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Radiation Oncology—Linking Technology and Biology in the Treatment of Cancer

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Technical advances in radiation oncology including CT-simulation, 3D- conformal and intensity-modulated radiation therapy (IMRT) delivery techniques, and brachytherapy have allowed greater treatment precision and dose escalation. The ability to intensify treatment requires the identification of the critical targets within the treatment field, recognizing the unique biology of tumor, stroma and normal tissue. Precision is technology based while accuracy is biologically based. Therefore, the *intensity* of IMRT will undoubtedly mean an increase in both irradiation dose and the use of biological agents, the latter considered in the broadest sense. Radiation oncology has the potential and the opportunity to provide major contributions to the linkage between molecular and functional imaging, molecular profiling and novel therapeutics for the emerging molecular targets for cancer treatment. This process of 'credentialing' of molecular targets will require multi disciplinary imaging teams, clinicians and basic scientists. Future advances will depend on the appropriate integration of biology into the training of residents, continuing post graduate education, participation in innovative clinical research and commitment to the support of basic research as an essential component of the practice of radiation oncology.

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In the introduction to the lecture which was the basis for this article, Dr Jens Overgaard announced the recent passing of Dr Juliana Denekamp. Dr Juliana Denekamp, known to all as just 'Julie', was a major driving-force in the field of radiation biology (1, 2) and her legacy can be seen in many aspects of today's radiation biology and radiation oncology research and practice.

PERSPECTIVE

Julie's tireless efforts, enthusiasm, stimulating comments and questions, creativity and support for students and young scientists were inspirational and motivating. She touched so many of us with her work on tumor biology, hypoxia and, more recently, angiogenesis She was invariably pushing, pulling, cajoling and leading radiation biology into new fields and bringing laboratory science into the clinic. Her untimely death from metastatic breast cancer creates a gap that will not easily be filled. She will be sorely missed and her courage and grit have been inspirational.

While many in science and clinical medicine are justifiably pleased with the advances that have been made recently, Julie, in her words and in her life, reminds us just how far we have to go. As with virtually all medically related disciplines, we in radiation oncology and biology stand at a threshold unlike none before. As we enter the molecular era with the human genome being sequenced, there are opportunities before us in the radiation oncology-related sciences that will enable us to make important advances to reduce the burden of suffering from cancer. In the process, the biologists, chemists and physicists have new tools by which to understand the interaction of radiation with living beings and the clinicians have unique opportunities in the prevention, detection and treatment of cancer.

Julie encouraged us to embrace the challenges and also to endeavor to keep our complex multidisciplinary radiation research field working together. Important advances in any research discipline are not sufficient to translate basic discovery into clinically relevant applications. She would likely have reminded us that the focus of cancer research is on new knowledge and on bringing advances to the clinic—it is on people, on cancer patients and on those who, because of research, will never become cancer patients. Why is this integration of clinical practice and research important and, indeed, urgent? Without research, tomorrow's treatments, like those that helped but could not cure Julie, will be no better that today's.

Opportunities and challenges

This article provides an overview of what I believe to be some exciting opportunities available to our field that can put us in the forefront where technology, biophysics, tumor biology, clinical medicine and molecular biology meet. The article includes aspects of the Radiation Oncology Sciences Program (ROSP) at the National Cancer Institute (NCI) and indicates that the mission of ROSP and the many supporting groups within NCI is to help our field take advantage of the basic and translational research opportunities before us. The rapid and stunning advances in basic science may seem rather daunting to a clinical specialty built largely on technological advances. But radiation technology, physics and biology are inherently linked such that the advances yet to be made in technology will depend on our field's collective knowledge and research efforts in basic science. This requires substantially more than nominal commitment to the basic science education of radiation oncologists and more than nominal efforts by radiation oncologists, particularly those in the academic departments, to help support basic research and encourage young clinician scientists (3).

RADIATION SCIENCES—THE BLIND MAN AND THE ELEPHANT OR THE 'POWER OF 10'

In approaching the field of radiation oncology research, one can use the analogy of the 'blind man and the elephant', in that one investigator may see a very different field than another investigator working in the same general field. Building on the concept of 'microenvironment' so familiar to radiation biology, a number of research and clinical realms can be described (4). The opportunities for translational research in radiation oncology are addressed in Fig. 1, which is reprinted from a presentation from the International Conference on Translational Research (ICTR) (4).

