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Editorial

When Less is More: The Rising Tide of Hypofractionation

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Hypofractionation, defined as the delivery of radiation in >2 Gy fractions, is not a new phenomenon. Hypofractionated regimens have long been used as convenient schedules for palliation, with use in the radical setting generally reserved for patients in whom tolerance of conventionally fractionated schedules was of concern. Ultra-hypofractionation, referring to the use of fraction size ≥5 Gy, has become increasingly fashionable over recent years and is now an accepted standard of care for many indications. The rapid rise of ultra-hypofractionation has been facilitated by advances in radiotherapy technology and image guidance enabling high precision radiation delivery, most notably the advent of stereotactic ablative radiotherapy (SABR).

So, what makes ultra-hypofractionated radiotherapy so attractive? On a practical level, reducing treatment attendances is appealing to both patients and healthcare providers. This has been of particular relevance during the COVID-19 pandemic, during which hypofractionated regimens were rapidly adopted across the UK and internationally [1,2]. Radiobiologically, hypofractionation may be advantageous, particularly for tumours with low alpha/beta ratios, where increasing fraction size results in a relative increase in tumour dose [3]. Additionally, the shorter treatment duration provides flexibility in scheduling around other treatment modalities.

Historically, the major concern has been the potential for increased toxicity and the journey to hypofractionation has not necessarily been a smooth one. For example, early studies in pancreatic cancer showed unacceptable rates of high-grade gastrointestinal toxicity, leading to the approach temporarily falling out of favour [4,5]. However, advances in technology in all aspects of treatment, including tumour localisation, on-treatment imaging, planning techniques and motion management, together with an improved understanding of appropriate fractionation schedules, have permitted safer delivery of hypofractionation in recent times.

The aim of this special issue of *Clinical Oncology* is to bring together a comprehensive review of the current status of hypofractionation and examine its role in various disease sites.

The special issue is opened by a review by Brand *et al.* [3] summarising the therapeutic rationale of hypofractionation and its radiobiological effects on toxicity and tumour control. This provides not only a pertinent reminder of the impact of hypofractionation on the '5 Rs' but highlights the opportunities for triallists to contribute to our currently imperfect knowledge of the underlying radiobiology through well thought out trial design.

In order to mitigate the risk of toxicity with SABR, dose limits to organs at risk (OARs) must be respected. In the second general article, Diez *et al.* [6] give a timely update to their original 2017 publication, providing an updated UK consensus on normal tissue constraints for SABR [7]. They review and update the recommended constraints based on the published literature, adding single-fraction recommendations to the existing fractionation schemes. This will no doubt prove to be an invaluable resource for oncologists and physicists alike, joining the recent HyTEC special issue as essential reading in this area [8].

While discussing the benefits of magnetic resonance-guided radiotherapy (MRgRT), Gough *et al.* [9] focus on pancreatic cancer as an exemplar tumour site. Magnetic resonance imaging facilitates clearer delineation of anatomy, whereas online daily plan adaption and ability to track and treat are additional features that make MRgRT an attractive option, particularly for upper abdominal tumours, given the complex anatomy. Dose escalation using SABR in pancreatic tumours remains challenging, given the proximity to OARs. However, higher doses appear deliverable with MRgRT, and studies of dose escalation and further hypofractionation are underway [10]. Other scenarios where precise imaging and precision delivery are of particular importance, for example, re-irradiation, are also likely to benefit from MRgRT.

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Macbeth and Treasure [11] and Chapman and colleagues [12] debate the role of SABR for oligometastatic disease, perhaps the single-most prominent indication that has defined the role of ultra-hypofractionated radiotherapy in a point–counterpoint argument. Whereas, Macbeth and Treasure [11] question the evidence base for SABR, attributing its popularity to 'cognitive and technical biases' and 'the unconscious tendency of individuals to fit their processing of information to conclusions that suit some end or goal', Chapman and colleagues [12] explore the biological underpinnings for oligometastatic disease and highlight six randomised controlled trials that argue the case in its favour. However, they acknowledge the need for careful patient selection and for molecular-based strategies to define suitable candidates. The role of SABR over conventional single or five-fraction palliative radiotherapy for oligometastatic or oligoprogressive spinal metastasis is discussed by Dunne and colleagues [13]. In randomised studies, a single fraction (24 Gy) and two fractions (24 Gy in two fractions) showed superior pain control outcome at 3 months with low rates of radiation toxicity, although one randomised controlled trial comparing 16–18 Gy to 8 Gy failed to demonstrate a benefit.

