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Radiation Research Special Issue: New Beam Delivery Modalities are Shaping the Future of Radiotherapy

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INTRODUCTION

The Radiosurgery Society (RSS) and Radiation Research Society (RRS), in collaboration with the National Cancer Institute (NCI), are pleased to present a special issue showcasing recent work and leading-edge ideas from some of the world's experts on innovative modalities for advancing radiotherapy. Following from a workshop sponsored by the RSS and NCI (*1*), this special issue is dedicated to the concepts developed during that meeting, which were focused on the ultimate implementation of new radiation modalities in an attempt to improve the therapeutic index.

This issue highlights recent advances in spatially fractionated (GRID/LATTICE) and microbeam (MRT) radiotherapy, as well as ultra-high-dose-rate (FLASH) radiotherapy. The GRID and LATTICE techniques have already undergone significant, if not sporadic, clinical implementation over the past several decades. These modalities utilize an engineered shield or collimation strategies (i.e., the GRID or LATTICE) to enable delivery of spatially distributed radiation in defined patterns, thereby minimizing total doses delivered to normal tissues, especially for larger target volumes. In the case of MRT, several preclinical models have shown promise, where dose differentials between high ''peak'' to lower ''valley'' regions derived from collimated synchrotron radiation sources have been shown to minimize normal tissue injury. Lastly, in a variety of tissue types, small and large preclinical animal models, and to date, one clinical case report, FLASH radiotherapy has been shown to elicit remarkable normal tissue sparing without compromising, and potentially enhancing, tumor response. Based on these exciting developments in radiation delivery, we present a cross section of articles aimed at evaluating the translational potential and clinical implementation of these fascinating and advanced technologies.

GRID/LATTICE

The term GRID stems from the parent term ''spatially fractionated radiotherapy.'' In reality, it refers to a pattern of on and off regions of dose, administered typically to large, locally advanced tumors with limited other treatment options. Another similar approach has been termed LATTICE, since it is a method for delivering high-dose nodes in a 3D pattern using advanced treatment planning. This focus issue contains articles on both the patterns and terminologies. Fractionating a large dose into a pattern of on and off volumes (although the ''off'' volume also receives a dose, referred to as the valley dose, which may be critical to optimizing and standardizing the approach) allows for preferential sparing of overlying or underlying normal tissues. This normal tissue sparing is generally thought to be accomplished by virtue of maintaining stem cell numbers and modifying the inflammatory/necrosis cascade that would be expected in whole beam exposures.

In addition, the gradient of dose between the on and off regions may induce some very unique and therapeutically beneficial reactions, such as bystander effects and possible differential regenerative signaling cascades in the normal tissues relative to the tumor volume. As the full potential of immunotherapy has garnered increasing attention in recent years, the ability of spatial fractionation, to improve the response rate to immunotherapy or to better synergize with immunotherapy and potentially contribute to abscopal effects, has given the field of spatial fractionation a further recent boost in interest.

An important aspect of any spatial fractionation or altered beam property-based treatment is the standardization of various aspects related to treatment planning. This is essential for multi-institutional clinical or laboratory studies to generate best practices and knowledge. It also serves to standardize what the terms actually mean when used in various contexts. A physics and dosimetry white paper by Zhang *et al.* in the current issue reviews many of these topics for clinical implementation and makes suggestions and give guidance to the best-case expansion of consistent treatment-planning and delivery for GRID-type therapy. This practical consensus article makes recommendations across spatially fractionated radiation therapy technologies, GRID field dosimetric properties, techniques for generating GRID fields, GRID therapy planning methods, GRID therapy documentation metrics, and clinical practice

recommendations that can serve as guides for clinical administration of these techniques.

Importantly, the LATTICE approach, while fractionated into on and off volumes, has specific differences compared to the more traditional 2D patterns of GRID dosing. The work by Wu and colleagues over recent years to develop a methodology for consistent clinical use of LATTICE is reviewed and further dissected in this issue. Additional complementary and directly relevant work in this issue comes from Amendola and clinical colleagues, who have arguably the most current experience in LATTICE therapy. They report on the treatment and follow-up of 10 patients with advanced cervical cancer, including some imaging and molecular correlates. It is the beginning of an intriguing approach that can be adopted fairly easily by standard radiotherapy equipment.

The work of Johnsrud *et al*. adds to the literature related to stimulation of an anti-tumor immune response of a primary tumor to GRID-patterned irradiation. Previously published work in both LATTICE (*2*) and microbeam (*3*), among others, has introduced the research community to the possibility that the unique dose depositions created with spatial fractionation are somehow able to better allow for the interaction of the host immune system with the irradiated volumes via antigen availability or possibly retention of more functional physiological status. The current article follows these reports with results that indeed suggest that, compared to high-dose whole-tumor irradiation, the use of GRID may be valuable as a primer for anti-tumor immunity in the context of a standard course of immunotherapy.

