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CRITICAL REVIEW

HYPOFRACTIONATED WHOLE-BREAST RADIOTHERAPY FOR WOMEN WITH EARLY BREAST CANCER: MYTHS AND REALITIES

JOHN YARNOLD, F.R.C.R.,* SØREN M. BENTZEN, D.SC.,† CHARLOTTE COLES, PH.D.,‡ AND JOANNE HAVILAND, M.SC.¶

*Section of Radiotherapy, Institute of Cancer Research and Royal Marsden Hospital, Sutton, United Kingdom; †Department of Human Oncology, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin; ‡Oncology Centre, Cambridge University Hospitals NHS Foundation Trust, Cambridge, United Kingdom; ¶Institute of Cancer Research Clinical Trials and Statistics Unit, Section of Clinical Trials, Sutton, United Kingdom

INTRODUCTION

Hypofractionation for treatment of women with early breast cancer is being used again after addressing past causes of failure. Data from randomized trials confirm the safety and efficacy of schedules using fraction sizes of around 3 Gy, provided the correct downward adjustments to total dose are made. Unjustified concerns relating to heart tolerance, nonuniform dose distribution, and duration of follow-up need not discourage the routine adoption of a 15- or 16-fraction schedule. Potential benefits of the overall shorter treatment time include greater convenience and improved local tumor control, although the latter benefit remains to be tested. Adjusting fraction size across the breast is a good way of matching dose to tumor relapse risk. A modest reduction in fraction size to breast tissue remote from the tumor bed and at low risk of local tumor relapse is expected to reduce late adverse effects without significant loss of tumor control. The corollary is that dose escalation to the index quadrant, whether by hypofractionation or by a sequential boost dose, will result in a greater relative increase in late adverse effects than tumor control, a therapeutic disadvantage that can be overcome only by exploiting a marked dose-volume effect.

BRIEF HISTORY OF HYPOFRACTIONATION

Hypofractionation: What went wrong and why

It has been understood for more than 100 years that the relationship between total radiation dose and biological effect depends on the dose per fraction. As fraction size increases, total dose must be reduced in order to maintain the same level of antitumor or normal tissue effect. True, the dose reduction is relatively modest for epidermis and some tumors, as correctly estimated by the Ellis isoeffect formula proposed in the late 1960s (1). When a regimen is changed from 25 × 2.0-Gy fractions to a 15-fraction regimen delivered over the same overall treatment time, the Ellis formula estimated a dose reduction from 50 Gy to 45 Gy in 15 fractions of 3.0 Gy to match acute skin reactions. Ellis felt that the healing of skin epithelium reflected "the condition of the underlying connective-tissue stroma" and, as a consequence, he hypothesized that "apart from bone and brain…the normal tissue tolerance dose, could be based on skin tolerance." It was realized in the late 1970s and early 1980s that dose reductions estimated using the Ellis formula were insufficient for matching late side-effects (2–5). Late effects such as subcutaneous fibrosis and skin telangiectasia are more sensitive than acute reactions to altered fraction size (6–7). In fairness, Ellis proposed his formula as a hypothesis to be tested in the clinic, but radiation oncologists applied the formula in what, with hindsight, was an uncritical way.

The distinct fractionation sensitivities of early and late responding normal tissues are well described using a linear-quadratic model in which an endpoint-specific quantity, the α/β ratio, offers a reliable way of describing these differences (8–9). Assuming a typical α/β value of 3.0 Gy for late normal tissue responses, a 15-fraction regimen reproducing the effects of 25 fractions of 2.0 Gy requires a reduction in total dose from 50 Gy to 42.8 Gy in fractions of 2.85 Gy

Reprint requests to: John Yarnold, Section of Radiotherapy, Institute of Cancer Research and Royal Marsden Hospital, Sutton SM2 5PT, UK. Tel: (+44) 208 661 3388. Fax: (+44) 208 661 3107; E-mail: john.yarnold@icr.ac.uk

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Table 1. Randomized clinical trials testing fraction size in adjuvant external beam radiotherapy

Trial year range	Test schedule (total dose/fraction no./treatment time (weeks) (fraction size))	No. of patients	% of patients undergoing breast-conserving surgery	% of patients prescribed a boost dose	Median follow up (months)
RMH/GOC 1986–1998	39.0/13/5.0 (3.0) 42.9/13/5.0 (3.3)	1,410	100	74.5	116
Ontario 1993–1996	42.5/16/3.2 (2.66)	1,234	100	0	> 132
START A 1999–2002	39.0/13/5.0 (3.0) 41.6/13/5.0 (3.2)	2,236	85	60.6*	61
START B 1999–2001	40.0/15/3.0 (2.67)	2,215	92	42.6*	72

Data compare designs of randomized clinical trials testing fraction size in adjuvant external beam radiotherapy to whole breast after local excision of early breast cancer. All trials used a control arm delivering 50 Gy in 25 fractions over 5 weeks.
* Breast conservation patients only.

