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UC RADIOLOGY

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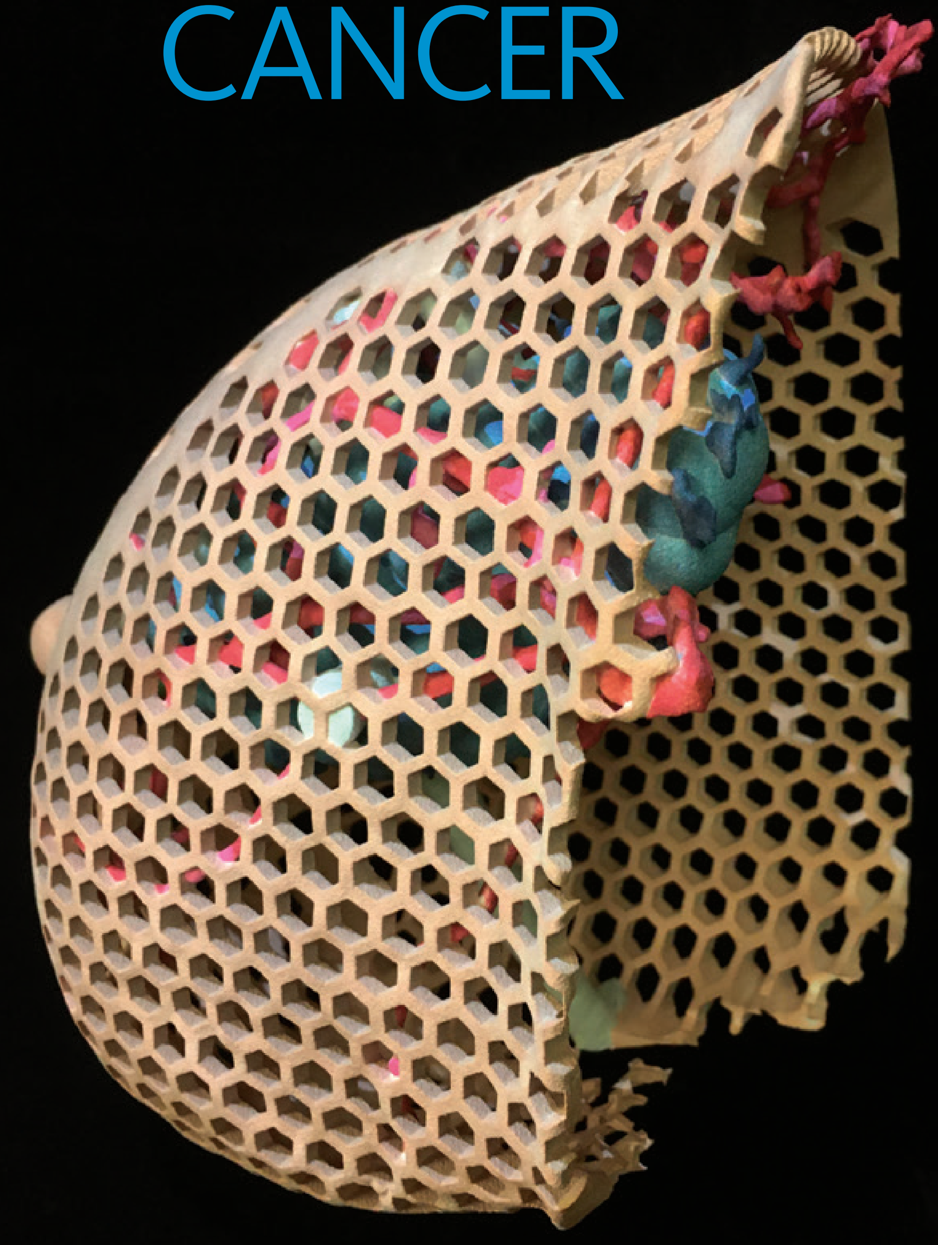

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Welcome from the Chairs

Dear Friends,

As you know so well, patients often learn and experience the expertise of our profession through screening, diagnosis, and treatment of their cancers. In modern practice, subspecialty radiologists are physicians acting in the patient's best interest as consultants par excellence by reducing uncertainty, establishing diagnoses, and moving patients along their unique roads to treatment. Our important work is all too often not fully appreciated as much of it takes place "behind the scenes." As we turn our focus to the theme of *Imaging Cancer* in this third issue of our joint UC Radiology newsletter, we highlight the centrality of radiologists and imaging scientists to multidisciplinary cancer care.

Every step in a patient's cancer journey involves imaging – from diagnosis to accurately detecting and characterizing the location, extent, and aggressiveness of a malignancy, to surgical planning and monitoring treatment response. In each of these steps, radiologists are uniquely positioned to help guide and direct the care of our patients. In these pages, we are pleased to share recent accomplishments and exciting new developments led by our faculty and trainees at each of these waypoints.

For commonly diagnosed malignancies such as breast and prostate cancers, our clinicians and researchers deploy artificial intelligence, 3D-printing, and advanced diffusion MR to extract useful information from images to personalize care and minimize invasive treatments :

- Researchers in the Applied Artificial Intelligence Research (AIR) Center at UC Irvine are developing methods to better understand individualized breast cancer risk, using deep learning algorithms to quantitatively score breast tissue density on screening mammograms and improve MRI evaluation of breast lesions.

- At UCLA, a multidisciplinary research program seeks to evaluate the performance of AI in interpreting and triaging screening mammograms and in determining how AI should be practically and efficiently integrated into a very high-volume clinical workflow.

- Clinicians at UCSF explore applications of 3D-printing in managing breast cancer, resulting in patient-specific presurgical planning and customized approaches to breast conservation and reconstruction.

- Researchers in the UCSD Women's Imaging Lab test restriction spectrum imaging (RSI) as a tool to differentiate breast cancer from healthy and benign tissue; the technique also shows promise for evaluating post-treatment response for cervical cancers.

From left: Vahid Yaghmai, MD; Dieter Enzmann, MD; Alexander Norbash, MD; Christopher Hess, MD, PhD; Elizabeth Anne Morris, MD

■ At UC Davis, Dr. Elizabeth Morris, a pioneer in high-risk breast cancer screening received her own diagnosis. Dr. Morris's personal experience as a patient strengthened her resolve to ensure that women have access to the best possible screening technology such as contrast-based imaging such as MRI or contrast-enhanced mammography.

Regarding imaging prostate cancer, UCLA clinician researchers in an integrated diagnostic program have found that multiparametric MRI visible tumors tended to have much higher predominance of aggressive histological and genomic features. This information may help determine which lesions in the prostate to biopsy and whether patients should be triaged to active surveillance, tumor ablation, surgical resection or radiation therapy.

"In modern practice, subspecialty radiologists are physicians acting in the patient's best interest as consultants par excellence by reducing uncertainty, establishing diagnoses, and moving patients along their unique roads to treatment."

Integrating the tools of diagnostics and therapy opens the door for revolutionary new *theranostics* — an exciting transformation of nuclear medicine to enable personalized medicine. In late 2020, UCSF and UCLA researchers gained FDA approval for prostate-specific membrane antigen PET imaging, or PSMA PET, a new technique for more effective imaging of prostate metastasis. UC Davis is building a state-of-the art theranostics clinic, slated to open in late 2023, where clinicians will care for patients with established and emerging radiopharmaceuticals.

Targeted, minimally invasive interventional radiology therapies show great promise for improving outcomes and reducing the collateral effects of cancer treatments. At UC Irvine, radiologists use image-guided interventions to manage patients with bone metastasis in concert with oncologists, surgeons, and pharmacists. Interventional radiologists at UCSD have established a multidisciplinary clinic to tailor pharmacological and non-pharmacological therapies for patients with difficult-to-manage cancer pain.

We hope that you will be inspired by these remarkable innovations across the University of California. We are proud to play a pivotal role in advancing the frontiers of imaging science and clinical practice to improve outcomes for our patients.

Sincerely,

Dieter Enzmann
Christopher Hess
Elizabeth Morris
Alexander Norbash
Vahid Yaghmai

BREAST / UCD

Pioneer in High-Risk Breast Cancer Screenings Becomes Cancer Patient Herself

Dr. Elizabeth Morris has an impressive resume as a pioneer in high-risk breast cancer screening. She also gained international prominence as coauthor of the book *Breast MRI: Diagnosis and Intervention.*

The UC Davis Department of Radiology chair has conducted research on imaging biomarkers to assess risk and treatment response. She also advocates for getting women at risk for breast cancer the screenings they need to detect cancer when it is most responsive to treatment.

And now, she is a breast cancer survivor herself.

"For me, the whole experience of being a cancer patient felt like a confluence of my personal and professional lives," said Morris. "I've been on a mission to detect breast cancer early in women so it can be found in time, and then suddenly I was facing my own breast cancer diagnosis."

Morris came to UC Davis from New York's Memorial Sloan Kettering Cancer Center, where she was chief of Breast Imaging Services. Her cancer was caught as she was getting elective breast reduction surgery before leaving for California to accept her new post at UC Davis Health in January 2021.

Never did Morris think she would start radiation therapy at the UC Davis Comprehensive Cancer Center the same month she started her new position across campus.

Risk factors low

"I didn't have any family history of breast cancer, and my only risk factors were being a female over 50 with extremely dense breasts," said Morris as she openly shared her story to benefit other women who wonder if they might contract breast cancer.

Tissue removed during the breast reduction surgery was sent to pathology, which is routine during such procedures. Morris is highly appreciative of the attentive pathologist who picked up her cancer, demonstrating how cancer detection is often a team effort.

"My 3D mammogram and screening ultrasound were negative, so I didn't wait apprehensively for my pathology results," said Morris. "I was surprised when my doctor told me they discovered a four-millimeter tumor called invasive lobular carcinoma, named for the way it grows in a single–file linear pattern. The shape of the tumor makes it difficult to spot in a traditional mammogram and ultrasound."

Advanced screening technology key to early detection

Lobular cancers are the second most common type of invasive breast cancer, meaning cancer that has spread to surrounding tissue.

"It just goes to show that mammograms don't detect all cancers, and that's why we need to make contrast-based imaging such as MRI or contrast-enhanced mammography available to women — perhaps not annually but at least every few years," said Morris.

Tests using an injection of contrast dye, such as MRI and contrast-enhanced mammography, are better at detecting all types of cancer compared with traditional mammograms.

"If I had to take on cancer, I'm glad I was at UC Davis," said Morris who is from Davis and obtained her undergraduate degree from UC Davis.

"My own personal journey has only strengthened my resolve to give women the best possible chance of surviving breast cancer by getting them access to the best possible screening technology," said Morris. "I'm so excited to contribute to UC Davis' world-class reputation as a leader in imaging technology and contemporary research programs as it continues to serve a large and diverse community."

Formidable cancer fighters forming a strong bond

Megan Daly and Elizabeth Morris have more than a couple of things in common: They are female physicians at UC Davis Health, both in the radiology field, and both determined to cure Morris' breast cancer.

