHO) statement, our aim and obligation should be "to stop, contain, control, delay and reduce the impact of this virus at every opportunity". In our roles as healthcare professionals and/or breast cancer experts this translates to minimising exposure of our patients to COVID-19 without compromising oncological outcome.

It is imperative that hospital visits are kept to the absolute minimum and that the complexity of RT planning/treatment is reduced where possible to ease pressure on our workforce. Given that breast RT accounts for 30 per cent of delivered RT fractions, the following recommendations require particularly urgent consideration. By adopting these recommendations where RT is minimised and targeted to those with the highest risk of relevant breast recurrence, we aim to protect our patients and health care professionals from potential exposure to COVID-19 as well as reducing the workload for health care providers and/or infrastructure at the moments that resources face strain due to the pandemic. A general guiding principle in this unusual setting is that: (i) where clinical equipoise has been sufficient to support the conduct of randomised trials testing a less resource-intensive approach, and (ii) results available to date have not provided evidence that such a test arm is clearly inferior, then (iii) the approach involving fewest

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patient visits and duration should be encouraged in the context of a pandemic like COVID-19 even when level 1-2 evidence has not formally been delivered.

We suggest that the following guidelines are **considered** and the **risks and benefits are discussed with patients** to facilitate shared decision-making. Centres may need/ choose to delay RT depending on local circumstances with reference to expert consensus following previous natural disasters [1] and also amend current systemic therapy pathways, but this is outside the remit of these guidelines.

1. Omit RT for patients 65 years and over (or younger with relevant co-morbidities) with invasive breast cancer that are up to 30mm with clear margins, grade 1–2, oestrogen receptor (ER) positive, human epidermal growth factor receptor 2 (HER2) negative and node negative who are planned for treatment with endocrine therapy [2].

Trials investigating safe omission of RT can be considered if they do not impact on patients visits and resources are available. Centres may also consider omitting RT for ductal carcinoma in-situ (DCIS) depending on individual risk and benefit.

2. Deliver RT in 5 fractions only for all patients requiring RT with node negative tumours that do not require a boost. Options include 28–30Gy in once weekly fractions over 5 weeks or 26Gy in 5 daily fractions over 1 week as per the FAST and FAST Forward trials respectively [3–5].

N.B. 5-year local relapse data are not yet available for FAST Forward but imminent publication is anticipated. In the meantime, 26Gy in 5 fractions has already been demonstrated to be equivalent with 40 Gy in 15 fractions with respect to 3-year normal tissue outcome. Furthermore, local control is likely to be within acceptable limits given the low local relapse rates in this patient group generally [6]. The FAST Forward protocol and RT planning pack are available at:

https://www.icr.ac.uk/our-research/centres-andcollaborations/centres-at-the-icr/clinical-trials-andstatistics-unit/clinical-trials/fast_forward_page/

Partial breast RT using 28.5-6Gy in 5 fractions over 1–2 weeks [7,8] can also be considered for selected patients if resources are available for increased complexity and/or to avoid deep inspiration breath hold (DIBH) for left-sided tumours in the upper half of the breast (if DIBH impacts on treatment time). N.B. IMPORT Low [6] has the same fractionation schedule in the control group as FAST Forward so 26Gy in 5 fractions over 1 week could also be proposed in the partial breast irradiation setting.

3. Boost RT should be omitted to reduce fractions and/or complexity in the vast majority of patients unless they 40 years old and under, or over 40 years with significant risk factors for local relapse [9]. Boost RT has no proven survival advantage so risks and benefits during the COVID-19 pandemic need to be reevaluated. An example of a significant risk factor is the presence of involved resection margins where further surgery is not possible. Any boost should be either simultaneous and integrated to minimise fractions if resource permits or hypofractionated sequential, e.g. 12Gy in 4 fraction over 4 days.

4. Nodal RT can be omitted in post-menopausal women requiring whole breast RT following sentinel lymph node biopsy and primary surgery for T1, ER positive, HER2 negative G1-2 tumours with 1–2 macrometastases [10].

This approach gives this group of patients the option of 5 fractions of RT, and may reduce complexity of planning/ treatment.

5. Moderate hypofractionation should be used for all breast/chest wall and nodal RT, e.g. 40Gy in 15 fractions over 3 weeks [11–14].

