Evolution to Revolution:

THE (ACCELERATING) TECHNOLOGICAL PROGRESSION OF RADIATION THERAPY

By Donald B. Fuller, MD, Radiation Oncologist

Introduction and Brief History

Therapeutic radiation has a history that dates back over 100 years, with the discovery of X-rays by Roentgen in 1895 and the discovery of radium by the Curies in 1898. Remarkably, antineoplastic effects of this new modality were already described by 1899, with radium tubes being implanted into tumors as early as 1910, and the specialty of radiotherapy beginning in 1922, with the reported cure of laryngeal cancer by radiation.

The development of megavoltage radiation treatment in the 1950s, initially using 60Cobalt, and followed shortly thereafter by the more powerful and sharply defined linear accelerator beams, led to an ability to concentrate radiation deeply within the body, better restricting the high dose to the tumor-bearing area. In parallel with advancing technology, the radiobiologic discovery that fractionation (multiple treatments) created a differential effect favoring the death of neoplastic cells relative to normal cells formed the biologic basis of contemporary radiation oncology.

In the 1980s, the advent of electronic importation of advanced imaging techniques, such as CT, PET, and MRI, directly to the radiotherapy-planning computer defined the next major advance, enabling the direct modeling of a higher radiation dose around a more completely and accurately defined tumor volume — a process known as three-dimensional conformal radiotherapy (3DCRT). From there evolved an even larger technological advance in computing technology and treatment delivery known as intensity modulated radiotherapy (IMRT), leading to the contemporary ability to literally sculpt a high dose of radiation conformally around a tumor volume of virtually any configuration, resulting in vastly better normal tissue sparing from the high-dose region. This has enabled more powerful radiation doses to be applied, further increasing the effectiveness and safety of radiation treatment.

Although 3DCRT and IMRT represent tremendous technological advances, the radiation oncology technology revolution is not finished. It seems that every time we solve an old problem, we confront a new one.

> [T]he radiation technology revolution is not finished.

Tumor Motion and "4D" Radiotherapy: The Next Frontier

Many tumors are prone to moving during treatment, sometimes by as much as 5 cm, and not always along a simple linear path. Sources of tumor motion include patient movement after initial set-up, organ motion such as bowel peristalsis, and respiratory-induced motion.

The relatively recent full appreciation of the tumor motion problem and its potential to degrade the accuracy of highly conformal radiation methods such as IMRT has led to the next wave of technological development: Image-Guided Radiotherapy (IGRT). Briefly, IGRT means radiographically checking the position of the tumor before each and every radiation treatment and using this feedback to correct the patient's position correspondingly each day to bring treatment back into proper alignment. The obvious benefit of this approach is the ability to more accurately strike the tumor every day with the full radiation dose, while simultaneously shrinking the high-dose radiation margin further, protecting more normal tissue from radiation injury.

IGRT Methods

A number of innovative methods have been devised to perform IGRT, using ultrasound, conventional X-rays, or tomographic X-rays to fulfill the image-guidance step.

Ultrasound-based IGRT (Commercial Examples: BAT, Z-Med): This method is primarily applied for prostate cancer and utilizes a daily trans-abdominal ultrasound to visualize the position of the prostate and compare it with a three-dimensional computer reconstruction of prostate position based on the original treatment planning images. The ultrasound IGRT computer then prescribes X-Y-Z positional adjustments to compensate for daily organ-motion-induced prostate movement. The primary challenge of ultrasound-based IGRT is that these images are not always easy to interpret, and this introduces subjectivity into this method, potentially degrading its accuracy in some patients.

Fiducial-based IGRT (Commercial Examples: Brain Lab, Novalis): Fiducials are gold seeds that are easily visualized by kilovoltage X-rays that may be mounted in the ceiling of the treatment room or attached directly to the linear accelerator. These fiducials are implanted directly into the tumor-bearing region and then stereoscopically imaged, providing three-dimensional target volume location information, providing another X-Y-Z daily targeting adjustment mechanism, that is potentially less subjective than ultrasound-based methods. The primary disadvantages of fiducial-based IGRT include the need for an additional invasive step in the planning process and the potential for migration of the fiducials, which degrades their targeting accuracy.

