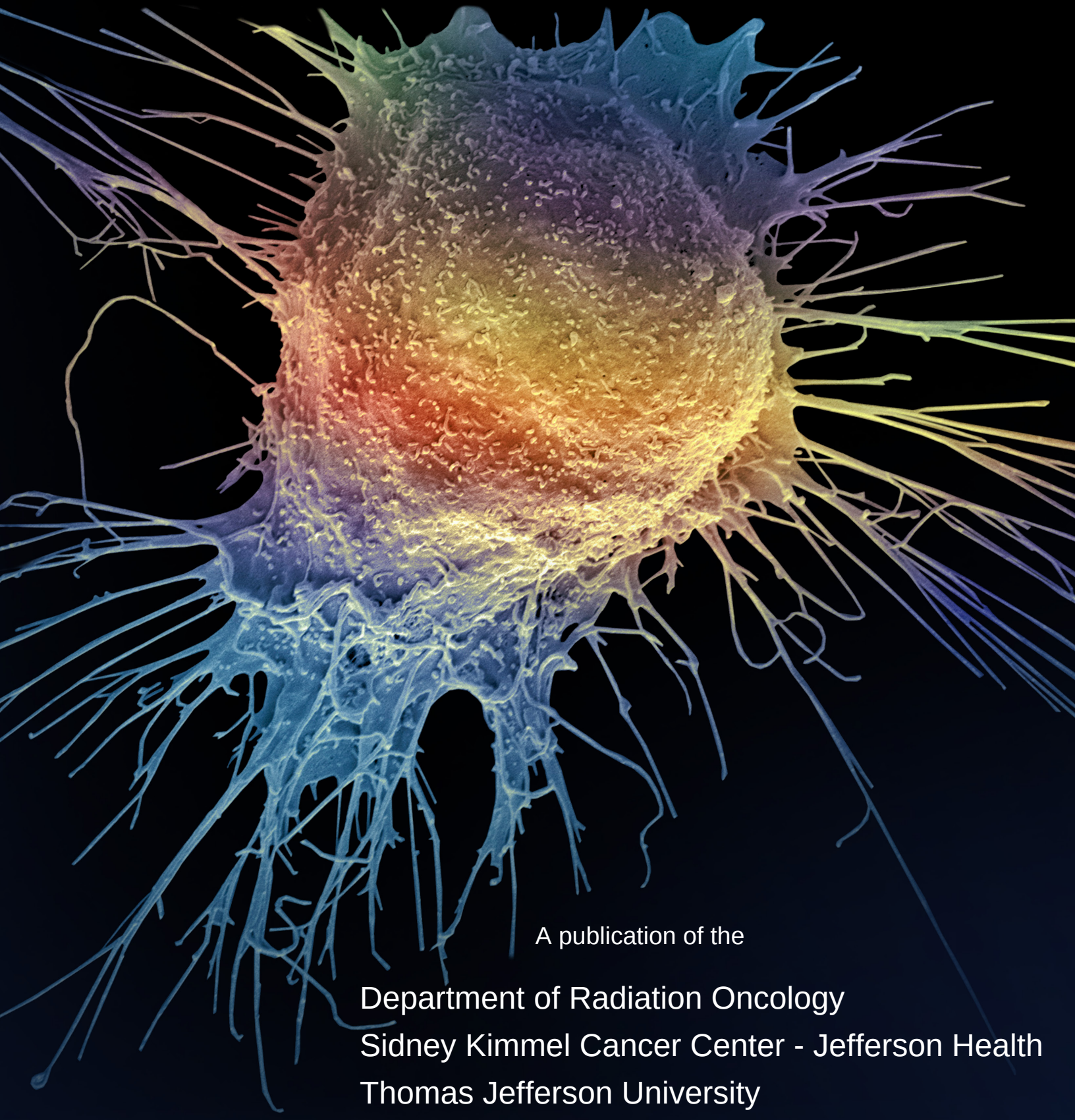
Jefferson Radiation Oncology Review

Volume 1, Number 1, Spring, 2018



A publication of the

Department of Radiation Oncology
Sidney Kimmel Cancer Center - Jefferson Health
Thomas Jefferson University

Jefferson Radiation Oncology Review
Volume 1, Number 1, Spring, 2018

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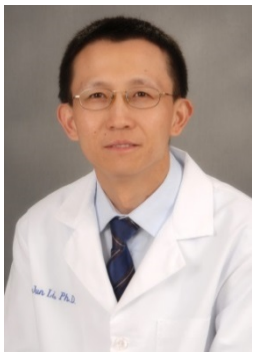
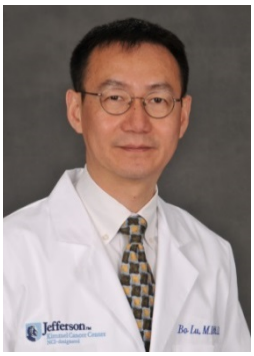

Jun Li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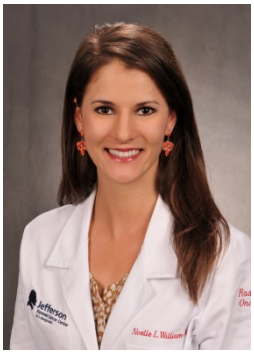
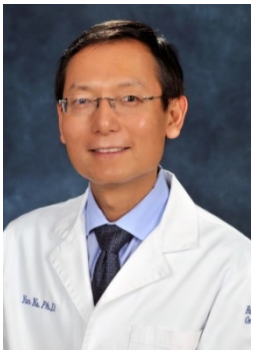

Noelle Williams


Yan Yu

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ISSN: 2576-5566

- Comparison of Online 6 Degree-of-freedom image registration of Varian TrueBeam cone-beam CT

  Technology in Cancer Research and Treatment. 2017 Jun;16(3):339-343.
  PMID: 28462690
  Li J, Shi W, Andrews D, Werner-Wasik M, Lu B, Yu Y, Dicker AP, Liu H
  Permission to Reprint from Sage Journals and Open Access Pages: 12/27/2017

- mHealth: Mobile technologies to virtually bring the patient into an oncology practice.

  American Society of Clinical Oncology Education Book.
  2017;37:144-154. PMID: 28561720
  Pennel NA, Dicker AP, Tran C, Jim, HSL, Schwartz DL, Stepanski EJ
  Permission to Reprint Granted, Order ID: 18-002

- Decreased survival after combining thoracic irradiation and an Anti-PD-1 antibody correlated with increased T-cell Infiltration into cardiac and lung tissues.

  International Journal of Radiation Oncology*Biology*Physics.
  2017 Dec 1;99(5):1129-36. PMID: 29165283
  Myers CJ, Lu B
  License Number to Reprint: 4254360369300 (Elsevier)

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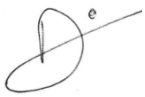
Dear Colleague:

I am pleased to send you a copy of the "Jefferson Radiation Oncology Review", one of our department's newest publications which will be distributed on a quarterly basis, highlighting our recent accomplishments.

I hope you enjoy our new journal and welcome your feedback.

Sincerely,



Adam P. Dicker, M.D., Ph.D., FASTRO
Senior Vice President and Chair, Enterprise Radiation Oncology
Professor of Radiation Oncology, Pharmacology and Experimental Therapeutics

Digital Health and Personal Connected Health Minisymposium

Thursday, July 12, 2018

1-3 PM Eastern Time

NRG Oncology Semiannual Meeting

Philadelphia Marriott Downtown - Philadelphia, PA

Aimed to help provide a conceptual framework for better mechanistic understanding of the pathways by which digital tools can impact cancer care.

Questions regarding the minisymposium can be directed to Dr. Dicker at adam.dicker@jefferson.edu

SPEAKERS

Paul G. Kluetz, MD
Food and Drug Administration CDER
"FDA Oncology Center of Excellence: Core Patient Outcomes and Digital Health"

Heather S. Jim, PhD
Moffitt Cancer Center
"Emerging Trends in Cancer Research Using Patient-Generated Data"

Amir Kishon, PhD
RMDY Health Inc.
"Platforms for Patient Engagement and Research"

S. Percy Ivy, MD
National Cancer Institute CTEP
"Technology APPlications for Digital Safety and Compliance in Drug Development"

Alexi Wright, MD MPH
Harvard Medical School
Dana-Farber Cancer Institute
"Harnessing Patient-Reported Outcomes and Digital Phenotyping to Improve Cancer Care"

Bradford W. Hesse, PhD
National Cancer Institute HCIRB, BRP
"Improving Cancer Outcomes Through Connected Health"

PROGRAM CO-CHAIRS

Adam P. Dicker, MD, PhD, FASTRO
Thomas Jefferson University

Matthew F. Hudson, PhD, MPH
Greenville Health System

Debra Ritzwoller, PhD
Kaiser Permanente

Register for the NRG Oncology Semiannual Meeting to attend.

nrgoncology.org/About-Us/Meetings/July-2018-Semiannual-Meeting-Resources

www.nrgoncology.org

DEPARTMENT OF RADIATION ONCOLOGY

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Mark D. Hurwitz, M.D.
Bo Lu, M.D., Ph.D.
Wenyin Shi, M.D., Ph.D.
Nicole Simone, M.D.
Maria Werner-Wasik, M.D., FASTRO

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Wayne Pinover, M.D.

Delaware Valley Urology Cancer Treatment Center
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John Smyles, M.D.

Jefferson Radiation Oncology at Riddle Hospital
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Shefali Gajjar, M.D.

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Tamara LaCouture, M.D.

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Shari B. Rudoler, M.D.

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Jefferson Torresdale Hospital
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Maryanne Kahmar, RT, CMD

RESIDENCY TRAINING PROGRAMS

Radiation Oncology Residency
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Program Director

Medical Physics Residency
Amy Harrison, Ph.D.
Program Director

Marlene Folino, Residency Program Coordinator

2017-18
Christian Fernandez, M.D.
Shivank Garg, M.D.
Benjamin Greenberger, M.D.
Gregor Manukian, M.D.
Joseph Marascio, M.D.
Gaurav Shukla, M.D., Ph.D.
Brittany Simone, D.O.
Andrew Song, M.D.
Noelle Williams, M.D.

2017-18
Peter Florio, MS
Emily Hubley, MS
Kara Lambson, MS
Graham Owen, MS
Andrew Soldner, MS
Michael Trager, MS

2018-2019
Victor Chen, M.D.
James Taylor, M.D.

2018-2019
Kai Kiang, Ph.D.
Angelia Landers, MS
Alisha Shutler, MS

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Ryan Pollock, AA
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Nicholas DeGregorio, BS
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James Turner
Joseph White

In Memoriam, Carl Mansfield, M.D.

Carl Mansfield, M.D. was the second chairman of the Department of Radiation Oncology at Thomas Jefferson University and an Emeritus Professor at the Sidney Kimmel Medical College (formerly Jefferson Medical College). Dr. Mansfield died at the age of 89 on January 11, 2018, in Philadelphia, PA.

Dr. Mansfield was born and raised in Philadelphia, graduating from West Philadelphia High School in 1946. He procured a senatorial tuition scholarship and attended Lincoln University in Oxford, PA., majoring in chemistry and minoring in mathematics. He then worked for a year for the quartermasters of the military and was admitted to Howard University, earning his medical degree in 1956.

At Episcopal Hospital in Philadelphia, he completed an internship and began a residency in radiology. He was drafted and assigned to Strategic Air Command Headquarters in Omaha, Nebraska, where, as a Captain, he served as the leader of the Department of Radiology at the air force base hospital. Since this facility was regarded as a primary target of the Russians in the cold war, it was located six stories underground. Dr. Mansfield returned to the Episcopal Hospital in 1960 and trained there for a full year in therapeutic radiology under the tutelage of Dr. Simon Kramer, who helped secure a one year NIH fellowship for him at Middlesex Hospital in Great Britain. Upon his return, he was appointed Chief of the Nuclear Medicine Division at Jefferson. He was a diplomate of the American Board of Radiology and the American Board of Nuclear Medicine.

Dr. Mansfield became an expert in breast cancer, developing an innovative technique of radioactive seed implantation. In 1974 he became the first African American appointed to the rank of full professor. In 1975 he became a fellow of the American College of Radiology (ACR) and was recruited to the University of Kansas as Professor and Chairman of Radiation Oncology from 1976 to 1983, where he further pioneered the use of iridium-192 perioperative implants for early stage breast cancer.

In 1984, Dr Mansfield agreed to return to Jefferson as Chairman with one major stipulation: a bigger and better center for cancer treatment that to this day has been the cornerstone of Jefferson's Department of Radiation Oncology. With the help of Dr. Kramer and his staff, with the support of Dr. Bluemle, the University President, and the generosity of the estate of Mr. William Bodine, President of Jefferson Medical College from 1959 to 1966 and Chairman of the Board from 1970-1977, The Bodine Centre for Cancer Treatment was dedicated on March 25, 1987. Dr. Mansfield served as chairman of the Department of Radiation Oncology at then Jefferson Medical College from 1987 to 1994. The Bodine Centre for Cancer Treatment is a three floor, 57,000 square feet building which expanded facilities for clinical oncology, radiobiology, and radiation physics research. Dr. Mansfield helped develop one of the biggest breast cancer practices in Philadelphia, working with a strong multidisciplinary team. He strived to raise awareness of African American accomplishments in oncology and to educate the

community in the prevalence and incidence of cancers in the African American population. In recognition of these efforts, he was awarded the Bronze Medal, the highest national tribute awarded by the American Cancer Society for public service. He extended his cause to level the playing field for all races, creeds and religions and also for underserved residents in the community. He obtained a grant for "Special Populations Networks for Cancer Awareness Research and Training" in order to continue his efforts into the 21st century.

Dr. Mansfield helped train over forty residents during his stay at Jefferson, and during his lifetime, published more than 100 articles and monographs and obtained two NIH grants for his research. In 1994, he became Associate Director of the Division of Cancer Treatment for the NCI, and was recruited as Chairman of the Department of Radiation Oncology at the University of Maryland from 1997-2002.

Dr. Mansfield served as the President of the American Radium Society in 1989, becoming the first African American to head a national radiologic society. In 1990, he received an Honorary Doctor of Science degree from his undergraduate alma mater, Lincoln University. In 2015, he became the first African American to be awarded the American Society for Radiation Oncology (ASTRO) Gold Medal. The Gold Medal is ASTRO's highest honor bestowed on revered members who have made outstanding contributions to the field of radiation oncology.

Prepared by Eric Gressen, M.D., and Maria Werner-Wasik, M.D., FASTRO

Photo: ASTRO/Adam Donohue

Thomas Jefferson University
Department of Radiation Oncology

CARL MANSFIELD, MD

Professor and Chair
1983-1994

- He raised social awareness for managing and treating the underserved community

- 1987: Bodine Center for Cancer Treatment opens under Dr. Mansfield's direction.

- Developed one of the largest breast cancer practices in Philadelphia

RESEARCH 2017-2018
Department of Radiation Oncology

Basic Research Studies/Grants

Optimizing first line treatment for men with castrate resistant prostate cancer.
Prostate Cancer Foundation. Principal Investigator: Wm. Kevin Kelly, D.O.,
Co-Investigator: Robert B. Den, M.D.

CARAVAN: Checkpoint-radiation-vaccine neoadjuvant trial for metastatic prostate cancer. Prostate Cancer Foundation.
Principal Investigator: Adam P. Dicker, MD, PhD, FASTRO

NRG Oncology Network Group Operations Center.
Principal Investigator: Maria Werner-Wasik, MD, FASTRO

Compare various metrics between two radiosurgery techniques for a large number of brain metastasis. Varian Medical Systems, Inc.
Principal Investigator: Wenyin Shi, MD, PhD

Chinese radiation oncologist observation program in the Radiation Oncology Program of Kimmel Cancer Center, Thomas Jefferson University, Philadelphia, PA.
Elekta Instruments, Inc.

Preclinical assessment of efficacy and safety of combining PD-1 inhibitor and radiotherapy. Merck Sharp & Dohme.
Principal Investigator: Bo Lu, MD, PhD

Overcome crizotinib resistance through Jak inhibition. Pfizer, Inc.
Principal Investigator: Bo Lu, MD, PhD

Role of Smac in lung carcinogenesis and therapy. Department of Defense.
Principal Investigator: Bo Lu, MD, PhD

Technical and procedural improvements for optimizing clinical use of Pyrexar HT equipment. Pyrexar Medical, Inc.
Co-Principal Investigators: Dario Rodrigues, PhD, and Paul Stauffer. MSEE, CCE

Clinical Research Studies/Grants

NRG-GU0002: (CIRB) Phase II-III trial of adjuvant radiotherapy and androgen deprivation following radical prostatectomy with or without adjuvant docetaxel.

NRG-GU0003: (CIRB) A randomized Phase III trial of hypofractionated post-prostatectomy radiation therapy (Hyport) versus conventional post-prostatectomy radiation therapy (CoPort).

NASBP B-51; RTOG-1304: A randomized Phase III clinical trial evaluating post-mastectomy chestwall and regional nodal XRT and post-lumpectomy regional nodal XRT in patients with positive axillary nodes before adjuvant chemotherapy who convert to pathologically negative axillary nodes after neoadjuvant chemotherapy.

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.

Phase I study of hyperthermia combined with high dose rate.

CAREFOR Study: Precision nutrition caloric restriction for oncology research: Precision medicine driving precision nutrition during neoadjuvant chemotherapy for breast cancer.

Caloric restriction for oncology research: Pre-operative caloric restriction prior to definitive oncologic surgery.

NRG-GY006: (CIRB) A randomized phase II trial of radiation therapy and cisplatin alone or in combination with intravenous triapine in women with newly diagnosed bulky stage IB2, Stage II, IIIB, or IVA cancer of the uterine cervix or Stage II-IVA vaginal cancer.

A phase I-11 dose-escalation study of NBTXR3 activated by external beam therapy or external beam radiotherapy with brachytherapy in subjects with newly diagnosed unfavorable intermediate risk or high risk prostate adenocarcinoma treated with androgen deprivation.

ARN-509 + abiraterone acetate + leuprolide with stereotactic, ultra-hypofractionated radiation (AASUR) in very high risk prostate cancer: A single arm, Phase II study.

SAVE THE DATE: Thursday, July 12, 2018

Inaugural Radiation Oncology and Medical Physics Residency Alumni Gathering

5:30 – 7:30 P.M.

The Bodine Center at
Thomas Jefferson University
Northeast corner of 11th & Sansom Streets
111 S. 11th Street
Philadelphia, PA 19107

RESIDENT RESEARCH ACTIVITIES

During their residency training, our graduating Residents, Dr. Gaurav Shukla and Dr. Noelle Williams participated in several research projects. We would like to share some of their research activities with you.

Gaurav Shukla, M.D., Ph.D.
Dr. Shukla, along with Drs. Taoran Li, Cheng Peng, Virginia Lockamy, Haisong Liu, and Wenyin Shi conducted research on the "Dosimetric impact of a tumor treating fields device for glioblastoma patients undergoing simultaneous radiation therapy". In this study, the impact from tumor treating field (TTField) electrodes on the dosimetry of VMAT treatment plans for patients with glioblastoma was quantitatively evaluated in two ways: (1) in the treatment planning system using advanced dose calculation algorithm and (2) using physical measurements on surface and deep doses. This work provides evidence that radiation doses to planning target volumes is not significantly changed due to the presence of TTFields electrodes, although the impact on skin dose was notable. This research was published in the journal Frontiers in Oncology (2018;8:51. PMID: 29594036).

Dr. Shukla was one of the members of team of researchers from Penn and Jefferson (included Drs. Rathore, Akbari, Doshi, Rozycki, Bilello, Lustig and Davatzikos) published a paper which presented their research efforts to develop a method for estimating peritumoral edema infiltration using radiomic signatures determined via machine learning methods, and tested it on 90 patients with *de novo* glioblastoma. This article, "Radiomic signature of infiltration in peritumoral edema predicts subsequent recurrence in glioblastoma: implications for personalized radiotherapy planning" appeared in the *Journal of Medical Imaging (Bellingham)* in April, 20918 (Volume 5, number 2; PMID: 29531967).

During his residency, Dr. Shukla had an additional five publications including:

Advanced magnetic resonance imaging in glioblastoma: a review. **Shukla G,** Alexander GS, Bakas S, Nikam R, Talekar K, Palmer JD, Shi W. Chin Clin Oncol. 2017 Aug;6(4):40. Review. PMID: 28841802.

Re-irradiation for recurrent glioblastoma multiforme. Barney C, **Shukla G,** Bhamidipati D, Palmer JD. Chin Clin Oncol. 2017 Aug;6(4):35. PMID: 28841798

Biochemical control and toxicity for favorable-and intermediate-risk patients using real-time intraoperative inverse optimization prostate seed implant: Less is more!
Shukla G, Sarkar A, Hanlon A, Crockett E, chen HC, Martelli-Raben J, Glick A, Benge B, Lobis M, Terranova S, Desperito T, Cozzolino D, Kemmerer E, Mourtada F, Raben A
Brachytherapy. 2017 May-Jun; 16(3):490-96. PMID: 28185762

Lung cancer screening: not all nodules are created equal. **Shukla G**, **Williams NL,** Luminais C, Lu B, Shi W, J. Thorac Dis. 2016 Oct;8(10):E1257-59. PMID: 27867602

Stereotactic body radiation therapy delivery in a genetically engineered mouse model of lung cancer. Du S, Lockamy V, Zhou L, Xue C, LeBlanc J, Glenn S, **Shukla G,** Yu Y, Dicker AP, Leeper DB, Lu Y, Lu B. Int J Radiat Oncol Biol Phys. 2016 Nov 1;96(3):529-37. PMID: 27681749

Dr. Shukla has several additional manuscripts in preparation and is continuing several research projects with his Penn Co-Investigators including a RT dose escalation study and having presented a clinical trial concept for image-guided supratotal resection at a recent NRG Oncology meeting, notes that the initial components of the trial are now ongoing.

Noelle Williams, M.D.
During her residency, Dr. Williams was very involved in research projects related to Patient Reported Outcomes (PROs) including: (1) The role of patient engagement and electronic patient reported outcomes in patients undergoing treatment for head and neck cancer: A quality improvement project; (2) Pilot feasibility trial examining the use of electronic patient-reported outcomes in prostate cancer patients with Apple ResearchKit smartphone application; (3) "Strength through insight" – evaluates the feasibility of ePROs via an Apple ResearchKit mobile application in patients with prostate cancer. This application was developed in collaboration with colleagues from Information Systems and Technology at Jefferson and is available to any patient with the diagnosis of prostate cancer undergoing treatment at Jefferson. We hypothesize that the collection of ePROs via a digital mobile-based platform will be feasible and acceptable to patients. This is the first use of the Apple ResearchKit for prostate cancer patients. The concept was funded in part by a grant from the Prostate Cancer Foundation.
Dr. Williams was an author, along with Drs. Garg, Ip and Dicker on a publication recently accepted by the Journal of Clinical Oncology: Clinical Cancer Informatics entitled, "Clinical integration of digital solutions in healthcare: An overview of the current landscape of digital technologies in cancer care".

Dr. Williams also conducted a "Pilot study of metformin in head and neck cancer and its effects on pro-inflammatory cytokines and exosomes implicated in acute and chronic toxicity" and a "Pilot study of metformin to mitigate sequelae of radioactive iodine treatment for well-differentiated thyroid cancers". She has also completed research projects related to prostate cancer, melanoma, and lung cancer.

During her residency, Dr. Williams had additional publications including:

Sleep disturbances in men receiving androgen deprivation therapy for prostate cancer: The role of hot flashes and nocturia. Gonzalez BD, Small BJ, Cases MG, **Williams NL,** Fishman MN, Jacobsen PB, Jim HSL. Cancer. 2018 Feb. 1;124(3):499-506. PMID: 29072790.