Most clinical radiation therapy occurs in the realm of the macroenvironment, in which the effort is to identify the tumor and the critical normal tissues and then construct a treatment plan. The technical capabilities being implemented include intensity-modulated radiation therapy (IMRT), 3D conformal treatment, respiratory and/or motion gating, various brachytherapy techniques, neutrons (and neutron capture therapy), protons and ligand-bound radio-isotopes (e.g., radioimmunotherapy). Electronic portal imaging devices (EPIDs), real-time dosimeters and real-time video monitoring help define patient and organ motion during external beam treatment and may provide real-time correction, although the complexities of implementing such a strategy including appropriate quality assurance are challenging. Hitting the target requires defining the target, the latter being not just the tumor outline on the image but also subregions within the tumor volume that may contain invasive cancer, preinvasive or *in-situ* cancer, normal tissue such as vasculature and stroma, and cells representing the host response to the tumor, such as immune cells and the inflammatory reaction. In short, the sophistication of radiation delivery has come a very long way and the questions now relate to target definition and understanding 'dose' in biological terms and dose-response relationships.

The macro-environment for radiation research extends well beyond the individual patient, including population-based studies for radiation risk, carcinogenesis, radiation protection and important regulatory and safety issues.

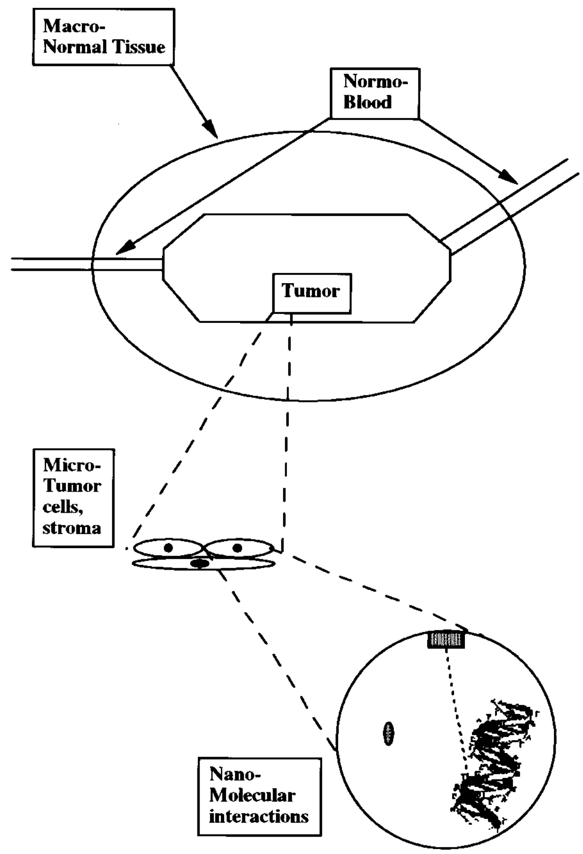

Fig. 1. Perspectives of radiation oncology sciences. Radiation oncology related research involves different 'environments' ranging from the macro- environment to the nano- and subnano-environments. The former include epidemiology studies of radiation exposure and risk and large randomized clinical trials. The micro- and nano-environments involve basic biological, chemical and physical sciences. The analogy of the 'blind man and the elephant' is useful in that investigators focusing in one discipline are seeing only a part of a larger research endeavor. Collaboration and interaction across such a broad field will strengthen the radiation research community and facilitate the application of science to people with or at risk for developing cancer. (Reprinted from (4)).

Nowadays, epidemiology is merging population-based studies, statistical analyses and molecular endpoints to better define risk and susceptibility to an environmental substance, e.g., alcohol or smoking addiction (5–7). Similarly, genetic polymorphisms may determine susceptibility to radiation-induced mutagenesis (8, 9).

Prognostic factors that emerge from the 'normo-environment' relate to the biology of the patient and the tumor. Concurrent illness, such as collagen vascular disease or diabetes, altered nutrition, advancing age, and the social situation of a patient may impact adversely on the patient's ability to undergo a course of curative radiation therapy so that 'adjustments' can be made that could represent a compromise in the overall treatment plan; for example, breaks may be required in a treatment regimen. Tumor burden as indicated by blood studies such as lactate dehydrogenase (LDH) and tumor markers such as PSA, CA-125, CEA, α-fetoprotein, βHCG, and so forth, are useful in predicting outcome and also in determining the likelihood of the presence of regional and metastatic disease as well as quantifying the tumor cell burden and the outcome of therapy (10–13). Anemia may require correction (14). The presence of certain inflammatory proteins such as TGFβ may help predict who will have pulmonary damage following treatment (15, 16) and who can tolerate dose escalation (17).

