UT Southwestern

THE TARGET

News from the Department of Radiation Oncology

WINTER 2017

First Gamma Knife Icon arrives in Texas

New radiosurgery tool allows frameless treatment option for brain cancer and metastases.

For decades, Gamma Knife radiosurgery has been the gold standard for cancer patients with inoperable brain tumors or brain metastases. With highly precise delivery of gamma rays, the system can also eliminate arterio-venous malformations and certain other pain and movement disorders that originate in the brain.

Gamma Knife Icon.

What's Inside

Until now, Gamma Knife treatment has been a single-day procedure that required the attachment of a head frame to the patient's skull to prevent movement during treatment. But now a new frameless system installed at UT Southwestern will free patients from the head frame and allow multiple treatments over several days.

The new Gamma Knife Icon, which specialists this month began using to treat patients in the Annette Simmons Stereotactic Treatment Center at Zale Lipshy University Hospital, is designed to allow stereotactic radiosurgery without placement of a frame. It uses cone beam CT imaging to verify patient positioning prior to treatment and continuous monitoring to further ensure submillimeter accuracy throughout treatment delivery.

"Our new Gamma Knife Icon, the sixth and latest generation of the device, is specifically designed to deliver a highly effective dose of radiation to an intracranial tumor or vascular malformation with the lowest possible radiation exposure to the surrounding normal brain and cranial nerves," says Bruce Mickey, M.D., Professor of Neurological Surgery. "This emphasis on brain protection, one of the founding principles of the UT Southwestern Peter O'Donnell Jr. Brain Institute, drove the decision to upgrade to this technology."

The new Gamma Knife will enable patients to receive treatments over the course of several days, rather than in just one session.

Continuous imaging replaces the head frame.

"Radiation is more tolerable to normal tissues if given in multiple, smaller daily doses called 'fractions' as compared to single potent doses called radiosurgery," says Robert Timmerman, M.D., Professor of Radiation Oncology and Director of the stereotactic center. "Some targets in patients are close to or even intermingled with normal tissue, making radiosurgery difficult to tolerate. Fractionating the treatment can be useful in these circumstances."

Previous versions of the Gamma Knife could not feasibly deliver fractionated treatments because the rigid head frame could not be put on daily or left on for many days.

The updated Gamma Knife offers several other advantages, including an expanded treatment area that includes the face and upper neck, as well as the ability to deliver staged treatments in which only a portion of the total target is treated.

The new technology will be particularly advantageous for patients with brain metastases who, more and more at UT Southwestern, are being treated with radiosurgery instead of whole-brain radiation.

"More than almost any other center, we aggressively treat patients with brain metastases using radiosurgery in order to spare them the neurocognitive toxicity associated with whole-brain radiation," says Assistant Professor of Radiation Oncology Zabi Wardak, M.D., a member of the clinical team specializing in treating central nervous system disease. "With improvements in systemic therapy offered by medical oncologists, patients are living longer after developing metastatic disease and are more likely to suffer long-term neurocognitive toxicity from whole-brain radiation. Thus, it becomes even more imperative to offer them treatments that lower the potential of neurocognitive toxicity."

For patients with numerous separate tumors (more than six), it could be exhausting for the patient to have all the targets treated in a single day. The new Gamma Knife enables a more tolerable treatment schedule distributed over several days.

The head frame, physicians emphasize, is still useful in instances where ultimate precision is demanded, such as when a tumor is located close to critical structures in the brain or when it is desirable to deliver a full dose in a single fraction.

"Combining the Gamma Knife Icon with our new CyberKnife gives us a full suite of capability to treat central nervous system disease with precision unmatched anywhere in North Texas," Dr. Timmerman says.

Dr. Mickey holds the William Kemp Clark Chair of Neurological Surgery.

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

Disease-oriented teams in the Department of Radiation Oncology

Each physician in the Department of Radiation Oncology specializes in the treatment of a particular cancer type, enabling individual specialists to bring familiarity and expertise to each patient encounter. They also participate in larger disease-oriented teams within UT Southwestern's Simmons Comprehensive Cancer Center, in which physicians and scientists bring a multidisciplinary approach to bear on the scientific and clinical challenges unique to different cancers.

