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

Beam arrangement for hippocampus-sparing treatment
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.

“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.

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Dr. Kevin 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.

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.

The study is expected to open in May.

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.

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 microslide. 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 for 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’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, 20 percent survived to year five, compared to 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 Hsi 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.
Physicians who would like to make a referral may call the Department’s main clinic number 214-645-8525 or UT Southwestern’s physician referral line at 214-645-8300 (toll-free 866-645-5455) for adult patients, or 877-445-1234 for pediatric patients.

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