Radiation Oncology Research: An Exclusive Update

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Advancing Radiation Therapy

These are very exciting times in Cleveland, as we have opened Seidman Cancer Center, home of our freestanding cancer hospital at University Hospitals Case Medical Center. This issue of Innovations in Cancer focuses on radiation therapy and our Radiation Oncology Department, which now occupies a floor in the new UH Seidman Cancer Center that is complete with the latest, most-advanced equipment in the field and access to natural light in the waiting area.

In these pages, we have assembled our experts to address several topics in radiation therapy. These include image-guided radiation therapy for brain and spinal tumors (Simon Lo, MD), the Radiation Therapy and Oncology Group and its vision for clinical trials in radiation therapy (Mitchell Machtay, MD), combined modality treatments that are curative for cervical cancer (Charles Kunos, MD, PhD), and a number of clinical trials in prostate cancer that are being conducted through UH Seidman Cancer Center and our affiliated institutions (Rodney J. Ellis, MD).

We have found that by selecting the most appropriate radiation therapy treatment for an individual patient from our incredible array of equipment options, we can provide the best and most innovative care tailored to the needs of the patient, and with the least toxicity. We conclude with a brief update about UH Seidman Cancer Center and a look at two fall conferences sponsored by Case Western Reserve University School of Medicine.

I also would like to draw your attention to our new tag line, “Curing Cancer Every Day,” which speaks to our aspiration to provide the very best cancer care that we can. We take every opportunity with each of our treatment options to cure cancer. Where we cannot cure it today, we have a powerful interdisciplinary research engine behind us to cure cancer tomorrow. Our mission is to advance cancer therapy to the point where we can truly cure every cancer every day.

The UH Seidman Cancer Center multidisciplinary team approach is further enhanced by a Magnet-certified, dedicated and caring nursing staff, and the support and resources that come from being part of UH Case Medical Center. Among the nation’s leading academic medical centers, UH Case Medical Center is the primary affiliate of Case Western Reserve University School of Medicine, a nationally recognized leader in medical research and education.

For the sixth consecutive year, UH Case Medical Center is recognized by Thomson Reuters as one of the top 15 major teaching hospitals in the country – the only hospital in Northeast Ohio to achieve this designation. In addition, UH Case Medical Center is the only hospital in the state of Ohio and one of only three nationally with five or more Beacon Award-winning intensive care units.

Warm regards,

Stanton L. Gerson, MD
Director, University Hospitals Seidman Cancer Center and Case Comprehensive Cancer Center
Asa and Patricia Shiverick - Jane Shiverick (Tripp)
Professor of Hematological Oncology, Case Western Reserve University School of Medicine

Contact Us

We have many trials, including early stage trials, linked to our innovative approach to care. We would be glad to discuss interest or questions about these trials. You can contact any of the physicians listed in this issue. A more complete listing of our current trials can be found at UHSeidman.org. This Web site also features a video that introduces patients to clinical trials.
In the past, radiation oncology relied on somewhat rudimentary methods to verify the fields to treat, but with newer, image-guided techniques, radiation oncologists can now more clearly visualize a tumor and verify precise positioning of radiation beams. With our teams of physicians, physicists, dosimetrists and therapists, University Hospitals Seidman Cancer Center, located on the campus of UH Case Medical Center, offers patients treatments that involve focused delivery of radiation to the brain and spine. A review of the protocols and technology utilized reveals why these newer approaches can result in improved clinical outcomes.

**Radiosurgery Techniques**

CyberKnife® and Gamma Knife® radiosurgery target tumors by using a high dose of radiation while sparing healthy tissue. CyberKnife has broader applications for tumors elsewhere in the body, in addition to the brain and spine, while Gamma Knife is specifically designed to treat, with very high accuracy, intracranial and skull base tumors. Our newest Gamma Knife version, Perfexion™, employs 192 independent Co-60 sources delivering radiation beams that accurately target malignant lesions, arteriovenous malformation, small benign tumors such as vestibular schwannomas and meningiomas, tumors in surgically inaccessible areas of the brain, and lesions that lie close to vital structures.

**Controlling Pain and Tumor Growth**

UH Seidman Cancer Center is one of the relatively few sites that offer stereotactic body radiation therapy (SBRT), a powerful tool for targeting both primary and metastatic tumors in the spine, in addition to occasional benign spinal tumors. Primary cancers of the lung, prostate, kidney or breast cause most metastatic tumors in the spine, but almost any tumor can spread there. Even if a spinal tumor cannot be eradicated with SBRT, a patient who has spinal tumors may benefit from this approach both for pain management and for more durable control of tumor growth.

