Dr. Mark Dewhirst joined Duke in 1984, and he and Dr. James Oleson set up a multidisciplinary hyperthermia research program. Duke and the College of Veterinary Medicine at NCSU were successful in obtaining a program project grant from the National Cancer Institute lasting for 23 years. The program project grant, combined with R01 and Breast SPORE funding, allowed Dr. Dewhirst to pursue his other passion of identifying underlying causes, consequences, and potential mitigators of tumor hypoxia.

Dr. Dewhirst’s collaborations with Dr. David Brizel are particularly notable. They were the first to report that tumor hypoxia is associated with greater likelihood for development of distant metastases in human patients with soft tissue sarcomas and that hypoxia in head and neck cancer is an independent predictor of local tumor control after radiotherapy.

Dr. Dewhirst successfully conducted the first phase III trial showing the importance of thermal dosimetry in thermoradiotherapy treatment response when he was at Arizona. But the Duke/NCSU/CSU consortium subsequently published the first phase III trial proving that prospective control of thermal dose impacted on local tumor control following thermoradiotherapy. In collaboration with Dr. David Needham in the Pratt School of Engineering, Dr. Dewhirst tested a novel thermally sensitive drug carrying liposome, which has been successfully translated to human clinical trials. As a predicate to human trials, the first phase I trial of this liposome was carried out in companion dogs with cancer.

Throughout his career, Dr. Dewhirst has placed high value on mentoring. There is no doubt that his successes are largely reflective of the exceptional list of graduate students, postdoctoral fellows, medical students, junior faculty members, and clinical fellows with whom he has worked.

In 2011, Dr. Dewhirst was selected to become the first associate dean of Faculty Mentoring in the Duke University School of Medicine. Over the past six years, Dr. Dewhirst established multidisciplinary grant coaching programs for first-time R01 and K-grant applicants. The program was so successful that it has now been incorporated into the core curriculum offered by the Office for Faculty, under the leadership of Vice Dean Ann Brown, MD, MHS. Dr. Dewhirst is now leading efforts to improve mentoring practices and competence across the medical school.

Dr. Dewhirst is the recipient of multiple awards including the Failla Medal from the Radiation Research Society, the Eugene Robinson Award for Excellence in Hyperthermia Research, and a similar award from the European Society for Hyperthermia Oncology. He was named a Fellow of ASTRO, and in 2012 ASTRO awarded the Gold Medal to Dr. Dewhirst, who has more than 600 peer-reviewed publications, book chapters, and reviews.

We will celebrate Dr. Dewhirst’s distinguished career on June 10 and 11, 2017.
“Should I Stay or Should I Go Now?” It was 1999, but I was pondering the question Mick Jones asked in the early 80’s Clash tune. Should I stay in academia or go into private practice? My co-residents and I in Duke’s Radiation Oncology program were facing what I came to believe was one of the toughest decisions of my life. Ultimately, my choice to join New Hanover Radiation Oncology in coastal North Carolina came with a promise to myself that clinical trials would be a part of my career, despite moving to “the Dark Side.”

When I joined our group in 2000, New Hanover Regional Medical Center (NHRMC) had a tiny clinical trials program. The handful of offerings available to patients were focused on medical oncology questions. Over the next couple of years, we opened a few Radiation Therapy Oncology Group (RTOG) trials. Early enrollment was slow but steady. I also published our community experience utilizing David Brizel’s chemoirradiation regimen for patients with advanced head and neck cancer. Around this time, the National Cancer Institute (NCI) announced its request for grant applications for its new Cancer Disparities Research Partnership (CDRP) program.

The CDRP, brainchild of Norm Coleman, Frank Govern, and Rosemary Wong at the NCI, was designed as a new vehicle to address differences in cancer outcomes between the predominantly upper- and middle-class white patients enrolling onto NCI-sponsored oncology trials nationally and underserved populations including minorities and poor whites. Targeted at oncology programs in community hospitals with minimal or no past NCI funding history, CDRP funding was to establish infrastructure for clinical research programs. Since our population in coastal NC is 25 percent black and approximately 15 percent of our patients overall lived at or around poverty level, I felt the CDRP program would be a good fit for us, so we applied.