Tomographic IGRT: (Commercial Examples: Varian Trilogy, TomoTherapy): The linear accelerator itself, or an attached kilovoltage head, may be made to rotate completely about the patient before each treatment, creating a volumetric CT image that displays the entire region to be treated each day. This cone-beam CT image (Varian Trilogy, Elekta Synergy) or helical CT image (TomoTherapy) may be matched with the original planning CT image and appropriate positional corrections made to bring the two image sets into daily alignment, again resulting in X-Y-Z target position correction before each daily treatment. The primary advantage of this method is the availability of a more complete image set for daily review, and, in the case of TomoTherapy, the ability to precisely treat very large segments of the body. Disadvantages include longer image processing time and sometimes difficult image interpretation, again introducing potential subjectivity into the alignment process.

Stereotactic Radiosurgery / Stereotactic Body Radiotherapy

Stereotactic Radiosurgery (SRS): The original SRS platform, the Gamma Knife, was actually developed decades ago by Swedish neurosurgeon Lars Leksell. This treatment system makes use of a frame to rigidly immobilize the head with an attached three-dimensional stereotactic reference frame, which may localize a tumor from a CT or MRI reference image series with sub-millimeter precision, and transfer that tumor position data to the treatment planning computer, which then directs 201 precisely focussed 60Cobalt beams to crossfire through the target volume. Subsequently, this same stereotactic, frame-based targeting methodology has been adapted to standard medical linear accelerators.

This degree of targeting precision has enabled a biologically more potent form of radiation — essentially ablative to all viable tissue within the targeted region in a single, large dose, yet with such sharp surrounding radiation fall off, that adjacent structures are well spared. Compared with standard radiotherapy, stereotactic radiosurgery has resulted in more durable control of intracranial lesions — particularly those that are "radioresistant," such as metastatic melanoma, providing an outcome comparable to surgical resection. Unfortunately, this technology does not address lesions beyond the head.

Stereotactic Body Radiotherapy (SBRT): The ability to target body areas beyond the head with precisely directed ablative radiation is the most recent innovation in radiation oncology, with early systems using an external body frame as the targeting reference system. Frame-based body systems are inherently less accurate than intracranial radiosurgery systems due to the greater degree of internal body target volume motion, though some impressive tumor ablation results have been reported with this approach, including one series report-

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reminds me of the child who presented recently with scissors sticking out of his skull.

The faculty here is personable and professional. They exhibit that balance of family, career, and self that so many preach but seldom live. Time in the OR is actually pleasant. People call each other by name, and there is no ducking of chucked instruments or responsibility. There is a focus on teaching not only the instruction of surgical skill but also how to empathetically care for a sick child and his or her family. It is comfortable here while still challenging, technically and intellectually.

January 18, 2006

Without much going on in the OR this afternoon, I sneak out and make it to another one of South Africa's many World Heritage Sites, Robben Island. Here, Nelson Mandela spent eighteen of his twenty-seven years of incarceration. As I sit on the ferry, I try to imagine what the political prisoners traveling in this same direction several decades ago must have thought. My tour of the prison is led by an ex-prisoner who recounts, with personal details, his experience during his five-year sentence. He shows us where he slept, where he ate, and brings everyone to Nelson Mandela's cell. This island, for me, has an eerie feel, but at times I feel the whole country is haunted. South Africans do not feel the same solemn reserve that I do visiting this place. They celebrate the end of Robben Island as it was once known. Now this site hosts New Year parties and dozens of weddings.

January 19, 2006

As I walk into the OR to help position our morning case, I hesitate. This five-year-old boy, operated on previously for a glioblastoma multiforme, is back for further resection. Locating the lesion is not difficult as it is protruding out of his skull 7 cm and is at least that wide in diameter. We start to operate, but we find we have to replace over 2.5 times his blood volume. The child is unstable, and the ever-cool anesthesiologist, in a flurry of vials and pacing, does his best to keep the child alive. Having replaced the bone on his skull, we close and send the patient and family home to wait for the pressure of the now inwardly expanding tumor.