Imaging is rapidly progressing from the basic anatomical imaging to functional and molecular imaging, as recently reviewed in Seminars in Radiation Oncology (18–28). CT simulation serves as the basis for 3D treatment planning. However, an entire treatment plan is often based on a single image and organ motion and variable position are not accounted for. Motion can be significant, as has been well studied for prostate cancer. This results in using multiple imaging procedures to understand and account for motion (29–31) and also in the need for a margin of normal tissue to prevent underdosing owing to organ motion (32–34). This may require a substantial increase in normal tissue treated to high dose so that new techniques for real-time target localization, gating, or real-time treatment adaptation are of potential value, particularly if they can be done in the routine clinical setting so that they can be widely applied.

The study of tumor subregions is becoming a reality. The concept of biological treatment volume (BTV) has been coined by Ling (35) to indicate that there are regions within the planning target volume that might require or benefit from a higher tumor dose that can be delivered with the modern techniques listed above. One critical issue is that of validating the image. What is the biochemical process that produces the abnormal functional image? Is the tumor only in areas of abnormal signal or might extensive but 'subthreshold' amounts of tumor be elsewhere in the target volume that, too, might benefit from increased dose? Do changes that occur in an image during treatment indicate a response to therapy and are they predictive of outcome? How should one compare imaging modalities?

The preceding questions are fairly obvious but the technology and biology available for issues such as a) image co-registration among imaging modalities and patient registration between serial images must be very precisely determined; b) stereotactic techniques are likely to be required for tissue sampling; c) reasonably inexpensive techniques are needed to perform multiple samples in high through-put studies such as cDNA microarrays and proteomic analyses; and d) precise knowledge of treatment dose for both radiation and drugs in order to understand the relationship between a therapeutic intervention and a change in imaging and molecular profile. In essence, understanding the relationship between imaging and biology brings one down to the next realm, that of the microenvironment.

The microenvironment has been a province of radiation biology for many decades, the radioresistance of hypoxic cells being an area of intense interest for tumor biologists and radiation oncologists. The complexity and, indeed, importance of the tumor microenvironment in cancer development and progression at the molecular level have been discussed by Hanahan & Weinberg (36) who emphasized the importance of the 'heterotypic' environment within cancer that may be substantially different from tumor cells grown and studied in clonogenic cultures. As contained in Fig. 1 (4), the microenvironment contains many normal tissue and stromal cells that may have an impact on the outcome of radiation treatment and which, in turn, may become targets for therapeutic intervention, including blood vessels, inflammatory cells and their cytokines, immune cells, cell-to-cell contact (bystander effect) (37) and other interactions that can occur between tumor cells and between tumor and stroma. The consequences of intermittent blood-flow-produced ischemia, reperfusion and oxidative stress present a very complex picture in which a tumor cell *in situ* will likely behave quite differently from what one encounters in the artificial environment of the laboratory. Thus, the need to understand tumor biology in the patient is essential.

Completing the picture is the nano-environment. While radiation is not limited by cellular barriers and is far more homogeneously delivered than are drugs, at the track structure level, radiation is deposited heterogeneously (38–40). The consequences of this heterogeneity within the cell have still to be fully determined but there are data indicating that cellular targets for radiation effect and, indeed, cell death may occur in DNA and non-DNA targets including the cell membrane (41, 42) and possibly other organelles such as the mitochondria (43).

There are many molecular perturbations that can be produced by ionizing radiation and oxidative stress. What is of interest is that very low doses of radiation can produce substantial changes in gene expression that persist for many hours (44). The identification of radiation-inducible genes will be greatly facilitated by the cDNA microarray, high through-put techniques (45–47).

In summary, the various basic sciences that contribute to the knowledge of radiation oncology may have a very different perspective, depending on the vantage point of a specific field of radiation research. Excellent science must be done within the expertise and realm of the individual scientist, described as 'focus' by various grant review groups, yet such a narrow field of view may limit the broader perspective required to bring advances to the patient. All fields of research benefit from cross-fertilization but few probably span the range from large epidemiology studies with many hundred-thousand patient-year observations and randomized clinical trials involving tens of thousands of patients down to subnanometer to picometer track structure and charge transfer along molecules that occurs at Angstrom distances (48, 49). Thus, using the 'Power of 10' motif, radiation sciences span approximately 15 orders of magnitude, yet we are all looking at the same body of science and knowledge.