(10). The linear-quadratic model predicts that the Ellis formula estimate of 45 Gy in 15 fractions is equivalent to 54 Gy in 2.0 Gy fractions, or to 56.3 Gy in the case of tissues like the brachial plexus with an assumed α/β value of 2.0 Gy. Thus, using the Ellis formula for estimating biologically isoeffective doses for late effects leads to an overdose of the tissues where these effects are dose-limiting.

What recent trials show

It should now be clear that it is always possible to identify a hypofractionated schedule equivalent to a conventionally fractionated regimen in terms of a specific late adverse effect. For fraction sizes in the range of 1 to 6 Gy, the linear-quadratic model appears to offer a reliable guide. The next question is how local tumor control is affected. It has long been assumed that most human tumors, especially squamous carcinomas, are relatively insensitive to fraction size (6, 11). If correct, the sharp reduction in total dose appropriate for late normal tissue effects leaves tumors effectively underdosed. As α/β value estimates from human data became available, it turned out that breast cancer and some other human malignancies appear to be more sensitive to fraction size than previously thought, comparable to the sensitivity of critical late reacting normal tissues (11–13). The underlying cell and molecular processes that explain these differences are not clear, but a mechanistic understanding is not needed to apply the linear-quadratic model safely and effectively. Over the last 20 years, several randomized trials involving a combined total of >7,000 women compared hypofractionated adjuvant radiotherapy to a standard regimen of 50 Gy in 25 fractions (Tables 1 and 2) (14–19). UK Royal Marsden Hospital/Gloucestershire Oncology Centre (RMH/GOC) and Standardisation of Breast Radiotherapy Trial A (START A) trials tested two dose levels of a 13-fraction regimen in terms of late adverse effects and tumor control; the study design allowed direct estimates of α/β for each trial (15–17). Based on a combined total of 278 local-regional tumor relapses in the two trials, the adjusted α/β value for tumor control was 4.6 Gy (95%

Table 2. Randomised clinical trials testing fraction size in adjuvant external beam radiotherapy

Trial	Dose schedule (total dose/fraction no./treatment time (weeks) (fraction size))	5-year rate for: Any change in breast appearance (%)	5-year rate for: Good/excellent breast cosmesis (%)	5-year rate for: Local tumour relapse (%)
RMH/GOC	50.0/25/5.0 (2.0)	35.4	–	12.1
1986–1998	39.0/13/5.0 (3.0)	27.4	–	14.8
	42.9/13/5.0 (3.3)	42.3	–	9.6
Ontario	50.0/25/5.0 (2.0)	–	79.2*	3.2†
1993–1996	42.5/16/3.2 (2.66)	–	77.9*	2.8†
START A	50.0/25/5.0 (2.0)	42.9	–	3.2
1999–2002	39.0/13/5.0 (3.0)	32.1	–	4.6
	41.6/13/5.0 (3.2)	43.6	–	3.2
START B	50.0/25/5.0 (2.0)	42.2	–	3.3
1999–2001	40.0/15/3.0 (2.67)	36.5	–	2.0

Results of randomised clinical trials testing fraction size in adjuvant external beam radiotherapy to whole breast after local excision of early breast cancer. All trials used a control arm delivering 50 Gy in 25 fractions over 5 weeks.
* 71.3% and 69.8% at 10 years.
† 6.7% and 6.2% at 10 years.

confidence interval [CI], 1.1-8.1), comparable to 3.4 Gy (95% CI, 2.3-4.5) for late change in photographic breast appearance. The two trials' results suggested a 13-fraction regimen delivered over 5 weeks can be as safe and as effective as 50 Gy in 25 fractions.