Elizabeth Morris, MD (left), and Megan Daly, MD (right)

"As a breast imaging expert, with an extensive background in diagnostic radiology, Liz had a very thorough understanding of our radiation treatment plan before we even spoke. So, if anything, she asked fewer questions than many patients who don't understand the concept of radiation or why we use it," said Daly, a radiation oncologist. She treated Morris with 16 fractions, or small doses, of radiation starting the first month of her tenure as chair of radiology at UC Davis.

Daly and Morris share a doctor-patient relationship and have also become peers and personal friends as they took an aggressive approach to treating Morris' breast cancer.

"Megan has such a personable style with her patients and is so effective at explaining the advances in radiation oncology now available to breast cancer patients treated at the UC Davis Comprehensive Cancer Center," Morris said.

Daly specializes in a variety of radiotherapy techniques, including the image-guided radiation therapy used to treat Morris.

"Liz was a great patient and, now as a breast cancer survivor, is in a unique position to understand the journey our patients take as they bravely face and conquer cancer," Daly said. ■

BREAST / UCSF

Current and Future Applications of 3D Printing in Breast Cancer Management

3D printing technology has been available for nearly 40 years, with recent rapid uptake in many medical subspecialties. Key applications are in pre-surgical planning, production of patient-specific surgical devices, simulation, and training.

Though all 3D-printed medical models are based on radiologic imaging, there is a notable lack of literature on the applications of 3D printing in breast cancer management.

Dr. Tatiana Kelil, an assistant professor in the Breast Imaging Section at UCSF, along with Arpine Galstyan, an MD candidate at UCSF, were corresponding authors on a recent review and discussion of the current applications of 3D printing in breast cancer management and potential impact on future practice. The paper was published in *3D Printing in Medicine* (https://doi.org/10.1186/s41205-021-00095-8) and assessed five applications of 3D printing in breast cancer management:

1. Breast-conserving surgery (BCS) and tumor localization
2. Breast reconstruction surgery
3. Physician-patient and interdisciplinary communication
4. Education and simulation
5. Quality control

"Overall, 3D printing is fundamentally changing breast cancer surgery. It allows for patient-specific presurgical planning and more customized surgical intraoperative surgical guides for both breast conservation and breast reconstruction surgeries," says Dr. Kelil.

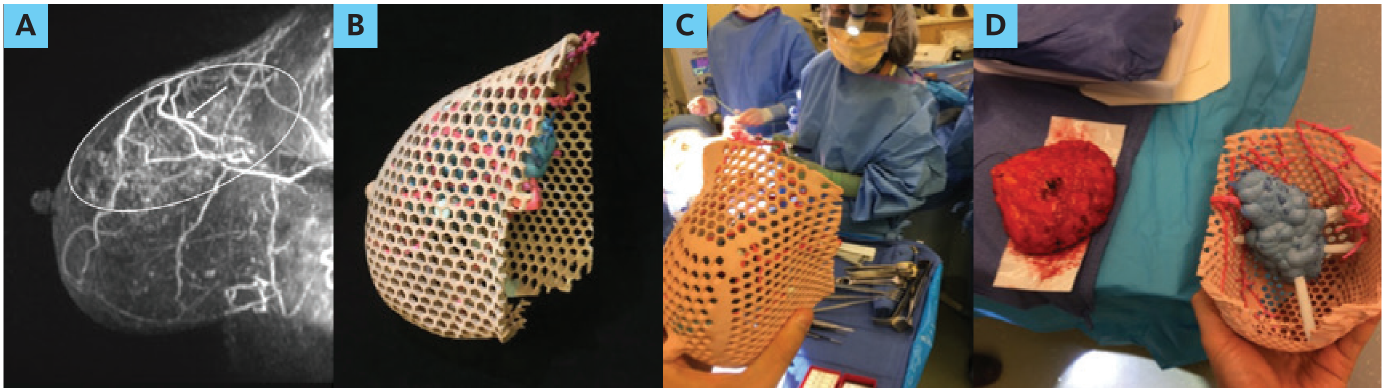
This review article was a collaboration with the UCSF Center for Advanced 3D+ Technologies (CA3D+) and the University of Central Florida (UCF). Michael Bunker from the CA3D+ participated in the creation of 3D printed models along with Fluvio Lobo, Robert Sims, James Inziello and Jack Stubbs from UCF. Surgical procedures were performed by Rita Mukhtar, MD from the UCSF Department of Surgery.

"Dr. Mukthar and I collaborate often to create precise 3D models of patients' breasts for cancer surgeries," says Dr. Kelil. "In addition to leading to better aesthetic surgical outcomes and negative surgical margins, these models serve as teaching and explanation tools for patients and trainees, and they can improve interdisciplinary communication between healthcare providers. For example, a 3D-printed model is a powerful visual for showing the extent of disease to a patient preparing for surgery. For trainees, 3D-printed models are tools to practice on before seeing patients. Similarly, a library of 3D-printed models is an

Tatiana Kelil, MD
Assistant Professor, Breast Imaging
Co-Director, UCSF Center for Advanced 3D+ Technologies

opportunity for trainees to encounter rare abnormalities that they may formerly only see in textbooks. For surgical management of breast cancer, 3D-printed models can provide a better spatial understanding and relationship of tumor to vital structures."

The UCSF Center for Advanced 3D+ Technologies was formed as a multidisciplinary collaboration between the departments of Pediatric Cardiology, Orthopaedics and Radiology and Biomedical Imaging thanks to a grant from the School of Medicine. The Center uses 3D printing and virtual reality to help doctors prepare for surgery and explain procedures to patients. The team is now working on emerging fields in 3D printing and breast cancer management, including bioprinting and personalized radiation therapy to address challenges encountered with current breast cancer management approaches. ■



A) Sagittal 3d maximum intensity projection (MIP) image from a contrast-enhanced MRI showing extent of abnormal non-mass enhancement in the right upper breast (white ellipse) and surrounding vessels (arrow). B) A 3D printed model derived from this breast MRI. C) A breast surgeon using the 3D printed model intraoperatively to visualize the location of the tumor as well as its relationship to adjacent vessels. D) Side-by-side comparison of the excised specimen and the 3D model.

BREAST / UCLA

Using Artificial Intelligence to Interpret Screening Mammograms

AUTHORS:
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Professor of Radiology
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Director of Iris Cantor Breast Imaging Center

Hannah Milch, MD
Assistant Professor of Radiology

“Screening mammography is the cornerstone of breast cancer detection,” says Cheryce Poon Fischer, MD, professor of radiology, section chief and director of the Iris Cantor Breast Imaging Center.

During the 12 months ending in October 2021, over 38 million screening mammograms were performed in the U.S. “The sheer volume of screening mammograms is staggering, requiring a large number of highly subspecialized radiologists for accurate interpretation,” continues Dr. Fischer.

UCLA is currently exploring what role machine learning (ML) and artificial intelligence (AI) can play in managing the high daily workload for radiologists by aiding in the interpretation of screening mammograms. “A reliable AI system could help with workflow by efficiently triaging patients with suspicious findings on screening exams and by helping mammographers reduce callback rates,” explains Dr. Fischer. Decreasing callback rates reduces patient radiation exposure, allays patient anxiety and frees up physician time to increase overall efficiency.

Cheryce Poon Fischer, MD

While computer-aided detection (CAD) systems have been under development for decades, the first CAD software was not approved for use by the FDA until 1998. CAD systems are very different from the ML algorithms that are currently generating a great deal of interest in many areas of radiology. While CAD could highlight focal areas of increased breast tissue density and microcalcifications, it has not proved to be impactful in helping radiologists interpret image data or in increasing efficiency.

AI systems for mammography use deep convolutional neural networks that learn how to classify image data. Such systems are able to aid in breast cancer detection in a more nuanced way than could earlier CAD systems by more adeptly handling ambiguous data. Today’s AI systems evaluate mammography images and assign numerical values to indicate the risk of breast cancer. These AI systems provide a score for each finding on a mammogram, calculating the probability of cancerous tissue for each suspicious area of interest.

Hannah Milch, MD

Dr. Fischer points out that current AI systems are not intended to replace the human radiologist, but to serve as a smart assistant in interpreting screening mammograms. The numerical results of the AI system's evaluation are available to radiologists in real time as they review images, helping them better and more quickly interpret the entire study.

> **"A reliable AI system could help with workflow by efficiently triaging patients with suspicious findings on screening exams and by helping mammographers reduce callback rates."**
> –*Cheryce Poon Fischer, MD*

UCLA is embarking on an extensive and multi-pronged research program to evaluate the performance of AI in assisting the interpretation of screening mammograms and contributing to the clinical practice of screening mammography, as well as how AI should be practically integrated into the high-volume clinical workflow. The research is starting with a retrospective study testing ML algorithms on 5,000 screening mammograms performed at UCLA from 2010 to 2015. Various competing ML algorithms have been tested by their developers, who have reported their findings and made claims about their algorithm's accuracy based on that data. "There is, however, concern that the performance measures of these ML algorithms using the vendors' test cases may not be fully generalizable to the screening mammograms performed at UCLA," explains Hannah Milch, MD, assistant professor of radiology, who serves as one of the lead investigators in this research. "There might be differences in patients' diversity, breast density, medical and surgical history, race, ethnicity and breast cancer risk." After assessing how the different ML algorithms perform on our own archived data set, UCLA will install one of the systems and perform a prospective clinical trial to fully evaluate how it performs in UCLA's everyday screening mammography workflow. "While there are some interesting clinical trials coming out of Europe, we're expecting to be at the forefront of actually using and prospectively studying AI in reading screening mammograms," explains Dr. Milch.

Drs. Fischer and Milch and their colleagues are also thinking about the practical adoption and future developments needed. "Present AI systems do not look at prior films when they do their interpretation, whereas the human radiologist does," says Dr. Fischer. "If the AI system could look at prior films and add that information to what it detects in the present films, it will be more useful, more accurate, and more able to diagnose very early stages of cancer by detecting subtle digital imaging changes in the breast tissue that may be difficult for the human eye to perceive." Other information that could be incorporated to improve future AI systems includes demographics such as patient age, cancer history, genetic information and even social determinants of health.

Foreseeing a day when AI will play an even larger role in triaging screening mammograms, Dr. Fischer notes that many of the breast imaging radiologist's hours are currently spent assessing healthy women. "With a robust, dependable AI system, we could decrease the time spent on evaluating normals in the daily workload, freeing us to spend more time on complex diagnostic exams, cross sectional MRI exams, biopsies and other interventional procedures — areas where AI cannot replace humans." ■

BREAST / UCSD

Improving Women's Imaging with Advanced Diffusion MRI

AUTHORS:
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Summer Joyce Batasin
Undergraduate Students in the Women's Imaging Lab, UC San Diego Health

The Women's Imaging Laboratory (WIL) in the Center for Multimodal Imaging and Genetics (CMIG) at UC San Diego Health develops state-of-the-art imaging technology and techniques to improve care for women across their lifespan. Current research focuses on advancing MRI for breast and cervical cancer.