Phase I study of Ipilimumab combined with whole brain radiation therapy or radiosurgery for melanoma patients with brain metastases. **Williams NL,** Wuthrick EJ, Kim H, Palmer JD, Garg S, Eldredge-Hindy H, Daskalakis C, Feeney KJ, Mastrangelo MJ, Kim LJ, Sato T, Kendra KL, Olencki T, Liebner DA, Farrell CJ, Evans JJ, Judy KD, Andrew DW, Dicker AP, Werner-Wasik M, Shi W. Int J Radiat Oncol, Biol, Phys. 2017 Sep 1;99(1):22-30. PMID: 28816150

A pilot study to determine if the use of a virtual reality education module reduces anxiety and increases comprehension in patients receiving radiation therapy. Marquess M, Johnston SP, **Williams NL,** Giordano C, Hurwitz MD, Dicker AP, Den RB: J Radiat Oncol. Epub 2017 Mar 25.

Management of Stage I lung cancer with stereotactic ablative radiation therapy. Dan T, **Williams NL:** Surg Oncol Clin N Am. 2017 Jul;26(3):393-403. PMID: 28576179

Radioisotopes in management of metastatic prostate cancer. Raval A, Dan TD, **Williams NL,** Pridjian A, Den RB. Indian J Urol. 2016 Oct-Dec;32(4):277-81. Review. PMID: 27843209

Dr. Williams' ongoing projects include:
RAMP Protocol – (remote Activity Monitoring Pilot): A feasibility study invstigating daily step and sleep data in combination with elecrtronic patient-reported outcomes in adult patients with head and neck cancer.

ADAMM Study: A pilot study investigating the feasibility of ADAMM (Automated Device for Asthma Monitoring and Management) in combination with electronic patient-reported outcomes in adult patients with lung cancer.

Sidney Kimmel Cancer Center at Jefferson Health
PATIENT SUPPORT OPPORTUNITIES
Spring 2018

For Registration, and more information, please contact 215-955-1800.
Please visit www.Jefferson.edu/CancerSupport.

All programs, unless otherwise noted, will be held at the Cancer Support and Welcome Center, 914 Chestnut Street, Philadelphia, PA, 19107.

The Cancer Support and Welcome Center is now open at 914 Chestnut Street! Please stop in for a tour and a gift! Our staff will be happy to help you and your family from cancer diagnosis through survivorship. Our services include; individualized assistance in finding information on diagnosis, treatment and support services, help with way-finding to cancer center appointments, assistance with MyChart, referrals to support resources and support groups, nutritional classes and seminars, educational workshops, exercise classes and more!
For more information stop in or call the Cancer Support & Welcome Center between 9:00am-5:00pm Monday through Friday at 215-955-1800, CancerSupportCenter@Jefferson.edu.

Survivorship Programs

Brain Tumor Support Group at Jefferson
A monthly group for individuals diagnosed with a brain tumor and their supporters.
The group meets year round, on the 2nd Thursday of every month from 6:30 to 8:00 pm
Jefferson Hospital for Neuroscience
900 Walnut St, third floor conference room
For registration and details: Judy.Boldurian@Jefferson.edu

Buddy Program
What can I expect from treatment? Does ANYONE know what I'm going through? Will my life ever be normal again?
ASK a Buddy.
The program is for newly diagnosed cancer patients who are matched by diagnosis, treatment, age, and gender with a trained cancer survivor for one-on-one telephone support.
Call 215-955-8370 if you would like to be matched with a "Buddy" or if you would like to become a "Buddy."

Look Good… Feel Better
A workshop for women with cancer to learn more about caring for themselves during treatment. Participants will learn tips on skin care, wig styling, scarf tying and make-up tips.
Co-sponsored by the American Cancer Society.
Monday, 1/08/2018 1:30 - 3:30 PM
Friday, 4/13/2018 10:00 -12:00 PM
Monday, 5/07/2018 1:00 - 3:00 PM
Tuesday, 7/17/2018 1:00 - 3:00 PM
Location: Cancer Support and Welcome Center at Jefferson
914 Chestnut Street, Philadelphia
To register, please call the American Cancer Society at 1-800-227-2345.

Nu-Voice Club of Center City
This monthly program is a support group for patients, Laryngectomee family members and friends.
The program meets the 3rd Thursday of each month from 12-1:30 pm.
Gibbon Building, Room 9490
111 South 11th Street, Philadelphia,
Call Nancy Travers, or Barbara Baskin, 215-955-2554, for more details.

Esophagectomy Survivorship and Support Group
This program is for patients and their family members who are to undergo or have undergone an esophagectomy.
The group meets quarterly.
April 25th, August 15th at 4:30 pm
Cancer Support and Welcome Center at Jefferson
914 Chestnut Street, Philadelphia
For more information, contact Sung.Whang@jefferson.edu.

Online/Telephone Primary and Metastatic Ocular Melanoma (OM) Support Groups
Thomas Jefferson University (TJU) Hospital's Oncology Support Services Program is excited to partner with the Melanoma Research Foundation's CURE OM to offer virtual support groups to the primary and metastatic ocular melanoma (OM) community. These support groups meet the first Wednesday of the month via a virtual platform so that individuals from across the country can join either by phone or internet. Licensed TJU social workers facilitate the groups in a private and confidential setting. If you would like to join a group, or want more information, please contact Lauren Johnston, CURE OM Program Manager, at ljohnston@melanoma.org

Support Group for Caregivers of Leukemia Patients
Anne M. Delengowski, RN, MSN, AOCN
Oncology Clinical Nurse Specialist
Wednesdays, 2nd and 4th of the month, starting with March 14, and 28, 1- 2 pm
Nurse Anne Delengowski will present an overview of Leukemia in relation to the needs of caregivers of Leukemia patients, in this supportive group setting.

Fighting Cancer Together: People Living with Cancer
Monthly Support Group
3rd Monday of the Month 12pm-1:15pm, starting April 16, 2018
Adult group members with different types of cancer come together each week to get support and learn from each other. People in active treatment, who have recently completed treatment or are having treatment-related side effects up to two years after treatment ends are welcome. This group is led by professional oncology social workers.

Coffee & Conversation with a Buddy
Every other Monday, beginning March 26th, 2:00-3:00PM
All are welcome to come have a cup of coffee and informally meet with a Buddy--a trained cancer survivor volunteer who has been through similar procedures and treatments and can help answer questions and provide support and companionship.

Children's Lives Include Moments of Bravery
CLIMB® is a new support program specifically for children who have a parent or grandparent diagnosed with cancer. Through art projects and discussion, this program will help children cope with their feelings, while improving communication between children and parents. Separate groups will be held at the same times for children ages 6-12, teens ages 13-17, and parents/grandparents.

CLIMB® is a six-week closed group support program that will meet once a week for six weeks. There is no cost to participate. Pre-registration is required.

When: dates to be determined
6:00-7:30 PM
Location: Cancer Support and Welcome Center
For more information or to register, please contact Jodi Sandos
(215) 503-7711 or Lora Rhodes (215) 503-5482 or email
oncologysocialwork@jefferson.edu.

Gentle Chair Yoga for Patients and Caregivers
Michelle Stortz, Certified Yoga Therapist (C-IAYT)
2nd Tuesday of the Month, 12-1:15 pm
Michelle specializes in yoga therapy for those who have had a cancer experience. Come and enjoy the many benefits of adaptive chair yoga for cancer survivors and for caregivers. This yoga experience is flexible for your unique needs and no experience is necessary.
Cancer Support and Welcome Center at Jefferson
914 Chestnut Street
For more information and registration, email M@michellestortz.com or call 215-955-8370

Temple Legal Clinic for Cancer Patients
Temple Legal Aid Office Lawyers and Legal Interns
Mondays, January 8 through April 16, 1-4 pm
Come and receive free legal advice and assistance with your legal problems. Advice is provided on many issues and representation is available for clients who meet Legal Aid's low-income criteria in areas in which they have expertise. The most common matters the Legal Aid office handles are the following:

1. Disability benefits, including Social Security and SSI Disability benefits and other public benefits;
2. Advance directives, durable powers of attorney, disability custody planning (standby guardianship), and estate planning.
3. Primarily advice on other civil legal problems, including private disability insurance, housing, family law, health insurance, discrimination, and other matters.

Optimizing Nutrition During and after Treatment
Heather Bell-Temin, MS, RDN, LDN, CSO
Outpatient Oncology Dietitian
March 15, 12-1:30 pm
Heather Bell-Temin will present helpful nutritional information based on cancer prevention guidelines,
and will provide guidance on which foods to eat and which foods to avoid during and after treatment.

Neuropathic Complications of Cancer Treatments: Help with treating symptoms
Goran Rakocevic, MD
Associate Professor of Neurology
Tuesday, March 20, 12-1:30 pm
Neurologist Goran Rakocevic will help you understand about chemotherapy-induced neuropathies and treatment options to better manage and improve symptoms in a supportive environment.

Medical Marijuana: What are the benefits, risks, and what does the Pennsylvania Program entail?
Brooke Worster, MD, FACP
Assistant Professor of Medicine
Medical Director, Neu Center for Supportive Medicine and Cancer Survivorship
Gregory D. Garber MSW, LCSW
Director of Support Services, Neu Center for Supportive Medicine and Cancer Survivorship
Director, SKCC Support and Welcome Center
Tuesday, March 27th, 12 – 1: 30 pm

Getting help with cancer-related symptoms when they occur = having better days and less symptoms. Symptoms such as cancer-related pain, depression, difficulty sleeping, and poor appetite can be helped with symptom management. Please join us to learn about the benefits and risks of using medical marijuana and how the certification program in Pennsylvania works and how to access it.

Please contact the Neu Center for Supportive Medicine and Cancer Survivorship, 215-955-1888, for a consult to receive help in getting signed up for Pennsylvania certification for medical marijuana.

Understanding Medicare, Medicaid and the Affordable Care Act
Angie Santiago, CRCS-I-ask
Certified Revenue Cycle Specialist- Institutional Lead Financial Counselor, Oncology
Crystal Sypherd, CPhT, Financial Counselor, Oncology, Business Services Department at Jefferson
Tuesday, April 3, 12-1:30 PM
In this program, learn about the basics of Medicare, Medicaid, and the Affordable Care Act (ACA) and an update on the status of the health insurance through the Affordable Care Act. You will also learn about co-pay assistance and pharmaceutical program assistance.

Managing Uncertainty and Coping with a Cancer Diagnosis
Gregory D. Garber MSW, LCSW
Director of Support Services, Neu Center for Supportive Medicine and Cancer Survivorship
Director, SKCC Support and Welcome Center
April 17th, 12-1:30 PM
Living with uncertainty is a challenge that anyone who has experienced a cancer diagnosis encounters.
This discussion will address the coping challenges that patients and family members encounter and provide strategies to help manage these. Anyone whose life has been affected by cancer is welcome to attend.

Novel Treatment for Hematological Malignancies
Lindsay Wilde, MD
Hematology / Medical Oncology
Thursday, April 26, 12 – 1:30 PM
Dr. Wilde will share information about new and promising treatments for hematologic cancers (leukemia, lymphoma, multiple myeloma), including the use of CAR-T cells and other targeted approaches, to help you gain a better understanding of how these therapies are helpful.

Help with Managing Fatigue and Insomnia for Better Days
Molly Hanson, CRNP
Nurse Practitioner
Alison Petok, MSW, LCSW, MPH

Neu Center for Supportive Medicine
Tuesday, May 1, 12-1:30 PM
The management of insomnia through a combination of pharmacologic and healthy sleep habits can have a positive impact not only on insomnia but also on related symptoms such as fatigue, and consequently, on overall health and quality of life. The presenters will provide strategies to help you improve fatigue and insomnia.

Oncology Nutrition: Myth versus Fact
Heather Bell-Temin, MS, RDN, LDN, CSO
Outpatient Oncology Dietitian
Thursday, May 3, 12-1:30 pm
There is confusing information when it comes to nutrition and cancer. Heather Bell-Temin will review common cancer nutrition myths and give you the facts so you can be the most informed while dealing with your diagnosis.

Tools for Stress Reduction thru Mindfulness
Aleeze Sattar Moss, PhD
Associate Director, Mindfulness Institute
Myrna Brind Center of Integrative Medicine at Jefferson
May 10, 12:00- 1:30 pm
This program provides a taste of the fundamentals of "mindfulness-based stress reduction," which has been shown to reduce anxiety, depression, and pain, and to improve well-being during cancer treatment and survivorship. Through meditation and awareness exercises, we will explore this practical time-proven approach to living fully in the present moment that has helped many achieve greater balance, vitality, and health.

Discovering Spiritual Strength during Difficult Times
Rev. Marianne Robbins, MDiv, BCC
Associate Director, Department of Pastoral Care and Education
Thomas Jefferson University Hospital
May 15th, 12 – 1:30 PM
Rev. Robbins will have an interactive session to help you discern what your needs are for support and comfort on your journey as you navigate your course of treatment and beyond.

Facing Breast Cancer with Information and Support
An informational and supportive seminar for women with Breast Cancer

Help with the Management of Lymphedema
Judith Folweiler, OTR/L, CHT, CLT
Clinical Specialist, Jeff FIT
Mary Michelle Loquias, PT, DPT, CLT, Physical Therapist, MHD,
Physical Medicine and Rehabilitation at Jefferson
May 17, 12 – 1:30 PM
In this program, Lymphedema experts will present on therapeutic approaches to reduce the swelling associated with lymphedema and the variety of treatments available, including skin care, manual lymph drainage, gentle massage and light exercises to help stimulate the lymphatic system.

Unite for HER Wellness Day
Thursday, May 18, 1-5 pm
Bluemle Building, Rooms 105/107
At the Jefferson Unite for HER Wellness Day event, Breast Cancer patients will learn about the benefits of complementary therapies and create a personal plan for incorporating those

valuable tools into their treatment and recovery. In small group settings, trained professions will lead discussions in the areas of acupuncture, massage, Reiki, yoga, meditation and nutrition, as well as a caregiver session. Participants leave the day with a Wellness Passport to cover the costs of the complementary therapies they choose to pursue.
For more information, contact Caitlin Tapper, 215-955-6040.

Journaling through the Journey
Monday, May 14th 10a-12pm
Journaling with mixed media arts can help relieve stress, worry and anxiety. Journaling with mixed media starts out the same as a written journal. Thoughts, feelings and emotions are written and released in the journal, then fully or partially covered with paint, collage, markers, stencils etc.
You do not have to be an artist or have any artistic talent! The focus is on the process, playing with art supplies while practicing mindfulness and being present in the moment. Registration required.

Art Discovery Workshop
Erin Cavanaugh, Art Therapist
Monday May 21, 10am-12pm
Explore your creativity through various art techniques, including drawing, painting, collage, and more in a supportive and playful environment.
Program open to patients, caregivers and survivors
No previous artistic experience required.

Prostate Cancer Networking Group
Helpful Strategies for Erectile Dysfunction
Irvin Hirsch, MD
Clinical Professor, Department of Urology, Thomas Jefferson University
Thursday, April 12, 12-1:30 PM
For men who have gone through a prostate cancer experience, erectile dysfunction may be a side effect after treatment. In this program, Dr. Hirsch will present options for surgical, medical, and behavioral strategies in the management of these possible side effects of treatment.

Novel Treatments for Advanced Prostate Cancer and New Hopes for Patients
William Kevin Kelly, DO
Professor Medical Oncology and Urology
Director, Division of Solid Tumor Oncology
Leader, Biology of Prostate Cancer Program
Associate Director, Clinical Research, Sidney Kimmel Cancer Center at Jefferson Health
Date: May 24, 12-1:30 PM
Treatment for advanced prostate cancer can help to control the cancer for prolonged periods of time. In this presentation, Dr. Kelly will discuss novel treatments and new therapies for men with an advanced Prostate Cancer diagnosis.

Survivorship Celebration

June 6, 2018, 12-2:00 pm
Dorrance H. Hamilton Building, Connelly Auditorium
1001 Locust Street, Philadelphia, PA 19107
12-1 pm Lunch and Health Fair
1-2 pm Presentation

"IV'S, Finish Lines, & Happy Dances"
Stephen Brown, Author and Cancer Survivor
As an athlete his entire life, Stephen Brown ran marathons and ironman triathlons, and a cancer diagnosis was the furthest thing from his mind.

When Stephen was diagnosed with chronic lymphocytic leukemia, he made choices that helped him to live above this disease, including maintaining his fitness level and running home from chemotherapy treatments when possible. Steve will talk about the importance of family, of not allowing a cancer diagnosis to be all-consuming,

And the doors that have opened up in his life because of his cancer experience. Please join us to hear Steve's story of courage and hope.

Additional Jefferson Locations:

Abington Jefferson Health
Please call 215-481-6700 or email Bethc@cancersupportphiladelphia.org
for information or to register for activities.

Aria Health
For programs contact: Jill Lefkowitz, MSW, LCSW at 215-612-5208
https://www.ariahealth.org/wellness-programs/support-groups/cancer-center-support-groups

Jefferson Health New Jersey
Abigale Hassel, MSW, LCSW, OSW-C - Social Worker
Patient support and information.
856-218-5322
https://www.kennedyhealth.org/services/cancer-center

What Sidney Kimmel Cancer Center at Jefferson Health Offers

Support Services
The Sidney Kimmel Cancer Center at Jefferson Health is your partner on the road to recovery. As we navigate this journey together, we understand that cancer can affect many aspects of your life. That's why the Jefferson staff works with you and your family, helping to meet your physical and emotional needs during this difficult time.
Supportive Services we offer:

- Oncology Social Workers
- Nutrition and Dietetic Counseling
- Financial Assistance Services
- Fertility Preservation

Cancer Support & Welcome Center
The Cancer Support and Welcome Center promotes wellness and healing by providing you and your family with supportive care services and cancer-related information. A range of programs are free and offered to anyone living with cancer, regardless of where they receive care.
The Cancer Support and Welcome Center is open Monday through Friday from 9 a.m. to 5 p.m.

914 Chestnut Street, Philadelphia, PA 19107
215-955-1800 | CancerSupportCenter@jefferson.edu

Neu Center for Supportive Medicine and Cancer Survivorship
While you are receiving state of the art oncologic care at the Sidney Kimmel Cancer Center at Jefferson Health, The Neu Center for Supportive Medicine and Cancer Survivorship will be available to help you along this path by addressing the issues that affect the quality of your life during and after your cancer care including the physical, emotional, social, financial, and spiritual effects among others.

Clinical Trials
A clinical trial is a type of research study that tests how well new medical approaches work. Jefferson offers a number of Clinical Trials.
To find out if there is a clinical trial available that might be right for you, ask your healthcare providers, visit our website, or contact the Sidney Kimmel Cancer Center at Jefferson Health Clinical Research Management Office at 215-955-1661. Jefferson.edu/ClinicalTrials

Original Article

Adjuvant Radiation Therapy, Androgen Deprivation, and Docetaxel for High-Risk Prostate Cancer Postprostatectomy: Results of NRG Oncology/RTOG Study 0621

Mark D. Hurwitz, MD[1]; Jonathan Harris, MS[2]; Oliver Sartor, MD[3]; Ying Xiao, PhD[1]; Bobby Shayegan, MD[4]; Paul W. Sperduto, MD[5,6]; Kasra R. Badiozamani, MD[7]; Colleen A. F. Lawton, MD[8]; Eric M. Horwitz, MD[9]; Jeff M. Michalski, MD[10]; Kevin Roof, MD[11]; David C. Beyer, MD[12]; Qiang Zhang, PhD[2]; and Howard M. Sandler, MD[13]

BACKGROUND: Phase 3 trials have demonstrated a benefit from adjuvant radiation therapy (ART) for men who have adverse factors at radical prostatectomy (RP). However, some patients have a high risk of progression despite ART. The role of systemic therapy with ART in this high-risk group remains to be defined. **METHODS:** Patients who had either a post-RP prostate-specific antigen (PSA) nadir > 0.2 ng/mL and a Gleason score ≥7 or a PSA nadir ≤0.2 ng/mL, a Gleason score ≥8, and a pathologic tumor (pT) classification ≥ pT3 received 6 months of androgen-deprivation therapy (ADT) plus radiotherapy and 6 cycles of docetaxel. The primary objective was to assess whether the addition of ADT and docetaxel to ART resulted in a freedom from progression (FFP) rate ≥ 70% compared with an expected rate of 50%. Multivariate logistic and Cox regression analyses were used to model associations between factors and outcomes. **RESULTS:** In total, 74 patients were enrolled. The median follow-up was 4.4 years. The pathologic tumor classification was pT2 in 4% of patients, pT3 in 95%, and pT4 in 1%. The Gleason score was 7 in 18% of patients and ≥8 in 82%. Post-RP PSA levels were ≤0.2 ng/mL in 53% of patients and >0.2 ng/mL in 47%. The 3-year FFP rate was 73% (95% confidence interval, 61%-83%), and the 3-year cumulative incidence of biochemical, distant, and local failure was 26%, 7%, and 0%, respectively. In multivariate models, postprostatectomy PSA nadir was associated with 3-year FFP, Gleason score, and PSA with biochemical failure. Grade 3 and 4 neutropenia was common; however, only 3 episodes of febrile neutropenia occurred. Late toxicities were not impacted by the addition of systemic therapy. **CONCLUSIONS:** Combined ADT, docetaxel, and ART for men with high-risk prostate cancer after prostatectomy exceeded the prespecified study endpoint of 70% 3-year FFP. Phase 3 trials assessing combined local and systemic therapies for these high-risk patients are warranted. ***Cancer*** **2017;123:2489-96.** *© 2017 American Cancer Society.*

KEYWORDS: androgen deprivation, chemotherapy, docetaxel, high risk, postprostatectomy, radiation.

INTRODUCTION

Radical prostatectomy (RP) is common treatment for prostate cancer. Although a majority of patients with favorable risk features do well, those with high-risk features have a substantial risk of disease recurrence. Patients with persistently elevated prostate-specific antigen (PSA) levels postprostatectomy or who experience biochemical failure within 3 years of surgery have a significantly increased risk of death from prostate cancer.[1]

Patients commonly receive radiation therapy (RT) after prostatectomy. Randomized trials of adjuvant RT (ART) have demonstrated an improvement in progression-free survival and, with long-term follow-up, an overall survival advantage.[2-4] Despite this overall benefit, 50% of patients with pT3 and Gleason ≥ 8 disease or Gleason ≥ 7 and a PSA nadir >0.2 ng/mL experienced treatment failure within 3 years. Patients in this subset fail despite receipt of both surgery and RT and thus are expected to be at greater risk of death from prostate cancer than those who fail only surgery.

Optimal therapies remain to be defined for patients who have high-risk disease despite the receipt of RT in the postprostatectomy setting. Standard care for high-risk patients who receive primary RT includes androgen-deprivation

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therapy (ADT).[5] It has been demonstrated that docetaxel improves survival in men with metastatic prostate cancer,[6-8] and a potential survival benefit was recently noted with docetaxel in the treatment of high-risk, clinically localized disease.[9] The current study was designed to test the hypothesis that the addition of docetaxel and ADT to RT for men at high risk of failure despite ART would result in improved freedom from progression (FFP) compared with historic controls.

MATERIALS AND METHODS

Patient Eligibility

Protocol approval was received from the institutional review board at each site. Informed consent was obtained from patients before participation. Eligible patients had prostatic adenocarcinoma with either a Gleason score $\geq$7 at prostatectomy and a PSA nadir >0.2 ng/mL or a Gleason score $\geq$8 at prostatectomy, a PSA nadir $\leq$0.2 ng/mL, and a pathologic tumor (pT) classification $\geq$ pT3a. Patients were enrolled within one year of RP. Subjects had no lymph node or distant metastases determined by bone scan and magnetic resonance imaging or computer tomography of the pelvis.

A Zubrod performance status $\leq$1 was required. A PSA level was obtained $\leq$6 weeks before registration. Absolute neutrophil count $\geq$ 2000 cells/mm^3, platelet count $\geq$ 100,000 cells/mm^3, hemoglobin $\geq$ 8.0 g/dL, alanine and aspartate transaminase $\leq$1.5 times, alkaline phosphatase $\leq$ 2.5 times, and total bilirubin $\leq$1.2 times the institutional upper normal limit were required.