Six multimillion-dollar five-year CDRP grants were awarded nationally, and we were fortunate to receive one. The first two awardees in 2002 were Laredo Medical Center in Texas and Rapid City Regional in South Dakota, hospitals in regions with predominantly Hispanic and Native American populations, respectively. In 2003, we joined the remaining awardees: Centinela Freeman in California, UPMC McKeesport in Pennsylvania, and Singing River Hospital in Mississippi, where blacks were the main minority population. Our grant funding allowed us to hire a clinical research associate, full-time director, regulatory officer, and patient navigator. We also were able to purchase hardware and software for telemedicine conferencing with our academic partner, the University of North Carolina, where Joel Tepper, MD, served as my original mentor in my new role as principal investigator. Ed Shaw, MD, at Wake Forest University was my other partner and mentor. Community outreach was a major component of our grant, which I thoroughly enjoyed, speaking in churches and writing articles for the local newspaper. Over these first five years, we increased our enrollment onto RTOG trials significantly and continued our in-house clinical research into minimizing treatment toxicity for patients with head and neck cancer.

Continue on page 8
http://radonc.duke.edu
I’m presenting two posters at ACRO 2017 in Orlando, Florida titled:
- “Toxicity analysis of lung stereotactic body radiation therapy (SBRT) at a community hospital”
- “How low is low? Radiation dose assessment of low dose chest computed tomography for lung cancer screening”

Both projects use data from a community hospital in Wisconsin where I completed my transitional year. The main findings are:
- Lung SBRT was generally well tolerated; however, roughly one-fourth of patients developed radiographically-proven rib fracture(s) within the radiation field, and those with documented low bone density had significantly higher risk of radiation-induced rib fractures (RR 2.95 [95% CI 1.25-6.96], p=0.008).
- We calculated the size-specific dose estimate (SSDE), or scanned volume absorbed radiation dose, using two different methods: (1) patient effective diameter (SSDE\textsubscript{\text{DE}}) and (2) water equivalent diameter (SSDE\textsubscript{\text{DW}}). We found that radiation dose from low dose CT scans is approximately 20% the 7 mSv effective dose commonly quoted for standard chest CT. SSDE\textsubscript{\text{DW}} was 23-30% higher than SSDE\textsubscript{\text{DE}}, indicating that if patient diameter but not tissue attenuation is considered, the dose estimate will be too low.

**Interim FDG-PET imaging during neoadjuvant chemoradiotherapy for esophageal cancer: Correlation with pathologic response**

I presented our research "Interim FDG-PET imaging during neoadjuvant chemoradiotherapy for esophageal cancer: Correlation with pathologic response" at the 2017 Gastrointestinal Cancers Symposium in San Francisco. The 26 patients included in this prospective study underwent a PET/CT scan before neoadjuvant chemoradiotherapy followed by an intra-treatment PET/CT scan after a median of 30 Gy. All patients then went to surgery. The relative changes in PET metrics (SUV\text{max}, SUV\text{mean}, metabolic tumor volume, total lesion glycolysis) between pre-treatment and interim PET were compared between histopathologic responders and non-responders using the Mann-Whitney test and binary logistic regression. We observed a decrease in metabolic tumor volume/activity on intra-treatment PET among all patients. However, changes on intra-treatment PET did not distinguish histopathologic responders from histopathologic non-responders. Further research will expand the sample population and explore different PET and CT metrics for their correlation with pathologic response.
Spiegel’s Research and Conference Presentations

During my year of research, I have had the opportunity to work on a number of different clinical research projects, both internally at Duke Radiation Oncology and through the Veterans Health Administration (VHA). With support and guidance from Dr. Salama and Dr. Lee, I examined testosterone recovery in patients with intermediate and high-risk prostate cancer who had been treated at the Durham VA Medical Center (DVAMC) with radiation and androgen deprivation therapy (ADT). In collaboration with a fellow resident, Dr. Julian Hong, we were able to create a predictive nomogram to allow for more accurate estimation of time to testosterone normalization. The results were recently presented at the Genitourinary ASCO Symposium in Orlando, Florida. The next step will be to examine a similar cohort of patients at Duke, which will allow for validation of our current nomogram. This is currently an ongoing project in collaboration with Dr. Koontz. Hopefully, at completion, we will have created a tool that can be used to help guide both patient expectations of testosterone and symptom recovery as well as physician administration of ADT.