The Women's Imaging Lab led by Rebecca Rakow-Penner, MD, PhD, is a relatively new lab at UC San Diego, addressing imaging health care needs for women. The lab has attracted bright talent and collaboration including members of UCSD's bioengineering program, medical school, and multiple hospital departments including radiology, gynecology and obstetrics, radiation oncology, breast surgery and oncology, and pathology. Women's Imaging Lab members also collaborate with Anders Dale, PhD, CMIG Director, and other CMIG members.

With funding from the National Cancer Institute, the California Breast Cancer Research Program, General Electric Healthcare, and the Kruger Wyeth Research Grant, the WIL is focusing on non-contrast MRI for breast and cervical cancer using Restriction Spectrum Imaging (RSI), a technique based on a diffusion weighted imaging (DWI). RSI is an organ-specific diffusion weighted imaging frame-work and thus needs to be modeled independently for each organ of interest. An organ-specific model has been developed and implemented

Continued on next page

for breast cancer and a model is in development for cervical cancer.

Breast Cancer Imaging

WIL Project Scientist Ana Rodríguez-Soto, PhD, and team developed an advanced diffusion model specific to the breast. This model decomposes the diffusion signal into three distinct water pools:

1. a restricted diffusion compartment (C_1) theoretically capturing signal from intracellular cancer cells,

2. a hindered diffusion compartment (C_2) common to both cancer and fibroglandular tissue, and

3. a fast flow compartment (C_3) such as flow in vessels (Figure 1).

Compared to DCE-MRI, the restricted diffusion compartment demonstrated similar specificity (C_1=82% vs. DCE-MRI=81%) and increased area under the curve (AUC) (C_1=0.90 vs. DCE-MRI=0.79), which highlights the effectiveness of the model in differentiating malignancy from healthy and benign tissues without the use of exogenous contrast.

The project was developed for biopsy-proven malignancies initially greater than 2 cm. A validation study, led by Alexandra Besser, MD, PhD, and Lauren Fang, BS, showed that the model discriminated concurrent biopsy-proven malignant, benign, and healthy tissue, particularly using the restricted diffusion C_1 compartment and product of the restricted and hindered diffusion compartments (C_1C_2). However, benign lesions and healthy tissue did not significantly differ in diffusion characteristics (Figure 2). The next phase of the project is to implement and adapt this technique for higher resolution diffusion imaging in the breast cancer screening population.

In addition to model development, the technique has also been implemented and evaluated. DWI has the potential to evaluate response to treatment at an earlier time point, and possibly more effectively than DCE-MRI. RSI quantifies tumor cellularity and is less susceptible to post-treatment edema and local perfusion changes, thus providing a complementary technique in evaluating true tumor response to neoadjuvant treatment.

Led by Fulbright Visiting Scholar Maren Andreassen, the group examined the diagnostic performance of RSI, classic DWI, and DCE-MRI in evaluating response to neoadjuvant treatment. Images were registered across timepoints using a novel non-rigid deformable registration technique called FLIRE (also developed in the lab led by Michelle Tong), reducing the number of regions of interest (ROI) that need to be manually defined. RSI was able to better predict early response to treatment than gold-standard DCE-MRI and ADC, and demonstrated higher post-treatment specificity than DCE-MRI and ADC (Figure 3). Findings underscore the potential of RSI as a quantitative imaging biomarker for breast cancer detection and treatment surveillance.

Cervical MRI

The WIL also focuses on imaging female pelvic cancers, such as cervical cancer. Evaluation of treatment response for cervical cancer is generally performed by PET/CT, which is confounded by post-treatment changes (e.g. inflammation or edema) in the few months after chemotherapy and radiation treatment. To decrease false positive sensitivity to benign post-treatment changes, patients typically wait at least three months post-treatment to determine treatment efficacy.

Currently, standard DWI is limited by post treatment inflammation/edema, hemorrhage, benign lesions, and distortion artifacts from magnetic field inhomogeneity. As demonstrated in the breast and other organs, RSI isolates cancer by separating the diffusion signal from different water pools within tissues, thus overcoming challenges like edema. Like the aforementioned breast studies, their proposed DW-RSI methodology may offer an alternative approach to evaluate post-treatment response, with additional advantages of being a radiation-free and contrast-free exam.

The group is actively gathering data to develop a cervix-specific model. Early cases fitted preliminarily with an existing (based on breast) RSI model showed promising results (Figure 4). The tumor was similarly conspicuous on RSI as it was on PET/CT, demonstrating both restricted diffusion (C_1) and hindered diffusion (C_2). A healthy volunteer, on the other hand, demonstrated only hindered diffusion signal (C_2) in the endocervical canal, without detectable restricted diffusion.

In addition to developing a non-contrast MRI technique for breast cancer screening, the group is also committed to taking the next steps in developing an ovarian-specific model. ■

Members of the Women's Imaging Laboratory (WIL) at UC San Diego Health

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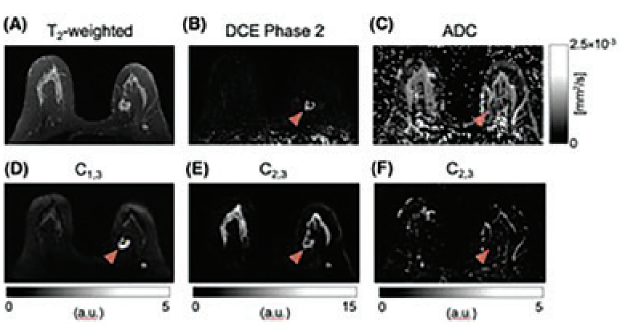

Figure 1. Processed images for a patient are shown, including (A) T_2-weighted and (B) DCE-MRI images, (C) conventional ADC map, and (D-F) the signal contributions ($C_{i,3}$) of the 3-component model (restricted, hindered, fast flow). Arrowheads indicate tumor location. Signal contribution in tumors was higher than surrounding tissues in both $C_{1,3}$ and $C_{2,3}$. The compartment $C_{3,3}$ displays vascular flow information. (Adapted from Rodríguez-Soto et al., 2021, Magn Reson Med, 87(4):1938-1951.)

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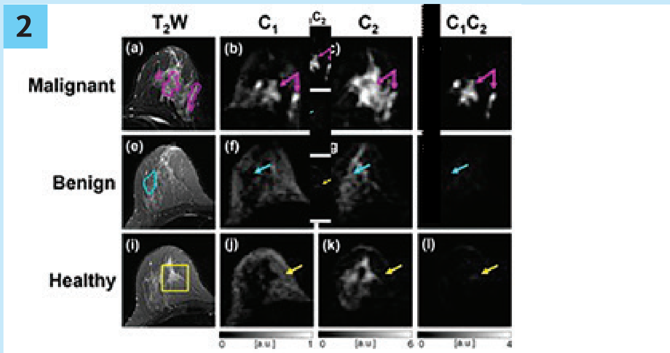

Figure 2. Representative RSI maps for a patient with concurrent biopsy-proven malignant and benign lesions, with (a-d) malignant lesions, (e-h) benign lesions, and (i-l) healthy tissue ROIs delineated. The product of the restricted and hindered diffusion compartments (C_1C_2) highlights malignant tissue (c), whereas benign and healthy tissues display no significant signal.

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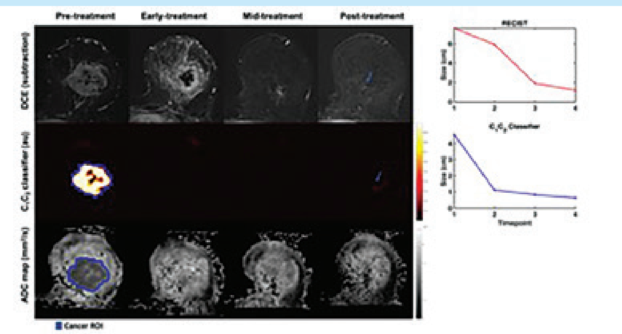

Figure 3. Post-contrast DCE-MRI images, RSI probability maps (C_1C_2 classifier) and ADC maps for all imaging timepoints for a subject with no remaining tumor tissue on final post-surgical pathology. The C_1C_2 classifier captured response to treatment already at the early treatment timepoint compared to DCE-MRI and ADC. Both determined that there was still some remaining tumor left within the tumor bed at the post-treatment timepoint (blue arrow). Also note that the RSI classifier is well-defined within the cancer ROI at the pre-treatment timepoint (blue outline). (Adapted from Andreassen et al. Abstract #1434, Presented at ISMRM 2021)

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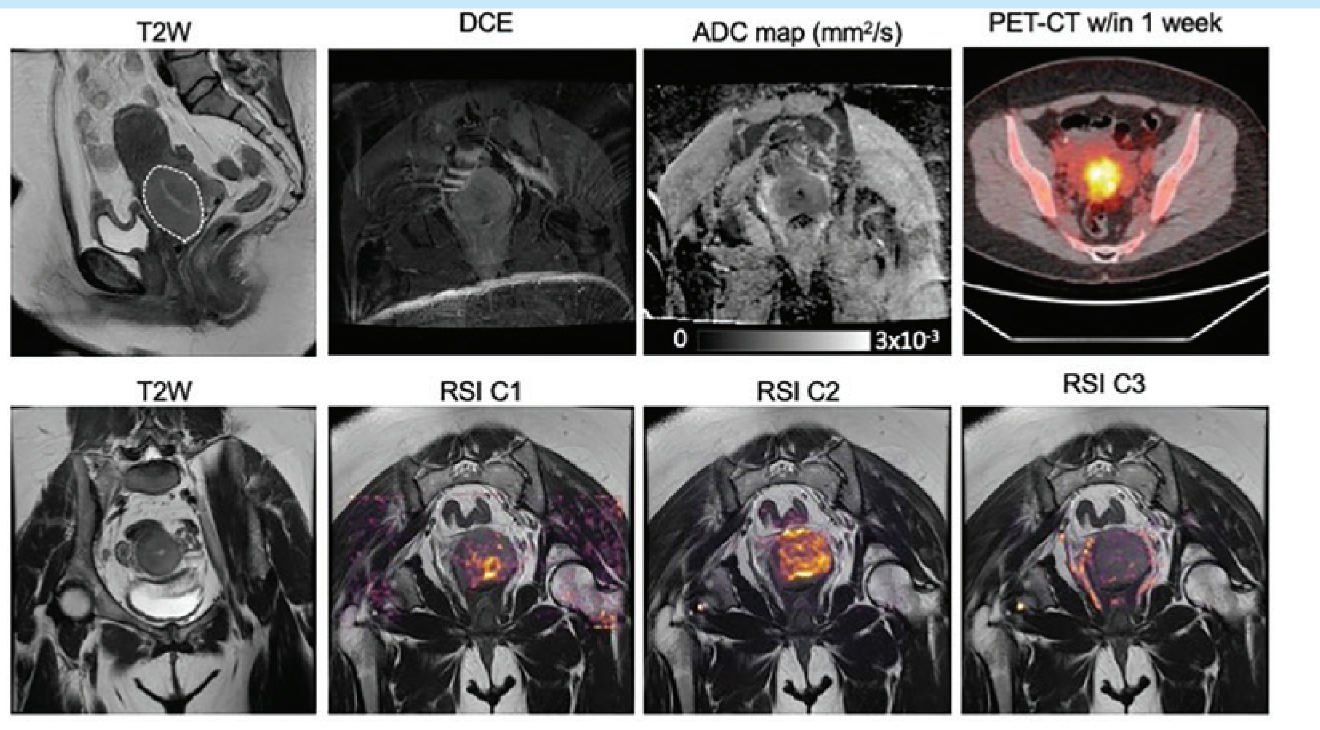

Figure 4. Processed images for a cervical cancer patient pre-treatment. T2-weighted, DCE-MRI, conventional ADC, PET-CT, and RSI compartment maps C1-C3 are shown. The lesion demonstrates hyperintense signal in the restricted and hindered diffusion compartments, in alignment with PET-CT.