Results from the Ontario and START B trials are consistent with this interpretation. The Ontario trial compared 42.5 Gy in 16 fractions of 2.66 Gy (3.2 weeks) with 50 Gy in 25 fractions over 5 weeks (14, 19). Schedules are expected to be equivalent in terms of late normal tissue and tumor responses assuming an α/β value of 3.0 Gy for each and no influence of treatment time. Rates of breast cosmesis at a median follow-up of >11 years were virtually identical in both treatment arms, consistent with this expectation. Given that tumor control might conceivably be sensitive to a 2-week difference in treatment duration, it is not possible to estimate tumor fractionation sensitivity from these two trials. The UK START B trial compared 40 Gy in 15 fractions of 2.67 Gy (3.0 weeks) to 50 Gy in 25 fractions and recorded a lower rate of change in breast appearance after the 15-fraction regimen (hazard ratio [HR] = 0.83; 95% CI, 0.66–1.04; $p = 0.06$) (17). An HR of <1 for late adverse effects is likely to be real, since 40 Gy in 15 fractions is equivalent to 45.5 Gy in 2.0-Gy fractions if the α/β ratio = 3.0 Gy. In other words, 40 Gy in 15 fractions is gentler on late reacting normal tissues than 50 Gy in 25 fractions. The important question is whether it is also gentler on breast cancer. If the α/β value for tumor control is $\geq$10 Gy, tumor control should be inferior after such a large reduction in total dose (from 50 Gy to 40 Gy), unless there is a major effect of shortening overall time, but tumor control does not appear to be worse. Although there were only 65 local-regional tumor relapses in START B at the time of reporting, the HR for this endpoint was 0.79 (95% CI, 0.48–1.29), indicating similar rates of local-regional relapse after 40 Gy in 15 fractions compared with 50 Gy in 25 fractions. The residual imprecision indicated by the upper and lower 95% CI limits for the absolute difference between 40 Gy in 15 fractions and the control schedule in START B suggests that local-regional tumor relapse is unlikely to be more than 1% higher, and perhaps 1% or 2% lower, than after 50 Gy in 25 fractions.

It is important to understand that population-based estimates of the α/β value represent averages and that values are likely to vary within tumor types as well as between them. The goal of correlative research is to identify biomarkers of fractionation sensitivity that can be used in the clinic to stratify patients for hypofractionation. An unplanned subgroup analysis of the Ontario trial suggested tumor grade as a predictive factor for fractionation sensitivity, but a statistically more powerful analysis of the UK START fractionation trials did not confirm this (19–20). It has also been speculated that a hypofractionated schedule may leave less opportunity for reoxygenation and reassortment due to the lower number of fractions, but these processes are unlikely to play a major role in determining the outcome of radiation therapy for subclinical disease.

Results of clinical trials need to be applied to the population from which patients were recruited, but there is no clinical rationale for excluding underrepresented subgroups without very good cause. In our view, hypofractionation trials based predominantly on patients undergoing breast conservation surgery are informative for postmastectomy radiotherapy. Local tumor relapse risks in the two surgical groups are broadly comparable, according to the systematic overview of radiotherapy effects by the Early Breast Cancer Trialists Collaborative Group (21). For the 7,311 women entered into randomized trials testing radiotherapy after breast conservation surgery, the 10-year local relapse rate was 29.2% in node-negative patients and 46.5% in node-positive patients in groups allocated to surgery without radiotherapy. In 8,505 women with node-positive disease entered into trials testing radiotherapy after mastectomy and axillary clearance, local relapse at 10 years occurred in 29% of patients allocated to surgery without mastectomy. Contemporary rates of local relapse after breast conservation surgery and mastectomy are lower, due to the effects of adjuvant systemic therapies and other factors, but the principle remains that the two surgical groups of patients are comparable with respect to local relapse risk (22). In conclusion, on the basis of level I evidence from four clinical trials, there appears to be no reason to avoid modest hypofractionation for the adjuvant treatment of women requiring whole-breast or postmastectomy chest wall radiotherapy in any identifiable subset of subclinical breast cancers. However, there are some residual concerns expressed in the literature that are immediately addressed below.

Concerns relating to organs at risk

All four clinical trials of hypofractionation provided photographs of breast appearance and reported palpable breast induration. The most common change in breast appearance is shrinkage (atrophy), but edema, retraction, and telangiectasia also contribute. Change in breast appearance is a complex phenotype, and the α/β estimate represents a synthesis of different pathogenetic processes. Induration many years after radiotherapy usually signifies underlying fibrosis, but fat necrosis and breast edema contribute to induration scores in the early years. Neither photographic appearance nor induration records damage to underlying pectoral muscle or rib cage. Prospective patient self-assessments of symptoms, body image, and quality of life offer ways of assessing the overall impact of these changes.

The sensitivity of lung tissue to larger fractions is a concern, but lung doses delivered by tangential fields exceed tolerance in whatever fractionation schedule is used. It is unusual for patients to develop clinically significant pneumonitis or fibrosis following radiotherapy confined to the whole-breast (23, 24). Where the heart is concerned, the priority is to protect this organ from exposure regardless of radiation schedule, since there appears to be no safe lower dose limit, however fractionated (25, 26).

