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Hypofractionation: The standard for external beam breast irradiation

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ABSTRACT

This overview provides the historical perspective of external beam breast hypofractionation over the last 50 years. It highlights the serious harm suffered by patients with breast cancer in the 1970's and 1980's because of new hypofractionation regimens based on a theoretical radiobiology model being adopted into clinical practice to solve a resource issue without testing within clinical trials and without the essential radiotherapy quality assurance.

It then describes the high-quality clinical trials comparing 3-week with 5-week standard of care regimens that were initiated based on a strong scientific rationale for hypofractionation in breast cancer. Today, there are still challenges with universal implementation of the results of these moderate hypofractionation studies, but there is now a substantial body of evidence to support 3-week breast radiotherapy with several large randomised trials still to report.

The limit of breast hypofractionation is then explored and randomised trials investigating 1-week radiotherapy are described. This approach is now standard of care in many countries for whole or partial breast radiotherapy and chest wall radiotherapy without immediate reconstruction. It also has the advantage of reducing burden of treatment for patients and providing cost-effective care.

Further research is needed to establish the safety and efficacy of 1-week breast locoregional radiotherapy and following immediate breast reconstruction. In addition, clinical studies are required to determine how a tumour bed boost for patients with breast cancer at higher risk of relapse can be incorporated simultaneously into a 1-week radiotherapy schedule. As such, the breast hypofractionation story is still unfolding.

1. Introduction

Hypofractionation, defined as more than 2Gy daily treatments or fractions (Fr), for breast external beam radiotherapy is now the widely accepted, though not universally, international standard [1–4]. The optimal dose and fractionation and extent of hypofractionation for all indications is yet to be determined. It has taken decades to arrive at this point but there remain on-going questions. The historical story of breast hypofractionation will be described in detail.

2. Hypofractionation radiobiological models

In 1969 Ellis published a paper describing time, dose and fractionation as a clinical hypothesis [5]. He suggested testing the 'Nominal Standard Dose' (NSD) formula based on published radiotherapy trial results. The NSD formula was introduced into standard practice rather than within clinical trials and was found subsequently to have underestimated the dose reduction required to match late adverse effects. In 1975 Bates published a prospective clinical trial of post-operative radiotherapy delivered in 6Fr twice-weekly or 12Fr thrice-weekly post-mastectomy with the doses derived from over 25 years of clinical data with long-term follow-up [6]. Both schedules produced similar local control and similar and acceptable late radiation effects. Applying the NSD formula would have suggested 10% higher dose for the 6Fr schedule and could have produced unacceptable late radiation effects if this had been used.

In 1977 the Danish Breast Cancer Group (DBCG) was established with the aim of optimising treatment using evidence-based multidisciplinary guidelines. In 1978, despite reports of increased complications, for practical reasons the DBCG switched to a twice-weekly fractionation

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for all adjuvant breast radiotherapy using the NSD formula. 73 patients received a median minimum target dose of 36.7Gy in 12Fr over 6 weeks. In 1981 they reverted to 5Fr per week with a median minimum target dose of 41.0Gy in 22 fractions for 4+ weeks due to the severity of late complications with 2Fr per week, in particular to chest wall soft tissue, arm lymphoedema and shoulder movement restriction. The report published in 1987 described these consecutive cohorts of patients (73 and 66 respectively), with reference to the NSD formula used for dose calculation [7]. Late complications are particularly well-documented in this publication though it is one of many reports that led to widespread caution regarding hypofractionation.

In 1983 Withers and colleagues proposed a new method for calculating adjustment in total dose required to achieve an equal tissue response when the dose per fraction was changed [8]. Their method used the α/β ratio of the coefficient of the linear quadratic survival formula. This accounted for the effect of repair of cellular injury and they suggested that the isoeffect curves varied for different tissues. They stated that late effects curves were uncertain and cautioned applying them until new data allowed for more accurate definition. John Yarnold acknowledged this and other contemporary information to pioneer the modern era of breast hypofractionation research [9]. He led the Royal Marsden Hospital and Gloucestershire Oncology Centre trial in the UK (later known as the START Pilot trial (START-P)) which not only tested moderate hypofractionation but also used a novel design concept to allow radiobiological testing of the experimental trial groups [10].