Artificial Intelligence for Personalized Breast Cancer Care

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The World Health Organization reports that breast cancer affects approximately 2.3 million women each year and is the leading cause of cancer-related deaths amongst women worldwide.

However, despite the tremendous heterogeneity in tumor pathophysiology and unique patient characteristics, current guidelines for breast cancer management are primarily informed by generic, population-level risk factors. As part of the Applied Artificial Intelligence Research (AIR) Center, researchers at UC Irvine are developing novel machine learning methods to better understand individualized breast cancer risk. Led by Dr. Peter Chang, the AIR team applies a specific machine learning technique known as deep learning neural networks, characterized by the ability to identify patterns in data with minimal human guidance. “After separating patients into relevant cohorts, a neural network can automatically identify key characteristics of each group without a priori assumptions or biases,” explains Dr. Chang.

Breast Density and Beyond

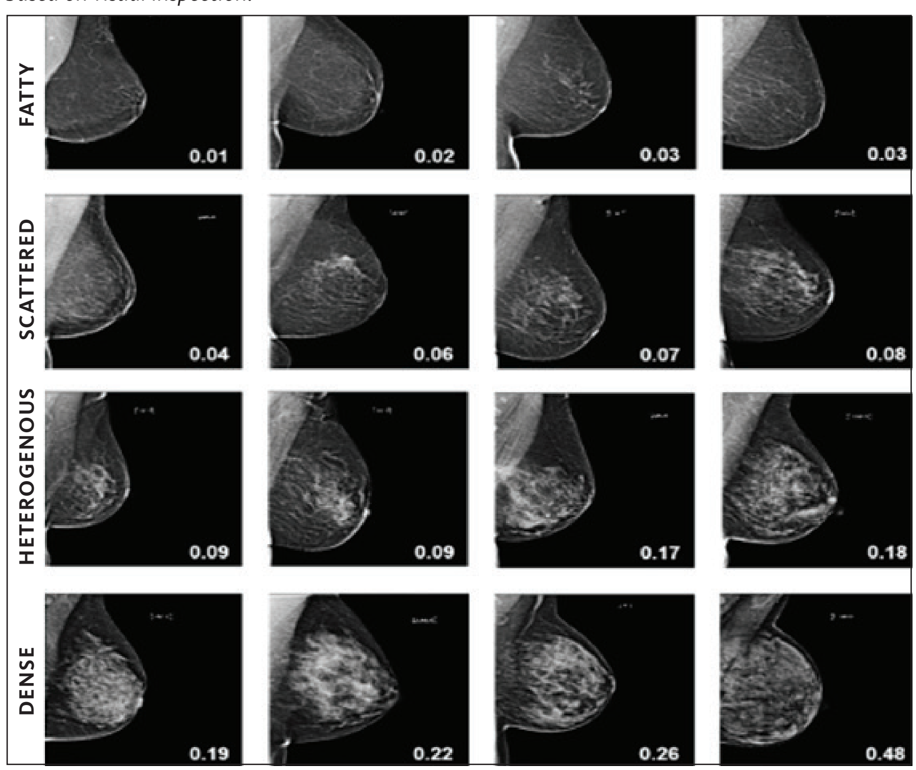
In breast cancer, a key focus of the AIR team at UCI is to identify imaging biomarkers for personalized cancer risk assessment. One well-known risk factor is breast tissue density on mammogram, traditionally evaluated visually by human experts on a four-point scale. “Women classified as BI-RADS extremely dense are four to six times more likely than women with BI-RADS almost entirely fatty to develop breast cancer, in part due to the limitations of mammography in

Peter D. Chang, MD

patients with denser tissue,” explains Dr. Irene Tsai, Chief of Breast Imaging at UCI. To improve on the current standard of care, the AIR team has developed a deep learning algorithm for quantitative scoring of breast tissue density on a scale of 0-100% on routine mammogram for each patient (Figure 1). In addition to providing more detailed density measurements, the algorithm is trained using a novel unsupervised strategy that does not require explicit human feedback. “This cutting-edge strategy could allow an AI system to continuously learn on new data, potentially giving rise to custom models at each hospital in the world adjusted to the unique features of each local patient population,” Dr. Chang further elaborates.

Beyond simply measuring the total amount of breast density, the specific pattern or configuration of fibroglandular tissue may also offer important clues to cancer risk. In ongoing collaborations with Columbia University Medical Center, AIR researchers have developed deep learning algorithms capable of estimating personalized cancer risk based on unique patterns in breast fibroglandular tissue. More specifically, the algorithm evaluates each individual mammogram pixel to determine the likelihood that any single region in the breast may develop cancer in the future (Figure 2). While the resulting

Figure 1. An unsupervised deep learning AI algorithm can estimate quantitative breast fibroglandular density, further refining the standard four-category BI-RADS scoring system based on visual inspection.



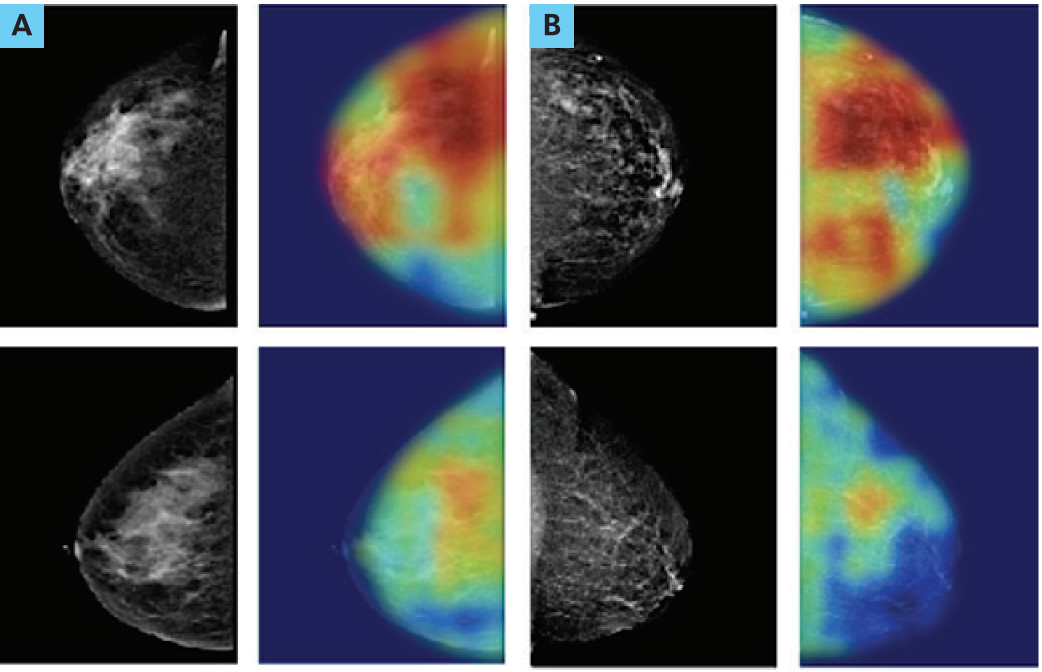


Figure 2. A deep learning AI algorithm provides personalized breast cancer risk based on patterns of fibroglandular tissue density. Note that high-risk (red regions; top row) and low-risk (blue-green regions; bottom row) patient cohorts are identified in both dense (column A) and fatty (column B) breasts.

> **"This cutting-edge strategy could allow an AI system to continuously learn on new data, potentially giving rise to custom models at each hospital in the world adjusted to the unique features of each local patient population."**
>
> *–Peter D. Chang, MD*

heatmap does overall correlate with breast density, the algorithm is also able to identify individual patients who are exceptions to rule: some patients with extremely dense breasts nonetheless have low cancer risk, while other patients with almost entirely fatty breasts yield regions suspicious for future cancer development. In a follow-up longitudinal study on 541 patients, researchers demonstrated that breast cancer likelihood assessed by the same AI system decreased over time in patients who had undergone risk-reducing chemoprevention treatment.

MRI and Genomics

In addition to screening mammograms, breast MRI is a powerful tool that facilitates more detailed characterization once a potential abnormality has been discovered. However, "many benign lesions also show strong contrast enhancement, and may lead to false positive diagnosis, unnecessary biopsy or over treatment," explains Dr. Lydia Su, Professor of Radiology at UCI. "With increasing screening and preoperative MRI performed, particularly in community settings, efficient characterization of the enhancing lesions is important to improve diagnostic accuracy." To this end, Dr. Su and Dr. Chang have collaborated on various machine learning models for improved MRI evaluation of breast lesions. In one study, an AI system was able to differentiate benign and malignant tumors on dynamic contrast-enhanced MRI in 133 patients with over 91% accuracy. Importantly, the research team notes that while the tumor appearance itself is critical in diagnosis, the AI model was able to identify important patterns in stromal tissues immediately surrounding the tumor that offer important prognostic information.

Dr. Su's team has also applied various AI methods for diagnosis of more challenging non-mass enhancement lesions on MRI as well as the prediction of tumor molecular subtypes. From a technical perspective. Dr. Su's group is interested in combining multimodal MRI and mammographic images to improve the diagnostic accuracy, and to improve model generalizability between different hospitals and heterogenous image quality using transfer learning techniques.

Clinical and Multimodal Analysis

While imaging biomarkers are important for assessment of cancer risk, clinical variables including patient age, demographics, family history, exposures, and genetics remain the primary determinants of risk stratification based on recent management guidelines. However, current standard methods for evaluation of clinical risk factors such as the Tyrer-Cuzick model were originally derived from a small population of non-Hispanic white females using a limited number of patient risk factors. In a collaboration with the Athena Breast Health Network spanning over 150,000 patients and over a decade of longitudinal follow-up, the AIR team is developing machine learning based methods for more individualized risk prediction using dozens of clinical covariates. The current highest-performing AI system is over 97% accurate and has identified important risk factors such as smoking history previously overlooked by traditional models. As a crucial next step, the team is actively investigating deep learning strategies to combine both clinical and imaging biomarkers into a single aggregate cancer risk score.