Treatment

ADT, including a luteinizing hormone-releasing hormone agonist and a nonsteroidal antiandrogen (bicalutamide 50 mg daily) were administered for 6 months beginning 8 weeks before RT.

RT was administered with either 3-dimenisonal conformal RT (3DCRT) or intensity-modulated RT (IMRT) using energies $\geq$ 6 MV. The total dose to the prostate bed was 6660 $\pm$ 180 centigray (cGy), including an initial pelvic field of 4500 cGy using daily fractions of 180 cGy. Pelvic fields included a superior border extending at a minimum to the bottom of the sacroiliac joint and at most superiorly to the lumbar 5-sacral 1 interspace. Seminal vesicle remnants if present received a minimum of 5040 cGy and could receive full dose at the discretion of the treating physician.

Patients received docetaxel 3 to 6 weeks after completion of RT and 6 cycles of 75 mg/m^2 intravenously every 3 weeks. Premedication with dexamethasone was required. If granulocytes were $\leq$ 1500 cells/mm^3 or platelets were $\leq$ 100,000 cells/mm^3, as measured within 1 day of docetaxel administration, then treatment was held and counts were repeated weekly with modification of subsequent docetaxel doses. If neutropenia/thrombocytopenia did not resolve to a point that allowed a patient to receive docetaxel by 15 days of scheduled chemotherapy, then chemotherapy was discontinued. Docetaxel was also modified or held because of abnormal liver function tests. The dose was reduced by 25% for grade 2 neuropathy without treatment delay or was discontinued for grade $\geq$3 neuropathy.

Follow-Up

Follow-up assessments occurred every 3 months for 2 years, every 6 months for 3 more years, and annually thereafter. The PSA level was obtained at each visit. PSA $\geq$ 0.4 ng/mL was verified with a repeat level to confirm progression. Bone scans and computed tomography or magnetic resonance imaging studies were recommended at least annually after PSA progression to determine rates of metastatic progression.

Statistical Design and Analysis

The primary endpoint was FFP, with failure defined as PSA $\geq$0.4 ng/mL after the end of RT confirmed by a second higher PSA, nonprotocol hormones, locoregional progression, distant metastasis, or death within 3 years after registration. According to Southwest Oncology Group (SWOG) Study 8794, the expected FFP rate was 50% for patients who underwent prostatectomy and also received RT. The experimental therapy was to be deemed effective if the FFP rate was $\geq$70%. According to the Fleming multiple testing procedure with 3 stages, 69 patients were required to test the null hypothesis (FFP $\leq$ 50%) against the alternative (FFP $\geq$ 70%) with 90% power and a significance level .025. Allowing for 10% patient ineligibility or nonevaluability, the total sample size was 76. At final analysis, if $\geq$44 of 69 patients had no FFP event (ie, if they were alive and progression free), then the null hypothesis would be rejected, and we would conclude that the FFP rate was $\geq$0.7. The 95% confidence interval (CI) for the FFP rate was calculated using the Clopper-Pearson method.

Secondary endpoints included FFP (at any time), locoregional progression, distant metastases, biochemical failure, overall survival, prostate cancer death, nonprostate-cancer death, and acute (within 90 days of treatment end, 3 weeks after the last planned docetaxel

dose) and late (≥91 days after treatment end) treatment-related (definitely, probably, or possibly related to treatment) adverse events. Adverse events were scored using Common Terminology Criteria for Adverse Events, version 3.0. The FFP and survival rates were estimated using the Kaplan-Meier method, and all others were estimated using the cumulative incidence method, with death before failure as a competing risk. Age, Gleason score, PSA, tumor classification, lymph node status, and surgical margin status were correlated with outcomes by using logistic or Cox regression.

RESULTS

Eighty patients from 33 sites were enrolled between April 2008 and September 2010, of which 74 who met eligibility requirements were included in the analysis. Details of patient enrollment are provided in Figure 1, and patient characteristics are listed in Table 1. The post-RP PSA level was ≤0.2 ng/mL in 39 patients (52.7%) and >0.2 ng/mL in 35 patients (47.3%). Among men who had post-RP PSA levels > 0.2 ng/mL, the median level was 0.60 ng/mL (interquartile range, 0.40-2.49 ng/mL). Surgical margins were positive in 43 patients (58.1%).

FFP in the First 3 Years

Because the final analysis included 74 patients, ≥ 46 patients who had no FFP event (ie, they were alive and progression free) were required to reject the null hypothesis (rather than 44 patients). Fifty-four of 74 patients had no FFP event, so the null hypothesis was rejected. The estimated FFP rate was 73% (95% CI, 61.4%-82.6%). A post-RP PSA level > 0.2 ng/mL was associated with an increased risk of failure in univariate analysis (odds ratio, 10.94; 95% CI, 2.68-65.81; $P < .001$) and multivariate analysis (odds ratio, 16.27; 95% CI, 3.51-108.17; $P < .001$) adjusted for Gleason score (8-10 vs 7).

Time-to-Event Outcomes

The median follow-up among surviving patients was 4.4 years (range, 3.3-5.6 years). The 3-year FFP rate was 73% (95% CI, 62.9%-83.1%) (Fig. 2). Twenty-six patients experienced treatment failure, including 20 within 3 years. Biochemical failure was the first event noted in 24 patients (92.3%), including 2 (7.7%) who presented with metastases as the initial sign of treatment failure. Eleven patients developed metastases. Three deaths occurred, including 2 from prostate cancer. The 3-year estimates are presented in Table 2. Gleason scores from 8 to 10 and post-RP PSA levels > 0.2 ng/mL were associated with an increased risk of failure for the endpoints FFP and biochemical failure in multivariate analysis, but only PSA levels >0.2 ng/mL were associated with an increased risk in univariate analysis (Table 3). Discrepant results for Gleason score between univariate and bivariate analyses were likely because of the eligibility criteria, in which patients who had a Gleason score of 7 were only eligible if they had a PSA level >0.2 ng/mL. In univariate analysis, post-RP PSA levels > 0.2 ng/mL were also associated with an increased risk of distant metastasis (hazard ratio, 12.62; 95% CI, 1.61-98.65; $P = .02$).

Treatment Delivery

Sixty-six of 74 patients (89.2%) were scored by study chairs according to protocol or with acceptable variation for RT. Seventy of 74 patients (94.6%) were scored according to protocol for chemotherapy, and 61 of 70 had no modifications or delays. For RT, 89.2% of patients received IMRT, 9.5% received 3DCRT, and 1 received no RT. All 73 patients who started RT received 66.6 ± 1.8 gray. Sixty-seven of 74 patients (90.5%) received 6 cycles of docetaxel, and 1 patient did not receive any docetaxel. All patients received luteinizing hormone-releasing hormone agonist, and all but 1 received oral antiandrogen.

Adverse Events

Chemotherapy side effects were common but manageable and did not increase long-term toxicity. Thirty-five patients (47.3%) experienced at least 1 grade 4 treatment-related adverse event at any time, and an additional 23 (31.1%) experienced at least 1 grade 3 treatment-related adverse event at any time. Acute treatment-related adverse events are summarized in Table 4. The most common acute toxicities were hematologic, including grade 3 and 4 neutropenia (16.2% and 40.5% of patients, respectively), leukopenia (35.1% and 13.5%, respectively) and lymphopenia (13.5% and 2.7%, respectively). However, only 4.1% of patients developed febrile neutropenia, and infection was limited to a single episode of grade 3 urinary tract infection. Grade 2 and 3 peripheral neuropathy occurred in 13.5% and 1.4% of patients, respectively. Late treatment-related toxicities included 6 episodes (8.1%) of various grade 3 toxicities and 2 episodes (2.7%) of grade 4 urinary incontinence (Table 5). The 2-year cumulative incidence of grade 3 and 4 late toxicity was 8.1% (95% CI, 3.3%-15.8%).

DISCUSSION

Phase 3 trials have consistently demonstrated a benefit from the receipt of ART by men who have adverse pathologic findings after prostatectomy, including extracapsular

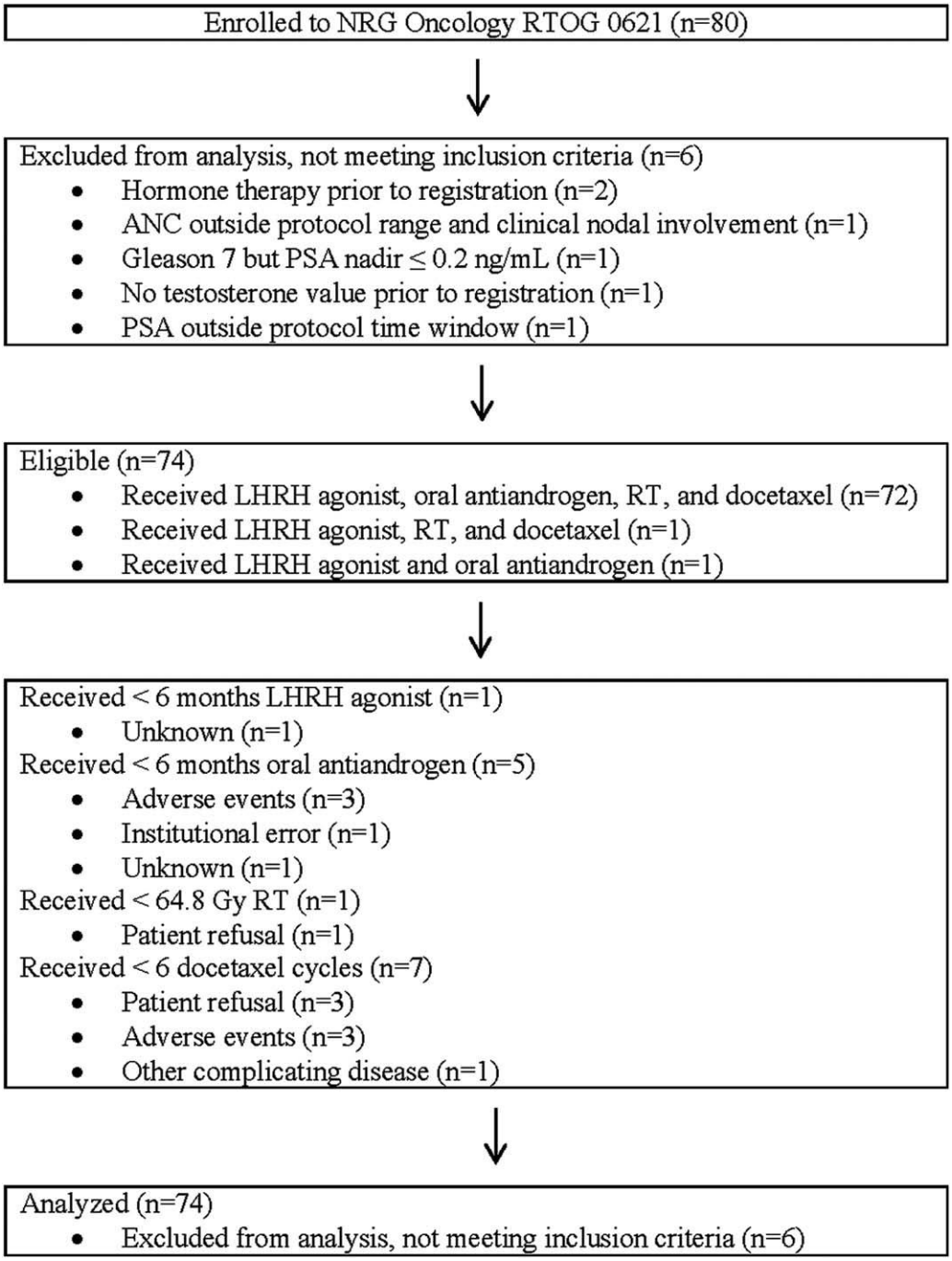

Figure 1. This is the NRG Oncology/Radiation Therapy Oncology Group (RTOG) 0621 Consolidated Standards of Reporting Trials (CONSORT) flow diagram. ANC indicates absolute neutrophil count; Gy, gray; LRHR, luteinizing hormone-releasing hormone; PSA, prostate-specific antigen; RT, radiation therapy.

disease extension, seminal vesicle invasion, and positive margins.[2-4] All 3 of those randomized studies reported a benefit in progression-free survival; and, in the SWOG 8794 trial with long-term follow-up, an overall survival benefit was noted.

Postprostatectomy ART will benefit many men; however, a review of studies that assessed postprostatectomy RT revealed subsets of patients at high risk of failure after both surgery and RT. In a large series from Johns Hopkins, men who experienced treatment failure within

TABLE 1. Patient and Tumor Characteristics, n = 74

Characteristic	No. of Patients (%)
Age, y	
Median	62 [43-75]
First/third quartile	55/66
≤65	52 (70.3)
>65	22 (29.7)
Race	
American Indian or Alaskan Native	2 (2.7)
Black or African-American	6 (8.1)
White	6 (87.8)
Unknown	1 (1.4)
Ethnicity	
Hispanic or Latino	1 (1.4)
Not Hispanic or Latino	66 (89.2)
Unknown	7 (9.5)
Zubrod performance status	
0	69 (93.2)
1	5 (6.8)
Prostatectomy margin	
Positive	43 (58.1)
Negative	31 (41.9)
Pathologic tumor classification	
pT2a	1 (1.4)
pT2c	2 (2.7)
pT3 (not otherwise specified)	2 (2.7)
pT3a	28 (37.8)
pT3b	40 (54.1)
pT4	1 (1.4)
Postoperative PSA nadir, ng/mL	
≤0.1	33 (44.6)
>0.1 to 0.2	6 (8.1)
>0.2	35 (47.3)
PSA at study entry, ng/mL	
≤0.1	27 (36.5)
>0.1 to 0.2	7 (9.5)
>0.2	40 (54.1)
Gleason score, combined	
7	13 (17.6)
8	19 (25.7)
9	41 (55.4)
10	1 (1.4)

Abbreviation: PSA, prostate-specific antigen.

3 years of prostatectomy had a 15-year risk of prostate cancer-specific mortality of 59% compared with 13% who experienced treatment failure after a longer postoperative period. In designing the current study, a subgroup of patients from the SWOG 8794 study was identified that, on average, had a 50% risk of failure by 3 years despite the addition of ART. Because these patients are at high risk of failing 2 local therapies, the current study was designed to assess the potential benefit of adding docetaxel and ADT to RT in this high-risk population.

Although the roles of ADT and chemotherapy in combination with postoperative RT have yet to be defined, a survival benefit with ADT and a potential benefit with docetaxel in other high-risk settings have been noted. The addition of ADT to primary RT is standard in the setting of high-risk prostate cancer and has an established survival benefit. Phase 3 trials have also revealed a survival benefit with docetaxel in metastatic prostate cancer, initially in the setting of castration-resistant disease[6,7]; and, more recently, a large survival benefit was noted in the CHAARTED study when docetaxel was received at the initiation of ADT for newly diagnosed, metastatic castration-sensitive disease.[8] The STAMPEDE trial demonstrated a benefit from docetaxel in metastatic disease and its potential utility in the locally advanced setting, and initial results from Radiation Therapy Oncology Group (RTOG) study 0521 indicate there may be a survival benefit in the primary treatment of high-risk patients.[9,10] Benefits observed with the use of docetaxel at earlier points in the course of prostate cancer support the investigation of its use in high-risk patients postprostatectomy who are without frank evidence of metastases but are likely to fail despite local therapy. The findings of the currently study support the hypothesis that the use of systemic therapy benefits men without established metastatic disease who nevertheless are at high risk of local treatment failure despite both RP and postoperative RT. The 3-year FFP rate was 73% compared with a projected rate of 50% observed among patients who had high-risk features in the adjuvant radiation arm of SWOG 8794. Although comparisons between studies must be viewed with caution, on review of patient characteristics and known prognostic factors, men enrolled on the current study appeared to be a higher risk cohort compared with the SWOG historic controls. In the current study, 82% of patients had Gleason scores from 8 to 10 versus 9% in the historic control series. PSA failed to nadir to ≤0.2 ng/mL in 47% of patients in the current study versus 36% of patients in SWOG 8794. Fifty-seven percent of patients in the current study had seminal vesicle involvement versus 31% in SWOG 8794, and fewer had positive margins. All of these factors have been associated with a greater risk of treatment failure in prior studies, including SWOG 8794.[11] Furthermore, both PSA nadir and Gleason score were associated with an increased risk of treatment failure on multivariate analysis in the current study, suggesting that the benefit from adding systemic therapy in these very-high-risk patients may exceed the estimated 23%.

Additional study of docetaxel in high-risk patients postprostatectomy is indicated noting both the potential benefits and toxicities. High rates of hematologic toxicities, including grade 3 and 4 neutropenia and leukopenia, occurred on the current study. These rates appear to be higher than those reported previously in series that assessed the use of docetaxel in treatment for metastatic prostate cancer, likely reflecting the initiation of docetaxel

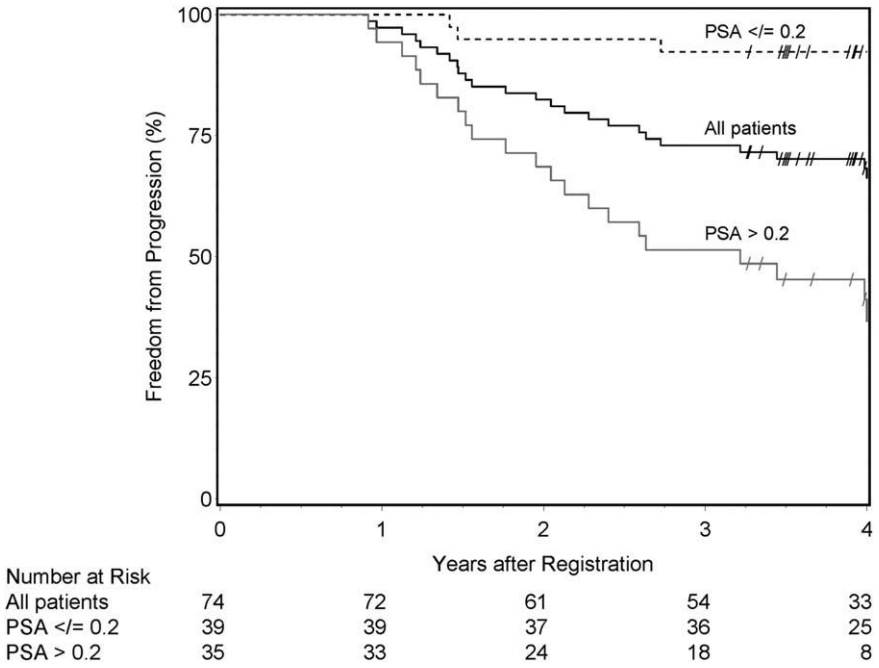

Figure 2. Kaplan-Meier estimates of freedom from progression (FFP) are shown. Overall, the estimated 3-year FFP rate was 73% (95% confidence interval [CI], 62.9%-83.1%). The 3-year FFP rates were 92.3% (95% CI, 83.9%-100%) and 51.4% (95% CI, 34.9%-68%) for patients with postradical prostatectomy nadir prostate-specific antigen (PSA) levels $\leq$ 0.2 and $>$0.2 ng/mL, respectively. Slashes (/) along each line indicate censored observations.

TABLE 2. Three-Year Time-to-Event Estimates

Endpoint	No. of Events		3-Year Estimate, %	95% CI, %
	First 3 Years	Total		
Freedom from progression	20	26	73	62.9-83.1
Local-regional progression	0	0	0	NA
Distant metastasis	5	11	6.8	2.5-14
Biochemical failure	19	25	25.7	16.3-36.1
Overall survival	1	3	98.6	96-100
Prostate cancer death	0	2	0	NA
Nonprostate cancer death	1	1	1.4	0.1-6.5

Abbreviations: CI, confidence interval; NA, not applicable.

3 to 6 weeks after completion of pelvic RT.[7,11-13] The impact of the timing of docetaxel initiation after RT on hematologic toxicities warrants further investigation. Although the concurrent receipt of docetaxel and RT may have sensitizing effects, as commonly observed in the treatment of other malignancies, the rates of hematologic toxicity noted in the current study support the sequential use of pelvic RT and docetaxel in this clinical setting. It is important to note that, although the rates of these laboratory toxicities were high, rates of febrile neutropenia and infection were similar to these in previously reported series.[7,12] Rates of other toxicities commonly associated with docetaxel, including peripheral neuropathy, were in line with the expected rates.[13] It is noteworthy that receipt of docetaxel and ADT in the current study was not associated with increased long-term toxicities, including the exacerbation of genitourinary and gastrointestinal side effects commonly observed with RT.[4,14]

It is important to note limitations of the current study. Because of the nonrandomized phase 2 design, the impact of each intervention, including RT, ADT, and docetaxel, on improving the FFP rate compared with historic controls remains to be defined. Improved surgical techniques and changes in Gleason grading since the completion of SWOG 8794 might have accounted for some of the benefit observed on NRG Oncology/RTOG 0621.

TABLE 3. Univariate and Multivariate Analysis of Prognostic Factors for Freedom From Progression and Biochemical Failure

Endpoint	HR (95% CI)	*P*
Freedom from progression		
Univariate analysis		
Gleason[a]	0.87 (0.33-2.32)	.78
PSA[b]	13.45 (4.00-45.22)	< .001
Multivariate analysis		
Gleason[a]	3.14 (1.16-8.50)	.02
PSA[b]	20.01 (5.81-68.95)	< .001
Biochemical failure		
Univariate analysis		
Gleason[a]	1.14 (0.39-3.32)	.81
PSA[b]	12.26 (3.64-41.27)	< .001
Multivariate analysis		
Gleason[a]	4.13 (1.39-12.28)	.01
PSA[b]	19.72 (5.72-67.99)	< .001

Abbreviations: CI, confidence interval; PSA, prostate-specific antigen.
[a] Patients who had Gleason scores of 7 were compared with those who had scores from 8 to 10.
[b] Patients who had postoperative nadir PSA levels >0.2 ng/mL were compared with those who had levels ≤0.2 ng/mL.

TABLE 4. Selected Treatment-Related Acute Adverse Events, n = 74

	No. of Events (%)		
CTCAE Category and Terms	Grade 2	Grade 3	Grade 4
Maximum	15 (20.3)	23 (31.1)	34 (45.9)
Blood/bone marrow			
Hemoglobin decreased	12 (16.2)	0 (0)	0 (0)
Leukopenia	2 (2.7)	26 (35.1)	10 (13.5)
Lymphopenia	10 (13.5)	10 (13.5)	2 (2.7)
Neutropenia	2 (2.7)	12 (16.2)	30 (40.5)
Infection			
Febrile neutropenia	0 (0)	2 (2.7)	1 (1.4)
Urinary tract infection [with grade 3-4 ANC]	0 (0)	1 (1.4)	0 (0)
Neurology			
Peripheral sensory neuropathy	10 (13.5)	1 (1.4)	0 (0)
Constitutional symptoms			
Fatigue	42 (56.8)	1 (1.4)	0 (0)
Gastrointestinal			
Constipation	8 (10.8)	1 (1.4)	0 (0)
Diarrhea	14 (18.9)	2 (2.7)	0 (0)
Ileus	0 (0)	1 (1.4)	0 (0)
Nausea	7 (9.5)	0 (0)	0 (0)
Vomiting	4 (5.4)	1 (1.4)	0 (0)
Renal/genitourinary			
Urinary frequency	15 (20.3)	1 (1.4)	0 (0)
Urinary incontinence	15 (20.3)	0 (0)	1 (1.4)

Abbreviations: ANC, absolute neutrophil count; CTCAE, Common Terminology Criteria for Adverse Events (version 3.0).

