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How Low Can You Go? The Radiobiology of Hypofractionation

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Abstract

Hypofractionated radical radiotherapy is now an accepted standard of care for tumour sites such as prostate and breast cancer. Much research effort is being directed towards more profoundly hypofractionated (ultrahypofractionated) schedules, with some reaching UK standard of care (e.g. adjuvant breast). Hypofractionation exerts varying influences on each of the major clinical end points of radiotherapy studies: acute toxicity, late toxicity and local control. This review will discuss these effects from the viewpoint of the traditional 5 Rs of radiobiology, before considering non-canonical radiobiological effects that may be relevant to ultrahypofractionated radiotherapy. The principles outlined here may assist the reader in their interpretation of the wealth of clinical data presented in the tumour site-specific articles in this special issue.

Key words: Hypofractionation; radiobiology

Introduction

Fractionated radiotherapy delivers a total radiation dose, to a target volume, in a series of smaller dose increments, termed fractions. Conventional fractionation refers to treating with one fraction per day, Monday to Friday, with a dose per fraction of 1.8–2 Gy. The choice of 2 Gy by convention evolved empirically in the early 20th century, based largely on the intensity of early skin reactions and local control rates in squamous cell carcinomas of the head and neck (HNSCC) and uterine cervix [1]. Hypofractionation is defined as >2 Gy/fraction. Here we refer to moderate hypofractionation (>2 to <5 Gy/fraction) and ultrahypofractionation (≥5 Gy/fraction). These thresholds are biologically arbitrary, but are useful in the discussion of clinical trials.

Hypofractionation is an older concept than many oncologists realise. A moderately hypofractionated schedule for laryngeal cancer (50 Gy/16 fractions) was developed in Manchester during the 1930s and is still in use today. In the decades following, there was heterogenous use of hypofractionation in the clinic. A 1989 UK survey revealed dozens of different regimens used for common radical and palliative indications [2]. Recent homogenisation of practice towards moderately hypofractionated schedules (e.g. for breast cancer and prostate cancer [3,4]) was achieved through randomised comparison of schedules derived from those in common usage. These recent studies confirm that common cancers vary more than previously assumed, in terms of sensitivity to fraction size.

Current ultrahypofractionated schedules owe as much to empirically derived historical data as to novel radiobiological derivation. An ultrahypofractionated regimen for prostate cancer (36 Gy/six fractions, 3 weeks) was in use at St Thomas's Hospital during the 1960s, with efficacy and toxicity similar to contemporary reports [5]. For adjuvant breast cancer, an ultrahypofractionated approach (32.5 Gy/five fractions, weekly) was developed in France during the 1980s [6]. In both cases, these regimens were developed with tolerability for elderly patients as a key motivating factor.

Other articles in this hypofractionation special issue discuss the accumulated clinical evidence for the use of hypofractionation in specific tumour sites. Here we look at the underpinning radiobiological rationale for hypofractionation and consider how triallists might best approach future hypofractionated trial designs.

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Clinical Considerations of Hypofractionation

Trials of hypofractionated radiotherapy will typically report acute toxicity, late toxicity and tumour control as the core clinical outcomes of interest. For the adoption of a new hypofractionated standard of care, trial-level results for all three must be acceptable. We therefore proceed to examine each of these in detail, from a hypofractionation perspective.

Hypofractionation and Acute Toxicity

We start with acute toxicity, as it is the most straightforward clinical outcome to consider. Hypofractionated regimens will commonly alter overall treatment time (OTT) and total dose, but may also change volume, due to the use of more conformal dose delivery, such as stereotactic body radiotherapy (SBRT).

Overall Treatment Time

Increasing OTT was recognised very early on to reduce acute toxicity, with Coutard in the 1930s reporting better tolerability of HNSCC regimens over 4–6 weeks, as compared with 2–3 weeks [7]. Reducing OTT without altering dose fractionation (pure acceleration), by using six rather than five daily fractions per week, increased HNSCC radiotherapy acute toxicity in the DAHANCA 6/7 [8] and IAEA-ACC [9] studies. Assuming the use of daily fractions, a hypofractionated regimen OTT will be shorter than its conventionally fractionated comparator, potentially worsening acute toxicity, although this can be offset by reducing total dose, as discussed below.