Our nine teams and their specialists are:

Breast

Nathan Kim, M.D., Ph.D.
Assistant Professor
Trained: Vanderbilt University Medical Center

Asal Rahimi, M.D.
Assistant Professor and Director of Clinical Research
Trained: University of Virginia

Ann Spangler, M.D., MACM
Associate Professor
Trained: Shands Hospital at the University of Florida

Central nervous system

Tu Dan, M.D.
Clinical Instructor
Trained: University of Florida

Lucien Nedzi, M.D.
Associate Professor
Trained: Harvard Medical School

Robert Timmerman, M.D.
Vice Chair, Professor and Medical Director, holder of the Effie Marie Cain Distinguished Chair in Cancer Therapy Research
Trained: The Johns Hopkins Hospital

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

Gastrointestinal

Jeffrey Meyer, M.D., M.S.
Associate Professor
Trained: Duke University Medical Center

Genitourinary

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

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

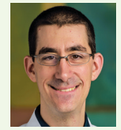
Aaron Laine, M.D., Ph.D.
Assistant Professor
Trained: UT Southwestern Medical Center

Gynecologic

Kevin Albuquerque, M.D.
Associate Professor
Trained: University Hospital of Brooklyn

Head and neck

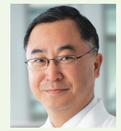
Nhat-Long Pham, M.D., Ph.D.
Assistant Professor
Trained: University of California, San Diego



David Sher, M.D., M.P.H.
Associate Professor
Trained: Harvard Medical Center

Tobin Strom, M.D.
Assistant Professor
Trained: University of South Florida College of Medicine

Lung



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

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

Kenneth Westover, M.D., Ph.D.
Assistant Professor
Trained: Harvard Radiation Oncology Program

Ocular and other brachytherapy

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

Pediatric

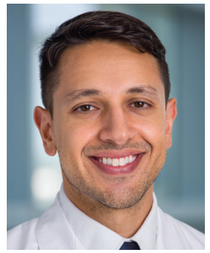
Larry Kun, M.D.
Professor
Trained: Penrose Cancer Hospital

New doctors to focus on patient care, research

Five physicians have recently joined the patient care team of the Department of Radiation Oncology.

Nhat-Long Pham, M.D., Ph.D.

Nhat-Long Pham, M.D., Ph.D., joins as Assistant Professor and member of the team treating head and neck cancer. Dr. Pham graduated with distinction from the University of Virginia, where he earned degrees in biochemistry and biology. He then entered the medical scientist training program at University of Iowa, where in addition to earning his medical degree he earned a Ph.D. in immunology. He completed his residency in radiation oncology at the University of California, San Diego.



Zabi Wardak, M.D.

Zabi Wardak, M.D., has been appointed Assistant Professor, joining the team focused on treating central nervous system (CNS) cancer. Dr. Wardak earned his medical degree at SUNY Upstate Medical University in New York and completed his residency training in radiation oncology here at UT Southwestern, where he received a Roentgen Resident/Fellow Annual Research Award for outstanding research. He has additional advanced training and certification in the use of Gamma Knife stereotactic radiosurgery and CyberKnife stereotactic radiotherapy.

Tobin Strom, M.D.

Assistant Professor Tobin Strom, M.D., earned his medical degree at the University of Colorado Health Sciences Center and completed his residency in radiation oncology at Moffitt Cancer Center in Tampa, Florida. A widely published and dedicated researcher, his practice will focus on treating head and neck cancer as well as skin malignancies.

Tu Dan, M.D.

Instructor Tu Dan, M.D., is a member of the team devoted to treating CNS disease. After graduating from the University of Florida College of Medicine, he completed a residency in radiation oncology at Thomas Jefferson University in Pennsylvania. In addition to seeing patients, Dr. Dan is also engaged in research in the laboratory of Howard Hughes Investigator Joshua Mendell, M.D., Ph.D.

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

Nathan Kim, M.D., Ph.D., has joined the faculty as Assistant Professor. An experienced and board-certified radiation oncologist, Dr. Kim will have a primary focus on treating breast cancer patients. He earned a master's degree in biomedical engineering at Johns Hopkins and then a combined M.D./Ph.D. at Boston University. He then completed a residency in radiation oncology at Vanderbilt University Medical Center.

Construction update

Opening 2017
Radiation Oncology Center

Work is proceeding rapidly on the new Radiation Oncology facility scheduled to open to patients in April 2017. Linear accelerators are installed, and the building exterior is finished. Visit our home page to see a live web cam of the construction site at **utsouthwestern.edu/radonc**.

Jiang garners $4m for heavy ion research

Steve Jiang, Ph.D.

