Modern Radiotherapy—Exploiting Technology Integration

a report by
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DOI: 10.17925/OHR.2006.00.00.17

Soon after the discovery of X-rays in 1895, ionizing radiation was established as a potent therapeutic agent. From these origins, practitioners of radiotherapy (RT) have focussed on limiting radiation damage in healthy tissue while delivering a lethal dose to the tissues burdened with cancer. This principle has driven a number of important technological advances, including:

- accurate and precise delivery using robotically controlled linear accelerators and collimation systems;
- imaging modalities capable of providing accurate volumetric anatomical and physiological data for treatment planning;
- software systems that exploit imaging to construct virtual patient models;
- numerical algorithms for simulating and optimizing dose distributions during planning; and
- data and networking standards for the verify-and-record software used to manage patient-specific information and to transmit complex treatment plans.

Exploiting the integration of these advances has led to the development of novel therapeutic approaches, such as intensity modulated radiation therapy (IMRT).

Advances in Treatment Planning

Computed tomography (CT) imaging has shifted the focus of treatment planning and guidance from inferring disease location based on radiographic bony landmarks to a more direct method of using soft-tissue to define both the tumour target and the normal organs in three dimensions. Magnetic resonance imaging (MRI), positron emission tomography (PET), and single positron emission computed tomography (SPECT) are being increasingly used to augment the process with more anatomical detail, and with physiological data. The importance of volumetric imaging in treatment planning cannot be over-emphasized. The radiographic approach is expedient, but requires large radiation fields to ensure that all of the diseased tissue is included in the treated volume. This is carried out at the cost of including excess normal tissue and limiting the radiation dose prescription to prevent unreasonable side effects. In contrast, the anatomically conformal approach attempts to maximally avoid normal tissues, reducing the toxic effects of treatment and enabling dose escalation.

After the appropriate imaging has been performed, treatment planning proceeds in the patient's absence. Imaging data are transferred to the planning computer, and are used to create a virtual patient model. In a largely manual process, physicians delineate target volumes and the essential normal tissues that may be affected by treatment toxicity. The direct delineation of anatomical structures in three dimensions supports a confined-field approach in which a multi-leaf collimator (MLC) shapes beams to conform to the target volume. The ability to precisely locate diseased tissue and delineate normal structures leads to a geometric approach in directing therapeutic beams, with multiple beams traversing the body from a wide range of angles and converging on the target. Target coverage can be optimized with beams directed to avoid sensitive normal tissues. It is equally important to note that the segmentation of images into anatomical structures also supports detailed dose accounting to accompany records of target and normal tissue effects monitored in clinical trials, and in the follow-up of individual patient outcomes.

Intensity Modulated RT

Achieving a feasible trade-off between target coverage and normal tissue avoidance is not always feasible by purely geometric conformation. Target volumes can be embedded in large organs that are highly sensitive to radiation, such as the lung and liver, or be wrapped around small sensitive organs, such as the salivary gland, an optic nerve, or the spinal cord. A greater degree of flexibility is required in these situations and can be achieved by using a larger number of incident beams and by sub-dividing the beam area into a series of smaller beam segments. This approach began to emerge in the middle of the 1990s and is known as intensity-modulated radiation therapy (IMRT). IMRT is a logical evolution of the 3-D conformal therapy approach. It addresses the compromise between targets and normal tissues by using segments of varying intensity to sculpt a much tighter dose distribution around the target, sparing more healthy tissue in turn. The IMRT treatment of head and neck cancers and prostate cancer has already begun to produce clinical evidence demonstrating its utility.

For IMRT treatments, the treatment team typically specifies beam angles, target volumes, and the dose prescription—a computer calculates the optimum beam segments to provide the specified dose to the tumor and the specified degree of protection for normal adjacent structures. Tomotherapy is a fairly recent innovation in the field of IMRT. It uses a rotational delivery and moving table approach, so that the radiation source traverses in a dynamic helical pattern. Treating with a rotational arc and modulating the radiation field in a dynamic fashion can achieve a very high degree of modulation. Regardless of the particular aspects of the associated technologies, IMRT is highly patient-specific and requires a high degree of automation to manage the complexities of optimizing and delivering treatment. IMRT also requires the dissemination of new skills and knowledge to build the required staff expertise. It also requires more effort from physicians to define specific model of the patient and to provide a more detailed dose prescription. IMRT can also consume large amounts of time to optimize the treatment plan, and to verify that the treatment is safe and effective.