MICROBEAM THERAPY

As alluded to, the field of microbeam therapy (MRT), which uses a synchrotron-generated, high-fluence-rate beam of much less than 1 mm in diameter, has had a rich history in preclinical spheres. Many concepts in MRT parallel those in the clinical use of GRID or LATTICE, yet the specific nature of the extremely high dose rates and sharp dose gradients between on and off regions with MRT present unique variables that have been found to markedly affect tumor physiology and response and minimally perturb many normal tissues. The challenge has been translating the beam line and hardware into a clinically acceptable treatment facility that is accessible to a large number of patients. The article by Potesz *et al*. is a fine example of the compelling responses and useful immune activation that may be obtainable using the power of microbeam technology and certainly suggests that efforts to create clinical study facilities remain worthwhile.

In this focus issue, Fukunaga and colleagues assess the use of MRT to achieve tissue-sparing effects for spermatogenesis. Using an *ex vivo* mouse spermatogenesis model, they assessed different proportions of irradiated to nonirradiated tissues and identified optimal ratios that can achieve essentially complete spermatogenesis sparring. Given the extent of radiosensitivity in testes, this work is thought provoking and, if translatable to human patients, may allow for better preservation of male fertility while still optimizing tumoricidal irradiation doses.

A major area of research and clinic interest is harnessing the ability to achieve the currently rare abscopal effects of radiation-induced cell death within an irradiated field with disease regression outside of the irradiated field. Abscopal effects are believed to occur at higher rates when radiation therapy is combined with immunotherapy and when radiotherapy is delivered at high doses per fraction, as is performed for stereotactic body radiation therapy, GRID, MRT and FLASH (*4*). Given that synchrotron radiation emits limited irradiation scatter, MRT can be an optimal model for studying out-of-field events such as abscopal effects. Forrester and her colleagues from Australia assess abscopal gene expression in response to MRT. Using mouse models and gene expression of out-of-field skin samples, the authors found that there is a role for immunological and DNA damage response genes in abscopal effects, and that the innate immune system is likely involved in out-of-field tissue responses.

Next, Lamirault and his colleagues from France report on a series of *in vivo* experiments performed to evaluate the tumor control effectiveness of proton minibeam radiation therapy (pMBRT) in glioma-bearing rats. In comparison to rats irradiated with standard proton therapy, those irradiated with pMBRT achieved equivalent increases of lifespan and no significant differences in the histopathological analysis of the tumors or the remaining brain tissue. While toxicities were not assessed in these experiments, these findings suggest a means to achieve comparable tumor kill but potentially with a reduction in long-term toxicities.

FLASH RADIOTHERAPY

The current significant interest in FLASH is reflected in the breadth of the 13 articles related to this highly topical area of research. The broad range of manuscripts reflects the diversity of the science required to dissect the nuances of this burgeoning irradiation modality and includes subject matter ranging from physics to chemistry and biology. Specific topics include a variety of dosimetry and modeling approaches, radiochemical considerations, treatment planning strategies and pre-clinical rodent models that demonstrate the hallmark sparing of normal tissues toxicities, termed the FLASH effect.

One of the more important requirements for moving the FLASH technology into the clinic is the need for real-time dosimetry, a current standard of care in clinical practice for non-FLASH radiotherapy. Challenges with monitoring dosimetry at ultra-high dose rates are addressed by Konradsson *et al*. in work that is aimed at investigating the feasibility of implementing a built-in transmission chamber of a clinical linear accelerator for real-time

dosimetry of electron beams. Data demonstrate the feasibility of developing an online monitor by quantifying the drop-in ion collection efficiency as a function of dose-per-pulse, linked via a logistic model to the transmission chamber to correct for ion recombination, which may prove useful in the clinical setting.

In other work focused on the important issue of dosimetry at ultra-high dose rates, Gondre *et al*. provide a new strategy for optimizing alanine dosimetry based on electron paramagnetic resonance spectra obtained with a Bruker spectrometer. With this approach, reading parameters (scan times and replicates) could be reduced without sacrificing signal-to-noise ratios, thereby improving accuracy between measured and reference doses to facilitate dose calculations for more precise biological applications of FLASH.

From the physical considerations, this issue transitions to a manuscript by Wardman who evaluates recent advancements in FLASH in the context of the long-standing literature of pulse radiolysis. Radiochemical considerations are used to evaluate possible mechanisms for the FLASH effect involving depletion of an important radioresponsive chemical and/or the role of radical-radical reactions within high-intensity pulsed beams. Potential differences in the radiolytic production of reactive oxygen species produced under vastly different dose rates are also discussed.

