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SUMMARY: ACHIEVEMENTS, CRITICAL ISSUES, AND THOUGHTS ON THE FUTURE

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Abstract

The number of individuals exposed to particle radiations in cancer treatment worldwide is increasing rapidly, and space agencies are developing plans for long-duration, deep-space missions in which humans could be exposed to significant levels of radiation from charged particles. Hence, the NCRP 47th Annual Meeting on “Scientific and Policy Challenges of Particle Radiations in Medical Therapy and Space Missions” was a timely opportunity to showcase the current scientific knowledge regarding charged particles, enhance cross-fertilization between the oncology and space scientific communities, and identify common needs and challenges to both communities, as well as ways to address those challenges. This issue of *Health Physics* contains papers from talks presented at that meeting and highlights provocative questions and the ample opportunities for synergism between space and particle-therapy research to further understanding of the biological impacts of particle radiations.

Keywords

National Council on Radiation Protection and Measurements; particle radiotherapy; space radiation; heavy charged particles

The number of individuals being treated for cancer using charged particles (primarily protons, but some carbon ions) is increasing rapidly worldwide, and space agencies around the world are making long-term plans for long-duration, deep-space missions in which humans could be exposed to significant levels of charged-particle radiation. However, many critical questions exist about the biological impacts of protons and heavier charged particles relevant to both patients and astronauts. This issue of *Health Physics* presents papers from talks given at the 47th Annual Meeting of the National Council on Radiation Protection and Measurements on the topic of “Scientific and Policy Challenges of Particle Radiations in Medical Therapy and Space Missions.” The goals of the meeting were to:

1. showcase the current state-of-the-knowledge regarding charged particles as relevant to space and medicine;
2. enhance cross-fertilization between the oncology and space scientific communities; and

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3. identify needs and challenges common to both communities and discuss ways to collaboratively address those provocative issues.

As discussed in many papers in this issue, but particularly by Blakely (2012), Durante (2012), and Zeitlin (2012), charged particles differ in significant ways from photons, particularly with regards to energy distributions and the resulting biological changes, and it is these differences between charged particles and photons that tie the fields of space radiation biology and particle-therapy research together. Particle interactions with matter being traversed produce a region of relatively dense ionization along the particle trajectory, as well as “knock-on” electrons, or delta rays, which can result in energy deposition at significant distances laterally from the track, depending on the charge and energy of the particle. The energy loss as the charged particle interacts with matter continuously slows the incident particle and increases its linear energy transfer (LET) to a maximum at the Bragg peak. In charged-particle therapy, advantage is taken of that dose distribution to localize the biologically effective dose in the spread-out Bragg peak on the tumor while minimizing dose to normal tissue distal to the spread-out Bragg peak. In space, the radiation field is more complex including galactic cosmic rays, composed of continuous fluxes of protons, helium, and heavier ions with energies of hundreds to tens of thousands of MeV n^{-1} , and solar particle events, which are predominantly protons of energies up to a few hundred million electron volts. In both space and medicine charged-particle research, a major consideration is the higher relative biological effectiveness (RBE), at least for cell killing, that is well-documented to increase with LET to about $100\text{--}200 \text{ keV } \mu\text{m}^{-1}$. However, as discussed by several authors herein (e.g., Blakely 2012; Durante 2012), ions with the same LET but different charge or velocity may have different track structure and fragmentation properties, and, hence, different RBE values. Consideration of track structure is an area of heavy ion biology ripe for further research.

There are some notable differences in the emphases of research on charged particles in the fields of radiation oncology and space radiation research. Simplistically, the increased RBE compared to photons is a threat for astronauts in space, but an advantage in therapy, as long as the RBE increase can be confined to the tumor. There are also major differences in the radiation exposure conditions, such as the total doses (high to tumors in the clinic, lower in space), dose rate (much lower in space), dose localization (total body in space vs. localized in the clinic), omnidirectional particle traversals in space vs. directed in therapy, complexity of mixed fields in space, generally higher particle energies and LETs in space, and substantial differences in characteristics of the persons exposed in terms of health status, age, etc.

