Emergency guidelines for pre-operative breast radiotherapy during the COVID-19 pandemic

Introduction

National and international emergency guidelines[1] have strongly advised the use of 5 fractions for the vast majority of patients who still require adjuvant breast radiotherapy (RT) during the COVID-19 pandemic. The major aims of these earlier guidelines were to reduce footfall within RT departments and minimise exposure to patients and staff, whilst maintaining safe cancer treatment.

The COVID-19 pandemic continues to accelerate, creating greater impact on the resource available for cancer treatment. For example, many hospitals have either stopped or are planning to stop routine cancer surgery including breast surgery. As a result, it is likely there will be increased demand for local treatment in the form of RT. Therefore, it is vital that the oncology community develops safe, pragmatic and joined up plans in order to tackle this crisis so that patients have the best care possible and available resource is used responsibly. **As per adjuvant guidelines, it is recommended that the majority of patients who need pre-operative RT receive 5 fractions.**

Pre-operative breast RT: background

Breast RT has always had an accepted role as local therapy in those patients who are inoperable after systemic therapy and older patients who are too frail for surgery. Recently, pre-operative breast RT is being investigated more within the trial setting and early results suggest that this is safe with no additional peri-operative complications[2]. Most pre-operative studies have used conventionally or moderately hypofractionated RT, but there are reassuring 5-year results available from the PAPBI phase II trial using 30Gy in 5 fractions over 1 week to the partial breast[3].

Timing of breast surgery after pre-operative RT remains controversial, but data from the UK PRADA study: NCT02771938 suggests that surgery within a few weeks (2-6 weeks) is feasible. Surgery scheduled 20-24 weeks after pre-operative 3-week RT with simultaneous integrated boost (SIB) followed by endocrine therapy is also under investigation within the on-going Neo-RT feasibility study: NCT03818100.

Pre-operative RT: emergency guidelines

Emergency guidelines have been developed by a group of breast cancer specialists who have experience in breast hypofractionation and/or pre-operative RT. **It is recognised that these are not based on level 1 evidence in the pre-operative setting, but have been developed to facilitate RT departments in providing a safe and simple framework for managing breast cancer patients ONLY during this emergency situation. Therefore, this should be regarded as an opinion document only.**

Patient selection

Centres will develop criteria for patient selection along the lines of other UK emergency guidelines: these will reflect local available resource and will require flexibility to react to fluctuations during the COVID-19 pandemic. As per other national guidelines, a tumour clip should be inserted for any neo-adjuvant therapy including RT if possible. Overarching principles when breast surgery is postponed are to consider breast RT for the following broad patients groups:

1. Newly diagnosed invasive breast cancer with no systemic therapy option (chemotherapy or endocrine), e.g. patient with oestrogen receptor (ER) negative breast cancer but deemed unsuitable for chemotherapy as significantly increased risk of COVID-19 mortality
2. Completion of all neoadjuvant therapy with no option of endocrine and/or human epidermal growth factor receptor 2 (HER2) directed therapy e.g. patients with triple negative breast cancer
3. Loco-regional cancer progression/poor response despite use of all available neo-adjuvant therapies including HER2-directed and/or endocrine therapy

Radiotherapy technique and dose/fractionation

As per adjuvant guidelines, it is recommended that the majority of patients who need pre-operative breast RT **receive 5 fractions**. There is no reason to believe that 26Gy in 5 fractions in the pre-operative setting would be any different to 40Gy in 15 fractions in the pre-operative setting or any different to 26Gy in 5 fractions in the adjuvant setting, in relation to normal tissue toxicity. Dose/fractionation regimens suggested are based on a combination of clinical experience within clinical trials in the adjuvant setting and radiobiological modelling (see Table 1 and Appendix 1).

Simultaneous integrated boost (SIB) would be encouraged where possible to provide a targeted boost dose to gross breast tumour in 5 fractions. Simultaneous integrated boost is under investigation within the UK IMPORT High trial: NCT00818051 and 3-year toxicity results have been published in abstract form[4]. Five fraction nodal RT with SIB is currently being tested within the Indian HYPORTAdjuvant trial: NCT03788213. If SIB is not possible due to inability to localise the tumour on RT planning CT and/or lack of planning/delivery resource, then a sequential boost can be considered where needed.

Table 1: Suggested approach for emergency pre-operative RT

Patient and tumour characteristics	Emergency pre-operative RT	
	Breast	**Nodes**
Clinical/radiological complete response following primary systemic therapy or impalpable tumour	26 Gy/5F/1week to breast	
Palpable tumour	26 Gy/5F/1week to breast Boost: *SIB 32Gy/5F/1week (additional 6Gy/5F boost) OR Sequential boost 10Gy/2F/2 days	
Clinically/radiologically negative axilla		None OR consider 26 Gy/5F/1week to levels 1-4 if node positive at presentation prior to primary systemic therapy
Clinically/radiologically positive axilla: N1		26 Gy/5F/1week to levels 1-4
Clinically/radiologically positive axilla: N2-3		Standard 3week RT OR consider 26 Gy/5F/1week to levels 1-4 + **internal mammary nodes (IMN)

*Dose used in HYPORTAdjuvant trial

**V11Gy <35% (i.e. V42% of 26Gy <35%) for ipsilateral lung MUST be met

Dose constraints and objectives

This is based the FAST Forward trial including nodal substudy and SIB is aligned with HYPORTAdjuvant trial. Please see link for FAST Forward trial documentation including RT planning pack: https:///www.icr.ac.uk/fastforward

See Table 2 for summary of dose constraints and objectives:

