UT SOUTHWESTERN

THE TARGET

News from the Department of Radiation Oncology

VOLUME 2, SPRING 2011

Will the frontiers of space exploration impact cancer therapy?

UT Southwestern researchers gain $7.5 million NASA grant to find the answer.

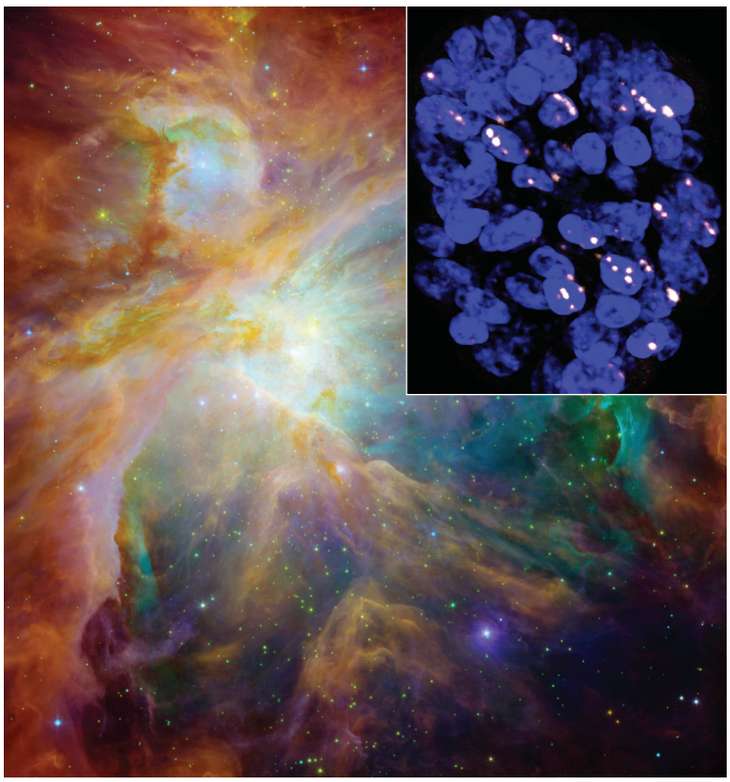

Image Courtesy of NASA, ESA, T. Megeath (University of Toledo) and M. Robberto (STScI). (Inset) Department of Radiation Oncology, UT Southwestern Medical Center

NASA deep-space image from the Hubble telescope and (inset) elemental iron tracks overlaid on 3D cell culture to mimic tissue.

Cancer is probably not the first thing that comes to mind when most people think about astronauts traveling in outer space. Yet cancer-causing, high mass and energy (HZE) particles like iron or silicon found in galactic cosmic rays currently pose a significant barrier to long-term manned space missions—a challenge that has opened promising new lines of investigation for cancer researchers.

Understanding and minimizing the health risks of space radiation is the primary goal behind a recent $7.5 million NASA Specialized Center of Research (NSCOR) grant awarded to UT Southwestern researchers in the Nancy B. and Jake L. Hamon Center for Therapeutic Oncology Research and the Department of Radiation Oncology. It follows on the heels of a $9.8 million grant that first established UT Southwestern as a NASA research center in 2005.

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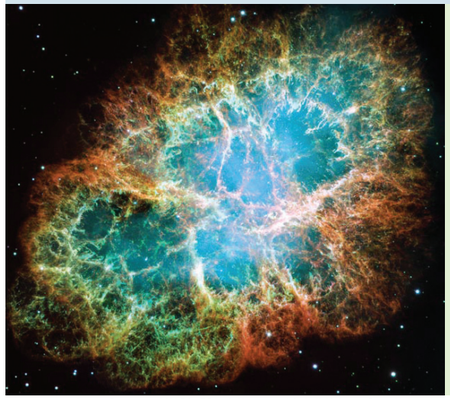


Image Courtesy of NASA, ESA, J. Hester and A. Loll (Arizona State University)

Understanding radiation's impact on the molecular and cellular level may lead to better assessment of the risk for cancer, as well as impacting other aspects of space exploration, from materials and design of aircraft to the creation of habitats for long-term missions.

