UT SOUTHWESTERN

THE TARGET

News from the Department of Radiation Oncology

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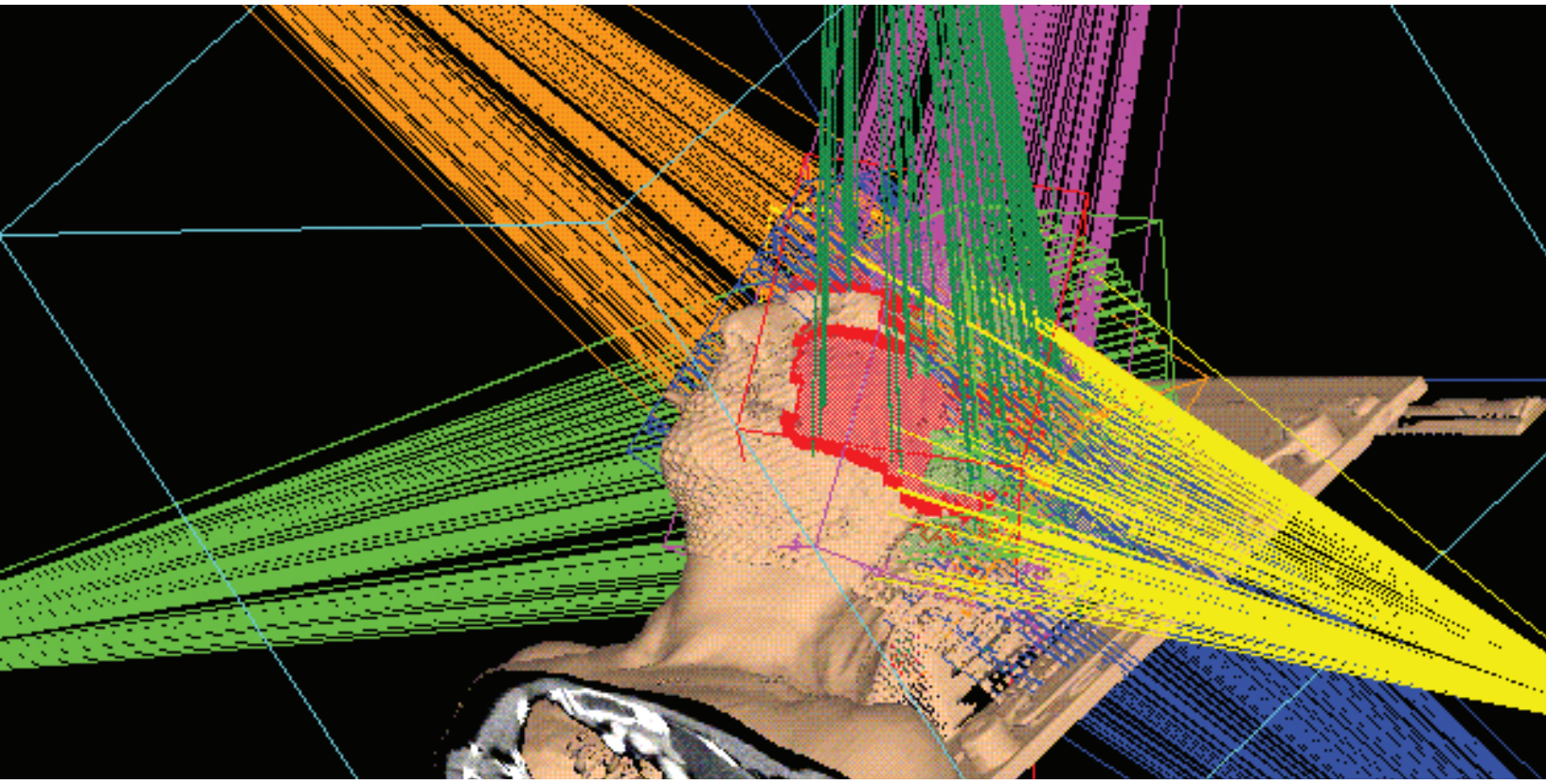
Hippocampus-sparing trial of whole brain radiation seeks to preserve memory



Beam arrangement for hippocampus-sparing treatment

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What's Inside

Trial with integrated boost may improve quality of life for WBRT patients.

Whole-brain radiotherapy (WBRT) is the most widely used treatment option for patients with multiple brain metastases. In addition to providing rapid relief of neurologic symptoms and improved local control as an adjuvant to resection or radiosurgery, WBRT also prolongs time to neurocognitive function (NCF) decline.