Steve Jiang, Ph.D., Professor and Vice Chair of Radiation Oncology and Chief of the Division of Medical Physics and Engineering, has been awarded a $4 million grant by the Cancer Prevention and Research Institute of Texas (CPRIT).

His project is titled "Towards Carbon Beam Stereotactic Body Radiation Therapy (C-SBRT) for Higher Risk Early Stage Lung Cancer."

"One of the focuses of our future carbon ion therapy center is to transform lung cancer treatment by delivering carbon beam SBRT (C-SBRT) for higher-risk, early-stage lung cancer," Dr. Jiang says.

"However, prior to conducting clinical trials, we need to develop novel and carbon therapy-specific technologies to realize lung cancer C-SBRT."

The program will include three projects: 1) spectral CT for accurate patient modeling (co-PI is Assistant Professor Ming Yang, Ph.D.); 2) Monte Carlo-based treatment planning (co-PI is Associate Professor Xun Jia, Ph.D.); and 3) real-time volumetric imaging and dose reconstruction for treatment safety and adaptation (co-PI is Associate Professor Jing Wang, Ph.D.).

Says Dr. Jiang, "Upon completion, it is expected that key technologies will have been developed and we will be ready to treat patients in what is likely to be the first heavy ion facility in the U.S."

More grants

- Associate Professor **Sandeep Burma**, NIH grant $1.6m (five years) NIH (R01)/ $387,541 (two years), NIH (R21).
- Assistant Professor **Asaithamby Aroumougame, Ph.D.**, $1.6m (five years) from the NIH National Institute of Aging.
- Associate Professor **Xun Jia, Ph.D.**, $463,117 (two years) from the National Institute of Biomedical Imaging and Bioengineering (R21).
- Assistant Professor **Ken Westover, M.D., Ph.D.**, $561,420 (two years) from the Department of Defense/Lung Cancer Research Program (Idea Development Award).
- **Robert Timmerman, M.D.**, Professor and Vice Chair of Radiation Oncology, $500,000 from the Once Upon a Time Foundation.
- Assistant Professor **Raquibul Hannan, M.D., Ph.D.**, $250,000 from the Lupe Murchison Foundation.
- Assistant Professor **Neil Desai, M.D., Ph.D.**, $600,000 (four years), part of Dr. Desai's appointment as a Dedman Family Scholar in Clinical Care at UT Southwestern.

Folkert to lead residency program

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

Michael Folkert, M.D., Ph.D., has been charged with leading the department's Radiation Oncology Residency Program.

Dr. Folkert says he relishes the opportunity to be more closely engaged with the training of the medical residents.

"Our program has grown significantly over the last few years," Dr. Folkert says. "I look forward to continuing our momentum in attracting top candidates and ensuring they receive a well-rounded and diverse educational experience."

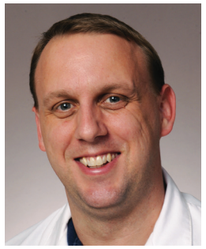
Formerly at 12 residents, the program will expand to 13 trainee positions in 2017.

New faculty appointments

- **Sarah McGuire, Ph.D., DABR**, joins the Physics Division as Associate Professor. She received her Ph.D. and completed postdoctoral training at Duke University. Dr. McGuire's research has focused on incorporating functional imaging in radiation treatment planning design and response assessment.
- **Andrei Pugachev, Ph.D.**, is a new Assistant Professor in our Physics Division. He earned his Ph.D. at Stanford University and performed his postdoctoral training at Memorial Sloan Kettering Cancer Center. Dr. Pugachev has extensive experience in molecular imaging for radiation therapy and preclinical validation of novel PET tracers.
- Molecular Radiation Biology Instructor **Heeyoun Bunch, Ph.D.**, joins us from Harvard Medical School and will conduct her research in the lab of Associate Professor Benjamin Chen, Ph.D.
- Scientific editor **Damiana Chiavolini, Ph.D.**, and former postdoctoral researchers **Nan Qin, Ph.D.**, and **Troy Long, Ph.D.**, have been elevated to the Radiation Oncology faculty with the title of Instructor.

Pictured left to right, first row: Bunch, Chiavolini, second row: Long, McGuire; third row: Pugachev, Qin

New laboratory opens under Davis



Anthony Davis, Ph.D.

Assistant Professor Anthony Davis, Ph.D., has been made an independent investigator in the department's Division of Molecular Radiation Biology and will oversee a laboratory dedicated to examining the response and repair of DNA damage, in particular DNA double-strand breaks, the most toxic kind of DNA lesion.