3. Moderate hypofractionation

Moderate hypofractionation is used here to describe regimens of 13–16Fr. In 2016, an updated systemic review of hypofractionated radiation therapy for early breast cancer was published in the Cochrane database [11]. Four trials were identified reporting 10-year outcomes, START trials -P, -A and -B from the UK and the Ontario Clinical Oncology Group (OCOG) trial from Canada [12–15]. The START -P and -A trials were 3-arm trials with two experimental hypofractionated schedules over 5 weeks to allow a direct estimate of α/β ratios for effects on normal tissues and local control with no confounding effect of time. START-B and the OCOG trial were both pragmatic trials testing 15 or 16Fr of 2.7Gy over 3 weeks with the historical normofractionation (defined as 2Gy Fr) standard of 50Gy in 25Fr daily over 5 weeks.

START-P recruited 1410 patients (1986–1998) requiring adjuvant radiotherapy (T1-3N0-1M0) following conservative surgery to the breast±axilla and/or supraclavicular lymph nodes. Randomisation (1:1:1) was to 50Gy in 25Fr daily over 5 weeks (control) versus two schedules of 13Fr in 5 weeks delivering 39Gy and 42.9Gy with 3Gy and 3.3Gy per fraction respectively. The trial was designed to examine normal tissue effects on the breast, specifically photographic appearance (primary endpoint) and palpable induration, and to generate α/β ratio estimates which could inform a larger multicentre trial. START-P was not powered for local control. The photographic assessment showed significant differences between schedules with an α/β ratio of 3.6Gy (95%CI 1.8–5.4Gy) for any change (mild or marked) and 2.9Gy (95%CI 1.0–4.8Gy) for marked changes in photographic breast appearance. Clinician assessments of late normal tissue effects differentiated between the two test arms; breast induration producing estimated α/β value of 3.1Gy (95%CI 1.8–4.4), similar to that for the photographic assessment. Using interpolation an equivalent 13Fr schedule to the control arm can be derived for late normal tissue effects. The earlier results of START-P informed the design of the subsequent START -A and -B trials which commenced recruitment in 1998.

Meanwhile the Canadian OCOG trial recruited from 1993 to 1996 (n = 1234), comparing a 3-week schedule with the 5-week international standard [16]. A pilot study in the 1980s had randomised patients with node negative breast cancer to radiotherapy or not, giving 40Gy in 15Fr in 3 weeks whole breast irradiation (WBI) followed by a primary site boost of 12.5Gy in 5Fr over a week [17]. The 1990s trial compared 50Gy in 25Fr over 5 weeks with a hypofractionated schedule more typically used in Canada of 42.5Gy in 16Fr over 22 days for patients post-lumpectomy with pathologically negative axillary lymph nodes. No radiation boost was given. Long-term results were reported at median 12-year follow-up [18]. The primary outcome was invasive recurrence in the ipsilateral breast; cumulative incidence at 10 years was 6.7% in the 25Fr group compared with 6.2% in the hypofractionated-radiation group (absolute difference 0.5%; 95%CI −2.5 to 3.5). At 10 years excellent/good cosmetic outcome was seen in 71.3% and 69.8% (absolute difference 1.5%; 95%CI −6.9 to 9.8) in the 25Fr and 16Fr groups respectively. There was no significant difference between groups for skin and subcutaneous tissue adverse effects.

START-P had a secondary endpoint of local tumour control. Results were consistent with the hypothesis that both late-reacting normal tissue effects and breast cancer have a similar sensitivity to an increase in fraction size, which informed the development of the START-A and -B trials. START-A and -B ran concurrently investigating local tumour control, normal tissue effects, quality of life and health economic evaluation. START-A continued the START-P design but with a reduction in total dose of the higher dose arm to 41.6Gy in 3.2Gy/Fr due to a slight increase in late normal tissue effects seen with 3.3Gy/Fr against the 50Gy control [13]. As with START-P this allowed interpolation between the 13-fraction test doses to find an equivalent dose to the control arm and to plan a joint analysis of START-P and -A. 40Gy in 15Fr over 3 weeks was widely used in the UK but had not been reported in a head-to-head trial with conventional fractionation, START-B was the pragmatic trial to do this [14]. The START-B schedules had been used to randomise patients receiving therapy in a UK West Midlands trial of radiotherapy or not which reported later [19].

