Ultrahigh dose-rate radiotherapy: The cat's whiskers or a flash in the pan?

Kevin J. Harrington

The Institute of Cancer Research

Division of Radiotherapy and Imaging

237 Fulham Road

London SW3 6JB

United Kingdom

Tel: 00 44 207 153 5077

E-mail: Kevin.Harrington@icr.ac.uk

Acknowledgement: KJH acknowledges support from The Royal Marsden/The Institute of Cancer Research National Institute of Health Research Biomedical Research Center

Disclosure/Conflict of Interest: KJH is a member of the MR-Linac Global Clinical Steering Committee which is sponsored by Elekta. He declares no other conflicts of interest.

Summary

A new way of delivering radiotherapy at very high dose-rates is described and compared to conventional radiotherapy. The ultrahigh dose-rate therapy reduces damage to normal pig skin and exerts potent activity against spontaneous nasal tumours in cat patients. The implications for clinical development of this approach are discussed. (48 words)

In this issue of CLINICAL CANCER RESEARCH, Vozenin and colleagues[1] describe the use of ionising radiation delivered at very high dose-rates as a means of modifying normal tissue damage. Radiotherapy represents one of the central pillars of modern oncological management, with roles in curative and adjuvant therapy across many tumour indications. For decades, standard-of-care practice has been based on the bedrock of conventional dose-fractionation regimens that were initially established through empirical observation rather than detailed, mechanistic understanding of the biological effects of radiotherapy. Such treatments have traditionally comprised fractions of 2 Gy/day on 5 days each week (Monday through Friday) for upto 7 weeks. Such schedules exploit differential responses of tumour and normal tissues to radiation. Classical radiobiological dogma states that, by using such conventional dose-fractionation regimens, normal tissues recover from the harmful effects of radiation to a greater extent than tumours, whose radiation response is dictated by the total dose delivered rather than by the dose given at each fraction. On these foundations, radiation oncologists have derived treatment strategies that cure a proportion of cancers without inflicting intolerable immediate and long-term damage on surrounding normal tissues.

Conventional dose-fractionation approaches have been perpetuated by a natural conservatism on the part of its practitioners, an understandable position given the potentially irreversible, harmful (or even fatal) effects of radiotherapy. Consequently, a substantial body of radiation research has focused on technologies that improve the precision of radiation delivery rather than studies that exploit biological differences between tumours and normal tissues. Certainly, this technological emphasis has revolutionised the discipline, leading to the development of practice-changing approaches such as intensity-modulated radiotherapy, volumetric-modulated arc therapy, stereotactic body radiotherapy (SBRT), the magnetic resonance linear accelerator and proton beam therapy. Nonetheless, most treatments, with the exception of SBRT, delivered using these platforms still cling to conventional dose-fractionation schedules derived decades ago. Recently, insights from basic radiobiology and carefully conducted clinical trials of abbreviated dose-fractionation regimens in common tumours, such as breast and prostate cancer[2,3], have driven increasing use of modestly hypofractionated treatment regimens involving daily delivery of dose-fractions of >2 Gy per day. In the case of SBRT,

extreme hypofractionation regimens are the norm for patients with early stage tumours confined to the local site or for those with symptomatic metastatic disease.

In all of the clinical practice discussed above, the rate of radiation dose delivery has been relatively constant (e.g. approximately 0.03 Gy per second (Gy/s)) and has not, until now, been seen as an important, manipulable treatment variable. Vozenin et al seek to change this paradigm by extending their previous preclinical work in mouse models[4] to demonstrate clinical efficacy of ultrahigh dose-rate (or FLASH) radiotherapy in mini-pig and cat patients[1]. This new approach fuses technological development and novel radiobiology by delivering electron therapy at dose-rates around 300 Gy/s, yielding remarkable results.