Adjuvant breast cancer is a prime example of how robust evidence generated through sequential UK-led randomised controlled trials has resulted in ultra-hypofractionation becoming the new international standard of care. Yarnold *et al.* [14] provide an elegant commentary detailing the evidence base supporting the reduction in fractionation schedule from 5 weeks to 1 week and provide insight on future avenues for research, including more extreme hypofractionation and the potential for biomarker-driven 'personalised' fractionation.

The CHHiP trial, which many readers will be familiar with, helped to establish moderate hypofractionation as a standard of care in localised prostate cancer [15]. Corkum *et al.* [16] focus on more extreme hypofractionation, reviewing the evidence base for fewer than five fraction treatments with SABR and high dose rate brachytherapy. The authors address the hot topic of 'How low can you go?', acknowledging the lessons learnt from the disappointing biochemical failure rates of single-fraction compared with two-fraction high dose rate brachytherapy [17].

Tjong *et al.* [18] review the role of single-fraction SABR as an alternative to multi-fractionated SABR in non-small cell lung cancer. They discuss the data in support of single-fraction regimens as a safe and efficacious alternative to the more commonly utilised three-to five-fraction regimens for stage I peripheral tumours, an approach recommended during the COVID-19 pandemic by an ASTRO-ESTRO consensus. However, in the context of treating lung metastases, the SAFFRON II trial showed higher local failure rates in colorectal cancer patients treated with 28 Gy single-fraction regimens compared with a multi-fractionated approach [19] and the authors recommend that a dose-escalated single-fraction approach should be investigated in this group.

Lewis *et al.* [20] review the role of SABR and hypofractionated radiotherapy (one to 10-fraction schedules) in hepatocellular carcinoma. Studies that were reported in the last 10 years and had a minimum of 25 patients were reviewed. The authors conclude that the optimum dose fractionation is yet to be defined, and a risk-adapted approach, based on baseline liver function and normal liver volume, tumour size and location, is preferable, with one-to three-fraction regimens proposed for peripheral and smaller lesions and a more fractionated regimen preferable for larger lesions and those near critical organs. Local control exceeds 80%, with radiation-induced liver disease noted in less than 5% of cases in appropriately selected patients.

Slevin and colleagues [21] provide a comprehensive review of short-course radiotherapy (SCRT) in rectal cancer. Although the overall merits of SCRT over long-course chemoradiotherapy is a matter of debate, SCRT remains an attractive option in conjunction with chemotherapy as a part of a total neoadjuvant therapy approach for localised cancer or in the presence of resectable metastatic disease, and in combination with transanal endoscopic microsurgery as an organ-preservation approach for early stage rectal cancer. Ongoing research focuses on radiotherapy dose escalation, technical advances (e.g. MRgRT) and combination with novel biological agents.

Finally, Tsao *et al.* [22] bring the special issue to a close with an overview of hypofractionation in the management of non-melanomatous skin cancers, highlighting how well suited the approach is to an often elderly and frail patient group. This is supported by meta-analysis findings of similar cosmesis compared with fractionated approaches and acceptable local control rates, albeit in the context of retrospective data.

In summary, we hope this special issue showcases how the rise in hypofractionation has changed the landscape of radiation therapy. For a number of tumour sites, conventional fractionation has already become obsolete and this trend will probably extend to further indications over the next decade.

So, what does the future hold? Further improvements in technology are anticipated – integrating the full complement of novel imaging, daily plan adaptation, tracking/gating and auto-contouring into treatment will add further technical precision and improve the efficiency of the pathway, whereas combination with systemic agents may improve the efficacy of the treatment. Conventionally accepted OAR constraints will need to be questioned as they were based on previous imprecise imaging, localisation and delivery. Our understanding of the 'ground truth' of OAR constraints should improve as newer technologies, such as MRgRT, shed light on delivered versus planned dose. With increased precision in contouring and delivery, we will probably see a 'greater' radiation tolerance for OARs than previously anticipated. Finally, clinicians may become the 'weakest link' in the pathway as the precision of target and OAR contouring will ultimately define the success and failure of the treatment – highlighting the need to formally incorporate radiology in radiation oncology training, and to work collaboratively with our radiology colleagues.

Conflicts of Interest

K. Aitken reports a relationship with Elekta that includes: speaking and lecture fees and travel reimbursement.

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