TABLE 5. Selected Treatment-Related Late Adverse Events, n = 74

	No. of Events (%)		
CTCAE Category and Terms	Grade 2	Grade 3	Grade 4
Maximum	36 (48.6)	6 (8.1)	2 (2.7)
Blood/bone marrow			
Lymphopenia	0 (0)	1 (1.4)	0 (0)
Infection			
Sepsis [with normal or Grade 1-2 ANC]	0 (0)	1 (1.4)	0 (0)
Skin infection [with normal or Grade 1-2 ANC]	0 (0)	1 (1.4)	0 (0)
Urinary tract infection [with unknown ANC]	1 (1.4)	0 (0)	0 (0)
Pain			
Pain [not otherwise specified]	0 (0)	1 (1.4)	0 (0)
Gastrointestinal			
Proctitis	2 (2.7)	0 (0)	0 (0)
Renal/genitourinary			
Cystitis	2 (2.7)	1 (1.4)	0 (0)
Ureteric obstruction	0 (0)	2 (2.7)	0 (0)
Urinary frequency	6 (8.1)	0 (0)	0 (0)
Urinary incontinence	16 (21.6)	0 (0)	2 (2.7)

Abbreviations: ANC, absolute neutrophil count; CTCAE, Common Terminology Criteria for Adverse Events (version 3.0).

However, this concern is significantly mitigated by the comparatively higher risk factors among the men enrolled on NRG Oncology/RTOG 0621, including more patients with persistently detectable postoperative PSA. It is unlikely that changes in Gleason grading over time can account for the large discrepancy in the numbers of men with high-risk disease (Gleason ≥ 8) between studies. The current study also differed from prior phase 3 trials of ART in the use of an initial pelvic field and a prescribed dose of 6660 cGy compared with the 6000 to 6400 cGy doses used in previous phase 3 trials, including SWOG 8794, which was the comparator study for the current series. The results from a DART01/05 trial indicating benefit to extended ADT in addition to dose-escalated RT as primary treatment for high-risk patients suggests that the benefit observed in the current study is unlikely because pelvic RT was used along with slightly higher doses, as now commonly used.[15] The use of ADT may also provide a lead-time bias in defining treatment failure because of the time required for testosterone recovery. Ultimately, the contribution of docetaxel and ADT and whether extended duration of ADT would provide further benefit are questions that only a phase 3 trial can definitively answer.

The optimal approach to managing high-risk patients remains an important question to be answered in the postprostatectomy setting. The NRG Oncology/RTOG 0621 study has revealed a very-high-risk subset of patients postprostatectomy at near-term risk of disease progression even with combined local and systemic therapy. The results of the current study strongly support further investigations into integrating systemic therapies,

including both ADT and chemotherapy, with postoperative RT in this patient population.

Conclusions

The addition of docetaxel and ADT to ART for men at high risk of failure despite receiving both surgery and RT resulted in a significant improvement in 3-year FFP compared with historic controls who received RT alone. Although past randomized trials have proven the efficacy of ART in selected subsets of men after RP, the individual contribution of hormone therapy and docetaxel in this setting will require additional, appropriately designed, prospective randomized studies.

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CONFLICT OF INTEREST DISCLOSURES

Mark D. Hurwitz reports personal fees from Medivation and Astellas outside the submitted work. Oliver Sartor reports personal fees and grants from Sanofi outside the submitted work. Howard M. Sandler reports grants from Myriad and personal fees from AstraZeneca, Medivation, Janssen, Blue Earth Diagnostics, Ferring, Bayer, Eviti, and Varian outside the submitted work. The remaining authors made no disclosures.

AUTHOR CONTRIBUTIONS

Mark D. Hurwitz: Conception and design of the study; acquisition, analysis, and interpretation of data; writing–initial draft and final revisions; and approval of the final article. **Jonathan Harris**: Design of the study, analysis and interpretation of data, writing–initial draft and final revisions, and approval of the final article. **Oliver Sartor**: Conception and design of the study; acquisition, analysis, and interpretation of data; writing–initial draft and final revisions; and approval of the final article; and approval of the final article. **Ying Xiao**: Design of the study; acquisition, analysis, and interpretation of data; writing–initial draft and final revisions; and approval of the final article. **Bobby Shayegan**: Design of the study; acquisition, analysis, and interpretation of data; writing–initial draft and final revisions; and approval of the final article. **Paul W. Sperduto**: Acquisition of data, writing–final revisions, and approval of the final article. **Kasra R. Badiozamani**: Acquisition of data, writing–final revisions, and approval of the final article. **Colleen A. F. Lawton**: Design of the study, acquisition of data, writing–final revisions, and approval of the final article. **Eric M. Horwitz**: Design of the study, acquisition of data, writing–final revisions, and approval of the final article. **Jeff M. Michalski**: Design of the study, acquisition of data, writing–final revisions, and approval of the final article. **Kevin Roof**: Acquisition of data, writing–final revisions, and approval of the final article. **David C. Beyer**: Acquisition of data, writing–final revisions, and approval of the final article. **Qiang Zhang**: Design of the study; acquisition, analysis, and interpretation of data; writing–initial draft and final revisions; and approval of the final article. **Howard Sandler**: Conception and design of the study; acquisition, analysis, and interpretation of data; writing–initial draft and final revisions; and approval of the final article.

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Original Article

Expression of the DNA Repair Gene *MLH1* Correlates With Survival in Patients Who Have Resected Pancreatic Cancer and have Received Adjuvant Chemoradiation: NRG Oncology RTOG Study 9704

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BACKGROUND: The majority of patients with pancreatic cancer who undergo curative resection experience rapid disease recurrence. In previous small studies, high expression of the mismatch-repair protein mutL protein homolog 1 (MLH1) in pancreatic cancers was associated with better outcomes. The objective of this study was to validate the association between MLH1 expression and survival in patients who underwent resection of pancreatic cancer and received adjuvant chemoradiation. **METHODS:** Samples were obtained from the NRG Oncology Radiation Therapy Oncology Group 9704 prospective, randomized trial (clinicaltrials.gov identifier NCT00003216), which compared 2 adjuvant protocols in patients with pancreatic cancer who underwent resection. Tissue microarrays were prepared from formalin-fixed, paraffin-embedded, resected tumor tissues. MLH1 expression was quantified using fluorescence immunohistochemistry and automated quantitative analysis, and expression was dichotomized above and below the median value. **RESULTS:** Immunohistochemical staining was successfully performed on 117 patients for MLH1 (60 and 57 patients from the 2 arms). The characteristics of the participants who had tissue samples available were similar to those of the trial population as a whole. At the time of analysis, 84% of participants had died, with a median survival of 17 months. Elevated MLH1 expression levels in tumor nuclei were significantly correlated with longer disease-free and overall survival in each arm individually and in both arms combined. Two-year overall survival was 16% in patients who had low MLH1 expression levels and 53% in those who had high MLH1 expression levels ($P < .0001$ for both arms combined). This association remained true on a multivariate analysis that allowed for lymph node status (hazard ratio, 0.41; 95% confidence interval, 0.27-0.63; $P < .0001$). **CONCLUSIONS:** In the current sample, MLH1 expression was correlated with long-term survival. Further studies should assess whether MLH1 expression predicts which patients with localized pancreatic cancer may benefit most from aggressive, multimodality treatment. ***Cancer*** **2017;000:000-000.** © *2017 American Cancer Society.*

KEYWORDS: biomarkers, chemotherapy, adjuvant, clinical trial phase 3, mutL protein homolog 1 (MLH1), pancreatic neoplasms, radiotherapy, adjuvant, tumor.

INTRODUCTION

Over 48,000 individuals are diagnosed with pancreatic cancer each year in the United States, and overall 5-year survival is 7%.[1] At diagnosis, approximately 20% have resectable disease; however, even among these patients, the median survival is only 15 months because of the early development of regional and metastatic disease.[2] There is an unmet need for the upfront identification of the subset of patients who demonstrate prolonged survival and derive benefit from such an aggressive approach.

Adjuvant chemotherapy is the standard of care for patients with resected pancreatic cancer.[3] Additional adjuvant options include radiation therapy (RT) to the tumor bed and regional lymphatic drainage.[4] The NRG Oncology-Radiation Therapy Oncology Group (RTOG) 9704 study was a randomized, phase 3 clinical trial comparing 2 different adjuvant

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protocols in patients with grossly resected pancreatic adenocarcinoma.[5] All patients received concurrent 5-fluorouracil (5-FU) plus RT; in addition, the control arm received 5-FU before and after RT, whereas the experimental arm received gemcitabine. Five-year overall survival (OS) was 18% and 22% in the 5-FU and gemcitabine arms, respectively (not significant).[6] On multivariate analysis, patients in the gemcitabine arm who had tumors of the pancreatic head experienced a trend toward improved OS ($P = .08$).

The DNA-mismatch repair (MMR) pathway corrects base substitution and insertion-deletion errors.[7] MMR dysfunction leads to the cellular acquisition of both point mutations and the instability of long, repetitive DNA sequences (ie, microsatellite instability [MSI]). Inherited MMR dysfunction is associated with increased rates of carcinogenesis (hereditary nonpolyposis colon cancer or Lynch syndrome).[8] The MMR machinery has an additional function of sensing DNA lesions, triggering cell-cycle checkpoints and apoptosis.[9]

MutL protein homolog 1 (MLH1) is a pivotal member of the MMR pathway, and complete loss of MLH1 is the most common cause of MSI.[10] Germline mutations in *MLH1* are rare in pancreatic cancer, with an estimated frequency of <1%.[11] Likewise, whole-genome sequencing has demonstrated that structural somatic mutations in *MLH1* are rare (approximately 2%); however, single allelic loss is observed in approximately 9% of tumors.[12] Whole-exome sequencing of 15 pancreatic cancer-derived cell lines revealed that the expression of MLH1 protein was decreased in cells that had *MLH1* allelic loss.[13] Cells that were haplodeficient for *MLH1* had decreased MLH1 expression and an increased number of indel mutations; however, they nonetheless tested negative on a polymerase chain reaction-based MSI assay. Thus, it appears that even a relative decrease in MLH1 expression may impair DNA fidelity without inducing MSI.

The clinical significance of decreased MLH1 expression in the absence of MSI is unknown; 1 small, retrospective series indicated that elevated MLH1 expression was significantly associated with favorable differentiation, fewer lymph node metastases, and improved OS.[14] In another study, increased MLH1 was associated with high tumor differentiation, fewer lymph node metastases, and tumor location.[15]

In the current study, we hypothesized that resected pancreatic tumors with decreased MLH1 expression would demonstrate impaired MMR function and resistance to adjuvant chemoradiation, influencing OS.

MATERIALS AND METHODS

Inclusion criteria for NRG Oncology RTOG 9704 included patients with nonmetastatic, histologically confirmed pancreatic adenocarcinoma who had undergone gross total tumor resection. Patients with poor performance status, inadequate organ function, or previous cytotoxic treatments were excluded. Protocol therapy was required to begin 3 to 8 weeks after resection.

Specimen and Biomarker Analysis

Tissue microarrays (TMAs) with 0.6-mm cores were prepared from standard paraffin blocks of tissue that was removed during surgery (ie, before the delivery of systemic therapy). MLH1 was detected using a primary monoclonal antibody (clone EPR3894; Epitomics, Burlingame, CA) and was observed using the EnVision + system (K4011; DAKO, Carpenteria, CA). Pan-cytokeratin was detected with polyclonal antibody (BP5069; Acris, San Diego, CA) and was observed with Alexa-555–conjugated secondary antibody (A21435; Life Technologies, Burlington, ON, Canada).

Automated image acquisition was performed using the HistoRx PM-2000 imaging platform (HistoRx Inc, Branford, CT), and digital images were analyzed using the HistoRx AQUAnalysis program (version 2.3.4.1; HistoRx Inc), as previouslydescribed.[16,17] Briefly, high-resolution digital images were obtained for each TMA core using separate filters to define the nuclear (4′,6-diamidino-2-phenylindole dihydrochloride [DAPI]), tumor (indocarbocyanine [Cy3]), and MLH1 (indodicarbocyanine [Cy5]) compartments. An analysis algorithm was constructed to generate a tumor-specific mask by thresholding the pan-cytokeratin images, and the tumor nuclear compartment was created by isolating DAPI-positive tumor nuclei within that area. The nuclear automated quantitative analysis (AQUA) score (nAQUA) (Supporting Fig. 1; see online supporting information), representing MLH1 expression, was defined as the average Cy5 pixel intensity within the tumor nuclear area for each TMA core.

Unusable areas were removed before each image was processed using optimized threshold values. Images were validated according to the following: 1) > 10% of the tissue area was pan-cytokeratin positive, 2) > 50% of the image was usable (ie, there was no overlapping or out-of-focus tissue), and 3) the thresholding produced accurate masked areas. An example of the staining for MLH1 is presented in Supporting Figure 1 (see online supporting information). Of note, immunohistochemical staining

and scoring were performed on blinded, nonannotated specimens.

Statistical Methods

MLH1 expression data were forwarded to the RTOG central office, where the samples were matched with clinical outcomes and a survival analysis was performed. Failure for OS was defined as death from any cause and was measured from the date of randomization to the date of death or of last follow-up for censored patients. Failure for disease-free survival (DFS) was defined as local, regional, or distant relapse; the appearance of a second primary lesion; or death from any cause and was measured from the date of randomization to the date of first failure or last follow-up for censored patients. The following baseline characteristics were dichotomized: pathologic tumor (T)-classification (T1 and T2 vs T3 and T4) and American Joint Committee on Cancer stage (I and II vs III and IV). Race was categorized as white versus African American/other. Statistical comparisons to assess potential associations between baseline characteristics and MLH1 grouping were carried out using the chi-square test or the Fisher exact test. OS and DFS were estimated univariately with the Kaplan-Meier method,[18] and MLH1 groups were compared using the log-rank test.[19] The reported median survival and DFS are the times (in years) at which 50% of the patients had failed.

Antibody staining for MLH1 expression was analyzed as a continuous variable and as a categorical variable using the median level for all patients as a cutoff point (below the median [<median] vs at or above the median [≥median]). Univariate and multivariate Cox proportional-hazards models[20] were used to determine whether there were any associations between MLH1 expression and survival (OS and DFS). The first level in the MLH1 grouping (<median) was used as the reference level. A hazard ratio (HR) > 1.00 indicated an increased risk of failure for patients who had ≥median versus < median MLH1 expression. For the multivariate analysis, only the MLH1 grouping was forced into the models, and a stepwise selection procedure was used to choose other variables using $\alpha = .05$ as the entry and exit criteria for the model building. The following variables were assessed in the models along with MLH1 expression: treatment arm, age, sex, race, tumor location, lymph node status, greatest tumor dimension, and surgical margin status. All analyses were performed on all patients and then within each treatment arm.

To adjust for the multiple comparisons in this exploratory analysis, a 2-sided P value < .01 was considered statistically significant. P values ≥ .01 and <.05 were considered to indicate a trend toward statistical significance. All analyses were performed using SAS/STAT software (version 9.4; SAS Institute Inc, Cary, NC).

The analysis was performed on tissue collected in the setting of a prospective clinical trial sponsored by the National Institutes of Health. The trial was performed with the approval of each medical center's institutional review board, in accordance with an assurance filed with and approved by the US Department of Health and Human Services; in addition, each participant provided informed consent.

RESULTS

In total, 538 patients were enrolled on the trial, and tissue was available for 220 patients, of whom MLH1 expression was quantifiable in 131 patients. MLH1 expression could not be quantified for 74 patients because of the low quantity/quality of tumor in the core and, for 15 patients, because of variations in immunohistochemical staining for pan-cytokeratin and DAPI. Fourteen patients were excluded from this analysis because they did not meet eligibility requirements for NRG Oncology-RTOG 9704. Thus, there were 117 eligible and analyzable patients. Figure 1 breaks down the 117 eligible and analyzable patients by treatment arm, and Table 1 provides baseline characteristics. There were no statistically significant associations observed between pretreatment characteristics and MLH1 nuclear expression, nor were there significant differences in OS or DFS between patients who could and could not be analyzed (Supporting Table 1; see online supporting information). Supporting Table 2 (see online supporting information) provides a follow-up and outcomes summary for the 117 patients by treatment arm and for the entire study. The median follow-up for surviving patients was 7 years in each arm (range, 2-9 years). For all 117 patients, the median expression of MLH1 in tumor nuclei was 3636.1 (range, 408-6321).

Increased expression of MLH1 in tumor nuclei was associated with longer OS and DFS in both treatment arms (5-FU: OS, 9% vs 33% 4-year survival; $P < .005$; gemcitabine: OS, 8% vs 33% 4-year survival; $P < .005$). Because MLH1 expression was similarly predictive in both arms, and overall outcomes in the 2 arms were very similar, the arms were combined in subsequent analyses. The 4-year OS rate for patients who had MLH1 nuclear expression < median versus ≥ median was 9% (95% confidence interval [CI], 3%-18%) and 33% (95% CI, 22%-45%), respectively ($P < .0001$; log-rank test) (Table 2,

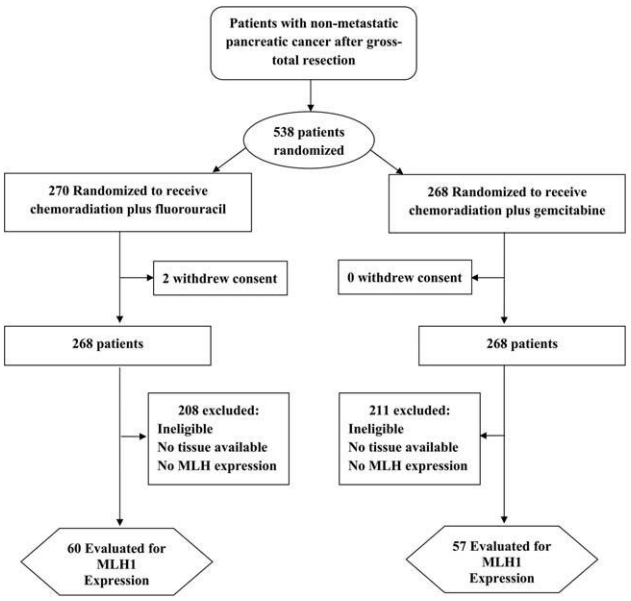

Figure 1. The flow of patients through the study is illustrated. MLH, mutL homolog; MLH1, mutL protein homolog 1.

Fig. 2). On univariate Cox analysis, patients who had MLH1 nuclear expression ≥ median had a 57% decrease in the risk of dying compared with those who had MLH1 nuclear expression < median (HR, 0.43; 95% CI, 0.28, 0.64; $P < .0001$). Similarly, the 4-year DFS rate for patients who had MLH1 nuclear expression < median versus ≥ median was 2% (95% CI, 0%-1%) and 18% (95% CI, 9%-29%), respectively ($P = .0002$; log-rank test) (Supporting Fig. 2; see online supporting information). Patients who had tumors with high MLH1 expression had a 51% decrease in the risk of failing than those who had tumors with low MLH1 nuclear expression (HR, 0.49; 95% CI-0.33, 0.72; $P = .0003$). When MLH1 expression in tumor nuclei was analyzed as a continuous variable, a 500-unit increase in MLH1 nuclear expression corresponded to an 11%/10% reduction in the risk of dying/failing (OS: HR, 0.89; 95% CI, 0.81-0.98; $P = .013$; DFS: HR, 0.90; 95% CI, 0.83-0.98; $P = .017$).

The multivariate Cox proportional-hazards models for OS are provided in Table 3. After adjusting for lymph node status, a 500-unit increase in MLH1 nuclear expression was associated with a 12% decrease in the risk of dying (HR, 0.88; 95% CI, 0.80-0.96; $P = .0045$). Likewise, after adjusting for lymph node status, patients who had MLH1 nuclear expression ≥ median were associated with a 59% reduction in the risk of dying compared with patients who had MLH1 nuclear expression < median (HR, 0.41; 95% CI, 0.27-0.63; $P < .0001$). In the multivariate Cox proportional-hazards models for DFS, only MLH1 nuclear expression had a statistically significant association with DFS; no other variables were added to the models (results not shown).

DISCUSSION

This study has demonstrated that higher MLH1 expression in tumor cell nuclei correlates with improved OS in patients with resected pancreatic cancer who receive adjuvant chemoradiation, with an HR of 0.41 on multivariate analysis. Furthermore, the Kaplan-Meier survival curves start to separate at year 1 and then stay apart (Fig. 2), suggesting that MLH1 expression predicts long-term outcomes. These findings are in keeping with the hypothesis that tumors with low MLH1 expression may have impaired MMR function and, consequently, demonstrate treatment resistance.

Function and Expression of MLH1

The *MLH1* gene is a pivotal member of the MMR pathway. *MLH1* presence/function may be assessed on the genetic, protein, or functional level. Structural mutations within the MLH1 gene are rare events in pancreatic cancer (<1% of sporadic cancers), although single allelic loss is more frequent.[12]

Multiple factors that impact MLH1 expression include copy number, allelic loss,[13] promoter hypermethylation,[15] histone acetylation,[21] and microRNA expression.[14] On the molecular level, the transcription factor

TABLE 1. Baseline Characteristics of the Patients, the Overall Study Population, and by Mut-L Protein Homolog 1 Nuclear Expression, Including Patients From Both Arms of the Study

	No. of Patients (%)			
		MLH1 Nuclear Expression		
Characteristic	Entire Population With MLH1 Evaluation, n = 117	<Median, n = 58	≥Median, n = 59	P[a]
Age: Median [range], y	63 [35-80]	63 [37-80]	63 [35-80]	
Sex				.31
Men	62 (53.0)	28 (48.3)	34 (57.6)	
Women	55 (47.0)	30 (51.7)	25 (42.4)	
Race				.21
White	105 (89.7)	50 (86.2)	55 (93.2)	
African-American/other	12 (10.3)	8 (13.8)	4 (6.8)	
Primary tumor location				.48
Head	98 (83.8)	50 (86.2)	48 (81.4)	
All others	19 (16.2)	8 (13.8)	11 (18.6)	
KPS				.65
60, 70, 80	42 (35.9)	22 (37.9)	20 (33.9)	
90, 100	75 (64.1)	36 (62.1)	39 (66.1)	
Tumor classification, surgical				.96
T1, T2	28 (23.9)	14 (24.1)	14 (23.7)	
T3, T4	89 (76.1)	44 (75.9)	45 (76.3)	
Lymph node classification, surgical				.51
N0	37 (31.6)	20 (34.5)	17 (28.8)	
N1	80 (68.4)	38 (65.5)	42 (71.2)	
AJCC stage, fifth edition				.64
I, II	36 (30.8)	19 (32.8)	17 (28.8)	
III, IV	81 (69.2)	39 (67.2)	42 (71.2)	
Greatest dimension of primary tumor, cm				.52
<3	47 (40.2)	25 (43.1)	22 (37.3)	
≥3	70 (59.8)	33 (56.9)	37 (62.7)	
Surgical margin status				.12
Complete resection/negative margins	47 (40.2)	21 (36.2)	26 (44.1)	
Complete resection/positive margins	40 (34.2)	25 (43.1)	15 (25.4)	
Complete resection/unknown margins	30 (25.6)	12 (20.7)	18 (30.5)	
Treatment				.23
RT + 5-FU	60 (51.3)	33 (56.9)	27 (45.8)	
RT + gemcitabine	57 (48.7)	25 (43.1)	32 (54.2)	

Abbreviations: 5-FU, 5-fluorouracil; AJCC, American Joint Committee on Cancer; KPS, Karnofsky performance status; RT, radiation therapy.
[a] *P* values were determined using either the chi-square test or the Fisher exact test.

GLI1 (human glioma-associated oncogene homolog 1), which is associated with the hedgehog signaling pathway, decreases MLH1 expression and consequent MMR activity.[22] In addition, it has been observed that external factors, such as hypoxia,[23] exposure to chemotherapy,[24] and epigenetic modifiers,[23,25] influence MLH1 expression levels.