After irradiation of the axilla and/or supraclavicular fossa, there were no cases of brachial plexopathy recorded in 82

patients given 40 Gy in 15 fractions in the START B trial at a median follow-up of 6.0 years (interquartile range [IQR], 5.0–6.2 years) (18). The regimen is equivalent to 47 Gy in 2.0-Gy fractions if the α/β value for brachial plexus is 2.0 Gy or to 49 Gy in 2.0-Gy fractions, if $\alpha/\beta = 1.0$ Gy. If radiotherapy centers are confident that their technique is safe when prescribing 50 Gy in 25 fractions, there will be no excess risk after 40 Gy in 15 fractions by using the same treatment position, field arrangement, dosimetry, and reference point.

Concern about duration of follow-up

The hypofractionation trials were published at median follow-up times, varying from 5.1 years (IQR, 4.4–6.6 years) in START A to 9.7 years (IQR, 7.8–11.8 years) in the RMH/GOC trial, and >11 years in the Ontario trial (16, 17, 19). New adverse effects, both nonstochastic and stochastic, will appear for as long as patients are alive. However, the critical concern is not whether a complete description of adverse effects has been gained—it clearly has not. The important question is whether the fractionation sensitivities of responses developing at the time of reporting are representative of those developing over the entire life span of a patient.

Convincing evidence has been generated by European Organization for Research and Treatment of Cancer (EORTC) trial 22881–10882, where the relative risk of induration at 5 years after tumor bed boost compared to no boost was comparable to that at 10 or more years, even though absolute rates of induration increased in the interval (27). In the RMH/GOC fractionation trial, 5-year and 10-year actuarial estimates of the rates of 10 different late endpoints were presented (15). Figure 1 compares a scatter plot of 5-year versus 10-year relative risk estimates for several late effects in two of the RMH/GOC trial arms, 42.9 Gy in 13 fractions relative to 50 Gy in 25 fractions. As the incidence of various late toxicity endpoints were generally higher in the 42.9-Gy schedule, these relative risk values are generally significantly larger than 1. There is, however, no indication that the relative risk estimated at 10 years is higher than the risk estimated at 5 years. On the contrary, all except one of the data points fall below the identity line ($x = y$), consistent with a relatively earlier onset of late effects after more intense treatment, as previously observed for other data sets. This observation is statistically significant as shown with a two-tailed p value of 0.02 (sign test). In conclusion, it is unjustified to consider follow-up a factor limiting the interpretation of current hypofractionation trials (28).

Concern relating to "triple-trouble"

"Double trouble" was the term coined by Withers (29) to illustrate the significance of a hot spot in a dose plan that receives not only a higher total dose but also a higher dose per fraction. When fraction size is increased, the total dose needs to be reduced, as already described. However, due to the mathematical form of the linear-quadratic dose-effect relationship, hot spots will be penalized more severely in a hypofractionated treatment, a phenomenon called triple-trouble (30). One way to look at this is by noticing that the steepness of the dose-response curve increases with increasing dose per fraction (31) and that this will tighten the required dose uniformity. Table 3 shows the impact of dose in homogeneities on the dose intensity of hypofractionated regimens that are isoeffective with 50 Gy in 25 fractions at a 100% reference point for whole-breast radiotherapy. For distributions falling within International Commission on Radiation Units and Measurements recommendations (95%-107% of reference isodose), triple-trouble has no clinically relevant

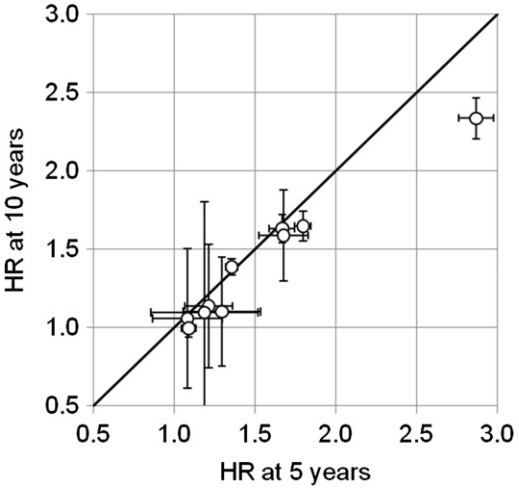

Fig. 1. Scatter plot of 5-year versus 10-year relative risk estimates for late adverse effects (expressed as hazard ratios [HR]) after 42.9 Gy in 13 fractions relative to 50 Gy in 25 fractions, in the RMH/GOC randomized breast radiotherapy fractionation trial (15). HRs for 10 late endpoints were analyzed: any change in breast appearance, marked change in breast appearance, clinical assessment of cosmesis, breast shrinkage, breast distortion, breast edema, induration, telangiectasia, arm edema, and shoulder stiffness. Error bars indicate the estimate ± standard error of 1, and the diagonal line is the identity line, $x = y$. The figure shows that HRs at 5 years for these 10 late adverse effects tend to be lower than the HRs for the same adverse effects at 10 years ($p = 0.02$, sign test).