In homage to old-school, classical radiobiology experiments, they used multiple sites on the back of a single mini-pig to demonstrate strikingly different cutaneous toxicity outcomes when large single doses of radiotherapy (28-34 Gy) were delivered either at conventional (0.083 Gy/s) or ultrahigh (300 Gy/s) dose-rates. Conventional dose-rate therapy was associated with all of the anticipated clinico-pathological late effects of radiotherapy, such as depilation due to stem cell loss in hair follicles, collagen deposition/scarring, skin contracture and fibronecrosis. Remarkably, these effects were not seen with ultrahigh dose-rate therapy, which at time points beyond 6 months resulted in healthy, supple skin that showed some pigmentary change and depilation (although hair follicles and their stem cells were preserved microscopically) but none of the hyperkeratosis, collagen deposition and ulceration that are hallmarks of long-term radiation-induced cutaneous toxicity (**Figure 1**).

The authors then conducted what they, rather fancifully, describe as a phase I dose escalation trial in spontaneously-arising squamous cell cancers of the nasal planum in six domestic cats. Using a dose escalation scheme that appeared to obey no pre-specified rules, cats received single fractions (25 to 41 Gy) of ultrahigh dose-rate radiotherapy using electron fields. Dose-escalation was curtailed at 41 Gy because all six cats treated to that point had achieved complete remissions. No dose-limiting toxicity was reported, although animals treated with higher radiation doses experienced moist desquamation within the irradiated area that healed some weeks after treatment. Interestingly, the authors reported no major disturbance of nutrition or olfaction in the post-treatment period, without sharing details of how one objectively scores smell function in a cat with cancer of the nose. Long-term toxicity was reported as relatively mild and, certainly, the clinical photographs presented portrayed impressively reassuring results. In total, durable disease control was achieved in 5 of 6 animals at 16 months, with one additional animal suffering disease relapse at a later time point.

This truly fascinating, rather idiosyncratic, study potentially opens the door to a new approach to the delivery of curative radiotherapy. Certainly, the data presented provide clinicians and regulators with sufficient justification for immediate clinical translation of ultrahigh dose-rate radiotherapy into early phase trials. Having said

that, a number of unresolved issues remain that will need to be addressed if this approach is to become anything other than a radiobiological curio. The most pressing issue is the need for a mechanistic explanation for the differential effects seen in tumour and normal tissues, without which these observations will remain merely phenomenological. In tandem with such studies, it will be important to understand how modulation of radiation dose-rate and the use of extreme hypofractionation might affect the so-called 5 Rs of radiobiology (repair, reoxygenation, redistribution, repopulation, radiosensitivity). Undoubtedly, a number of these factors, which have traditionally been seen as central to the radiobiology of fractionated therapy, will become irrelevant in the context of a single dose of radiotherapy delivered in less than a second. For example, reoxygenation, cell cycle redistribution and radiation-induced altered/accelerated repopulation of the tumour would no longer occur during the course of radiotherapy. In addition, our increased appreciation of the importance of the tumour microenvironment in determining both tumour responses and late normal tissue damage demands that we understand the potential effects of ultrahigh dose-rate therapy on the entire tumour ecosystem and not just on the cancer cells within it[5]. It will also be important to examine how the damage induced with this form of irradiation might affect radiation-induced anti-tumour immunity.

Assuming that the radiobiological effects of ultrahigh dose-rate radiotherapy are clarified, there are still be a number of technical considerations that must be resolved if this approach is to find a place in clinical practice. For example, if this approach is restricted to relatively superficial tumours within the range of standard electron beams (e.g. upto 20 MeV electrons) its clinical applicability will be very limited. In addition, the data presented in the current study were generated with very small field sizes, indeed below the usual lower limit of what might currently be accepted in the clinic due to potential dose inhomogeneities with field dimensions of less than 4 cm. Further studies with more clinically relevant field sizes will be needed as this approach progresses through clinical studies.