Image-guided RT

A majority of RT procedures, including IMRT, spread the radiation delivery over a period of weeks. Each treatment session delivers a fraction of the total dose. Fractions are delivered daily, or are at least separated by several hours, to allow healthy tissue repair to occur. Fractionation is predicated on the fact that healthy tissue repairs radiation damage promptly, while cancer cells are unable to completely repair the damage before the next treatment is given. A disadvantage of fractionated treatment is the need to re-establish the planned patient geometry prior to each treatment, and the need to account for uncertainties in patient position, organ movement, and positioning. Margins are included around treatment volumes, to compensate for uncertainties and physiologic motion, although these margins must be as small as possible to assure normal tissue protection. Some disease sites are unaffected by physiological motion, and set-up uncertainties can be controlled using mechanical fixation. Small brain tumors and certain benign brain disorders can be treated with stereotactic radiosurgery, which is based on a mechanical fixation frame adopted from neurosurgery applications. Radiosurgery involves a single ablative dose of radiation to a small and precisely localized volume and, like a surgical procedure, everything within this volume is destroyed with minimal side effects in the healthy tissue.

There has been a burgeoning interest in extending radiosurgery principles to diseases throughout the entire body. Stereotactic body RT (SBRT) imposes more stringent requirements on the accuracy and precision of treatment planning, patient positioning, and management of organ motion. Image-guidance reduces uncertainties by acquiring images before each treatment to permit verification and adjustment of the target position. Similar to the treatment planning process described in the previous sections, verification of treatment delivery with image guidance has begun a shift from localization inferred from radiographs to a more direct method of using CT scans in the treatment suite to establish the target location at any point during a treatment session.

New innovations in image-guided radiation therapy (IGRT), such as cone-beam CT (CBCT), are making this practical by aiding in the visualization of soft tissues, and creating the confidence needed to further reduce the safety margins that account for patient set-up uncertainty. Emerging improvements may also facilitate compensation for respiratory movements and shape distortion over the course of treatment through measurement of explicit motion, and even image-based treatment gating and target tracking.

What the Future Holds

Technological innovation continues to advance the accuracy and precision of RT. Heavy ion and proton beams have physical properties that can help to reduce normal tissue damage. Owing to their mass, heavy ions and protons interact intensively along their tracks and stop when they reach a depth related to their initial energy. Consequently, very little dose is deposited in the normal tissues that lie beyond the target volume—this is advantageous in certain pediatric diseases and in eye tumors; however, due to the associated costs of building and operating facilities, proton and ion beams are currently limited to only a few centers worldwide.

It is exciting to reflect on the future in the broader oncology context. IMRT and IGRT give radiation oncologists the capacity to respond to the laboratory developments emerging from the field of genomics and proteomics. Early clinical research has already begun on a number of fronts. Advances in the understanding of the genes and proteins that regulate the formation and growth of cancer and blood vessels

Photographed with the cooperation of Edward Hospital, Naperville, Illinois.

Everyday Triumphs in Oncology

Today, we turned improbable into possible. Advancing cancer care depends on more accurate detection and more precise treatment planning. Too often, though, "state-of-the-art" technology seems engineered for the future without enough day-to-day return on investment. Then we discovered some real breakthroughs in oncology. First, a hybrid SPECT/CT system. One flexible enough to increase patient throughput with stand-alone CT or SPECT exams. Next, a new big bore CT for more accurate radiation therapy planning, with a unique 85cm center opening for easier patient positioning. Finally, the first and only open PET/CT system. Combining localization accuracy with increased patient comfort and system flexibility. Improved detection and seamlessly integrated treatment planning. With the potential to provide immediate financial rewards for our department. Now, we give patients a better chance for more successful therapy. Futuristic systems ready for molecular medicine, designed for everyday use. Philips. It just makes sense.

