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THE TARGET

News from the Department of Radiation Oncology

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Immune therapy + stereotactic radiation = i-SABR

UT Southwestern is launching two innovative trials for metastatic prostate and renal cell cancers that will combine either a personalized cancer vaccine or an immuno-stimulatory agent with stereotactic ablative radiotherapy (SABR, also known as SBRT). SABR itself is known to generate a systemic immune response. The new trials will evaluate whether these two approaches can work synergistically to teach the patient's own body to rid itself of cancer.

Assistant Professor of Radiation Oncology Raquibul Hannan, M.D., Ph.D., is leading the new i-SABR trials (combining immunotherapy and stereotactic ablative radiotherapy).

Story continues on page 2

What's Inside

Collectively known as the i-SABR trials (immunotherapy + SABR), the studies led by Assistant Professor of Radiation Oncology Raquibul Hannan, M.D., Ph.D., are an effort to capitalize on the fact that tumors treated with radiation remain inside the body, leaving a source of tumor-specific antigens from the dying tumor cells. These dying tumor cells can essentially act as an in-place cancer vaccine, attracting dendritic cells that may notify the body's immune system to seek out and destroy cancer cell metastasis elsewhere in the body.

The so-called "abscopal effect," in which radiation delivered to a primary site of cancer results in shrinkage or elimination of cancer in the metastatic sites, is primarily noticed with the high radiation dose levels given in SABR as opposed to conventional radiotherapy.

This spring, UT Southwestern Radiation Oncology, along with colleagues in the Departments of Urology and Medical Oncology in the Simmons Cancer Center, opened a phase II clinical trial combining the prostate cancer vaccine sipuleucel-T with SABR for patients with metastatic, castrate-resistant prostate cancer.

The systemic part of the treatment—sipuleucel-T, which is for prostate—is also the first and so far only immunotherapy approved by the FDA for any type of cancer.

"There have been multiple phase III, randomized clinical trials of sipuleucel-T with adequate follow-up, so we know there is a survival benefit to its use," Dr. Hannan says. "Our goal is to see if we can make the therapy even more potent by combining it with the immunogenic effects of SABR."

> "We are going to do extensive studies to explore the specific biological aspects of how SABR interacts with immunotherapy."
>
> *—Raquibul Hannan, M.D., Ph.D.*

Dr. Hannan explores the biological basis for SABR's immune response.

Optimized for stereotactic treatments, the Vero linear accelerator at UT Southwestern—the first in North America—is often used to treat metastases.

Eligible patients may have any number of metastatic lesions; however, a maximum of six lesions will be treated with SABR in the trial. "The lesions that get priority are larger lesions, which we already know are more difficult for a systemic treatment alone to eradicate," Dr. Hannan explains. "We will also give priority to treat lesions causing pain or symptoms, as well as lesions that could cause debilitation, such as an impending fracture or spinal cord compression."

After their initial consultation and eligibility verification, patients would first go to an approved blood center to undergo leukapheresis, a process in which white blood cells are harvested. Those cells are sent to Dendreon, the maker of sipuleucel-T (trade name Provenge), which has a proprietary method of incubating a patient's dendritic cells with a prostate cancer antigen combined with an immunostimulant, creating an autologous cancer vaccine. The patient then returns to Simmons Cancer Center a few days later to receive an infusion of his own cells, which are now trained to be active against the prostate cancer.

The process is repeated twice over five weeks; meanwhile, radiation is delivered in one to three fractions, depending on the tolerability of the site, beginning with the second week of treatment.

"The idea is that while the activated dendritic cells from the vaccine are in circulation, stereotactic radiation therapy will kill cancer cells, making countless additional patient-specific tumor antigens available for cross-presentation and priming of the immune system, leading to a synergistic therapeutic effect between the two treatments," Dr. Hannan says.

The metastatic renal cancer trial, expected to open later this summer, is also a phase II study combining high-dose interleukin-2 (HD IL-2) with SABR.