Unfortunately, WBRT itself can be the cause of later NCF decline. There is a component of early neurocognitive decline, within the first one to four months, which primarily affects memory. Long-term serious and permanent adverse effects, including cognitive deterioration in other domains and cerebellar dysfunction, have also been documented.

There is much emerging evidence to suggest radiation damage to a particular portion of the brain – the hippocampus – is responsible for these losses in NCF. The two paired hippocampi, located at the base of the brain in the medial temporal lobe, have been studied extensively in connection to spatial memory and navigation, and are one of the first regions of the brain to be damaged in Alzheimer's disease.

By using a conformal plan to exclude the hippocampi from treatment, UT Southwestern researchers hope to significantly reduce neurodegenerative side effects in patients undergoing WBRT. In a new phase II clinical trial, patients receive hippocampus-sparing WBRT using intensity-modulated radiotherapy (IMRT) of 20 Gy in 10 fractions, in addition to an integrated boost of 40 Gy in 10 fractions to the individual metastases.

Although avoiding the hippocampus poses the risk of attenuating the benefit of WBRT due to increased metastatic disease within the hippocampal avoidance region, that risk is considered to be reasonably low. In a 2007 study of 100 patients with 272 metastases, 3.3% of metastases were within 5 mm of the hippocampi; 4.4% were between 5 and 10 mm from the hippocampi; and 6.3% lay between 10 and 15 mm from the hippocampi. Of all metastases, 86.4% were greater than 15 mm from the hippocampi and none lay within the hippocampi themselves.

The UT Southwestern trial is modeled on a similar national trial (RTOG 0933), currently being conducted by the Radiation Therapy Oncology Group, which examines the effects of hippocampal avoidance during whole-brain radiotherapy for brain metastases, but without the addition of a boost.

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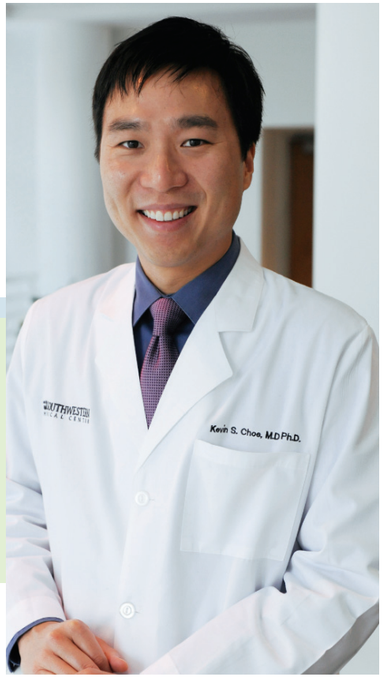
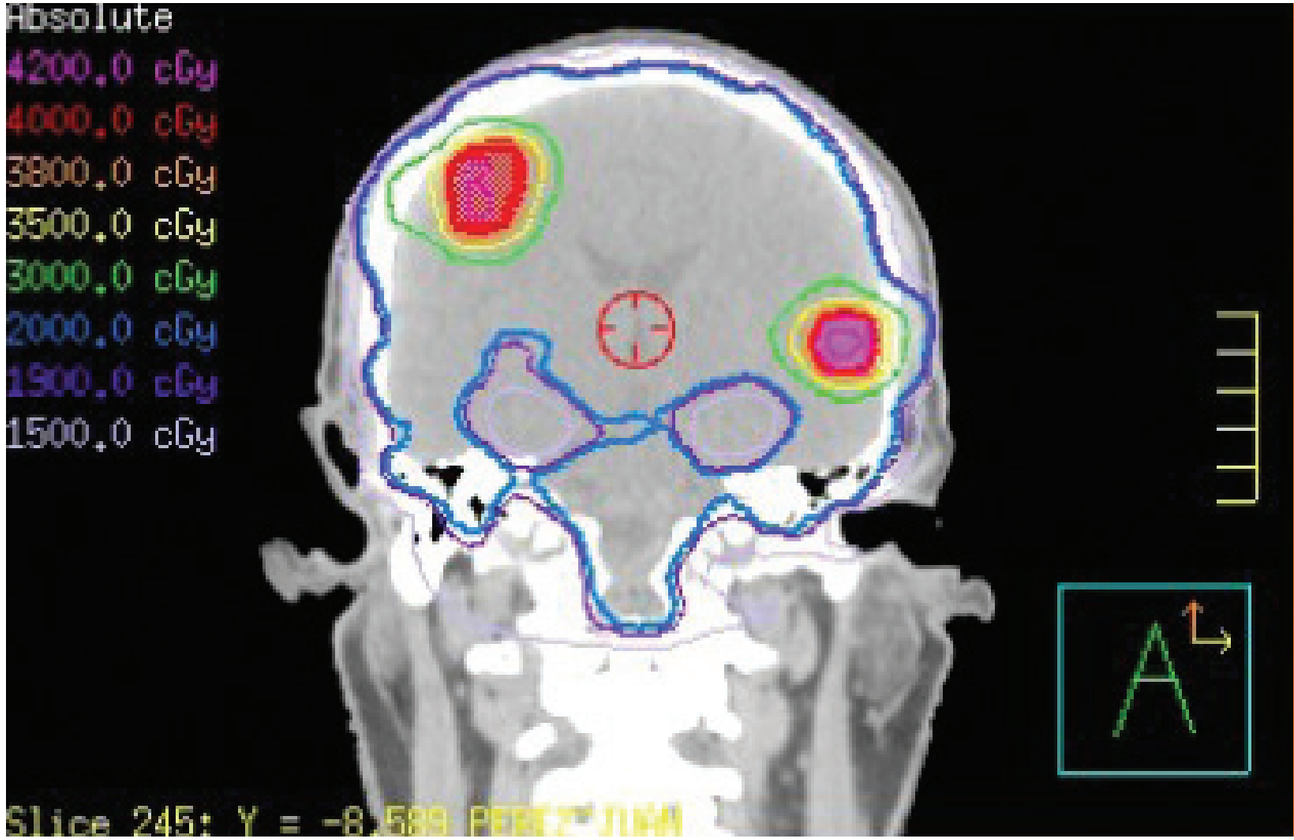