The 2008 publications of 5-year follow-up in the START -A and -B trials led to UK guidelines for 40Gy in 15Fr in the UK in 2009 [20]. In 2013, the pre-planned 10-year follow-up results of START-A and -B were published [21]. The primary endpoint of START -A and -B was ipsilateral local-regional relapse, with a non-inferiority hypothesis for START-B. Normal tissue effects were assessed by clinicians, patient self-assessment and photographic change from pre-radiotherapy baseline. Direct estimates of the α/β ratio were obtained for breast cancer and the dose-limiting normal tissues.

In START-A (N = 2236) median age at randomisation was 57 years, 1900 (85%) had breast-conserving surgery, 643 (29%) had confirmed positive lymph nodes and 318 (14%) underwent lymphatic radiotherapy. At 9.3 years median follow-up 139 (6·2%) patients had local-regional tumour relapse; hazard ratios relative to the 50Gy schedule were 0·91 (95%CI 0·59–1·38) for the 41·6Gy test dose and 1·18 (0·79–1·76) for 39Gy. The α/β estimate for local-regional relapse in START-A was 4Gy (95%CI 0·0–8·9) adjusting for age, tumour size, mode of primary surgery, adjuvant chemotherapy use, tamoxifen use, lymphatic radiotherapy and boost radiotherapy to the tumour bed. Meta-analysis of START-A and -P trials gave an adjusted α/β value for local-regional relapse of 3·5Gy (95%CI 1·2–5·7) with data on 349 events in 3646 women. Moderate or marked breast induration, telangiectasia and breast oedema were significantly less common with the 39Gy schedule patients than in the 50Gy control group but adverse effects did not differ significantly between 41·6Gy and 50Gy groups. Adjusted α/β estimates for normal tissue endpoints in START-A were 3·5Gy (95%CI 0·7–6·4) for breast shrinkage, 4Gy (2·3–5·6) for breast induration, 3·8Gy (1·8–5·7) for telangiectasia, and 4·7Gy (2·4–7·0) for breast oedema.

In START-B (N = 2215) median age at randomisation of 57 years, 2038 (92%) had breast-conserving surgery, 504 (23%) had confirmed positive lymph nodes and 161 (7%) underwent lymphatic radiotherapy. At 9.9 years median follow-up 95 (4·3%) patients had a local-regional tumour relapse; hazard ratio for the 40Gy schedule compared with the 50Gy control was 0·77 (95%CI 0·51–1·16). The estimated absolute difference in local-regional relapse by 10 years for 40Gy versus 50Gy was −1·2% (95%CI –2·6% to 1·0%); the upper limit of the one-sided 95%CI gave a 0·4% excess risk associated with the 15-fraction schedule.

Moderate or marked breast shrinkage, telangiectasia and breast oedema were significantly lower with 40Gy versus 50Gy. At 10 years, ischaemic heart disease, symptomatic rib fracture and symptomatic lung fibrosis were rare and occurred in similar proportions with all regimens in START-A and -B.

Recent publications of trials investigating moderate hypofractionation add to the Cochrane 2016 systemic review findings. The DBCG commenced recruitment into the HYPO trial in 2009. The trial used the same schedules as START-B with a primary endpoint of 3-year grade 2–3 breast induration. Patients with DCIS were eligible in addition to early invasive breast cancer and pre-specified sub-groups for analysis included large-breasted patients. 86.7% were treated for invasive cancer and 13.3% DCIS, the median age for the population was 59 years (only patients >40 years eligible). The 3-year rate of grade 2–3 induration was 11.8% (95%CI 9.7–14.1) in the 50Gy group and 9.0% (95%CI 7.2–11.1) in the 40Gy group, satisfying the statistical criteria for noninferiority of 40Gy compared with 50Gy (risk difference −2.7%; 95%CI -25.6%–0.2%; p = 0.07). At >7 years median follow-up induration risk was 13% with the 50Gy schedule and 11% in the 40Gy group (odds ratio 0.80; 95%CI 0.65–0.98). No difference in locoregional recurrence risk between the two regimens was seen overall, or for invasive cancer or DCIS when analysed separately. The hazard ratio for locoregional recurrence for invasive carcinoma was similar for HYPO (0.75; 95%CI 0.37–1.49) and START-B (0·77; 95%CI 0·51–1·16) trials for the 40Gy schedule compared with 50Gy.