This FDA-approved, nonspecific immunostimulant is given as an IV infusion every eight hours for a total of three weeks (including a one-week break) but must be given in an ICU setting because of its toxicity. This cycle is typically repeated once more if patients respond.

Although not an ideal treatment, HD IL-2 "gives the only chance of a cure for metastatic kidney cancer patients, as it results in a durable, long-term response in about seven to nine percent of patients," Dr. Hannan says. "But that's not very high, especially compared to its toxicity. Our goal is to increase this response rate by combining it with SABR."

An important part of both trials will be correlative laboratory studies.

"We are going to do extensive studies to explore the specific biological aspects of how SABR interacts with immunotherapy," says Dr. Hannan, whose earlier laboratory studies have shown that SABR initiates and augments a tumor-specific immune response by altering the tumor microenvironment. "Fully understanding how this process works will enable us to design more effective i-SABR treatment combinations for all cancer patients, not just prostate and kidney."

Endowed chair honors longtime leader

Department Chair Hak Choy, M.D. (left), with honoree David Pistenmaa, M.D., Ph.D.

Professor of Radiation Oncology David Pistenmaa, M.D., Ph.D., was honored with a dinner on March 14 to celebrate the elevation of the endowed position that bears his name.

Established in 2005, the David A. Pistenmaa, M.D., Ph.D., Distinguished Professorship in Radiation Oncology is now a university-designated Distinguished Chair with an endowment of $1 million. Dr. Pistenmaa, who chaired the Department of Radiation Oncology from 1996 to 2003, was presented with a chair and scroll at the event by UT Southwestern President Daniel K. Podolsky, M.D.

Dr. Pistenmaa graduated from West Point and received his medical degree in 1969 from Stanford Medical School and his Ph.D. in medical physics from the University of California at Berkeley.

He completed an internship in medicine at Cornell University Medical School and then returned to California and Stanford for a three-year residency in radiation therapy.

He was invited to join the Stanford faculty in Radiation Oncology and followed that with a stint at the National Cancer Institute (NCI) as chief of the Radiotherapy Development Branch. He left the NCI for private practice and headed the largest radiation oncology private practice group in the Washington, D.C./Virginia area.

Dr. Pistenmaa was recruited to UT Southwestern in 1992 to help form the new Harold C. Simmons Comprehensive Cancer Center. He was named Chair of the Department of Radiation Oncology in 1996 and led the planning and design efforts that resulted in the 2003 opening of the UT Southwestern Moncrief Radiation Oncology Building.

Dr. Pistenmaa is a Fellow of the American College of Radiology and he has consistently been on "Best Doctor" lists for Dallas.

Radiation oncology professionals complete training

This spring a new batch of health professionals graduated from each of the department's specialized radiation oncology programs.

Senior medical residents John Anderson, M.D., and Sheena Jain, M.D., have successfully completed four years of residency training in radiation oncology, and are now qualified to seek board certification.

In the Department's division of medical physics and engineering, medical physics resident Brian Hrycushko, Ph.D., was awarded his diploma for completing the two-year medical physics residency program.

And finally, six students in the Radiation Therapist Training Program (jointly operated by the university's School of Health Professions and the Department of Radiation Oncology) successfully completed that two-year program, earning either a Bachelor of Science degree or a post-baccalaureate certificate in radiation therapy.

Congratulations to all our trainees!

Graduates of UT Southwestern's Radiation Therapy Program

Superficial voltage system excels at treating skin cancer

The Department of Radiation Oncology's new superficial voltage system is geared to precisely treat small areas on the surface of the skin, including skin cancer, cutaneous lymphomas, and keloids, providing more pleasing cosmetic outcomes for patients.

"Just like its name, superficial voltage delivers the maximum dose right at the surface to a depth of about one centimeter, so we are able to limit the dose to the underlying tissue," says Assistant Professor Susie Chen, M.D..

It's a treatment that has come full circle in the history of the development of therapeutic radiation devices.

Low-energy superficial voltage (5-200 kilovolts) and orthovoltage (200-500 kilovolts) machines were originally the first radiation therapy devices used to treat all kinds of cancer prior to the invention of linear accelerators and the onset of cobalt-60 units. Orthovoltage and superficial voltage were then relegated to treating superficial tumors.