Few investigators have examined the clinical significance of MLH1 expression in pancreatic cancer. In agreement with the current results, 2 small Chinese studies noted that increased MLH1 expression, as assessed by manual pathologist grading, was associated with good prognostic factors and possibly survival,[14,15] although another small study challenged those findings.[26] These studies were limited by their lack of clinical details and the diverse methods used to quantify MLH1 expression. Single nucleotide polymorphisms (SNPs) within MMR genes correlate with various outcomes in pancreatic cancer, including the response to chemoradiation and OS[27]; however, it is unclear how the presence of these SNPs relates to gene expression or MMR function. Conversely, Japanese investigators noted that cancers with a high frequency of MSI were associated with a better prognosis[28,29]; however the incidence of MSI in those studies was an order of magnitude greater than that noted in North America and Europe, raising questions regarding the generalizability of the findings.

MLH1, MSI, and Response to DNA-Damaging Agents

MSI is considered a functional demonstration of MMR dysfunction. MSI may be caused by germline, somatic, or epigenetic silencing of 1 of several MMR genes, including *MLH1*, *MSH2*, *MSH6*, and *PMS2*. The incidence of MSI in pancreatic cancer is much higher in Japan (approximately 15%[29] than in North America and Europe

TABLE 2. Overall and Disease-Free Survival by Nuclear Mut-L Protein Homolog 1 Expression, n = 117

Survival	MLH1 Level <Median	MLH1 Level ≥Median	P^a	HR (95% CI)[b]
OS (95% CI), %			< .0001	0.43 (0.28-0.64)
2 y	16 (8-26)	53 (39-64)		
4 y	9 (3-18)	33 (22-45)		
DFS (95% CI), %			.0002	0.49 (0.33-0.72)
2 y	10 (4-20)	37 (25-49)		
4 y	2 (0-8)	18 (9-29)		

Abbreviations: CI, confidence interval; DFS, disease-free survival; HR, hazard ratio; MLH1, mutL protein homolog 1; OS, overall survival.
[a] *P* values were calculated using the log-rank test.
[b] HRs < 1.00 indicate a decreased risk of failure for MLH1 expression at or above the median relative to MLH1 expression less than the median.

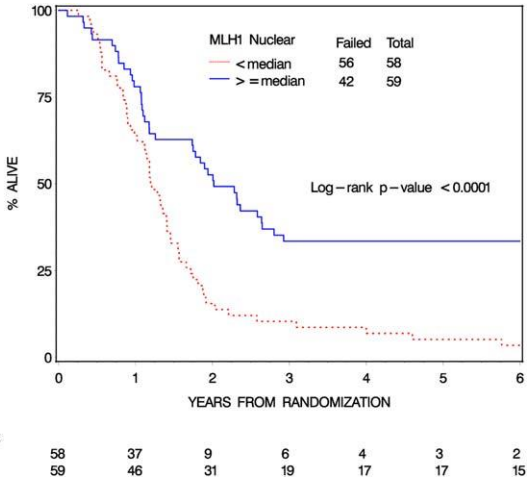

Figure 2. Overall survival is illustrated according to nuclear mutL protein homolog 1 (MLH1) expression for all patients (n = 117).

TABLE 3. Overall Survival by Nuclear Mut-L Protein Homolog 1 Expression: Multivariate Cox Proportional Hazards Model, n = 117

Variable	Adjusted HR (95% CI)	P^a
MLH1 nuclear expression		
Continuous: Unit increase = 500	0.88 (0.80-0.96)	.0045
Lymph node status		
Negative	1.00	
Positive	1.74 (1.12-2.71)	.013
MLH1 nuclear expression		
<Median	1.00	—
≥Median	0.41 (0.27-0.63)	< .0001
Lymph node status		
Negative	1.00	—
Positive	1.68 (1.09-2.61)	.019

Abbreviations: CI, confidence interval; HR, hazard ratio; MLH1, mutL protein homolog 1.
[a] *P* values were determined with chi-square tests using a Cox proportional-hazards model.

(approximately 1%[30]. However MSI is an imperfect measure of MMR function: heterozygous loss of *MLH1* is associated with decreased MLH1 expression and increased frequency of indel DNA mutations, but not with classic MSI.[13]

Tumors with dysfunctional DNA repair are generally considered sensitive to DNA-damaging agents.[31] Although the MMR pathway is concerned with DNA repair, paradoxically, MMR dysfunction in the preclinical setting has repeatedly been associated with primary resistance to cytotoxic therapies, including methylating agents, 6-thioguanine, cisplatin, carboplatin, temozolomide, and etoposide.[32,33] It is noteworthy that several studies have demonstrated that cells with low expression of MMR proteins may demonstrate therapeutic resistance even in the absence of MSI.[33,34] The role of MMR in determining primary sensitivity to radiation and to nucleoside analogues like 5-FU and gemcitabine[35,36] is more controversial.

An alternative mechanistic explanation for our findings relates to the role of MMR in maintaining genomic integrity. MMR-deficient cells exhibit genomic instability associated with increased rates of sporadic mutations, as demonstrated by increased rates of carcinogenesis but also more rapid development of secondary resistance to therapeutic agents, such as cisplatin, topotecan, gemcitabine and etoposide.[37] Furthermore, when exposed to mutagenic agents, MMR-deficient cells generate resistant variants more rapidly than MMR-intact cells.[38] Wang et al demonstrated a dose-response effect between MLH1 expression and the degree of genomic instability (as measured by somatic indels).[13] Hence, compared with MMR-proficient cells, cells with MMR dysfunction may more rapidly develop resistance during adjuvant chemoradiation, facilitating disease recurrence.

A strength of the current study is that it was based on a large, prospectively gathered, multicenter clinical trial, representing a homogenous tumor population that, at the time of tissue collection, was treatment-naive. Another strength is the use of HistoRx AQUA technology, which has been established as objective, reproducible, and suitable for clinical practice. Blinding of the pathologic samples helped avoid bias. The 2 treatment groups were well balanced (Table 1), and their characteristics were similar to those of the patients who did not have

tissue samples available (Supporting Table 1; see online supporting information).

A limitation of the study is that a genomic analysis of the samples was not performed. MSI was assumed to be very low based on previous studies[30,39]; however, the frequency of minor genetic changes (eg, indels) was not known. Furthermore, it is unknown which factors influence MLH1 protein expression (eg, promoter hypermethylation or allelic loss) within this population. Although we hypothesized that lower levels of MLH1 expression would be correlated with dysfunctional MMR, additional mechanistic studies are required. The current study was based on the use of archival specimens derived from a TMA that lacked normal tissue samples; consequently, we were unable to assess intratumoral heterogeneity of MLH1expression, and we could not compare tumor expression levels with those in normal (eg, pancreatic) tissues. We plan to perform such comparisons in future studies.

Although these current findings are in line with 2 smaller studies that have correlated MLH1 expression with outcomes in patients with pancreatic cancer,[14,15] ideally, the results would be validated in a similar, large data set from an additional prospective clinical trial. These findings raise several questions: Is MLH1 expression a predictive or prognostic factor? Does MLH1 expression correlate with prognosis in other stages of pancreatic cancer (eg, metastatic or postresection not in those who do not receive radiation)? Is the profound effect of MLH1 expression on OS demonstrated here the result of MMR dysfunction-induced primary or secondary resistance? Based on the proposed mechanism that low MLH1 expression is associated with the rapid development of resistance, we may hypothesize that patients who have tumors with high MLH1 expression may especially benefit from aggressive adjuvant regimens, such as the chemoradiation used in RTOG 9704. Conversely, those who have tumors with low MLH1 expression and have a poor prognosis may be best served by receiving chemotherapy alone. Hence MLH1 should join the list of potential biomarkers (eg, impaired homologous recombination, molecular subtypes based on genomic analysis) to be considered for use in a personalized approach to pancreatic cancer treatment.

In conclusion, the current results suggest that patients who have resected pancreatic tumors with above-average MLH1 expression have a good prognosis in the context of adjuvant chemoradiation. Once validated, MLH1 expression may prove to be a useful stratification factor for future trials of DNA-damaging agents in pancreatic cancer and also potentially may predict which patients can benefit from an aggressive, multimodality approach.

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CONFLICT OF INTEREST DISCLOSURES

Alexander C. Klimowicz is currently employed by Boehringer Ingelheim Pharmaceuticals, Inc. Jeffrey P. Simko reports grants from the National Cancer Institute during the conduct of the study; nondirected research funds from Genomic Health Inc. and Myriad Inc outside the submitted work; personal fees from 3D Biopsy Inc, GenomeDx Inc, Genomic Health Inc, and 3Scan outside the submitted work; and membership on the Scientific Advisory Boards and equity ownership in 3D Biopsy Inc and 3Scan. Anthony M. Magliocco reports grants from Ventana Medical Systems and BioTheranostics; personal fees from Illumina, Genoptixs, BioTheranostics; Janssen Diagnostics LLC, Bristol-Myers Squibb, Merck, and Johnson & Johnson; travel support from Illumina, Guardant Health, and Definiens International, all outside the submitted work; and travel support and related expenses associated with being the Co-chair of pathology for NRG Oncology. The remaining authors made no disclosures.

AUTHOR CONTRIBUTIONS

Yaacov R. Lawrence: Conceptualization and writing–original draft. **Jennifer Moughan**: formal analysis, investigation and resources, and writing–original draft. **Anthony M. Magliocco**: Methodology, resources, investigation, and writing–original draft. **Alexander C. Klimowicz**: Methodology, resources, investigation, and writing–review and editing. **William F. Regine**: Investigation, resources, and writing–review and editing. **Rex B. Mowat**: Writing–review and editing. **Thomas A. DiPetrillo**: Investigation, resources and writing–review and editing. **William Small, Jr**: Investigation, resources, and writing–review and editing. **Jeffrey P. Simko**: Methodology, resources, investigation, and writing–review and editing. **Talia Golan**: Investigation, resources, and writing–original draft. **Kathryn A. Winter**: Formal analysis, writing–original draft, supervision, project administration, and funding acquisition. **Chandan Guha**: Conceptualization and writing–review and editing. **Christopher H. Crane**: Conceptualization and writing–review and editing. **Adam P. Dicker**: Conceptualization, writing–original draft, supervision, project, administration and funding acquisition.

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Comparison of Online 6 Degree-of-Freedom Image Registration of Varian TrueBeam Cone-Beam CT and BrainLab ExacTrac X-Ray for Intracranial Radiosurgery

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Abstract

Purpose: The study was aimed to compare online 6 degree-of-freedom image registrations of TrueBeam cone-beam computed tomography and BrainLab ExacTrac X-ray imaging systems for intracranial radiosurgery. **Methods:** Phantom and patient studies were performed on a Varian TrueBeam STx linear accelerator (version 2.5), which is integrated with a BrainLab ExacTrac imaging system (version 6.1.1). The phantom study was based on a Rando head phantom and was designed to evaluate isocenter location dependence of the image registrations. Ten isocenters at various locations representing clinical treatment sites were selected in the phantom. Cone-beam computed tomography and ExacTrac X-ray images were taken when the phantom was located at each isocenter. The patient study included 34 patients. Cone-beam computed tomography and ExacTrac X-ray images were taken at each patient's treatment position. The 6 degree-of-freedom image registrations were performed on cone-beam computed tomography and ExacTrac, and residual errors calculated from cone-beam computed tomography and ExacTrac were compared. **Results:** In the phantom study, the average residual error differences (absolute values) between cone-beam computed tomography and ExacTrac image registrations were 0.17 $\pm$ 0.11 mm, 0.36 $\pm$ 0.20 mm, and 0.25 $\pm$ 0.11 mm in the vertical, longitudinal, and lateral directions, respectively. The average residual error differences in the rotation, roll, and pitch were 0.34° $\pm$ 0.08°, 0.13° $\pm$ 0.09°, and 0.12° $\pm$ 0.10°, respectively. In the patient study, the average residual error differences in the vertical, longitudinal, and lateral directions were 0.20 $\pm$ 0.16 mm, 0.30 $\pm$ 0.18 mm, 0.21 $\pm$ 0.18 mm, respectively. The average residual error differences in the rotation, roll, and pitch were 0.40° $\pm$ 0.16°, 0.17° $\pm$ 0.13°, and 0.20° $\pm$ 0.14°, respectively. Overall, the average residual error differences were <0.4 mm in the translational directions and <0.5° in the rotational directions. ExacTrac X-ray image registration is comparable to TrueBeam cone-beam computed tomography image registration in intracranial treatments.

Keywords

cone-beam computed tomography, TrueBeam, ExacTrac X-ray imaging, 6 degrees of freedom, image registration, intracranial, radiosurgery

Abbreviations

6DOF, 6 degrees of freedom; ABMP, automatic brain metastases planning; CBCT, cone-beam computed tomography; SRS, stereotactic radiosurgery; SRT, stereotactic radiotherapy

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Introduction

Image guidance is widely used in radiation therapy for patient setup corrections. In linear accelerator–based stereotactic radiotherapy (SRT) and stereotactic radiosurgery (SRS), usually cone-beam computed tomography (CBCT) or planar X-ray imaging, for example, ExacTrac X-ray imaging system (BrainLab, Feldkirchen, Germany), is used for image guidance.[1-12] Compared to planar imaging, CBCT provides better visualization of anatomy and soft tissue. ExacTrac X-ray imaging system that uses 2 orthogonal X-rays, with 2 X-ray sources located on the floor and 2 detectors mounted on the ceiling, is free of couch collision. Compared to CBCT, it has the advantage of providing image guidance for noncoplanar treatments and allowing faster setup. ExacTrac X-ray imaging, however, is a 2-dimensional planar X-ray imaging and uses less information for image registration, in comparison with CBCT, which is a 3-dimensional volumetric imaging. It is of interest to compare image registrations of ExacTrac X-ray imaging and CBCT. Most of the publications of ExacTrac X-ray imaging and CBCT were focused on evaluating setup accuracy under image guidance.[1-13] Ma *et al* had conducted a study on a hybrid system, Varian Novalis Tx treatment unit (Varian Medical Systems, California), to compare image registrations of ExacTrac X-ray and CBCT.[14] Because 6 degree-of-freedom (6DOF) online CBCT registration was unavailable at the time of study, Ma *et al* were unable to perform online comparison of 6DOF image registrations of CBCT with ExacTrac X-ray. Instead, they performed online 3DOF image registration comparison and offline 6DOF image registration comparison by use of Eclipse treatment planning system (Varian Medical Systems, CA, USA).

A newer hybrid system, TrueBeam STx (Varian Medical Systems, CA, USA), which incorporates current CBCT and ExacTrac X-ray imaging techniques, has been used in clinics. It would be interesting to compare image registrations, especially, online 6DOF image registrations, of the 2 current imaging systems.

In our institution, brain multiple metastases are treated on a TrueBeam STx, with single isocenter treatment plans using dynamic arcs, which are generated on a recently emerged treatment planning system, automatic brain metastases planning (ABMP; BrainLab). In our practice, to ensure patient setup accuracy, both CBCT and ExacTrac X-ray imaging are used in the metastasis radiosurgery. It is important to know whether image registrations agree between ExacTrac and CBCT.

This study aimed to compare 6DOF online image registration of current BrainLab ExacTrac X-ray imaging and CBCT of TrueBeam STx linear accelerator for intracranial radiosurgery. Phantom study and patient study based on brain multiple metastasis radiosurgery were performed.

Materials and Methods

Figure 1 shows the TrueBeam STx linear accelerator system (version 2.5) used in the study, which was equipped with a BrainLab ExacTrac system (version 6.1.1). The coordinate system used in the study is indicated in the figure.

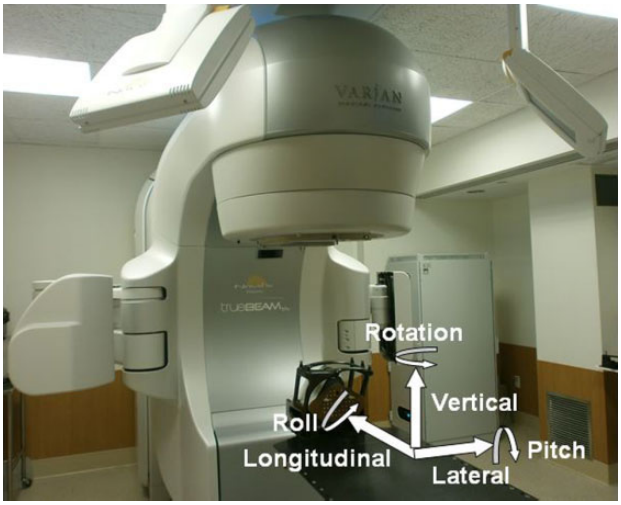

Figure 1. Picture of the TrueBeam STx linear accelerator, which is equipped with CBCT and BrainLab X-ray imaging systems. Rando head phantom was immobilized with a BrainLab mask on the treatment couch. The coordinate system used in the study is shown. CBCT indicates cone-beam computed tomography.

Phantom Study

A Rando head phantom (The Phantom Laboratory, NY, USA) was used (Figure 1). The phantom was scanned with a GE LightSpeed CT scanner (General Electric Company, Fairfield, Connecticut), with a slice thickness of 1.25 mm. Treatment plans were generated on the CT images. The phantom study was designed to evaluate isocenter location dependence of the image registrations. To include various situations that isocenters are located at various locations, treatment plans were generated with an iPlan treatment planning system (BrainLab, version 4.5) instead of ABMP treatment planning system because iPlan allows a user to select isocenter locations, whereas ABMP does not. In an ABMP system, an isocenter is automatically determined by the system. In planning with the iPlan, tumors (or targets) were assumed to be located at various locations and each isocenter was selected at the geometric center of the individual tumor: isocenters were located in the regions of brain stem, left cerebellum, right cerebellum, left temporal lobe, right temporal lobe, left frontal lobe, right frontal lobe, thalamus, and left and right cerebellopontine angles where acoustic neuroma occurs. Table 1 lists the isocenter locations. The CT images of the phantom were transferred from iPlan to ExacTrac and TrueBeam CBCT, which were used as reference images in the image registrations.

In the treatment unit, the phantom was immobilized with a BrainLab mask (BrainLab) on the treatment couch. After the phantom was moved to isocenter with the ExacTrac 6DOF couch (BrainLab), 2 orthogonal ExacTrac X-ray images were taken. The phantom was then shifted using the 6DOF couch according to the image registration results. After shift, ExacTrac X-ray images and TrueBeam CBCT images were taken, and X-ray image registrations and CBCT image registrations were performed and the results were compared. The study was conducted for each of the 10 isocenters.

Table 1. Isocenter Locations in the Head Phantom.

Isocenters	Isocenter Location
1	Brain stem
2	Left cerebellopontine angle
3	Right cerebellopontine angle
4	Left cerebellum
5	Right cerebellum
6	Left temporal lobe
7	Right temporal lobe
8	Left frontal lobe
9	Right frontal lobe
10	Thalamus

Patient Study

Thirty-four patients were studied. The patients were CT scanned with the GE LightSpeed CT scanner, with a slice thickness of 1.25 mm. Treatment plans for the multimetastasis patients were generated on an ABMP treatment planning system using single isocenter dynamic arcs. The isocenters were automatically determined by the treatment planning system, which were located at the geometric center of multiple tumors. The study procedure was the same as that of the phantom study: the patient was immobilized with a BrainLab mask on the treatment couch. After initial setup using the ExacTrac infrared photogrammetry guidance system, X-ray images were taken and the patient position was corrected with the X-ray imaging registrations. After correction, the patient was imaged with TrueBeam CBCT and ExacTrac X-ray imaging, respectively, and the image registrations of the 2 imaging modalities were compared.

In both phantom and patient studies, 6DOF online image registrations were performed and residual errors in the 3 translational directions (vertical, longitudinal, and lateral) and in the 3 rotational directions (rotation, pitch, and roll) were evaluated. In CBCT, the head protocol was used in the scan and bone window was used in the image registration. In ExacTrac imaging, 80 kV and 8 mAs were applied to the X-ray generator tubes and bony match was used in the image registration.

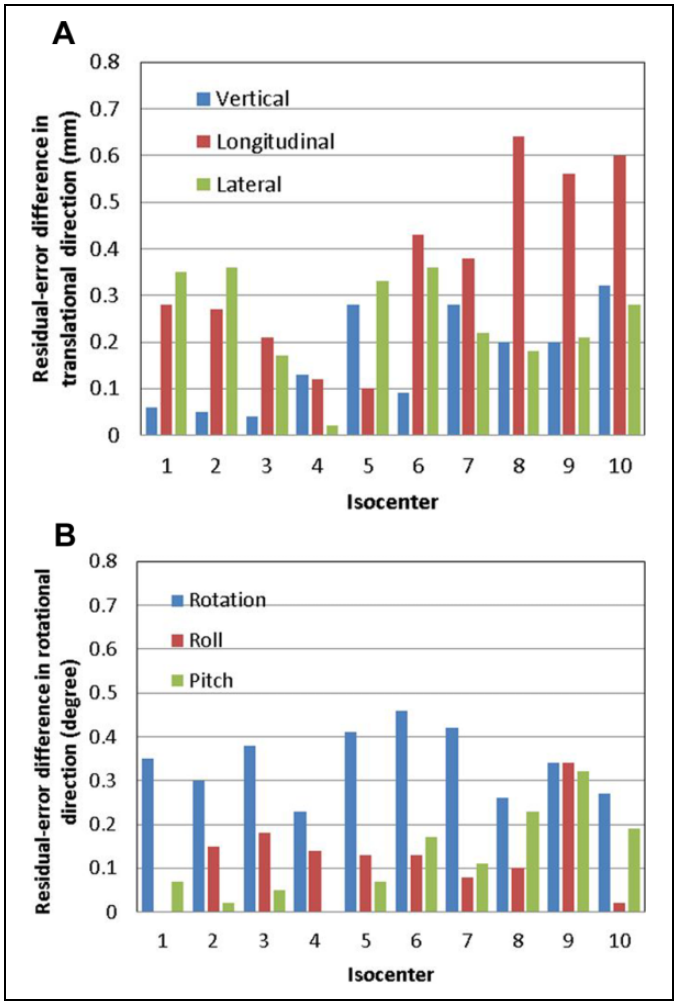

Figure 2. Results of the phantom study of the 10 isocenters: absolute differences in calculated residual errors between ExacTrac X-ray imaging registration and TrueBeam CBCT imaging registration (difference = ExacTrac − CBCT) in (A) translational (vertical, longitudinal, and lateral) and (B) rotational (rotation, roll, and pitch) directions, respectively. CBCT indicates cone-beam computed tomography.

Results

Figure 2 shows the results of the phantom study: absolute differences in the calculated couch residual errors between ExacTrac X-ray imaging registration and TrueBeam CBCT imaging registration (difference = ExacTrac − CBCT) of the 10 isocenter studies in translational (vertical, longitudinal, and lateral) and rotational (rotation, roll, and pitch) directions, respectively. Table 2 lists the summary of the absolute differences. The average residual error differences in the vertical, longitudinal, and lateral directions were 0.17 ± 0.11 mm, 0.36 ± 0.20 mm, and 0.25 ± 0.11 mm, respectively. The average residual error differences in the rotation, roll, and pitch were 0.34° ± 0.08°, 0.13° ± 0.09°, and 0.12° ± 0.10°, respectively. It was noticeable that the longitudinal residual error differences at isocenters 8, 9, and 10 were larger than those at the other isocenters.

Figure 3 shows the absolute differences in the calculated couch residual errors between ExacTrac X-ray imaging registration and TrueBeam CBCT imaging registration in the patient study. Table 3 lists the summary of the absolute differences. The average residual error differences in the vertical, longitudinal, and lateral directions were 0.20 ± 0.16 mm, 0.30 ± 0.18 mm, 0.21 ± 0.18 mm, respectively. The average residual error differences in the rotation, roll, and pitch were 0.40° ± 0.16°, 0.17° ± 0.13°, and 0.20° ± 0.14°, respectively.

The average residual error differences in the phantom study had similar magnitudes as those in the patient study. The phantom and patient studies showed that among the results in the 3 translational directions, larger differences occurred in the longitudinal direction, and among the results in the 3 rotational directions, larger differences occurred in the rotation direction.