4. Ultra-(5Fr) hypofractionation

Postulating that 15-/16-Fr regimens should not be the limit of hypofractionation the schedules to be tested in the UK FAST trial were developed using the linear quadratic equation and α/β values of 3Gy and 4Gy for normal tissue late effects and tumour responsiveness respectively [23]. FAST (N = 915) aimed to devise schedules of once weekly radiotherapy for 5 weeks that would be similar in outcome to 50Gy in 25Fr over 5 weeks. As with START-P/-A the 3-arm design allowed for interpolation between test arms. Total doses of 28.5Gy and 30Gy in fractions of 5.7Gy and 6Gy were tested. FAST commenced recruitment in 2004 with the primary endpoint of change in photographic breast appearance at 2 years compared with baseline. At 2 years a statistically significant dose response was seen between 28.5 and 30Gy. 28.5Gy was similar (odds ratio 1.15; 95%CI 0.82–1.60, p = 0.489) and 30Gy higher (1.70; 95%CI 1.26–2.29, p < 0.001) for mild or marked change compared with the 50Gy standard.

10-year follow-up of FAST reported on clinician assessment of side effects and 5-year photographs [24]. At 5 years none/mild/marked change in photographic breast appearance was seen in 79.5%/17.7%/2.8% of 615 patients respectively. Rates of mild/marked change in photographic breast appearance at 2 or 5 years were not significantly different for 28.5Gy (odds ratio 1.10; 95%CI 0.70–1.71; p = 0.686) compared with 50Gy but were significantly higher for 30Gy (OR 1.64; 95%CI 1.08–2.49; p = 0.019) for 30Gy. Annual clinician assessments over follow-up for any moderate/marked breast normal tissue effect were not significantly different between 28.5Gy and 50Gy (OR 1.22; 95%CI 0.87–1.72; p = 0.248) but were significantly higher for 30Gy versus 50Gy (OR 2.12; 95%CI 1.55–2.89; p = 0.001). The FAST trial was not powered for comparisons of local recurrence; it was reported for 11/915 patients (50Gy-3; 30Gy-4; 28.5Gy-4), with an estimated 10-year cumulative incidence rate of 1.3% (95%CI 0.7–2.3) overall. The FAST trial identified 28Gy in 5Fr daily as estimated to be radiobiologically-equivalent to the 25Fr standard regarding late normal tissue effects.

The START and FAST trials' early results and design informed the development of the UK FAST-Forward trial. The control arm for FAST-Forward was 40Gy in 15Fr over 3 weeks versus 2 test schedules of 5Fr delivered daily in a week. Using α/β values generated from START and FAST together with modelling as explained in a subsequent publication [25], test doses of 26Gy and 27Gy were selected. The primary endpoint was local recurrence and key secondary endpoints included acute and late normal tissue effects. Acute toxicity sub-studies showed that with both 5Fr schedules erythema was less intense and settled a fortnight earlier than with the 40Gy/15Fr regimen [26]. Acute reactions were also milder in both FAST 5-Fr schedules than for the 50Gy schedule [23].

In FAST-Forward (N = 4110), 5-year estimated cumulative incidence of local recurrence was 2.1% (95%CI 1.4–3.1) for the 40Gy schedule, 1.7% (95%CI 1.2–2.6) with 27Gy and 1.4% (95%CI 0.9–2.2) with 26Gy, conclusively showing both 5Fr schedules as non-inferior to 40Gy [27]. At 5 years, the prevalence of any moderate/marked normal tissue effect in the breast or chest wall (shrinkage, induration, telangiectasia or oedema) assessed by clinicians was 9.9%/15.4%/11.9% for patients in 40Gy/27Gy/26Gy respectively, with a statistically significant difference between 40Gy and 27Gy (p = 0.0003) but not between 40Gy and 26Gy (p = 0.17). In the patient-reported outcomes sub-study change in breast appearance was the most prevalent moderate/marked effect reported at 5 years, with 32% for 40Gy, 36% for 27Gy (p = 0.28 versus 40Gy) and 32% for 26Gy (p = 0.83 versus 40Gy). There were no statistically significant differences in 5-year prevalence of patient-reported adverse effects between schedules. There was some evidence for an increase in patient-reported moderate/marked breast hardness/firmness at 5 years for 27Gy compared with 40Gy and more breast swelling in both 5-Fr schedules (although prevalence of swelling was very low in all schedules), but these were not statistically significant at the pre-specified cut-off of p = 0.005 used due to multiple testing. Given the large number of adverse effect outcomes assessed the chances of a type 1 error (false positive result) are increased, hence use of a stringent cut-off is advisable. 26Gy in 5Fr over a week was deemed the clinically relevant regimen with non-inferiority of efficacy and similar normal tissue effects.