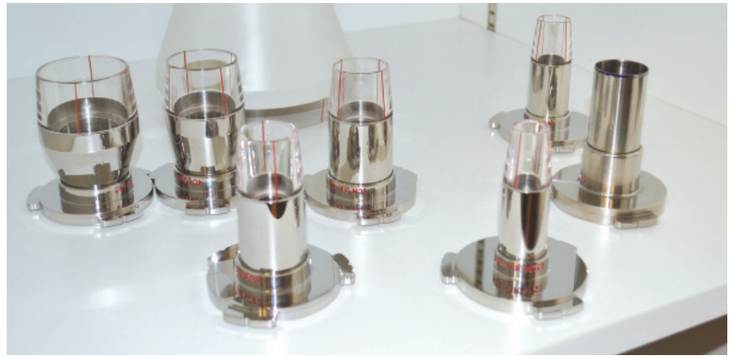
When electron beam therapy came into use, it supplanted both of these older technologies. But more recently, some have been reconsidering the use of orthovoltage and superficial voltage.

"The margin we treat is much tighter with superficial voltage due to the physics of it," Dr. Chen says. "This is a very specialized technology for skin that many other centers do not yet have."

UT Southwestern's superficial device is expected to be put to use most often in the facial area, where cosmetic results are better due to the system's limited field size and penetration. The tumor or other target will be outlined on the skin, and the information transferred to a sheet of lead in which a hole is cut out to match that shape. A cylindrical cone, with sizes ranging from 1.5 cm to 15 cm in diameter, is selected to cover the area and direct the radiation.

While it will not replace electron beam therapy, which is still extremely useful for large field sizes, superficial voltage will enable physicians in the Department of Radiation Oncology to choose from the widest range of tools available to best treat patients with superficial lesions of the skin.

The new superficial voltage system was installed this spring at the Harold C. Simmons Comprehensive Cancer Center–Radiation Oncology clinic.



Cylinders of different sizes shape the size of the radiation beam.

Clinical Trials Listing

BRAIN

072012-094 A prospective, multi-center trial of NovoTTF-100A together with temozolomide compared to temozolomide alone in patients with newly diagnosed GBM

052012-050 A randomized, double-blind, phase II, dose-ranging study to evaluate the safety and efficacy of veliparib and whole brain radiation therapy versus placebo and whole brain radiation therapy in subjects with brain metastases from non-small cell lung cancer

042011-075 Interstitial radioactive iodine implants for the treatment of pan-invasive pituitary macroadenomas

042011-050 Phase II trial of hippocampal-avoiding whole brain irradiation with simultaneous integrated boost for treatment of brain metastases

E3F05 Phase III study of radiation therapy with or without temozolomide for symptomatic or progressive low-grade gliomas

BREAST

102012-020 A phase II trial of ixabepilone and stereotactic body radiation therapy (SBRT) for patients with triple negative metastatic breast cancer

092012-058 Randomized, double-blind, vehicle-controlled pilot study of the efficacy and safety of HylaCare™ in the treatment of acute skin changes in patients undergoing external beam radiotherapy for tumors of the breast

072010-015 A phase I study of CyberKnife® partial breast irradiation (PBI) for early-stage breast cancer

RTOG 1014 A phase II study of repeat breast preserving surgery and 3D-conformal partial breast re-irradiation (PBRI) for local recurrence of breast carcinoma

RTOG 1005 A phase III trial of accelerated whole breast irradiation with hypofractionation plus concurrent boost versus standard whole breast irradiation plus sequential boost for early-stage breast cancer

GASTROINTESTINAL

032012-025 Phosphatidylserine-targeting antibody bavituximab in combination with capecitabine and radiation therapy for the treatment of stage II and III rectal adenocarcinoma

072010-093 Dose escalating study of single fraction stereotactic body radiation therapy (SBRT) for patients with hepatic metastases