MOLECULAR TARGET CREDENTIALING—A UNIQUE OPPORTUNITY FOR RADIATION RESEARCH

The annual National Cancer Institute Bypass Budget includes Scientific Priorities for Cancer Research: NCI's Extraordinary Opportunities (found on www.nci.nih.gov). These are areas of investigation that through advice and input from many individuals within and outside the Institute are deemed to be of particular interest in the near future. Three priorities that fit well within the practice of clinical radiation therapy and the scope of basic research conducted within radiation biology programs are: Cancer Imaging, Defining the Signatures of Cancer Cells: Detection and Diagnosis, and Molecular Targets of Prevention and Treatment. Other area of relevance include Genes and the Environment and Research on Tobacco and Tobacco-related Cancers.

Radiation oncology will increasingly depend on functional and molecular imaging for target definition (35). How the image and the molecular abnormality are related remains to be defined. Imaging modalities such as PET discriminate cancer from normal tissue based on general metabolic abnormalities in cancer. MRI can determine oxygen concentration. Future imaging may be able to define cancer-specific molecular processes; for example, apoptosis or abnormal angiogenesis. Thus, since radiation oncology depends on anatomic localization, cancer imaging is of interest in target definition but research into the relationship between imaging and molecular signatures would be relevant to radiation oncology. The ability to define the molecular lesions in the cancer will likely be relevant to both prognosis but potentially useful in predicting the response to radiation therapy and the use of combined therapy with radiation plus new molecular targets.

Many new types of treatments have been designed for more specific molecular targets than the drugs of the past. An excellent example is STI-571 (Gleevac), which targets the BCR-ABL tyrosine kinase of chronic myelogenous leukemia (50–52). As occurs frequently, anti-cancer agents often find important roles when used in combination with radiation therapy. Clinical development will continue to be based on preclinical tumor models and, in part, on empirically designed clinical trials. Yet, the future will likely include treatments designed for specific targets, as defined by both molecular imaging and molecular signatures. These will include signatures of the individual cancer cells, but also phenotypes that occur within the complex tumor microenvironment, with hypoxia being an excellent example. It is reasonable to assume that the hypoxia-directed therapies could be used more effectively with knowledge of the presence of hypoxia and also its natural history during a course of therapy (53–55).

REDEFINING DOSE IN MOLECULAR TERMS

To administer radiation treatment safely and for comparison among institutions and laboratories, radiation dose is appropriately defined in terms of energy deposition and exposure. There is an enormously valuable practical experience that helps the clinician understand the dose–volume relationships for tumor control and normal tissue damage. There are a number of theories as to why certain organs have different tolerance to radiation and there are debates on the critical target for normal tissue and, indeed, tumor control. Is it the individual cell? the epithelial or the cancer cell? the stromal cell? the endothelial cell (56)? For normal tissue injury, what is the ongoing process between the time of treatment and a late reaction years or decades later? For treatment-related carcinogenesis, can the development of the secondary malignancy be prevented?

What is needed is the understanding of the molecular events within the tissue and tumor cells. For molecular targets, one can envision using the 'Gleevac' analogy for employing specific agents that target radiation-induced events. Some of these events may be produced at relatively low doses of irradiation (44) so that a radiation dose may be chosen based on the molecular events it produces rather than on the energy deposition in an ionization chamber or tissue-equivalent material. Furthermore, as is well known to clinical oncologists, agents that are not very effective in eradicating a local tumor per se can become effective when combined with radiation therapy. Many of the new molecular therapeutics are only cytostatic and might require an additional cytotoxic treatment, such as standard chemotherapy and/or radiation therapy.

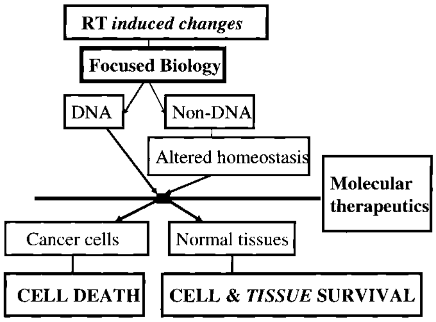

Fig. 2. Molecular targets for radiation therapy: focused biology. Radiation therapy will have novel uses by virtue of its ability to create molecular changes within a targeted volume. For systemic agents that produce changes in cancers that are cytostatic, radiation can be used as the 'killing agent'. A novel use for radiation therapy is to take advantage of the lesions that are produced and use these as the target for novel molecular therapeutics. The targets include the complex tumor-cancer cells and stroma- as well as the normal tissues that limit the amount of radiation that can be administered.