Kevin Choe, MD, PhD



Isodose images for hippocampus-sparing radiation treatment

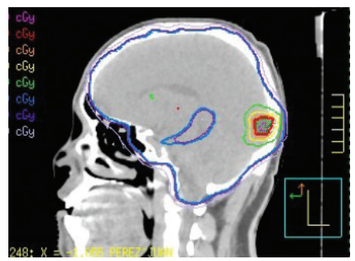
"Compared to the RTOG trial, our study will give us good proof of principle of whether the integrated boost makes a difference," says Kevin Choe MD, PhD, of the Department of Radiation Oncology.

The rationale for an integrated boost is improved local control. With IMRT, boost doses comparable to radiosurgery are generally achievable, with the possibility of delineation and avoidance of the hippocampal regions thought to be related to radiation-induced neurocognitive decline. There is a logistic advantage to the simultaneous integrated boost in that it can be administered in a single course of radiotherapy rather than a combination of conventionally fractionated radiotherapy and radiosurgery. Additionally, the treatment can be administered with linear accelerators that are common in most community-practice settings.

There is a dosimetric advantage as well, in that the composite plan can be fully optimized to achieve a relatively homogenous whole-brain dose, a steep gradient for the radiographically evident disease, and adequate hippocampal sparing, all at once.

Measured outcomes of the study will include neurocognitive function up to 24 months post-treatment, as well as fatigue and quality of life. "We're hoping this approach will benefit patients who can now expect to live longer after improved treatments for metastatic cancer," says Dr. Choe.

Side view



Department gains dedicated gynecologic cancer physician

Kevin Albuquerque, MD, FRCS, has joined the faculty of UT Southwestern's Department of Radiation Oncology, complementing the clinical practice with a focus on gynecologic cancer.

Kevin Albuquerque, MD, FRCS

Dr. Albuquerque was previously an associate professor of radiation oncology at Loyola University Medical Center in Chicago, where he held numerous roles including director of research for radiation oncology and section chief of the breast and gynecologic oncology program. He was also responsible for establishing LUMC's breast brachytherapy program.

Dr. Albuquerque has authored numerous peer-reviewed articles and book chapters on the subject of breast and gynecologic cancer. He has been involved in translational research comparing the effects of partial breast radiation (brachytherapy) and standard whole-breast radiation with reference to patient quality of life, fatigue, and immune status. He has also been involved in an NIH-funded study investigating mindfulness-based stress reduction for management of the distress associated with cancer.

Board certified in radiation oncology, Dr. Albuquerque brings "substantial depth and experience in women's cancers to our disease-oriented teams," says Hak Choy, MD, Chair of Radiation Oncology.

Dr. Albuquerque earned his medical degree from L.T.M. Medical University at Bombay University, India, and an MS in research and epidemiology from Loyola University. He has also completed residencies in surgical oncology, general surgery, and radiation oncology.

