frontiers in ONCOLOGY

SPECIALTY GRAND CHALLENGE ARTICLE
published: 27 May 2011
doi: 10.3389/fonc.2011.00007

Radiation oncology: today and tomorrow

Timothy James Kinsella*

Department of Radiation Oncology, Rhode Island Hospital, Warren Alpert Medical School of Brown University, Providence, RI, USA
**Correspondence: tkinsella@lifespan.org*

The twentieth century witnessed the birth of the medical discipline of Radiation Oncology, beginning with the discovery and clinical application of radium in the early 1900s. Subsequently, clinical radiation oncology evolved as a major modality for the treatment of most solid cancers with the initial use of orthovoltage x-rays, to the use of supervoltage photons and electrons and, most recently, to the use of neutrons, protons, and other charged particles. In the last quarter of the century, Radiation Oncology readily adapted and integrated the use of supercomputers and new imaging modalities (CT, MRI, PET/CT) into radiation treatment planning and delivery to transition from 2-dimensional (2-D) to 3-D, and now to 4-D treatment. As we moved through the first decade of the twenty-first century, our ability to carefully conform the radiation dose to the outlines of irregularly shaped tumor or target volumes while also creating a steep radiation dose gradient to adjacent normal tissues is now becoming standard-of-care with the use of image-guided and intensity-modulated radiation therapy (IGRT and IMRT, respectively) or with the use of stereotactic radio surgery (SRS). This rapid evolution in imaging and radiation treatment technologies was only made possible by the simultaneous integration of specialty trained medical physicists and dosimetrists as essential members of Radiation Oncology departments.

The latter half of the twentieth century also witnessed the development of radiation biology as an essential basic-translational component of Radiation Oncology. With the overall goal of better understanding the acute and late side effects of ionizing radiation (IR) on both malignant and normal cells/tissues, five major biologic concepts have emerged from these research efforts that currently influence clinical radiation oncology. These concepts (the so-called "5 R's") include: intrinsic cellular **r**adiosensitivity; acute/chronic hypoxia and **r**eoxygenation; differential DNA damage-**r**epair processing; cell cycle **r**edistribution; and tumor cell **r**epopulation. When combined with today's sophisticated 3-D and 4-D radiation treatment planning/delivery, the radiation oncologist attempts to interpolate the 5-R concepts into clinical practice for a particular tumor in a particular patient so as to maximize the therapeutic index (TI). However, since few cancers are now treated with radiation therapy as a single modality, determination of the maximum TI is complicated by the spatial and temporal interactions of radiation therapy with surgery, conventional chemotherapy, and newer biologics/small molecules. As such, close interactions amongst radiation oncologists, surgeons, and medical oncologists are clearly needed today and more so in the future as we attempt to improve the "complication-free" cure rates in certain cancers or to provide more effective and less toxic palliative treatment in other cancers. With newer combined modality approaches, treatment of some cancers as chronic diseases involving effective treatment of limited metastatic disease will be an emerging area for clinical research in Radiation Oncology.

Looking back over the last one to two decades, one can conclude that few medical disciplines have undergone such rapid change in treatment concepts and technologies as Radiation Oncology. However, looking ahead, many, many (Grand) challenges remain, particularly as we enter the era of "personalized" cancer therapy. As part of this introduction to *Frontiers of Radiation Oncology*, I will briefly describe three such challenges.

One major challenge for Radiation Oncology in the near future will be to broaden the current cross-disciplinary team of radiation oncologists, medical physicists, and radiation biologists to include engineers and mathematicians in a systems science/biology approach. The recent development of more cost–effective technologies to comprehensively assess DNA, RNA, protein, and metabolites in patients' tumors provides opportunities to tailor cancer care. We currently have validated molecular tests in breast and colorectal cancers which drive chemotherapy decision making. Is the radiation-chip on the horizon?

The promise of personalized radiation therapy will necessitate overcoming many theoretical and regulatory challenges. The new high-throughput technologies of genomics, proteinomics, and metabolomics when applied to patients' tumor or blood samples results in huge masses of data which are challenging to manage, visualize, and then convert to knowledge in a meaningful way to impact patients' tumor responses and/or normal tissue toxicities. A cross-disciplinary integrated systems biology approach involving engineering, physics, and mathematics with biological and medical insights will be necessary to convert the information from these multidimensional data sets into useful biomarkers to predict tumor response to treatment and to identify the key drivers (genes, proteins, metabolites) of tumor behavior that are potential targets for therapy. Such a systems understanding of the effects of targeted therapeutics (i.e., small molecules and biologics combined with radiation therapy) on signaling networks and homeostatic regulatory loops on tumor and normal tissues will be necessary to prevent excessive normal tissue toxicities and to develop more rational combinatorial therapies with radiation including the emerging treatment paradigm of synthetic lethality.