Another interesting theoretical article, by Azzam *et al*., describes some potential advantages of hadron therapy delivered at ultra-high ''FLASH'' dose rates. Radiation oncology has long hypothesized the advantages of superimposing spread-out Bragg peaks to make use of the beneficial dose-depth profiles of charged particles for maximizing tumor cell kill. Based on radiochemical principles, the authors point to the capability to radiolytically-produce molecular oxygen in the Bragg peak region of carbon ion beams. The possibility to generate this potent radiosensitizer in hypoxic tumors at FLASH dose rates in regions of maximal LET is discussed, with provocative clinical implications.

As the number of published studies from various groups regarding the FLASH effect continue to climb, the importance of characterizing beam parameters has become increasingly critical and necessary for experimental rigor and reproducibility. In this light, Breitkreutz *et al*. used existing treatment planning software to generate whole brain radiotherapy plans for pediatric patients using opposing 40 MeV electron beams. Monte Carlo simulations indicated that FLASH dose rates sufficient for neurocognitive sparing could be obtained with sufficient beam homogeneity for the intended pediatric irradiations.

To date, most preclinical FLASH reports have utilized relatively lower energy (5–6 MeV) electron beams to irradiate rodents. In efforts to provide conformal photon FLASH irradiators, Ko *et al*. endeavored to develop a collimated X-ray FLASH linear accelerator system incorporating a rotational rodent system compatible with conformal FLASH delivery from multiple beam directions. Details of this innovative approach describe the imaging approach necessary for registering precise anatomical landmarks under rotational speeds compatible with FLASH conformal radiotherapeutic applications.

Moving to preclinical models of FLASH-RT, this issue features three reports implementing mice to evaluate further the extent that ultra-high-dose-rate electron irradiation minimizes normal tissue toxicities. In the work of Soto *et al*., a dose-response study was performed comparing FLASH and conventional-dose-rate (CONV) irradiation on skin toxicity. These novel datasets demonstrate a rightward shift in the dose-response curve for FLASH versus CONV irradiation, where reductions in the incidence and severity of radiation-induced skin ulcerations after FLASH suggest an improved therapeutic index.

As for the brain, two relevant studies further document the beneficial effects of FLASH on preserving normal tissue from radiation-induced toxicities. In their work, Montay-Gruel *et al*. sought to elucidate the differential response of reactive astrogliosis to FLASH and CONV irradiation modalities. The investigators found that markers of activated astrogliosis were expressed at reduced levels after FLASH, particularly the TLR4 receptor, compared to animals that received CONV irradiation. These data confirm previously reported studies showing the capability of FLASH-RT to attenuate neuroinflammation.

In another study on the effect of encephalic irradiation, Allen *et al*. provide some of the first evidence that FLASH can spare microvasculature integrity in the irradiated brain. High-dose (25 Gy) and lower-dose (10 Gy) irradiations with FLASH and CONV were used to evaluate the integrity of the vasculature and blood-brain barrier over a course of days to many weeks after irradiation. Vascular dilation, elevated eNOS expression and reduced tight junction protein levels found after CONV were all mitigated after FLASH, pointing to additional normal tissue benefits that define the FLASH effect.

Finally, as the field contemplates the translational feasibility of FLASH radiotherapy, powerful proton accelerators including cyclotrons and synchrotrons may be optimal means to achieve ultra-high-dose-rate radiation therapy. Many have moved to ascertain if and how proton irradiation platforms can be adapted and used to achieve the FLASH effect. Grilj *et al*. assembled, optimized and tested two proton irradiation platforms capable of delivering therapeutic doses to thin biological samples at dose rates equal to and above 100 Gy/s. They also manufactured a microfluidic flow-through device for irradiations of biological samples in suspension. These investigators used these platforms to conduct preliminary studies on the role of proton dose rate on cell survival in cancer cell lines and to investigate the depletion of oxygen from aqueous solution by water radiolysis after short intense proton pulses.

Similarly, Zhang and colleagues from Massachusetts General Hospital report on the development of a proton irradiation platform in a clinical proton facility. Using their

double scattering system, they report on the ability to deliver a homogeneous dose distribution while keeping the dose rate >100 Gy/s, and they report on their preliminary studies of partial-abdominal irradiation in mice.

SUMMARY

We hope you find the important work discussed in this special issue to serve as a provocative and valuable resource for your future research endeavors.

Sincerely yours,
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Guest Editors, *Radiation Research*

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The National Cancer Institute Radiation Research Program in collaboration with The Radiosurgery Society (RSS) organized a collaborative effort with the purpose of investigating clinical, radiobiology and medical physics scientific facets of GRID, Lattice, FLASH and microbeam radiotherapy, with the ultimate goal of advancing treatments for patients. Three Working Groups (Clinical, Physics and Biology) were formed to progress the understanding of these emerging technologies. This special FOCUS issue of Radiation Research is a joint effort of the three Working Groups and addresses the current understanding of GRID, Lattice, FLASH and microbeam radiotherapy.

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