Biologically, acute effects occur in tissues with a rapidly proliferating cell compartment (e.g. gut lining), where radiation inhibits functional cell replacement from surviving stem cells [10]. Repopulation rates increase during radiotherapy, attenuating acute toxicity over more protracted courses. However, other factors may influence this. In 1995, Nyman and Turesson [11] reported a trial of 49 breast cancer patients receiving adjuvant bilateral parasternal electron irradiation (50 Gy/25 fractions) as a component of adjuvant radiotherapy. In a self-controlled design, each patient had the right field treated daily (5 weeks) and the left field treated twice daily (8 h intervals, 2.5 weeks). Surprisingly, acute toxicity was less with 2.5 weeks of treatment, suggesting that reduced redistribution (a factor discussed further below) may attenuate acute responses.

Equivalent Dose in 2 Gy Fractions

Hypofractionated regimens do not purely accelerate treatment; this is accompanied by an alteration of the equivalent dose in 2 Gy fractions (EQD2), which accounts for the non-linear changes in tissue response with increasing dose per fraction. This is commonly expressed using the linear-quadratic model [12]:

$$EQD2 = d \times n \times \left(\frac{d + \alpha/\beta}{2 + \alpha/\beta}\right)$$

Here, d is the dose per fraction, n is the number of fractions and the α/β ratio describes the relative fraction size sensitivity of an end point (tumour or normal tissue). Lower α/β ratios imply a greater change in EQD2 through hypofractionation. A relatively high α/β ratio of 10 Gy is commonly applied to acute toxicity reactions, although human studies are few [1]. A similarly high α/β ratio is usually applied to more rapidly dividing tumours, such as HNSCC or cervical SCC. However, lower α/β ratios are more characteristic of late toxicities and certain tumours, such as breast and prostate cancers. This means that hypofractionated regimens designed for isoeffectiveness to an end point with a low α/β ratio (e.g. late toxicity) will have a lower EQD2 for acute toxicity.

Hypofractionation therefore typically produces two competing effects on acute toxicity: increasing it through acceleration and decreasing it through lower EQD2. As an example, the FAST-Forward study examined acute toxicity for a moderate hypofractionated regimen (40 Gy/15 fractions/3 weeks) versus two ultrahypofractionated regimens (27 or 26 Gy/five fractions/1 week) [13]. The $EQD2_{\alpha/\beta=10}$ for these regimens (42.2 $Gy_{\alpha/\beta=10}$ versus 34.7/32.9 $Gy_{\alpha/\beta=10}$) compares with observed grade 3+ Radiation Therapy Oncology Group (RTOG) toxicity 13.6% versus 9.8/5.8%. Here, acute toxicity is reduced more by the EQD2 reduction with ultrahypofractionation than any countervailing increase from reduced OTT.

Volume and Acute Toxicity

Irradiated normal tissue volume is also an important predictor of acute toxicity severity. That larger head and neck radiotherapy fields cause worse mucositis has long been understood [7]. Clearly, SBRT has enabled safe delivery of ultrahypofractionated doses by minimising irradiated normal tissue volumes, with highly conformal radiotherapy. Trials comparing ultrahypofractionation (as SBRT) to conventional fractionation (e.g. PACE-B [14]) therefore change both dose fractionation and irradiated normal tissue volume. This should be remembered when interpreting toxicity (acute and late) from such trials.

Hypofractionation and Late Toxicity

EQD2 and Late Toxicity

Late toxicity end points, often dose-limiting, are characterised by lower α/β ratios than acute toxicities [1]. This greater fraction size sensitivity makes the assumed α/β ratios for late toxicity very important in clinical trial designs testing hypofractionation.

The influence of α/β ratio assumptions can be seen by designs for two phase III trials of moderately hypofractionated radiotherapy in prostate cancer. The HYPRO trial (78 Gy/39 fractions versus 64.6 Gy/19 fractions) was designed as isotoxic for a late normal tissue (rectal and bladder) α/β ratio of 4–6 Gy [15], an estimate derived from animal data [16]. Subsequent gastrointestinal and genitourinary toxicity was worse for the hypofractionation arm, with higher grade 3+ genitourinary toxicity (19% versus 12%, $P = 0.021$). Unfortunately, disease control was also not improved with the

escalated EQD2 in the hypofractionation arm. This highlights the potential risk of using animal-derived normal tissue α/β ratio estimates in trial design.