"Prior studies including our own efforts have demonstrated that the addition of breast density provides incremental improvement in the performance of clinical risk stratification tools," says Dr. Tsai. "In turn, improved risk assessment may help better identify patients who require additional supplemental screening modalities such as ultrasound or MRI, ultimately leading to enhanced patient outcomes." ■

PROSTATE / UCLA

MRI Can Improve Prostate Cancer Screening by Adding Individualized Tumor Information

Steven S. Raman, MD, FSAR, FSIR

AUTHOR:
Steven S. Raman, MD, FSAR, FSIR
Professor of Radiology, Urology and Surgery
Director, UCLA Prostate MRI and Interventional Program
Director, UCLA Abdominal Imaging Fellowship

Prostate cancer presents management challenges that make it unique among solid organ cancers.

"Unlike other cancers, for men it's not a matter of *if* you get prostate cancer, it's a matter of *when* you get prostate cancer," explains Steven Raman, MD, professor of radiology and director of the UCLA Prostate Imaging and Image Guided Treatment Program. "Over 80 percent of men over the age of 80 have some prostate cancer, which is not true of other cancers."

The key to managing the disease is to know what type of prostate cancer an individual man has and how aggressively it is likely to behave, which helps determine how aggressively it should be treated. Non-aggressive prostate cancers could be managed conservatively with active surveillance and MRI, but usually are left untreated to avoid the morbidity of sexual and urinary dysfunction associated with prostate cancer treatments.

Despite the usefulness of individualized information, the standard of care for prostate cancer screening has been uniform. Men typically present with an elevated blood PSA (prostate specific antigen) level > 4 or the presence of a nodule on digital rectal examination, both of which are nonspecific and do not differentiate between aggressive and non-aggressive prostate cancer subtypes. Typically this is followed by a transrectal ultrasound (TRUS) guided systematic biopsy of the prostate gland to try to detect prostate cancer, which can then be categorized according to the Gleason grading system. However, this fails to accurately estimate individual cancer risk in up to 50 percent of patients.

"Since the early 1990s, men have been getting tested for PSA, which is a good test but not a great test because it leads to overdiagnosis," explains Dr. Raman. "It does pick up the majority of men with prostate cancer, however it doesn't discriminate between aggressive and non-aggressive subtypes." The widespread use of PSA resulted in a significant decrease in prostate cancer mortality in the 1990s, but it came at the cost of very widespread sexual and urinary morbidity and overtreatment for many other men.

This may be in the process of changing as MRI (magnetic resonance imaging) is proving to be useful in identifying the most aggressive prostate cancer tumors for biopsy and, importantly, in returning a negative result when non-aggressive tumors don't present immediate threats to men's health.

"UCLA data shows that using MRI, we can detect 80 to 90 percent of the aggressive disease (Gleason score > 7) while detecting less than 50 percent of the non-aggressive disease," states Dr. Raman. "For the last 11 to 12 years, we've also pioneered the use of MRI targeted biopsy — taking a biopsy of the most aggressive disease we see under MRI using a variety of fusion imaging techniques as well as direct

> "For the last 11 to 12 years, we've also pioneered the use of MRI targeted biopsy — taking a biopsy of the most aggressive disease we see under MRI using a variety of fusion imaging techniques as well as direct MRI-guided biopsy in the MR scanner." — *Steven S. Raman, MD, FSAR, FSIR*

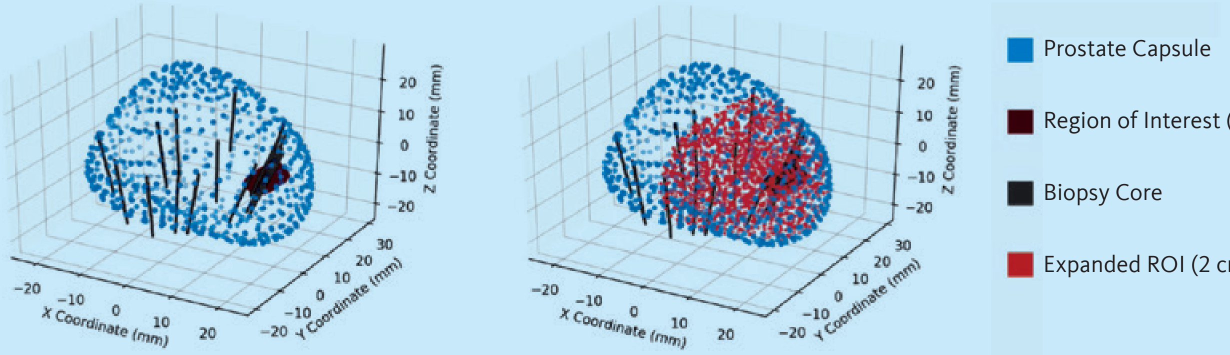


Figure 1: A landmark study by Drs. Corey Arnold and Steven Raman (Raman et al. J Urol 2021; 206(3): 595-603) of detailed 3D biopsy analysis of 16,459 biopsy cores in 1,000 patients showed that over 97 percent of clinically significant prostate cancers (red dots) were within 2 cm of the MRI target (brown spot), further validating the technique and decreasing the need for extensive systematic biopsies, which add risk of bleeding, infection and pain.

MRI-guided biopsy in the MR scanner. Our most recent analysis (Figure 1) shows that 97 percent of clinically significant prostate cancers were within 2 cm of the MRI target, requiring less extensive prostate biopsy samples.

A recent population-based study in Sweden enrolled 12,750 men to compare standard prostate cancer screening to a screening program that adds the use of MRI in detecting clinically significant disease. Men with PSA scores of 3 and higher (1,532 men met the study criteria) were randomized to receive either standard systematic TRUS biopsy or an MRI followed by a targeted TRUS biopsy and a standard systematic biopsy if the imaging indicated the presence of aggressive prostate cancer.

Clinically significant prostate cancer — defined as a Gleason score of 7 or higher following histological examination of the biopsy tissue — was detected in 21 percent of those in the MRI arm of the study, compared to 18 percent for those in the standard-of-care arm. In addition, only four percent of the men in the MRI arm detected as positive for prostate cancer but proved to have clinically insignificant disease. In the standard-of-care arm, 12 percent of those detected positive proved clinically insignificant for prostate cancer. "This study mirrors our long experience at UCLA, initially published 10 years ago," says Dr. Raman. "MRI is very good at detecting significant prostate cancer while not detecting insignificant prostate cancer."

Screening for prostate cancer is poised for a significant step forward with MRI imaging to help discriminate when biopsy is called for and when prostate disease should be monitored without invasive testing. "With the introduction of MRI, prostate cancer care has entered a whole new phase where the risk of each individual man is more personalized than it was in the past," says Dr. Raman. "Based on UCLA research, MRI is the single best marker for predicting clinically significant cancer and also predicting the underlying tumor molecular biology, including hypoxia genes. The combination of artificial intelligence, MRI and PSMA PET scans may be better than any of them alone for diagnosing prostate cancer in the near future." ■

UCSF, UCLA Gain FDA Approval for Prostate Cancer Imaging Technique

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In December 2020, the University of California's two nationally ranked medical centers, UC San Francisco and UCLA, and their nuclear medicine teams obtained approval from the U.S. Food and Drug Administration to offer a new imaging technique for prostate cancer that locates cancer lesions in the pelvic area and other parts of the body to which the tumors have migrated.

Known as prostate-specific membrane antigen PET imaging, or PSMA PET, the technique uses positron emission tomography in conjunction with a PET-sensitive drug that is highly effective in detecting prostate cancer throughout the body so that it can be better and more selectively treated. The PSMA PET scan also identifies cancer that is often missed by current standard-of-care imaging techniques.

"UCLA and UCSF researchers studied PSMA PET to provide a more effective imaging test for men who have prostate cancer," said Jeremie Calais, MD, MSc, an assistant professor at the David Geffen School of Medicine at UCLA. "Because the PSMA PET scan has proven to be more effective in locating these tumors, it should become the new standard of care for men who have prostate cancer, for initial staging or localization of recurrence."

A clinical trial conducted by the UCSF and UCLA research teams on the effectiveness of PSMA PET proved pivotal in garnering FDA approval for the technique at both universities. The PSMA drug used in the technique was developed outside the U.S. by the University of Heidelberg.

"It is rare for academic institutions to obtain FDA approval of a drug, and this unique collaboration has led to what is one of the first co-approvals of a drug at two institutions," said Thomas Hope, MD, an associate professor at UCSF. "We hope that this first step will lead to a more widespread availability of this imaging test to men with prostate cancer throughout the country."

How It Works

For men who are initially diagnosed with prostate cancer or who were previously treated but who have experienced a recurrence, a critical first step is to understand the extent of the cancer. Physicians use medical imaging to locate cancer cells so they can be treated.

PSMA PET works using a radioactive tracer drug called 68Ga-PSMA-11, which is injected into the body and attaches to proteins known as prostate-specific membrane antigens. Because prostate cancer tumors overexpress these proteins on their surface, the tracer enables physicians to pinpoint their location.

The current standard of care in prostate imaging is a technique called fluciclovine PET, which involves injecting patients with fluciclovine, a synthetic radioactive amino acid. Since prostate cancers consume more amino acids than normal prostate cells, the tumors accumulate large amounts of the synthetic tracer, making them easier to detect during scans.

In their research comparing PSMA PET and fluciclovine PET, the UCLA and UCSF research teams found that imaging with PSMA PET was able to detect significantly more prostate lesions than fluciclovine PET in men who had undergone a radical prostatectomy but had experienced a recurrence of their

Continued on next page

Thomas Hope (left), MD, and Peter Carroll, MD, MPH stand at the PACS workstation where the images from the PSMA PETs are viewed and interpreted. Photo by Maurice Ramirez

cancer. Their findings indicate that PSMA PET should be strongly considered both before initial treatment in men with high-risk cancers and in cases of cancer recurrence after surgery or radiation to provide more precise care. The PSMA tracer also can be used in conjunction with CT or MRI scans.

"I believe PSMA PET imaging in men with prostate cancer is a game changer because its use will lead to better, more efficient and precise care," said Peter Carroll, MD, MPH, a professor at the UCSF Helen Diller Family Comprehensive Cancer Center.

"Prostate cancer is one of the most common cancers in men, with more than 190,000 newly diagnosed cases expected just this year alone," said Johannes Czernin, MD, chief of the Ahmanson Translational Theranostics Division at UCLA. "That's why this major effort between the UCLA and UCSF nuclear medicine divisions and our many partners was important and will significantly change for the better how this cancer is detected and treated."

The UCLA research team was led by the nuclear medicine faculty from the molecular and medical pharmacology department's Ahmanson Translational Theranostics Division. They worked in collaboration with the departments of urology, radiation oncology and radiology, along with support from the Geffen School of Medicine, the UCLA Jonsson Comprehensive Cancer Center and the Prostate Cancer Foundation.

The UCSF research team was led by faculty from the molecular imaging and therapeutics section of the department of radiology and biomedical imaging, who worked in collaboration with the departments of urology, radiation oncology and medical oncology. Support was provided by the UCSF Helen Diller Family Comprehensive Cancer Center and a philanthropic gift to the UCSF Department of Urology, and by the Prostate Cancer Foundation.