The potential new uses of radiation therapy in the "molecular era" are presented in Fig. 2. Radiation can be the 'killing agent' for cytostatic agents and radiation can also be the 'target-inducer' so that a molecular targeted drug may be useful after radiation triggers a critical process. Radiation has the advantage of going where it is aimed. In that vein, we at the Radiation Oncology Sciences Program refer to this use of radiation as 'focused biology', with the idea that radiation interaction with tissue is indeed a molecular event. Future units of measure for radiation, in addition to the currently used measures of exposure, might be molecular units, e.g, ability to induce certain signaling pathways or to alter expression of certain molecules.

TRANSLATIONAL RADIATION RESEARCH

The Radiation Oncology Sciences Program at the NCI has as its goal the advancement of radiation oncology research by helping to enhance collaborative programs as well as generating support and interest in new research concepts. Ongoing reorganization of the grant review process by the Panel on Scientific Boundaries for Review (PSBR) of the Center for Scientific Review, CSR (http://www.csr.nih.gov/EVENTS/updatephase2.htm) will have an impact on the review process for the radiation oncology sciences and technology with the intention of making the study section organizational structure more current and flexible. There is an emphasis on cross-fertilization, of which radiation oncology is an excellent example, involving multiple disciplines. This reorganization is being accomplished at the NIH and not the NCI level. Working with whatever structure emerges, ROSP will endeavor to be a resource for the field, using the extra- and intramural resources to enhance the productivity, efficacy and visibility of the research done by the greater radiation oncology sciences community.

Translational research requires an intellectually interactive environment in which researchers and clinicians aim to bring new advances to cancer care and prevention and clinicians bring observations, insights and material to the laboratory to enhance the understanding by basic scientists and physicists of the problems and issues encountered in the clinic. Through the conduct of workshops, the Radiation Research Program (RRP) brings together experts to help define the state of the art and science in various areas of radiation research and to formulate critical research questions. Should areas of research not be supported sufficiently, the RRP endeavors to find solutions. Given the complex and multiple areas of translational research, there is a need for a range of investigators including single institutions, industrial collaborations and cooperative groups. Some degree of coordination and/or information-sharing can optimize the flow of information and knowledge from the laboratory or technological development to Phase I and early Phase II trials and then into the national and international cooperative groups. The RRP has initiated a new program that is working closely with the Developmental Therapeutics Program (DTP) of the Division of Cancer Treatment and Diagnosis, in which the RRP is located. The Radiation Modifier Evaluation Module (RAMEM) is being established to study radiation–drug interactions, which is intended to serve as a resource, as is the DTP, to individual investigators and to industry. The goal is to develop novel molecular therapeutics for the radiation oncology community to study in the clinic. For the intramural program within the Center of Cancer Research (CCR), the Radiation Oncology Branch and Radiation Biology Branch are working on the concept of molecular target credentialing, as described above. Through fellowships, such as those recently developed by ASTRO, and other forms of collaboration, ROSP hopes to serve as a national and international resource for the field. A new program just recently approved is the Cancer Disparities Research Program (CDRP), which involves radiation oncology that helps to bring advances in cancer research to communities that historically have been underserved.

CONCLUSION

Radiation oncology, by virtue of its pillars of physics, chemistry, biology and medicine, is at a critical juncture. The benefits to be accrued by the development and proper use of technology are being enhanced by computer technology, imaging and highly sophisticated treatment delivery systems. While technology is the basis of daily practice, fundamental biology, chemistry and physics form the basis for understanding the etiology, prevention and treatment of cancer. For the good that can be derived from radiation

