UT Southwestern breaks ground on Radiation Oncology center

The Department of Radiation Oncology’s new facility will be the largest in North Texas when it opens to patients in 2017.
Surgery vs. SABR: ‘Stablemates’ trial to directly compare treatments in operable lung patients

The results of a national trial evaluating stereotactic ablative radiotherapy (SABR) in lung cancer patients too frail to receive surgery were so positive that physicians, led by researchers in Boston and Dallas, have opened a multi-institutional study to directly compare surgery versus SABR in operable patients.

More than 30 institutions in the U.S. and Canada are planning to participate in the “Stablemates” trial, which is being administered independently by UT Southwestern. The trial’s nickname, says Dr. Robert Timmerman, M.D., Professor of Radiation Oncology at UT Southwestern Medical Center in Dallas, was chosen because “the two therapies [surgery and SABR] are both fiercely competitive, like thoroughbreds in a race. Yet when not competing on the track, they reside together in a stable enjoying each other’s company—ready and eager to be called on for the next challenge.”

SABR is a newer therapy that utilizes advanced image guidance and a high number of treatment beams to deliver a more powerful dose of radiation than with standard radiation therapy. The higher dose is delivered in a small number of treatments. The new study will offer SABR delivered in five sessions. Although image guidance in radiotherapy has improved dramatically over the last few years, with SABR in particular being touted for its “surgical” precision, only a few, mostly retrospective, studies have directly compared surgery with SABR.

He notes that surgical techniques have improved over the years just as they have in radiation therapy.

“This study will help doctors understand the advantages and disadvantages of each therapy so that they can better advise patients about their treatment options,” Dr. Fernando says. “The study may also help physicians identify which patients are more likely to benefit from one therapy compared to the other.”

In Dallas, the Stablemates trial is being conducted by radiation oncologists Punetha Iyengar, M.D., Ph.D. (also the study’s principal investigator), and Hak Choy, M.D., along with cardiothoracic surgeons Kemp Kernstine, M.D., Ph.D., and Scott Reznick, M.D.

“As a noninvasive, relatively convenient outpatient treatment, SABR may benefit patients by offering them a treatment that is easier to tolerate and that doesn’t interfere greatly with their normal daily living activities,” Dr. Timmerman says.

“We hope this landmark study will help us come closer to understanding the optimal role for SABR in treating lung cancer,” Dr. Fernando is Chief of Thoracic Surgery at Boston Medical Center; Director of the Barrett’s Esophageal Program; Director of Thoracic Surgery Clinical Research; Associate Professor of Surgery, Boston University School of Medicine; and Director of the Center for Minimally Invasive Esophageal Surgery.

Dr. Timmerman is Professor, Vice Chair, and Medical Director of Radiation Oncology at UT Southwestern Medical Center. He holds the Ebbie Marie Cain Distinguished Chair in Cancer Therapy Research.

For more information, visit the Stablemates trial website at joltca.org.
Physician added to genitourinary team

Neil Desai, M.D., M.H.S., has joined the UT Southwestern faculty as Assistant Professor of Radiation Oncology, specializing in the treatment of genitourinary cancers, including bladder, kidney, urethra, prostate, and testes. He also specializes in the treatment of leukemia and lymphoma patients.

Dr. Desai earned his medical degree at Yale University, where he also conducted cancer biology research that led to a master’s degree. He completed residency training in radiation oncology at Memorial Sloan Kettering Cancer Center in New York.

His clinical interests include finding improved treatments for bladder cancer and prostate cancer. Dr. Desai is the author of several papers in prominent medical journals, including the Journal of Clinical Oncology and The Red Journal.

Dr. Desai notes that patients are increasingly faced with multiple options for treating their cancer. “My goal is to match patients with the best treatment for them as individuals after taking their goals into account,” he says.

“We have well-recognized urology and medical oncology programs at UT Southwestern,” Dr. Desai adds. “We can offer a comprehensive spectrum of proven cancer treatments, as well as newer therapies still in development that are not available elsewhere. Just as importantly, we do so by vetting those therapies with the prospective trials and transparency that are found only at top-tier academic institutions.”