The use of moderate hypofractionation is already the standard of care in many countries and in the altered riskbenefit context of a pandemic should be strongly considered in patients with breast reconstruction. However, many centres will halt immediate reconstruction during the pandemic as this is not essential cancer surgery.

References

- [1] Gay HA, Santiago R, Gil B, Remedios C, Montes PJ, López-Araujo J, et al. 3rd lessons learned from hurricane maria in puerto rico: practical measures to mitigate the impact of a catastrophic natural disaster on radiation oncology patients. *Pract Radiat Oncol* 2019 Sep - Oct;9(5):305–321.
- [2] Kunkler IH, Williams LJ, Jack WJ, Cameron DA, Dixon JM. PRIME II investigators. Breast-conserving surgery with or without irradiationin women aged 65 years or older with early breast cancer (PRIME II): a randomised controlled trial. *Lancet Oncol* 2015 Mar;16(3):266–273. https://doi.org/10. 1016/S1470-2045(14)71221-5.
- [3] Brunt AM, Haviland J, Sydenham M, Algurafi H, Alhasso A, Bliss P, et al. FAST Phase III RCT of Radiotherapy Hypofractionation for Treatment of Early Breast Cancer: 10-Year Results (CRUKE/04/015). IJROBP 2018;102(5):1603–1604.
- [4] Brunt AM, Wheatley D, Yarnold J, Somaiah N, Kelly S, Harnett A, *et al.* FAST-Forward Trial Management Group. 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;120:114–118.
- [5] Brunt AM, Haviland JS, Sydenham MA, Alhasso A, Bloomfield D, Chan C, *et al.* OC-0595: FAST-Forward phase 3 RCT of 1-week hypofractionated breast radiotherapy: 3-year normal tissue effects. *Radiother Oncol* April 2018;127(Supplement 1):S311–S312.
- [6] Coles CE, Griffin CL, Kirby AM, Titley J, Agrawal RK, Alhasso A, *et al.* IMPORT Trialists. 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 Sep 9;390(10099):1048–1060.

- [7] Livi L, Meattini I, Marrazzo L, Simontacchi G, Pallotta S, Saieva C, *et al.* Accelerated partial breast irradiation using intensity-modulated radiotherapy versus whole breast irradiation: 5-year survival analysis of a phase 3 randomised controlled trial. *Eur J Cancer* 2015 Mar;51(4):451–463.
- [8] First results of the preoperative accelerated partial breast irradiation (PAPBI) trialvan der Leij F, Bosma SC, van de Vijver MJ, Wesseling J, Vreeswijk S, Rivera S, *et al.* First results of the post-operative accelerated partial breast irradiation (PAPBI) trial. *Radiother Oncol* 2015 Mar;114(3):322–327.
- [9] Bartelink H, Maingon P, Poortmans P, Weltens C, Fourquet A, Jager J, et al. European Organisation for Research and Treatment of Cancer Radiation Oncology and Breast Cancer Groups. Whole-breast irradiation with or without a boost for patients treated with breast-conserving surgery for early breast cancer: 20-year follow-up of a randomised phase 3 trial. *Lancet* Oncol 2015 Jan;16(1):47–56. https://doi.org/10.1016/S1470-2045(14)71156-8.

- [10] Bloomfield DJ. Core Group facilitated by The Royal College of Radiologists. Development of postoperative radiotherapy for breast cancer: UK consensus statements – a model of patient, clinical and commissioner engagement? *Clin Oncol R Coll Radiol* 2017 Oct;29(10):639–641.
- [11] Haviland JS, Owen JR, Dewar JA, Agrawal RK, Barrett J, Barrett-Lee PJ, et al, START Trialists' Group. The UK standardisation of breast radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. *Lancet Oncol* 2013 Oct;14(11):1086–1094.
- [12] https://www.nice.org.uk/guidance/ng101.
- [13] Whelan TJ, Pignol JP, Levine MN, Julian JA, MacKenzie R, Parpia S, *et al.* Long-term results of hypofractionated radiation therapy for breast cancer. *N Engl J Med* 2010 Feb 11;362(6): 513–520.
- [14] Leong N, Truong PT, Tankel K, Kwan W, Weir L, Olivotto IA. Hypofractionated nodal radiation therapy was not associated with increased patient-reported arm or brachial plexopathy symptoms. *Int J Radiat Oncol Biol Phys* 2017 Dec 1;99(5): 1166–1172.