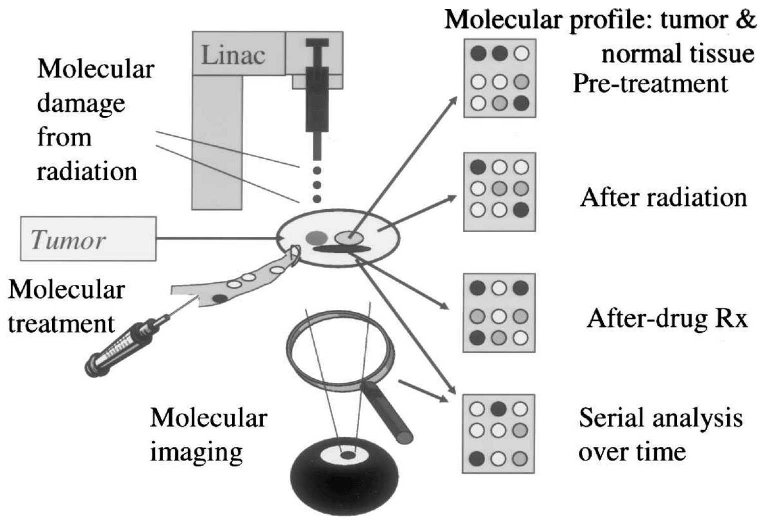

Fig. 3. Radiation therapy is a molecular event. The interaction between radiation and biological systems might best be thought of as a molecular event. While in clinical practice for treatment planning and quality assurance and for communication among laboratories, dose must be defined in terms of exposure; in effect dose is only a superficial description of the effects of radiation. Radiation oncology research should be a major contributor to molecular target credentialing, which involves imaging, molecular signatures and molecular targets. Information and knowledge can be derived both from large studies in which some information is obtained from each patient and also from small studies in which there is a 'dense study' of a limited number of patients. The latter is outlined in this figure in that multiple images and molecular correlates are studied before, during and after therapy. Conclusions from this type of 'dense study' are then used to optimize the design of the larger scale trials. The circles on the microarrays represent gene expression profiles of genes that are increased, decreased or unchanged in comparative analyses. Comparisons can be made between normal cells and tumor cells, pretreatment, and between cells before and after treatment with ionizing radiation and/or drug treatment. Comparisons can also be made from areas of a tumor that do and do not have a specific image; for example, an abnormal choline:citrate ratio, uptake of a hypoxic marker, or uptake of a PET isotope. Such studies will help optimize the time for post-treatment imaging and possibly provide an understanding of the tumor response to treatment sufficiently early in a course of therapy to allow for individualization of treatment.

oncology, I believe that we need an increased effort to bring together expertise that can be brought to bear to enhance the outcome of cancer therapy. Fig. 3 is a new cartoon for this millennium. One might think of the radiation source as a source of molecular events and not just a set of isodose curves. Understanding the nature of the interaction of radiation at the nano-level is essential for the optimal use at the micro-, normo- and macro-levels.

In our current world of healthcare in which many participants consider the "bottom line" to be the financial balance sheet, it is important to remember that while responsible use of resources is important, the aim of health and cancer care is to help people. Julie Denekamp is a reminder of the millions of people for whom our best efforts in 2001 are not yet good enough. We have much to do and we have better and better tools with which to combine superb technology with truly marvelous biology. We are fortunate to be in an era with such opportunity and advances. It is up to us to use them wisely and well.

REFERENCES

1. Fowler J. Juliana Littbrand-Denekamp. Radiother Oncol 2001; 60: 233–5.
2. Fowler J. The Denekamp diadems. Acta Oncol 2001; 40: 903–12.
3. Coleman CN. Young investigators' workshop—radiation research program, radiation oncology sciences program, National Cancer Institute, NIH, August 1–2 2000. Int J Radiat Oncol Biol Phys 2001; 49: 1505–16.
4. Coleman CN. International conference on translational research and preclinical strategies in radio-oncology (ICTR)-conference summary. Int J Radiat Oncol Biol Phys 2001; 49: 301–9.
5. Pastorelli R, Bardazzi G, Saieva C, et al. Genetic determinants of alcohol addiction and metabolism: a survey in Italy. Alcohol Clin Exp Res 2001; 25: 221–7.
6. Cheng LS, Swan GE, Carmelli D. A genetic analysis of smoking behavior in family members of older adult males. Addiction 2000; 95: 427–35.
7. Spitz MR, Shi H, Yang F, et al. Case-control study of the D2 dopamine receptor gene and smoking status in lung cancer patients. J Natl Cancer Inst 1998; 90: 358–63.
8. Wiese C, Gauny SS, Liu WC, et al. Different mechanisms of radiation-induced loss of heterozygosity in two human lymphoid cell lines from a single donor. Cancer Res 2001; 61: 1129–37.
9. Hollander MC, Kovalsky O, Salvador JM, et al. Dimethylbenzanthracene carcinogenesis in Gadd45a-null mice is associated with decreased DNA repair and increased mutation frequency. Cancer Res 2001; 61: 2487–91.
10. Partin AW, Kattan MW, Subong EN, et al. Combination of prostate-specific antigen, clinical stage, and Gleason score to predict pathological stage of localized prostate cancer. A multi-institutional update. JAMA 1997; 277: 1445–51.
11. Blute ML, Bergstralh EJ, Partin AW, et al. Validation of Partin tables for predicting pathological stage of clinically localized prostate cancer. J Urol 2000; 164: 1591–5.