In addition to creating a nomogram for testosterone recovery using DVAMC patient data, I have worked with the national Veterans Affairs Central Cancer Registry (VACCR) to evaluate outcomes of locally advanced rectal cancer (LARC) patients treated with definitive chemoradiation either with or without surgery. I sought to identify a subgroup of patients with LARC who may be candidates for non-operative management without sacrificing disease outcomes. Results have been submitted to ASTRO and will hopefully be presented in the Fall of 2017. An ongoing project with the same VACCR cohort will examine the utility of adjuvant chemotherapy, which has largely been extrapolated from colon cancer data, following chemoradiation and surgery.

Finally, outside of my research interests, I have had the unique opportunity to pursue a GME concentration as a “Resident as Teacher.” The course provides a didactic lecture series designed to teach residents the principles of adult learning theory. Based on these philosophies, I have been developing a new course for radiation oncology residents on fiberoptic laryngoscopy, which will be integrated into the 2017-2018 academic year curriculum.
In the treatment of cancer, carbon ion radiotherapy offers potential advantages compared with photon and proton radiotherapy: increased biological efficacy and more conformal dosimetry. The Relative Biological Effectiveness (RBE) of carbon ions has been experimentally determined in cell lines, normal tissues, and syngeneic/xenograft tumor models. Primary (autochthonous) tumor models differ from syngeneic/xenograft models in that the tumors are induced in vivo rather than artificially implanted into the host. Thus, primary tumor models may better approximate the de novo neoplasia and radiation response observed in human cancers. However, to date, the RBE of carbon has not been determined in a primary tumor model.

In the Kirsch lab, we generated primary soft tissue sarcomas in the hind limbs of Kras^{LSL-G12D/+};p53^{FL/FL} mice by intramuscular injection of adenovirus-Cre recombinase. Mice were transported to the NASA Space Radiation Laboratory (NSRL) in Upton, New York, for carbon ion treatment. A 109.5 MeV/n beam was modulated with a custom 30-step compensator wheel to yield a 3 cm spread out Bragg peak. Twenty-five mice were treated with a single dose of 10 Gy. Forty-four unirradiated litter mates were followed as controls. The growth delay observed in mice treated with carbon radiotherapy compared favorably with our prior experience using X-rays to treat this radioresistant tumor.

I am currently treating sarcomas in mice with various single fraction doses of X-rays at Duke. Comparison of the tumor growth delay seen in the carbon and x-ray cohorts will allow me to calculate the RBE. Additionally, IHC/immunofluorescence and RNA sequencing of harvested tissue will allow me to better understand the differences in the radiation response between these two modalities. I plan to report the results at ASTRO and RRS later this year.
A phase 1b study of the safety and tolerability of veliparib combined with capecitabine plus radiotherapy in patients with locally advanced rectal cancer

Brian Czito, MD

Rectal cancer remains a major cause of cancer–related morbidity and mortality, with an estimated 40,000 cases occurring this year in the United States. Although neoadjuvant chemoradiotherapy followed by resection remain a standard of care in stage II–III patients, newer strategies attempting to improve upon this approach are the subject of ongoing investigation. One approach involves the integration of novel radiation sensitizers in combination with conventional chemoradiation approaches.

One potentially attractive class of radiation sensitizers are PARP (Poly (ADP-ribose) polymerase) inhibitors. The mechanism of action of PARP inhibitors results in the inhibition of single-strand DNA break repair. Combined with radiation therapy, this inhibition could lead to increased production of DNA double-strand breaks and therapeutic efficacy, including downstaging and pathologic complete response, ultimately resulting in fewer local failures and even potential non-operative management in highly selected patients. Brian Czito, MD, and colleagues at Duke University helped lead a multi-institutional, multinational phase I study investigating the PARP inhibitor veliparib in combination with radiation and capecitabine in neoadjuvantly treated rectal cancer patients. In this study, investigators from six institutions, including Duke, enrolled patients using a dose escalation approach of veliparib. Following a planned accrual of 32 patients, trial outcomes indicated that this combination was well-tolerated with minimal rates of high-grade toxicity. Additionally, encouraging pathologic complete response rates (29% entire group, 33% at the highest veliparib dose level/recommended phase II dose) were seen. This manuscript was recently accepted to the The Lancet Gastroenterology & Hepatology for publication. Based on these outcomes, this approach is currently being investigated by the NRG (former RTOG/GOG/NSABP) group in a national phase II study (NCT02921256) in which rectal cancer patients receive induction chemotherapy, followed by the combination of radiation, capecitabine and veliparib, followed by resection. These patients will be compared to a similar, “active comparator” arm that does not contain veliparib.
Phase II Randomized Trial Comparing Percutaneous Ablation to Hypofractionated Image-Guided Radiation Therapy in Veteran, Non-surgical Hepatocellular Carcinoma Patients (PROVE-HCC)