Table 2. Results of the Phantom Study.[a]

Difference	Vertical (mm)	Longitudinal (mm)	Lateral (mm)	Rotation (°)	Roll (°)	Pitch (°)
Minimum	0.04	0.10	0.02	0.23	0.00	0.00
Maximum	0.32	0.64	0.36	0.46	0.34	0.32
Mean	0.17	0.36	0.25	0.34	0.13	0.12
Standard deviation	0.11	0.20	0.11	0.08	0.09	0.10

Abbreviation: CBCT, cone-beam computed tomography.
[a]Residual error differences (absolute values) in translational and rotational directions, between ExacTrac X-ray imaging registration and TrueBeam CBCT registration among 10 isocenter studies.

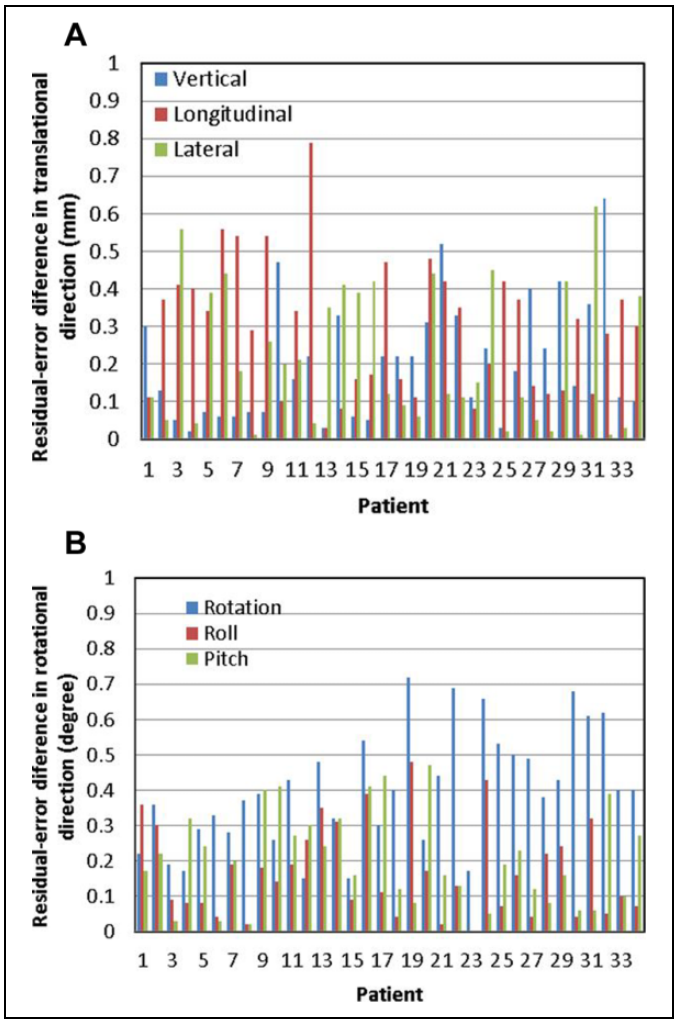

Figure 3. Results of the patient study: absolute differences in calculated residual errors between ExacTrac X-ray imaging registration and TrueBeam CBCT imaging registration (difference = ExacTrac − CBCT) in (A) translational (vertical, longitudinal, and lateral) and (B) rotational (rotation, roll, and pitch) directions, respectively. CBCT indicates cone-beam computed tomography.

Discussion

The phantom study, which was designed to evaluate the image registrations for various isocenter locations, demonstrated that longitudinal residual error differences showed isocenter location dependence: the longitudinal residual error differences at isocenters 8, 9, and 10 were larger than the residual error differences at other isocenters. The isocenters 8, 9, and 10 were located in the regions of the left frontal lobe, right frontal lobe, and thalamus, respectively, that is, in the frontal lobe or close to the frontal lobe. In the patient study, the longitudinal residual errors in patients 6, 7, 9, and 12 were larger than those in other patients. The isocenters of these 4 patients were all located in the frontal lobes. The results showed that in general, if isocenters were located in or close to the frontal lobes, that is, located more superior in the head, the longitudinal residual error differences could be larger. Residual error difference up to 0.79 mm was observed in the longitudinal direction in patient 12. It was noticed that when isocenters were located superficially, less patient anatomy information was captured in the images. The reduced anatomy information might result in larger uncertainties in image registrations and as a consequence larger differences between the 2 image registrations in those cases. Based on this assumption, we used "virtual isocenter" functionality in ExacTrac for superiorly located isocenters in patients 13–34, and the longitudinal difference was reduced, as can be seen from Figure 3A. This function allows the user to select a "setup" isocenter other than the treatment isocenter at the correction X-ray imaging step, so that more bony structures can be included in the X-ray imaging receptors' field of view and more accurate registration can be obtained. The difference between setup isocenter and treatment isocenter locations is applied in addition to the calculated shifts when couch correction is made so that patient is positioned at final treatment isocenter.

In general, the residual error differences in the longitudinal direction were larger than those in the lateral and vertical directions, which were observed in both the phantom and patient studies. The phenomenon could be related to CT slice thickness. The reference CT images in the study had a slice thickness of 1.25 mm and a pixel size of 0.9 mm. That is, the CT image resolution was 1.25 mm in the longitudinal direction and 0.9 mm in the vertical and lateral directions. The image registration thus had larger uncertainty in the longitudinal direction compared to the vertical and lateral directions.

Isocenter location dependence was not observed in rotational residual error differences. Further investigation on the cause of residual error differences between ExacTrac X-ray and CBCT is expected in the future study.

In Ma *et al*'s study on a Novalis Tx system,[14] average residual error differences were found to be <0.5 mm for phantom

Table 3. Results of the Patient Study.[a]

Difference	Vertical (mm)	Longitudinal (mm)	Lateral (mm)	Rotation (°)	Roll (°)	Pitch (°)
Minimum	0.02	0.03	0.01	0.15	0	0
Maximum	0.64	0.79	0.62	0.72	0.48	0.47
Mean	0.20	0.30	0.21	0.40	0.17	0.20
Standard deviation	0.16	0.18	0.18	0.16	0.13	0.14

Abbreviation: CBCT, cone-beam computed tomography.
[a]Residual error differences (absolute values) in translational and rotational directions, between ExacTrac X-ray imaging registration and TrueBeam CBCT registration among 34 patient studies.

and <1.5 mm for patients, which are larger than our results. In our study, similar differences were observed in phantom and patients, and the average differences in phantom and patients were <0.4 mm. Compared to Ma *et al*'s study, the smaller differences observed in our study could be attributed to the improvement in CBCT and ExacTrac X-ray techniques (a new generation of X-ray imaging receptor was used in ExacTrac version 6 and above, and the X-ray image quality has been improved visually), and the fact that the differences were similar in our phantom and patient studies might imply improvement in immobilization.

Conclusion

The phantom and patient studies showed that average residual error differences between ExacTrac X-ray and TrueBeam CBCT registrations were <0.4 mm in the translational directions and <0.5° in the rotational directions. Compared to the previous publication that was based on earlier versions of the imaging systems, better agreement between ExacTrac X-ray and CBCT image registrations was found in our study. The result indicates that image registrations of current ExacTrac X-ray and TrueBeam CBCT are comparable in intracranial treatments. The study provides confidence for using ExacTrac X-ray for image guidance of brain multiple metastasis radiosurgery.

Declaration of Conflicting Interests

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mHealth: Mobile Technologies to Virtually Bring the Patient Into an Oncology Practice

Nathan A. Pennell, MD, PhD, Adam P. Dicker, MD, PhD, Christine Tran, MS, Heather S. L. Jim, PhD, David L. Schwartz, MD, FACR, and Edward J. Stepanski, PhD

OVERVIEW

Accompanied by the change in the traditional medical landscape, advances in wireless technology have led to the development of telehealth or mobile health (mHealth), which offers an unparalleled opportunity for health care providers to continually deliver high-quality care. This revolutionary shift makes the patient the consumer of health care and empowers patients to be the driving force of management of their own health through mobile devices and wearable technology. This article presents an overview of technology as it pertains to clinical practice considerations. Telemedicine is changing the way clinical care is delivered without regard for proximity to the patient, whereas nonclinical telehealth applications affect distance education for consumers or clinicians, meetings, research, continuing medical education, and health care management. Technology has the potential to reduce administrative burdens and improve both efficiency and quality of care delivery in the clinic. Finally, the potential for telehealth approaches as cost-effective ways to improve adherence to treatment is explored. As telehealth advances, health care providers must understand the fundamental framework for applying telehealth strategies to incorporate into successful clinical practice.

Telehealth encompasses a broad variety of technologies with clinical applications to deliver virtual health care services. Because there is no universal definition, the terms telehealth, telemedicine, eHealth, digital health, or mobile health (mHealth) often are used interchangeably. However, the U.S. Department of Health & Human Services defines telehealth as the use of electronic information and telecommunication technologies to support and promote long-distance clinical health care, patient and professional health-related education, public health, and health administration.[1] Although this broad definition includes both clinical and nonclinical applications, the term telemedicine is confined to clinical services in remote locations and is defined as allowing health care professionals to remotely evaluate, diagnose, and treat patients using telecommunications technology.[2] These clinical applications encompass services that support remote electronic clinical consultation, such as diagnosis, patient communication, disease management, remote monitoring, and clinician support. Meanwhile, nonclinical applications can include distance education for consumers or clinicians, administrative meetings, research, continuing medical education, or health care management.[3] Telehealth innovations enable the delivery of care irrespective of geographic location, bringing about a fundamental shift in U.S. health care by bringing health care to the patient. Moreover, the need to improve quality, access, equity, and affordability of health care supports the utilization of telehealth across several medical disciplines. The potential shortage of oncology services is pointed out in ASCO's report, *The State of Cancer Care in America: 2016*[4]; evidence-based health research supports the use of telehealth in the oncology setting and its ability to increase access to patients with cancer.[5-7] For example, in a systematic review of experiences for patients with cancer who have participated in telehealth interventions, telehealth was noted to be an advantageous approach to reduce treatment burden and disruption to patient lives.[8] Health care professionals who use telehealth to export their clinical expertise enable patients to experience decreased travel time, immediate access to care, early detection of health issues, increased patient autonomy, reduced caregiver burden, and increased patient satisfaction with health care.

TELEHEALTH TECHNOLOGY

The most commonly used telehealth technology employs video conferencing to connect a patient to a health care provider.[9] Video conferencing integrates telecommunications

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technology to allow patients and providers to "electronically collaborate face to face, in real time, and share all types of information, including data, documents, sound, and picture."[9] This type of interactive video conferencing environment allows for patient-provider consultation, discussion, education, and patient monitoring. The use of telehealth technology offers great promise and currently is being used in health care in a number of ways. The clinical applications of telehealth range from drug formulary apps to reference programs, educational apps, medical tools (patient documentation apps, patient monitoring apps, nursing apps, imaging apps, and clinical apps), payer tools, decision support tools, and patient support tools.[10] The technological advances of telehealth include wearable sensors (pedometer/accelerometer, or sensors of sleep, weight, blood pressure, heart rate, temperature, environment exposure, blood levels, falls, and geolocation), data entry technologies (exercise testing, diet, mood/stress levels, symptoms, health-related quality of life, functional status, social support, medication, tobacco use, pillbox sensors, and alcohol use), ingestible/implantable sensors, biometric sticker sensors, and the ability of smartphones to be used as otoscopes, ophthalmoscopes, and microscopes. This technology can be used to remotely collect and send data for interpretation by a health care provider.[11] Telehealth interventions also have been expanded to social media sites such as Twitter to foster healthy lifestyles through the use of wearables for self-monitoring and social media to facilitate support for behavioral changes.[12] The U.S. Food and Drug Administration also has approved imaging apps, which allow radiologists to interpret images or ophthalmologists to use color vision plates for clinical evaluation when a more traditional outlook is not available. Digital images also are a type of store-and-forward technology, which permits the electronic transmission of medical files to be used at the convenience of providers to then make diagnoses, recommendations, and treatment plans. Whether the device exists as a standalone item, such as a smartphone, wearable, or hybrid (e.g., smartwatch), the information can be used by remotely monitoring health, medical behavior (e.g., compliance, movement, symptoms, vital signs, diet) or a person's location.[11]

Moreover, the demand to satisfy uniform quality of telehealth services has been met recently through the American Telemedicine Association. These practice guidelines and technical standards include practice guidelines for videoconferencing-based telemental health, evidence-based practices for telemental health, core standards for telemedicine operations, practice guidelines for teledermatology, telehealth practice recommendations for diabetic retinopathy, home telehealth clinical guidelines, and clinical guidelines for telepathology.[13] The standardization of telehealth guidelines may help reduce the cost of equipment and increase adoption by making telecommunication independent of hardware used.

HEALTH CARE CONSUMER AND PROVIDER PERSPECTIVES

The goal of telehealth is equal efficiency with in-person care, and physician-patient encounters via telehealth recently have reported consistent performances compared with standard face-to-face care.[14] In a randomized, controlled trial for patients with prostate cancer that used telehealth after radical prostatectomy to assess the efficiency, satisfaction, and cost of remote virtual visits versus traditional office visits, telehealth was equivalent in patient and provider satisfaction and time allocated to care.[15] In another study to evaluate the opinion on the use of telehealth in oncology, a majority of responders cited advantages of oncologic apps that included better documentation, improved and continual care for patients, enhancement of communication between provider and patient, improved patient compliance, possible use of data for scientific evaluation, and potential for patient-independent information.[16] Overall, 84.3% supported the use of oncologic apps complementary to traditional treatment.[16] Critics of telehealth cited issues related to legal uncertainty, data privacy, and insecure data transfer and storage.[16] Moreover, in a group of surveyed health care professionals, the most common medical app functions included drug-referencing tools, clinical decision-support tools, communication, electronic health record (EHR) access, and medical education materials.[17] The amount of scientific material that clinicians must memorize is large, so reference programs and educational apps help enable clinicians to choose clinically appropriate and cost-effective drugs, quickly search and access information/textbooks, perform calculations, log experiences, communicate, and input specific patient information for diagnosis.[10]

The adoption of telehealth technology relies on patient participation and the motivation of patients to become partners in their health care. With a consumer-based foundation, telehealth shifts medicine to more participatory care and an improved health care system composed of patient empowerment. This paradigm shift in responsibility allows patients to manage their health, health network, and heath information, and it leverages emerging technologies for a patient-centered ecosystem. In a survey to assess patient

KEY POINTS

- **Oncology health care is ripe for digital health disruption with the convergence of mobile technology, platforms, networks, and the introduction of machine learning.**
- **Digital platforms that include telemedicine, internet of things, and wearables are scalable.**
- **mHealth technology, including virtual scribes, real-time location systems, and peer-to-peer messaging apps, has the potential to improve the efficiency and quality of clinical cancer care.**
- **Treatment nonadherence in oncology occurs at a high rate and is associated with worse outcomes.**
- **Innovative, collaborative research will be pivotal to transform mHealth into a standard part of modern cancer care relevant to the 21st century health care marketplace.**

attitudes toward telehealth, patients had a positive overall attitude and cited an opportunity for improved self-efficacy and improved provider-driven medical management.[18] Moreover, respondents mentioned comfortableness in being remotely monitored with confidence in privacy protection. Findings about telehealth from the experience of a cancer survivor illustrated analytic themes that included how telehealth limited the disruption to people's lives, how telehealth could enable close and personalized relationships between cancer survivors and service providers, and how survivors felt that they had immediate access to professional advice, which acted as a safety net for possible issues in treatment.[8] Nevertheless, individual differences in digital literacy (i.e., the competency and technical skills to operate digital devices and conceptually understand their functionality) have the potential to widen health disparities and must be addressed as telehealth becomes more widespread.[19,20]

TELEHEALTH CHALLENGES FOR CLINICAL PRACTICE

Despite its potential, telehealth issues of privacy and security remain ongoing concerns for health care professionals and patients alike. For telehealth to complement traditional approaches in the delivery of health care, it must be delivered to both clinicians and patients with confidence that the privacy, confidentiality, and security of their data will be safeguarded within compliance of the Health Insurance Portability and Accountability Act (HIPAA). In an emerging field, the means for securing data includes understanding the roles of cybersecurity and developing a mobile technology policy to ensure that protected health information data are safe. Moreover, patient portals tethered to EHRs include advanced technology as part of their system to provide scheduling, billing, and clinical support, but there is no policy for telehealth applications to be fully integrated into health information systems in hospitals or provider organizations.[21] The variation in telehealth data and a patient's EHR displays the difficulty of management for telehealth and need for integration. In the progression of telehealth, health care institutions must establish a method for health care providers to access the EHR at the time of a telehealth encounter and establish a foundation of interoperable standards.

Multiple factors on both the individual and organizational levels are crucial to clinician acceptance and adoption of telehealth technology. Clinician acceptance of telehealth technology depends on a full integration into the workflow, added value to patient care, administrative convenience, and facilitated communication among multidisciplinary teams.[22] Although usefulness and ease of use were cited as important factors to the adoption of telehealth, the argument of whether it is an affordable option is still in discussion among health care professionals, who have referenced cost issues as limiting the adoption of telehealth tools.[23,24] Elements related to costs (e.g., the question of how to bill for telehealth) act as barriers to its adoption. Reimbursement regulations for medical services were planned before telehealth technology, which thus gives each state the option of whether to cover telehealth. These variations in reimbursement relate to service coverage, payment methodology, distance requirements, eligible patient populations, authorized technology, and patient consent.[25] Moreover, traditional concepts of liability and malpractice still apply to telehealth practitioners, who are more vulnerable to legal issues and who may face an additional fee for malpractice insurance.[26]

Despite technological advances, legal and regulatory challenges concerning provider licensure, credentialing, and privileging processes remain an obstacle for all allied health professionals. Mutual recognition models such as the multistate Nurse Licensure Compact or the Interstate Medical Licensure Compact are just beginning to develop to help facilitate telehealth interactions across state boundaries and into the mainstream. Additionally, the mandate for credentialing and privileging in multiple, separate health care facilities offer similar challenged for health care providers to deliver telemedicine.

FUTURE DIRECTIONS FOR TELEHEALTH

Telehealth is the future to improved access to specialized medicine, preventive care, monitoring of chronic conditions, and improved patient outcomes and satisfaction. It has the potential to reduce fragmentation of care and allow access to care despite the distance from major medical centers. In a 2014 study, telehealth industry growth and its potential to decrease care costs within the health care system were demonstrated; the study outlined $5 billion in savings on the basis of an estimated 100 million telemedicine visits across the world.[27] Demands for improved access to care in rural areas or to underserved populations that have been a challenge historically because of a shortage of clinicians or because of financial or geographic barriers also create the potential for a new telehealth ecosystem and novel health care model. Telehealth can overcome many of these barriers; it already has increased the quality of care and reduced costs by reducing the readmissions and emergency visits in rural communities.[28] Telehealth effectiveness also has been demonstrated through research in rural and remote areas, where telehealth satisfaction reached 94%.[29] These findings suggest a general acceptance of therapies delivered via telehealth, which advocates for its unparalleled opportunity. Growing interest in tele-oncology also shows the potential to increase access from a comprehensive cancer center to patients in rural areas by offering consultations, supervision of chemotherapy administration, oral medication adherence, or symptom management.[30]

THE POTENTIAL OF MHEALTH TECHNOLOGY TO IMPROVE EFFICIENCY AND CLINICAL CARE

mHealth technology has a tremendous potential to improve clinical care; its uses range from telemedicine patient encounters to the collection of patient-reported outcomes and improved adherence to therapies with apps and mobile devices. However, there is a lack of research about what patients will benefit the most, what the efficiency of telehealth

is at saving costs or time, and whether its contribution to a greater provider burden significantly hinders the advancement of telehealth. Apps for electronic patient-reported outcomes are available now from the Apple and Android app stores. One example is the Strength Through Insight app (Fig. 1).[31] The Strength Through Insight study aims to assess the feasibility of collecting survey data from patients through digital technologies and hand-held devices.[31] Practitioners may worry about the impact these technologies have on their day-to-day workflows and how demands for increasing technological innovation may interfere with their primary job of caring for patients. To what extent are these changes taking into account improvements in the efficiency of patient care? Efficiency has not been a major consideration in the design of much of health care technology, but there are a number of areas in which mHealth tools can be used not just to improve compliance or billing but also to benefit day-to-day practices.

REDUCING THE BURDEN OF DOCUMENTATION IN THE EHR WITH VIRTUAL SCRIBES

The primary components of health care technology that practitioners interact with on a day-to-day basis are the EHR, clinical decision support tools, and clinical physician order entry.[32] The primary intent behind adoption of these tools has been the reduction in preventable medical errors, as outlined in the Institute of Medicine report "To Err is Human; Building a Safer Health Care System,"[33] and their use is encouraged through the Health Information Technology for Economic and Clinical Health (HITECH) Act.[34] Although much time and money have been spent on their adoption, little time has been spent making these systems user friendly or efficient. Additional requirements specific to oncology, such as meeting criteria for participation in the Oncology Care Model,[35] only worsen the bureaucratic burden. There is a growing realization that documentation in the EHR places a substantial time burden on practitioners and is drastically reducing the amount of time physicians can spend face to face in direct patient interaction. This has consequences in reduced patient and physician satisfaction as well as in reduced clinical productivity and income.[36]

The need for documentation in an EHR is not going away anytime soon, so a workaround, the medical scribe, has allowed practitioners to spend more time with patients. Scribes, who usually are unlicensed professionals hired to retrieve from and transcribe data into the EHR, have been shown in various clinical settings to decrease time spent in documentation and to improve both the quality of documentation and patient satisfaction.[37] Scribes introduce challenges too, including space issues in the exam room, patient discomfort with a stranger in the room during sensitive conversations, and—of course—expense and availability of trained scribes issues. However, the capacity of telemedicine for instantaneous, real-time communication anywhere in the world now means that the scribe does not have to be in the same room or even in the same country as the practitioner.

Virtual scribes, connected by audio and video to the patient and practitioner through a wireless connection such as Google Glass,[38,39] could provide the same advantages as an in-person scribe but without the space issues or intrusiveness of an additional person in the room. There could also be cost advantages, such as reduced expense in hiring and training scribes in a HIPAA-compliant location that can link out to clinics around the world, even, potentially, in countries where highly educated individuals are available at reduced cost. Patients would still have to consent to this service, and there are important issues related to protection of protected health information and data security that must be addressed, but hospital systems around the country already are adopting this model with some success.[39] A pilot study to investigate the impact of virtual scribes on documentation time and on patient and physician satisfaction is planned (unpublished observation).

