

THE TARGET

DEPARTMENT OF RADIATION ONCOLOGY



+ RUNS IN THE FAMILY

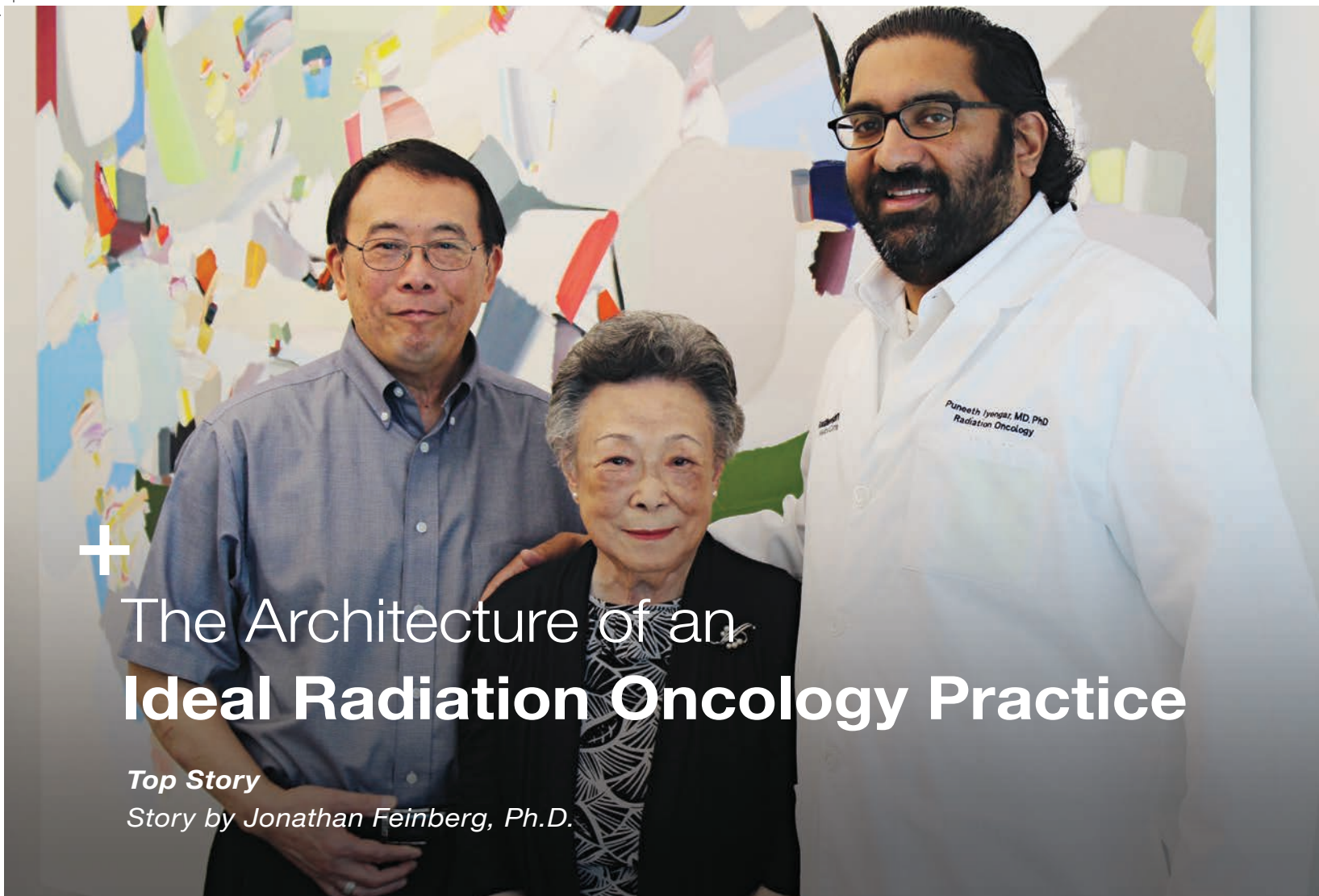
Elsie Wong and her son, Clifford Wong, share their experience of surviving cancer and their perspectives on the new Radiation Oncology clinic at UT Southwestern

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The Architecture of an Ideal Radiation Oncology Practice

Top Story

Story by Jonathan Feinberg, Ph.D.

Elsie Wong, 89, of Richardson, Texas, sits quietly next to her son, smiling modestly as he praises her artistic gifts.

“She’s very talented, my mother is,” Clifford Wong, 64, of Plano, Texas, says with obvious pride. “Right now, she’d even make things that you wouldn’t believe,” producing intricate works of origami and Chinese painting. Mr. Wong shares his mother’s artistic ability – he remembers drawing on each floor tile in the front corridor of the family’s home as a child, and he now runs a successful architecture firm.

Unfortunately for the Wongs, artistic talent is not the only thing that runs in the family. The Wong family also has a history of cancer: Mrs. Wong had a tumor removed from her bladder in 2004, and her husband died of lymphoma almost thirty years prior. More recently, both mother and son have been treated for lung cancer.

When Mr. Wong was diagnosed with stage IIIB non-small cell lung cancer in 2013, he turned to UT Southwestern Medical Center. There, he was treated by a team of doctors and therapists, including Puneeth Iyengar, M.D., Ph.D., Assistant Professor of Radiation Oncology. After a seven-week course of combined treatment with chemotherapy and radiation, followed by two full doses of chemotherapy, Mr. Wong’s cancer was in complete remission. “I’m thankful to be alive today,” Mr. Wong says, attributing his survival to “being treated by a doctor like Dr. Iyengar, his team of doctors, and assistants.”

When his mother was diagnosed with stage I lung cancer in the spring of 2017, Mr. Wong knew where to turn. As Mrs. Wong was not a candidate for surgery because of her age, Dr. Iyengar treated her with three fractions of stereotactic body radiation (SBRT) in the summer of 2017.

Between the time of Mr. Wong’s treatment and his mother’s, the Department of Radiation Oncology opened the new William P. Clements Jr. University Hospital Radiation Oncology Clinic, part of the Harold C. Simmons Comprehensive Cancer Center. Mr. Wong had

been treated in the Department’s more traditional clinic environment, which is widely recognized as a state-of-the-art facility, but he also accompanied his mother to her appointments at the new Radiation Oncology Clinic, which was designed to go beyond the current state of the art and includes features never implemented before. An architect with his own firm, Mr. Wong appreciates how a building’s design drives workflow and efficiency and can create a sense of calm and stability. This gives him a unique perspective, as both a patient and an architect, on the differences between the two facilities.