RTOG 1010 A phase III trial evaluating the addition of trastuzumab to trimodality treatment of Her2-overexpressing esophageal adenocarcinoma

GYNECOLOGIC

RTOG 1203 A randomized phase III study of standard vs. IMRT pelvic radiation for postoperative treatment of endometrial and cervical cancer (TIME-C)

GOG 0274 / RTOG 1174 A phase III trial of adjuvant chemotherapy following chemoradiation as primary treatment for locally advanced cervical cancer compared to chemoradiation alone: The Outback Trial (ANZGOG 0902 /GOG 0274 / RTOG 1174)

GOG-0238 A randomized trial of pelvic irradiation with or without concurrent weekly cisplatin in patients with pelvic only recurrence of carcinoma of the uterine corpus

GOG-0263 Randomized phase III clinical trial of adjuvant radiation vs. chemoradiation in intermediate risk, stage I/IIA cervical cancer treated with initial radical hysterectomy and pelvic lymphadenectomy

GOG 279 A phase II trial evaluating cisplatin and gemcitabine concurrent with intensity-modulated radiation therapy (IMRT) in the treatment of locally advanced squamous cell carcinoma of the vulva

GOG 0258 A randomized phase III trial of cisplatin and tumor volume directed irradiation followed by carboplatin and paclitaxel vs. carboplatin and paclitaxel for optimally debulked, advanced endometrial carcinoma

GOG 0724 Phase III randomized study of concurrent chemotherapy and pelvic radiation therapy with or without adjuvant chemotherapy in high-risk patients with early-stage cervical carcinoma following radical hysterectomy

HEAD AND NECK

RTOG 3501 A phase II randomized, double blind, placebo-controlled study of lapatinib (Tykerb®) for non-HPV locally advanced head and neck cancer with concurrent chemoradiation

072010-48 A phase II multi-center study of concomitant cetuximab and cisplatin with re-irradiation using intensity-modulated radiotherapy (IMRT) in patients with recurrent squamous cell carcinoma of the head and neck

072010-046 A phase I/II study of nab-paclitaxel, cisplatin, and cetuximab with concurrent radiation therapy for local-regionally advanced head-and-neck squamous cell carcinoma

RTOG 0920 A phase III study of postoperative radiation therapy (IMRT) /- cetuximab for locally-advanced resected head and neck cancer

RTOG 1008 A randomized phase II study of adjuvant concurrent radiation and chemotherapy versus radiation alone in resected high-risk malignant salivary gland tumors

LUNG (THORACIC)

Small Cell Lung Cancer

CALGB 30610/RTOG 0538 A phase III comparison of thoracic radiotherapy regimes with cisplatin and etoposide in limited small cell lung cancer

RTOG 0937 Randomized phase II study comparing prophylactic cranial irradiation alone to prophylactic cranial irradiation and consolidative extracranial irradiation for extensive disease small cell lung cancer (ED-SCLC)

Non-Small Cell Lung Cancer

062012-53 A randomized phase I/II study of nab-paclitaxel, or paclitaxel, plus carboplatin with concurrent radiation therapy followed by consolidation in patients with favorable prognosis inoperable stage IIIA/B NSCLC

RTOG 1021 A randomized phase III study of sublobar resection (+/- brachytherapy) versus stereotactic body radiation therapy in high-risk patients with stage I NSCLC

RTOG 0813 Seamless phase I/II study of stereotactic body radiotherapy (SBRT) for early-stage, centrally located non-small cell lung cancer (NSCLC) in medically inoperable patients

052011-093 Phase III randomized study of standard versus accelerated hypofractionated image-guided radiation therapy (IGRT) in patients with stage II-III non-small cell lung cancer and poor performance status

PROSTATE

102012-026 Phase II trial of sipuleucel-T and stereotactic ablative body radiation (SABR) for patients with metastatic castrate-resistant prostate cancer (mCRPC)

RTOG 0815 A phase III prospective randomized trial of dose-escalated radiotherapy with or without short-term androgen deprivation therapy for patients with intermediate-risk prostate cancer