His appointment brings the total number of independent labs in the division to 10.

The Davis lab will look at several specific mechanisms involved in DNA repair, including:

- DNA-PKcs: The Division has already generated a significant body of work on the critical role this enzyme plays in non-homologous end-joining (one of two ways that cells repair DNA double-strand breaks). Dr. Davis will continue to work closely with Dr. Ben Chen in investigating the role of DNA-PKcs.
- BRCA-1: Dr. Davis has published findings on how this tumor suppressor – which is mutated in inherited breast, ovarian, and pancreatic cancers – regulates non-homologous end-joining. His lab will continue to elucidate how this protein promotes precise repair of DNA double-strand breaks and how mutations in *BRCA1* drive development of cancer due to defective DNA repair.

Dr. Davis earned his Ph.D. in cell regulation while in the Pharmacology Department here at UT Southwestern, and after a year's postdoctoral work he switched to the lab of Dr. David Chen in Radiation Oncology, where he rose from a postdoctoral fellow to Assistant Professor.

"I think the future for this department is very bright," he says. "It's the best place in the country for radiation-based research; some of the best scientific minds are here."

Industry partnerships

The department has renewed its three-year research partnership with Novocure, a company that has made headlines with its unusual approach to treating glioblastoma.

Novocure markets a wearable transducer array in the form of a cap that generates a low intensity alternating electric field (so-called "tumor treating fields") that disrupts tumor cell division. The FDA has approved this technology, marketed as Optune™, for the treatment of recurrent and newly diagnosed glioblastoma. It has met with some early success in extending the lives of glioblastoma patients.

Division of Molecular Radiation Biology researchers are working to better define the fundamental tumor cell killing mechanisms of tumor treating fields and will also investigate the technology's application to sites outside the cranium.

Researchers have also recently been funded by Dallas-based Peloton Therapeutics to further study its first-in-class inhibitor of hypoxia inducible factor-2α (HIF-2).

HIF-2 helps cells survive in the same hypoxic conditions that also cause tumors to be radioresistant. Previous research in the lab of Associate Professor Benjamin Chen, Ph.D., examined the radiosensitization effect of this HIF-2 inhibitor in clear cell kidney cancer. The new project will examine the radiosensitization effect in head and neck cancer which, like renal cell cancer, often becomes hypoxic and radioresistant.

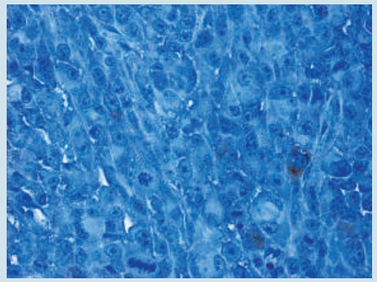
Publications

Takeshima T, Pop LM, **Laine A, Iyengar P**, Vitetta ES, Hannan R. Key role for neutrophils in radiation-induced antitumor immune responses: Potentiation with G-CSF. *Proc Natl Acad Sci U S A*. 2016 Oct 4;113(40):11300-11305.

Nakada Y, Canseco DC, Thet S, **Abdisalaam S, Asaithamby A**, et al. Hypoxia induces heart regeneration in adult mice. *Nature*. 2016 Oct 31. (Epub)

White DA, **Zhang Z**, Li L, Gerberich J, **Stojadinovic S**, Peschke P, **Mason RP**. Developing oxygen-enhanced magnetic resonance imaging as a prognostic biomarker of radiation response. *Cancer Lett*. 2016 Sept 28;380(1):69-77.

Story M, Pompos A, Timmerman R. On the value of carbon-ion therapy. *Phys Today*. 2016 Nov;69(11):14.



Radiation therapy-recruited neutrophils damage tumor tissues and induce apoptosis (as seen in PNAS*).*

Clinical Trials

BRAIN

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

NRG BN001 Randomized phase II trial of hypofractionated 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

BREAST

New– 032011-073 A randomized phase III trial of the value of early local therapy for the intact primary tumor in patients with metastatic breast cancer

052015-047 Intra-patient comparison of active breathing coordinator-based vs. Vision RT-based deep inspiration breath-hold for left chest wall irradiation, a pilot study for breast cancer

062015-085 Phase I dose-escalation trial of single fraction adjuvant stereotactic body partial-breast irradiation (SB-PBI) for early-stage breast cancer