The five-year grant "Risk Estimates and Mechanisms of Lung Cancer Pathogenesis After Space Radiation" is led by Dr. John Minna, director of the W.A. "Tex" and Deborah Moncrief Jr. Center for Cancer Genetics and the Nancy B. and Jake L. Hamon Center for Therapeutic Oncology Research. Other principals include Dr. David Chen, professor of radiation oncology and head of the molecular radiation biology division; Dr. Jerry Shay, professor of cell biology; Dr. Michael Story, associate professor of radiation oncology and director of the Simmons Cancer Center Genomics Core Facility; Dr. Yang Xie, assistant professor of clinical sciences; and Dr. Adi Gazdar, professor of pathology.

The grant is just one of several NASA grants in which the Department of Radiation Oncology participates through its Division of Molecular Radiation Biology [see box].

Currently, NASA astronauts are limited to radiation exposure equal to a 3 percent lifetime risk for a fatal cancer. For deep space missions that might be as little as a single mission, given the current margin of error in cancer risk estimation.

"That's a problem," pointed out Dr. Michael Story. "You can't spend a million dollars to train someone to go into space one time." Understanding radiation's impact on the molecular and cellular level, he said, may lead to better assessment of the risk for cancer, as well as impacting other aspects of space exploration, from materials and design of aircraft to the creation of habitats for long-term missions.

Dr. Story's portion of the NSCOR grants aims to determine how the combination of mass and energy of various particles affects the response of normal lung cells at the molecular and cellular level, including the rate of cellular transformation—one of the first steps in the oncogenic process. From there, using cell lines from Dr. John Minna's laboratory, the goal is to determine the variability in response to radiation between individual human lung cell lines, which may help NASA more precisely assign individual risk for cancer.

Another line of investigation is the examination of DNA damage and repair. Dr. David Chen, whose laboratory was the first to identify a key process (phosphorylation of DNA-PK) in DNA double-strand break rejoining, is examining DNA damage and repair in differentiated cell cultures that closely model cells of the lung. Dr. Jerry Shay is using mouse models to examine the role that chronic inflammation from very low dose rate radiation exposures may play in the onset of cancer.

Finally, Drs. Minna, Xie, and Gazdar are using an extensive tissue bank collected by Dr. Gazdar and colleagues from non-smokers with lung cancer to develop biomarkers for lung cancer in non-smokers. Drs. Minna and Xie will collaborate with all projects to build a similar set of biomarkers denoting the post-irradiation response, and compare and contrast those with Dr. Gazdar's biomarkers.

"By doing that, we essentially provide a toolkit for NASA for predicting lung cancer risk, possibly even before someone goes into space, just by assessing them genetically and looking at particular biomarkers," said Dr. Story. "Or we could enable them to assess these individuals throughout their careers to see if certain biomarkers appear."

From the viewpoint of radiation oncology, there is another important benefit to this program. Heavy particles are now being used for therapy—carbon in particular—yet the mechanisms by which they generate a clinical response are not yet well understood. Carbon therapy is being used in Europe and Asia, particularly in Japan and China. Currently there is no heavy particle treatment facility in North America.

Said Dr. Story, "By doing these kinds of studies we're leading the way for the use of these therapies in the United States, by developing an understanding of the molecular and cellular basis for response to therapy, for protons as well as for carbon and other particles that eventually may be used."

Department of Radiation Oncology NASA research

Shared NSCOR Grants

John Minna, Michael Story,* Jerry Shay, David Chen,* Yang Xie, Adi Gazdar; "Risk Estimates and Mechanisms of Lung Cancer Pathogenesis After Space Radiation" $7,500,000 (2011-16)

Michael Story;* "Genomic Analysis" $1,042,907, part of "NASA Specialized Center of Research on Radiation Carcinogenesis"‡ (June 2009–May 2014)

Individual Grants

Sandeep Burma; "Radiation and Gliomagenesis: A Sensitive Model System to Evaluate the Tumorigenic Potential of HZE Particles" $1,348,172 (January 2010-13)

David Chen; "Mechanisms of the Repair of HZE Induced DNA Double-Strand Breaks in Human Cells" $1,249,896 (September 2007-11)

Benjamin Chen; "Impact of HZE Particles on Adult Neural Stem Cells and Neurogenesis," $1,337,800 (August 2007-11)

* Department of Radiation Oncology

‡ Prime institution University of Texas Medical Branch in Galveston

News

Aspirin may enhance prostate cancer survival

Aspirin was recently linked to a reduced risk of prostate cancer death in a study of 5,295 men led by UT Southwestern physician and researcher Kevin Choe, MD, PhD.