“They did a really nice job here,” Mr. Wong says. “Everything is very bright, you know – a little better sense of comfort when you come in.”

The new clinic features a calm, comforting environment for patients, characterized by a bright, spacious waiting area where patients can move freely and choose from a variety of entertainment and comfortable seating options. In the treatment areas, skylights bathe the vaults in natural light, and patient apparatuses have been moved out of the vaults and into the technical corridor, where they are accessible to therapists but invisible to patients.

These improvements in the patient experience were a deliberate part of the clinic’s design. Following evidence-based principles for patient-centered medicine and connected workplaces, the Department, led by Professor and Chairman Hak Choy, M.D., set out to develop an Ideal Radiation Oncology Practice Model that would improve efficiency, quality, and the doctor/patient relationship.

Achieving this goal meant not only creating the comforting patient environment that Mr. Wong experienced, but also completely reorganizing the clinic’s operations behind the scenes. Central to this reorganization is the disease-oriented team (DOT) concept, which entails multidisciplinary teams of physicians, therapists, biologists, dosimetrists, and physicists focusing on one specific disease site to provide what Nathan Kim, M.D., Ph.D., Associate Professor of Radiation Oncology, describes as “specialized care at its best.” The DOTs allow experts to “refine their expertise with a specified team” and to build a strong, collaborative rapport with that team to improve the clinic’s efficiency and provide patients with the highest quality personalized treatment plans. Dr. Kim believes that the DOT concept should be the future standard of care for radiation oncology. A recent survey of the new clinic by the Joint Commission

commended the facility and the DOT approach in particular.

The building has been designed to facilitate the DOT approach. An open office floor plan and “team rooms” – rather than separate stations for nurses and doctors – foster collaboration and communication among team members, which Chief Radiation Therapist Jay Dwyer says has increased comradery. Doctors, dosimetrists, and physicists are all in the same building – having previously been separate – and sit in close proximity to each other, which helps them to coordinate on treatment plans. Now, says Dr. Kim, his dosimetrist knows and understands what he wants when developing a plan. Their close collaboration “translates into smoother care for patients.”

The comradery and collaborations that the new facility supports also extend to new connections between researchers and clinicians. The initial effort to establish disease-oriented teams focused on physically integrating academic research and excellent patient care by moving part of the Department’s research closer to the clinics. Ultimately, this integration is closing the gap between experiments and real life, ensuring that clinical practice is informed by cutting-edge scientific research and that research remains grounded in the reality of everyday clinical practice.

By incorporating efficiency, collaboration, and patient comfort into the design of the new Radiation Oncology Clinic, UT Southwestern is striving to create and implement an ideal model to improve the overall health outcomes of cancer patients. “I truly believe that the design of this building will save lives,” says Professor and Vice Chair of Radiation Oncology Robert Timmerman, M.D.

Which means that Elsie Wong may be making art for years to come.

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

Dr. Timmerman holds the Effie Marie Cain Distinguished Chair in Cancer Therapy Research.



+ NEW FACULTY

Department News

CLINICAL



Larry Kun

M.D., FASTRO, Professor and Director of Educational Programs

Dr. Kun received his bachelor's degree from Penn State University, his medical degree from Jefferson Medical College, and did his residency at Penrose Cancer Hospital, Colorado Springs. In 2016, after 32 years, Dr. Kun retired from St. Jude Children's Research Hospital where he served as Chair of Radiation Oncology and Diagnostic Imaging, later as Executive Vice President and Clinical Director. He chaired the Pediatric Brain Tumor Consortium and the Brain Tumor Committees of the Pediatric Oncology Group and the Children's Oncology Group; he also served in leadership positions for the American Society for Radiation Oncology and the American Board of Radiology. Dr. Kun has received numerous honors, including *Memphis Business Journal's* 2017 Lifetime Achievement Award in Healthcare, the Gold Medal from the American Society for Radiation Oncology, the Janeway Medal from the Radium Society, and the Pediatric Award from the American Society for Clinical Oncology.



Todd Aguilera

M.D., Ph.D. Assistant Professor

Dr. Aguilera is a physician-scientist trained as a radiation oncologist with expertise in molecular engineering and imaging, tumor microenvironment, and tumor immunology. He completed the Scientist Training Program and an internship at the University of California San Diego (UCSD), followed by a residency at Stanford University. In addition to his clinical work, Dr. Aguilera has a research lab with a focus on factors in the tumor microenvironment that promote immunologic tolerance and developing therapeutic approaches to improve immunotherapy responses in solid tumors.



Prasanna Alluri

M.D., Ph.D. Assistant Professor

Dr. Alluri, who received his medical degree from the University of Minnesota, is a physician-scientist working at the interface of clinical breast oncology and translational breast cancer research. His laboratory studies molecular mechanisms underlying treatment resistance in breast cancer with the goal of developing targeted therapies to overcome such resistance.



Jennifer Shah

M.D., Assistant Professor and Associate Director of Medical Residency Program

Dr. Shah received her medical degree from Stanford University. Her clinical focus is the treatment of malignancies of the head and neck.

MOLECULAR RADIATION BIOLOGY



Guo-Min Li

Ph.D., Professor, Director of Translational Research and the Reece A. Overcash Jr. Chair for Center for Research on Colon Cancer

Dr. Li received his B.S. and M.S. degrees in biology from Wuhan University in China and his Ph.D. in chemistry from Wayne State University. Before joining UT Southwestern, Dr. Li was a professor at the University of Southern California. Dr. Li studies cellular mechanisms maintaining genome stability—in particular, the DNA mismatch repair (MMR) pathway and its role in cancer susceptibility and therapy.



Liya Gu

Ph.D. Professor

Dr. Gu received both her bachelor's and master's degrees in biochemistry from Wuhan University. She received her Ph.D. in chemistry at Wayne

State University in Detroit. Dr. Gu was a postdoctoral fellow at NIEHS/NIH and a postdoctoral fellow UNC at Chapel Hill.



Hanzhi Wang

Ph.D. Instructor

Dr. Wang received her degree in biology from Nanjing University and a Ph.D. in biochemistry and molecular biology from the Institute of Biochemistry and Cell Biology, Shanghai Institute for Biological Sciences, Chinese Academy of Sciences. Her research interests include molecular mechanisms of autophagy, hypoxia, and genome instability-related potential cancer therapy.