Manisha Palta, MD

Primary liver cancer, also known as hepatocellular carcinoma (HCC), is the world’s third most common cause of cancer death. In the United States, the incidence of HCC is increasing. United States veterans are more likely to have HCC, due to higher rates of Hepatitis C infection and alcoholic cirrhotic liver disease, both of which are leading causes of HCC. To combat this higher incident, the Durham Veterans Affairs Medical Center (DVAMC) has implemented robust early detection screening programs. While surgery is the optimal treatment, less than a third of HCC patients are medically fit for surgery or liver transplant. This means that a majority of patients are treated with non-operative, liver-directed treatments.

In response to this increasing incidence and complexities of management, a multi-disciplinary tumor board at the Durham Veterans Affairs Hospital—made up of gastrointestinal doctors, medical oncologists, surgeons, and radiation oncologists, as well as diagnostic and interventional radiologists affiliated with Duke and the Durham VA Medical Center—was created. All patients with imaging concerning for HCC are reviewed in this multi-disciplinary conference, and treatment recommendations are made.

The current standard of care for patients who are not candidates for surgery is percutaneous ablation. Radiation, for non-surgical candidates, has typically been considered only in cases where the lesion is too large to do an ablation, in a location where ablation is less than ideal, or when prior liver-directed treatments have been exhausted or ineffective.

Drs. Fumiko Chino and Manisha Palta have developed a new phase II randomized trial comparing two non-surgical alternatives—percutaneous thermal ablation and hypo-fractionated image-guided radiation therapy (HIGRT)—in patients with early-stage HCC. The trial (PROVE-HCC) is being sponsored and funded by the Duke University Department of Radiation Oncology and is open to accrual. The primary goal is to determine which of these effective treatments is tolerated best by measuring quality of life before and after the treatments, in addition to secondary endpoints of local control and hospital associated costs. This will be the first randomized trial to be conducted at the Durham VA Department of Radiation Oncology in decades.
The success of the CDRP program during its initial five years allowed the NCI to repeat funding requests. We were fortunate to receive another major grant from 2009 through 2013. When Larry Marks, MD, took the chairman position at UNC, he became my academic partner and mentor there. During this time in coastal NC, we focused on trials for prostate cancer, aided in large part by my partner and co-PI Mike Papagikos, MD. Our goal was to be able to offer a clinical trial to virtually every man with prostate cancer who presented for radiation oncology consultation. Trials included RTOG 0232 testing brachytherapy +/- external beam for men with intermediate risk disease, RTOG 0415 evaluating non-inferiority of 70 Gy in 28 fractions versus standard fractionation, and the Duke stereotactic body radiation therapy trial of 27 Gy in 5 fractions for men with low/intermediate risk disease. Our enrollment success on these and earlier trials resulted in our practice being awarded an American Society of Clinical Oncology Clinical Trial Participation Award in 2010, the first radiation oncology practice in the country to receive the award.

Throughout and after completion of our decade of CDRP grant funding, our clinical oncology research program has been fortified and expanded. Now under the umbrella of the South East Area Health Education Center (SEAHEC), affiliated with both NHRMC and UNC-Chapel Hill Hospitals, clinical cancer research in coastal NC continues to thrive. My personal involvement with radiation oncology clinical trials has contributed significantly to my career satisfaction in private practice. Looking back over the past 17 years since my initial tough decision at Duke, I feel so fortunate to have had the best of both worlds.

**Promotions:** Rachel Blitzblau, MD, PhD - promoted to associate professor

**Farewells**

For many years these three have been familiar faces here in radiation Oncology. We were sad to see them go but wish them the best in retirement.

Susan Anderson,
Therapist/Medical secretary
30 years at Duke

Kevin Smith, Dosimetry
33 years at Duke

Beverly Steffey, Physics
20 years at Duke