**Imaging with CT**

Our center also offers the options of TomoTherapy-based and LINAC (linear accelerator, with conebeam CT)-based SBRT. Both devices allow for GPS-like image guidance to locate the tumor prior to radiation delivery. This tool allows treatment to be adjusted daily as the tumor changes in volume or position. This technique also adjusts for changes in the patient’s body contour and variations in tissue density.

**Higher Doses, Fewer Treatments**

With the availability of advanced treatment devices, radiation therapy treatment planning techniques and image guidance plus the considerable experience and expertise available at UH Seidman Cancer Center, we can deliver a focused high dose of radiation to the tumor accurately and precisely in fewer treatments while sparing healthy tissue of damage from radiation. A large number of beams, which can be stationary or moving during treatment, are used to precisely deliver radiation to the target. This also provides a potential option for salvage treatment in patients who have already received significant doses of conventional radiation therapy but have recurrence in the same area.

**Further Research Directions**

The Radiation Therapy and Oncology Group (RTOG) 0631, a phase II/III study of image-guided SBRT for localized spine metastasis, currently undergoing central interim analysis, will reopen soon at UH Seidman Cancer Center.

**Integrated Care**

At UH Seidman Cancer Center, our teams of radiation and medical oncologists, surgeons and medical physicists work together to provide each patient a personalized treatment plan. We believe that having a broad set of treatment options allows us the greatest flexibility in designing optimal treatment plans for patients who have tumors of the brain and spine.
The Radiation Therapy Oncology Group (RTOG) asserts that hypothesis-driven, multidisciplinary, prospective trials are the superior way to advance knowledge of cancers and their cures. Single institution, retrospective research can be helpful, but by its nature is less rigorous and limited to older treatments. In addition, we believe that the path to improving cancer treatment is not just about radiation but also about combined modality therapy, especially as new and exciting agents and techniques in surgery and tissue acquisition are developed. The RTOG is a highly multidisciplinary group that includes medical, surgical and radiation oncologists. Many promising research initiatives are under way, and scientists and clinical researchers at University Hospitals Case Medical Center and Case Western Reserve University School of Medicine are playing key roles, including my international role as the RTOG’s Deputy Chair. UH Seidman Cancer Center recently became a Full Member of the RTOG, one of only 41 such centers in the U.S. and Canada.

Technology-Driven Trials
Radiation itself is the single most effective agent against almost every type of cancer cell. Technological limitations, however, inhibit our ability to provide enough radiation to certain tumor cells without producing dose-limiting adverse effects. One key type of radiotherapy trial evaluates technology-driven research, where we leverage advances in our knowledge of physics, engineering and computer software to develop better ways of irradiating and killing tumors and improving outcomes. An example is a series of ongoing studies at UH Seidman Cancer Center evaluating extracranial radiosurgery.

One of the department’s largest studies uses the CyberKnife® Robotic Radiosurgery System to treat prostate cancer. The research is novel in that we are able to provide what would otherwise be an eight- or nine-week course of radiation treatment in a week and a half, giving high, pinpointed doses in just five treatments. This is a total dose that we think will destroy all cancer cells in the prostate, but because it is targeted so precisely, we can avoid or limit radiation exposure and associated adverse effects to the urinary system, bladder, rectum and bowel. Eventually, we hope to use this approach to limit or avoid radiation to critical nerves and blood vessels that are important for sexual function. The principal investigator is Lee Ponsky, MD, Director, Urologic Oncology Center, UH Case Medical Center, and Associate Professor, Case Western Reserve University School of Medicine. Several members of our faculty are co-investigators, including Rodney J. Ellis, MD, Vice-Chairman, Clinical Research; Director, Genito-Urinary Oncology, Brachytherapy and Advanced Image-Guided Radiotherapy, Radiosurgery, UH Seidman Cancer Center; and Clinical Assistant Professor, Case Western Reserve University School of Medicine, an expert in image-guided radiation treatment for prostate cancer.

We believe it is important for our patients that this work is conducted as a prospective clinical trial with meticulous treatment planning and quality assurance, rather than administering it on an ad hoc basis. The early data look very promising, and UH Case Medical Center is one of the principal institutions proposing this to the RTOG as a national multicenter trial. The in-house study continues to enroll new participants, but we also anticipate that this larger RTOG protocol will open for further enrollment later this year.

Additional radiosurgery clinical trials are currently available in kidney cancer and gynecologic cancer, with plans soon for a clinical trial in pancreatic cancer.