Huiming Lu

Ph.D. Instructor

Dr. Lu graduated from Zhejiang University with a bachelor's degree in agronomy. He continued his graduate studies there focusing on biophysics. His research interests include the molecular mechanisms of DNA double-strand break repair and targeting key players of DNA double-strand break repair for potential cancer therapy. Dr. Lu will be part of Dr. Anthony Davis's lab.



Janice Ortega Rodriguez

Ph.D. Instructor

Dr. Rodriguez received her degree in chemistry from the University of Puerto Rico, Río Piedras Campus, and a Ph.D. in toxicology from the University of Kentucky.



Vinesh Kumar Thidil Puliappadamba

Ph.D. Instructor

Dr. Puliappadamba received his master's degree in biotechnology from Cochin University in India and his Ph.D. in biotechnology from the University of Kerala. Before joining UT Southwestern, he was a postdoc fellow in the Department of Radiation Oncology at the University of Alabama in Birmingham. Dr. Puliappadamba studies chemo resistance in brain cancer targeting DNA repair mechanism and cell signaling.



Qihuang Jin

Ph.D. Instructor

Dr. Jin received his Ph.D. degree from Shanghai Institute of Biochemistry and Cell Biology, Chinese Academy of Sciences. His research covers many fields, including apoptosis, adipogenesis, epigenetics, and cell signaling transduction, but his main focus now is on epigenetic regulation of DNA repair. Before joining UT Southwestern, he was a visiting fellow at the National Institutes of Health in Maryland and an instructor at UT MD Anderson Cancer Center. In addition, he led a 3DMed team in Shanghai, China, developing techniques on DNA mutation detection with next generation sequencing (NGS) in tissue DNA and circulating tumor DNA (ctDNA).

PHYSICS



Amir Owрани

Ph.D. Assistant Professor

Dr. Owрани is a physicist-scientist trained as a radiation oncology medical physicist with expertise in adaptive radiation therapy, brachytherapy, and MRI guidance in radiotherapy. He received his B.S. and M.S. degrees in physics and radiation medicine from Shiraz University in Shiraz, Iran, and his Ph.D. in biomedical engineering from the University of Western Ontario in London, Canada. He completed his medical physics residency at the University of Michigan. Before joining UTSW, Dr. Owрани was an Assistant Professor in the Department of Radiation Oncology at the University of Toronto, where his research was focused on developing new methods for generating synthetic CT images from MRI images.



Dan Nguyen

Ph.D. Instructor

Dr. Nguyen did his undergraduate studies at the University of Texas at Austin and his graduate work at the University of California, Los Angeles.

+ PUBLICATIONS

Department News

Albuquerque K, Folkert M, Mayadev J, et al. Adjuvant external radiation impacts outcome of pelvis-limited stage III endometrial carcinoma: a multi-institutional study. *Am J Clin Oncol*. 2017 Feb 20; 6:175-187.

Davis AJ, Wang SY, Chen DJ, Chen BPC. Imaging of fluorescently tagged ATM kinase at the sites of DNA double strand breaks. *Methods Mol Biol*. 2017;1599:277-285.

Folkert MR, Setton J, Apte AP, Grkovski M, et al. Predictive modeling of outcomes following definitive chemoradiotherapy for oropharyngeal cancer based on FDG-PET image characteristics. *Phys Med Biol*. 2017 Jul 7; 62(13):5327-5343.

Guo G, Gong K, Ali S, Ali N, Shallwani S, Mickey B, Burma S, et al. A TNF-JNK-Axl-ERK signaling axis mediates primary resistance to EGFR inhibition in glioblastoma. *Nat Neurosci*. 2017 Aug;20(8):1074-1084.

Hrycushko BA, Chopra R, Sayre JW, Folkert MR, Timmerman RD, Medin PM, et al. Local hypothermia as a radioprotector of the rectal wall during prostate stereotactic body radiation therapy. *Int J Radiat Oncol Biol*. 2017 May 1; 98(1):75-82.

Iqbal Z, Verma G, Kumar A, Thomas MA. Covariance J-resolved spectroscopy: theory and application in vivo. *NMR in Biomed*. 2017 May 8.

Jones RT, Rezaeian NH, Desai NB, Jia X, Hannan R, Kim DWN, Dubas J, Laine AM, Timmerman RD, Folkert MR, et al. Dosimetric comparison of rectal-sparing capabilities of rectal balloon vs injectable spacer gel in stereotactic body radiation therapy for prostate cancer: lessons learned from prospective trials. *Med Dosim*. 2017 Jul 3.

Kalimutho M, Bain AL, Mukherjee B, Harris JL, Burma S, et al. Enhanced dependency of KRAS-mutant colorectal cancer cells on RAD51-dependent homologous recombination repair identified from genetic interactions in *Saccharomyces cerevisiae*. *Mol Oncol*. 2017 May; 11(5):470-490.

Karanam NK, Srinivasan K, Ding L, Sishc B, Saha D, Story MD. Tumor-treating fields elicit a conditional vulnerability to ionizing radiation via the downregulation of BRCA1 signaling and reduced DNA double-strand break repair capacity in non-small cell lung cancer cell lines. *Cell Death Dis*. 2017 Mar 30; 8(3):e2711.

Li B, Lee HC, Duan X, Shen C, Zhou L, Xia X, Yang M. Comprehensive analysis of proton range uncertainties related to stopping-power-ratio estimation using dual-energy CT imaging. *Phys Med Biol*. 2017 Jul 5.

Mohamad O, Sishc BJ, Saha J, Pompos A, Rahimi A, Story MD, Davis AJ, Kim DWN. Carbon ion radiotherapy: a review of clinical experiences and preclinical research, with an emphasis on DNA damage/repair. *Cancers*. 2017 Jun 9;9(6).

Qin N, Pinto M, Tian Z, Dedes G, Pompos A, Jiang SB, Parodi K, Jia X. Initial development of goCMC: a GPU-oriented fast cross-platform Monte Carlo engine for carbon ion therapy. *Phys Med Biol*. 2017 May 7;62(9):3682-3699.

Rahimi A, Thomas K, Spangler A, Albuquerque K, Ding C, Ahn C, Timmerman RD, et al. Preliminary results of a phase 1 dose-escalation trial for early-stage breast cancer using 5-fraction stereotactic body radiation therapy for partial-breast irradiation. *Int J Radiat Oncol Biol*. 2017 May 1; 98(1):196-205.