Table 2: Dose objectives/constraints for 5 fractions

RT planning region	Dose objectives/constraints	
	Mandatory	**Optimal**
Breast SIB	V95%≥90% V105%≤7% V107%≤2% Dmax2cc≤110%	V95%≥95% V105%≤5%
Breast PTV	V95%≥90% V105%≤7% V107%≤2% Dmax2cc≤110%	V95%≥95% V105%≤5%
Nodal PTV	**Max point MUST not exceed 110% of prescribed dose**	V90%≥90% V107%≤2%
Region outside PTVs		V107%≤2cc
Brachial plexus Not mandatory to contour outside trial setting		0.1cc≤105%

Table 3: Dose objectives/constraints for organs at risk

Organs at risk	Dose objectives/constraints	
	Mandatory	**Optimal**
Ipsilateral lung	V30%≤17% V30%≤25% if nodal RT	V30%≤15%
Heart	V25%≤5% V5%≤30%	

RT technique and delivery

Please refer to FAST Forward planning packs as above. A clinical target volume (CTV) boost margin of 5mm around gross tumour visible on CT planning scan could be considered as per Neo-RT protocol.

For SIB, please refer to IMPORT High protocol for over-arching principles including image-guidance: https://www.icr.ac.uk/our-research/centres-and-collaborations/centres-at-the-icr/clinical-trials-and-statistics-unit/clinical-trials/import_high

Sequential boost can delivered with photon or electrons, but the use of mini-tangents is cautioned due to the large volume irradiated unless tumour is locally advanced.

References

1. Coles CE et al. International guidelines on radiation therapy for breast cancer during the COVID-19 pandemic. Clinical Oncology 2020 (in press)
2. Lightowlers SV, Boersma LJ, Fourquet A, Kirova YM, Offersen BV, Poortmans P, Scholten AN, Somaiah N, Coles CE. Preoperative breast radiation therapy: Indications and perspectives. Eur J Cancer. 2017 Sep;82:184-192.
3. Bosma SCJ, Leij F, Vreeswijk S, Maaker M, Wesseling J, Vijver MV, Scholten A, Rivera S, Bourgier C, Auzac G, Foukakis T, Lekberg T, Bongard D, Loo C, Rutgers E, Bartelink H, Elkhuizen PHM. Five-year results of the pre-operative accelerated partial breast irradiation (PAPBI) trial. Int J Radiat Oncol Biol Phys. 2020 Apr 1;106(5):958-967.
4. Coles C, Griffin C, Kirby A, Haviland J, Titley J, Benstead K, ... Yarnold J. (2019). Abstract GS4-05: Dose escalated simultaneous integrated boost radiotherapy for women treated by breast conservation surgery for early breast cancer: 3-year adverse effects in the IMPORT HIGH trial (CRUK/06/003). *Cancer Research, 79*(4 Supplement), pp. GS4-05-GS4.

Appendix 1

Schedule	Alpha/beta (Gy)				
	Late NTE			Breast cancer	
	3.0	*2.5*	*2.0*	***⁺3.5***	***3.5 + *time***
50Gy/25F (2.0)					
EQD2	50	50	50	50	50
40Gy/15F (2.7)					
EQD2	45	46	47	45	**+8=53
53Gy/15F (3.5)					
EQD2	69	71	73	67	+8=75
26Gy/5F (5.2)					
EQD2	43	44	47	41	+8=49
28Gy/5F (5.6)					
EQD2	48	50	53	46	+8=54
30Gy/5F (6.0)					
EQD2	54	57	60	52	+8=60
32Gy/5F (6.4)					
EQD2	60	63	67	57	+8=65
33Gy/5F (6.6)					
EQD2	63	67	70	60	+8=68

Explanation:
EQuivalent total Doses in 2 Gy fractions (EQD2) of 50 Gy/25F/5W, START-B 40GY/15F, IMPORT High 53 Gy/15F/3W and 4 dose intensities of 5F/1W schedules assuming apha/beta values of 3.0, 2.5 and 2.0 Gy for late NTE. START-P/-A generated a/b=3, FAST a/b=2.5 and FF a/b=2 with 95%CI overlapping between all trials and all NTE endpoints. START-P/-A & FAST controlled for time, but FF estimates do not attempt to correct for any time-related effects. If real (very slow incomplete repair, no repopulation) and corrected for, time corrections tend to increase a/b *very* slightly BUT barely change EQD estimates. The a/b values in the table based on START, FAST and FAST-Forward are estimates of clinical reality in the contexts tested within each trial, whether or not they incorporate a time element representing very slow (>24hr) repair in addition to classical Elkind repair (24hr) or any other process that we are unaware of.

⁺Based on START-P/-A trials' estimate of a/b=3.5 Gy to tumours which controlled for overall time. Clinical literature in H/N cancer suggests accelerated repopulation, the main time-related effect, does not kick in earlier than day 21, but it is conceivable that repopulation in BC starts from day 1 RT if prior surgery &/or systemic therapy stimulate proliferation.

**Hypothesis-generating* analysis of START trials suggests 0.6 Gy wasted dose per 2 Gy fraction during weeks 4 & 5 in Control group, which would explain why in START-B 40 Gy/15F with EQD2=45 has lower local relapse risk than 50 Gy/25F. If this effect operates from day 1 after surgery and/or systemic therapies, a 1-week RT schedule replacing a 3-week regimen saves EQD2 of 14x0.6=8 Gy, partly compensating for the loss of therapeutic ratio associated with large fraction sizes. If RT is first anti-cancer modality, there is no case for time correction that I know of.
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**This value was generated for START-B using a/b value=3.5 estimated by START-P/-A which controlled for time (5w), so it does not take account of the 14 fewer days of wasted dose when 15F are used. In the *footnote above, this effect is postulated to account for the apparent over-performance of 40Gy/15F compared to 50Gy/25F.

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