CPRIT IGRT trial gathers momentum

Eleven investigators statewide will participate in a UT Southwestern clinical trial designed to test whether proper use of hypofractionated technology will improve cure rates across later stages (2 and 3) of non-small cell lung cancer.

The study is part of an $8.8 million grant from the Cancer Prevention Research Institute of Texas (CPRIT) to extend sophisticated image-guided radiation therapy (IGRT) to lung cancer patients across the state.

UT Southwestern will provide training to participating institutions in advanced IGRT techniques and quality assurance. In doing so, researchers hope to create a strong regional clinical trials network that can rapidly test and bring new advances to patients.

Participating institutions include: Baylor Research Institute, Dallas VA Medical Center, Georgetown Cancer Center, Greater Houston Radiation Oncology, Harrington Cancer Center, John Peter Smith, Methodist Richardson Cancer Center, MD Anderson, Scott & White Memorial, UT Health Science Center San Antonio, and UTMB Galveston.

The study is expected to open in May.

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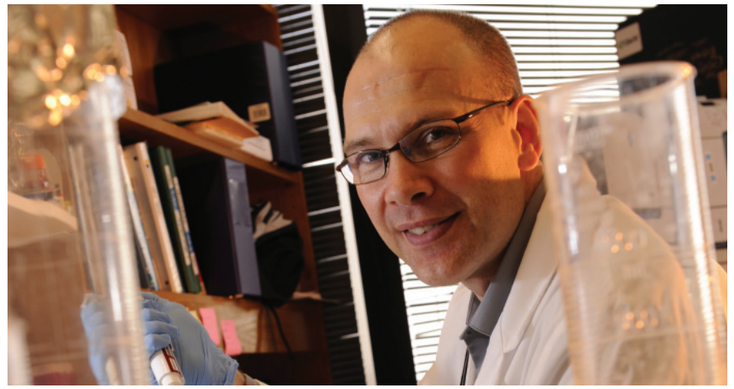
New screening program ramps up search for radiation-enhancing cancer drugs

Physician scientist John Yordy, MD, PhD, is leading a new effort at UT Southwestern to exponentially increase screening efforts to identify potential compounds that can be combined with radiation to treat cancer.

"The current paradigm for locally advanced disease is to combine radiation with chemotherapy," Dr. Yordy says. "It provides some benefit but it also increases the toxicity. We would like to find drugs that enhance the effect of radiation without increasing the toxicity to normal tissues."



John Yordy, MD, PhD

Turning up the volume

In the past, Dr. Yordy says, it's been difficult to do high throughput screening with radiation because the traditional assay that's used to study drug and radiation combinations is a clonogenic assay.

"With this assay we would plate single cells, maybe a hundred cells in a petri dish, and then we would treat with radiation and the drug, and then let it sit and incubate for two weeks," Dr. Yordy says. "Any cell that survives will form a colony. At the end of the two weeks you count the number of colonies on the plate.

"It's very accurate but very time-consuming and labor-intensive. You can do it with one or two drugs but you can't do it with a thousand drugs. There's just not enough time or incubator space."

To get around this, Dr. Yordy, who joined the UT Southwestern faculty in 2011, plans to incorporate high throughput imaging using an IN Cell Analyzer 2000 by General Electric. This machine "miniaturizes" the study by counting individual cells, rather than colonies. It's performed in an automated fashion on a machine that can both image and count, removing the potential for human bias and error, and increasing the potential volume of experiments by a thousand fold.

"Initially, the drugs we would look at that are already in phase 1 or 2 clinical trials are on the order of 10 to 20," Dr. Yordy says. "But we're also interested in previously uncharacterized molecules as well as combinations of drugs. Once we start looking at combinations, the number of permutations goes way up. There really is no upper limit."

Protein effects

The second aspect of the program involves reverse-phase protein arrays. Component proteins from normal or tumor cells are spotted onto a microscope slide. Each slide is then probed with a specific antibody against one protein, and a microscope slide reader is used to automatically measure the density of the signal in each spot on the slide, which corresponds to the amount of the measured protein in that sample.

"We can determine whether radiation causes the phosphorylation of a specific protein we're interested in, and if we want to find a drug that can block the phosphorylation of that protein, we can then use these high throughput arrays to screen a lot of drugs for that one specific phosphorylation effect," Dr. Yordy says.