12. Zagars GK, Pollack A, Kavadi VS, et al. Prostate-specific antigen and radiation therapy for clinically localized prostate cancer. Int J Radiat Oncol Biol Phys 1995; 32: 293–306.
13. D'Amico AV, Whittington R, Malkowicz SB, et al. Pretreatment nomogram for prostate-specific antigen recurrence after radical prostatectomy or external-beam radiation therapy for clinically localized prostate cancer. J Clin Oncol 1999; 17: 168–72.
14. Thomas G. The effect of hemoglobin level on radiotherapy outcomes: the Canadian experience. Semin Oncol 2001; 28: 60–5.
15. Anscher MS, Kong FM, Marks LB, et al. Changes in plasma transforming growth factor beta during radiotherapy and the risk of symptomatic radiation-induced pneumonitis. Int J Radiat Oncol Biol Phys 1997; 37: 253–8.
16. Garipagaoglu M, Munley MT, Hollis D, et al. The effect of patient-specific factors on radiation-induced regional lung injury. Int J Radiat Oncol Biol Phys 1999; 45: 331–8.
17. Anscher MS, Marks LB, Shafman TD, et al. Using plasma transforming growth factor beta-1 during radiotherapy to select patients for dose escalation. J Clin Oncol 2001; 19: 3758–65.
18. Watson GA, Kadota RP, Wisoff JH. Multidisciplinary management of pediatric low-grade gliomas. Semin Radiat Oncol 2001; 11: 152–62.
19. Morris DE, Bourland JD, Rosenman JG, et al. Three-dimensional conformal radiation treatment planning and delivery for low- and intermediate-grade gliomas. Semin Radiat Oncol 2001; 11: 124–37.
20. Ricci PE, Dungan DH. Imaging of low- and intermediate-grade gliomas. Semin Radiat Oncol 2001; 11: 103–12.
21. Rosenman J. Incorporating functional imaging information into radiation treatment. Semin Radiat Oncol 2001; 11: 83–92.
22. Neeman M, Provenzale JM, Dewhirst MW. Magnetic resonance imaging applications in the evaluation of tumor angiogenesis. Semin Radiat Oncol 2001; 11: 70–82.
23. Chapman JD, Schneider RF, Urbain JL, et al. Single-photon emission computed tomography and positron-emission tomography assays for tissue oxygenation. Semin Radiat Oncol 2001; 11: 47–57.
24. Sullivan DC, Hoffman JM. In vivo imaging of gene expression. Semin Radiat Oncol 2001; 11: 37–46.
25. Munley MT, Marks LB, Hardenbergh PH, et al. Functional imaging of normal tissues with nuclear medicine: applications in radiotherapy. Semin Radiat Oncol 2001; 11: 28–36.
26. Mankoff DA, Bellon JR. Positron-emission tomographic imaging of cancer: glucose metabolism and beyond. Semin Radiat Oncol 2001; 11: 16–27.
27. Zakian KL, Koutcher JA, Ballon D, et al. Developments in nuclear magnetic resonance imaging and spectroscopy: application to radiation oncology. Semin Radiat Oncol 2001; 11: 3–15.
28. Krishna MC, Subramanian S, Kuppusamy P, et al. Magnetic resonance imaging for in vivo assessment of tissue oxygen concentration. Semin Radiat Oncol 2001; 11: 58–69.
29. Martinez AA, Yan D, Lockman D, et al. Improvement in dose escalation using the process of adaptive radiotherapy combined with three-dimensional conformal or intensity-modulated beams for prostate cancer. Int J Radiat Oncol Biol Phys 2001; 50: 1226–34.
30. Yan D, Wong J, Vicini F, et al. Adaptive modification of treatment planning to minimize the deleterious effects of treatment setup errors. Int J Radiat Oncol Biol Phys 1997; 38: 197–206.
31. Lattanzi J, McNeely S, Hanlon A, et al. Daily CT localization for correcting portal errors in the treatment of prostate cancer. Int J Radiat Oncol Biol Phys 1998; 41: 1079–86.
32. Li JG, Xing L. Inverse planning incorporating organ motion. Med Phys 2000; 27: 1573–8.
33. Zelefsky MJ, Crean D, Mageras GS, et al. Quantification and predictors of prostate position variability in 50 patients evaluated with multiple CT scans during conformal radiotherapy. Radiother Oncol 1999; 50: 225–34.