Ritter TA, Matuszak M, Chetty IJ, Wu J, Iyengar P, Xiao Y, Timmerman RD, et al. Application of critical volume-dose constraints for stereotactic body radiation therapy in NRG radiation therapy trials. *Int J Radiat Oncol Biol*. 2017 May 1; 98(1):34-36.

Saki M, Makino H, Javvadi P, Tomimatsu N, Saha D, Story MD, Burma S, et al. Mutations in epidermal growth factor receptor compromise hypoxia associated radiation resistance through impaired repair of replication fork associated DNA damage. *Mol Cancer Res*. 2017.

Saja J, Wang SY, Davis AJ. Examining DNA double-strand break repair in a cell cycle-dependent manner. *Methods Enzymol*.

2017 Apr 17;591:97-118.

Sishc BJ, Davis AJ. The role of the core non-homologous end joining factors in carcinogenesis and cancer. *Cancers*. 2017 Jul 6;9(7)81.

Thomas KM, Maquilan G, Stojadinovic S, Medin P, Folkert MR, Albuquerque K. Reduced toxicity with equivalent outcomes using three-dimensional volumetric (3DV) image-based versus non-volumetric point-based (NV) brachytherapy in a cervical cancer population. *Brachytherapy*. 2017 Jun 8.

Tomimatsu N, Mukherjee B, Potts PR, Khanna KK, Burma S, et al. DNA damage-induced degradation of EXO1 exonuclease limits DNA end resection to ensure accurate DNA repair. *J Biol Chem*. 2017 June 30;292(26):10779-10790.

Tumati V, Jackson WC, Lotan Y, Folkert MR, Laine A, Hannan R, Spratt DE, Desai NB, et al. Natural history of biochemical failure following post-operative radiation therapy for prostate cancer: a multi-institution study. *BJU International*. 2017 Jun 5.

Wang CJ, Lin M-H, Jung M, Desai N, Kim DWN, Pedrosa I, Laine A, Xie X-J, Choy H, Timmerman RD, Hannan R, et al. Safety and efficacy of stereotactic ablative radiation therapy for renal cell carcinoma extracranial metastases. *Int J Radiat Oncol Biol*. 2017 May 1; 98(1):91-100.

Yin Y, Li R, Xu K, Ding S, Li J, Ding S, Liu Z, Gao Y, Li X, Liu X, Xing C, Desai NB, Burma S, Chen BPC, et al. Androgen receptor variants mediate DNA repair after prostate cancer irradiation. *Cancer Res*. 2017 Jul 20.

Zhou Z, Folkert MR, Iyengar P, Westover K, Zhang Y, Choy H, Timmerman RD, Jiang S, Wang CJ. Multi-objective radiomics model for predicting distant failure in lung SBRT. *Phys Med Biol*. 2017 May 8; 62(11):4460-4478.

Zhou Y, Klages P, Yang M, Hrycushko B, Medin P, Pompos A, Jiang S, Albuquerque K, Jia X, et al. Automated high-dose rate brachytherapy treatment planning for a single-channel vaginal cylinder applicator. *Phys Med Biol*. 2017 Jun 7;62(11):4361-4374.

+ CLINICAL TRIALS

Department News

BREAST

STU 062015-085: A phase I dose-escalation trial of single-fraction adjuvant stereotactic body partial breast irradiation for early stage breast cancer.

STU 052016-046: A phase IIR/III trial of standard of care therapy with or without stereotactic body radiotherapy and/or surgical ablation for newly oligometastatic breast cancer.

NON-THERAPEUTIC

STU 012014-039: UTSW SBRT prospective clinical registry for oligometastatic disease, consolidation therapy, debulking prior to chemotherapy, or re-irradiation.

CENTRAL NERVOUS SYSTEM

STU 022015-106: A phase I dose-escalation study of stereotactic radiosurgery for brain metastasis without whole brain radiation.

STU 072010-134: A phase II study of stereotactic body radiation therapy and vertebroplasty for localized spinal metastasis.

STU 042011-075: Interstitial radioactive iodine implants for the treatment of pan-invasive pituitary macroadenomas.

GASTROINTESTINAL

STU 102015-019: A randomized phase III pancreatic cancer radiotherapy study evaluating modified FOLFIRINOX with or without stereotactic body radiotherapy in the treatment of locally advanced pancreatic cancer.

STU 102014-018: A phase I therapeutic dose-escalation study using percutaneous image-guided navigation for high-dose rate brachyablation of primary liver lesions.

GENITOURINARY

STU 102014-064: A phase III randomized trial of androgen deprivation therapy and high-dose radiotherapy with or without whole pelvic radiotherapy in unfavorable

intermediate or favorable high-risk prostate cancer.

STU 012013-041: A phase II trial of high-dose IL-2 and stereotactic ablative body radiation therapy for patients with metastatic clear-cell renal cell cancer.

STU 102012-026: A phase II trial of sipuleucel-T and stereotactic ablative body radiation for patients with metastatic castrate-resistant prostate cancer.

STU 062014-027: A phase I clinical trial of stereotactic ablative radiotherapy of pelvis and prostate targets for patients with high-risk prostate cancer.

STU 022015-058: Safety lead-in phase II trial of neoadjuvant for IVC tumor thrombus in newly diagnosed renal cell cancer.

STU 122015-052: A phase II trial of nivolumab and stereotactic ablative radiation therapy for metastatic clear-cell renal cell carcinoma.

STU 052016-044: A phase II trial of stereotactic ablative body radiation therapy for patients with primary renal cancer.

HEAD & NECK

STU 052016-044: A prospective phase II study of involved field elective volume de-intensification for oropharyngeal and laryngeal squamous cell carcinoma treated with intensity-modulated radiation therapy.

STU 022011-213: A randomized phase II study of adjuvant concurrent radiation and chemotherapy versus radiation alone in resected high-risk malignant salivary gland tumors.

STU 092010-061: A phase III study of postoperative radiation therapy (IMRT) +/- cetuximab for locally advanced resected head and neck cancer.

STU 072014-041: A randomized phase II and phase III study of individualized treatment for nasopharyngeal carcinoma based on biomarker Epstein-Barr virus deoxyribonucleic acid.

NON-THERAPEUTIC

STU 102016-004: A study on the reliability of using cone-beam CT for dose calculation and replanning in online adaptive radiotherapy for head and neck cancer.

