

## Personalized Treatment Approaches in Radiation Oncology: The Future Is Now

Significant recent research and technical advances now demand that our colleagues in other fields of oncology understand modern radiation therapy. This goes beyond the increasingly apparent benefit of multimodality cancer treatment. It is the surgical oncologist who identifies candidates for body radiosurgery. It is the medical oncologist who identifies patients for radionuclide therapy. And it is the responsibility of referring physicians to understand and critique the quality of radiotherapy services offered in their area. There has been a surge of new technological abilities in image guidance, radiation planning, and beam-targeting capabilities. Radiation oncology technology development has benefited from recent advances in computing power and software development, allowing more sophisticated and individualized treatment delivery. The focus of translational research in molecular targets and predictive assays holds the potential to benefit patients by allowing better prediction of both tumor response and normal tissue toxicity. These important advances in radiation oncology technology and biology will allow us to better personalize cancer treatment for individual patients. This personalization of radiotherapy is the focus of this issue.

Advances in imaging capabilities and in the integration of more sophisticated 3-D and 4-D imaging studies into radiation treatment planning procedures have resulted in increasingly precise target delineation and treatment delivery. Such research focuses on the physical properties of the tumor, target structures, and avoidance of normal organs at risk. More precise targeting allows for dose escalation as in the case of prostate cancer, hypofractionation as in the case of stereotactic radiation therapy for the brain and body, and better normal tissue avoidance as in the case of late toxicity to critical organs. In their article on stereotactic body radiation therapy (SBRT), Drs Dilling and Hoffe discuss the state-of-the-art approaches to areas of the body in the thorax and abdomen that were previously difficult to treat adequately. Lung SBRT is used to treat patients with early tumors who are medically inoperable, typically due to poor lung function, and in whom large radiation fields might result in fatal toxicity. Lung SBRT relies on 4-D imaging to account for the motion of the tumor in the chest based on individual patient respiratory patterns. This allows us to increase margins along axes with high mobility while shrinking margins along axes with little motion — thus delivering full tumor dose and minimizing dose to adjacent normal tissues. Several series have reported local control with SBRT in the range of 86% to 95%, with fairly minimal toxicity — these compare favorably with some surgical series. The abdomen is a difficult region of the body to treat due to the limited radiation tolerance of the normal organs, especially the small bowel, kidneys, and liver. Some liver masses are high-

ly mobile, while the normal liver parenchyma can be treated only up to certain limited volumes before fatal toxicity might be incurred. SBRT may be used to treat both primary liver tumors as well as oligometastases in the diseases in which liver resection of metastatic lesions may provide long-term survival. The advantage of SBRT is in its noninvasive nature, which is particularly appealing for patients with metastases or poor performance status but which may eventually be used in the majority of patients in lieu of surgery. Special equipment is required for SBRT, including specially designed linear accelerators with extremely accurate targeting capabilities, high resolution online imaging for daily setup and tumor localization, and strict immobilization techniques to prevent patient positioning errors between fractions. Such technological advances have led to improved individualization of radiation treatment for several diseases that were previously difficult to treat.

Advances in technology that allow more precise target delineation and treatment have also led to advances in treatment applications of physical principles for normal tissue dose and improvements in toxicity profiles. In general, greater normal tissue avoidance can allow higher doses to be delivered to primary tumors, which may improve the therapeutic ratio for diseases such as lung cancer, prostate cancer, and head and neck cancers. In the postoperative treatment setting, where dose escalation is not necessary, greater capability for normal tissue avoidance reduces acute and late toxicity, allowing for the safer use of concomitant systemic agents for radiosensitization. In their article on functional lung imaging, Dr Zhang and colleagues discuss how ventilation-perfusion imaging can be used to characterize the functionality of specific areas of lung in individual patients. Techniques to use deformable image registration from 4-D imaging with ventilation maps will allow radiation to be targeted through less functional areas of lung, thereby lessening potential pulmonary toxicity, increasing the feasibility of dose escalation and radiosensitization, and reducing toxicity. This also will allow the development of dose-function histograms, which should predict late pulmonary toxicity more accurately. In her article on late cardiac toxicity, Dr Harris discusses how studies of long-term toxicity outcomes over several decades of breast cancer treatment have consistently identified increases in cardiac toxicity, particularly coronary artery disease, in left-sided breast cancer patients and also how improvements in radiation technique over time designed to avoid the cardiac structures have resulted in reductions in these toxicities. Further individualized refinements in breast cancer irradiation techniques, such as intensity-modulated radiation therapy (IMRT), image-guided radiation therapy (IGRT), partial breast irradiation, and precision immobilization methods, should allow the mini-

mization of late cardiac toxicity from radiation in patients with left-sided breast cancer. Also of interest is how the patient's individual risk factors for other disease such as cardiac or lung disease, which are unrelated to cancer therapy but which may interact with treatments to modify toxicity profiles, and how personalized risk assessments may be incorporated into treatment planning design.