Novel Drugs Plus Radiation
We specialize in another type of trial that combines novel radiation-sensitizing agents with radiation therapy. Radiation does not always cure cancer because some cancer cells are able to repair the damage caused by radiation through certain molecular pathways. Unfortunately, these radiation-resistant cancer cells can survive, spread and behave even more aggressively. We now think it is necessary to identify those cancers that are particularly resistant to standard radiation therapies, understand the cause of resistance, and learn to reverse that resistance.

As an example, certain head and neck cancers that are not associated with HPV infection do not respond well to standard radiation plus chemotherapy, so we are investigating the addition of targeted agents to the treatment protocols. We are particularly interested in agents that target the signal transduction pathways...
that extend between EGFR and other receptors and the cell nucleus. One such agent that has provided intriguing results is cetuximab. Min Yao, MD, PhD, Radiation Oncologist, UH Seidman Cancer Center, and Associate Professor, Case Western Reserve University School of Medicine, is principal investigator for a trial that studies the combination of reirradiation plus cisplatin plus cetuximab for recurrent head and neck cancer. Dr. Yao and I are also major participants in the national trial (RTOG 0920) of radiation therapy with or without cetuximab for head and neck cancer patients who have had surgery but are at relatively high risk for cancer recurrence.

Investigating Molecular Subtypes of Cancers

Radiation has developed a negative reputation for causing toxicity and severe complications that can harm quality of life. At UH Seidman Cancer Center and in RTOG as a whole, we have a renewed, strong focus on improving quality of life by using more-precise and smarter forms of radiation that cause less collateral damage to healthy tissue. We are very excited about this, and we view it as one of the great advances of the past decade.

In pursuing these improved radiation techniques, our researchers are finding that almost every cancer type is actually a composite of many types of cancers. For example, oncologists have long lumped together a whole group of cancers that start below the brain and above clavicles, calling them “head and neck cancers” and treating them as a single entity in clinical research trials and in routine care. We now know more about the molecular subtypes of these cancers and have discovered they consist of dozens of different diseases.

To illustrate this, consider HPV-positive cancer of the head and neck. This subtype is more responsive to radiation and chemotherapy than most other types, and we now recognize the need for customized treatment strategies. UH Seidman Cancer Center will be a major participant in the soon-to-open RTOG randomized trial of standard radiation plus chemotherapy versus radiation plus cetuximab (a less toxic agent that is still very effective) in patients with HPV-positive head and neck cancer. We hope to see equivalence of cure with better quality of life with cetuximab plus radiotherapy compared with older treatments. For patients whose head and neck cancers are unlikely to respond to conventional treatment, UH Seidman Cancer Center will be starting an early phase clinical trial that combines chemoradiotherapy with a novel inhibitor of another important molecular pathway (the MTOR pathway).

The Role of RTOG

The Radiation Therapy Oncology Group® (RTOG®; rtog.org) is the world’s leading multicenter radiation oncology clinical trials organization. RTOG works to increase survival and improve the quality of life for cancer patients. RTOG, a clinical research arm of the American College of Radiology, is a multi-institutional, international clinical cooperative group funded primarily by the National Cancer Institute.

Enrolling Patients

Some of the trials being conducted by the Radiation Therapy Oncology Group are offered at University Hospitals-affiliated institutions. For information on enrolling a patient in a radiation therapy-related clinical trial at UH Seidman Cancer Center, contact Ellen Perme, RN, ACN, Oncology Research Nurse, at Ellen.Perme@UHhospitals.org or 216-844-2512.

Ask Our Expert

For more about the information in this article, please contact the office of Mitchell Machtay, MD, at Denise.Moore@case.edu.
Feature Story

Improved Treatment Outcomes in Cervical Cancer

A novel agent sensitizes tumors to radiation and cisplatin

By Charles Kunos, MD, PhD

University Hospitals Seidman Cancer Center, through Case Comprehensive Cancer Center, in partnership with the National Cancer Institute (NCI), has been developing the novel radiation sensitizing agent triapine as a clinically useful tool in the treatment of cervical cancer. More than 12,000 American women are diagnosed with this type of tumor each year, and 35 to 40 percent have locally advanced disease that is not amenable to surgery. These women often respond to the current standard of care, cisplatin plus radiation, but a small number do not do well. For them, adding a biologic agent like triapine may significantly improve treatment outcome.

Triapine’s Mechanism of Action

DNA precursor production by ribonucleotide reductase (RNR) is a rate-limiting step in the cellular repair of both single- and double-strand breaks in DNA caused by radiation and DNA replication fork blocks produced by cisplatin. Unfortunately, RNR activity increases in cervical cancer cells when a patient receives radiation therapy, which reduces the cancer’s sensitivity to radiation and enhances tumor cell repair with further cancer growth and metastasis. Triapine (3-aminopyridine-2-carboxaldehyde thiosemicarbazone, 3-AP) is a potent, irreversible inhibitor of RNR activity.