STU 112014-004: A prospective, single-arm cohort study of patients receiving endocrine therapy alone (without radiotherapy) after breast-conserving surgery for early stage, post-menopausal breast cancer patients whose tumors have favorable biologic features.

LUNG

STU 072013-085: A randomized phase II study of individualized combined modality therapy for stage III non-small cell lung cancer.

STU 052011-093: A phase III randomized study of standard versus accelerated hypofractionated image-guided radiation therapy in the definitive setting for patients with stage II-III or recurrent non-small cell lung cancer and poor performance status.

STU 022015-069: A randomized phase III study of sublobar resection versus stereotactic ablative radiotherapy in high-risk patients with stage I non-small cell lung cancer.

STU 082016-055: Randomized, double-blinded phase III trial of cisplatin and etoposide plus thoracic radiation therapy followed by nivolumab/placebo for locally advanced non-small cell lung cancer.

CALGB 30610: A phase III comparison of thoracic radiotherapy regimens in patients with limited small cell lung cancer also receiving cisplatin and etoposide.

NON-THERAPEUTIC

STU 062016-073: Investigating radiation-induced injury to airways and pulmonary vasculature in lung stereotactic ablative body radiotherapy (SABR).

For more information, please contact Sarmistha Sen, Clinical Research Manager, at 214-645-1477 or sarmistha.sen@UTSouthwestern.edu.

Overcoming Therapeutic Resistance

By Jonathan Feinberg, Ph.D.

Cancer cells' ability to develop resistance to conventional therapies poses one of the most daunting challenges to effective treatment.

Guo-Min Li, Ph.D., Professor in the Department of Radiation Oncology, compares cancer's therapeutic resistance to the natural selection of species. Just as random mutations leave some species better able than others to survive adverse environmental conditions, mutations allow some cancer cells to survive treatment while most of the cancer cells die. "They try to take advantage of mutation," Dr. Li says, "to transform into different forms that are resistant to anything."

Dr. Li recently joined UT Southwestern Medical Center, coming from the University of Kentucky via the University of Southern California, to pursue alternative cancer treatments that can overcome therapeutic resistance. "UT Southwestern has a great reputation in the sciences," says Dr. Li. "I think that the Medical Center is probably, in my opinion, one of the best in the world in biomedical research."

Dr. Li's lab studies the biological mechanisms that lead to cancer, focusing specifically on the DNA mismatch repair system. Dr. Li identified the link between defects in DNA mismatch repair and colorectal cancer while working as a postdoctoral fellow at Duke University in 1993 under future Nobel laureate, Dr. Paul Modrich (Chemistry, 2015).

"DNA mismatch repair is a very important pathway in our cells," Dr. Li explains, "because it maintains genomic stability by assuring replication fidelity." The DNA mismatch repair system corrects thousands of DNA replication mistakes made during each cell division cycle. Without these corrections, replication mistakes would lead to mutations and, eventually, tumorigenesis. Since DNA mismatch repair is not 100 percent accurate, mutations accumulate slowly over time, often leading to cancer late in life. However, defects in the DNA mismatch repair gene can create a genetic predisposition to tumorigenesis and a higher likelihood of cancer earlier in life, as unrepaired replication mistakes accumulate more rapidly with each successive cell cycle.

Dr. Li thinks the DNA mismatch repair system can be

used for cancer therapy. His lab has identified a mutant mismatch repair protein that recognizes and binds to DNA mismatches. This binding initiates the mismatch repair reaction, but the reaction is arrested at the excision step, generating single-stranded DNA gaps that can trigger cell death. Since only cancer cells undergo error-prone DNA replication that generates mismatches during cell division, Dr. Li is hopeful that they can use the mutant protein to develop a therapy that would target cancer cells specifically and spare normal cells, which contain no mismatches.

Such a therapy would contrast sharply with traditional cancer therapies, like chemotherapy and radiation therapy, that cannot distinguish cancer cells from normal cells and thus, kill both, leading to adverse side effects. Just as important, a mismatch repair-based therapy would avoid the pitfalls of therapeutic resistance, as it would target the very mutations that allow cancer cells to adapt and survive conventional therapies.

Targeting DNA mismatches could even be used for cancer prevention, especially among those with a defect in the mismatch repair genes, as cells with mismatches could be killed before they become tumorigenic, while normal cells would remain unaffected.

Delivering the mutant protein is the challenge, however. Dr. Li sees two possible approaches. The first is to use a nanoparticle or similar agent to deliver the protein directly to cancer cells, using distinctive surface molecules on the cancer cells to distinguish them from normal cells.

The second approach is to identify a small molecule that can make the wild type mismatch repair protein function like the mutant protein, ultimately triggering cell death in cells with mismatches. This molecule could be taken like a pill or a vitamin, allowing for easy, non-invasive delivery. In fact, Dr. Li says, one of the reasons why he came to UT Southwestern was because it has a small molecules library that his lab can screen to identify the right molecule.

"If we can find that," Dr. Li says, "that would be revolutionary for the whole field."

Dr. Li holds the Reece A. Overcash Jr. Distinguished Chair for Research on Colon Cancer.

+ Research Highlights

RESEARCH

Guo-Min Li, Ph.D.

Professor in the Department of Radiation Oncology

"UT Southwestern has a great reputation in the sciences. I think that the Medical Center is probably, in my opinion, one of the best in the world in biomedical research."

Predictive Research: Rectal Toxicity

By **Brian Hrycushko, Ph.D.**

Edited by **Mary Whitmore and Kevin Albuquerque, M.D.**

Cervical cancer is the third most common cause of female cancer mortality worldwide (Torre et al, 2015). Locally advanced cervical cancer is typically treated with external beam radiotherapy (Al-Mansour and Verschraegen, 2010), followed by brachytherapy, with or without chemotherapy. Randomized studies have shown excellent treatment outcomes in early stage cervical cancer (Gray, 2008; Haie-Meder et al., 2010), but treatment results aren't as favorable in advanced stages.

More and more clinical evidence correlates tumor control rate with dose, but with higher doses, comes greater risk for toxicity to nearby organs, including the rectum, sigmoid, bladder, and vagina. Delayed rectal morbidity (manifested as rectal bleeding) (Mazon et al., 2016) is directly proportional to the amount of dose received by the lower rectum, but it is difficult to tease out this dose-toxicity correlation. A better understanding of the relationship between organs-at-risk toxicity and dose is critical for safe-dose escalation to improve local control of large-sized advanced-stage cervical cancer tumors.