Table 3. "Triple trouble" relative change in equivalent doses

Dose inhomogeneity	% equivalent dose in 2.0 Gy fractions at different fraction sizes				
	2 Gy	3 Gy	4 Gy	5 Gy	6 Gy
105%	107.1%	107.1%	108.0%	108.3%	108.5%
110%	114.4%	115.5%	116.3%	116.9%	117.3%
115%	121.9%	123.6%	124.9%	125.8%	126.5%

"Triple trouble" describes the relative change in the equivalent dose in 2-Gy fractions as a function of magnitude of hot spot and dose per fraction for hypofractionated schedules that are isoeffective at the 100% reference point. For example, if 2.0 Gy is prescribed to the 100% reference point, a 110% hot spot receives a 14.4% higher dose, so if 25 fractions are prescribed, the 100% hot spot receives 114.4% of 50.0 Gy = 57.2 Gy. $\alpha/\beta = 3$ Gy. Original plan was normalized to 2 Gy per fraction at the 100% isodose contour.

impact: the main effect is double-trouble, already present in a 2-Gy-per-fraction schedule. Even for hot spots of >110%, evidence presented later (see section "A Strong Volume Effect" below) suggests a marked volume response for late effects such as breast shrinkage and induration. In other words, the clinical consequences of high doses to small volumes are much less than high doses delivered to large volumes.

Other reasons for poor outcomes in the past

Inadequate downward adjustment to total dose was not the only factor contributing to poor historical results of hypofractionated breast radiotherapy. Additional factors included poor dosimetry and high skin doses delivered by low-energy beams, use of nonstandard reference points, delivery of medial and lateral tangential fields on alternate days, failure to detect gross off-axis dose in homogeneities, and position errors causing overlap at field junctions. With the benefit of hindsight, it is easy to see how a prescribed mid-plane dose to the breast of 2.5 Gy delivered as an applied dose of 3.5 Gy to medial and lateral tangential cobalt-60 fields on alternate days led to worse cosmetic results than if both fields had been treated every day (32). Equally, it is now obvious that changing patient position between fields greatly increases the risk of overlap at field junctions and subsequent harm to patients (33).

ACCELERATED FRACTIONATION MIGHT IMPROVE TUMOR CONTROL, BUT RECOVERY MUST BE COMPLETE BETWEEN FRACTIONS

Retrospective analyses of treatment delay raised the possibility that tumor proliferation may have been underestimated in the past, with an estimated loss of 5-year survival of 1.8 percentage points per month of delay over 1 to 6 months (34, 35). Other reports were consistent with this finding, but an overview failed to detect a significant effect (36–38). Treatment time has no impact on the risk of late adverse effects, assuming a 24-hour interfraction interval and complete repair (39, 40). Current protocols for accelerated hypofractionation to partial breast, using three-dimensional (3D) conformal radiotherapy, include twice-daily fractions separated by 6 hours (41). Whatever the schedule, a twice-daily schedule will have a greater biological effect due to incomplete recovery. In the National Surgical Adjuvant Breast and Bowel Project B-39 trial (41), 38.5 Gy in 10 fractions delivered by external beam conformal radiotherapy in twice-daily fractions, Monday to Friday of a single week, delivers the equivalent of 53 Gy in 2.0-Gy fractions, assuming complete repair and an α/β value of 3.4 Gy. If the recovery half-time for late effects is taken as the 4.4 hours estimated for subcutaneous fibrosis in the Continuous Hyperfractionated Accelerated Radiotherapy head and neck trial, the twice-daily schedule delivers the equivalent of 65 Gy in 2-Gy fractions. The satisfactory interim cosmetic results reported with this schedule suggest a significant volume effect in sparing late adverse effects (as discussed below) (42, 43).

DOSE ESCALATION HAS A MUCH GREATER EFFECT ON NORMAL TISSUE RESPONSES THAN ON TUMOR CONTROL AFTER WHOLE-BREAST RADIOTHERAPY

The standard sigmoid dose-response models used in radiation oncology are completely specified by two parameters: a position parameter (often taken as the dose for 50% incidence of the endpoint in question, the D50) and a steepness parameter, most often the normalized dose-response gradient, γ_{50} (44). The parameter γ_{50} is defined as the absolute percentage increment in response rate per 1% increase in total dose at the 50% response level (45). For normal tissues, typical values for γ_{50} lie between 2 and 4, so a 2.0-Gy increment in total dose above 50 Gy in 25 fractions to the breast, representing a 4% increase in total dose, causes an 8% to 16% absolute increase in the probability of an adverse effect around the 50% response level (46). Due to the sigmoid shape of the dose response, the increase in incidence of an adverse effect occurring in 10% of patients will be less dramatic. The γ_{10} lies between 0.5 and 1.2, and the expected absolute increase in response from a 4% increase in total dose will be 2% to 5% (47).