Dr. Desai joins Raquibul Hannan, M.D., Ph.D., and Aaron Laine, M.D., Ph.D., as members of the Radiation Oncology team specializing in treating genitourinary cancers.

To refer a patient or schedule an appointment with Dr. Desai, please call 214-645-8525.

Leading physics researcher joins faculty

Yiping Shao, Ph.D., has joined the faculty of the Department of Radiation Oncology as Professor in the Division of Medical Physics and Engineering. A distinguished researcher in the field of medical imaging, Dr. Shao was part of the team at UCLA who, beginning in 1994, was the first to develop microPET for small animal imaging, as well as the first to combine positron emission tomography (PET) and MRI to locate tumors and quantify their response to cancer treatment.

Dr. Shao has held a number of positions in industry and academic medicine, most recently at MD Anderson in Houston, where he garnered a $1.2 million grant from the Cancer Prevention and Research Institute of Texas (CRPRIT) in 2011 to develop in-situ PET imaging to help guide proton therapy with real-time adaptation.

Dr. Shao expects to continue this research at UT Southwestern with the funding assistance of two NIH grants. These projects include an R21 grant entitled “Investigation of the molecular mechanism of DNA repair and DNA damage signaling” and an R01 grant entitled “Advanced Micro-PET/CT/RT System for Translational Radiation Oncology Applications.”

Dr. Shao notes that radiation physics research at UT Southwestern is tied very closely to clinical practice. “This gives us the opportunity to develop and apply new imaging techniques very quickly,” he says. “The close collaboration between the researchers and medical team here represents a great advantage to improving cancer care.”

The Medical Physics and Engineering Division currently comprises more than 80 employees and trainees, including 18 faculty members who advise students in the medical physics residency, biomedical engineering, and postdoctoral medical physics certificate programs.

Education and Research Seminar Series

Lectures sponsored by the Department of Radiation Oncology are free and open to interested professionals, including physicians, physicists, radiation therapists, biologists, and students. For more information, contact RadOncInfo@utsw.edu.

† Molecular Radiation Biology Seminar Series
‡ Radiation Oncology Residency Program

**February**

**Speaker:** Dipanjan Chowdhury, Ph.D.

**From:** Department of Radiation Oncology, Harvard Medical School

**Date:** Tuesday, February 23

**Time/Place:** Noon–1 p.m.

**Subject:** “Involvement of the molecular mechanism of DNA repair and DNA damage signaling”

**March**

**Speaker:** Reshma Jagi, M.D.

**From:** University of Michigan Health System

**Date:** Friday, March 4

**Time/Place:** Noon–1 p.m.

**Subject:** TBD

**Speaker:** Tarek Sarkaria, Ph.D.

**From:** Department of Oncology, Institute of Cancer Research, University of Wisconsin

**Date:** Tuesday, March 8

**Time/Place:** Noon–1 p.m.

**Subject:** “Using brain tumor patient-derived xenografts to interrogate the influence of the blood-brain barrier on treatment efficacy”

For more information, please contact Clinical Research Manager Juan Wu at 214-645-1892 or juan.wu@utsouthwestern.edu