Adding triapine to a patient’s treatment plan increases the sensitivity of cervical cancer cells to both radiation and chemotherapy, allowing us to stabilize patients who have metastatic disease and those with tumor cells that have reached the circulation but not yet created discernible metastases.

Impressive Early Results

Two studies of cervical cancer cells at UH Seidman Cancer Center demonstrated that triapine enhances radiation sensitivity in these tumors in vitro. We continued this research here with a small phase I study in 10 patients with cervical cancer who received radiation and intravenous cisplatin and triapine. We are cautious about the findings because of the small sample size, but the data were impressive. All the patients demonstrated complete response by the tumors in the pelvic region, a highly unusual and encouraging result.

We have now initiated a phase II clinical trial of patients with locally advanced stage IB2-IVA cervical cancer or stage II–IV vaginal cancer using this same regimen. All 19 women enrolled at the time this article was written had a complete response by the tumors in the pelvic region. These data were presented at a recent American Society of Clinical Oncology meeting. Furthermore, only two of the 29 patients treated to date in the phase I and II studies have developed metastatic disease after treatment, which is less than a fourth of the rate anticipated with standard therapies alone.

We are now planning a phase III trial, and UH Seidman Cancer Center hopes to be the lead institution for this international, multicenter investigation, in partnership with the NCI.

Possible Worldwide Applicability

One of the reasons that the planned phase III study is such exciting research is that triapine will be tested as an oral tablet for the first time in patients who have cervical cancer, which means trials can be undertaken in countries that lack the ability to easily refrigerate medications and provide nursing support during intravenous administration. These are the very countries where HPV-linked cervical cancer is most prevalent. Our hope is that oral triapine plus radiation may eventually replace the current standard of care, allowing a half-million women a year better access to high-quality treatment.

Other research in our laboratories focuses on another newer, orally administered radiation sensitizer, which also offers applicability beyond the traditional U.S. and European audiences.

Enrolling Patients

For more information about the ongoing triapine phase II trial and planned phase III trial, contact the office of Charles Kunos, MD, PhD, at 216-844-2537.
Innovations in Research

A Time for Trials

Four clinical studies offer prostate cancer patients new options for treatment

By Rodney J. Ellis, MD

University Hospitals Seidman Cancer Center, located at UH Case Medical Center, and through our affiliation with Case Western Reserve University School of Medicine, participates in many clinical trials that offer our patients novel options for cancer therapy. We are excited about the new opportunities afforded to us through the opening of UH Seidman Cancer Center, such as the recent announcement of our plans to become by 2014 the first proton therapy center to open in Ohio, and we look forward to advancing the standards of care in cancer treatment through successful accrual to leading-edge clinical trials. We are proud to be one of the foremost cancer centers in accrual for the Radiation Therapy Oncology Group (RTOG) trials nationally, especially for genito-urinary trials. Highlighted here are four ongoing, innovative trials for patients with prostate cancer.

Hormone Therapy for Intermediate Risk*

Intermediate risk prostate cancer patients often receive a combination of radiation and hormonal therapy. The current standard of care (SOC), however, employs higher doses of radiation than that used when this combination therapy was developed. RTOG-0815 was designed to determine whether hormonal therapy is still needed to maintain high cure rates in intermediate-risk patients who are given a high dose of radiation. This phase III, multicenter trial is enrolling patients with Gleason score 7 [3 + 4 or 4 + 3] and PSA less than 10 ng/mL.

 Physicians have considerable flexibility in determining how that radiation dose is delivered, either by electronic beam radiation therapy (EBRT) to 79.2 Gy or a combination of EBRT to 45 Gy followed by brachytherapy. The brachytherapy can be low-dose rate permanent seed implant or high-dose rate temporary seed implant depending on the study centers’ preferences. We are running two treatment arms at UH Seidman Cancer Center: (1) 45 Gy EBRT followed by permanent brachytherapy seed implant, and (2) 79.2 Gy EBRT.

Quality-of-Life Study*

RTOG-0831 explores how we can improve the quality of life for patients who have prostate cancer. It studies whether adding tadalafl to radiation therapy can prevent erectile dysfunction. The randomized, double-blinded, multicenter phase III trial compares daily, single-pill, six-month treatment with tadalafl versus placebo that is begun within seven days of initiating radiotherapy. Patients can receive the drug or placebo with either EBRT alone or brachytherapy alone.