In summary, Vozenin and colleagues provide an intriguing vision of how we might use dose-rate modulation of radiotherapy to improve outcomes for patients. In the coming years, it will be extremely interesting to understand the molecular radiobiological underpinnings of their approach and to observe if the data they have generated in pig and cat models can be replicated in cancer patients. (1200 words)

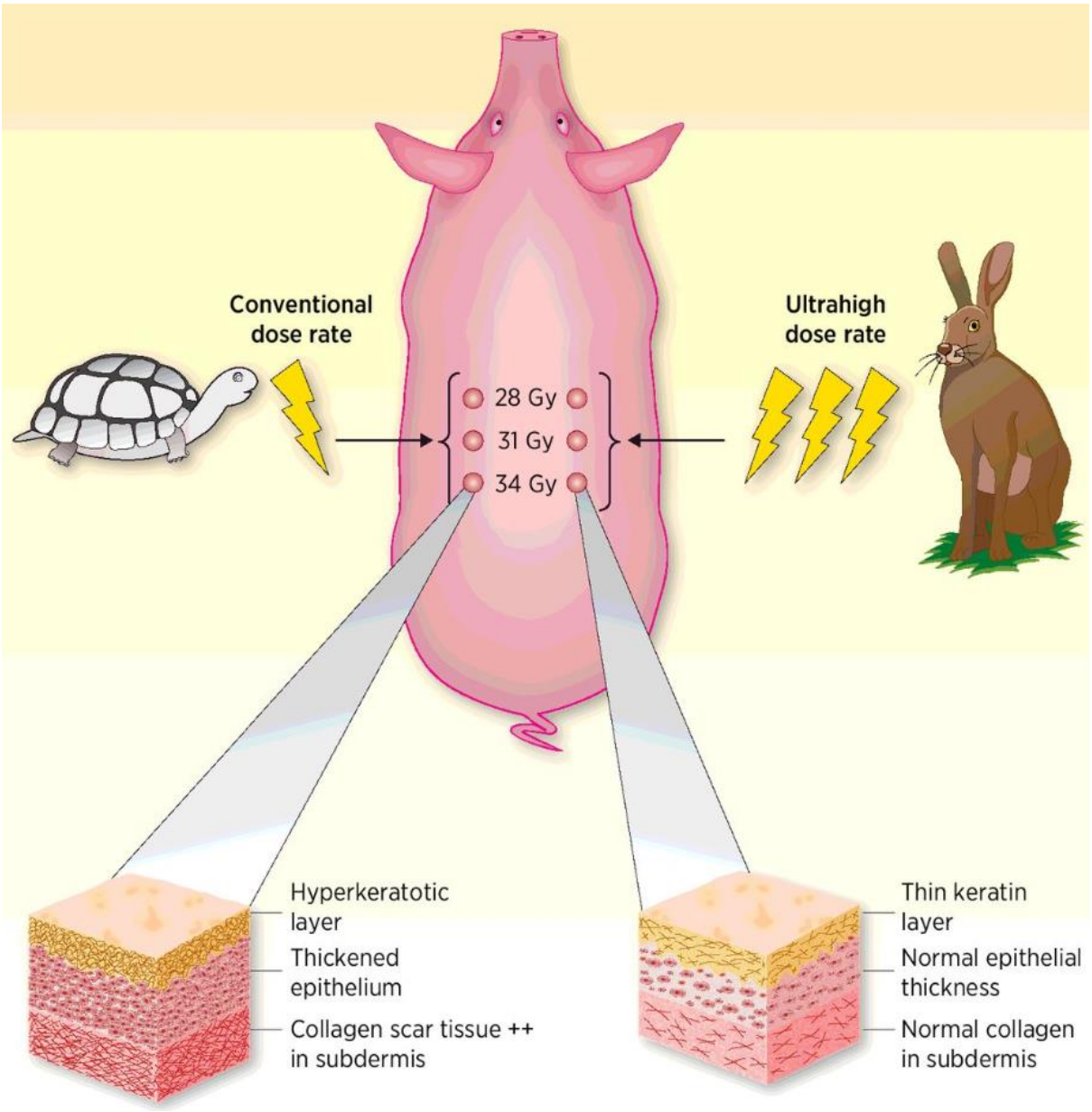

Figure 1. Differential normal tissue damage as a result of conventional versus ultrahigh dose-rate radiotherapy. Pig skin was irradiated to single-fraction radiation doses of 28, 31 or 34 Gy using either conventional or ultrahigh dose-rate electron therapy. Late normal tissue damage measured by standard clinical measures and light microscopic analysis was significantly greater in animals irradiated using conventional dose-rate therapy. In contrast, ultrahigh dose-rate (or FLASH) radiotherapy was associated with relative sparing of normal tissue damage.

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