The standard of care for locally advanced cervical cancer includes combined external beam radiotherapy and intracavitary brachytherapy. Modern adaptive image-guided brachytherapy utilizes a newly acquired 3-D image for each fraction; however, effective utilization of these 3-D images has yet to be achieved.

Most of a patient's brachytherapy radiation treatments plans are based on a few static 3-D image sets of their tumor region. Dose calculations are made for each of these treatment fraction events and are arithmetically summated to get the total dose to the normal organs—in this case, the rectum. But, because the organs and tumor can move and change throughout the fractionated treatment course, simple summation of dose will not give an accurate estimation of dose to the affected organ.

Current American Brachytherapy Society (ABS) organ at-risk dose limits are based on the simple arithmetic addition of the dose received by the rectum. However, because the geometry of organs at-risk relative to the target may change for each brachytherapy fraction, the same volume of at-risk organs does not always receive the highest dose and this toxicity metric will overestimate the dose making it



a conservative, worse-case scenario limit.

Understanding how the dose truly gets distributed from fraction to fraction within at-risk organs will help improve this adaptive therapy approach by allowing the planner to better control the dose to be delivered for each fraction. In turn, it will benefit the patient by reducing the probability for toxicity to organs at risk, such as the rectum, bladder, or sigmoid. It will also allow for escalation of the tumor dose, which appears to be necessary for higher stage disease.

Dr. Xuejun Gu, Associate Professor in the Department of Radiation Oncology and part of the gynecological disease-oriented team, is working on an approach to use novel deformable image registration techniques to propagate the contours of organs at-risk from fraction to fraction. She has developed an algorithm so we can better see fraction to fraction which volume of rectum is getting the maximum dose and, therefore, accurately assess the dose exposure.

In order to do this, Dr. Gu's group, which includes Xin Zhen, Ph.D., Jiawei Chen, Ph.D., Zichun Zhong, Ph.D., Brian Hrycushko, Ph.D., Linghong Zhou, Ph.D., Steve Jiang, Ph.D., Kevin Albuquerque, M.D., and Xuejun Gu, Ph.D., has developed seed-point auto-generation for random walks segmentation enhancement (SPARSE) and contour-guided deformable image registration (CG-DIR) algorithms—both of which will assist in automatic organ at-risk segmentation and clinical target volume propagation from fraction to fraction. Through the combination of her recently developed topography-preserved point-matching deformable image registration (TOP-DIR) and CG-DIR algorithms, accurate dose summations are enabled across all external beam radiation therapy and brachytherapy treatment plans.

After combining these deformable image registration tools with patient data, Dr. Gu is using artificial intelligence strategies and techniques utilized by companies such as Facebook, Google, and Amazon for auto-tagging, photo recognition, or product recommendations, to determine better correlates between the accumulated dose distribution map and tumor/normal organs compared to the current metrics. The hope is that these advanced tools will allow us to better plan where to distribute the dose from fraction to fraction in a way that maximizes tissue-sparing and the radiotherapy efficacy for late-stage cervical cancer.

Their paper, entitled “Transfer Learning Using Deep Convolutional Neural Networks for Rectum Toxicity Prediction in Cervical Cancer Radiotherapy,” was selected for the 2017 Science Council Session—one of only 12 accepted each year. Eventually, Gu wants to expand the study to prostate cancer.

References

Al-Mansour Z, Verschraegen C. Locally advanced cervical cancer: what is the standard of care? *Curr Opin Oncol.* 2010 Sep;22(5):503-512. PMID: 20473164.

Gray HJ. Primary management of early stage cervical cancer (IA1-IB) and appropriate selection of adjuvant therapy. *J Natl Compr Canc Netw.* 2008 Jan; 6(1):47-52. PMID: 18267058.

Haie-Meder C, Morice P, Castiglione M, ESMO Guidelines Working Group. Cervical cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. *Ann Oncol.* 2010 May;21(5):v37-40. PMID: 20555099.

Mazon R, Fokdal L U, Kirchheiner K, Georg P, Jastaniyah N, Segedin B, Mahantshetty U, Hoskin P, Jurgentliemk-Schulz I, Kirisits C, Lindegaard J C, Dorr W, Haie-Meder C, Tanderup K, Potter R, EMBRACE collaborative group. Dose-volume effect relationships for late rectal morbidity in patients treated with chemoradiation and MRI-guided adaptive brachytherapy for locally advanced cervical cancer: results from the prospective multicenter EMBRACE study. *Radiother Oncol.* 2016 Sep;120(3):412-419. PMID:27396811.

Torre L A, Bray F, Siegel R L, Ferlay J, Lortet-Tieulent J, Jemal A. Global cancer statistics, 2012. *CA Cancer J Clin.* 2015 Mar;65(2):87-108.

GRANTS & PARTNERSHIPS

David Chen, Ph.D. had his competing renewal for “Pathway Choice of DNA Double-Strand Break Repair” funded for another five years by the National Institutes of Health.

Guo-Min Li, Ph.D. received “Established Investigator Recruitment Award” from CPRIT for \$6 million.

Guo-Min Li, Ph.D. received the “UT Rising Star Investigator Award” for \$2 million.

Kenneth Westover, M.D., Ph.D. received “HTS for covalent GTP-competitive inhibitors of KRAS G12C” from CPRIT for \$823,500.

Todd Aguilera, M.D., Ph.D. received the “CPRIT Recruitment of First-Time, Tenure-Track Faculty Member Award” for \$2 million.

Raquibul Hannan, M.D., Ph.D. is the co-investigator on the recently awarded CPRIT HRHI grant “Radiation-Induced Release of Chemotherapeutic Agents in Vivo.”

Distributed Stereotactic Radiosurgery for Multiple Brain Metastases

By **Zabi Wardak, M.D.**

Edited by **Mary Whitmore and Claire Almanza**

Brain metastases are the most common brain tumor, with approximately 170,000 cases diagnosed each year (Claus, 2011). Due to continual improvements in systemic therapy, prolonged survival of cancer patients may be associated with an increased risk of developing intracranial metastatic disease.

At UT Southwestern, brain protection is a fundamental mission. As such, our radiation oncologists and neurosurgeons use stereotactic radiosurgery (SRS) as the preferred treatment method for patients with brain metastases. (Historically, treatment for patients with brain metastases was whole-brain radiation therapy (WBRT) and/or surgical resection.)