Frequencies of normal tissue effects were low overall in the FAST-Forward trial, and markedly less than observed in the START trials. The most prevalent clinician-assessed moderate/marked effect at 5 years was breast shrinkage with 5.5%/8.2%/6.8% for 40Gy/27Gy/26Gy, compared with 11.4% in 40Gy for the START-B trial. The only statistically significant difference between 26Gy and 40Gy in FAST-Forward for a clinician-assessed normal tissue effect was for moderate/marked breast induration outside the tumour bed, reported at 5 years in 0.1% for 40Gy (1 case) and 2.1% for 26Gy (20 cases). It is highly unlikely to be considered clinically significant, as the absolute numbers of patients experiencing these effects are very small.

5. Chest wall and hypofractionation

Information regarding chest wall hypofractionation was obtained from START-A/-B although the minority had mastectomy (336 (15%)/177 (8%) patients respectively). Wang et al. reported a single institution randomised non-inferiority trial of hypofractionation post-mastectomy without reconstruction, with locoregional recurrence as primary outcome [28]. Patients received radiotherapy to the chest wall and axillary levels 3 and 4 (supraclavicular fossa) following mastectomy with axillary dissection and neoadjuvant or adjuvant chemotherapy. Randomisation was between 50Gy/25Fr over 5 weeks or 43.5Gy/15Fr of 2.9Gy daily over 3 weeks. 820 patients, median age 49 years, were enrolled 2008–2016. At 58.5 months median follow-up the estimated 5-year cumulative incidence of locoregional recurrence was 8·1% (90% CI 5·4–10·6) in the 50Gy group and 8·3% (90%CI 5·8–10·7) in the hypofractionated arm confirming non-inferiority of the 15Fr schedule. The hypofractionated group had less frequent grade 3 acute skin toxicity (14/401, 3%) than normofractionated (32/409, 8%); p < 0·0001. There were no significant differences between schedules in the incidence of other acute or late toxicities, including symptomatic radiation pneumonitis, lymphoedema, ischaemic heart disease and shoulder dysfunction.

6. DCIS and hypofractionation

The Breast International Group (BIG) 3–07 and *Trans*-Tasman Radiation Oncology Group (TROG) 07.01 study (N = 1608) had dual aims, to investigate whether whole breast hypofractionation was appropriate for non-low-risk DCIS and also whether a tumour bed boost decreased local recurrence [29]. The former question is addressed here. Whole breast irradiation compared daily schedules of 50Gy/25Fr daily with 42·5Gy/16Fr. Five-year free-from-local-recurrence rates were similar with 25Fr (94·4%) and 16Fr (93·7%); (HR 0·94; 95%CI 0·51–1·73; p = 0·84). There was no statistically significant interaction between tumour bed boost and dose fractionation. Moderately-hypofractionated radiotherapy was concluded to be as safe and effective as normofractionation for DCIS.

7. Partial breast and hypofractionation

Using 40Gy/15Fr daily standard, the UK IMPORT LOW trial randomised 1:1:1 between WBI, partial breast irradiation (PBI), and reduced-dose radiotherapy to the whole breast and partial breast (this third group not discussed here as not used in clinical practice) [30]. Notably, treatment volume was tested unconfounded by external beam radiotherapy technique, dose, fractionation or time factors. At 72 months median follow-up, local relapse was reported for 9 (1%) WBI and 6 (1%) PBI, with 5-year estimated cumulative incidence of local relapse 1·1% (95%CI 0·5–2·3) and 0·5% (0·2–1·4) respectively. Non-inferiority was concluded for PBI. At 5 years patients reported fewer marked/moderate events for skin appearance change, overall breast appearance change, breast smaller, and breast harder or firmer to touch in PBI compared with WBI although this reduction was statistically significant for change in breast appearance only (p < 0·0001). 5-Year clinical assessment of normal-tissue effects showed a low occurrence of moderate/marked events across all treatment groups and HRs for all late effects were consistently less than 1 for PBI compared with WBI, although no statistically significant differences for individual effects were seen.