The dose response for control of subclinical tumor foci is even shallower due to much greater heterogeneity in terms of familiar factors known to influence tumor control probability, including variation in clonogen number, intrinsic radiosensitivity, hypoxia, and repopulation. Systematic overviews (21) of outcomes in patients treated with surgery alone suggest that an average of 70%, perhaps more, of patients have no residual disease in the breast at referral for radiotherapy, so the dose response curve is actually anchored at 70%, not 0%, local control (Fig. 2). Dose response data from the RMH/GOC and START A trials suggest a local γ value of

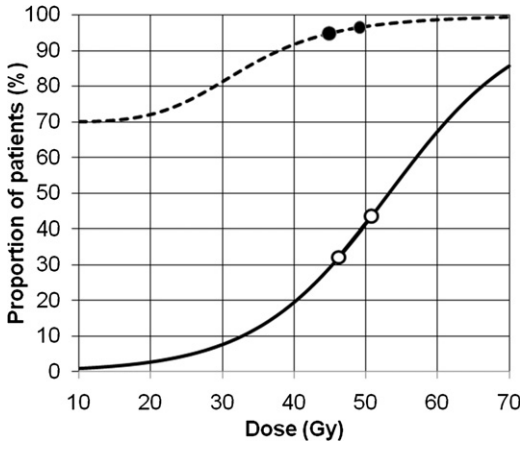

Fig. 2. Dose-response curves for local tumor control (dashed line) and for late photographic change in breast appearance (solid line) as a function of dose delivered in 13 fractions. The upper dashed curve is anchored at 70%, reflecting the proportion of patients predicted to have no residual disease requiring eradication by radiotherapy, *i.e.*, patients controlled by surgery alone. The two solid points represent local control estimated after randomization to 39.0 Gy and 41.6 Gy in 13 fractions. The lower solid line represents the dose response curve for late change in breast appearance in the same trial (17).

<0.2, so that a 2.0-Gy increase or decrease in total dose achieves a change in local tumor control of <1% (16,17).

There is a benefit here to be exploited in low-relapse-risk patients. A reduction in total dose is expected to reduce the complication risk by a much greater margin than local tumor control. An 8% reduction in dose intensity from 50 Gy to 46 Gy in 2.0-Gy fractions to the whole breast is expected to increase local tumor relapse by ≤1.5%. The absolute rate of mild/moderate adverse effects will fall by up to 30%, and for more marked effects occurring in up to 10% of cases, the expected reduction will be at least 4%. These estimates are consistent with the outcome of the UK START B trial, in which a 15-fraction regimen equivalent to 46 Gy in 23 fractions in terms of late adverse effects was tested without any significant inferiority in terms of tumor control (18).

It ought to be possible to take advantage of the differing gradients of the dose response curves for late adverse effects and tumor control to improve the therapeutic ratio in areas of the breast at low risk of tumor relapse. This possibility is being tested by reducing dose intensity outside the index quadrant in the UK Intensity Modulated and Partial Organ Radiotherapy (IMPORT) LOW trial of partial breast radiotherapy in women >50 years old with unifocal invasive ductal carcinoma (Fig. 3a and b). Patients are eligible if they are considered to have an annual risk of local recurrence of <1%: those who are ≥50 years old, have any grade of unifocal invasive ductal carcinoma ≤30 mm, and have 1 to 3 positive lymph nodes (48). Compared to 15 fractions of 2.67 Gy delivered to the whole breast (control), test arms 1 and 2 deliver 15 fractions of 2.4 Gy and zero dose, respectively, outside the index quadrant. Applying an α/β value of 3 Gy, test arm 1 delivers the equivalent to 40 Gy in 20 fractions to this volume, close to the quasi-threshold dose for nonstochastic late adverse effects. In contrast, improving tumor control by dose escalation in higher risk patients depends on a very strong volume effect, a requirement that will be considered next.