Clinical Trials

**Brain**

**Gynecology**

**Spine**

**Lung**

**Gastrointestinal**

**Genitourinary**

**Small Cell Lung Cancer**

**Non-Small Cell Lung Cancer**

**General**
Management of early-stage non-small cell lung cancer with SABR

Origins of SABR use in the treatment of malignancies

The concept of using SABR/SBRT for the treatment of lung cancer can be traced back to the use of radiosurgery in the treatment of CNS malignancies in the 1940s and 1950s. Radiosurgery, a noninvasive treatment, is defined by the use of a single, high-dose fraction of radiation in the treatment of intracranial conditions. Dr. Lars Leksell of Sweden, along with physicist and radiobiologist Borje Larsson, were the first to implement the concept of delivering high doses of ionizing radiation to ablate neoplastic activity while limiting normal tissue side effects. This was achieved through the use of a high precision treatment targeting. In early radiosurgery treatments, protons and gamma rays from a radioactive cobalt-60 source were used to irradiate patient lesions. To ensure precision and prevent movement, patients’ skulls were immobilized and fiducial markers delineating a coordinate system were used. Thus, a high dose could be delivered safely and effectively. Eventually, multiple linear accelerator and non-linear accelerator systems were employed to deliver high doses of radiation in a limited number of treatments. For extracranial treatment, stereotactic body radiation therapy (SBRT) has been the term applied to the relatively complex process of high-dose precision treatment of neoplasms. The term stereotactic ablative radiotherapy (SABR) has been gaining traction recently because “ablative” more accurately describes how radiation affects the tumor tissue at large dose levels, leading to high local control rates and limited toxicity. The latter characteristic of SABR is predicated on the use of multiple imaging modalities—before, during, and after treatment—to ensure maximum tumor targeting and limited collateral effect on adjacent normal tissues. The term image-guided radiation therapy (IGRT) describes this use of imaging in target delineation, especially for treatments involving high doses per treatment such as SABR. Both the American Society for Radiation Oncology (ASTRO) and the American College of Radiology (ACR) have defined SABR to include all radiation therapy requiring very large doses per fraction.

While treatment of CNS malignancies with radiosurgery has been standard, it is apparent that a leap in treatment paradigms has occurred with the use of SABR for early-stage NSCLC. The next section will discuss the indications, rationale, and methods of treating NSCLC with SABR.

SABR becomes possible for lung disease with improved technology

With the extremely high doses that can be used per fraction in SABR, normal tissue injury can have more profound consequences than in the setting of conventionally fractionated radiation. Several technological advances over the last 20 years have more closely approached the theory—and facilitated the acceptance—of SABR as a rational and safe treatment for lung tumors. Among these are tumor motion evaluation, patient immobilization, image guidance, and class solutions in radiation treatment planning.

It has been known for some time that lung tumors, especially those in the lower lobes of the lung, alter their positions in the thorax during the respiratory cycle as the diaphragm moves. The goal of SABR is to target disease while limiting normal lung parenchyma or critical structures from receiving any significant dose. With moving lung targets there is a risk of potentially missing the target at certain times of the respiratory cycle. With conventional radiation this would require treating larger volumes of normal lung parenchyma or thorax to compensate, but this approach cannot be implemented with the higher SBRT dose.

To counteract this problem, tumor motion tracking has become an intrinsic aspect of SABR treatment planning. Four-dimensional computed tomography (4D-CT) and fluoroscopy are utilized to assess the extent of tumor motion in all phases of the respiratory cycle. This information allows us to evaluate the radiation therapy team to account for motion when planning the fields of treatment with regard to margin on the moving target. To minimize the extra normal lung tissue added to the treatment field to ensure tumor coverage, strategies including abdominal compression, deep inspiration breath hold/respiratory gating, and tumor tracking with fiducials have been employed with varying degrees of success. Adequate patient immobilization is also a fundamental requirement of SABR treatment planning. The patient needs to be immobilized prior to each treatment to allow for reproducibility and consistency in target delineation over the one to five fractions normally given for SABR. Multiple types of immobilization systems are utilized nationally and internationally for lung SABR treatments, including vacuum cushions, stereotactic body frames, and thermal plastic restraints. With the advent of computed tomography, then 4D-CT, magnetic resonance imaging (MRI), and positron emission tomography (PET) combined with CT over the last 20-25 years, radiation oncologists are more accurately able to define the site of lung disease. The margins placed around tumors to ensure coverage and treatment of malignancy have become smaller as imaging is more frequently used to identify tumor location with respect to normal tissues in the thorax (carina, chest wall, esophagus, trachea, spinal column, heart, and lung borders, among other anatomic considerations) and bony landmarks. Daily cone-beam CTs prior to treatment, between beam treatments, and after treatment allow us to evaluate the patient and tumor positioning and make real-time changes that promote tumor targeting and limiting of normal tissue collateral exposure.

Finally, with continued treatment of patients with SABR, practitioners have become adept at determining which beam arrangements are optimal to treat lung disease while avoiding normal tissue toxicities. It has become apparent that the use of more beams (10-12, on average) is able to achieve objectives set on covering the tumor while limiting dose to the heart, rest of lung, spinal cord, esophagus, brachial plexus, chest wall, etc. (Figs. 1-2).