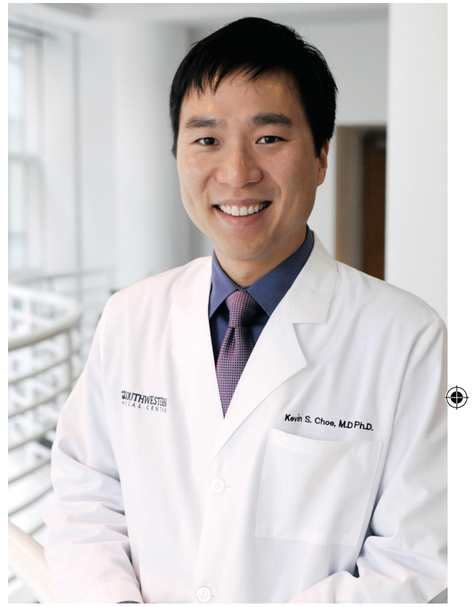
Participants in the study all had localized adenocarcinoma of the prostate treated either with radical prostatectomy (3,523 subjects) or radiotherapy (1,772 subjects). Thirty-seven percent of the total group were taking an anticoagulant, primarily aspirin, at enrollment or during follow-up.

After a median follow-up of 59 months, deaths attributable to prostate cancer were significantly reduced in the aspirin-taking group. The reduction in mortality was most prominent in patients with high-risk disease: at seven years only 2 percent of the high-risk patients who took aspirin had succumbed to prostate cancer versus 8 percent of the non-aspirin takers.

At 10 years the difference was even more striking: 4 percent mortality in the aspirin-taking group versus 22 percent of the non-aspirin takers. The benefit in prostate cancer mortality was not as significant in those taking other anticoagulants besides aspirin.

"Further studies are necessary to elucidate the underlying mechanism for this effect, but it may be that aspirin operates by suppressing metastasis," said Dr. Choe.

The findings were highlighted at the most recent annual meeting of the American Society for Radiation Oncology.



Kevin Choe, MD, PhD

After 10 years the study showed 4 percent mortality in the aspirin-taking group versus 22 percent of the non-aspirin takers.

Technology makes more women candidates for breast-sparing radiation treatment

Multilumen catheters for accelerated partial breast irradiation

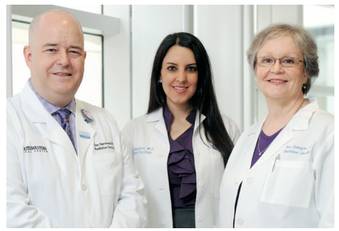
—by Ann Spangler, MD

Women whose tumors are located close to the skin or chest wall may now be considered for this treatment.

High dose rate intracavitary brachytherapy for early stage breast cancer has been in use for approximately five years. In this procedure, a balloon catheter delivers a high dose of radiation therapy (usually with iridium-192) to the breast tissue immediately surrounding the partial mastectomy tumor bed.

The advantage of this form of radiation is its ability to spare the remaining normal breast tissue from high doses of radiation, and to deliver treatment over a short time period, usually five days.

Initially, treatment was delivered using a MammoSite® single lumen catheter. The radioactive material was located in a single catheter in the center of the balloon, and delivered the radiation dose in a spherical distribution. By using several positions within the single lumen, a more elongated radiation distribution could be obtained, but the radiation dose was the same to all of the tissue at the same distance from the center of the catheter.



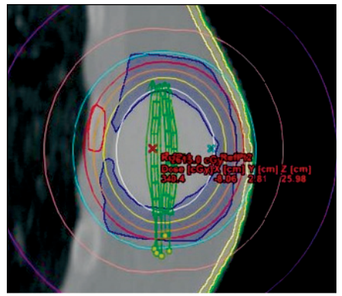
Breast specialists in the Department of Radiation Oncology: (l to r) Dr. Dan Garwood, Dr. Asal Shoushtari Rahimi (arriving July 2011) and Dr. Ann Spangler.

This generally provided an acceptable dose distribution, but in some patients with a smaller distance from the balloon to the skin or chest wall, those tissues would have received a higher dose than desired, and this treatment could not be offered.

Newer catheters now in use by the Department of Radiation Oncology at UT Southwestern have multiple lumens, permitting the iridium-192 source to be positioned either in the central catheter, as it would have been with the original single lumen catheter, or in one or more additional catheters offset from the central catheter. This permits differential shaping of the radiation dose to provide increased or decreased radiation dose depending on the shape of the cavity, or the normal tissues next to the balloon, specifically the skin and chest wall.

