www.rcr.ac.uk

Clinical Oncology
The Royal College of Radiologists

Postoperative radiotherapy for breast cancer: hypofractionation

RCR consensus statements

May 2021

Contents

Consensus statements

The Royal College of Radiologist's (RCR) 2016 breast consensus statements made recommendations on hypofractionation.[1] There was consensus, with strong support, that there was no indication to use more than 15 fractions for the breast, chest wall or nodal areas. FAST-Forward was recruiting to the nodal sub-study at the time and there were no results to discuss. The following statements, agreed in 2020 following the FAST-Forward trial primary endpoint publication,[2] are intended to supplement the 2016 statements rather than replace them.

The new consensus statements are listed below. Please also refer to the 2016 breast consensus statements for other aspects of breast radiotherapy.[1]

Consensus statement 1

- Offer 26 Gray (Gy) in five fractions over one week for whole breast radiotherapy.

Consensus statement 2

- Offer 26 Gy in five fractions over one week for chest wall radiotherapy.

Consensus statement 3

- Consider 26 Gy in five fractions over one week for chest wall radiotherapy with reconstruction.

Consensus statement 4

- Offer 26 Gy in five fractions over one week for partial breast radiotherapy.

Consensus statement 5

- Consider 28.5 Gy in five fractions over five weeks instead of 26 Gy in five fractions over one week for patients with significant co-morbidities and/or frailty that make daily radiotherapy difficult.

Consensus statement 6

- Fifteen fractions over three weeks is the current standard of care for breast nodal radiotherapy. Consider 26 Gy in five fractions for nodal radiotherapy (excluding the internal mammary chain [IMC]) only for patients with significant co-morbidities while awaiting the two-year normal tissue results of the FAST-Forward nodal sub-study (due to report in 2021).

Consensus statement 7

- For patients requiring a boost, offer:
  - 26 Gy in five fractions whole breast radiotherapy plus either a sequential normofractionated boost or a hypofractionated boost (delivered in no more than five fractions as per the RCR *Postoperative radiotherapy for breast cancer: UK consensus statements*, 2016)
    or
  - 15 fraction simultaneous integrated boost (SIB), for example, 48 Gy to boost volume and 40 Gy to rest of breast all over three weeks.

Introduction

What are consensus statements?

Consensus statements are developed by a group of experts on a topic for which 'consensus is sought using an explicit methodology to identify areas of agreement and disagreement'.[3] The consensus statements reflect the group's collective analysis and evaluation of the best available evidence as well as their expert opinion on a topic.

Clinical consensus statements are not to be confused with clinical practice guidelines. While clinical consensus statements and clinical practice guidelines both provide recommendations on clinical practice, there are subtle but important differences between them. Clinical guidelines are usually based on a formal systematic review of high-level evidence, while consensus statements are most appropriate for topics where evidence is limited or lacking and therefore consensus approach offers the best way to address variability in clinical practice and improve patient outcomes.

As with any treatment, the benefits, risks and uncertainties should be discussed and a shared decision reached with the patient, taking into account their wishes and views. As such, there may be situations whereby 15 fractions is deemed to be optimal compared to five fractions for the individual patient. However, it is important that patients have the opportunity to hear about new research that may be relevant to them so that they can make an informed choice about their treatment. This patient-centred approach is facilitated by the framework of national consensus statements as a starting point for discussion.

RCR consensus methodology

In light of the FAST-Forward publication and the rapid change of breast practice during the COVID-19 pandemic, the RCR's Clinical Oncology Professional Support and Standards Board agreed there was a need to update the RCR's breast radiotherapy consensus statements.[1,2]

In June 2020 a multidisciplinary working group of breast cancer experts and patients were brought together to lead on the development of consensus statements focusing on breast hypofractionation. Following an appraisal of the FAST-Forward trial results and other research literature, six statements were drafted and refined over a six-week period.

Breast radiotherapy leads from each of the 62 UK radiotherapy centres were invited to share the first draft of statements with their multidisciplinary breast radiotherapy teams and to provide feedback. They were also asked to complete a survey of their past, current and future hypofractionation practice. Feedback received was incorporated into a subsequent draft of statements for the virtual consensus meeting in October 2020.

Prior to the consensus meeting a detailed presentation of the FAST-Forward trial was recorded and made available via open access online (https://vimeo.com/465716195). On 15 October 2020 the virtual consensus meeting was run in two parts. The first session was a webinar open to all members of the multidisciplinary breast cancer team. It included presentations and a question and answer session with Professor Murray Brunt (FAST-Forward Chief Investigator), Professor Charlotte Coles (RCR Breast Consensus Working Group Chair) and Dr Imogen Locke (NHS England Radiotherapy Clinical Reference Group Chair). The pre-meeting survey results of hypofractionation practice and the implementation of FAST-Forward results were presented and discussed.