112014-004 The IDEA study (Individualized Decisions for Endocrine therapy Alone): 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

GASTROINTESTINAL

New– 102015-019 Pancreatic cancer radiotherapy study group (PanCRS) trial: A randomized phase III study evaluating modified FOLFIRINOX (mFFX) with or without stereotactic body radiation therapy (SBRT) in the treatment of locally advanced pancreatic cancer

New– 072015-013 Evaluation of targeted radiofrequency ablation and vertebral augmentation prior to or following radiation therapy to treat painful metastatic vertebral body tumor(s) [the STARRT study]

GENITOURINARY

NRG-GU001 Randomized phase II trial of postoperative adjuvant IMRT following cystectomy for T3/pT4 urothelial bladder cancer

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

022015-058 Safety lead-in phase II trial of neo-adjuvant 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 A phase II trial of sipuleucel-T and stereotactic ablative body radiation (SABR) for patients with metastatic castrate-resistant prostate cancer (mCRPC)

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

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

New– RTOG 1008 A randomized phase II/III study of adjuvant concurrent radiation and chemotherapy versus radiation alone in resected high-risk malignant salivary gland tumors

062013-052 A phase I CyberKnife accelerated hemilarynx stereotactic radiotherapy study for early-stage glottis larynx cancer

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

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 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

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

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

072015-013 Evaluation of targeted radiofrequency ablation and vertebral augmentation prior to or following radiation therapy to treat painful metastatic vertebral body tumor(s) (The STARTT Study)

072010-134 A phase II study of stereotactic body radiation therapy and vertebroplasty for localized spine metastasis

RTOG 0631 A phase II/III study of image-guided radiosurgery/SBRT for localized spine metastasis

For more information, please contact Clinical Research Manager Jean Wu at 214-633-1753 or jean.wu@utsouthwestern.edu

Continuing Medical Education

The Department of Radiation Oncology offers free Continuing Medical Education credit to readers who read the designated CME article and successfully complete a follow-up test online. You can complete the steps necessary to receive your *AMA PRA Category 1 Credit(s)™* by visiting **cme.utsouthwestern.edu/content/em1509a**.

Exploiting the immunomodulatory properties of radiation therapy

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

- Explain the immunomodulatory changes brought on by radiation therapy to a tumor microenvironment
- Differentiate between the immune-stimulatory and immune-suppressive properties of tumor irradiation
- Define the abscopal effect of radiation therapy and in what settings it is observed most commonly
- Describe the available clinical evidence in support of combining immunotherapy and radiation therapy.

Introduction

Radiation therapy (RT) is a classic treatment modality that achieves local control of various solid tumors by targeting a defined field of interest or disease. Hence, it is generally ineffective in controlling widespread disease and has previously had little purpose in this setting beyond palliation. Immunotherapy is an effective systemic treatment for metastatic cancer even though a large proportion of patients do not respond because of the immune-evasive and suppressive properties of cancer.[1] However, accumulating evidence suggests that these two treatment modalities in combination may complement each other's therapeutic impact and offer greater clinical efficacy. The combination of immunotherapy (IMT) and RT takes advantage of the demonstrated immunogenic properties of RT.[2,3] Because RT is targeted directly to the tumor, it does not inherently immunocompromise the host. By not surgically removing the tumor, the body retains an antigen depot of dying tumor cells to act as an in situ tumor vaccine. However, the rational combination of IMT and RT in the clinic is still in its early stages, and its use depends on further understanding of the underlying mechanisms and early immunogenic effects that RT has on the tumor microenvironment.

Radiation-induced immunomodulatory changes in the tumor microenvironment

The activation of immune cells during cancer therapy irradiation is increasingly being recognized.[4] Leukocytes themselves are highly radiation-sensitive and likely die from apoptosis in the irradiated field. Instead, the immune-activating effects of radiation appear to result from tumor antigens released following tumor cell death, which are then relayed to antigen-presenting cells (APCs) and propagated

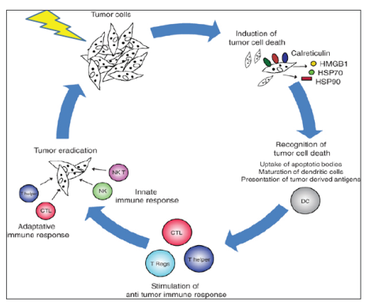


Figure 1: Proposed mechanism of radiation-induced abscopal effect.