A STRONG VOLUME EFFECT IS NEEDED TO COMPENSATE FOR THE ADVERSE EFFECTS OF DOSE ESCALATION, HOWEVER FRACTIONATED

The volume effect for a given endpoint is tested by comparing adverse effects after randomization to different volumes of breast tissue prescribed the same dose. If a volume effect exists, it may vary according to the endpoint chosen. Indirect measures of volume effect for induration can be gained from several sources, including (*i*) a retrospective study of nonrandomized variation in interstitial brachytherapy volumes and (*2*) a randomized EORTC trial of boost dose versus no-boost dose following whole-breast radiotherapy (49–50). In the retrospective

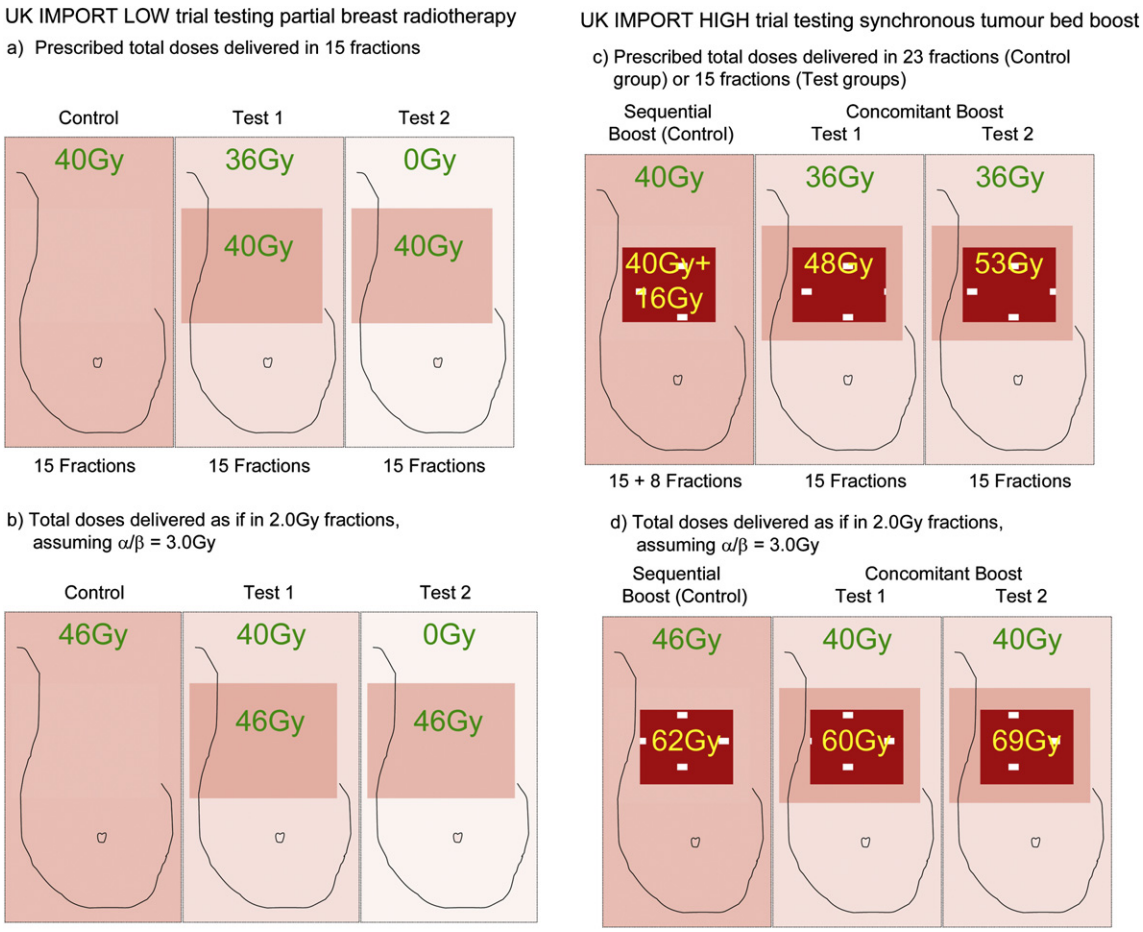

Fig. 3. Schemas of UK intensity modulated and partial breast (IMPORT) LOW and HIGH trials with women treated by breast conservation surgery.