34. Killoran JH, Kooy HM, Gladstone DJ, et al. A numerical simulation of organ motion and daily setup uncertainties: implications for radiation therapy. Int J Radiat Oncol Biol Phys 1997; 37: 213–21.
35. Ling CC, Humm J, Larson S, et al. Towards multidimensional radiotherapy (MDCRT): biological imaging and biological conformality. Int J Radiat Oncol Biol Phys 2000; 47: 551–60.
36. Hanahan D, Weinberg RA. The hallmarks of cancer. Cell 2000; 100: 57–70.
37. Mothersill C, Seymour C. Genomic instability, bystander effects and radiation risks: implications for development of protection strategies for man and the environment. Radiat Biol Radioecol 2000; 40: 615–20.
38. Nikjoo H, Uehara S, Wilson WE, et al. Track structure in radiation biology: theory and applications. Int J Radiat Biol 1998; 73: 355–64.
39. Goodhead DT. Initial events in the cellular effects of ionizing radiations: clustered damage in DNA. Int J Radiat Biol 1994; 65: 7–17.
40. Nikjoo H, Goodhead DT. Track structure analysis illustrating the prominent role of low-energy electrons in radiobiological effects of low-LET radiations. Phys Med Biol 1991; 36: 229–38.
41. Lozano J, Menendez S, Morales A, et al. Cell autonomous apoptosis defects in acid sphingomyelinase knockout fibroblasts. J Biol Chem 2001; 276: 442–8.
42. Haimovitz-Friedman A, Kolesnick RN, Fuks Z. Differential inhibition of radiation-induced apoptosis. Stem Cells 1997; 15: 43–7.
43. Taneja N, Tjalkens R, Philbert MA, et al. Irradiation of mitochondria initiates apoptosis in a cell free system. Oncogene 2001; 19: 167–77.
44. Amundson SA, Do KT, Fornace Jr AJ. Induction of stress genes by low doses of gamma rays. Radiat Res 1999; 152: 225–31.
45. Amundson SA, Bittner M, Meltzer P, et al. Physiological function as regulation of large transcriptional programs: the cellular response to genotoxic stress. Comp Biochem Physiol B Biochem Mol Biol 2001; 129: 703–10.
46. Amundson SA, Do KT, Shahab S, et al. Identification of potential mRNA biomarkers in peripheral blood lymphocytes for human exposure to ionizing radiation. Radiat Res 2000; 154: 342–6.
47. Amundson SA, Bittner M, Chen Y, et al. Fluorescent cDNA microarray hybridization reveals complexity and heterogeneity of cellular genotoxic stress responses. Oncogene 1999; 18: 3666–72.
48. Kelley SO, Barton JK. Electron transfer between bases in double helical DNA. Science 1999; 283: 375–81.
49. Boudaiffa B, Cloutier P, Hunting D, et al. Resonant formation of DNA strand breaks by low-energy (3 to 20 eV) electrons. Science 2000; 287: 1658–60.
50. Druker BJ, Sawyers CL, Kantarjian H, et al. Activity of a specific inhibitor of the BCR-ABL tyrosine kinase in the blast crisis of chronic myeloid leukemia and acute lymphoblastic leukemia with the Philadelphia chromosome. N Engl J Med 2001; 344: 1038–42.

51. Mauro MJ, Druker BJ. ST157 1: targeting BCR-ABL as therapy for CML. Oncologist 2001; 16: 233–8.
52. Gorre ME, Mohammed M, Ellwood K, et al. Clinical resistance to STI-571 cancer therapy caused by BCR-ABL gene mutation or amplification. Science 2001; 293: 876–80.
53. Hunjan S, Zhao D, Constantinescu A, Hahn EW, et al. Tumor oximetry: demonstration of an enhanced dynamic mapping procedure using fluorine-19 echo planar magnetic resonance imaging in the Dunning prostate 83327-AT1 rat tumor. Int J Radiat Oncol Biol Phys 2001; 49: 1097–8.
54. Taylor NJ, Baddeley H, Goodchild KA, et al. BOLD MRI of human tumor oxygenation during carbogen breathing. J Magn Reson Imaging 2001; 14: 156–63.
55. Krishna MC, Devasahayam N, Cook JA, et al. Electron paramagnetic resonance for small animal imaging applications. Ilar J 2001; 42: 209–18.
56. Paris F, Fuks Z, Kang A, et al. Endothelial apoptosis as the primary lesion initiating intestinal radiation damage in mice. Science 2001; 293: 293–7.