UT Southwestern

THE TARGET

News from the Department of Radiation Oncology

WINTER 2016

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.

Architectural rendering of the new Radiation Oncology center.

What's Inside

Page 1 story UT Southwestern breaks ground on Radiation Oncology center

UT Southwestern broke ground in late September on a new Radiation Oncology center that will feature state-of-the-art technology.

Daniel K. Podolsky, M.D., (center) President of UT Southwestern; Hak Choy, M.D., (left) Chairman of Radiation Oncology; and Arnem Dontes, Executive Vice President for Business Affairs, turn the soil at the opening ceremony.

The $66 million, state-of-the-art facility will have three floors and 63,000 square feet of space. Housed within the center will be seven patient treatment rooms and some of the world's leading technology for targeting tumors with radiation therapy.

One of the goals of the building's design is to further enhance disease-site specialization in the treatment of cancer patients. Each major disease site, such as brain, breast, or gastrointestinal cancer, will have its own dedicated area for the teams of doctors, mid-level providers, nurses, clinic researchers, and physicists attending those patients.

The groundbreaking marked the first construction in several years on UT Southwestern's East Campus on Inwood Road across from Harold C. Simmons Comprehensive Cancer Center. In 2008 the university opened the first building on the site—the BioCenter at Southwestern Medical District, a multitenant facility meant to help commercialize university technologies and attract biotech companies to the area.

Daniel K. Podolsky, M.D., President of the Medical Center and Professor of Internal Medicine, spoke at a groundbreaking ceremony attended by Radiation Oncology staff and UT Southwestern leadership. He pointed to the importance of the recent NCI designation of Simmons Cancer Center as a Comprehensive Cancer Center and described the growth of Radiation Oncology as a natural byproduct of the success of Simmons Cancer Center.

"One cornerstone of that dedication to delivering cancer care at the very highest level found anywhere in the country has been the development of our program in radiation oncology under the inspired leadership of Dr. Hak Choy," Dr. Podolsky said.

Dr. Choy, Chairman and Professor of Radiation Oncology, called the event a celebration of a new chapter in the story of the Department. He paid tribute to oil magnate and philanthropist Tex Moncrief, whose gift 12 years ago helped launch the Department.

The status of the Department of Radiation Oncology as a top destination for cancer patients has meant that the facilities across campus could soon be outgrown. Currently, the Department treats 160-170 patients daily across three facilities it operates on the Dallas campus, seeing about 2,300 new patients annually.

"The future of the Radiation Oncology program at UT Southwestern lies within all of us," Dr. Choy said. "We take our mission seriously, and our Department mission is to deliver world-class care to our patients with the best technology available."

Dr. Choy holds the Nancy B. & Jake L. Hamon Distinguished Chair in Therapeutic Oncology Research.

Dr. Podolsky holds the Doris and Bryan Wildenthal Distinguished Chair in Medical Science, and the Philip O'Bryan Montgomery, Jr., M.D. Distinguished Presidential Chair in Academic Administration.

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."

Robert Timmerman, M.D.

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 radiation therapy 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.

Dr. Timmerman, led the initial study (RTOG 0236), which offered SABR to patients with serious comorbidities (severe emphysema, heart disease, or diabetes) or poor pulmonary function. At three years, local control and survival were 98% and 56%, respectively. Five-year data has likewise shown a durable response with relatively high survival.

"This was very exciting," Dr. Timmerman says. "These patients previously had a poor prognosis but were given a very effective treatment that could be compared to surgery in terms of immediate tumor control and long-term survival. As a result of that study, SABR is now firmly established as a standard-of-care therapy for patients with early-stage lung cancer who are unable to tolerate surgery."

The results also begged the question: If a noninvasive treatment can deliver results comparable to surgery, what role should SABR have in the management of patients who would normally receive surgery?

Hiran Fernando, M.D., Chief of Thoracic Surgery at Boston Medical Center, championed the current study, which compares both approaches directly. The new trial is enrolling patients with early-stage lung cancer who are classified as high risk for surgery but are still eligible to receive a modified procedure (sublobar resection).

Hiran Fernando, M.D.

"While they can still tolerate a surgery, these patients have other conditions that put them at a higher risk for complications," Dr. Fernando says. "We selected this patient population to study SABR versus surgery because there would be a specific benefit to this group in finding an alternative to surgery."

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 Puneeth 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 Effie 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.

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 only by vetting those therapies with the prospective trials and transparency that are found only at top-tier academic institutions."