Between the high throughput imaging and the reverse-phase arrays, he says, "we're trying to establish a robust pipeline for drug discovery that will identify drugs that can be further validated with more in-depth experiments and from there into clinical trials."

UT Southwestern patients living longer after lung cancer

For the first time, five-year survival data has become available for lung cancer patients treated at UT Southwestern's Department of Radiation Oncology, showing that, in most cases, patients here are living longer post-treatment compared to a national average.

The outcome chart below shows the age-adjusted Kaplan Meier survival results of non-small cell lung cancer (NSCLC) patients who were diagnosed between 2003 and 2007 and who received radiation as part of their treatment. Patients treated at UT Southwestern include patients from Parkland Memorial Hospital (the Dallas county hospital), UT Southwestern hospitals, and outside referrals.

The UT Southwestern outcomes data were compared to the age-adjusted Kaplan Meier outcomes of patients in the National Cancer Institute (NCI)'s Surveillance, Epidemiology, and End Results (SEER) program Region 17 registry. This registry similarly included patients who were diagnosed between 2003 and 2007, and encompassed all NSCLC histology types and all ages, both male and female.

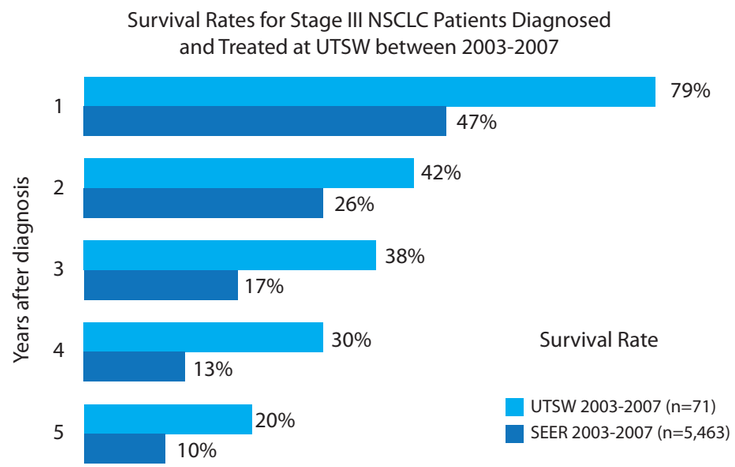
The increase in survival is most pronounced among stage 3 lung cancer patients: 79 percent of UT Southwestern patients were alive at year one and 20 percent survived to year five, compared with the national SEER average of 47 percent and 10 percent, respectively.

Assistant Professor of Radiation Oncology Nathan Kim, MD, PhD, says, "I think the numbers speak for themselves. While there is always a possibility of selection bias, we don't think this is the case because we treat a heterogeneous patient population from all walks of life.

"Certainly we can say that patients treated at UT Southwestern are getting state-of-the-art care. We offer the most sophisticated and advanced radiation treatments including SBRT, IGRT, and IMRT, and we are fortunate to have highly specialized experts in each disease site. We would hope that our outcomes would reflect this."

"Survival data is an important part of measuring our success in treating patients," says Radiation Oncology Chair Hak Choy, MD. "We hope to expand our outcomes measurements both to support our research and to anticipate the short- and long-term needs of our patients."

Data compiled by Joseph "Chip" Hodges, MD, MBA.



Clinical Trials Listing

BRAIN

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

RTOG 0837 Randomized, phase II, double-blind, placebo-controlled trial of conventional chemoradiation and adjuvant temozolomide plus cediranib versus conventional chemoradiation and adjuvant temozolomide plus placebo in patients with newly diagnosed glioblastoma

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

BREAST

042010-052 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

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

082010-335 A pilot and phase II study of altered chemotherapy sequencing during neoadjuvant therapy for patients with stage II or III rectal adenocarcinoma

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

GYNECOLOGIC

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

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 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

GOG 9918 A phase I trial of tailored radiation therapy with concomitant cetuximab (C225, NSC #714692) and cisplatin (NSC #119875) in the treatment of patients with cervical cancer

HEAD AND NECK

BMS CA 225314 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

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

—Stage 1

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

—Locally Advanced (Stage 3) or Inoperable (Stage 1 or Stage 2)

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

—Metastatic (2 or more sites)

42007003 A 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)

PROSTATE AND BLADDER

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

SPINE

SCCC-03Z08 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.

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Harold C. Simmons Cancer Center

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Department of Radiation Oncology
5801 Forest Park Rd.
Dallas, TX 75390-9183

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Department of Radiation Oncology at UT Southwestern

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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 University Hospital–Zale Lipshy

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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