to activate the immune system. RT also appears to induce changes in the tumor microenvironment that lead to the recruitment of radiation-naive immune cells from areas outside the radiation field, resulting in an increase in immune cell infiltration and the targeting and killing of tumor cells.[5]

In a recent study at UT Southwestern, we identified neutrophils as one of the key players in mediating early inflammatory changes caused by radiation therapy in the tumor microenvironment.[6] In this study we showed that after radiation there is a rapid infiltration of neutrophils as the first inflammatory mediator. We further showed that this is a key step because when it is prevented, anti-tumor efficacy and the radiation-caused immune response significantly decrease. We also explored the possibility of increasing neutrophil infiltration using G-CSF (granulocyte-colony stimulating factor) – a well-known drug currently in clinical use to increase neutrophil production – which successfully increased the anti-tumor immune response and thereby the therapeutic efficacy of radiation therapy.

Because RT causes local inflammation with the infiltration of neutrophils, dendritic cells (DCs) are also attracted into the tumor.[6,7] In vivo studies have shown that radiation induces the release of damage (or danger)-associated molecular patterns (DAMPs) such as HMGB1, HSP, and calreticulin into the extracellular matrix, thereby promoting the recruitment and activation of APCs such as DCs.[8-11] The DCs transport tumor antigens to regional lymph nodes where an adaptive anti-tumor immune response is initiated. The products of this response (T cells and antibodies) travel back to the primary and metastatic tumor sites to eliminate tumor cells (Figure 1).[12-13] Furthermore, RT causes dose-dependent increases in MHC class I tumor neo-antigen presentation by tumor cells,[14] which exposes the tumor's ploy to evade the immune system.[15] This, in conjunction with a demonstrated increase in FAS death receptors on the tumor cell surface in response to radiation, renders tumor cells particularly susceptible to the cytotoxic activity of CD8+ T cells.[16,17]

The abscopal effect as evidence of radiation-induced anti-tumor immune response

Tumor regression outside of the irradiation field following localized treatment is called the abscopal effect, first described by Robin H. Mole in the 1950s.[18] Until recently, the abscopal effect was poorly understood and regarded as an uncommon phenomenon. But a 2004 preclinical study (Demaria et al.) demonstrated that the abscopal effect was mediated by immune cells when RT inhibited distant, untreated disease in control mice while this effect was absent in immune-deficient nude mice.[19] Likewise, the abscopal effect was eliminated when RT in combination with Flt3-ligand was administered to immunocompromised mice as compared to immunocompetent mice, suggesting that the abscopal effect is immune-mediated. 19 In the clinic, the abscopal effect has been documented by multiple case reports in which RT to one tumor site resulted in a systemic complete response of tumor regression at metastatic sites.[20-23]

Immune-suppressive properties of radiation therapy

With all these immune-stimulating properties of radiation therapy, one has to wonder why the abscopal effect is not seen more frequently. In fact, the abscopal effect is so rare that it is difficult to see it outside of case reports. This is due to the simultaneous immunosuppressive properties of radiation therapy. While RT increases CD8+ T cells and DCs in the tumor microenvironment, fractionated RT can subsequently eradicate these cells, leading to tolerance. This is likely the reason the abscopal effect is seen more frequently in the hypofractionated or stereotactic radiation (SAbR) dose-fractionation settings. Tumor irradiation upregulates active transforming growth factor beta (TGF-β), which in turn can increase regulatory T cells (T-regs) and inhibit effector T cells.[24-25] Because T-regs are relatively more radioresistant, their proportional increase has been documented after tumor RT.[26-28] Increases in bone marrow-derived myeloid cells (MDSC) and immunosuppressive polarization of macrophages contribute to tumor proliferation and recurrence after irradiation.[29-32] Radiation therapy has also been shown to increase the expression of programmed death ligand 1 (PD-L1) protein on the tumors and monocytes/lymphocytes, which leads to deactivation of cytotoxic T lymphocytes (CTLs) – the so-called "exhausted" CTLs. [33-35] Together, these help the tumor escape an immune response.

Radiation and immunotherapy synergy

While it is clear that the immune system plays an active role in the irradiated tumor microenvironment, the activation of a systemic immune response by RT alone usually cannot overcome the threshold of immune-suppression in the tumor microenvironment except in a limited number of instances.[36-40] Therefore, a strategy that counters the immunosuppressive properties of radiation therapy and simultaneously augments its inflammatory properties will see the abscopal effect routinely and reproducibly in the clinic.