Clinical indications for early-stage lung cancer treatment with SABR

In order to understand why radiation oncologists moved toward use of SABR in treating primary NSCLC, one must appreciate the different benefits that SABR/SBRT can offer over conventional radiation therapy. Many have moved toward considering other ways to treat these patients. Many have moved toward considering other ways to treat these patients. Many have moved toward considering other ways to treat these patients. During the past several years, particularly with the introduction of new gamma knives and radiosurgery systems, there has been considerable interest in using radiosurgery for early-stage NSCLC. The change in usage paradigm has occurred with the use of SABR for early-stage NSCLC. The change in usage paradigm has occurred with the use of SABR for early-stage NSCLC. The change in usage paradigm has occurred with the use of SABR for early-stage NSCLC. The change in usage paradigm has occurred with the use of SABR for early-stage NSCLC. One of the reasons for this is the acknowledgement that radiation therapy is beneficial versus no treatment yet inferior to outcomes from surgery. Herein, it has been a push to escalate the radiation total dose as well as the dose per fraction in the hope of attaining better locoregional control. Studies from Memorial Sloan Kettering Cancer Center and the Radiation Therapy Oncology Group (RTOG) attempted to escalate the total dose with standard fractionation and found a survival benefit with final doses above 60 Gy. However, there was significantly increased acute and late pulmonary toxicity.

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Pulmonary toilet capabilities. On update six deaths were attributed to pneumo-
treatment-related deaths. Four of the eral tumors (46% vs. 17%) and included had more than twice as many severe
rate, survival rates achieved with this are: efficacy of an immobilization device for
involves the body having different parts with
that studies in this field have been limited by the
usually shows that these individuals could tolerate high doses of radiation in limited fractions quite well with signifi-
cancer control. A phase II study, also at Indiana University, that built off the phase I study included medical inoperable, early-stage NSCLC patients. A phase I study for T1-T2 N0 NSCLC patients evaluated doses ranging from 24 Gy in 3 fractions to 72 Gy in 3 frac-
tions to establish dose-limiting toxicity. No maximum tolerated dose (MTD) was reached for the T1 patients up to 60 Gy in 3 fractions or T2 tumors less than 5 cm up to 66 Gy in 3 fractions, effec-
tion equivalent to 54 Gy in 3 fractions with heterogeneity correction, which assumes the body has different parts with different densities). No centrally located primary tumors (within 2 cm of the bronchial tree) were included, a lesson learned from the earlier phase II Indiana study. The study’s findings were ultimately published in the Journal of the American Medical Association and ended up being one of the most impactful papers of 2010.
With overall, with a median follow-up of 2.9 years, the three-year tumor control was 98% (with one marginal failure at the primary tumor site), the three-year local (tumor plus lobe) control was 91%, three-year locoregional control was 87%, three-year distant metastasis (DM) rate was 22%, and median OS was 48 months. There was limited toxicity, with no deaths from treatment. Eleven of 55 patients failed distantly, potentially as a consequence of initial understaging of their disease. Despite this distant disease failure, survival rates achieved with this treatment regimen compare very favorably with surgical patients. Disease-free and overall survival at three years were 48% and 56%, respectively. At this time, studies nationwide and internationally are trying to address a number of questions related to SABR for early-stage NSCLC. RT05 0813, a phase I/II trial that has com-
located tumors, is attempting to identify an MTD for these lesions using a five-
fracti
tion regimen starting at 50 Gy and extending to 80 Gy (12 Gy/fraction). RT05 0813 is a phase II, multi-institutional study (accrual complete) that treated patients with SABR to a dose of 54 Gy in 3 fractions for NSCLC, early-stage operable lesions. Most criti-
cially there are at least three small trial to open or already activated that com-
Wang LT, Solberg TD, Medin PM, Boone R. Infrared patient positioning for stereotactic radiotherapy of extra-
Bob Goble, 71, a semiretired IT professional, first noticed something was wrong when he started waking up with a strange pain over his left eye combined with numbness to the skin in the area. After meeting with several doctors and receiving inclusive answers, he eventually came to UT Southwestern, where imaging revealed a mass sitting right on top of his eye, invading the periorbital space and threatening the optic nerve. By the time he received a biopsy and subsequent diagnosis of squamous cell carcinoma in 2011, the mass was pressing on his eye to such a degree that it blocked his vision inclusive answers, he eventually came to UT Southwestern, where imaging revealed a mass sitting right on top of his eye, invading the periorbital space and threatening the optic nerve. By the time he received a biopsy and subsequent diagnosis of squamous cell carcinoma in 2011, the mass was pressing

“The care at UT Southwestern was off-the-charts incredible. The collaboration between the team members was seamless. I can see out of this eye now because of those guys.”