REAL-TIME LOCATION SYSTEMS

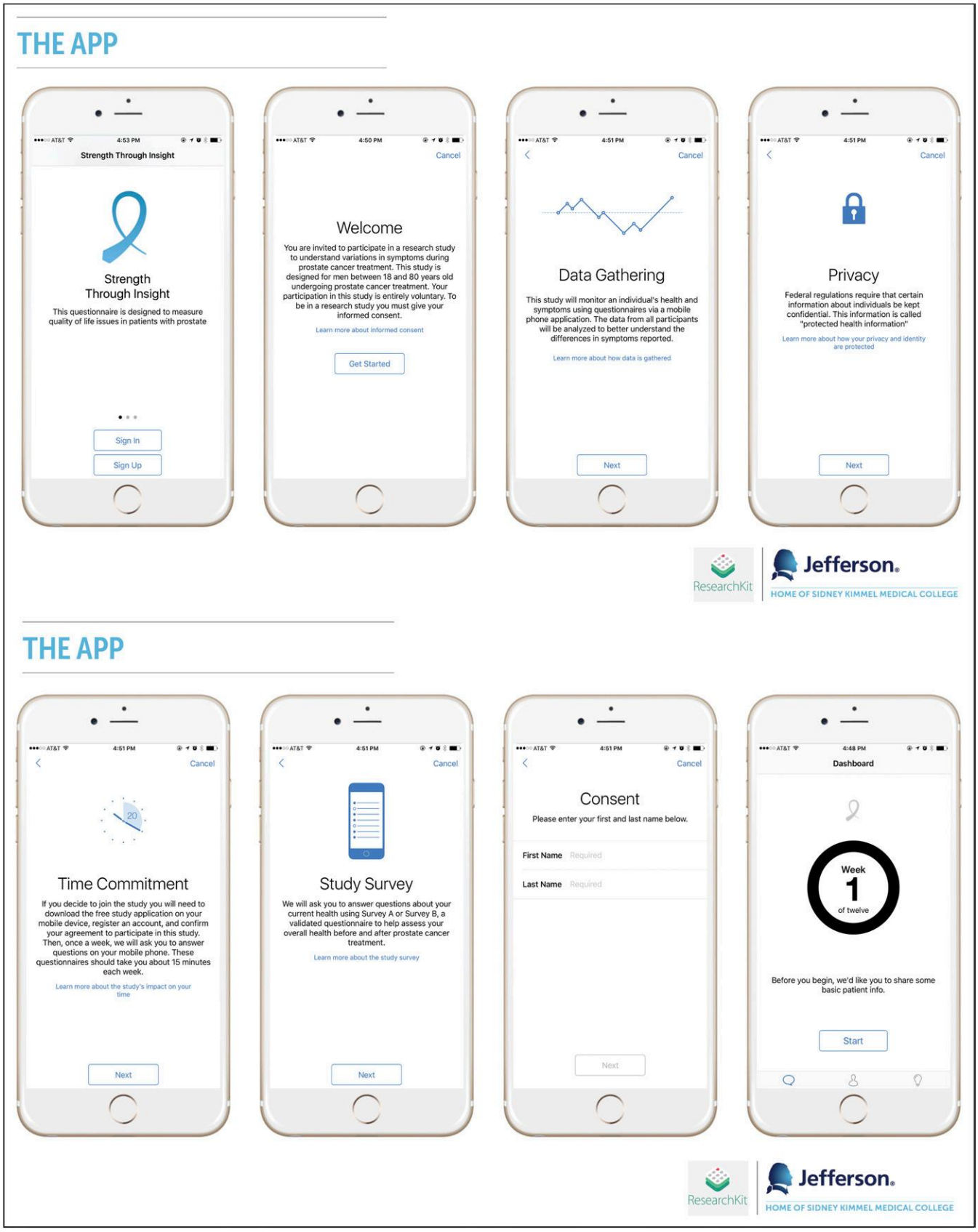
mHealth technology does not always have to connect to the outside world. Real-time location system (RTLS) technology is emerging as a useful tool to help improve patient flow within clinics and hospitals by allowing real-time localization of patients and practitioners.[40,41] In general, patients or practitioners wear a badge that allows them to be tracked in real time by a variety of possible means (e.g., wireless local area networking (Wi-Fi), radio-frequency identification (RFID), or global positioning system (GPS), and the patterns of movement and time spent in a particular location can be recorded. This can help with clinic flow and treatment chair management, and it can decrease room turnover time.[40,42] RTLS also can allow rapid localization (which can be a tedious process) of individual practitioners to sign orders, for example. Some RTLS systems allow hands-free verbal communication through the badges.[43]

Although little data exist specifically in the oncology field about the use of RTLS to improve efficiency, data in other health care settings supports RTLS as a viable option, and a number of prominent institutions, including a cancer center affiliation of one author (N. A. P.), has adopted this technology.[44,45] In an example of how RTLS can be used, a timer starts when patients are roomed; if no practitioner enters the room within 15 minutes, a nurse is alerted to find the practitioner and to reassure the patient. As a result of the positive effect on clinic flow as well as the possible impact of the Hawthorne effect (i.e., that watching someone tends to influence their behavior), studies have shown the patient wait times can be lowered and satisfaction scores can be improved by RTLS.[42]

USE OF MOBILE TECHNOLOGY FOR PHYSICIAN-TO-PHYSICIAN COMMUNICATION

Communication between health care practitioners is critically important to high-quality health care, especially in a field as multidisciplinary as oncology. This is true whether it occurs between nurse and physician, between resident and supervising physicians on a health care team, or between

FIGURE 1. The Strength Through Insight App



The app allows patients and their caregivers to build a partnership for communication throughout their cancer treatment. The survey uses standard questions that can be answered digitally via an app at a set schedule.

consulting services. Although there are a great many ways that practitioners communicate, ranging from alphanumeric pagers to email, the ubiquity of mobile phones and texting/instant-messaging apps opens up a whole new arena of opportunity for communication.

Mobile phones have been tested in medical settings and compared with pagers in terms of speed of communication and reduction in medical errors; results generally are in favor of mobile phones.[46] However, the speed and ease with which practitioners can be reached with mobile phones has drawbacks. Although replacement of pagers with mobile phones has been shown to improve efficiency and decrease the time needed to reach physicians, it may not improve nursing satisfaction with communication. In fact, in one study, use of mobile phones reduced face-to-face communication of nurses with doctors. Instead communication primarily occurred by texting or phone calls, which were considered less meaningful.[47] Studies also have suggested that the ease of mobile phone–based communication significantly increases the number of messages, which can be disruptive to workflow.[48] Finally, questions about the security of protected health information depend on the specific application used for texting; institutions that choose texting as a preferred communication method must provide a properly secure environment.[49]

Despite the risks of increased interruptions and security, mobile phones seem likely to replace pagers and other types of physician-to-physician communication, given their prominence in all other aspects of our lives. In middle-income countries, mobile phones may represent the best available means of communication. An example of the use of mobile technology in this manner is the widespread use of the web-based messaging app, WhatsApp (WhatsApp, Inc., Mountain View, CA), which has approximately one billion users worldwide and has been tested in a number of health care settings.[50]

WhatsApp has advantages compared with short message service texting in that closed groups can be created, and all communications can be viewed securely by all group members, which allows supervision of team communications. Notifications can be sent when a message has been read, and the app is fairly inexpensive, because practitioners can use their own phones and communicate with the wireless network of the institution. In some countries, such as Israel, WhatsApp is used by up to 96% of physicians, and up to 71% use it for communication of patient information and for consultations.[50] Several studies have shown WhatsApp to be a viable method of communicating patient information, asking questions of supervising physicians, and getting feedback among members of a health care team.[51,52]

Given the importance of teamwork and multidisciplinary care to oncology,[53] the availability of a secure and rapid method for team communication would have tremendous potential to aid patient care. However, there are concerns about the security of WhatsApp for communicating protected health information,[54] because the app security is end-to-end encrypted only if all members of a communication group have the most up-to-date version of the software. WhatsApp represents an intriguing illustration of the potential for web-based messaging for clinical communication. However, before adoption of a specific app for professional communication, the policy of the institution about the use of such technology must be clear.

Many oncologists and other practitioners view health information technology as a burden that decreases their face-to-face time with patients and contributes to burnout, but it is important to point out that technology also has the potential to improve efficiency and reduce time spent on low-value tasks. Although this is by no means a comprehensive list, the examples of virtual scribes to reduce time spent typing on the EHR, RTLS to reduce time spent moving patients or searching for providers, and use of mobile apps for better team communication should illustrate how technology may reduce burdens in caring for patients with cancer. As these technologies advance, however, it will be critically important to study their effects on patient care and practitioner well-being and to make sure that the rapid pace of technological development does not conflict with laws in place to protect patient confidentiality.

MHEALTH APPROACHES TO IMPROVING TREATMENT ADHERENCE

Decreased adherence to treatment is well documented for many chronic diseases. Adherence rates vary across diseases and patient factors, with an overall nonadherence rate of 24.8%.[55] This is an important topic, given that decreased treatment efficacy is a consequence of nonadherence.[56] The empiric data specific to adherence in oncology is more limited. Innovative use of mobile technology is well suited to support strategies to improve adherence in oncology, although study of these approaches is still limited. Given that use of telehealth approaches may provide a cost-effective way to improve outcomes for patients with cancer, validated approaches to use of this technology are highly desirable.

Although there are decades of experience in measuring and improving adherence in many chronic diseases, this topic has not received the same attention in oncology. Given the historical dominance of infused therapies in oncology, the concept of adherence as understood in other therapeutic areas was not relevant—antineoplastic treatment was delivered in direct view of the health care team. Empiric work conducted to understand adherence to cancer treatment is more limited, and strategies to optimize patient adherence have not been incorporated into usual care. A preponderance of the empiric work on treatment adherence in oncology has focused on imatinib for chronic myeloid leukemia, or on hormonal therapy for breast cancer (e.g., tamoxifen, aromatase inhibitors), because these were among the first widely used oral medications to require long-term administration in oncology.[57] Adherence rates in these indications are similar to those documented in other therapeutic areas; adherence to oral chemotherapy has ranged in empiric studies from 50% to 89%, depending on the definition of adherence and the study methodology.[57-59]

An important methodologic consideration in adherence research is the measure of adherence used. Measures can be described as direct measures (e.g., blood levels, provider observation) or indirect measures that are further subdivided into objective (e.g., prescription fills) or subjective (e.g., patient self-report) measures. Comparison of objective and subjective measures shows that patients systematically over-report adherence behavior.[60]

Treatment adherence is a critical issue for oncology, because studies consistently have shown that nonadherence leads to worse outcomes, including decreased survival.[61] Data from studies of infused therapies are instructive to define the risk of missed doses. A study of relative dose intensity of adjuvant chemotherapy delivered to patients with breast cancer found that the cohort of patients who received a relative dose intensity of less than 65% achieved an overall survival equivalent to a control group who received no adjuvant chemotherapy.[62] Increased mortality underscores another difference between the consequences of poor adherence in oncology and those in other diseases, in which the risk is limited to increased morbidity.

Nonadherence also leads to increased health care utilization and increased cost.[63] Predictors of nonadherence include patient factors (e.g., age, gender, amount of social support), treatment factors (e.g., frequency and severity of adverse effects), and health care team factors (e.g., education from physician about disease linked to treatment information).[58] Cost of treatment also has been linked to decreased adherence rates.[64,65] Given the emerging focus on improving outcomes while containing health care costs, the need to implement cost-effective strategies to improve treatment adherence is paramount. In addition, the ability to connect to patients outside clinical settings is a compelling approach, given the importance of patient engagement and symptom management in promoting adherence for patients with cancer. For both of these reasons, research into mHealth approaches to manage treatment adherence is desirable.

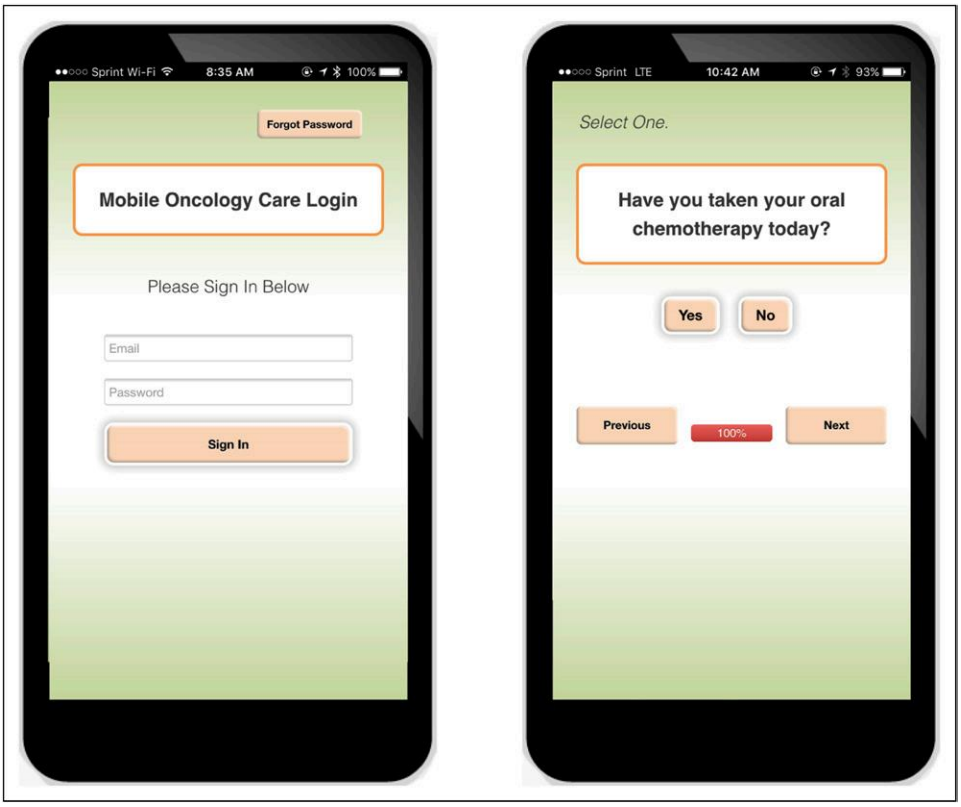
Given that smartphones are becoming ubiquitous, interventions to improve medication adherence through smartphone applications are broadly available.[66] Greater than 90% of American adults owned a cell phone in 2015, an increase from 65% in 2005.[67] There is a growing body of evidence that even simple interventions, such as text message reminders, improve adherence in a variety of chronic diseases.[68] Greater than 80% of cell phone users report sending or receiving text messages.[69] Essentially all (99%) texts are opened, and 90% are read within 3 minutes.[70] Short message service–and multimedia message service–based texting programs and smartphone applications are being introduced into the health care setting.[71-73] Prospective research remains limited, but early studies indicate that digital mHealth interventions can improve patient engagement and adherence to treatment.[69,74] Real-time mobile links between patients and providers can relieve logistic burdens of facility-based care, improve symptom tracking, enhance patient compliance, and shift symptom control to the at-home setting.[75] However, it is also true that the features present in basic smartphone apps vary enormously; therefore, not all apps can be expected to have the same usability or outcomes.[76] An evaluation of the features of 272 mobile phone apps purported to promote medication adherence, and readily available in an app store, found that only six of these apps had even half of the desirable features.[76] For example, flexible scheduling was the most common feature found across the 272 apps but was still available in only 56.3% of the apps. Password protection, as desired to optimize data privacy, was available for only 13.2% of these apps. Standard approaches to evaluate the quality of apps as required to meet their stated goals are needed to facilitate decision making by patients and providers.

In contrast to standard treatments for many chronic diseases, treatments in oncology are often associated with risks for toxicity. This cause of nonadherence may require a different approach than those effective in other therapeutic indications. That is, a text message reminder may not increase treatment adherence in a patient with severe diarrhea who is electing not to take his oral chemotherapy in response to treatment-related symptoms. Instead, approaches that include symptom monitoring of emerging toxicity that prompt the health care team to conduct proactive management would be expected to provide value to improve adherence in oncology. Basch et al[77] used an electronic system to routinely collect patient reported outcomes on common symptoms as part of usual care. Patients in this experimental condition continued to receive therapy for an average of 2 months longer, and they experienced increased 1-year survival, compared with a control group treated with usual care. These data provide evidence that symptom assessment and management may help improve outcomes in the context of oncology care.

A recent pilot study combined symptom monitoring and adherence assessment in patients with early-stage breast cancer who initiated treatment with aromatase inhibitors (Fig. 2).[78] Patients were stratified to receive text and/or email alerts reminding them to complete surveys or to a group that logged onto a website to complete surveys on an ad lib schedule. The group receiving text/email alerts completed 74% of surveys compared with 38% in the ad lib group. Post-study interviews found a high level of acceptance for the mobile surveys; patients stated that they felt that weekly surveys better captured their symptoms compared with waiting for their in-clinic appointment. Additionally, the alert group had nominally better quality of life than the ad lib group.

Beyond systemic therapy, patient-facing technology also may improve broader patient acceptance of their complex care journey, including locoregional treatment. Adherence to immediate postoperative care is ripe for mHealth engagement. Surgical recovery is a traumatic part of the overall cancer care continuum and is punctuated by discomfort, disability, and anxiety. For example, the emotional burden of cancer surgery in the head and neck region is heightened by disfigurement and debilitation. Surgeons and allied

FIGURE 2. Screen Shots From the Patient Care Monitor (Vector Oncology, Memphis, TN) Used for Mobile Health Adherence Monitoring



providers field drop-in visits to manage minor problems, but these visits distract from their urgent duties. Real-time or asynchronous mobile communication could empower appropriate patient self-care, preempt needless anxiety, and decompress clinic schedules. A pilot study that involved a surgical specialty team was conducted at an academic referral center and used a commercial automated text-based intervention to address the immediate postoperative care engagement needs of patients with head and neck cancer.[79] Thirty-two patients were approached, and 23 patients (72%) enrolled. All enrolled patients texted their providers, although frequency (median, seven texts; range, two to 44 texts) varied. Socially isolated patients and those who faced surgical complications used the platform more frequently. Patient satisfaction with the platform was high (mean,3.8 on a four-point Likert scale).

Radiation treatment is complex, lengthy (often 30 to 35 daily treatments during 6 to 7 weeks), costly, and toxic. It has been shown that gaps in treatment yield poorer outcomes for patients as a result of accelerated tumor regrowth during breaks in treatment. Compliance is crucial to ensure the best chance for local control and cure; unfortunately, adherence to radiation is a challenge. A review of 564 patients with head and neck cancer who received radiotherapy at a tertiary academic center was conducted to quantify the extent of this problem in a modern patient population covered by a spectrum of private insurance and public indigent care.[80] Three-hundred sixteen patients (56% of all enrolled) suffered a treatment break; 114 missed a single session, 202 missed multiple treatments. Seventy percent of uninsured patients had treatment delays compared with 47% of privately insured patients ($p \leq .0001$). Uninsured patients most often missed treatment because of nonmedical/logistic reasons. Delay was predictive for local recurrence ($p = .0002$) and overall survival ($p < .0001$). Among noncompliant patients, there was a higher likelihood for local recurrence in indigent patients. Our results highlight cancer control needs specific to disadvantaged communities at risk for poor radiotherapy adherence. A complex mix of social and human elements—including patient trust in providers, effectiveness of toxicity management, and quality of patient support—create a constellation of determinate factors. Emerging research has shown that mHealth informatics platforms can positively affect health care delivery in indigent cancer populations.[74,75] Interestingly, a pilot study published by Percac-Lima et al[81] found that telephone navigation directed to at-risk patients significantly improved cancer clinic visit adherence.

In summary, early patient-centered studies leveraging mHealth applications to engage patients with cancer about their treatments confirm an exciting beginning. However, these are just the first steps in a longer journey, on which all hype will wear thin quickly. Careful work is needed to refine personalized telehealth tools/utility measures, propel

stakeholder enthusiasm, and secure sustainable reimbursement models. Momentum toward mobile consumer self-fulfillment in our modern economy is undeniable. Our patients soon will demand dependable, useful, and thoughtfully designed mobile tools to optimize the acute, recuperative, and long-term survivorship phases of their cancer care. Inclusive multidisciplinary teams will be necessary to keep the cancer care experience relevant to the 21st-century patient, and the changes will require the buy-in and expertise of clinicians, social scientists, computer/data scientists, product designers, health systems experts, and health care policy makers among others. Additional work must focus on best practices to improve outcomes and balance patient and provider burden. Comparing approaches will be challenging because of the variability in features of apps and tools grouped under the mHealth label. Attention to scientific methodology will be especially important to ensure that potentially cosmetic improvements in patient satisfaction and adherence that we engender with technology actually lead to meaningful downstream clinical outcome improvements.

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BRIEF REPORT

Decreased Survival After Combining Thoracic Irradiation and an Anti-PD-1 Antibody Correlated With Increased T-cell Infiltration Into Cardiac and Lung Tissues

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Introduction

Lung cancer is the leading cause of cancer-related mortality in the United States, with the American Cancer Society estimating that ~155,870 Americans will die of the disease in 2017 (1). Of these lung cancer cases, 85% will be non-small cell lung cancer (NSCLC) (2, 3), which has a 49% 5-year survival overall rate. This proportion decreases to 1% for metastatic (stage IV) disease (1). Traditional treatments have centered around chemotherapy and radiation, providing both systemic and local treatment for patients with inoperable locally advanced lung cancer.

Although it can be an extremely effective therapy, thoracic radiation can have both acute and long-term detrimental effects to the highly radiation-sensitive lung tissue, in the form of pneumonitis and fibrosis, respectively, which can greatly affect patients' quality of life after treatment. Up to 15% of patients will develop pneumonitis within 2 to 3 months after radiation (4, 5). Evidence for an immunologic component in radiation pneumonitis is strong. Several groups have found that patients meeting radiologic (evidence of pulmonary infiltrates on chest radiographs) and clinical criteria respond positively to steroid treatment, with disease relapse occurring with treatment discontinuation (6). T cells constitute an important part of the immune cells infiltrating the lung tissue (4, 7-10), and patients have elevated CD4/CD8 ratios in bronchoalveolar lavage fluid (4, 6, 9, 10). Importantly, this increase has also been seen in animal models of radiation pneumonitis (11-13). However, it is still controversial whether cells from the innate and adaptive immune system directly contribute to radiation-induced tissue damage or only modulate disease progression. Evidence from preclinical and clinical investigations has shown that T cells constitute an important part of the immune cells infiltrating the lung tissue on irradiation of the thoracic region (4, 7-10).

In addition to pulmonary damage, cardiovascular effects such as pericardial effusion and carditis can occur acutely after thoracic radiation (14-24). Although cancer survivorship has been improving during the past several decades, this cohort must contend with a new source of potential health complications, including cardiovascular disease, which is now the second leading cause of death in this group (8). In particular, cardiac fibrosis and remodeling can cause extensive pathologic features that can severely limit cardiac function (25, 26). Multiple types of cancer can be treated with thoracic radiation, and in many of these

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cohorts, increased postradiation cardiovascular disease has been studied, including breast cancer (27-32) and Hodgkin lymphoma (33, 34). As serious as these complications are, their incidence has been low in patients treated with radiation alone (35, 36).

The relatively recent addition of immunotherapeutic treatment has proved immensely beneficial for cancer patients, including some with lung cancer. One target of immunotherapy is programmed cell death protein 1 (PD-1), a member of the same family as CTLA-4 (cytotoxic T-lymphocyte-associated protein 4), which functions to regulate T-cell activity by inhibiting activated T cells by engaging its ligand, PD-L1. PD-L1 expression is upregulated on tumor cells, including breast (37, 38), pancreatic (39), colorectal (38, 40), ovarian (38, 41), brain (42), and lung (38, 43-45) cancer. Isolation of tumor-infiltrating lymphocytes has shown that these cells express increased levels of PD-1 (46), indicating that they are active, yet susceptible to the protective PD-L1 upregulation seen almost ubiquitously across tumor types. Clinical trials have shown the efficacy of both anti-PD-1 and anti-PD-L1 blocking antibodies in enhancing the antitumor activity of chemotherapy and radiation therapy, and several drugs have been approved by the Food and Drug Administration for lung cancer treatment, including atezolizumab (TECENTRIQ; Genentech Oncology), erlotinib (Tarceva; Astellas Pharma), and nivolumab (Opdivo; Bristol-Myers Squibb). Pembrolizumab (Keytruda; Merck) has been approved as first-line treatment of stage IV NSCLC with a high level of PD-L1. PD-1 inhibitors have been combined with thoracic radiation therapy to treat stage III NSCLC, with concurrent initiation of both therapies in some studies.

Although the efficacy of anti-PD-1 treatment is being heavily investigated, and the deleterious effects of radiation on thoracic organs has been well-established, the effect of combining these therapies on nonmalignant lung tissue has not yet been investigated. In the present study, we provide evidence that the combination of anti-PD-1 antibody and thoracic irradiation results in T-cell infiltration into lung and heart tissue that increases mortality in an animal model used ubiquitously in the study of cancer.

Methods and Materials

Animals

C57Bl/6 mice were bred in a pathogen-free animal facility. The institutional animal care and use committee approved all protocols, which complied with the Guide for the Care and Use of Laboratory Animals. Commercially prepared food and water were provided without restriction.