Accurate human α/β ratio estimates are therefore of interest to predict toxicity from novel hypofractionated schedules. Table 1 summarises some recent human estimates for late normal tissue end points. When assuming a late toxicity α/β ratio for trial design, the lowest estimate (producing the largest EQD2) is most conservative. Researchers reporting hypofractionation trials might consider fitting α/β ratios for important end points, to improve human estimates. Consideration of this interest at the trial design stage can make such fitting easier. The unique START-P and -A breast trial design compared a 25-fraction regimen with two investigational 13-fraction hypofractionated regimens, with all treatment delivered over 5 weeks. This allowed investigators to derive direct estimates of α/β for normal tissue end points and tumour control, unconfounded by differences in OTT [3].

Repair

Inter-fraction repair time has a significant influence on late toxicity. The Nyman and Turesson study [11] (discussed above) found late skin telangiectasia were much more frequent with twice daily versus once daily treatment (very marked: 17% versus 0%), indicating 8 h as insufficient for sublethal radiation damage repair in human dermal capillary endothelium.

Repair times are thought of in half-lives; e.g. 5 half-lives ≥95% repair. Insufficient inter-fraction interval for complete repair has generally been more of a consideration for hyperfractionated, accelerated schedules, such as CHART for HNSCC (54 Gy/36 fractions/12 consecutive days versus 66 Gy/33 fractions/6.5 weeks) [27]. In CHART, despite a

Table 1
Some recent human estimates of late normal tissue α/β ratios

Organ Author [reference]	Number of patients	End point	α/β ratio (Gy)	95% confidence interval (Gy)
Bladder				
Fiorino *et al.* [17]	1176	CTCAE incontinence ≥ grade 3	0.8	0.1–4.8
	1176	CTCAE haematuria ≥ grade 3	0.7	0.0–1.8
Breast				
Yarnold *et al.* [18]	1202	Breast photograph: any change	3.6	1.8–5.4
	1202	Breast photograph: marked change	2.9	1.0–4.8
	806	Breast induration	3.1	1.8–4.4
	806	Cosmesis (fair/poor)	3.8	1.4–6.3
	806	Breast shrinkage	4.7	1.0–8.6
	806	Breast distortion	3.1	1.0–5.8
	806	Breast oedema	2.3	1.0–4.5
	806	Induration	3.1	1.8–4.4
	806	Telangiectasia	5.1	1.0–9.5
	806	Arm oedema	2.2	1.0–7.9
	806	Shoulder stiffness	1.8	1.0–3.6
Brunt *et al.* [19]	615	Breast photograph: any change	2.7	1.5–3.9
	774	Any clinical toxicity	2.5	1.8–3.3
	774	Breast shrinkage	2.7	1.9–3.5
	774	Induration	1.6	0–4.4
	774	Telangiectasia	3.1	2.3–3.9
Brunt *et al.* [20]	1309	Breast photograph: any change	1.8	1.1–2.4
	3975	Moderate/marked clinical toxicity	1.7	1.2–2.3
	1774	Patient reported breast change	2.3	1.8–2.9
Lung				
Scheenstra *et al.* [21]	64	SPECT perfusion reduction	1.3	0.5–2.1
Rectum				
Brenner [22]	Trial level data (8 studies)	RTOG rectal ≥ grade 2	5.4	3.9–6.9
Marzi *et al.* [23]	162	RTOG rectal ≥ grade 2	2.3	1.1–5.6
Tucker *et al.* [24]	509	RTOG rectal ≥ grade 2	4.8	68% confidence interval 0.6–46
Brand *et al.* [25]	2006	Rectal bleeding ≥ grade 2	1.7	0.7–3.0
	2021	Stool frequency ≥ grade 2	2.7	0.9–8.5
	2146	Proctitis ≥ grade 2	2.7	1.3–15.1
	2199	Sphincter control ≥ grade 1	3.1	1.4–9.1
	2206	Stricture/ulcer ≥ grade 1	2.5	0.9–8.2
Spinal cord				
Jin *et al.* [26]	Trial level data (25 studies)	Heterogenous: myelopathy	3.7	2.2–8.2

CTCAE, Common Terminology Criteria for Adverse Events; RTOG, Radiation Therapy Oncology Group; SPECT, single photon emission computed tomography.

reduced total dose, late toxicity was not markedly improved; from this, Bentzen *et al.* [28] calculated repair half-lives of (e.g.) 4.9 h for laryngeal oedema. The relevance to hypofractionation is that ultrahypofractionated regimens have sufficiently few fractions to enable every other day, or even more protracted, delivery [29]. A repair half-life of 4.9 h implies about 95% inter-fraction repair for a once daily regimen, versus >99.9% repair for every other day. This must be balanced against any tumour repopulation considerations (discussed below) and is a consideration for those designing hypofractionated trials.