Stereotactic radiosurgery for brain metastases has several advantages over whole brain radiation therapy and surgery and is becoming the preferred treatment choice in many cases. SRS can be performed in patients who are not surgical candidates due to medical comorbidities and can treat deep metastases that are not amenable to surgical resection. SRS is also a minimally invasive, outpatient procedure with no significant recovery time. In addition, compared with WBRT, SRS provides more potent biologic doses of radiation, which may be beneficial – especially in tumor types considered resistant to traditional radiotherapy.

Most significantly, with WBRT both the tumor and surrounding (healthy) tissues receive radiation, which can lead to side effects such as fatigue and cognitive decline – specifically, a decline in short-term memory. Recent clinical trials have shown that SRS alone is associated with lower rates of memory decline when compared with WBRT (Chang, 2009; Brown, 2016). Based on these trials, patients with limited brain metastases undergo SRS alone, with close surveillance, as the treatment of choice for the preservation of cognitive function. The candidacy for SRS has largely been determined by the number of metastases; however, at UT Southwestern we have expanded the eligibility for patients with multiple metastases thanks to improvements in our technology.

Our patients are being treated on the latest model of the Gamma Knife, known as the Icon, which provides several advantages over the previous model when treating multiple brain metastases. With the previous version of the Gamma Knife, patients were required to wait with a stereotactic headframe fixed to the skull during the treatment planning process, which, once begun, could last several hours when treating multiple metastases. With the introduction of the Gamma Knife Icon we're able to treat with a



mask – without the head frame – greatly improving patient comfort. This also allows us to distribute the treatment over several days by treating only a subset of the metastases on each day, with complete treatment delivered over one to five distributed radiosurgery sessions, each at a fraction of the time. Furthermore, we are able to maximize sparing of healthy brain when metastases are in close proximity to one another by distributing their treatment over multiple sessions.

Zabi Wardak, M.D., Assistant Professor in the Department of Radiation Oncology, has opened a clinical trial that aims to determine the safety and neurocognitive decline with SRS for patients with six or more brain metastases. By combining the latest in technology, he hopes to expand the eligibility of patients receiving SRS, improve patient outcomes, and maintain their quality of life. Dr. Wardak, Principal Investigator, will work closely with the Department of Neurosurgery, the Division of Radiation Physics, and the Department of Clinical Sciences, to enroll patients and follow them throughout the trial, which is slated to run for up to three years.

References

Brown PD, Jaeckle K, Ballman KV, et al. Effect of radiosurgery alone vs radiosurgery with whole brain radiation therapy on cognitive function in patients with 1 to 3 brain metastases: a randomized clinical trial. *JAMA*. 2016 Jul 26;316(4):401-409. PMID: 27458945.

Chang EL, Wefel JS, Hess KR, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. *Lancet Oncol*. 2009 Nov;10(11):1037-1044. PMID:19801201.

Claus EB. Neurosurgical management of metastases in the central nervous system. *Nat Rev Clin Oncol*. 2011 Dec 6;9(2):79-86. PMID: 22143137.

+ DISEASE-ORIENTED TEAM FACULTY

Our Team

BREAST



Ann Spangler, M.D.

Associate Professor

Trained: Shands Hospital at the University of Florida

Dr. Spangler has a primary focus on treating breast cancer. She can provide partial-breast irradiation with the CyberKnife, a noninvasive robotic radiosurgery system.



Asal Rahimi, M.D.

Assistant Professor and Director of Clinical Research

Trained: University of Virginia

Dr. Rahimi's practice focuses on breast cancer and she is administratively responsible for the clinical research infrastructure, including oversight of more than 90 current clinical trials.



Nathan Kim, M.D., Ph.D.

Associate Professor

Trained: Vanderbilt University Medical Center

Dr. Kim is focused on treating breast cancer. His research interests include combined modality therapy for breast cancer and the mitigation of normal tissue injury from radiation therapy.



Prasanna Alluri, M.D., Ph.D.

Assistant Professor

Trained: University of Minnesota

Dr. Alluri is a physician-scientist working at the interface of clinical breast oncology and translational breast cancer research. His laboratory studies molecular mechanisms underlying treatment resistance in breast cancer with the goal of developing targeted therapies to overcome such resistance.

CENTRAL NERVOUS SYSTEM



Robert Timmerman, M.D.

Vice Chairman, Professor and Medical Director
Holder of the Effie Marie Cain Distinguished Chair in
Cancer Therapy Research

Trained: The Johns Hopkins Hospital

Dr. Timmerman specializes primarily in treating adults and children with brain tumors and vascular malformations. He has achieved worldwide attention for his work in translating the specialized treatment techniques developed for brain tumors into the treatment

of cancer sites in the body. This technique, known as stereotactic ablative radiotherapy or stereotactic body radiation therapy, is often in the setting of hypofractionation.



Lucien Nedzi, M.D.

Associate Professor

Trained: Harvard Medical School

Dr. Nedzi treats patients with central nervous system malignancies, both primary brain cancers and brain metastases.



Tu Dan, M.D.

Clinical Instructor

Trained: Sidney Kimmel Medical College
at Thomas Jefferson University

Dr. Dan has a primary focus on adult and pediatric central nervous system diseases. He devotes a majority of his professional time to the laboratory study of radiation resistance and strategies to improve the efficacy of radiation.



Zabi Wardak, M.D.

Assistant Professor

Trained: UT Southwestern Medical Center

Dr. Wardak's clinical focus is on adult and pediatric central nervous system neoplasms and vascular malformations.

GASTROINTESTINAL



Michael Folkert, M.D., Ph.D.

Assistant Professor and Residency Program Director

Trained: Memorial Sloan Kettering Cancer Center

Dr. Folkert specializes in treating many disease sites with brachytherapy and coordinates the intraoperative radiation therapy program. His clinical sites also include gastrointestinal and pediatric cancers, sarcoma, eye, and spinal tumors.



Nathan Kim, M.D., Ph.D.

Associate Professor

Trained: Vanderbilt University Medical Center

Dr. Kim is focused on treating breast cancer. His research interests include combined modality therapy for breast cancer and the mitigation of normal tissue injury from radiation therapy.



Todd Aguilera, M.D., Ph.D.
Assistant Professor
Trained: UC San Diego School of Medicine

Dr. Aguilera is a physician-scientist trained as a radiation oncologist with expertise in molecular engineering, molecular imaging, tumor microenvironment, and tumor immunology. His lab is studying factors in the tumor microenvironment that promote immunologic tolerance and developing therapeutic approaches to improve immunotherapy responses in solid tumors.