Survival analysis

We pretreated 6- to 8-week-old C57Bl/6 mice with 200 μg of either control IgG or anti-PD-1 antibody in 100 μL of phosphate-buffered saline (PBS) 4 days before irradiation, 2 days before irradiation, and just before irradiation. Full thoracic x-ray irradiation was applied, with the head, neck, abdomen, and lower body shielded using a custom-designed lead cylinder. Five mice were irradiated in parallel. One irradiation provided 20 Gy at 170 cGy/min through a 0.25-mm copper 1-mm aluminum filter. The control mice were exposed to 0 Gy. After radiation, the mice were returned to a quarantine facility and monitored daily with weighing and behavior observation. They received booster injections of 100 μg of antibody at 3, 7, 10, 14, and 17 days after irradiation to maintain the circulation levels. The mice were followed up until death or weight loss of >20%, at which point they were killed using carbon dioxide. Death was confirmed by cervical dislocation, in accordance with the institutional animal care and use committee–approved protocols. Mice surviving until 21 days after irradiation were killed using carbon dioxide, and death was confirmed by cervical dislocation.

Lung tissue analysis

The lung tissue was collected from the mice and ground through a 70-μm filter. The resulting suspension was rinsed with Dulbecco's modified Eagle medium with 10% fetal bovine serum and placed on ice until staining and flow cytometric analysis.

Cardiac tissue analysis

Cardiac tissue was collected from the mice, cut into 2- to 3-mm slices, and ground through a 70-μm filter. The red blood cells were lysed. The resulting suspension was rinsed with Dulbecco's modified Eagle medium with 10% fetal bovine serum and placed on ice until staining and flow cytometric analysis.

Flow cytometry

All samples were pretreated with CD16/CD32 Fc receptor blocker before staining. The cells were labeled with anti-mouse CD3. Staining was performed in accordance with the manufacturer's protocols. Data were collected using a BD LSRII flow cytometer and analyzed using FlowJo software.

Histologic analysis and quantification

At death, the lungs of each mouse were collected for histologic analysis, as previously described (47). Also, the thorax and neck were dissected to expose the trachea and thoracic organs. The trachea was cannulated using a 22-gauge needle attached to rubber tubing filled with PBS, and the lungs were allowed to fill by gravity. The lungs were then removed and placed in formalin. After removal of the lungs, the cardiac vasculature was flushed with PBS,

and the heart was removed and placed in formalin. Whole organs were embedded in paraffin, and 5-μm-thick slices were mounted on slides. The slides were stained with anti-CD3 antibody, appropriate for paraffin-preserved samples, in accordance with the manufacturer's protocols. The slides were photographed at ×10 (heart) or ×20 (lung) magnification, and the number of positively staining cells was calculated by blinded analysis.

Statistical analysis

Kaplan-Meier analysis was used to determine the significant differences in survival. Analysis of variance with pairwise comparison was performed with Prism, version 5.0, software to accommodate multiple groups. Statistical significance was set at the level of $P<.05$.

Results

Combining thoracic radiation and T-cell stimulation decreased survival

We first examined whether the combination of thoracic radiation and anti-PD-1 antibody would decrease survival compared with irradiation and a control IgG antibody or treatment with anti-PD-1 antibody alone. The mice were pretreated with control or anti-PD-1 antibody and irradiated as described in the previous section. The first death occurred on day 4 in the IgG plus radiation group. The first deaths in the anti-PD-1 plus radiation group occurred on day 7 (Fig. 1). The last deaths occurred on days 12 and 14. At 21 days after radiation, 100% of the mice in the antibody-only groups were still alive, and 70% of the mice in the IgG plus radiation group survived, significantly more than in the anti-PD-1 plus radiation group (36%; $P=.0169$).

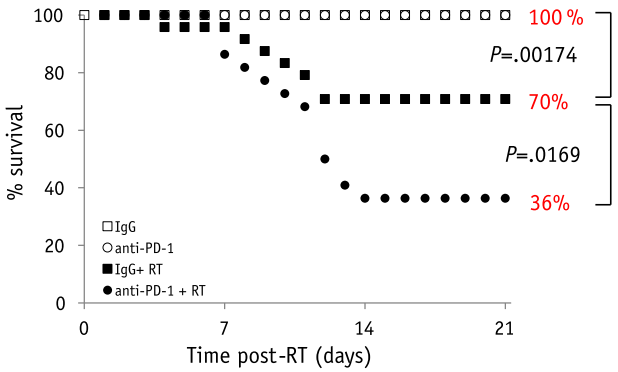

Fig. 1. Anti-programmed cell death protein 1 (PD-1) antibody decreases survival after thoracic radiation (RT). Combining anti-PD-1 antibody and 20 Gy of irradiation significantly decreased survival. IgG plus RT first death at day 4; anti-PD-1 plus RT first death at day 7; day 5 survival for IgG plus RT was 96% and for all other groups was 100%; n = 20 to 25 mice per group.

Combination immunotherapy and radiation significantly increased T-cell influx into thoracic organs

Flow cytometric analysis of T cells isolated from cardiac tissue or lung tissue showed a significant increase in the number of immune cells present after treating the mice with both radiation and anti-PD-1 antibody compared with anti-PD-1 antibody alone ($P=.0003$; $P=.0006$) or control IgG and radiation ($P=.02$; $P=.03$). Anti-PD-1 alone did not significantly alter the T-cell count in either organ compared with control IgG treatment (Fig. 2A). In the heart, the difference in infiltration was not different after control IgG and radiation compared with control IgG alone, although a significant difference was seen in the lungs ($P=.02$).

The histologic analysis findings support these results. The differences in the cardiac tissues (Fig. 2B) were significant when comparing control IgG against anti-PD-1 ($P=.000003$) or control IgG and radiation ($P=8.8 \times 10^{-11}$) or comparing anti-PD-1 antibody to anti-PD-1 plus radiation ($P=7.1 \times 10^{-10}$). The comparison of both groups receiving radiation also revealed a significant difference ($P=.0000002$). The differences in the lung tissues (Fig. 2C) were also significant when comparing control IgG against anti-PD-1 ($P=.008$), control IgG and radiation ($P=.001$), or anti-PD-1 antibody against anti-PD-1 plus radiation ($P=.0009$). Comparing both groups receiving radiation also revealed a significant difference ($P=.008$).

Discussion

Cancer immunotherapy officially began in the early 1980s when the Rosenberg group used adoptive therapy to treat several different types of cancers, infusing lymphocytes and attempting to induce tumor regression (48). In the 30 years since, therapy has become much more specific and much more aggressive, in some cases resulting in impressive decreases in tumor growth. With the increasing popularity of immunotherapy, many models have been developed to study how alteration of immune cell function can affect tumors. Combination immunotherapy and chemotherapy has been studied in a variety of cancers, and several studies combining immunotherapy and radiation therapy are underway, with promising preliminary results. The present report reflects the preliminary, yet critical, findings of increased mortality after immune cell infiltration in mice treated with a combination of radiation and anti-PD-1 blocking antibody, an immunostimulatory molecule.

Combining immunotherapy with traditional chemotherapy has been studied in many cancers, including bladder (49), esophageal (50), urothelial, hepatocellular (51), and colorectal (52) cancer and NSCLC (53), with promising results reporting synergistic effects but an accompanying increase in side effects. This might be because both treatments are systemic, leading to nonspecific activity that can affect more than the target tissues.

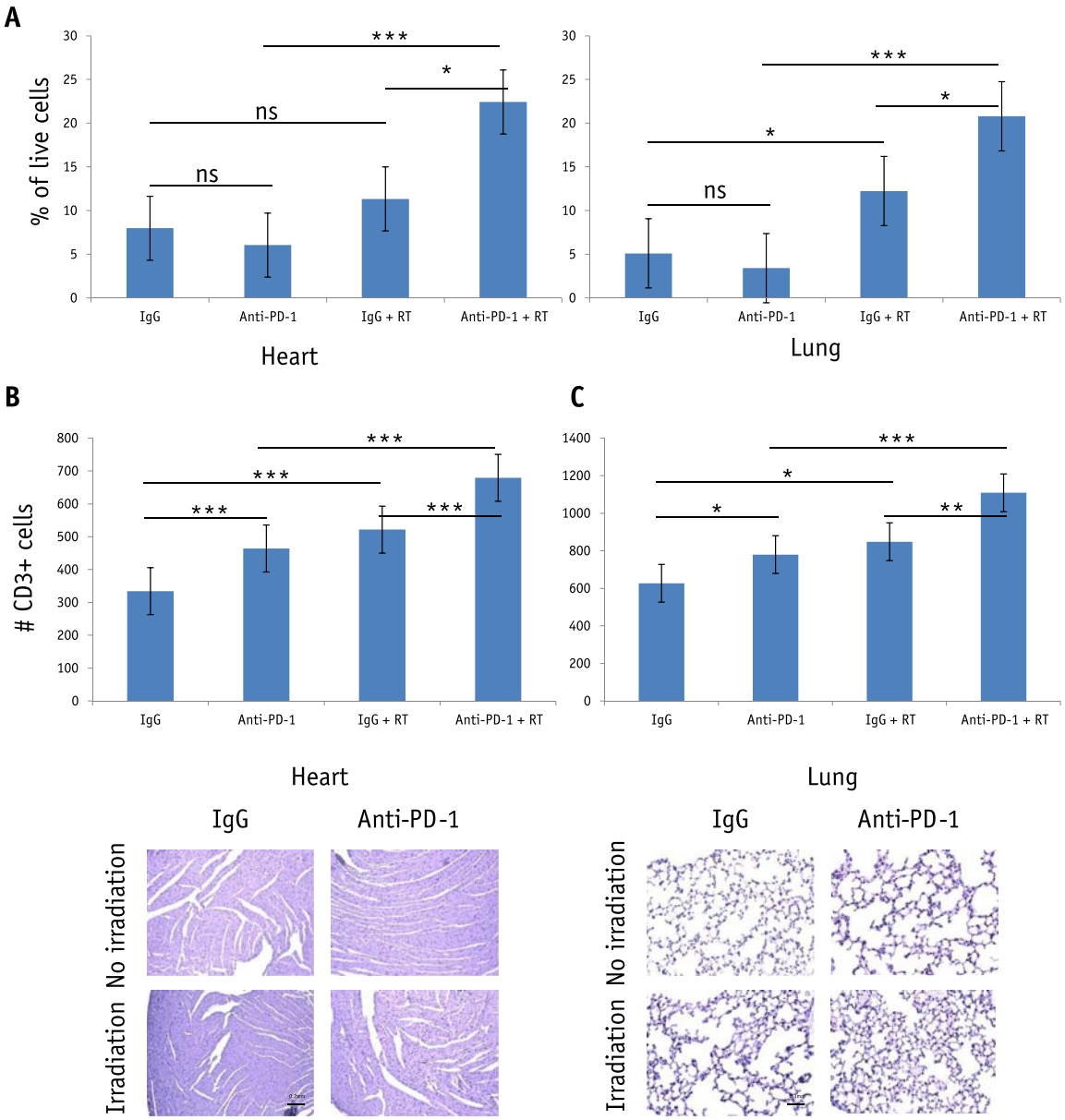

Fig. 2. $CD3^+$ cells were significantly increased in the heart and lungs of mice receiving immunotherapy and thoracic irradiation. (A) Combining irradiation and anti-programmed cell death protein 1 (PD-1) significantly increased the number of T cells isolated from heart and lung tissue. Irradiation alone significantly increased the number of T cells in the lung. Error bars represent standard error. (B, C) Analysis of $CD3^+$-stained samples showed a significant increase in T cells in both heart and lungs after treatment with radiation, with anti-PD-1 antibody, and with combination treatment. Three views of each sample, 10 samples per group, were analyzed by a blinded observer. Analysis of (B) heart and (C) lung tissue involved calculation of the average number of cells per field and comparisons between groups. (Bottom) Representative samples of tissues collected from each treatment group shown. *P<.05; **P<.01; and ***P<.001.

Radiation is a commonly used tool in the treatment of many cancers and can be applied selectively to limit damage to noncancerous tissue. Exploring the combination of radiation and immunotherapy is an exciting new area being studied in many tumor types, including melanomas (54), and breast (55, 56), colorectal (57), pancreatic (58), prostate (59), and lung (60) cancer.

In addition to analyzing the efficacy of this treatment in tumors being directly irradiated, the combination of anti-PD-1 and radiation has been analyzed for abscopal antitumor effects, with a small number of patients showing decreased metastatic disease. Radiation is able to affect change at abscopal sites by its effects on the immune system. At the site of treatment, dead cells release damage-associated molecular patterns, such as adenosine triphosphate, which in turn activate local dendritic cells, increasing antigen presentation (61, 62). Radiation can also increase the diversity of the presented antigens (63)

and localize macrophages to the tumor (64). However, these effects are primarily seen in immunostimulatory tumors such as renal cell carcinoma, melanoma, and hepatocellular cancer (65) and are dose- and method-dependent. For less immunogenic cancers, combining radiation with immunomodulatory molecules might provide the boost needed to see anticancer effects at distant sites. Preclinical data regarding the combination of radiation with interleukin-2, Flt3 ligand, toll-like receptor ligands (62), and CTLA-4 (cytotoxic T-lymphocyte-associated protein 4) (66, 67) have been reported, with promising results. A limited number of studies have treated lung cancer patients with radiation and granulocyte macrophage colony-stimulating factor (68), or ipilimumab (65). However, to the best of our knowledge, the combination of anti-PD-1 and irradiation has not been previously examined (although Deng et al (69) recently reported on the combination of anti-PD-L1 antibody and radiation in the TUBO breast cancer model).

This indicates that the effects of combining these treatments is not restricted to the target area (70, 71). Although this has potentially beneficial effects for treating metastatic disease, it also puts nontargeted tissue at risk. Typical tumor regression models involve inoculation with tumor cells on a limb, providing easy access to the site for radiation but lacking an assessment of how the surrounding tissues will be affected by irradiation. Ectopic models provide more accurate information regarding the role of the tumor microenvironment, because the tumor is located in the tissue from which the tumor would normally develop; however, these models are notoriously difficult to replicate uniformly. Thus, most preliminary studies are conducted in orthotopic models, with further exploration necessary before parallels can be drawn between the model system and clinical applications. Our laboratory's primary interest is lung cancer; therefore, we explored the consequences of combined thoracic radiation and anti-PD-1 antibody to understand how nonmalignant tissue might be inadvertently affected during the treatment of lung cancer.

Analysis of the damage to nontarget tissue has not been reported in these studies. With the increasing popularity of immunotherapy, many models have been developed to study how the alteration of immune cell function can affect tumors. We explored the consequences of combined thoracic radiation and anti-PD-1 antibody to understand how healthy tissue might be inadvertently affected during the treatment of lung cancer.

Both radiation (72) and anti-PD-1 antibody (73) given alone have been shown to cause acute pneumonitis in lung cancer patients. Although most patients with lung cancer will not experience this complication, for the 10% to 15% of patients that do, the consequences can be devastating, negatively affecting their quality and length of life. In addition, irradiation is known to cause both long- and short-term cardiac damage (74); however, the effect of anti-PD-1 on cardiac function has not been studied. Analysis of damage to cardiac and pulmonary nontarget tissue was not been reported in the previously cited combination treatment studies.

In our study, mice with no tumor burden showed increased mortality when given a combination of anti-PD-1 and total thoracic irradiation (a single dose of 20 Gy, an easily reproducible dose compared with that typically described as causing mortality in mice). Dosing and strength were optimized for survival to be used as an endpoint to demonstrate a difference in toxicity. The choice of C57Bl/6 mice, typically known for being fibrosis prone, for these experiments was a result of much research demonstrating physiologic (75), cytologic (76-80), and pathologic (75, 77, 81, 82) evidence of acute pneumonitis in this model in the setting of thoracic irradiation. These animals are prone to developing T-cell helper 1−weighted responses, and, because the T-cell population is weighted toward this response in acute radiation pneumonitis (83), they were an appropriate model for the present study. In addition, modeling this effect in mice that require more intervention to develop this response lends weight to the importance and universality of our findings. At 21 days after radiation, 70% of mice in the IgG plus radiation group survived (Fig. 1), significantly more than in the anti-PD-1 plus radiation group (36%; $P = .0169$).

Limited analysis of the breath rate and ejection fraction differences between these groups provided preliminary evidence that, with the accumulation of activated immune cells, organ function is compromised (data not shown). In addition, we found that cardiac-targeted irradiation does not decrease survival as dramatically as does total thoracic irradiation (data not shown), indicating that the significantly decreased survival resulted from damage to multiple organs. The consequences of this finding are critical, because patients undergoing combination therapy will be at greater risk of treatment-induced pathologic features. Understanding the origin of this phenomenon is key to specifically targeting cancer cells and inducing as little unnecessary damage as possible.

T-cell counts were significantly elevated in both cardiac and pulmonary tissue after combination therapy compared with treatment with radiation alone, indicating that, although prolonging the action of immune cells might enhance their antitumor activity, nonmalignant tissue damaged by irradiation is susceptible to accumulation of, and further damage by, activated T cells. Flow cytometric and histologic analysis of lung and cardiac tissue showed a significant increase in the number of immune cells present after treating mice with both radiation and anti-PD-1 antibody (Fig. 2).

Simply, the presence of these cells undoubtedly affected organ efficiency, because infiltrates of any type are known to interfere with normal functioning. Immune cell infiltrates can be particularly damaging, because activated cells can cause damage beyond disruption of the normal structure and connections, including tissue destruction. Early studies of PD-1 function, using knockout mice to assess its function, showed that animals develop immune infiltrates that cause premature mortality. To the best of our knowledge,

the present study is the first report of such a finding in an experimental treatment model, indicating that collateral damage induced when normal tissue is exposed to antitumor treatment has the potential to negatively affect the patient. Preliminary data (not shown) from these infiltrates indicated a greater level of interferon-γ expression in T cells isolated from mice in the combination treatment group. Further analysis of these cells' functionality will be critical to future studies.

The next step is to understand which cell types are responsible for this damage, including a more in-depth analysis of differences between the T-cell population in the mice that survived radiation alone or combination therapy. Understanding the differences in cytokine production and proportional representation of the cell subtypes will allow us to explore the influence of combination therapy on these cells in particular. Once a determination has been made regarding which T-cell subtypes are responsible for this damage and whether they are the same types active in the antitumor response, alterations in the therapeutic regimen designed to protect nontargeted tissue can be more thoroughly explored.

Our study had a few limitations, including the use of only 1 strain of mice. We have limited preliminary findings in Balb/c mice showing the same effect; however, further exploration of this nature in a variety of genetic backgrounds will provide more information on this phenomenon. In addition, the radiation dose chosen for these experiments is not directly comparable to that which would be used in a clinical setting. The 20-Gy radiation dose allowed us to use mortality as the endpoint; in contrast, translation of these experiments to the clinic would assess morbidity.

Currently, >60 studies investigating the combination of radiation and anti-PD-1 therapy are in various stages of development, including 12 currently recruiting patients with lung cancer (no lung cancer studies have begun treatment or data collection). None have yet reported data on efficacy or complications. Our experiments were an attempt to foresee the complications that might arise from applying these treatments at the same time, in particular, because of their known complications individually. We were also limited by the variables that exist in the clinic and might have an effect on the development of cardiopulmonary complications, such as genetic variations, chronic obstructive pulmonary disease, underlying heart disease, and overall functional status. However, seeing these effects in mice with overall healthy tissue makes it even more likely that they will be seen in patients with significant comorbidities. It is our hope that our findings will provide some insight regarding the potential complications of treatment and, after further study, might help to guide the development of treatment protocols to minimize complications.

Conclusions

Although the combination of radiation and immunotherapy has the potential to greatly decrease tumor burden and increase survival in lung cancer patients, healthy tissues can also be affected to the extent that the treatment might be as bad as the disease. A more extensive understanding of the mechanisms underlying these findings might provide information on how to best decrease the tumor burden with a minimum amount of collateral damage.

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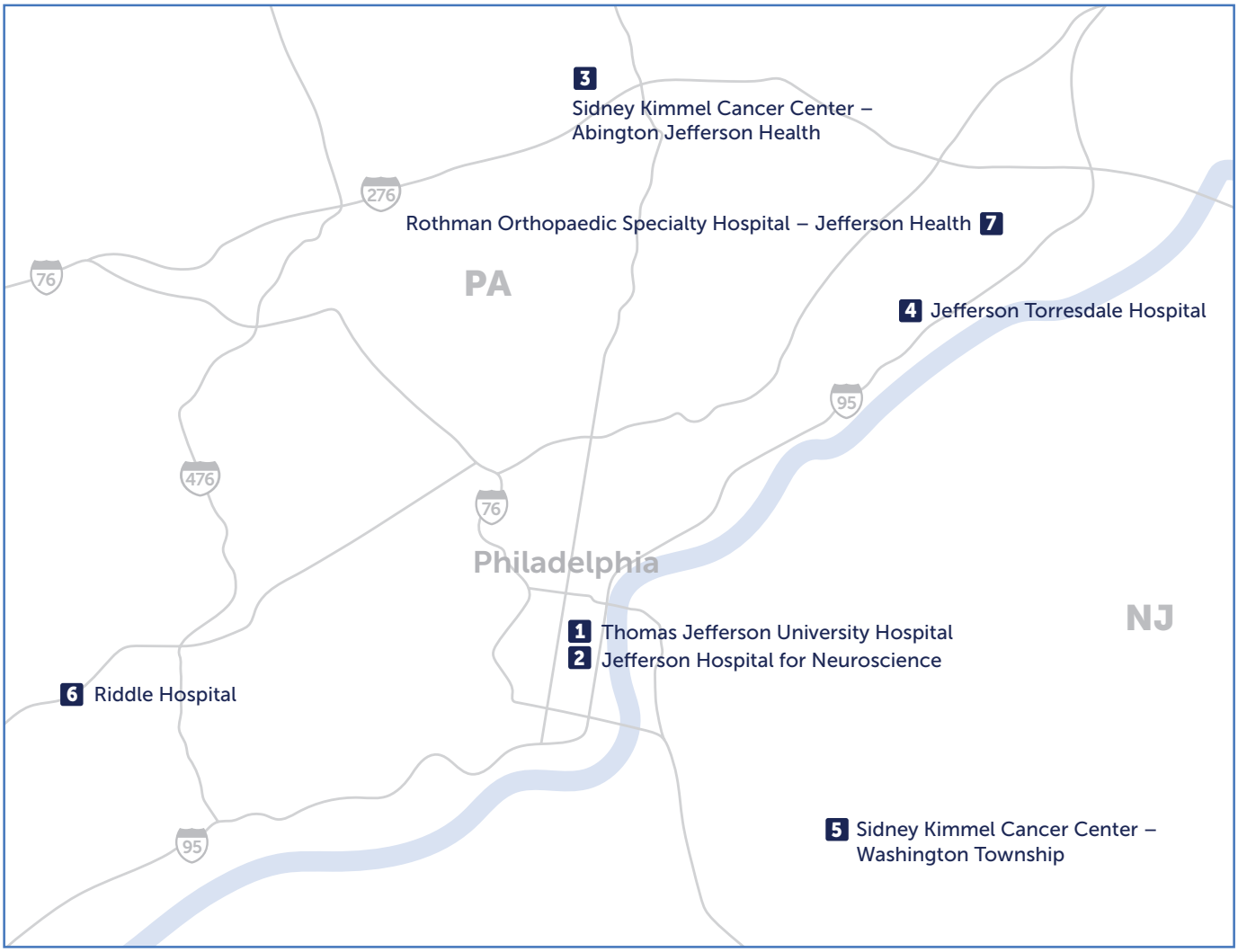

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3 Sidney Kimmel Cancer Center – Abington Jefferson Health
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4 Jefferson Torresdale Hospital
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5 Sidney Kimmel Cancer Center – Washington Township
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6 Riddle Hospital
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