A slow repair component has also been postulated, Turesson and James [30] suggested a $T_{1/2}$ of about 40 days for skin telangiectasia. This slow repair was suggested as an explanation for toxicity mitigation with time, given that repopulation was excluded through absence of mitotic figures. Such detail has proven important as a possible explanation for skin toxicity being slightly higher than anticipated in the isotoxically designed 27 Gy arm of the FAST-FORWARD trial [31].

Volume and Late Toxicity

Similar to acute toxicity, the volume of irradiated normal tissue is important in determining late toxicity. The IMPORT-LOW study demonstrated this, showing reduced late toxicity with partial versus whole breast adjuvant radiotherapy [32]. This applies principally to parallel architecture organs, rather than serial, where a maximum point dose might dominate.

Individual Patient Factors

As mentioned earlier, hypofractionated regimens have sometimes emerged as options for the elderly, where concerns such as cosmetic considerations may vary. Today in the UK, the most extremely hypofractionated skin schedules (18–20 Gy/one fraction) are recommended for small skin carcinomas in the elderly [33].

Genetic predisposition to late toxicity is a field that may expand rapidly, with several consortia undertaking genomic sequencing of large numbers of patients undergoing radiotherapy (e.g. Radiogenomics Consortium [34], REQUITE [35]). Through large data methods, such as genome-wide association studies, genomic polymorphisms can be identified that modulate late toxicity [34]. Incorporation of such genomic polymorphisms into clinical/dosimetric 'big data' predictive modelling may improve the prediction of normal tissue toxicities [36].

Hypofractionation and Tumour Control

EQD2 and Tumour Control

Hypofractionated regimens have been particularly successful for tumours such as breast and prostate cancers, which exhibit lower α/β ratios than the typical 10 Gy assumption (e.g. for HNSCC). The lower α/β ratio means hypofractionation exerts a relatively greater increase in EQD2, which is critical to tumour control. Therapeutic gain through hypofractionation can be achieved in such circumstances. In the case of prostate cancer, tumour α/β ratio (1.6 Gy, 95% confidence interval 1.3–2 Gy [37]) is lower than late rectal α/β ratios, meaning hypofractionation increases tumour EQD2 proportionally more than late rectal EQD2.

Non-isoeffective EQD2 Doses in Hypofractionation Trials

Even for tumours with higher α/β ratios, such as non-small cell lung cancer (NSCLC) [38], investigational hypofractionated schedules may represent EQD2 dose escalation. The CHISEL trial randomised 101 inoperable stage I NSCLC patients between ultrahypofractionated SBRT (48–54 Gy/three to four fractions/2 weeks) versus conventional (66 Gy/33 fractions or 50 Gy/20 fractions; daily) schedules [39]. Improved freedom from local failure with ultrahypofractionation (hazard ratio = 0.32, 95% confidence interval = 0.13–0.77) may in part reflect higher ultrahypofractionation EQD2s (88–126 $Gy_{\alpha/\beta=10}$ versus 52–66 $Gy_{\alpha/\beta=10}$). The possible impact of reduced OTT on tumour control after ultrahypofractionation will be considered later.

The Importance of Planning Processes in Stereotactic Body Radiotherapy Trials

The CHISEL planning processes further increased SBRT dosage. Conventional treatment was prescribed to the 100% reference point in the planning target volume (PTV) centre, whereas SBRT was prescribed to the 70–80% isodose at the PTV surface. Both had minimum PTV coverage by 95% isodose. Together, this means SBRT PTV doses of 95% to about 140% of prescription, whereas conventional treatment would typically be 95–107% per ICRU recommendations. Clinicians should be alert to the differences such planning techniques can make to tumour and normal tissue doses.

Uncertainty in EQD2 Calculations and Radiosensitivity

The CHISEL trial had higher EQD2s in the ultrahypofractionation versus standard of care arms. However, for prostate cancer, an appealing hypofractionation trial design is isoeffectiveness, aiming for equal tumour EQD2 between arms, with lower normal tissue EQD2, resulting in therapeutic gain. Although isoeffectiveness success was seen with moderate hypofractionation (e.g. PROFIT trial [40]), issues have been found at the extreme end of ultrahypofractionation. Morton *et al.* [41] randomised 170 low/intermediate-risk prostate cancer patients to high dose rate (HDR) brachytherapy in either 1×19 Gy (EQD2 111 $Gy_{\alpha/\beta=1.5}$) or 2×13.5 Gy, 1 week apart (EQD2 116 $Gy_{\alpha/\beta=1.5}$). (It is worth noting that, similar to SBRT, this is a minimum dose aim to the PTV, with much higher doses [>200%] present in the PTV.) Despite similar EQD2s and dosimetry, local failure was much worse with the single fraction (29% versus 3%).