In recent years, preclinical studies that combine RT with immunotherapy[37-41] have been able to reliably reproduce distant tumor regression outside of the irradiation field using syngeneic mouse models of cancer, thereby validating the combination of RT with immunomodulatory as a promising strategy. In our own syngeneic prostate tumor model, we demonstrated that RT and a Listeria-PSA vaccine synergize to reduce tumor volume and to generate tumor-specific CD8+ T cells.[42]

Clinical evidence for the combined use of RT and IMT is also emerging. In a retrospective analysis of 62 patients with stage II-IV breast cancer treated with preoperative (pre-mastectomy) RT, Konoeda et al. reported an abscopal effect in metastatic lymph nodes in 15 out of 42 cases (35.7 percent) by palpation.[20] Biopsy of the lymph nodes revealed a histopathological abscopal effect in 22 out of the 42 cases (52.4 percent). Notably, the patients who experienced the abscopal effect had CD8 and CD4-positive infiltrating lymphocytes around the degenerated cancer cells in the irradiated primary tumor nests. These results show that localized irradiation results in the generation of antitumor immune effector cells and their trafficking to the tumor site.

Wersall et al. reported that non-irradiated lesions in four of 28 patients (14 percent) with primary renal cell carcinoma (RCC) regressed following stereotactic treatment with 96 Gy (12 x 8 Gy).[23] Of the four patients with abscopal response, three patients received nephrectomy and none were noted as having undergone chemotherapy. Notably, one patient after nephrectomy received systemic interleukin-2, whose function is to enhance CTLs. Another recent prospective study reported an abscopal effect in patients with various metastatic solid tumors (44 percent non-small cell lung cancer and 34 percent breast cancer) following chemo-radiation therapy combined with immunotherapy using a cytokine granulocyte-macrophage colony-stimulating factor (GM-CSF) to stimulate dendritic cell maturation.[45] Patients enrolled in this study were treated with a total dose of 35 Gy in 10 fractions, and an abscopal response occurred in 11 of 41 accrued patients (27 percent). Similarly, a recent retrospective analysis of 21 melanoma patients who received palliative RT after they progressed from receiving the anti-CTLA4 antibody ipilimumab found 52 percent of patients experienced an abscopal response.[46] Importantly,

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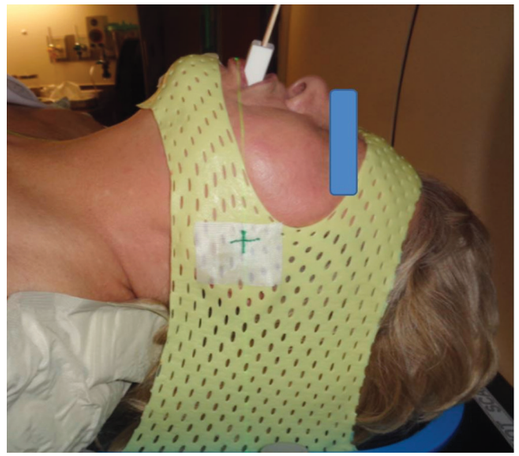
Open mask head and neck treatment using VisionRT



A patient receives treatment wearing an open mask.

A recent pilot study in the Department tested whether newer technology could make treatments more comfortable for patients who normally wear fully enclosed, rigid masks while receiving radiation therapy to the head and neck.

"Not only do the enclosed masks make some patients uncomfortable, but the masks also create a bolus effect that results in an increased radiation dose to the skin, which is an undesired effect," says Bo Zhao, Ph.D., a physicist and Assistant Professor in the Division of Medical Physics and Engineering.

Dr. Zhao developed a theory that if the masks were opened up, surface guidance technology already used in the clinic to detect body motion could potentially be used to track facial features. That technology, VisionRT, utilizes video cameras to constantly track motions within a grid of light beamed on the patient.

Dr. Zhao's team took standard thermoplastic masks and cut out large portions in the center and on the ends so that mainly a forehead and chin portion remained, removing about 60 percent of the standard mask surface area. Vacuum bags were used to secure the shoulders, allowing the neck area to remain open as well.

Twenty patients were enrolled in a clinical trial testing the new technique. Dr. Zhao reports that all were successfully treated with an average group mean setup error of <1mm compared to the initial cone-beam CT, a difference similar to standard full mask treatment. Patients reported feeling generally comfortable in the masks.