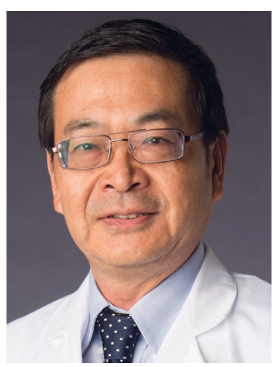
Dr. Desai joins Raquibul Hannan, M.D., Ph.D., and Aaron Laine, M.D., Ph.D., as members of the Radiation Oncology team specializing in treating genitourinary cancers.

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.



Yiping Shao, Ph.D.

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 (CPRIT) 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 "Road to PET Image-based On-line Proton Beam Range Measurement" 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 Visiting Lecturer

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: "Investigation of the molecular mechanism of DNA repair and DNA damage signaling"

March

‡ **Speaker:** Reshma Jagsi, M.D.
From: University of Michigan Health System
Date: Friday, March 4
Time/Place: Noon–1 p.m.
Subject: TBD

† **Speaker:** Jann 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"

Clinical Trials

BRAIN

New–022015-106 A phase I dose-escalation study of stereotactic radiosurgery for brain metastasis without whole brain radiation

New–NRG BN001 Randomized phase II trial of hypo-fractionated dose-escalated photon IMRT or proton beam therapy versus conventional photon irradiation with concomitant and adjuvant temozolomide in patients with newly diagnosed glioblastoma

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

GASTROINTESTINAL

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

GENITOURINARY

New–062014-027 Phase I clinical trial of stereotactic ablative radiotherapy (SABR) of pelvis and prostate targets for patients with high-risk prostate cancer

New–022015-058 Safety lead-in phase II trial of neoadjuvant SABR for IVC tumor thrombus in newly diagnosed RCC

092013-013 Phase II study of stereotactic ablative radiotherapy (SABR) for low-risk prostate cancer with injectable rectal spacer

RTOG 924 Androgen deprivation therapy and high-dose radiotherapy with or without whole-pelvic radiotherapy in unfavorable intermediate or favorable high-risk prostate cancer: a phase III randomized trial

122013-030 A phase II trial of stereotactic ablative body radiation therapy (SABR) for patients with primary renal cancer (RCC)

12013-041 A phase II trial of high-dose IL-2 and stereotactic ablative body radiation (SABR) for patients with metastatic clear-cell renal cell cancer (mRCC)

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

GYNECOLOGIC

082013-064 A phase II study for image-guided hypofractionated radiation boost therapy for definitive treatment of locally advanced cervical cancer

HEAD AND NECK

052014-085 A phase I trial of stereotactic HYpofractionateD RadioAblative (HYDRA) treatment of advanced laryngeal cancer

112013-007 A phase I study of reduced-volume hypofractionated, PET-directed, intensity-modulated radiotherapy concurrent with weekly cisplatin chemotherapy for T1/NO-2 squamous cell carcinoma of the head and neck

NRG-HN001 Randomized phase II and phase III studies of individualized treatment for nasopharyngeal carcinoma based on biomarker Epstein Barr virus (EBV) deoxyribonucleic acid (DNA)

RTOG 1216 Randomized phase II/III trial of surgery and postoperative radiation delivered with concurrent cisplatin versus docetaxel versus docetaxel and cetuximab for high-risk squamous cell cancer of the head and neck

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

LUNG

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

Non-Small Cell Lung Cancer

New–022015-069 [JoLT-Ca] A randomized phase III study of sublobar resection (SR) versus stereotactic ablative radiotherapy (SABR) in high-risk patients with stage I non-small cell lung cancer (NSCLC), the Stablemates trial. www.joltca.org

92013-070 Maintenance chemotherapy versus consolidative stereotactic body radiation therapy (SBRT) plus maintenance chemotherapy for stage IV non-small cell lung cancer (NSCLC): A randomized phase II trial

RTOG 1306 A randomized phase II study of individualized combined modality therapy for stage III non-small cell lung cancer (NSCLC)

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

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

SPINE

072010-134 A phase II study of stereotactic body radiation therapy (SBRT) 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 214-648-1892 or jean.wu@utsouthwestern.edu

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

After completing this activity, the participant should be better able to:

- Identify the types of patients and lung lesions suitable for SBRT as a curative treatment
- Describe the benefits that SABR can offer over conventional radiation treatment in the management of early-stage NSCLC
- Describe the evolution of treatment leading to the use of SBRT for early-stage NSCLC

Introduction

Non-small cell lung cancer (NSCLC) has had the highest rate of cancer incidence and patient deaths in the U.S. for decades. Due to poor health/comorbidities, many patients are not able to receive the standard of care for early-stage disease, namely, surgical resection with lobectomy. As an alternative, some of these patients have been treated with standard fractionation radiation, traditionally to doses of 60-70 Gy over six to seven weeks, with limited durable tumor control. The inadequacy in treatment response has led radiation oncologists to consider other ways to treat these patients. Many have moved toward stereotactic body radiation therapy (SBRT)—also known as stereotactic ablative radiotherapy (SABR)—in treating early-stage primary NSCLC.