Several multilumen catheters are available, including Contura® and MammoSite.® By using the multilumen balloon catheter, the improved dose distribution permits consideration of this treatment modality in more women than with the single lumen catheter dose distribution.

Women who previously were not candidates for partial breast irradiation because their tumors were located close to the skin or chest wall may now be considered for this treatment as a result of the ability to steer the dose away from these structures with the newer catheters.



Contouring for dosimetric planning:

***White line** = Contura® balloon surface*

***Red line** = 1 cm expansion*

***Blue contour and line** = planning target volume for evaluation (PTV_EVAL)*

***Yellow lines** = skin surface and 5 mm for skin sparing*

***Small bright red oval** = closest rib surface*

UT Southwestern one of top sites nationwide for lung cancer clinical trials

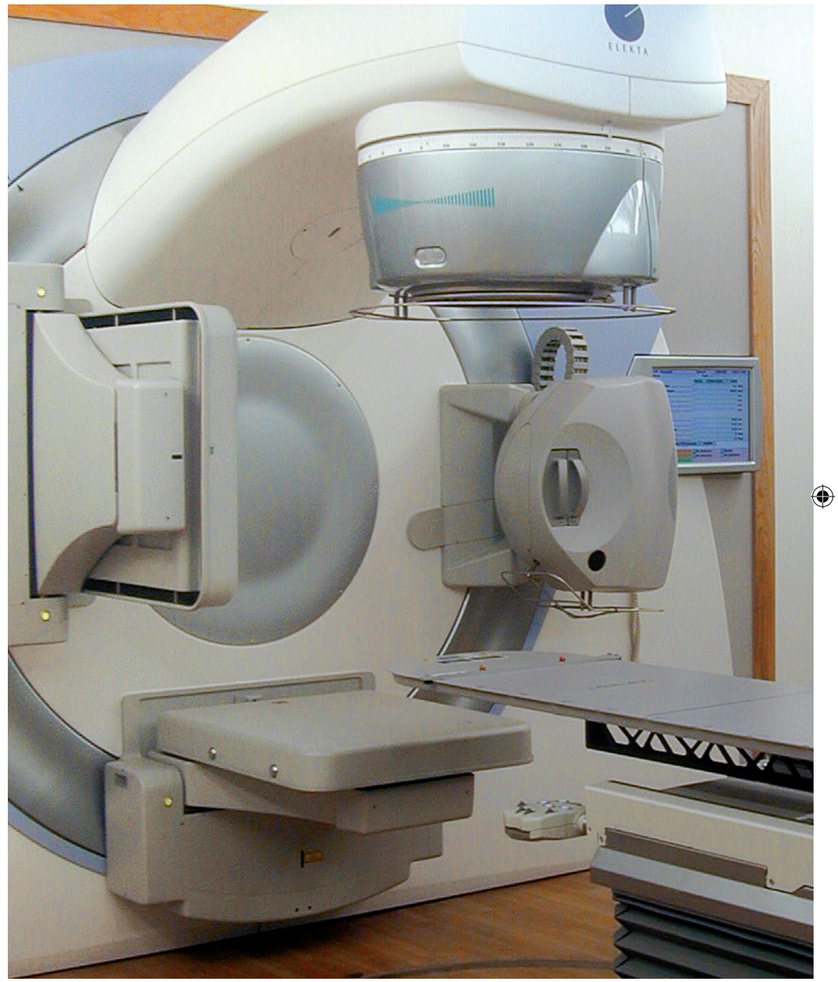
The Department of Radiation Oncology at UT Southwestern Medical Center is the 2nd highest-enrolling facility in the U.S. for lung cancer clinical trials initiated by the Radiation Therapy Oncology Group (RTOG), the leading multicenter research organization for radiation therapy trials.

According to the group's recent data, UT Southwestern has accrued more patients to lung cancer studies since joining the RTOG in 2005 than any other radiation facility except Cleveland Clinic Hospitals in Ohio.

"This ranking shows our commitment to research and to making leading-edge treatments available to our patients," says Dr. Robert Timmerman, professor of radiation oncology and neurosurgery, and director of clinical research in the Department of Radiation Oncology.