"Surface monitoring may even offer an advantage over the closed mask because patients do move inside the mask as well," Dr. Zhao notes. "This way you can track how much movement occurs, which can provide another indication of treatment accuracy."

Head and neck cancer is one of the most challenging areas to treat with radiation therapy because of the location of many critical structures in close proximity.

"Our aim was to show the feasibility and reproducibility of this technique," Dr. Zhao says. "To implement it requires significant physician involvement and additional planning. We hope to continue studying the potential benefits of this approach."

"Our aim was to show the feasibility and reproducibility of this technique. To implement it requires significant physician involvement and additional planning. We hope to continue studying the potential benefits of this approach."

— Bo Zhao, Ph.D.

Survivor Story: Putting stage 4 kidney cancer in remission

Clinical trials help patient through innovative use of radiation

Elizabeth Martinez, 42, of Irving, Texas, had been a five-year survivor of breast cancer when she was diagnosed in the summer of 2015 with stage III kidney cancer. She knew she was in urgent need of help.

"Everything goes through your mind," Ms. Martinez says. "You're trying to figure out what you need to do that you haven't done. That's when I met Dr. Hannan."

Raquibul Hannan, M.D., Ph.D., is an Assistant Professor of Radiation Oncology at UT Southwestern and co-leader of the Kidney Cancer Program at UT Southwestern Medical Center. He is also the principal investigator of several clinical trials using stereotactic ablatic radiation therapy (SAbR) to try to get improved results for patients with kidney cancer.

The immediate concern with Ms. Martinez's kidney cancer was that it had developed a venous extension into her inferior vena cava (IVC). Although surgery is the only treatment proven effective for IVC tumor thrombus, it is a challenge to eradicate cancer with this presentation, and survival rates are poor. Dr. Hannan proposed to administer SAbR prior to surgery to help increase the chance of surgical success as part of a clinical trial. While conventional radiation is typically ineffective against radioresistant renal cell cancer, the higher doses given in each treatment with SAbR have been shown to be successful in overcoming kidney cancer.

Ms. Martinez agreed and underwent five rounds of highly focused radiation to her IVC tumor thrombus followed by a radical nephrectomy.

Unfortunately, when she came back for postoperative follow-up six weeks later, the cancer had spread widely to the extent it was reclassified as stage IV.

"They told me it was everywhere, in my lungs and my stomach," Ms. Martinez recalls. "That's when I felt … I was going to give in."

Dr. Hannan proposed another clinical trial involving SAbR, from a series called i-SAbR (immunotherapy plus SABR).

Cancer survivor Elizabeth Martinez.

"Radiation is known for a property called the abscopal effect, in which radiation to one location alarms the body's immune system and the body starts developing an immune response to cancer outside the original field of treatment," Dr. Hannan says. "We see this primarily in the context of SAbR, when a very high dose of radiation is given in just a few treatments. But this kind of response is very unpredictable, which is why we strategically combine SAbR treatment with immunotherapy agents to try to trigger the abscopal response and improve the patient's curative chance."

Ms. Martinez enrolled in an i-SAbR trial in which interleukin-2 is administered soon after radiation treatment.

"Typically, about 20 percent of advanced-stage kidney cancer patients treated with interleukin-2 alone will see a response to treatment in which cancer stops growing or regresses," Dr. Hannan says. "In this clinical trial with combined therapy, so far we have had a 53 percent response rate."

Ms. Martinez received a radiation dose of 25Gy in a single treatment to one of her lung lesions and three treatments of 12Gy each to another lung lesion, followed by the interleukin-2. For her, it was a winning strategy.

Dr. Hannan reports after one year: "She's in complete remission, meaning that we cannot find any evidence of cancer anywhere in her body. To share that result with her was truly rewarding. I believe that someday stereotactic radiation will be integrated in the clinic with immunotherapy to become an integral part of the cancer treatment strategy."

Says Ms. Martinez, "I'm very thankful that they gave me the opportunity and it worked. I feel that I have another opportunity to live and enjoy life and enjoy my family."

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W.A. Monty and Tex Moncrief Radiation Oncology Building

5801 Forest Park Rd.
Dallas, TX 75390-9183

Annette Simmons Stereotactic Treatment Center at UT Southwestern Zale Lipshy University Hospital

5151 Harry Hines Blvd.
Dallas, TX 75390-9183

Harold C. Simmons Comprehensive Cancer Center–Radiation Oncology

2001 Inwood Rd.
Dallas, TX 75390-9183

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