This surprising result is of interest, given our reliance on the linear-quadratic model in hypofractionation EQD2 estimation. Could the actual prostate cancer α/β ratio estimate differ from the assumed 1.5 Gy? A large meta-analysis ($n = 13\,384$) supports a prostate cancer α/β ratio of 1.6 Gy (95% confidence interval 1.3–2.0 Gy) albeit in the range of 1.8–6.1 Gy/fraction [37]. As a note of caution, this α/β ratio estimate is derived from external beam radiotherapy data rather than brachytherapy data, where doses per fraction may be higher. Also, heterogenous brachytherapy dose

distributions make α/β ratio estimation highly sensitive to dose calculation methodology [42]. If, however, we accept the α/β ratio (radiotherapy fraction size sensitivity) as accurate, other reasons for differing tumour control rates using similar EQD2 dose fractionations must be considered. The other 4 Rs of radiobiology could of course alter the effective tumoricidal dose, e.g. repopulation in HNSCC [12], but adjustment of EQD2 to account for the 4 other Rs is uncommon. In this study, reduced redistribution and reoxygenation with single-fraction treatment may have contributed to the greater local control failure rate. We therefore turn to consider these other Rs of radiobiology and their relationships with hypofractionation.

Redistribution

Cells progressing through the cell cycle exhibit varying radiosensitivity [43]. Fractionation allows multiple chances to irradiate cells in their more radiosensitive phases (e.g. G2/M). Hypofractionation diminishes the role of redistribution, with it having no relevance to single-fraction treatments. The loss of redistribution with one- (versus two-) fraction prostate cancer HDR brachytherapy may have contributed to lower local control rates. However, it would be surprising if redistribution of cells in a single inter-fraction interval explained a 25% difference in local control.

Reoxygenation

In a laboratory setting, using photons, we see enhanced killing of oxygenated versus hypoxic tumour cells [1]. Fractionated radiotherapy is thought to permit reoxygenation of initially hypoxic tumour cells over the course of treatment, enhancing cell kill. Hypofractionation therefore risks diminishing such reoxygenation benefit; although it has been proposed that longer inter-fraction intervals with ultrafractionation may improve this [44]. A total absence of reoxygenation with single-fraction treatment may have contributed to the reduced efficacy with one-versus two-fraction HDR brachytherapy for prostate cancer, discussed above. Functional imaging provides an opportunity to assess tumour hypoxia, with the potential to vary the total dose and dose per fraction for radiotherapy treatments [45].

More tangibly, multiple major radiotherapy trials have had success modulating hypoxia. For example, adding agents to radical radiotherapy for bladder cancer: BC-2001 (mitomycin-C/5-fluorouracil) [46] and BCON (carbogen/nicotinamide) [47]. If hypofractionated regimens do suffer a penalty from insufficient reoxygenation time, then trials combining hypofractionation and hypoxia modulation may be fruitful. Recent meta-analysis of BCON and BC-2001 reassuringly showed moderate hypofractionation (55 Gy/20 fractions) had a lower risk of local failure than conventional radiotherapy (66 Gy/33 fractions) [48].

Repair

It is probable that tumour α/β ratios vary between patients with the same cancer type. Indeed, given intra-tumoural heterogeneity, different tumour cells within one tumour may have differential sensitivity to fraction size. Normal tissue/cellular studies suggest that the use of homologous recombination to repair radiation-induced DNA damage results in loss of fraction size sensitivity [49,50]. Similar to normal tissue, it has been shown that tumours defective in p53 are less sensitive to fraction size [51]. It has been proposed to use such genomic markers of tumour radiosensitivity to guide the dose for tumours such as breast cancer [52], although trial evaluation is awaited. Similarly, it is plausible that genomic markers of tumour fraction size sensitivity (e.g. P53/BRCA1&2) might permit a personalised α/β ratio for selection of dose fractionation [53]. Trials of hypofractionation would be advised to consider a collection of tumour and normal tissue to permit investigation of gene-based fraction-size sensitivity markers.