RTOG 0534 A phase III trial of short-term androgen deprivation with pelvic lymph node or prostate bed only radiotherapy (SPPORT) in prostate cancer patients with a rising PSA after radical prostatectomy

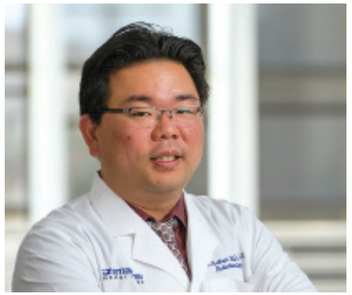
RTOG 1115 Phase III trial of dose-escalated radiation therapy and standard androgen deprivation therapy (ADT) with a GnRH agonist vs. dose escalated radiation therapy and enhanced ADT with a GnRH agonist and TAK-700 for men with high-risk prostate cancer

SPINE

072010-134 A phase II study of stereotactic body radiation therapy and vertebroplasty for localized spine metastasis

RTOG 0631 A phase II/III study of image-guided radiosurgery/SBRT for localized spine metastasis

For more information, please contact Clinical Research Manager Jean Wu at 214-633-1753 or jean.wu@utsouthwestern.edu.



Nathan Kim, M.D., Ph.D.

Clinic implements patient quality-of-life reporting

"We don't just forget about our patients once they've finished treatment here."

That's the message Assistant Professor of Radiation Oncology Nathan Kim, M.D., Ph.D., is hoping will be communicated to patients as the Department of Radiation Oncology this summer implements a new, Web-based, patient feedback system focusing on quality-of-life issues.

"This is an effort to not only look at our outcomes based on hard measures like survival or toxicity assessment, but also to get a sense of how patients are doing from their own perspective," Dr. Kim says.

"The idea behind getting patient-reported outcomes is to give the patient a voice, telling us how they feel they're really doing, not just how we think they're doing. It adds a new dimension to understanding how our treatments have impacted patients."

Radiation is known to have both acute (short-term) and long-term side effects, which makes follow-up particularly valuable, from both a scientific and patient perspective. "This new program allows us to follow up with patients, not only during their treatment but for months and years afterward, in order to evaluate the care our patients receive," Dr. Kim says.

In a pilot rollout beginning this summer, patients with gynecologic, head and neck, or genitourinary cancers will be enrolled in the program during their first consultation visit. They will complete a detailed series of questions tailored to the nature of their illness, either at workstations in the clinic or from home at their own convenience, using the Internet.

The clinic will use the VisionTree program, which encourages patients to participate by sending automated email reminders to patients at specified time intervals, up to two or three years after treatment.

"By collecting this information electronically using VisionTree, we are able to retrieve and analyze the data in real time, seamlessly. We can constantly assess how our patients are doing," Dr. Kim says. "It may alert us to make adjustments to our processes if we see discrepancies between our toxicity reporting and how our patients feel they are doing."

Physicians may also use the tool to compare the benefits of different treatment modalities.

"We have a vision for a comprehensive radiation therapy center, including plans for a particle therapy center here in the near future. One of the biggest questions in the field is how well this type of treatment modality measures up to current standards in terms of outcome, including quality of life," Dr. Kim says. "There are many ways the data can be used to further our understanding of how radiation therapy can be used to benefit cancer patients."

Indeed, the use of quality-of-life self-reporting for radiation patients is becoming a best practice at academic medical centers across the country.

"I think the message to patients is that they're not just treated and forgotten," Dr. Kim adds. "I believe it will strengthen our relationship with them and improve the overall quality of care."

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5801 Forest Park Rd.
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W.A. Monty and "Tex" Moncrief Radiation Oncology Building

5801 Forest Park Rd.
Dallas, TX 75390-9183

Annette Simmons Stereotactic Treatment Center UT Southwestern Zale Lipshy University Hospital

5151 Harry Hines Blvd.
Dallas, TX 75390-9183

Harold C. Simmons Comprehensive Cancer Center–Radiation Oncology

2001 Inwood Rd.
Dallas, TX 75390-9183

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