The second session was an online meeting with one nominated breast radiotherapy lead per centre, representing the wider multidisciplinary team. Attendees were invited to discuss and vote on the final consensus statements; 55 centres were represented.

The evidence for each of the statements was discussed, facilitated by working group members. Statements were refined based on the meeting discussion. Representatives were then asked to vote on each statement on behalf of their centre, with one vote per centre, using an online voting app.

The following voting categories were agreed to indicate strength of voting. Consensus in the responses was defined as an agreement of at least 70% from participants.

Unanimous support	100%
Very strongly supported	90–99%
Strongly supported	70–89%
Majority support	60–69%
Equipoise	50–59%
Rejected	<50%

Members of the working group and RCR staff took notes of the discussion.

Key references

1. The Royal College of Radiologists. *Postoperative radiotherapy for breast cancer: UK consensus statements*. London: The Royal College of Radiologists, 2016.
2. Brunt AM, Haviland JS, Wheatley DA *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. *The Lancet* 2020; **395** (10237): 1613–1626.
3. Jacobs C, Graham ID, Makarski J *et al*. Clinical practice guidelines and consensus statements in oncology – an assessment of their methodological quality. *PLoS ONE*; **9** (12): e116267.
4. Kwong JSW, Chen H, Sun X. Development of evidence-based recommendations: implications for preparing expert consensus statements. *Chin Med J (Eng)*. 2016; **129** (24): 2998–3000.
5. Rosenfield RM, Nnacheta LC, Corrigan MD. Clinical consensus statement development manual. *Otolaryngol Head Neck Surg* 2015; **153** (Suppl 2): S1–S14.

Background

The UK FAST-Forward randomised trial was carried out in 97 hospitals (47 radiotherapy centres and 50 referring hospitals) for adults with early invasive breast carcinoma (pT1-3, pN0-1, M0) after breast conserving surgery or mastectomy.[1] They were randomised on a 1:1:1 basis to either 40 Gy in 15 fractions over three weeks (UK standard of care), 27 Gy in five fractions over one week or 26 Gy in five fractions over one week.

A total of 4,096 patients were recruited between November 2011 and June 2014 with a median follow up of 71.5 months. The primary endpoint of five-year ipsilateral breast tumour relapse was estimated as 2.1% (95% confidence interval [CI] 1.4–3.1) after 40 Gy, 1.7% (1.2–2.6) after 27 Gy and 1.4% (0.9–2.2) after 26 Gy. The upper confidence limits excluded an increase in ipsilateral breast tumour relapse of 1.6% or more, meeting pre-specified non-inferiority criteria for both investigational groups with p=0.0022 for 27 Gy and p=0.00019 for 26 Gy schedules compared with 40 Gy in 15 fractions.

Moderate or marked clinician-assessed normal-tissue effects were observed in 98/986 (9.9%) of the 40 Gy group, 155/1005 (15.4%) of the 27 Gy group and 122/1020 (11.9%) of the 26 Gy group. The odds ratios versus 40 Gy across all clinician assessments in the five-year period were 1.55 (95% CI 1.32–1.83, p<0.0001) for 27 Gy and 1.12 (0.94–1.34, p=0.20) for 26 Gy. Both patient and photographic assessments showed that the risk of normal-tissue effects was higher for 27 Gy, but not for 26 Gy, compared with the control group.

Consensus statement 1

Statement	Voting outcome
Offer 26 Gy in five fractions over one week for whole breast radiotherapy.	Very strongly supported

Notes

Consensus statement 1 is applicable to all patients with pT1–3, pN0–1, M0 invasive breast cancer following breast conserving surgery. Patients classified as high risk (age <50 years or grade 3 or both) were represented as follows: 518 (31.1%) in the 40 Gy group, 513 (37.5%) in 27 Gy and 514 (37.6%) in the 26 Gy group.

Patients with ductal carcinoma in situ (DCIS) only were not included in FAST-Forward, but these patients can still be offered 26 Gy in five fractions over one week for whole-breast radiotherapy. This is based on the same pragmatic implementation of 40 Gy in 15F over three weeks for DCIS following publication of the UK START B trial,[2–3] especially as breast radiotherapy for DCIS has not been shown to have a survival advantage within randomised trials.[4] Given the very low ipsilateral breast relapse rate for DCIS, it would not be feasible to repeat the FAST-Forward trial for DCIS.