Enlarging Radiation Field Size*

RTOG-0534, the SPPORT study, is enrolling patients who have had surgery to remove the prostate but whose PSA values are increasing, indicating risk of locally recurring disease or tumor metastasis. These men are usually referred for radiation to the prostate bed as the current SOC, but the salvage rate is only approximately 50 percent. This phase III, randomized multicenter trial will determine whether enlarging the radiation fields or adding hormone therapy will improve outcomes.

Shortening Radiosurgery Treatment

Case Trial 13807 is unique to our institution, and this type of treatment is not available to patients elsewhere in our region. We are evaluating an expedited CyberKnife radiotherapy protocol for men with low- to intermediate-risk prostate cancer. This trial, which is enrolling patients with Gleason score 6 or 7 [3 + 4] and PSA less than 10 ng/mL, shortens the course of stereotactic body radiotherapy (SBRT) to five treatments while providing the full radiation dose. Lee Ponsky, MD, Director, Urologic Oncology Center, UH Case Medical Center, and Associate Professor, Case Western Reserve University School of Medicine, is principal investigator.

* Case Western Reserve University received funding for this study from NCI.
Upcoming Conferences and CME

2nd Annual Graft Versus Host Disease International Symposium
On Nov. 4, 2011, the Meredith A. Cowden Foundation, in collaboration with UH Seidman Cancer Center and Case Comprehensive Cancer Center, Case Western Reserve University School of Medicine, will host the second annual GvHD (Graft versus Host Disease) International Symposium at the Renaissance Cleveland Hotel in Cleveland. The symposium brings together physicians, patients and health care specialists from leading cancer research hospitals and educational institutions across the country; more than 300 participants are anticipated this year.

The meeting unites physicians, researchers and other leading authorities in hematology/oncology, bone marrow transplantation and immunology to share their knowledge and resources with the goal of finding a cure for GvHD.

Details and registration are available on the 2011 GvHD Symposium Web site at gvhdsymposium.org.

International Conference, Integrative Oncology
The Eighth International Conference of the Society for Integrative Oncology (SIO), jointly sponsored by UH Seidman Cancer Center, Case Western Reserve University School of Medicine and SIO, will be Nov. 10–12, 2011, at the InterContinental Hotel and Conference Center in Cleveland.

The meeting, titled “Innovating Integrative Oncology: New Science, New Solutions,” will highlight current science behind integrative clinical care and discuss why oncology patients are asking for more nutrition assistance, psychosocial support and mind-body medicine. Specific topics include oxidative stress and antioxidants, regulation of botanical medicine development, mitigation of treatment toxicity, circadian disruption, and the impact of obesity and energy metabolism on cancer biology.

The presentations are geared to a range of oncology and medical professionals – integrative and conventionally trained – including physicians, researchers, oncology nurses, health care administrators, nutritionists, and other complementary therapy practitioners.

The keynote speaker will be Francis S. Collins, MD, PhD, Director, National Institutes of Health. Special guest speakers will include Kris Carr, New York Times best-selling author; Stanton L. Gerson, MD, Director, UH Seidman Cancer Center and Case Comprehensive Cancer Center; Michael Lisanti, MD, PhD, Professor, Stem Cell Biology and Regenerative Medicine, Thomas Jefferson University; and Bharat Aggarwal, PhD, Professor, Department of Experimental Therapeutics, Division of Cancer Medicine, the University of Texas MD Anderson Cancer Center.

Registration and additional information are available at integrativeonc.org/8th-annual-sio-conference.

Additional CME Opportunities
UH Seidman Cancer Center also provides many free CME courses online; details are available at UHseidman.org/cme.

Hospital News
University Hospitals Seidman Cancer Center, which opened in the spring, is already having a very positive impact on our ability to care for patients. Our physicians are utilizing the new Philips PET-MRI technology; it provides both anatomic information and specific molecular data about a patient’s tumor. Right in the operating room, the innovative intraoperative radiation therapy is delivering a dose of radiation to tumors such as gliomas.

UH Transfer Referral Center Hotline
Expedite adult and pediatric transfers with one call.
Services include:
■ Basic or ALS transports
■ Ground and air medical evacuation
■ Critical care transports
216-844-1111 or 1-800-421-9199

Your Feedback Is Important
As a medical professional, your input is invaluable in helping us shape future issues of Innovations in Cancer. We want to know what’s important to you. Do you want to read about cutting-edge research, learn about the latest technology, or hear firsthand case studies of how others in your specialty are improving and saving lives? Tell us what you want to read about and your name will be entered to win one of two Apple iPad 2s! Simply visit UHhospitals.org/innovations.