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 through the use of high-precision treatment targeting.[1] 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 nonlinear 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.[2,3]

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.[4]

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.[5-6]

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.

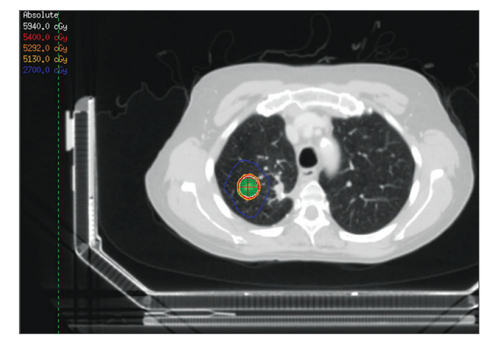

Figure 1. Axial computed tomography (CT) image of an early-stage NSCLC of the right lung. Isodose curves depict the tumor receiving the curative dose.

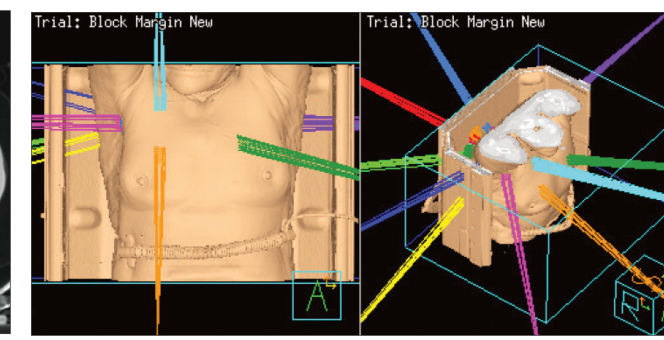

Figure 2. Skin rendering image set showing orientation and direction of SABR radiation beams entering the patient to converge on the tumor.

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 then allows the radiation 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.[3,7-8]

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 has to appreciate the poor outcomes in controlling this disease with standard fractionated radiation therapy (more than five treatments). Generally, the median OS for medically inoperable patients treated with standard radiation is 1.5 years, with a five-year OS of approximately 20%. These outcomes are significantly improved compared to no treatment but fall well below the outcomes from surgery. SEER data has suggested that radiation (with doses ranging from 45 Gy to 66 Gy at 1.8 to 2 Gy per fraction) versus no treatment offers a five- to seven-month OS benefit.[16] Multiple institutions, including MD Anderson Cancer Center, Indiana University, and various European centers, by 2005 had published their own experiences with fractionated radiation for medically inoperable stage I and II NSCLCs in comparison to no treatment. Clearly, radiation is beneficial versus no treatment yet inferior to outcomes from surgery.

Hence there 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 80 Gy.[19]

However, there was significantly increased acute and late pulmonary toxicity with both higher total doses and slightly increased dose per fraction above 2 Gy, suggesting the need for treatment refinement.

From diminishing returns from higher total doses with limited fraction sizes, it became apparent that SABR may offer the benefits of improved local tumor control while avoiding normal tissue toxicity with adequate image guidance, tumor motion assessment, modern patient immobilization, and treatment planning. Indiana University conducted a series of studies over the last decade that set the stage for large, cooperative group trials that have since verified the standard use of SABR in medically inoperable, early-stage NSCLC patients.[20-21]

A phase I study for T1-T2 N0 NSCLC patients evaluated doses ranging from 24 Gy in 3 fractions to 72 Gy in 3 fractions 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, effectively showing that these individuals could tolerate high doses of radiation in limited fractions quite well with significant tumor control.

A phase II study, also at Indiana University, that built off the phase I study included 70 medically inoperable, clinical T1 N0 NSCLC patients treated with SABR to a dose of 60 Gy in 3 fractions and T2 N0 (greater than 7 cm) patients treated to 66 Gy in 3 fractions.[22-23]

With a median follow-up of 17 months, two-year local control (LC) was 95%, median OS was 2.7 years, and two-year OS was 55%. These numbers started approaching surgical outcomes for the same group of resectable patients. The study also showed, however, that patients with centrally located lesions (near the bronchial tree), had more than twice as many severe grade 3 toxicities as those with peripheral tumors (46% vs. 17%) and included six treatment-related deaths. Four of the six deaths were attributed to pneumonia, potentially as a result of reduced pulmonary toilet capabilities. On update at 50 months, three-year LC was still very high at 88% and OS appreciable at 42%. Of note, multiple other studies from institutions in the U.S., Japan, and Scandinavia have performed similar trials and reported similar local control and survival rates with comparable total doses and dose per fraction schema.[24-27]

As part of the continuing evaluation of SABR, the RTOG in 2002 undertook a phase II, multi-institutional study based on the Indiana data to assess in a robust manner the efficacy of stereotactic treatments of early-stage NSCLC.[28] Fifty-five patients with medically inoperable T1-T2 N0 NSCLC disease were included with a few more specific parameters: lesions < 5 cm and all patients treated with 60 Gy in 3 fractions without heterogeneity correction (equivalent to 54 Gy in 3 fractions with heterogeneity correction, which assumes the body has different parts with different densities). No centrally located lesions (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.

