Over the past year, three outstanding academic radiologists received Peter Michael Fellowships to support their research in prostate cancer imaging at Memorial Sloan-Kettering Cancer Center (MSK): Dr. Andreas Wibmer of the Medical University of Vienna, Austria; Dr. Francois Cornelis, a Fulbright Scholar at MSK from the Pellegrin Hospital of Bordeaux, France; and Dr. Olivio F. Donati, who, thanks to his Peter Michael Fellowship, returned to the faculty of University Hospital, Zurich in May with highly-developed skills in prostate cancer MRI. In collaboration with other members of our prostate cancer management team, these investigators have examined the value of advanced MRI and PET-CT for improving numerous areas of prostate cancer care. Along with summarizing their extensive efforts (see below), we are pleased to report that the head of MSK’s prostate cancer imaging research team, Dr. Hedvig Hricak, has been awarded the 2014 Presidential Citation of the American Urological Association for her pioneering work in MRI of the prostate.

**Developing diffusion-weighted MRI for the prediction of tumor aggressiveness**

Many prostate cancers diagnosed today are likely overtreated, but better means are needed to identify appropriate candidates for active surveillance and other conservative management approaches. In particular, distinguishing tumors of Gleason score 6 from tumors of Gleason score ≥7 is critical. Several studies have identified associations between Gleason scores and apparent diffusion coefficient (ADC) values derived from diffusion-weighted MR imaging (DW-MRI). The ADC is a relatively simple metric that can be calculated on a pixel-by-pixel basis with most standard clinical MRI platforms. However, there is no consensus on the best metric to summarize the multiple ADC values contained within each prostate cancer lesion. To establish the ADC as a robust biomarker for predicting prostate cancer Gleason scores, standardization of quantitative ADC metrics is crucial. Dr. Donati led a study that compared the associations between Gleason scores and various ADC parameters used in prior research. The study indicated that the 10th percentile ADC was the parameter that enabled the most accurate differentiation of low-grade from intermediate- or high-risk prostate cancer. The study was published in *Radiology*.

Dr. Donati was also involved in a study assessing the value of the mean tumor ADC and the tumor volume on ADC maps for predicting tumor Gleason scores. The study showed that, independent of tumor volume, mean ADC could distinguish Gleason score 6 tumors from those with higher Gleason scores. The manuscript has been provisionally accepted by *Clinical Cancer Research* pending revision.
Using MRI to evaluate sexual function in patients with prostate cancer

Excellent prostate cancer control rates have led to increased interest in survivorship issues such as sexual function. A study by Dr. Donati and colleagues showed that penile dynamic contrast-enhanced (DCE)-MRI parameters were significantly associated with self-reported sexual function. These parameters can be readily obtained when performing multiparametric prostate MRI for cancer staging and may prove relevant to patient management, including treatment selection.

Improving clarity in the communication of prostate MRI findings

It has been established that the widely varying expressions radiologists use to indicate degrees of diagnostic certainty are often misunderstood by referring physicians. In 2009, to address this concern, MSK implemented a standardized lexicon that encourages the radiologist to use one of 5 predefined terms to express his/her level of diagnostic certainty. Dr. Wibmer was involved in a study that assessed the usefulness of this diagnostic certainty lexicon for communicating the likelihood of extracapsular tumor extension (ECE) of prostate cancer on prostate MRI. Before lexicon implementation, radiologists used 49 different terms to express their levels of certainty regarding ECE. Afterwards, they adhered to the lexicon in 83.6% of cases. The findings suggested that the use of a diagnostic certainty lexicon likely prevents miscommunications and helps referring clinicians incorporate radiologists’ assessments into clinical decision-making. A manuscript has been submitted to the American Journal of Roentgenology.

Examining the impact of second-opinion, subspecialist interpretation of prostate MRI

Dr. Wibmer and colleagues investigated whether second-opinion readings of prostate MRI by sub-specialized radiologists at dedicated tertiary care cancer centers. A manuscript is being prepared for submission.

Studying the feasibility and value of Haralick texture analysis of prostate MRI

Haralick texture analysis evaluates the spatial distribution of pixels in a gray-scale image to provide quantitative information about the image that cannot be discerned with the naked eye. It has been successfully applied for various purposes, including automated recognition of land use on satellite images. Dr. Wibmer worked on a study showing that Haralick texture analysis of prostate MRI is feasible and provides parameters that may help differentiate cancer from normal tissue and assess prostate cancer aggressiveness. A manuscript is being prepared.