IMPORT LOW and FAST-Forward were planned to be assessed together, with the same control schedule of 40Gy in 15Fr WBI. The results from both are therefore applicable to PBI and 26Gy/5Fr. IMPORT LOW showed reduced volume results in reduced late normal tissue toxicity for a constant dose/fractionation, therefore it follows that 26Gy/5Fr was adopted for PBI. This approach was agreed at a UK Royal College of Radiologists consensus meeting [31] and by the ESTRO breast consensus working group [32].

The DBCG investigated WBI and PBI using 40Gy/15Fr with the primary endpoint of 3-year grade 2–3 breast induration in a relatively low risk population aged ≥60 years [33]. 865 evaluable patients, median age 66 years, had median follow-up of 5 years for morbidity and 7.6 years for locoregional recurrence. The grade 2–3 induration at 3 years was WBI 9.7% (95%CI 7.0–12.9) and PBI 5.1% (95%CI 3.2–7.6); p = 0.014. Evaluating all assessments up to 5 years found large versus small breasts had a risk of induration of 12% versus 7%, (OR 1.71, 95%CI 1.23–2.38, p = 0.0014). For breast size and irradiated breast volume, a 3-year induration incidence was found in large-versus small-breasted patients of 13% (WBI) and 6% (PBI) versus 6% (WBI) and 5% (PBI) respectively. In a separate publication the DBCG concluded that breast induration risk increased significantly with larger irradiated breast volume, not the breast size itself, strongly favouring small volumes and therefore PBI [34]. The 5-year locoregional recurrence risk was WBI 0.7% (95%CI 0.2–1.9) and PBI 1.2% (95%CI 0.4–2.6), showing no significant difference (p = 0.47).

Long-term results of the Florence trial provide information on both PBI and a daily 5Fr schedule delivering 30Gy which was compared with 50Gy in 25Fr over 5 weeks WBI with a tumour bed boost. 520 patients, predominantly with low recurrence-risk characteristics, had a median 10.7-year follow-up [35]. The 10-year cumulative incidence of IBTR was estimated as 2.5% (n = 6) in 25Fr WBI with a tumour bed boost and 3.7% (n = 9) in the PBI arm (hazard ratio 1.56; 95%CI 0.55–4.37; p = 0.40). Overall survival was 91.9% in both arms at 10 years. PBI had significantly less acute toxicity, late toxicity and a better cosmetic outcome evaluated by patients and clinicians (all p = 0.0001).

8. Nodal irradiation and hypofractionation

The HYPORT-Adjuvant trialists describe their trial as a validation study of FAST-Forward and IMPORT High in a high-risk population [36]. It is a randomised phase III non-inferiority trial comparing 40Gy/15Fr over 3 weeks with 26Gy/5Fr over a week, with all patients receiving regional radiotherapy including the supraclavicular fossa ±internal mammary nodal irradiation. HYPORT-Adjuvant includes a simultaneous integrated boost (SIB) for breast conservation patients with the boost volume receiving 48Gy/15Fr or 32Gy/5Fr. The primary endpoint is local recurrence, and secondary endpoints include any grade 3 or more radiation-related adverse events. HYPORT-Adjuvant is currently recruiting. Interim analysis of acute toxicity reported grade 2/3 radiation dermatitis in 4 (2.9%) and 15 (11.1%) patients for the 1- and 3-week schedules respectively. Two patients in the 3-week schedule had a grade 2 transient cough considered infective and no patients reported grade 2 dysphagia.

The OCOG Hypofractionated LocoRegional Radiotherapy in Breast Cancer (RHEAL) trial (NCT04228991) is recruiting with a primary objective to determine if 26Gy/5Fr daily to the regional nodes (supraclavicular, axillary and internal mammary) in addition to the breast or chest wall is non-inferior to 40Gy/15Fr over 3 weeks in patients with node positive breast cancer. Study participants will be assessed for lymphoedema by measuring arm volume (primary outcome).