In addition to inter-fraction repair, intra-fractional tumour repair (potentially reducing biological effect) may need to be considered with the use of protracted fraction deliveries (e.g. >30 min via platforms such as CyberKnife) [54].

Repopulation

Repopulation of tumour cells, known to contribute to the failure of protracted radiotherapy courses [55], provides a strong motivation for acceleration via hypofractionation. Pure acceleration improves HNSCC local tumour control, as shown by DAHANCA 6/7 [8] and IAEA-ACC [10] (discussed earlier). It is possible that reduced OTT contributed to the improved local control seen with ultrahypofractionation in the CHISEL trial [39]. Given that accelerated repopulation is not thought to begin until several weeks into treatment [55], the relevance of repopulation in comparing moderately- and ultrahypofractionated regimens is diminished. However, it may be relevant if contemplating protracted (e.g. weekly) schedules.

Beyond EQD2 and the 5 Rs

EQD2 and the 5 Rs of radiotherapy principally concern the direct process of radiotherapy-induced tumour cell kill, i.e. DNA damage. Other indirect methods of radiation-induced cell kill have been proposed, such as vascular damage and immune stimulation. The need to invoke such mechanisms has stemmed from suggestions that tumour control following ultrahypofractionated radiotherapy exceeds that expected by DNA damage alone [56]. If present, indirect cell kill may mean the linear-quadratic model underestimates tumour control at high doses per fraction. However, others have suggested that the standard linear-quadratic model can account for the observed tumour control rates, e.g. for NSCLC SBRT [57]. Furthermore, we have seen in the one-versus two-fraction HDR brachytherapy case, tumour control may be overestimated by linear-quadratic model prediction, the opposite effect to that expected with indirect cell kill [41]. We will be fairly brief, given these topics have recently been reviewed in detail [56,58].

Vascular Injury

Even a decade ago, it had been shown by many studies, utilising a wide array of assays, that larger doses of radiation (>10 Gy) can cause vascular damage resulting in tumour cell kill [59]. This is therefore hypothesised to contribute to the efficacy of ultrahypofractionated radiotherapy [56].

Vascular injury and induced hypoxia appear as early as day 1 post-radiotherapy [60], giving further impetus to consider hypoxia modification for multi-fraction ultra-hypofractionated treatments.

Immune-mediated Cell Kill

Evidence that the immune system plays a role in radiotherapy-induced tumour control has existed for decades, but the most appropriate dose fractionation to exploit the synergy is not known. In 1964, Haddow and Alexander [61] reported that irradiated tumour antigen injection enhanced subsequent single-dose X-ray tumour growth delay. Unfortunately, translation of such studies into clinical application has proved challenging, which has been theorised to be due to large radiotherapy fields inhibiting the host immune response [58]. With much tighter dose distributions, it is possible that immune responses may play a larger role in the response to ultra-hypofractionated SBRT.

The recent success of immunotherapy in systemic cancer control has led many to the hypothesis that concurrent immunotherapy (e.g. PD-1/PDL-1 inhibition) might enhance radiation-related cell kill or vice versa. Although some early concurrent phase III trials have not succeeded (e.g. [62,63]), a better understanding of the mechanistic basis of differences in immune response according to fraction size may allow optimal selection of radiotherapy + immunotherapy combinations [64].

Conclusions

We hope that this piece will give readers a sense of some of the radiobiological issues underpinning hypofractionation. It is important to note that our understanding of these issues is imperfect, so those conducting hypofractionation studies should be conservative in their approaches. Much early hypofractionation work was carried out due to reasons of resource scarcity [7] or patient factors preventing intensive daily treatments [6]. Investigators must be particularly careful when investigating novel fractionation regimens for an indication that already has satisfactory treatments available. Consideration should be made to initially testing safety and efficacy in patients for whom standard treatment is undesirable. Thereafter, there is no substitute for the randomised trial, in determining the comparative safety and efficacy of any novel regimen. Given the uncertainties we have in underpinning the radiobiology of hypofractionation, investigators are encouraged to consider designs that might further our knowledge. Secondary randomisations might test different schedules or the addition of hypoxia modifiers/immunotherapy. Translational substudies might include genomic analyses (normal tissue and tumour), functional imaging for hypoxia or collection of blood/tissue for immune markers. Careful thought in trial design will allow us to maximise the contribution of each randomised patient, towards the goal of optimal hypofractionated radiotherapy.

Conflict of interest

The authors declare no conflict of interest.

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