study of brachytherapy volumes, low-dose-rate iridium implantation given as boost therapy after tumor excision and whole-breast radiotherapy to 404 patients was associated with a four-fold increase in risk of fibrosis (induration) for each 100 cm^3 increment in boost volume, suggesting a very steep volume response (49). In the EORTC study of electron boost therapy, univariate analysis of cosmesis in 364 patients treated with boost volumes of $\leq$200 cm^3 compared to >200 cm^3 reported a HR of 0.45 (95% CI, 0.29-0.76), suggesting a shallower volume response (50). A measure of the volume effect can also be derived by comparing dose responses (γ values) for late adverse effects following a randomized boost dose to the tumor bed compared with the same dose increment to the whole-breast volume. This test was performed with 723 patients entered into the RMH/GOC fractionation trial, randomized after whole-breast radiotherapy into those who would not receive a tumor bed boost versus those who would receive a boost dose of 15.5 Gy (100%) in 7 fractions via a direct electron field, typically 7 to 10 cm diameter and 8 to 12 MeV energy (15). In this trial, 27.5% of patients randomized to the no-boost group developed moderate or marked induration at 10 years compared to 44.5% of those randomized to receive boost therapy, generating a γ value of 0.5. The same trial randomized 940 patients to two dose levels of whole-breast radiotherapy using a 13-fraction regimen (Table 1), generating a γ value for induration of around 1.4 at 10 years after randomization. The volume and proportion of breast irradiated with electron boost can only be estimated crudely based on the above parameters, but values correspond to about 200 cc^3 and 25%, respectively. For this partial volume, the slope of the dose response for clinically assessed induration is about one-third that of whole-breast radiotherapy.

The scope for exploiting a dose-volume effect in dose escalation is undergoing testing in the UK IMPORT HIGH trial, designed for patients needing a tumor bed boost dose after breast conservation surgery, appropriate adjuvant systemic therapy, and whole-breast radiotherapy. The trial design compares sequential versus simultaneous integrated boost delivered to a standardized target volume (Fig. 3c and d). The test arm 1 boost dose is equivalent to that of the control arm in terms of late adverse effects, assuming an α/β value of 3.0 Gy. Thus, 40 Gy in 15 fractions plus sequential 16 Gy in 8 fractions (control) and 48 Gy in 15 fractions (test arm 1) to identical tumor bed volumes are each equivalent to 60 Gy in 30 fractions. If rates and severity of induration are comparable in both arms, this shows that a reduction in dose from 40 Gy in 15 fractions to 36 Gy in 15 fractions outside the index quadrant fails to increase tolerance inside the boost volume. If the induration score in test arm 2 is comparable to that in the control arm, it suggests a large and quantifiable sparing effect from reducing the dose to low-risk volumes. The reality may lie in between.

WHAT ARE THE LIMITS OF HYPOFRACTIONATED WHOLE-BREAST RADIOTHERAPY?

It is unlikely that a 15- or 16-fraction regimen represents the limits of hypofractionation for whole-breast radiotherapy. The UK prospective randomised clinical trial testing 5.7 Gy and 6.0 Gy fractions of whole breast radiotherapy in terms of late normal tissue responses and tumour control (FAST trial) (51) randomized 915 women 50 years old or older with node-negative tumors following breast conservation surgery to receive whole-breast radiotherapy delivered using 3D dosimetry to a total dose of 50 Gy in 25 fractions (control) versus 28.5 or 30 Gy in 5 once-weekly fractions of 5.7 or 6.0 Gy and no tumor bed boost. Assuming α/β = 4.0 Gy, the dose levels are equivalent to 46 Gy and 50 Gy in 2.0 Gy fractions, respectively. An interim analysis of moderate/marked breast shrinkage (photographic assessment) generated an α/β of 2.4 Gy (95% CI, 1.0-3.9) consistent with estimates generated by the START A trial (51). A schedule of 30 Gy in 5 fractions over 15 days to the whole breast using 3D dosimetry reported very mild acute reactions and satisfactory 2-year outcome in terms of change in breast appearance and induration compared to a matched sample of patients treated to 50 Gy in 25 fractions (52). This schedule is too intense to form the basis of a 5-day schedule, given current estimates of α/β values derived from the FAST and START trials, but a 5-day course of whole-breast radiotherapy that delivers 1 fraction per day can certainly be identified that is equivalent to standard fractionation in terms of late adverse effects in the breast (but not the lymphatic pathways). If the α/β value for late adverse effects is between 2 and 3 Gy and that for tumor control is between 4 and 5 Gy, a small loss of therapeutic gain might be compensated for by a time factor for tumor control when treatment times are compressed from 5 weeks to 1 week.

CONCLUSIONS

Recent randomized trials justify the routine use of modest hypofractionation for adjuvant whole-breast radiotherapy in women with early breast cancer. The standard UK schedule of 40 Gy in 15 fractions is gentler on normal tissues than 50 Gy in 25 fractions, without evidence of inferior local tumor control. This schedule, or 42.5 Gy in 16 fractions, can be recommended as safe and effective alternatives to 50 Gy in 25 fractions for whole-breast or postmastectomy chest wall radiotherapy.

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