The FAST-Forward nodal substudy (N = 469) has the same design as the main FAST-Forward trial but is restricted to patients prescribed radiotherapy to level I-III axilla and/or level IV axilla (supraclavicular fossa) in addition to the breast/chest wall. The principal comparison is between the 40Gy and 26Gy schedules since recruitment into the 27Gy group of the nodal substudy closed early following confidential review by the Independent Data Monitoring Committee of accumulating normal tissue data from the main FAST-Forward trial. The primary endpoint is 5-year patient-reported arm/hand swelling. Interim results for normal tissue effects up to 2 years for patient-reported outcomes and up to 3 years for clinician assessments have been reported [37]. Most patients reported no arm/hand swelling at 2 years: 73% in 40Gy, 76% in 26Gy and 66% in 27Gy, and with most symptoms graded as mild. Two-year prevalence of moderate/marked arm/hand swelling was 10%/7%/14% for 40Gy/26Gy/27Gy. Clinician-reported arm lymphoedema at 3 years was 8%, 12% and 11% in 40Gy, 26Gy and 27Gy. Primary analysis will be at 5 years' follow-up. The interim descriptive results up to 3 years suggest no cause for concern of an excess in normal tissue effects in the arm and shoulder for 26Gy/5Fr compared with 40Gy/15Fr.

9. Risk groups, breast size, boost and hypofractionation

The 2018 ASTRO guidelines recommended moderately-hypofractionated breast radiotherapy irrespective of age, tumour grade or receptor status [1]. Sub-group analyses of locoregional relapse were done in a meta-analysis of 10-year follow-up in the 5861 patients from the START-P/-A/-B trials [21]. There was no evidence of a differential effect of fractionation schedule for tumour control by age, type of primary surgery, axillary node status, tumour grade, use of adjuvant chemotherapy or boost radiotherapy. Central analysis of tumour blocks reported no disadvantage with moderate hypofractionation for patients with high-grade tumours in the OCOG trial and that tumour grade and molecular subtype did not predict response to hypofractionation [38].

Shaitelman et al. conducted a US randomised trial to address concerns regarding cosmesis with boost, in patients receiving chemotherapy or with larger breast size [39]. 287 patients with invasive disease or

DCIS were randomised to 50Gy/25Fr or 42.56Gy/16Fr with boost schedules of 10–14Gy/5-7Fr and 10–12.5Gy/4-5Fr respectively. Adverse patient-reported cosmesis at 3 years (primary outcome) was 8.2% (N = 8) with hypofractionated and 13.6% (N = 15) with normofractionated schedules (p = 0.002 for non-inferiority). The proportion with an adverse cosmetic outcome was 18.6% lower with hypofractionation among patients with D cup or larger breasts. Boost, chemotherapy and larger breast size were not found to be a contraindication for using hypofractionation.

Retrospective subgroup analyses of FAST-Forward comparing local recurrence in 26Gy versus 40Gy provide no evidence of a differential effect according to age, grade, pathological tumour size, nodal status, tumour bed boost, adjuvant chemotherapy, HER2 status and in triple negative patients [25]. Results should be interpreted with caution as the statistical power is low due to few events. Local recurrence was reported in 3/128 and 10/111 triple negative patients, 4/217 and 3/198 in patients age under 50 years, and 8/378 and 20/386 grade 3 patients for 26Gy and 40Gy respectively.

The HYPO trial pre-specified sub-group analysis according to breast volume [22]. Large-compared with small-breast volume was significantly associated with induration at 3-years but at no time-point did 40Gy result in worse outcome compared with 50Gy. In FAST-Forward adjusting for breast size made very little difference to the α/β estimate for photographic-assessment or clinician-assessed normal tissue effects [27]. Retrospective sub-group analyses provided no evidence of a differential effect of the 5-fraction schedule for clinician-assessed normal tissue effects according to breast size, although power for these analyses was low.