Over the last 5–10 years, the pre-clinical scientific literature has defined several molecular signaling pathways (or networks) which are activated by IR and which are potentially amenable to targeted therapies with biologics and/or small molecule inhibitors for tumor radiosensitization and, less commonly, for normal tissue radioprotection. Many of these potential targets have emerged from our improved understanding of the DNA damage and repair pathways. For example, in my inaugural article for *Frontiers in Radiation Oncology*, I describe in detail the results of several pre-clinical studies involving radiation biology and systems science approaches to enhance

iododeoxyuridine-mediated radiosensitization in DNA mismatch repair deficient (damage-tolerant) human cancers. Other potential direct modifiers of key signaling pathways involved in IR-induced DNA damage/repair include the use of biologics or small molecular inhibitors or ATM, DNA-PKcs, PARP, and DNA polymerases. Such modifiers can lead to increased residual IR-induced DNA strand breaks (both DSBs and SSBs) in tumor, and ideally less in irradiated normal tissues, to maintain a TI. Other direct modifiers of p53 and the cyclin dependent kinases, Chk1 and Chk2, have been shown experimentally to abrogate the G1 and G2/M IR-induced cell cycle checkpoints, also leading to increased unrepaired SSBs and DSBs and enhanced IR cytotoxicity.

The pre-clinical scientific literature has also designated the tumor microenvironment for potential IR-mediated targeted therapy. Acute and/or chronic hypoxia and a lowered (acidic) pH in the microenvironment result in tumor-associated alterations in cellular metabolism, angiogenesis, and genetic (DNA repair) stability. As such, newer targeted therapy attempting to target anaerobic glycolysis or tumor vasculature can also potentially enhance IR cytotoxicity. Finally, tumor targeted therapy using IR-inducible gene vectors offers a potential indirect approach to enhance tumor response through modification of a local immune (e.g., TNF release) pathway.

However, there are many translational challenges for the radiation oncology community involved in applying these exciting experimental findings to the clinic. In addition to the issues of the pharmacokinetics and pharmacodynamics of these biologics and small molecules, two of the greatest translational challenges involve the selection of appropriate patient/tumor groups and the determination of the optimal dosing schedules when combined with conventional or altered fractionated radiation therapy. Both of these challenges are multi-faceted. By definition, the target must be present in the tumor with sufficient differential expression from dose-limiting normal tissues to allow for an increased TI (or simply to maintain a TI). Currently, we do not have readily accessible diagnostics to provide molecular confirmation of the intended target nor available biomarkers (serum levels, imaging studies, etc.) to monitor the specificity of tumor targeting during treatment. While we can "image" hypoxia, for example, we cannot then simultaneously measure the effects of hypoxia on altering angiogenesis, DNA repair, or cellular metabolism. Given these current realities with respect to the integration of targeted therapies and radiation therapy, the overall challenge for the radiation oncology community in the future will be to begin to carefully design clinical trials with appropriate biomarker assessments for tumor and normal tissues. Hopefully, *Frontiers in Radiation Oncology* will provide a major forum for discussing the future successes (and failures) of such clinical trials as well as discussing new leads for targeted therapy using pre-clinical experimental models.

A second major challenge for Radiation Oncology will be to integrate the new insights on tumor and normal tissue radiobiology into a dynamic time-sensitive and spatial-sensitive treatment plan. Even with "sophisticated" IMRT and IGRT treatment planning and delivery, we assume that both tumor radiation sensitivity and normal tissue function are uniformly distributed within their respective volumes. We also assume that a particular patient's tumor and normal tissue radiobiological characteristics do not change during a several week course of radiation therapy. Unfortunately, both assumptions are probably wrong. More likely is the scenario where tumor and normal tissue biology changes during treatment and, as such, adaptive radiotherapy will be necessary to truly impact on the TI. The implementation of adaptive radiotherapy will require the development of newer functional imaging (MRI, MRS, PET) to monitor temporal and spatial variations in tumor radiation response and normal tissue function during the course of treatment.

Finally, in the era of medical cost containment for all medical fields, but especially for a high-tech discipline such as Radiation Oncology, we will need to develop new quantitative measures of comparative effectiveness. With our aging population in all parts of the world and the emergence of new forms of cancer (e.g., HPV-associated head and neck cancer), actuarial projections of the cancer burden may double over the next few decades. Toward this end, the discipline of Radiation Oncology must accept the challenge of making our treatment approaches more cost–effective while also striving to enhance the TI.

While I cite only three major challenges for the near future of Radiation Oncology, I know that there will be many others. With the support of the Editorial Board and the entire Radiation Oncology community, *Frontiers of Radiation Oncology* will be a major forum for addressing these and other future challenges. Welcome to the new journal and this new style of publishing!

Received: 18 February 2011; accepted: 17 May 2011; published online: 27 May 2011.
Citation: Kinsella TJ (2011) Radiation oncology: today and tomorrow. Front. Oncol. ***1****:7. doi: 10.3389/fonc.2011.00007*
This article was submitted to Frontiers in Radiation Oncology, a specialty of Frontiers in Oncology.