"'Game changer' is almost an understatement for how prostate cancer patient care could be improved by this technique," said Jonathan W. Simons, MD, CEO of the Prostate Cancer Foundation. "After investing more than $26 million in research on PSMA over many years, we are honored to congratulate the research teams at UCSF and UCLA on their milestone achievement." ■

Q&A with Dr. Hope

In September 2021, the team led by Thomas Hope, MD, at UCSF and Jeremie Calais, MD, at UCLA, published a paper in *JAMA Oncology* (doi:10.1001/jamaoncol.2021.3771) detailing the phase 3 diagnostic efficacy trial that led to FDA approval of PSMA PET.

In addition, the National Comprehensive Cancer Network (NCCN) and the Society of Nuclear Medicine and Molecular Imaging (SNMMI) included PSMA PET in published prostate guidelines and established appropriate use criteria (AUC) for this new imaging technique.

Dr. Hope answers some questions about the significance of these developments and gives insight into what's next for PSMA PET.

What is the main focus of the *JAMA Oncology* paper?

The paper focuses on the role of 68Ga-PSMA-11 PET at time of initial staging. The goal was to compare the imaging results to nodes found at time of surgery in order to determine the sensitivity and specificity of PSMA PET. This study showed that PSMA PET has a high specificity for the detection of nodal metastases, although the sensitivity for small pelvic nodes was lower than expected.

What is the significance of NCCN including PSMA PET in their published prostate guidelines?

This is a very important development. NCCN guidelines are used by many insurance companies to determine what tests to cover. The inclusion in these guidelines will help increase the likelihood of insurance coverage of PSMA PET at time of initial staging and biochemical recurrence. Additionally, the NCCN guidelines recently convinced the FDA to include 68Ga-PSMA-11 PET at time of initial staging for patients with prostate cancer.

What are some highlights from the SNMMI's appropriate use criteria for PSMA PET imaging?

Similar to the NCCN guidelines, the SNMMI AUC document will have an impact on insurance coverage. Through the Protecting Access to Medicare Act (PAMA), high-cost imaging studies will be required to use clinical decision support mechanisms. The AUC document will provide the required documentation to support the use of PSMA PET in the appropriate indications.

What's next for PSMA PET imaging?

Next up is to grow the use of PSMA PET for patient selection in PSMA radioligand therapy.

Currently there are no FDA approved agents for PSMA radioligand therapy, but we expect approval of 177Lu-PSMA-617 in the coming months, and so we will start using PSMA PET in this patient population. Additionally, now that PSMA PET will be widely available, we will need to complete clinical trials in order to understand how to manage patients better based on the results of PSMA PET imaging studies. ■

THERANOSTICS / UCD

Clinic Transforms Cancer Treatment by Combining Diagnosis and Therapy

Conventional treatments for cancer, such as chemotherapy, external beam radiation and surgery, don't always work, but hope is on the horizon for some patients with certain cancers.

Department of Radiology Chair Elizabeth Morris, MD, reviews clinic blueprints with Cameron Foster, MD, the new director of the theranostics division.

UC Davis Health is leveraging the next generation in nuclear medicine treatments to attack cancers in ways that traditional options cannot by themselves. The new approach, called *theranostics*, is revolutionizing cancer care by combining both diagnostics and therapeutics in delivering targeted radiotherapy. UC Davis Health is planning to expand its current theranostics therapy capabilities with a new clinic dedicated to the innovative treatment.

Typically injected into the patient's bloodstream, therapeutic radiopharmaceuticals travel and deliver radiation directly to a tumor site, destroying cancerous cells while leaving healthy tissue alone.

"The radiation dose is selected to ensure minimum radiation exposure to healthy tissues and maximum accuracy in targeting diseased tissues," said UC Davis Chief of Radiology Elizabeth Morris.

As part of its growing commitment to advancing radioactive targeted therapy, the UC Davis School of Medicine Department of Radiology appointed Cameron Foster, director of the new UC Davis theranostics division and professor of clinical nuclear medicine, to oversee the construction of the new theranostics clinic.

"Modern theranostics is transforming nuclear medicine," said Foster. "We are moving away from nuclear medicine being used largely for imaging. We're taking advantage of novel compounds that both pinpoint and target tumors, allowing for removal of diseased tissue with limited side effects while aiming to minimize the chances of the cancer returning."

Radiopharmaceuticals deliver targeted amounts of the required therapeutic agents. This burgeoning field of theranostics enables nuclear medicine doctors to progress beyond merely interpreting diagnostic scans and expand into involvement in treating patients. Consequently, UC Davis has begun to rethink the environment for patients being treated with nuclear medicine.

"There is a lot more patient interaction with theranostics," said Foster. "The same doctor who interpreted patients' scans identifying their active cancer may now also be the one treating them. That's exciting for patients because they are getting acute care from a nuclear medicine physician who is intimately aware of the characteristics of their tumor and will monitor it carefully while using targeted radiotherapy to treat."

The new dedicated theranostics clinic will reflect the evolving relationship between patient and doctor. Some features of the new clinic now under construction include consultation rooms to help physicians share images with patients and go over nuclear medicine treatment options. The facility, currently expected to be finished near the end of 2023, also will include space dedicated to supporting radiopharmaceutical therapy research and patients participating in nuclear medicine therapeutic clinical trials.

Private therapy rooms are being built to administer:

- Radioiodine therapies for thyroid disorders and cancers
- Strontium-89 and Samarium-153 therapies for bone metastases from a wide variety of cancers
- Radium-223 therapy for bone metastasis from prostate cancer
- Lutetium-177 dotatate therapy (Lutathera) for certain neuroendocrine tumors
- Emerging radiopharmaceutical therapeutic agents

"Often we see patients who have exhausted all other options," said Foster. "They are at a very expensive stage in their disease and we want to give them the best possible chance of survival while managing their cancer in the most efficient way."

The theranostics clinic will centralize care for patients. They'll receive their treatment and have their tumor tracked at the same location by the same medical staff who often become like family to them.

"It's a centralized brain trust where friendly and familiar faces detect, treat and track tumors all in one location," said Morris. "This one-stop shop for our patients is a real game changer for medicine, and we're proud to be at the forefront." ■

INTERVENTIONAL / UCSD

Interventional Radiologists Tackle Cancer Pain

Cancer pain is one of the most common reasons for emergency room visits and hospitalization and has been linked to increased 30-day mortality. With cancer pain inadequately treated in up to 80% of patients, UCSD Radiology launched a palliative interventional radiology service to bridge the gap.

From left: Sean Tutton, MD, Professor, Interventional Radiology; Anthony Tadros, MD, Assistant Clinical Professor, Interventional Radiology; Frank Chiarappa, MD, Assistant Professor, Orthopaedic Surgery; Marin McDonald, MD, PhD, Assistant Clinical Professor, Neuroradiology

> **"Patients are living longer but have more skeletal complications of their cancer therapy. That's where we come into play as interventional oncologists."**
>
> *— Sean Tutton, MD*

Led by Sean Tutton, MD, and Anthony Tadros, MD, interventional radiologists at UCSD, the palliative IR service was developed to provide innovative minimally-invasive procedures for cancer patients. Harnessing a multi-disciplinary approach, these therapies have helped alleviate suffering, reduce opioid needs, and help patients discharge so that they may spend their final days with family at home.

"We're turning many cancers into chronic diseases and that's a huge paradigm shift," Dr. Tutton said. "Patients are living longer but have more skeletal complications of their cancer therapy. That's where we come into play as interventional oncologists. We can focus on those patients, provide minimally invasive therapies that relieve pain, and improve quality of life."

Multidisciplinary palliative care

In September 2020, Dr. Tadros helped establish a weekly multidisciplinary palliative care conference to meet the needs of inpatients with difficult to manage cancer pain. A core group of physicians attends the tumor-board style conference. Representatives include interventional radiologists Dr. Anthony Tadros and Dr. Sean Tutton; palliative care faculty Kira Skavinski, DO, Kadee Winters, MD, and Paula Mesarwi, MD; anesthesiologist Joel Castellanos, MD; and radiation oncologist Drew Bruggeman, MD. Patients presented at the conference have significant pain medication needs with very high oral morphine equivalents (sometimes grams) in addition to salvage therapies such as ketamine and lidocaine infusions. The conference has led to the successful treatment of numerous patients, helping them discontinue their patient-controlled analgesia (PCA) and reach their goal of discharge to home. It has also facilitated the treatment of numerous outpatients through new interdisciplinary relationships with oncology providers across the health system.

To highlight the unmet need of these patients within the health system, the number of palliative IR procedures performed in 2020-2021 increased 569% compared to the previous academic year. Palliative IR procedures included nerve blocks, neurolysis (celiac, hypogastric, intercostal, pudendal, etc.), bone tumor ablation (radiofrequency ablation, cryoablation), vertebroplasty/kyphoplasty, and pelvic and extremity osteoplasty.

Given the success of this partnership, Dr. Tadros and Dr. Tutton are expanding its scope of practice to the outpatient setting with the development of a multidisciplinary cancer pain clinic. The clinic will offer a tailored approach of pharmacological and non-pharmacological therapies in an interdisciplinary fashion, including specialists from interventional radiology, palliative care, anesthesiology, and radiation oncology. The program is designed to rapidly schedule patients, provide preliminary assessment, and coordinate consultant visits to compress the care experience into the most efficient and patient-centric way possible. The target population is patients with cancer pain who are especially at risk for emergency department visits and hospitalization.

The cancer pain clinic will meet on a weekly basis to allow for urgent patient add-ons from both outpatient (e.g. oncologists) and inpatient (e.g. emergency physicians) referrals. Same-day interdisciplinary discussion will allow for developing personalized treatment plans and expedited therapy scheduling. Patients will be followed longitudinally with the objective to optimize cancer pain relief; decrease adverse effects related to opioid use; and reduce ED visits, hospital admissions, and readmissions secondary to cancer pain.

Radiology takes on spine metastases

As spinal metastases are among the leading causes of cancer pain affecting up to 40% of cancer patients, Dr. Tadros and Dr. Tutton have recently spearheaded a Metastatic Spine Working Group for the UCSD health system. The group aims to provide a comprehensive decision-making framework that facilitates a personalized treatment plan for patients. Collaborators include neuroradiologist Marin McDonald, MD, PhD; neurosurgeon Joseph Osorio, MD; orthopaedic surgeon Todd Allen, MD, PhD; and radiation oncologists Drew Bruggeman, MD, and James Urbanic, MD.

Managing metastatic spine disease requires a complex assessment of spinal stability, neurologic function, oncologic history and imaging. Wide-ranging therapies include biopsy, surgical decompression and stabilization, vertebroplasty and kyphoplasty, spinal ablation, and radiation (Figure 1). As early treatment is critical to improved patient outcomes, Dr. Marin McDonald, Director of MRI, is developing an imaging-based reporting tool to identify patients early in their disease for referral to the group for management. Through an innovative multidisciplinary clinic model that includes a consensus work-up and treatment algorithm, the group aims to streamline care for these patients and ultimately launch a regional second-opinion program.

