Multiscale Modeling in Radiation Oncology Mechanisms of Fast Neutron Relative Biological Effectiveness (RBE)

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Abstract

Why fast neutrons? The UW has a fast neutron beam that is used for research and for the treatment of patients with cancer. To generate neutrons, a cyclotron accelerates protons to 50.5 MeV and directs them towards a beryllium target. The fast neutron beam so produced is collimated by a primary iron collimator placed below the target and a 40 leaf iron (with polyethylene inserts) collimator, a so-called multi-leaf collimator (MLC), that can be adjusted to create regular and irregular shapes that conform to the beams-eye view of a tumor target. For salivary gland tumors, fast neutron treatments can achieve a 5-year local control rate of 75% compared to 35% for MV (megavoltage) x-rays. Although fast neutrons have been used to successfully treat salivary gland and selected other tumors for over 30 years, the physical and biological mechanisms underlying this form of cancer treatment are not fully understood.

Why Multiscale Modeling? The responses of cells, tissues and tumors to ionizing radiation emerge from an immensely complex sequence of events and processes spanning multiple time and spatial scales. On the smallest scale, the stochastic aspects of individual radiation tracks have a substantial impact on the nature and quantity of initial biomolecular damage. Molecular sensors detect the damage and activate an intricate network of molecular, cellular and intercellular signaling pathways controlling the rates of cell birth and death as well the migration and differentiation of cells. On even larger time and spatial scales, inflammatory and immunological processes may become important and alter the longer term consequences of radiation exposure.

Purpose of the Presentation: Quantify putative physical and biological mechanisms underlying fast neutron RBE and test the hypothesis that cell survival and double strand break (DSB) induction measured in vitro are predictive of fast neutron RBE for clinical (in vivo) endpoints.

Method and Materials: A MCNPX simulation of the therapeutic fast neutron beam (50.5 MeV $^1$H $\rightarrow$ Be target $\rightarrow$ n) at the UW has been developed to determine the physical characteristics of the neutral and secondary charged particles produced in a water phantom or patient. Estimates of fast neutron RBE for the endpoint of double strand break (DSB) induction were then computed as a dose-weighted average of the DSB yields for individual light ions ($^1$H, $^3$H, $^4$He, $^6$He, $^{12}$C) using information from the Monte Carlo Damage Simulation (MCDS). For comparison to estimates of neutron RBE derived from first principle Monte Carlo simulations, estimates of fast neutron RBE for the endpoint of repairable cell death were also derived from a re-analysis of published in vitro data for 30 cell lines using the Repair-Misrepair-Fixation (RMF) model. Estimates of the clinical RBE for normal tissues (bladder, femoral heads, skin, brain, spinal cord, parotid, esophagus, rectum and liver) were estimated from a linear-quadratic (LQ) analysis of equivalent tolerance doses (TDs) for photons and fast neutrons. The former were taken from the literature, and the latter are based on our clinical experience using the fast neutron beam at the UW and upon surveys of the clinical experience at other neutron radiotherapy centers in operation during the 1980s and 1990s.

Results and Conclusions: The analysis of in vitro data for fast neutrons gave a low-dose cell survival RBE of $3.3 \pm 1.6$. For comparison, the estimated fast neutron RBE for DSB induction derived from first principles (MCNPX + MCDS simulations) is 1.9 for cells irradiated under normoxic conditions and 4.1 for cells irradiated under anoxic (0% O$_2$) conditions. Estimates of neutron RBE derived from first principles and in vitro data are in reasonable agreement with estimates derived from the TDs for 16 clinical (in vivo) endpoints, i.e., RBE = $2.9 \pm 0.7$. The results provide evidence supporting a causal chain of events and processes linking the physical and dosimetric characteristics of fast neutrons to early molecular and cellular endpoints (DSB induction or cell death) and to the ultimate ability of normal tissues to tolerate fast neutron irradiation.
Bio

Professor Robert D. Stewart, Ph.D.
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Dr. Rob Stewart is currently an Associate Professor of Radiation Oncology and a Medical Physicist at the University of Washington (UW) Medical Center in Seattle, WA. The Department of Radiation Oncology is an integral part of the Cancer Program at UW, which has been consistently ranked by U.S. News & World Report as among the top cancer programs in the United States (ranked 6th in 2011-2012). Prior to joining the UW in 2010, he was the Assistant Head of the School of Health Sciences and the Director of the Radiological Health Science program at Purdue University (West Lafayette, IN). From 1997-2002, Dr. Stewart was a Senior Research Scientist in Radiation Biophysics at the Pacific Northwest National Laboratory (Richland, WA). Professor Stewart has been the recipient of over 1.2 million dollars in competitive grants, has published over 44 peer reviewed papers and 2 book chapters, and served as an associate editor of the Journal Radiation Research and on the executive council of the Radiation Research Society.

His formal education is in Nuclear and Mechanical Engineering, and he has 10+ years of post-doctoral experience teaching radiation physics, dosimetry and radiation biology. Early in his career, he was involved in loss of coolant analyses (LOCA) of advanced nuclear reactor designs and in climate change research. Over the last 19 years, Professor Stewart’s research interests have spanned a wide range of topics, including microdosimetry, DNA damage, DNA repair, and cell death mechanisms, including cell death mediated by intercellular signaling, so-called bystander effects. In 2005, Dr. Stewart and colleagues developed a novel Monte Carlo model to simulate the induction and base excision repair (BER) of clustered DNA lesions. The 2011 version of the Monte Carlo Damage Simulation (MCDS v. 3.1) developed by Stewart and colleagues is also a first of kind, and at present, the only Monte Carlo model capable of providing nucleotide-level maps of the clustered DNA lesions formed in cells irradiated under reduced oxygen conditions. The Monte Carlo models for the induction and repair of DNA damage are part of his more than decade-long effort to develop a multi-scale system of models to capture essential aspects of the early physical, chemical and biological processes underlying cell death kinetics. Dr. Stewart is also leading an effort, in collaboration with Greg Moffitt and Professor Tatjana Jevremovic (University of Utah Nuclear Engineering Program), to develop an MCNPX model of the UW fast neutron beam. The ultimate goal of Dr. Stewart’s research is to improve the prediction of treatment outcomes and to conduct virtual clinical trials to design and assess the potential impact of high-risk/high-benefit treatments using high Linear Energy Transfer (LET) radiations (i.e., protons, neutrons and carbon ions). Dr. Stewart is an internationally recognized authority on the applications of computer modeling in radiation biophysics.