Computer simulation to estimate ablation zones after ultrasound-guided irreversible electroporation of the prostate: Comparison with MRI and clinical outcomes

Irreversible electroporation (IRE) is a relatively new ablation modality that uses short pulses of DC electric current to create pores in the cell membrane that lead to cell death. During IRE ablation, particular care must be taken in needle placement to avoid side effects from distribution of the ablative electric field to non-targeted tissue. Dr. Cornelis and colleagues examined the accuracy of non-FDG PET-CT for guiding biopsies of suspicious bone lesions in patients with metastatic castration-resistant prostate cancer. Patients were biopsied using PET-CT imaging guidance 6-7 days after injection of Zr89-labelled anti-PSMA antibody. Whereas pre-procedure CT showed equivocal findings in bone, the PET-CT with the anti-PSMA antibody revealed bone lesions in all patients and allowed the acquisition of biopsy specimens that were adequate for pathological and molecular profiling. Biopsy results confirmed prostate cancer metastasis in every case. The findings suggest that PSMA-based PET-CT imaging can be used to guide needle biopsies with a high rate of technical success. An abstract was accepted for presentation at the 2014 annual meeting of the Society of Interventional Radiology.

Developing targeted molecular imaging for precision medicine

Recently, Dr. Cornelis participated in the first clinical study evaluating the accuracy of non-FDG PET-CT for guiding biopsies of suspicious bone lesions in patients with metastatic castration-resistant prostate cancer. Patients were biopsied using PET-CT imaging guidance 6-7 days after injection of Zr89-labelled anti-PSMA antibody. Whereas pre-procedure CT showed equivocal findings in bone, the PET-CT with the anti-PSMA antibody revealed bone lesions in all patients and allowed the acquisition of biopsy specimens that were adequate for pathological and molecular profiling. Biopsy results confirmed prostate cancer metastasis in every case. The findings suggest that PSMA-based PET-CT imaging can be used to guide needle biopsies with a high rate of technical success. An abstract was accepted for presentation at the 2014 annual meeting of the Society of Interventional Radiology.

Improving the accuracy of biopsies using intra-procedural low-dose FDG PET-CT

Dr. Cornelis and colleagues examined the accuracy of percutaneous biopsies performed under intra-procedural 18F-fluorodeoxyglucose (FDG) PET-CT guidance. The study included 105 consecutive patients who had FDG PET-CT-guided biopsies of 106 masses in bones, liver, soft tissues, lung and abdomen. Biopsies were positive for malignancy in 76/106 (71.7%) cases. For the vast majority of the biopsies (94.3%), the immediate results were considered adequate (no further exploration was required). Accuracy, sensitivity and positive predictive value of biopsies were all 100%. Complications occurred after only 3.7% of the biopsies. The findings suggest that intra-procedural FDG PET-CT-guided percutaneous biopsy, which may be applied in patients with various types of cancer, including metastatic prostate cancer, is safe and highly accurate. A manuscript has been submitted to Radiology.

Mixed tumor biology of bone metastases:

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a: CT component of FDG PET/CT
b: fused FDG PET/CT
c: fused FDHT PET/CT
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Several recently developed treatments have significantly improved upon the survival of patients with advanced prostate cancer. One of these treatments blocks the pro-cancer effects of the male hormone, androgen. Although these treatments can delay progression of cancer, cancer still finds a way around these treatments. Clearly, we need new treatments to block this hormone pathway more completely.
RNA is a key molecule in all cells and functions to translate genes (DNA) into proteins. However, this critical intermediate step is frequently manipulated in cancer cells, resulting in altered proteins and creation of growth and survival signals, promoting the uncontrolled growth of cells and development of cancer. Recent developments suggest these alternative RNA forms could be targets for treatments that would block the pro-cancer activity.

We have leveraged our support from the Peter Michael Foundation to bring together a team of experts at Duke University Medical Center and the University of North Carolina at Chapel Hill to create a critical mass of research in the field of RNA therapeutics focused on prostate cancer. Specifically, we have designed and synthesized a novel splice-switching oligonucleotide (SSO), which is a small nucleic acid that can produce a variant RNA, resulting in a protein that will block androgen activity. If successful, this SSO product should prevent the activation of genes required for prostate cancer growth and survival. Initial results have demonstrated that when this SSO is applied to prostate cancer cells it creates a protein product that blocks an androgen regulated gene. Our current studies are focusing on demonstrating that the SSO product is able to block additional androgen regulated genes and slow the growth of prostate cancer cells. Future studies will focus on using an innovative strategy to selectively deliver this SSO product to prostate cancer cells and localize it to the compartment within the cancer cells where such a product will have an effect, the cancer cell nucleus. Ultimately, this approach could be used in combination with current treatments, enabling a complete blockade of androgen activity in prostate cancer.