GENITOURINARY



Aaron Laine, M.D., Ph.D.
Assistant Professor
Trained: UT Southwestern Medical Center

Dr. Laine focuses on the treatment of genitourinary cancer. As a medical scientist, he directs laboratory research exploring cachexia where he, along with other researchers, have successfully identified genomic and inflammatory alterations in cells that are linked to its cachexia development.



Michael Folkert, M.D., Ph.D.
Assistant Professor and Residency Program Director
Trained: Memorial Sloan Kettering Cancer Center

Dr. Folkert specializes in treating many disease sites with brachytherapy and coordinates the intraoperative radiation therapy program. His clinical sites also include gastrointestinal and pediatric cancers, sarcoma, eye, and spinal tumors.



Neil Desai, M.D.
Assistant Professor
Awarded the Dedman Family Scholar in Clinical Care
Trained: Memorial Sloan Kettering Cancer Center

Dr. Desai focuses on the treatment of genitourinary disease and lymphoma, and is an expert in the use of brachytherapy for prostate cancer.



Raquibul Hannan, M.D., Ph.D.
Assistant Professor
Trained: Albert Einstein College of Medicine

Dr. Hannan, leader of the genitourinary radiation oncology team and a co-leader of the Cancer Center's kidney cancer program, has a clinical focus on the treatment of genitourinary malignancies—specifically in the application of SBRT for tumors in both the primary and metastatic settings. He leads a translational lab that examines the immune and inflammatory responses induced by tumor irradiation, which he utilizes in the clinical setting by strategically combining radiation therapy with immunotherapy to induce abscopal effects.

GYNECOLOGICAL



Kevin Albuquerque, M.D.
Professor
Holder of the Ken Sharma Professorship in Radiation Oncology
Trained: University Hospital of Brooklyn

Dr. Albuquerque focuses on the treatment of gynecologic cancers and melanoma. He is an expert in the use of brachytherapy for the management of these malignancies.



Michael Folkert, M.D., Ph.D.
Assistant Professor and Residency Program Director
Trained: Memorial Sloan Kettering Cancer Center

Dr. Folkert specializes in treating many disease sites with brachytherapy and coordinates the intraoperative radiation therapy program. His clinical sites also include gastrointestinal and pediatric cancers, sarcoma, eye, and spinal tumors.

HEAD & NECK



David Sher, M.D., MPH
Associate Professor
Trained: Harvard Radiation Oncology Program

Dr. Sher focuses on the treatment of head and neck cancer. His research interests include outcomes and comparative and cost-effectiveness analysis.



Jennifer Shah, M.D.
Assistant Professor and Associate Director of Medical Residency Program
Trained: Stanford University

Dr. Shah focuses on the treatment of malignancies of the head and neck, as well as lymphoma.



Nhat-Long Pham, M.D., Ph.D.
Assistant Professor
Trained: University of California – San Diego

Dr. Pham treats patients with head and neck disease. His scientific interest focuses on designing and implementing innovative strategies to improve the efficacy of radiation therapy in conjunction with tumor immunotherapy.

LUNG



Hak Choy, M.D., FASTRO
Chairman, Professor
Holder of the Nancy B. and Jake L. Hamon Distinguished Chair in Therapeutic Oncology Research
Trained: Ohio State University Hospital; UT Health Science Center at San Antonio

Dr. Choy is known globally for his pioneering work, beginning in the early 1990s, showing the benefit of combining paclitaxel and other chemotherapeutic agents with radiation treatment for lung cancer. He continues to be active in designing national clinical trials that combine chemotherapy with the latest radiation treatment techniques and focuses on lung cancer in the clinic.



Kenneth Westover, M.D., Ph.D.
Assistant Professor and Director of Clinical Innovation and Information Systems
Trained: Harvard Radiation Oncology Program

Dr. Westover is a practicing member of the thoracic oncology service, but also leads a research laboratory focusing on structural biology, enzymology, early stage drug development, and chemical biology. In his role of Director of Clinical Innovation and Information Systems, he brings together teams of technology developers and care providers to develop technology solutions that enhance patient care.



Puneeth Iyengar, M.D., Ph.D.
Assistant Professor
Trained: UT MD Anderson Cancer Center

Dr. Iyengar's clinical emphasis is on the treatment of lung cancer. His laboratory research focuses on the complex crosstalk between inflammatory states, cachexia, and lung cancer progression and therapeutic resistance.

LYMPHOMA



Jennifer Shah, M.D.
Assistant Professor and Associate Director of Medical Residency Program
Trained: Stanford University

Dr. Shah focuses on the treatment of malignancies of the head and neck, as well as lymphoma.



Neil Desai, M.D.
Assistant Professor
Awarded the Dedman Family Scholar in Clinical Care
Trained: Memorial Sloan Kettering Cancer Center

Dr. Desai focuses on the treatment of genitourinary disease and lymphoma, and is an expert in the use of brachytherapy for prostate cancer.

PEDIATRIC



Larry Kun, M.D., FASTRO
Professor
Trained: Penrose Cancer Hospital

Dr. Kun is the former Chair of Radiation Oncology and Radiological Sciences, and the former Clinical Director of St. Jude Children's Research Hospital. He is a world-renowned pediatric radiation oncologist, with particular expertise in pediatric brain tumors.



Tu Dan, M.D.
Clinical Instructor
Trained: Sidney Kimmel Medical College at Thomas Jefferson University

Dr. Dan has a primary focus on adult and pediatric central nervous system diseases. He devotes a majority of his professional time to the laboratory study of radiation resistance and strategies to improve the efficacy of radiation.



Zabi Wardak, M.D.
Assistant Professor
Trained: UT Southwestern Medical Center

Dr. Wardak's clinical focus is on adult and pediatric central nervous system neoplasms and vascular malformations.

ADVANCED PRACTITIONERS



Daniella Hall, MPAS, PA-C
Physician Assistant
Trained: UT Southwestern Medical Center



Shohreh Bahrimi, APRN, FNP-BC
Nurse Practitioner
Trained: Texas Woman's University



Tamara Dickinson, APRN, AGPCNP-BC
Nurse Practitioner
Trained: University of South Alabama



Terri Kelley-Griffis, APRN, FNP-C
Nurse Practitioner
Trained: Texas Woman's University



Gina Chorley, MSN, APRN-BC
Nurse Practitioner
Trained: Northern Illinois University

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Photos by Claire Almanza & Dave Gresham



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