Currently the department has 23 total studies open to accrual, including 12 RTOG studies and 11 investigator-initiated studies. Last year, 104 UT Southwestern and Parkland patients were enrolled in therapeutic studies. An additional 229 patients were enrolled in non-therapeutic studies, most of them to create a tissue bank to help researchers explore the individual genetic response to radiation.

A further 23 patients were enrolled last year by study subsites at University of Minnesota, University of Colorado, Medical College of Wisconsin, MD Anderson Orlando, Case Western Reserve University, and Baylor Medical Center, all of which participate in the department's investigator-initiated studies. This year, Stanford University joins the group by participating in the UT Southwestern study "Hypofractionated image-guided radiation therapy (IGRT) in lung cancer patients with poor performance status."



Lung cancer patients receive stereotactic treatment on the Elekta Synergy-S

Full Clinical Trials Listing

BRAIN

082009-040 Phase I study of the combination of vorinostat and radiation therapy for the treatment of patients with brain metastases

RTOG 0825 Phase III double-blind placebo-controlled trial of conventional concurrent chemoradiation and adjuvant temozolomide plus bevacizumab versus conventional concurrent chemoradiation and adjuvant temozolomide in patients with newly diagnosed glioblastoma

BREAST

042010-052 Phase I study of CyberKnife partial breast irradiation (PBI) for early stage breast cancer

GASTROINTESTINAL

052010-013 Dose escalating study of single fraction stereotactic body radiation therapy (SBRT) for patients with hepatic metastases

GYNECOLOGIC

GOG 0249 Phase III trial of pelvic radiation therapy versus vaginal cuff brachytherapy followed by paclitaxel/carboplatin in patients with high-risk, early stage endometrial cancer

HEAD AND NECK

BMS CA 225314 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

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

LUNG (THORACIC)

Small Cell Lung Cancer

CALGB 30610/RTOG 0538 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 extra-cranial irradiation for extensive disease small cell lung cancer (ED-SCLC)

Non-Small Cell Lung Cancer

—Locally Advanced (III) or Inoperable (I/II)

RTOG 0617 Randomized phase III comparison of standard-dose (60 Gy) versus high-dose (74 Gy) conformal radiotherapy with concurrent and consolidation carboplatin/paclitaxel /- cetuximab (IND #103444) in patients with stage IIIA/IIIB non-small cell lung cancer

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

072009-061 Phase I study of accelerated hypofractionated image-guided radiation therapy (IGRT) in patients with stage II-IV non-small cell lung cancer and poor performance status

RTOG 0915 Randomized phase II study comparing 2 stereotactic body radiation therapy (SBRT) schedules for medically inoperable patients with stage I peripheral non-small cell lung cancer

—Metastatic (2 or more)

42007003 Phase II trial of erlotinib (Tarceva®) in combination with stereotactic body radiation therapy (SBRT) for patients with locally advanced or metastatic non-small cell lung cancer (NSCLC)

—Non-Therapeutic

SCCC-01508 Bold contrast magnetic resonance imaging (MRI) of lung tumors: physiological characterization of lung cancer

PROSTATE AND BLADDER

62006010 Phase I and II study of stereotactic body radiation therapy (SBRT) for low and intermediate risk prostate cancer

062009-014 Hypoxia assessment in localized prostate cancer: a companion protocol to a phase II study of stereotactic body radiation therapy (SBRT) for low and intermediate risk prostate cancer

122009-038 Phase I/II study of adjuvant prostate irradiation and ixabepilone for high risk prostate cancer post-prostatectomy

RTOG -0534 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 0815 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 0524 Phase I/II trial of a combination of paclitaxel and trastuzumab with daily irradiation or paclitaxel alone with daily irradiation following transurethral surgery for non-cystectomy candidates with muscle-invasive bladder cancer

SPINE

SCCC-03Z08 Phase II study of stereotactic body radiation therapy and vertebroplasty for localized spine metastasis

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

GENERAL

Non-Therapeutic

Tissue procurement and outcome collection for radiotherapy treated patients

Case Study

Customized radiation therapy for a rare sarcoma

John Bacon of Irving, Texas, age 63, didn't think he had much to worry about when he was told the lump in his right forearm didn't warrant immediate treatment. Lipomas, or masses of fatty tissue, are fairly common and benign.

"I let it go for about a year," recalled Mr. Bacon. "I assumed it was benign. But it was so big—about the size of a small egg—that it bothered me. I finally scheduled a surgery to have it removed."