Bob Goble, cancer survivor

Survivor Story: CyberKnife saves eye of cancer patient

The findings are available in Molecular Cancer Research, a journal of the American Association for Cancer Research. @

New brachytherapy operating room

Intraoperative team at William P. Clements Jr. University Hospital

Bob Goble, cancer survivor

Researchers develop classification model for cancers caused by most frequently mutated cancer gene

UT Southwestern Medical Center researchers have developed a classification for cancers caused by KRAS (Kirsten rat sarcoma viral oncogene homolog), the most frequently mutated gene in cancer, that could eventually help oncologists choose more effective, customized cancer therapies.

“New strategy is based on models that researchers developed to classify cancers caused by KRAS mutations, which cause KRAS-driven cancer mutations have long been a focus of cancer research, effective targeted therapies are not available. “This work further supports the idea that new strategy is based on models that researchers developed to classify cancers caused by KRAS mutations, which cause KRAS-driven cancer mutations have long been a focus of cancer research, effective targeted therapies are not available. “This work further supports the idea that any treatment to kill his cancer could potentially also result in the loss of vision or of the eye itself. His UT Southwestern treatment team, including radiation oncologist Lucien Nedzi, M.D., ophthalmologist Ronald Mancini, M.D., and medical oncologist Randal Hughes, M.D., presented the challenge to him in realistic yet hopeful terms. “Dr. Nedzi told us he had a 50 percent chance of keeping the eye and beating the cancer, so we could look at the glass as being half empty or half full, and we are choosing to look at it as half full,” recalls Teena Goble, Bob’s wife of 41 years. “That positivity was huge.”

“To realize the gravity of it but I was never really scared,” Mr. Goble says. “I felt like this was something God had told me I had to walk through. And I felt like I was in the right place.”

Normally Mr. Goble’s place is in the classroom, where for 16 years he has taught students at Dallas Baptist University about information systems and project management. He also serves as project manager for a company that helps churches and schools discover new revenue streams. “My passion is seeing the ‘lights’ come on when teaching kids about how technology impacts every facet of their lives,” he says. Working in the yard, reading, and teaching were his pastimes until cancer treatment also became part of his daily regimen. The prescribed treatment for his tumor was six weeks of daily intensity-modulated radiation treatment (IMRT) combined with three infusions of cetuximab—a combination therapy typical for head and neck cancer patients. What was unusual was the decision of Dr. Nedzi, a head and neck cancer specialist, to complete this treatment with a strategy developed using the CyberKnife for a total dose of 72 Gy (60 Gy IMRT + 12 Gy CyberKnife). The robotic CyberKnife is designed to deliver an extremely tight dose of radiation that spares surrounding tissue from injury. The hope was to give a tumor-killing dose of radiation that would at the same time avoid damaging the optic nerve. Mr. Goble received five final treatments using the CyberKnife. His journey through treatment was not easy and included two hospitalizations, including one for a treatment-related complication that caused potentially dangerous swelling around the affected eye. He developed fatigue and lost weight. But eventually he was able to complete his entire course of therapy. When Mr. Goble returned for a follow-up MRI three months afterward, he said, “I’ll never forget how Dr. Nedzi came to me and said ‘Bob, we got it’.”

“Bob is a real success story”, Dr. Nedzi says. “Not everyone with such a disease presentation is able to keep their eye after receiving such a high level of radiation. We think the ability to tailor the dose delivery with CyberKnife made a difference in his outcome. Now his vision is fine, he has unrestricted eye motion, and his cancer is cured.”

“The care at UT Southwestern was off-the-charts incredible”, says Mr. Goble. “The collaboration between the team members was seamless. I can see out of this eye now because of those guys.” Thank you, UT Southwestern!”

Publications


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