References

1. Brunt AM, Haviland JS, Wheatley DA *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. *The Lancet* 2020; **395** (10237): 1613–1626.

2. Bentzen SM, Agarwal RK, Aird EGA *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:** 1098–1107.
3. Haviland JS, Owen JR, Dewar JA *et al*. 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; **14:** 1086–1094.
4. Early Breast Cancer Trialists' Collaborative Group (EBCTCG), Correa C, McGale P *et al*. Overview of the randomized trials of radiotherapy in ductal carcinoma in situ of the breast. *J Natl Cancer Inst Monogr* 2010; **2010**(41): 162–177.

Consensus statement 2

Statement	Voting outcome
Offer 26 Gy in five fractions over one week for chest wall radiotherapy.	Very strongly supported

Notes

Mastectomy rates within FAST-Forward were as follows: 91 patients (6.7%), 89 patients (6.5%) and 84 patients (6.1%) in the 40 Gy, 27 Gy and 26 Gy groups respectively. Immediate reconstruction rates were <1% across all groups with only ten patients receiving immediate implant-based reconstruction in the entire group. Given these very small numbers for immediate reconstruction, it was agreed at the consensus meeting that the consensus statement should be divided into chest-wall radiotherapy with and without reconstruction. However, it was noted that there was no biological reason why patients with an immediate reconstruction should have a higher risk of normal tissue toxicity/capsular contracture with 26 Gy in five fractions compared with 40 Gy in 15 fractions.

Consensus statement 3

Statement	Voting outcome
Consider 26 Gy in five fractions over one week for chest wall radiotherapy with reconstruction.	Strongly supported

Notes

As for consensus statement 2. It was recommended that centres may wish to audit their practice of 26 Gy in five fractions in this group and record rates of normal tissue toxicity/capsular contracture given the very small numbers of patients with immediate reconstruction in FAST-Forward.

Consensus statement 4

Statement	Voting outcome
Offer 26 Gy in five fractions over one week for partial breast radiotherapy.	Very strongly supported

Notes

The FAST-FORWARD trial was designed in parallel with IMPORT LOW with the same dose/fractionation for the control group in each study.[1] FAST-FORWARD showed non-inferiority with 40 Gy in15 fractions for efficacy and similar toxicity, while IMPORT LOW showed non-inferiority with 40 Gy in 15 fractions for efficacy *and* reduced toxicity. It was always envisaged that a five-fraction partial breast regimen would be adopted if these trial results were demonstrated. It is considered unnecessary and impractical to run a follow-on trial testing five fractions with partial breast radiotherapy given the very low ipsilateral breast relapse rates observed in IMPORT LOW. In addition, equipoise for randomisation to such a trial would be questionable for both clinicians and patients.

Of note, 84% voted 'yes' at the consensus meeting to the question: Do you plan to be offering partial breast radiotherapy in 2021?

References

1. Coles CE, Griffin CL, Kirby AM *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.

Consensus statement 5

Statement	Voting outcome
Consider 28.5 Gy in five fractions over five weeks instead of 26 Gy in five fractions over one week for patients with significant co-morbidity and/or frailty that makes daily radiotherapy difficult.	Very strongly supported

Notes

The long-term FAST trial results published in 2020 showed that at ten years, there was no significant difference in normal tissue event rates with 28.5 Gy in five fractions compared with 50 Gy in 25 fractions over 25 weeks.[1] However, normal tissue event rates were higher after 30 Gy in five fractions. The cumulative local relapse rate in all groups of this low-risk group of patients was 1.3% at 10 years.

References

1. Brunt AM, Haviland JS, Sydenham M *et al.* Ten-year results of FAST: A randomized controlled trial of 5-fraction whole-breast radiotherapy for early breast cancer. *J Clin Oncol* 2020; **38:** 3261–3272.

Consensus statement 6

Statement	Voting outcome
15 fractions over three weeks is the current standard of care for breast nodal radiotherapy. Consider 26 Gy in five fractions for nodal radiotherapy (excluding internal mammary chain [IMC]) only for patients with significant co-morbidities while awaiting the two-year normal tissue results of the FAST-Forward nodal sub-study (due to report in 2021).	Strongly supported

Notes

Nodal radiotherapy was not included in the FAST-FORWARD trial in *The Lancet* 2020 publication as the FAST-FORWARD nodal sub-study recruited participants after the main study with the first results of normal tissue effects expected in 2021. Therefore, five-fraction nodal radiotherapy should not be considered a current standard of care at this stage.