When he did, lab analysis of the tumor revealed that it actually contained a 5 cm soft tissue sarcoma, a rare but aggressive cancer. Mr. Bacon came to UT Southwestern for his definitive treatment, which included a re-excision of the tumor bed to remove all positive margins, followed by radiation therapy.

Radiation oncologist Thomas Boike, MD, felt that a customized brachytherapy treatment, in which catheters are placed into the wound at the time of surgery, would deliver the most tightly controlled radiation dose to the tumor bed while sparing healthy tissue. In this case, the goal was to preserve the skin and elbow joint, which closely abutted the tumor bed.

Mr. Bacon's personal circumstances were also a consideration. "Typically a six-week course of radiation therapy could be offered," Dr. Boike explained. "But Mr. Bacon works full-time to support his family and it would have been difficult to take time off for six weeks. With brachytherapy, we can deliver the same dose in a more focused manner, in just five days."

Working with Rohit Sharma, MD, of the surgical oncology department at UT Southwestern's Simmons Cancer Center, Dr. Boike implanted 12 hollow brachytherapy catheters into Mr. Bacon's arm. After healing from his surgery for a few days, Mr. Bacon came to the Department of Radiation Oncology for a CT scan. Medical physicist and brachytherapy expert Strahinja Stojadinovic, PhD, precisely outlined each individual wire on the patient's CT scans, and then used a computer model to simulate the placement of a live source inside each of the catheter tubes in order to optimize coverage of the planned tumor volume.

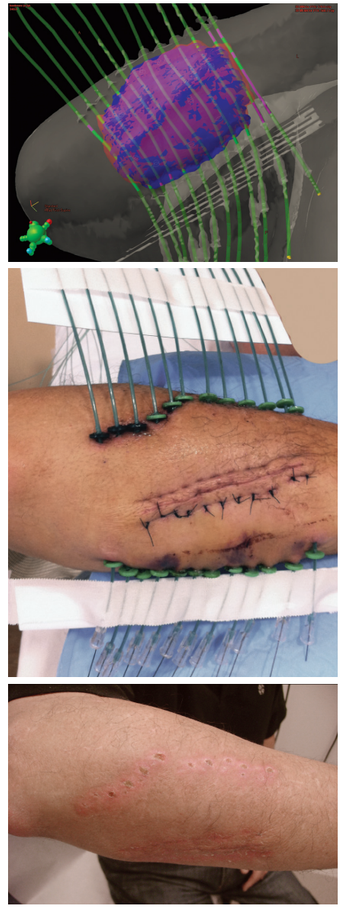
"This is as close as it gets to personalized radiation treatment," said Dr. Stojadinovic. "With the interstitial implant we custom-make the actual delivery vehicle of the radiation. This goes beyond looking at a patient's scans and delineating a target volume."

"The advantage of brachytherapy over external beam therapy is that the radiation dose is placed where it needs to be, so there is no entry or exit dose," continued Dr. Stojadinovic. "The dose fall-off is also very sharp, which means a minimal dose to healthy tissue."

Afterwards, Mr. Bacon was treated twice a day for five days, receiving a total dose of 34 Gy, or the biological equivalent of 45 Gy due to the hypofractionated course of therapy. "Brachytherapy is the original hypofractionated treatment," noted Dr. Boike, "although most physicians don't refer to it that way anymore."

A "seed" of radioactive iridium-192 placed on the end of a wire traveled through the various catheters into the tumor bed, where it released radiation at different points along the treatment canals. After Mr. Bacon's final treatment, the catheters were removed and the wounds sutured shut. Two months later, the visible traces of his treatment are almost gone.

"Sarcoma is a rare tumor and very histologically diverse," said Dr. Boike. "We see a fair number of them here at UT Southwestern sent by referring physicians because they are so unusual."



The customized brachytherapy treatment sought to preserve the skin and elbow joint, which closely abutted the tumor bed.

"Our multidisciplinary team of medical, surgical, and radiation oncologists specialized in treating sarcoma is proud to have the option of high dose rate brachytherapy to offer our patients," he added. "Our emphasis is interdisciplinary care."

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UT Southwestern Patient Services Ambassadors: 214-648-7001

Physicians who would like to make a referral may call the department's main clinic number or UT Southwestern's physician referral line at 214-645-5455 (toll free 866-645-5455) for adult patients or 800-5379 for pediatric patients.

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