While research on the physical properties of tumors and normal tissue has led to rapid advancements in personalized radiation treatment in recent years, important advances in the understanding of tumor biology and normal tissue response are also making their way into clinical trials. Lung cancer has been a major focus of such studies due to its prevalence, its high mortality rate, the challenges in treating this disease successfully, and the high inherent toxicity in treating lung cancer. In their article on molecular-based treatment approaches for small cell lung cancer, Dr Bepler and associates discuss emerging molecular markers that predict for outcomes in this disease. These include prognostic markers, which help define tumor behavior and patient survival outcomes, as well as markers of therapeutic response. Prognostic markers that reflect tumor biology may be targeted for drug interventions that specifically address the genetic defects in the tumor and contribute to personalized treatment approaches based on the inherent biology of the specific tumor. For small cell lung cancer, these markers include ERCC1 and RRM1. Therapeutic response markers also aid in the individualization of cancer treatment by allowing the choice of the best drugs for use against a specific tumor. For example, low BRCA1 expression predicts for good platinum response but poor taxane response in small cell lung cancer, thus directing the clinician toward particular systemic therapy regimens. In their article on serum biomarkers to predict radiation lung toxicity, Dr Kong and coauthors focus on the ability to use molecular markers to customize radiation treatment plans in the treatment of thoracic malignancies, accounting for likely normal tissue response and allowing the clinician to monitor closely and specifically for radiation-induced lung toxicity. These markers may also allow for identification of patients who are optimal candidates for dose escalation. Useful markers in this regard include a number of cytokines, and proteomic studies are ongoing. Drs Torres-Roca and Stevens review the use of molecular predictive assays to provide individualize risk assessment for both tumor and normal tissue radiosensitivity. Such assays will ultimately allow for complete individualization of dose prescription based on the sensitivity of the tumor and not solely by the tolerance of the surrounding normal tissues, as dose prescription has typically been derived heretofore. For example, a gene expression profile has been characterized with significant accuracy in predicting radiosensitivity in a variety of tumor cell lines, and genes in the profile were found to be involved in molecular radioresponse pathways. Gene expression profiles may also be useful in predicting normal tissue tolerance.

As these articles highlight, a great deal of exciting and innovative research is focused on the ability to personalize cancer treatment by characterizing the inherent sensitivity of individual tumor to systemic therapies and to radiation therapy. Similarly, additional efforts are being focused

on the avoidance of critical normal organs and the characterization of normal tissue response in order to reduce toxicity to normal tissue and allow for dose escalation and other techniques that would improve therapeutic response. Approaches taking advantage of new technologies in imaging, computing, and radiation therapy equipment to characterize the physical properties of both tumor and normal tissues seek the same end. These techniques and assays are currently available for clinical use or are on the immediate horizon. While much remains to be studied and understood, an explosion of advancement in personalized cancer care is here now, for the benefit of cancer patients, with the goal of improving tumor control while reducing acute and late toxicity of treatment.

In addition to the articles on radiation, this issue of the *Cancer Control* also includes three research reports that address screening for cancer. The first two articles are part of our "Cancer, Culture and Literacy" section. The first focuses on colorectal cancer screening specifically in the Latino community. Dr Natale-Pereira and coauthors suggest strategies that could be used to overcome the top four barriers to screening in this population: low awareness, language barriers, lack of insurance, and undocumented legal status. In the second article, Dr Smith and colleagues provide results from a study of cervical cancer screening among Northern Plains Native Americans. Women were most comfortable with Pap test providers who offered information and were reassuring, encouraging, personable, constant, familiar, and female! Clearly, attention to the aspects of culture and literacy are of paramount importance in maximizing cancer screening practices in special populations. Lastly, a special report from Dr Hannon and associates on the status of colorectal screening by primary care physicians in Washington State suggests that three interventions should improve screening. Thus, physicians should know the current screening guidelines, they should strongly encourage their patients to undergo screening, and they should employ a tracking system to monitor compliance.

We hope you enjoy and benefit from reading this issue of *Cancer Control*.

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