However, as is clearly evident from the collective impression of the papers in this issue, the enterprises of space radiation research and particle therapy share many more similarities in research needs than differences, as summarized well by Durante in his Warren K. Sinclair Keynote Address in this volume (Durante 2012). These many similarities provide unique opportunities for synergism between the space and therapy communities, and emphasize the need for knowledge gained by one field to help advance research and application in the other field. Briefly, several of the opportunities for synergism as shown in the papers in this issue are highlighted here. The same physical interactions of particles with matter occur in space and in particle therapy, as summarized by Zeitlin (2012). As a result of the basic energy deposition differences between charged particles and photons, the physico-chemistry of DNA interactions and the resulting biology differ qualitatively, as well as quantitatively. Charged-particle radiations produce more clustered DNA lesions, less efficient and less accurate DNA repair, more complex chromosome aberrations, different gene expression patterns and altered roles for tissue microenvironment compared to photons [as discussed by, e.g., Blakely (2012), Durante (2012), and Tabocchini et al. (2012)]. Consideration of

such qualitative differences raises questions about the appropriateness of using “simple” multiplicative approaches as embodied in RBE and quality factors for determining biologically relevant doses to be used in therapy as well as weighting factors for calculation of risks of cancer or damage to normal tissues in medicine or space. For cancer induction, particles differ from photons with regards to RBE values, fractionation/dose/dose rate dependencies, latency and endpoint/tumor type. The latter is clearly illustrated by the intriguing work of Weil and colleagues, discussed in this issue (Bielefeldt-Ohmann et al. 2012), on the incidence of acute myeloid leukemia and hepatocellular carcinoma in mice treated with ^{137}Cs gamma rays or 1 GeV n^{-1} ^{56}Fe ions. Research is well underway on risks of proton-induced second cancers in the radiation oncology arena (Paganetti 2012; Yock and Caruso 2012). Can such research be informative to the space radiation community in their efforts to estimate cancer risk in astronauts?

For many years the issue of radiation-induced late normal tissue damage has been of paramount concern in radiation oncology, and the space radiation community also has increasing concern about normal tissue degenerative effects, such as cataract induction or effects on the central nervous system. Normal tissue effects are discussed from the proton clinical perspective by Mahajan (2012), from the space perspective for protons and heavier ions by Kronenberg and Cucinotta (2012), and from both the clinical and space outlook by Blakely (2012). It is quite evident from several articles in this issue that relatively little is known about RBE values for late noncancer effects. RBEs may be large in some cases, as suggested by cataracts and behavior effects in rodents (Durante 2012; Kronenberg and Cucinotta 2012), with large uncertainties and substantial inter-individual variability. Clearly, opportunities for synergism between clinical and space researchers exist in this arena.

Another issue of ever increasing interest in both space radiation biology and radiation oncology is that of individual radiosensitivity. Papers in this issue point out the importance of genotype in HZE-induced mutations in cultured cells (Kronenberg and Cucinotta 2012), chromosome aberrations (Peng et al. 2012), tumor induction (Bielefeldt-Ohmann et al. 2012; Peng et al. 2012), and gene expression (Story et al. 2012). For space travel, such findings raise thorny issues about selection of astronauts for space missions, and, in the therapy realm, the findings raise the exciting possibilities of individualizing, and thus improving, therapy by understanding differences between normal tissue and tumor sensitivities to radiations of varying LET, as discussed by Story et al. (2012). However, in both the space and therapy situations, there are many “omics” to consider – genomics, transcriptomics, proteomics, metabolomics – so the opportunities and needs for interactive laboratory and translational research are many-fold.

In both medical applications of charged particles and space radiation biology, characterizing the secondary particles, fragments and neutrons produced by incident particles interacting with accelerator apertures, shielding, spacecraft and the bodies of astronauts or patients is critical for estimating absorbed doses and subsequent biological effects and risks of undesirable outcomes. Several papers in this issue deal with relevant physics matters such as track structure simulations (Dingfelder 2012), transport codes (Kim et al. 2012), and nuclear fragmentation (Norbury and Miller 2012).