Radiology partners with Orthopaedic Surgery

In November 2021, Alex Norbash, MD, chair of radiology, and Susan Bukata, MD, chair of orthopaedic surgery, created an extraordinary partnership with the joint recruitment of Sean Tutton, MD. Dr. Tutton is a nationally and internationally recognized interventional radiologist who has helped propel the field of image-guided musculoskeletal interventions. Board-certified in hospice and palliative medicine, his research focuses on ablation of soft tissue tumors including desmoids, and ablation and stabilization for patients suffering from painful cancer-related spine and pelvic fractures. His shared faculty appointment in the Departments of Radiology and Orthopaedic Surgery has created an unprecedented collaborative paradigm for the UCSD health system that will dramatically advance the field of minimally invasive interventions for cancer-pain.

Prior to joining UCSD, Dr. Tutton pioneered several percutaneous interventions for unstable pelvic metastatic disease including osteoplasty, ablation, and screw fixation. In collaboration with orthopaedic surgeon Frank Chiarappa, MD, Dr. Tutton has used cone-beam CT and needle guidance software (3D-augmented fluoroscopy) in the interventional radiology suite to perform minimally-invasive stabilization procedures that have significantly improved patient cancer-pain and function (Figure 2). As he partners with team members from across the health system, the shared vision is to build a multidisciplinary bone health program at UCSD that will transform the patient experience. ■

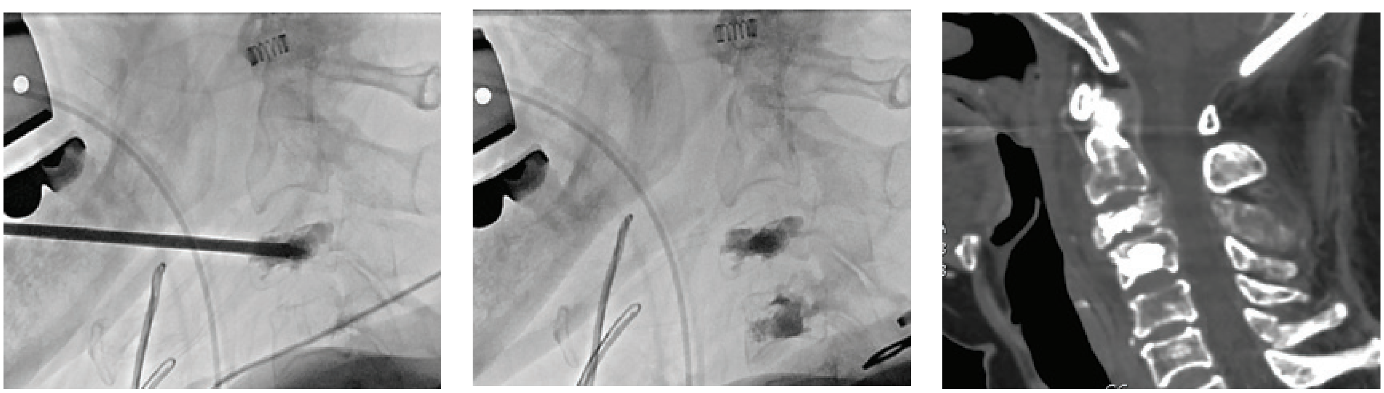


Figure 1: 78 year-old female with metastatic lung cancer and intractable neck pain with opioid-related complications. Interventional radiologists Dr. Sean Tutton and Dr. Anthony Tadros performed C3 and C4 vertebroplasty for pathologic fractures via trans-oral approach with significant improvement in pain and mobility. Patient subsequently underwent consolidative radiation therapy managed by radiation oncologist Dr. Drew Bruggeman.

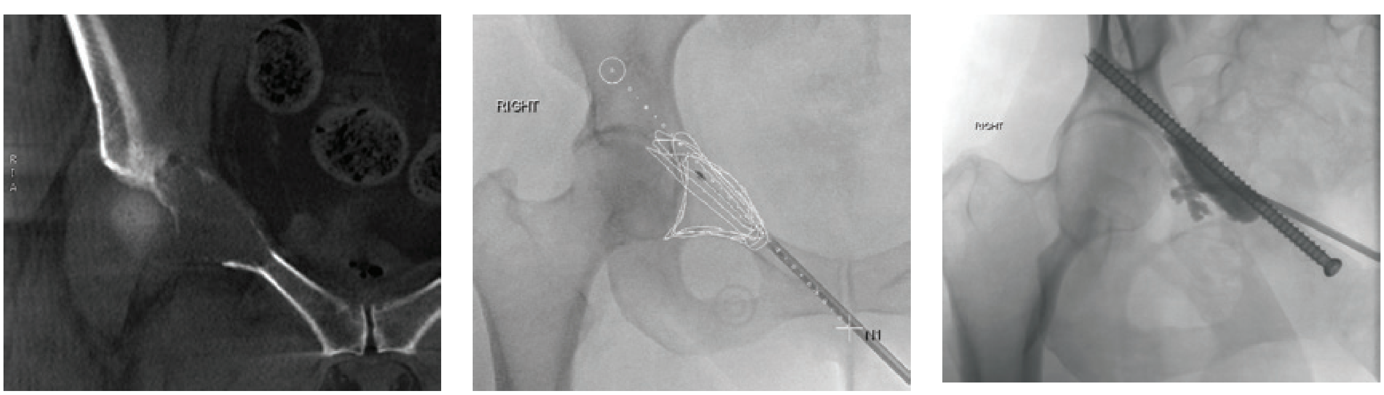


Figure 2: 46 year-old female with metastatic sarcoma to right pubic ramus and mechanical hip pain. Interventional radiologist Dr. Sean Tutton and orthopaedic surgeon Dr. Frank Chiarappa performed collaborative single-session percutaneous microwave ablation, screw fixation and cementoplasty using 3D augmented fluoroscopy in IR suite. Patient had significant pain relief with improved ambulation.

INTERVENTIONAL / UCI

Musculoskeletal Interventional Oncology at UC Irvine

AUTHORS:

Andy Tomasian, MD, Associate Professor and MSK Fellowship Program Director

Christina Boyd, MD, Assistant Clinical Professor

Bone is the third most common site involved by cancer metastases, and skeleton-related events such as intractable pain, pathologic fracture, and neurologic compromise often will negatively affect patients' quality of life and functional independence. In fact, the annual medical-economic burden related to bone metastases is a substantial component of the total direct medical cost estimated by the National Institutes of Health.

There have been substantial recent advances in percutaneous image-guided minimally invasive interventions for the management of patients with osseous metastatic disease, particularly thermal ablation, cementoplasty, as well as embolization. These interventions are performed in conjunction with or are supplemented by adjuvant radiation therapy, systemic therapy, surgery, or opioids. Together, they help achieve timely and durable pain management, local tumor control, and skeletal stabilization in a subset of patients. Such minimally invasive interventions have been incorporated in the patient treatment algorithms as part of the National Comprehensive Cancer Network and American College of Radiology guidelines.

Our team of radiologists at UC Irvine involved in care of patients with bone metastases, as well as benign bone tumors, perform these interventions in a multidisciplinary setting with close collaborations with the orthopedic oncologic surgeons as well as other referring physicians and provide patients who primarily suffer from skeletal related events with minimally invasive, safe, and efficacious treatment options.

There are seemingly vast opportunities to advance the field of musculoskeletal interventional oncology and our team looks forward to continuing the collaborations with our colleagues at various clinical services to provide alternative state-of-the-art percutaneous treatment options to many patients with musculoskeletal tumors.

CASE 1: A 62-year-old man with metastatic liposarcoma and T4–T7 metastatic lesion with spinal cord compression who presented with progressively intractable biologic, mechanical, and radicular pain and no evidence of myelopathy. This complex case demonstrates multidisciplinary approach to patient care.

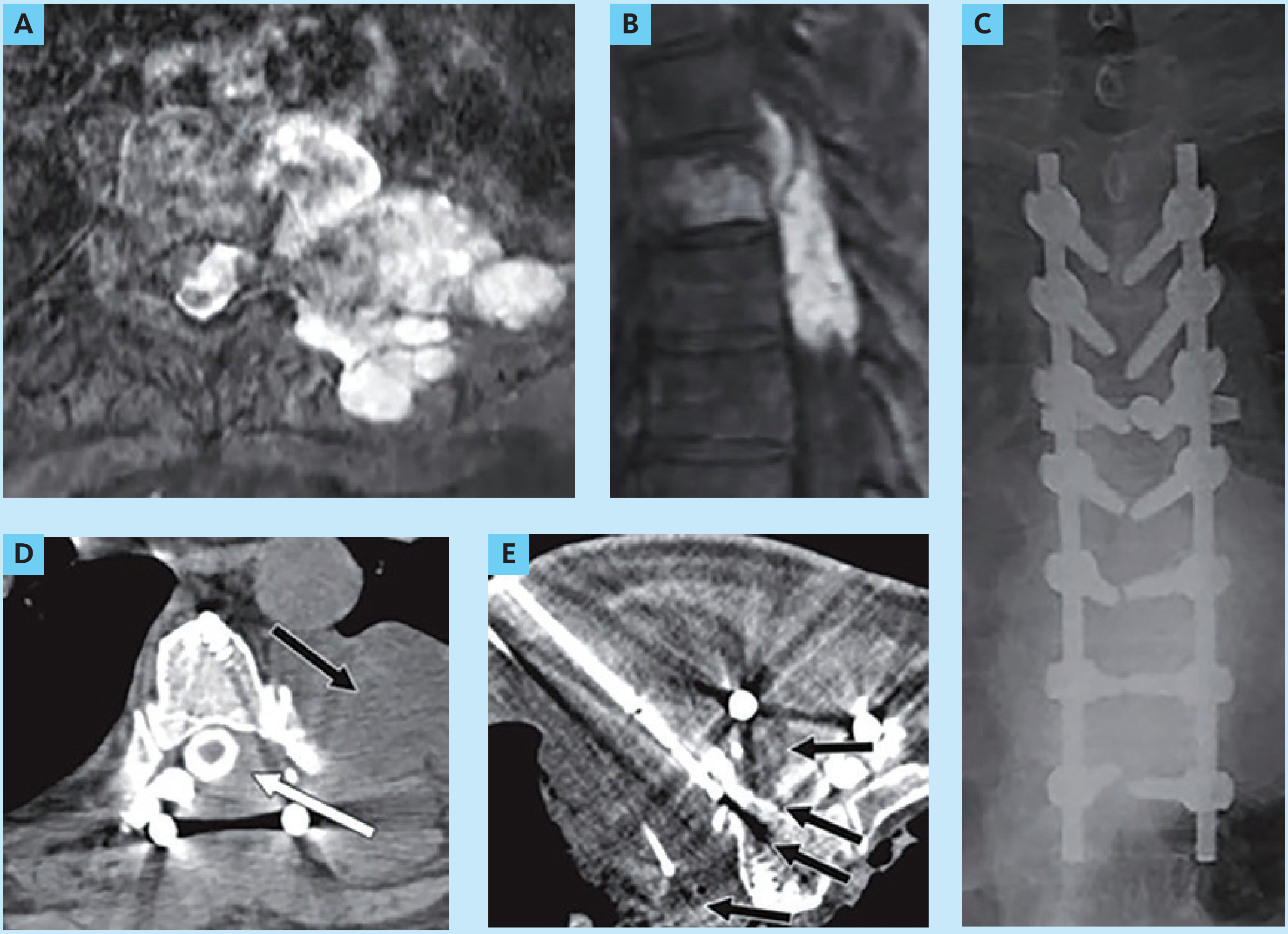
IMAGES:

- Axial (A) and sagittal (B) T1-weighted fat-suppressed contrast-enhanced MR images show heterogeneously enhancing left paraspinal T4–T7 mass extending into central canal and left neuroforamina with mass effect on, anterolateral displacement, and deformation of thecal sac with involvement of left aspect of vertebral body and left pleural component.
- The patient initially underwent surgical resection with gross tumor removal from central canal, decompression and instrumented spinal fusion (**C**).
- The patient re-presented with new progressive upper back pain. Axial CT myelogram (**D**) shows recurrent tumor (white arrows) in central canal and left neuroforamina as well as progression of pleural component (black arrow). Following stereotactic body radiation therapy (21 Gy in three fractions), symptoms persisted, and patient underwent CT-guided cryoablation under general anesthesia for pain palliation and local tumor control.
- Prone CT image during cryoablation (**E**) shows placement of multiple cryoprobes with hypoattenuating ice ball extending to central canal, neuroforamina, vertebral body, and encompassing pleural component (arrows). Note that intraprocedural myelogram is performed to identify spinal cord and provide thermal protection. Evoked potential monitoring was also performed for thermal protection. Post-cryoablation MRI (not shown) showed local tumor control and the patient remained nearly symptom free.

CASE 2: Metastatic clear cell renal cell carcinoma with painful right humerus osteolytic metastasis. Patient was on chronic opioids and unable to use his right arm. Pre-operative embolization was performed to decrease hemorrhage followed by cooled radiofrequency ablation of the metastatic lesion for pain control and local tumor control. Prophylactic intramedullary nailing was performed by orthopedic oncologic surgery with only 50 cc blood loss. Patient has no pain in his arm, has returned to work, and is no longer on pain medications.

IMAGES:

- Right proximal humerus shaft osteolytic metastasis (**F**) at risk for impending pathologic fracture.
- Angiograms (**G**, **H**) of the hypervascular right humerus metastasis before and after embolization.
- CT-guided, cooled radiofrequency ablation of the right humerus osteolytic metastasis after Embolization (**I**).
- Prophylactic intramedullary nailing with only minimal blood loss to minimize pathologic fracture (**J**). ■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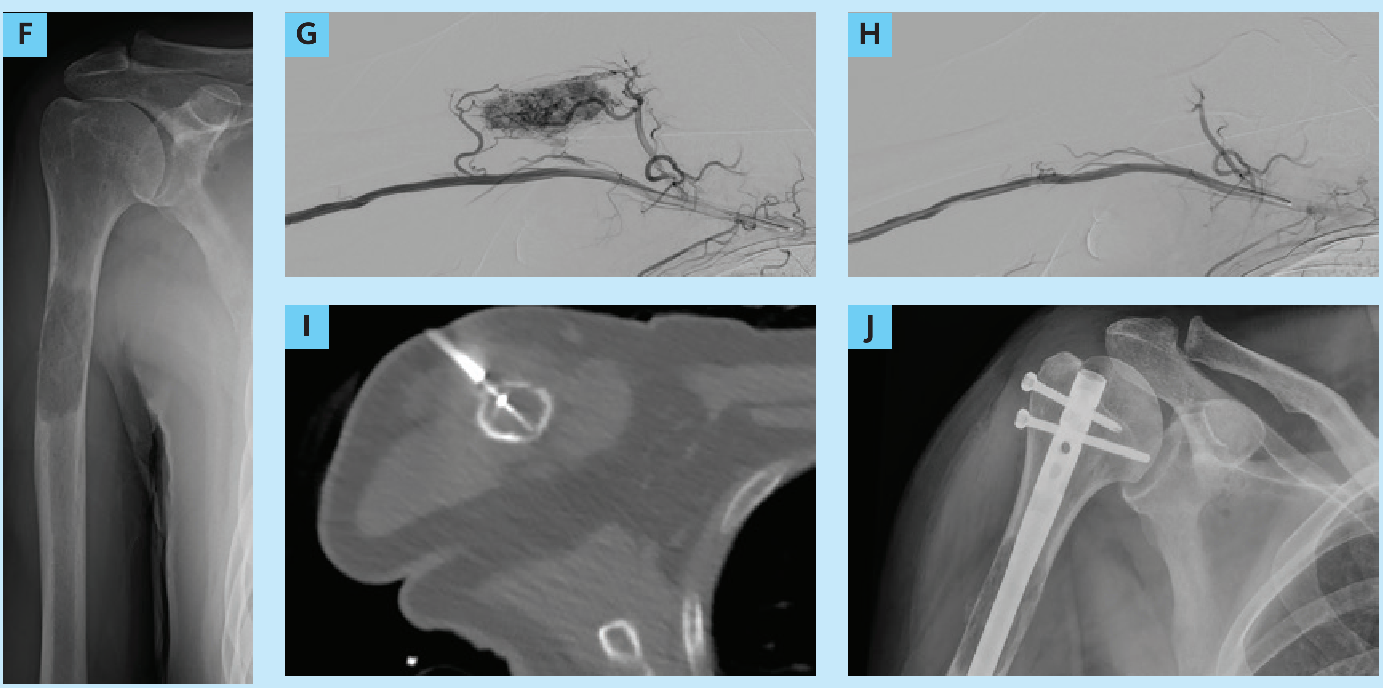
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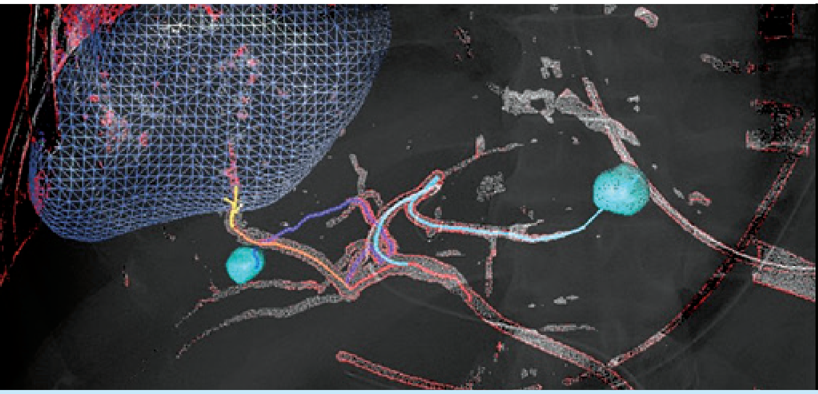

Figure 1: A large hepatocellular carcinoma was segmented (blue mesh) as were two smaller tumors (green mesh). The vessels supplying the tumors are shown in various colors guiding the physician to the treatment area. The conventional image is displayed in grey scale in the background.

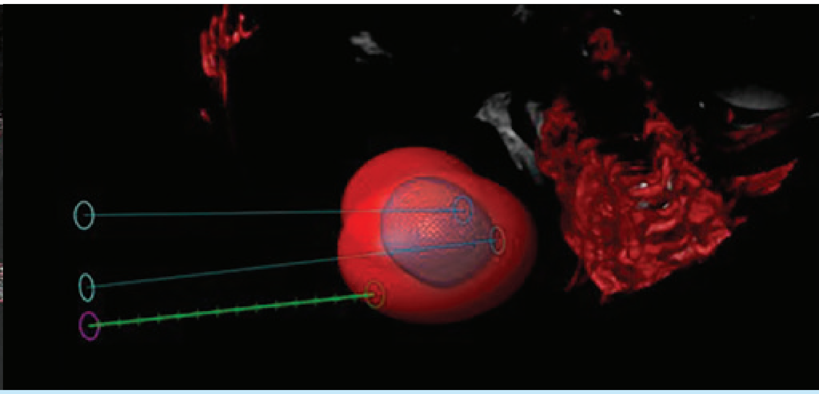

Figure 2: Renal cell carcinoma (blue mesh) is localized among benign kidney tumors by fusion of the contrast enhanced MRI and intraprocedural cone beam CT. This enables localization of the target tumor and planning of the treatment.

INTERVENTIONAL / UCI

Targeting the Invisible: Advanced Imaging in Interventional Radiology

AUTHOR:

Nadine Abi-Jaoudeh, MD, Professor and Division Chief of Vascular and Interventional Radiology

PET scans and contrast enhanced magnetic resonance imaging (MRI) have improved lesion detection but definitive diagnosis and/or molecular profiling still requires biopsy specimens.

These procedures are performed with ultrasound and computed tomography guidance. The challenge of targeting a lesion visible on imaging technologies not available in the procedure room is resolved with the use of navigation technologies. Using fusion, images from pre-procedural modalities can be registered to intra-procedural ultrasound, CT or even CBCT enabling advancement of a needle or an ablation probe to the lesion.

Research by UCI interventional radiologists has shown that these technologies allow targeting lesions not visible on conventional imaging and/or targeting a specific area in a lesion such as guiding a biopsy needle into the PET avid area or the non-necrotic portion of a lesion. A prospective randomized trial by Dr. Nadine Abi-Jaoudeh, Division Chief of Interventional Radiology at UCI, comparing navigation technologies to conventional imaging for lesions seen on ultrasound or CT demonstrated that use of these technologies reduced the time and the number of needle repositioning required to reach a target tumor. Needle repositioning is associated with increased risk of complications and, therefore, this technology improves patient safety.

Nadine Abi-Jaoudeh, MD

These image fusion techniques can be used to plan ablation and embolization procedures. The tumor can be segmented on advanced intra-procedural imaging, the ablation probe trajectories can be planned in advance and displayed in real time. The predicated ablation zone can be displayed to ensure coverage of the tumor with a safety margin. Finally, once completed the ablation zone is segmented to confirm complete treatment coverage of the tumor. The use of image fusion and navigation technologies resulted in changes in number of ablation probes and/or duration of ablation in 1/3 of patients with technical effectiveness of 96.1%.

During embolization, these technologies have been shown to improve detection of the number of vessels supplying a tumor that need to be treated. The post embolization scans can be overlaid to the pre-treatment scan to ensure that the entire tumor has been treated. Complete tumor coverage by embolization has been shown to increase the rate of complete response and progression free survival in patients with hepatocellular carcinoma. Therefore, use of these advanced imaging technologies is correlated with improved patient outcome.

Another potential advantage of these technologies is the possibility of reduction in radiation and contrast material dose. Indeed, in the prospective biopsy trial, the skin entry radiation dose decreased by 29%. Also, there was a 50mL reduction in contrast use compared to conventional imaging. ■