IMPORT HIGH tested SIB versus sequential boost using hypofractionated radiotherapy [40]. Patients were randomised 1:1:1–40Gy/15Fr to the whole breast plus 16Gy/8Fr sequential boost (control) versus 36Gy to the whole- and 40Gy to the partial-breast and either 48Gy or 53Gy SIB to the tumour bed in 15Fr. 2617 women were consented, with median age 49 years. Primary endpoint was ipsilateral breast tumour relapse (IBTR). Estimated 5-year IBTR incidence was 1.9% (95%CI 1.2–3.1) for control, 2.0% (95%CI 1.2–3.2) for 48Gy and 3.2% (95%CI 2.2–4.7) for 53Gy. Hypofractionated 48Gy SIB shows non-inferiority in terms of IBTR compared with standard sequential boost and with incidence of relapse much lower than expected. 5-Year rates of moderate/marked normal tissue effects were similar between each test group and control, with higher risk of clinically-assessed breast induration, breast distortion and patient-assessed breast hardness/-firmness for 53Gy versus 48Gy.

10. Health economics and global health with hypofractionation

Deshmukh et al. performed a US value-based comparative cost-effectiveness analysis of WBI delivered with conventional and moderate hypofractionated radiotherapy following conservative breast surgery [41]. Hypofractionation resulted in higher quality-adjusted life-years (QALYs) and lower cost than normofractionation in all scenarios tested, indicating that it was most cost-effective.

Glynn et al. formally evaluated IMPORT LOW and FAST-Forward for costs and health consequences associated with PBI and 5-fraction hypofractionation in a UK population [42]. Health impacts were captured using QALYs. In patients receiving WBI and not eligible for PBI 5Fr was expected to provide more QALYs and have lower costs compared with 15Fr. The expected cost savings were predominantly due to reduced fractions. Similar results were found for PBI favouring 5Fr. Resource savings would enable the same number of patients to be treated whilst freeing linear accelerator capacity. 5Fr schedules reduce hospital attendance and burden of treatment for patients.

Globally access to radiotherapy is extremely heterogeneous with infrastructure severely under resourced in many low- and middle-income countries (LMICs) [43]. The investment to set up radiotherapy programmes and associated training is challenging for LMICs particularly with ongoing operational and maintenance needs whilst balancing all other health needs. An international ESTRO-GIRO survey investigated use of hypofractionated radiotherapy [44]. It found a relative lack of uptake of hypofractionated radiotherapy in LMICs compared with higher income countries: use of hypofractionation was preferred in the node-negative setting following breast conservative surgery by respondents in Europe (88·5%) and North America (97.3%) and Africa (40.0%) respectively.

5Fr over 1 week could go some way to alleviating inequity of access to radiotherapy. Given that many patients in LMICs present with more advanced disease the results of HYPORT-Adjuvant will add to the evidence for 5Fr-nodal irradiation. This shortened fractionation could reduce health system costs and limit potential financial toxicity for patients who would have received up to 5 weeks of radiotherapy.

11. Future research and hypofractionation

The future focus on 5Fr hypofractionation trials follows the current areas of interest, namely SIB and nodal especially internal mammary chain lymph nodes (IMC). RHEAL, HYPORT and FAST-Forward nodal substudy will add regional nodal data but for IMC in particular more will be required. HYPORT-Adjuvant will contribute data on 32Gy/5Fr as SIB but other schedules may need to be studied such as 30/31Gy.

12. Conclusions

The evidence supporting hypofractionated 15/16 daily fractions over 3 weeks compared with the historical normofractionation 50Gy/25Fr over 5 weeks is considerable. Regarding efficacy, non-inferiority of the hypofractionated schedules has been shown with regard to the 25Fr regimen, with no exceptions shown according to patient characteristics, tumour features or sites to be irradiated. For normal tissue effects the hypofractionated schedules are at least similar and in the case of 40Gy/15Fr over 3 weeks there is evidence of reduced adverse effects. There is no longer any situation for which 50Gy/25Fr over 5 weeks can be justified for breast adenocarcinoma. Evidence is accumulating regarding 1-week schedules; 26Gy in 5 daily fractions over a week can be used as a standard regimen for whole breast, chest wall without reconstruction or PBI. More trial evidence is required for nodal (especially internal mammary) and boost (especially SIB) irradiation and post-reconstruction 1-week radiotherapy.

Declaration of competing interest

Professor Brunt is Chief Investigator of the FAST-Forward trial.
The authors have no other declarations.

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