January 20, 2006

By now I have made my way through the tourist's checklist of Cape Town: hideous baboons and hilarious penguins at Cape Point, the cable car to Table Mountain, concerts in Kirstenbosch National Botanical Gardens, a jazz festival at the Waterfront, and hikes up Lion's head and through Constantia National Forest. I have spent nearly every night watching the Africa's Cup on television with my friends from Zambia and Benin. We go out to a bar to watch a game, where two dozen avid fans yell, cry, and throw bar peanuts at the television screen. The next morning when I ask one of my colleagues if he had seen the game, he replies with a matter-of-fact tone, "White people don't watch soccer." The World Cup will be in South Africa in 2010.

January 24, 2006

When the mother carries her baby into the examination room, she unwraps the dressing from her 20-month-old baby's head. Underneath, a 5 cm diameter portion of brain covered in a thin layer of skin and dripping CSF protrudes from between her eyebrows. They have traveled three hours from a neighboring township for this visit. The mom politely asks my attending to fix her baby. She cannot take the child out of the house (and is therefore herself confined) for fear of judgment by her community.

January 28, 2006

It is my last weekend, and I am spending it with my South African friends on the western coast, two hours north of Cape Town. There is a lull, with each moment blending into the next, without the haste and urgency I am accustomed to at home. We spend all day chatting, stirring pots, and tending to the braii, which means "barbecue" in Afrikaans. My friend and I look out on the sunset together, a landscape that you could mistake for Baja if you didn't know you were on the other side of the world. She turns to me and says, "You know, people have been telling us our whole lives that we're not good enough, that our lives don't mean anything. But you have a choice. You can believe them or you can live your life for you, knowing that you have value even if no one ever tells you so. This is the position we are all in." SDP

While the extremes of wealth and poverty seem more accentuated here in South Africa, I realized our communities in San Diego are no more integrated.

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ing a 98 percent local control rate for early stage lung cancer lesions, without undue toxicity — a result that appears superior to conventional radiotherapy.

Robotic Radiosurgery: The most contemporary SBRT/SRS targeting platform, known as CyberKnife, makes use of continuous target volume tracking, extending the IGRT concept beyond initial set-up, carrying it through the entire treatment, continuously updating the target centroid. It accomplishes this without the need for rigid frame-based fixation.

Briefly, this method uses multiply repeated stereotactic kilovoltage X-ray imaging to identify fixed body landmarks such as skull or spine, or implanted gold seeds (fiducials), providing full, six-dimensional positional location data to the treatment computer, which then instructs the robotically mounted linear accelerator to make precise translational and rotational positional corrections every time the image set is updated, directing up to several hundred radiation beams through this continuously updated target volume with millimeter precision. The CyberKnife also has the distinction of being the only radiation delivery system capable of tracking respiratory-based tumor motion with millimeter precision, transferring this precision to the treatment of targets that move with respiration.

In summary, the CyberKnife system is the only current method that brings radiosurgical precision throughout the entire body, as well as enabling frameless cranial radiosurgery. An example of the benefit of the CyberKnife treatment system is provided by the Stanford University pancreatic carcinoma series, which reported a 100 percent local tumor control rate, using a single conformal ablative radiation dose, with an absence of serious toxicity. Spinal neoplasms, the majority of which were metastatic and recurrent after prior external beam radiotherapy, were treated with the CyberKnife in a series reported by Gersten, et al, with a 94 percent response rate, and absence of serious neurologic toxicity, again reflecting the precision of this device. Throughout the body, the benefits of this powerful targeting and treatment platform are only beginning to be fully defined.

Conclusion

At its core, radiation is a purely mathematical function. As such, this modality is uniquely well suited to computer modeling. As the computer becomes more powerful, so does the applied radiation, with no end of progression in sight. It is probably not a coincidence that the explosion of advanced technology radiation delivery devices and precision has paralleled the computer revolution.

The only unfortunate corollary is that computers tend to evolve more rapidly than clinical outcome data may be collected — a conundrum that threatens to leave patients, physicians, and payers frustratingly behind the coverage curve, waiting for the data to catch up with the technology, potentially negating the highest and best use of this amazing cancer killing technology. SDP

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