Consensus statement 7

Statement	Voting outcome
For patients requiring a boost, offer: ▪ 26 Gy in five fractions whole breast radiotherapy plus either a sequential normofractionated boost or a hypofractionated boost (delivered in no more than five fractions as per the RCR's *Postoperative radiotherapy for breast cancer: UK consensus statements,* 2016)[1] or ▪ 15 fraction simultaneous integrated boost (SIB), for example, 48 Gy to boost volume and 40 Gy to rest of breast all over three weeks.	Strongly supported

Notes

A permissive approach was adopted given the lack of new evidence regarding boost dose/fractionation. This will be revisited following publication of the UK IMPORT High trial (expected 2021).[2]

References

1. The Royal College of Radiologists. *Postoperative radiotherapy for breast cancer: UK consensus statements*. London: The Royal College of Radiologists, 2016.
2. Coles C *et al*. 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* 2019; **79** (Suppl 4): DOI 10.1158/1538-7445.SABCS18-GS4-05.

Acknowledgements

Members of the working group

Clinical oncology

- Charlotte Coles (Department of Oncology, University of Cambridge) – Chair
- Tom Roques (RCR Medical Director, Professional Practice, Clinical Oncology)
- Murray Brunt (Chief Investigator, FAST-Forward trial)
- Anna Kirby (Royal Marsden Hospital)
- Imogen Locke (NHSE Radiotherapy Clinical Reference Group)
- Marj Maclennan (Edinburgh Cancer Centre)
- Pippa Lewis (National Radiotherapy Fellow, NHS England)

Therapeutic radiography

- Heidi Probst (Chair of the Breast Radiotherapy Interest Group)

Radiotherapy physics

- Karen Venables (East and North Herts NHS Trust / Radiotherapy Trials Quality Assurance)

Patient representatives

- Mairead MacKenzie (Independent Cancer Patients' Voices)
- Hilary Stobart (Independent Cancer Patients' Voices)

Project support

- Sarah Griffin (RCR Clinical Oncology Projects and Development Officer)

Consensus participants

The following centres were represented at the RCR virtual consensus meeting held on 15 October 2020.

Aberdeen Royal Infirmary
Addenbrooke's Hospital
Beatson West of Scotland Cancer Centre
Belfast City Hospital
Bristol Haematology & Oncology Centre
Castle Hill Hospital
Cheltenham General Hospital
Colchester General Hospital
Dorset Cancer Centre, Poole Hospital
Edinburgh Cancer Centre
Guy's & St Thomas' Cancer Centre
Imperial College Cancer Centre
Ipswich Hospital
Kent Oncology Centre
Leeds Cancer Centre, St James' University Hospital
Leicester Royal Infirmary
Lincoln County Hospital
Mount Vernon Cancer Centre
Musgrove Park Hospital
NCCC, Freeman Hospital
New Cross Hospital
Ninewells Hospital & Medical School
Norfolk and Norwich University Hospital
North Middlesex University Hospital
North West Cancer Centre, Altnagelvin Hospital
Northampton General Hospital
Oxford Cancer Centre
Peterborough City Hospital
Plymouth Oncology Centre, Derriford Hospital
Portsmouth Oncology Centre, Queen Alexandra Hospital
Queens Hospital, Romford
Raigmore Hospital
Royal Berkshire Hospital
Royal Cornwall Hospital
Royal Derby Hospital
Royal Devon and Exeter Hospital
Royal Free Hospital
Royal Marsden Hospital
Royal Preston Hospital
Royal Shrewsbury Hospital
Royal Stoke University Hospital
Royal Surrey County Hospital
Royal Sussex County Hospital
St Bartholomew's Hospital
The Christie Hospital
The Clatterbridge Cancer Centre
The James Cook University Hospital
Torbay Hospital
University College London Hospital
University Hospital Southampton
University Hospital, Coventry
University Hospitals Birmingham, Queen Elizabeth Hospital
Velindre Hospital
Weston Park Hospital
Worcester Oncology Centre

The Royal College of Radiologists
63 Lincoln's Inn Fields
London WC2A 3JW

The Royal College of Radiologists is a Charity registered with the Charity Commission No 211540.

+44 (0)20 7405 1282
enquiries@rcr.ac.uk
www.rcr.ac.uk
@RCRadiologists

The Royal College of Radiologists. *Postoperative radiotherapy for breast cancer: hypofractionation. RCR consensus statementss.* London: The Royal College of Radiologists, 2020.

The Royal College of Radiologists is a Charity registered with the Charity Commissino No, 211540

Ref No. BFCO(21)1