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 failure rate, 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.[28]

At this time, several studies nationally and internationally are trying to address a number of questions related to SABR for early-stage NSCLC. RTOG 0813, a phase I/II trial that has completed accrual of patients with centrally located tumors, is attempting to identify an MTD for these lesions using a five-fraction regimen starting at 50 Gy and extending to 60 Gy (12 Gy/fraction). RTOG 0618 is a phase II, multi-institutional study (accrual complete) that treated patients with SABR to a dose of 54 Gy in three fractions for NSCLC, early-stage operable lesions. Most critically, there are at least three studies set to open or already activated that compare SABR versus surgery head-to-head. A national phase III study supported by the Joint Lung Cancer Trialists' Coalition (JoLT-Ca) has just opened for accrual that will randomize high-risk, early-stage T1/T2 N0 (tumors less than or equal to 5 cm) NSCLC patients to either SABR (54 Gy in 3 fractions) or sublobar resection. "High-risk" refers to those patients who could potentially have excessive toxicity outcomes from a lobectomy and thus would receive only sublobar surgeries. Similar trials are expected to open at the U.S. VA Hospital System and in Europe.

Conclusion

In reviewing the literature, it is obvious that SABR should be the primary modality in the treatment of medically inoperable NSCLC patients because it offers outcomes approaching surgical equivalence. The natural extension of this finding is to assess SABR's outcomes versus surgery outcomes in patients at high risk of morbidity from lobar resections. Such studies are in the early stages of patient accrual. The roles for SABR continue to increase and should be maintained as an integral aspect of any academic or private practice treatment repertoire.

Puneeth Iyengar, M.D., Ph.D.

Puneeth Iyengar, M.D., Ph.D., is Assistant Professor of Radiation Oncology at UT Southwestern Medical Center.

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New brachytherapy operating room

Intraoperative team at William P. Clements Jr. University Hospital

The new William P. Clements Jr. University Hospital on the UT Southwestern Medical Center campus recently opened a specially shielded operating room to allow physicians to perform intraoperative brachytherapy procedures.

The state-of-the-art, 970-square-foot room is shielded with two-inch thick, interlocking lead bricks and fitted with a specialized door and exterior controls to guide the delivery of radiation in the operating room. Select cancer patients can now be treated immediately following surgery with applicators placed directly in or adjacent to the tumor bed via the open surgical incision.

This approach delivers an extremely conformal dose, sparing healthy tissue from radiation, and can be a lifesaving procedure, particularly for patients with widespread cancer in the abdominal cavity.

A multidisciplinary, intraoperative team under the leadership of Radiation Oncology physician Michael Folkert, M.D., Ph.D., has accomplished a number of institutional firsts in the new operating room, including: the first abdominal intraoperative radiation therapy (for retroperitoneal sarcoma), the first endobronchial brachytherapy procedure, and the first esophageal brachytherapy procedure. The team is also treating ocular melanoma with the temporary placement of radioactive eye plaques in conjunction with UT Southwestern's Department of Ophthalmology.

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.

That new strategy is based on models that researchers developed to classify cancers caused by KRAS mutations, which cause cells to grow uncontrollably. Although 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 not all oncogenic KRAS mutations function in the same way to cause cancer," says Kenneth Westover, M.D., Ph.D., Assistant Professor of Radiation Oncology and Biochemistry. "The model we developed may help subclassify KRAS-mutant cancers so they can be treated more effectively, using therapies that are tailored to each mutation. Furthermore, this study gives new fundamental understanding to why certain KRAS-mutant cancers behave as they do."

KRAS is one of the main members of the RAS family. About a third of all human cancers, including a high percentage of pancreatic, lung, and colorectal cancers, are driven by mutations in RAS genes, which also make cells resistant to some available cancer therapies.

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

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Survivor Story: CyberKnife saves eye of cancer patient

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.

Bob Goble, cancer survivor

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 ability to look up. Doctors were concerned 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."

"I realized 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 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

The prescribed treatment for his tumor was six weeks of daily intensity-modulated radiation treatment (IMRT) combined with three infusion sessions of cisplatin—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 boost of radiation from 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!"

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