However, although radiation dose can be measured or simulated, and biological effects can be quantified, risks of tissue damage, including carcinogenesis, can only be estimated. Recommendations for radiation protection limits currently are largely based on cancer risk. In this issue, Paganetti (2012) describes the current state-of-the-art in risk modeling for induction of second malignancies in radiation therapy, and Kronenberg and Cucinotta (2012) and Cucinotta et al. (2012) describe the continuing development of National Aeronautics and Space Administration’s (NASA) cancer risk projection model (Cucinotta et

al. 2011), including considering possible synergism between radiation and tobacco smoking. The importance of uncertainties in NASA's cancer risk projection model have been highlighted in several earlier publications (Durante and Cucinotta 2008; Cucinotta et al 2011) and are summarized in Kronenberg and Cucinotta (2012). The uncertainties include: the low-LET epidemiology data, transfers for population characteristics/differences, radiation physics (e.g., space environment), RBEs or quality factors applied, dose and dose-rate effectiveness factor used, and whether there are low dose thresholds or nontargeted effects. Many of these uncertainties apply to charged-particle therapy risk projections, as well.

Many of the papers in this issue, directly or indirectly, call attention to personnel and infrastructure needs for charged-particle studies. Research to understand the biological impacts of charged particles and extend that to prediction of risks of various outcomes in humans – patients or astronauts – is interdisciplinary, requiring interactive teams of physicists (track structure experts, medical physicists, health physicists, theorists, and experimentalists), chemists, biologists (molecular, cellular, whole organism), clinicians, epidemiologists, and ethicists, as well as many ancillary specialists. Ground-based accelerators are used for most space radiation biology studies, and the same facilities are or should also be used for clinically-relevant fundamental research. A noteworthy example of how the combined use of a facility for clinical and space research can work effectively is the program that was based at the cyclotron at Lawrence Berkeley National Laboratory, but is no longer operational. Some of the important research conducted there is elegantly summarized in the Lauriston S. Taylor Lecture on Radiation Protection and Measurements by Dr. Blakely, in this issue (Blakely 2012). Currently, most ground-based research with heavy ions is conducted at only one facility in the United States, the NASA Space Radiation Laboratory at Brookhaven National Laboratory (BNL 2012); internationally, research is ongoing at the GSI Helmholtz Center for Heavy Ion Research and the Heidelberg Ion Therapy Center in Germany (GSI 2012) and the National Institute of Radiological Science (NIRS 2012) in Japan. The German and Japanese institutes conduct both space radiation biology studies and clinically-relevant research, and the former could also be used for that dual purpose, if appropriate funding were available.

Lastly, but certainly not least important, are numerous scientific policy challenges with regards to particle radiations that are addressed in several papers here (Alonso 2012; Deye 2012; Dosanjh et al. 2012). Among obvious policy challenges faced by space agencies in the United States and internationally are setting of radiation dose limits for astronauts, currently embodied, for example, in the permissible exposure limits for NASA, decisions on whether to pursue long-duration, human missions beyond low-Earth orbit, and use of “omics” in astronaut selection. Some of those matters are discussed by Kronenberg and Cucinotta (2012). The recent, rapid worldwide, expansion of particle therapy facilities, mostly protons, but some with heavier ions, is built on demonstrable clinical efficacy in several tumor sites (Durante and Loeffler 2010; Blakely 2012; Durante 2012). In this issue, Deye (2012) has summarized the substantial role played by the National Cancer Institute in support of charged-particle research and patient treatment, and the coordination of hadron therapy efforts through the European Network for Light Ion Hadron Therapy (ENLIGHT) is described by Dosanjh et al. (2012). Important issues related to protection of patients and staff need to be considered, and “personalization” of treatment is growing in importance, as discussed by Story et al. (2012). Critical decisions about costs, or more specifically the benefit:cost ratio for particle therapy, are being and will continue to be made, influenced by and influencing the development of new accelerators (Alonso 2012), gantries and other technologies including active scanning and organ motion tracking. Applied and basic biology and physics research needs, that, from a practical standpoint, will ultimately affect costs include assessing the role and use of hypofractionation and determining whether

carbon is the best heavier-than-proton ion for therapeutic use. Support for research and development is needed from both governments and the private sector. The challenges to expanding the scientific knowledge base regarding charged particles in space and medicine remain formidable and include, for example, the need for infrastructure, sound long-term scientific policies and sufficient funding. Future progress to benefit both clinical use of charged particles and understanding of their risks and development of countermeasures for astronauts can be facilitated by increased sharing of valuable accelerator-based facilities, interagency cooperation, inter-institutional and international collaborations, public/private partnerships, and shared education and training programs.

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