Our research team includes Dr. Dan George, MD, Director of Genitourinary Oncology at the Duke Cancer Institute, Dr. Steve Patierno, PhD, Deputy Director of the Duke Cancer Institute, Dr. Bruce Sullenger, PhD, Director of the Duke Translational Research Institute, Dr. Rudy Juliano, PhD, Boshamer Distinguished Professor of Pharmacology at the University of North Carolina at Chapel Hill, Dr. Zefeng Wang, PhD, Associate Professor of Pharmacology at the University of North Carolina at Chapel Hill, and Dr. Jennifer Freedman, PhD, recently promoted to Assistant Professor of Medicine at Duke, thanks in large part to the support of the Peter Michael Foundation.

Publications

Understanding the effects of immunotherapies within human cancer

To understand what an immunotherapy does within a patient, we have developed a program at UCSF to administer immunotherapies to prostate cancer patients prior to them undergoing a planned surgery to remove the prostate. This allows us to study the resected tissues in our laboratory. We have just completed a study where men with localized prostate cancer received sipuleucel-T (Provenge) prior to surgery. We show for the first time that this treatment recruits helper and killer T cells to the cancer site. Moreover, these T cells are activated and dividing, indicating that the T cells are responding to targets within the tumor. These results afford us not a greater understanding of what these treatments are doing in people, but also help guide us in developing new treatments and as well as providing the rationale for combining different treatments together. We have opened a clinical trial combining the anti-CTLA-4 (ipilimumab) with sipuleucel-T.

Identifying biomarkers that may predict who responds to an immunotherapy

While immunotherapy can lead to long-lasting responses in cancer patients, unfortunately, only a small proportion of patients (20-30%) may respond to our current immunotherapies. Identifying who may respond to a treatment is a major question within the field. We have been studying the many different activation markers present on immune cells contained in the blood of treated cancer patients. We have identified several pre-existing biomarkers that correlate with improved survival. We are now confirming this finding in a larger clinical study. If successful, this finding will allow the selection of patients that will benefit the most from this treatment. In addition, these biomarkers give us insight into the underlying biology within these cancer patients that may enable the development of new treatments or treatment combinations for the patients that at present do not respond to our current treatments.

Publications
Fong et al. Recruitment of activated lymphocytes into the tumor microenvironment following reaudaciation of sipuleucel-T in localized prostate cancer. JNCI, 2014 in press.

above: high and low magnification images of the CD3/CD8 double stain

Defining the targets that the immune system sees following cancer immunotherapy

We have used blood from prostate cancer patients treated with immunotherapies to decipher what target proteins (antigens) are being recognized by the immune system in treated patients. We define the spectrum of antibody responses to over 8000 different human proteins and find that patients who clinically improved with treatment developed a significantly larger magnitude of responses than people who did not. Moreover, these immune responses induced by the treatment where actually amplified from pre-existing immune response already present in the patient, rather than generating new immune responses. We have now continued this work to examine whether immune responses are also induced to mutated proteins within the cancer cells. Cancer can arise from errors in the DNA of the these cells. These errors can give rise to mutated proteins that are different from normal proteins, which can be great targets for the immune system to see. We found that both pre-existing and induced antibody responses as a result of immunotherapy treatment could be found in prostate cancer patients. These antigens could represent great candidates as potential cancer vaccine antigens because they are specific to the cancer and not found in normal cells.

Principals

Principal Investigator: Lawrence Fong, MD
Department of Medicine, Hematology & Oncology

Peter Michael Postdoctoral Fellow: Serena S. Kwek, PhD
De ar Dr. Hricak:

It gives me great pleasure to officially select you as a recipient of a 2014 AUA Presidential Citation. I am proud to acknowledge your pioneering work in magnetic resonance imaging of prostate cancer.

The presentation of this honor will be held in conjunction with the 2014 AUA Annual Meeting. The award will be presented during the Awards Dinner on Tuesday, May 20, 2014. There are also many complimentary benefits provided by the AUA to you as a recipient of this prestigious award. Enclosed is a letter from Ms. Liz Asplin, Conventions & Meetings Manager, which outlines the travel, hotel and

Congratulations and thank you for your contributions to the field of urology and, specifically, to the AUA.

With warmest regards,

Pramod C. Sogani, MD, FACS, FRCS (C)
President, American Urological Association