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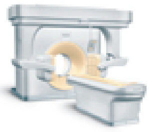
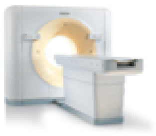


Precedence
SPECT/CT



Brilliance
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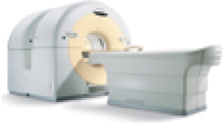

GEMINI
PET/CT

PHILIPS
sense and simplicity

can be expected to generate targeted therapies which work synergistically with RT. For example, new types of drugs are able to manipulate the formation of blood vessels by moderating angiogenesis or alter the hypoxic fraction of some tumors. Radiation could also be used promote stress-inducible genes implanted via gene therapy. Irradiation of the genes involved in the stress response could help to kill cancer cells. Compounds are also being developed to protect normal tissues. In addition to these therapeutic synergies, the continuing trend toward individualized medicine will be driven by the explosion of information originating from molecular biology and medical imaging, which is expected to support improved decision-making in selecting treatment options, and confidence in the delivery of radiation treatment.

The availability of soft-tissue imaging in the treatment suite is setting open the door to adaptive approaches to RT that provide the precision needed to push personalized therapies even further. Currently, radiation delivery is implemented on the basis of a single CT scan acquired prior to treatment. While the patient responds to radiation, to chemotherapy, or as surgical wounds heal, the tumour may change in size or shape, and uncertainties may arise regarding the patient's position and the geometry of internal organs. Adaptive therapy exploits the imaging acquired for IGRT to provide feedback of the therapy response. It seeks to adjust the treatment plan in response to changes measured over the course of fractionated treatment.

If measurable tumour shrinkage or patient weight loss occurs, the plan would be adjusted to conform to the updated shape of the tumour and position of normal tissues. At some level, adaptive RT can be practiced in many centers, at least in an 'off-line' capacity where measured patient changes are addressed by a new treatment plan, which is implemented at a later date. To realize its full potential, two important technical hurdles should be addressed to allow 'on-line' treatment planning, or 're-planning'.

One important hurdle is the need to accurately accumulate doses in deforming organs. This requires non-rigid, or deformable, anatomical registration of volumetric images in a manner that resolves anatomical distortions and tracks the trajectory of a tissue element over time. There is also a need to automate the segmentation of images to delineate targets and normal tissue. This task currently requires significant manual intervention. Automatic segmentation is the second crucial barrier, and a crucial element in the workflow required to implement an adaptive therapy approach. Automatic segmentation is needed to facilitate the repeated propagation and adaptation of structures over the course of treatment. Ideally, online adaptive re-planning would support a realtime evaluation of the patient in the treatment position by acquiring a CT scan, determining if there is a need to adjust the treatment plan on the basis of anatomical changes, and assist in the immediate implementation of the required adjustments. Tools for deformable image registration and automatic organ propagation are major steps toward realizing this goal.

There are certainly groups of patients who will not benefit from the exquisite precision afforded by IMRT, IGRT, and stereotactic methods. When using moderate doses to alleviate pain in palliative patients, or to treat diffuse diseases, such as certain lymphomas, the increased precision may not be warranted and the added complexity may impose an undue risk of technical error. On the other hand, the same technologies used to support adaptive re-planning of treatment could be used to perform *de novo* planning in the treatment room for patients requiring prompt emergent care (to alleviate the pain from metastatic disease in the spine, or the trauma associated with blocked airways). This would improve the delivery of palliative care and improve the patient's quality of life by reducing the time they spend in the RT department.

Using new and emerging technologies offers a number of provocative opportunities to improve RT effectiveness and efficiency, but the applications will only be as good as the basic clinical information and understanding of oncology will allow.

Ionizing radiation has been a proven therapy for more than 100 years. Steady technological advancement has led to continuing improvement and expanding applications of RT. IGRT has already begun to facilitate the extension of radiosurgery concepts and principles to the chest, abdomen, and pelvis. Cancer patients stand to gain tremendous benefit in terms of durable local control of disease, a reduced number of hospital visits, and fewer treatment side effects. This is true for frail and elderly patients who were unable to endure the toxic effects of conventional treatments, and for patients receiving aggressive schedules of RT integrated with surgery and chemotherapy. Ionizing radiation is firmly entrenched as a proven and effective therapeutic agent.

Continuing technological advances and integration with molecular medicine virtually assure that it will continue to improve and fulfil the challenges of expanding applications, and to provide benefits for cancer patients. ■