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INNOVATIONS
IN CANCER

SUMMER 2015

Quality Improvement: A 24/7 Proposition

To achieve ever-improving outcomes for our patients requires constant commitment – from an expansive vision to the single-mindedness to attend to the seemingly smallest detail.

In this issue of Innovations in Cancer, we explore some of the quality-improvement investigations and efforts under way at University Hospitals Seidman Cancer Center.

Our cover story features the work of radiologist **Donna Plecha, MD**, as well as surgeons **Robert Shenk, MD**, and **Julian Kim, MD**. Drs. Plecha and Shenk have shown that wire localization of metastatic axillary lymph nodes dramatically increases successful surgical removal in breast cancer patients, even in the growing number of women undergoing neoadjuvant therapy. Their simple innovation promises to open the option of less-invasive sentinel lymph node biopsy to many more women with metastatic disease. Similarly, Dr. Kim's three-year follow-up study of the radiopharmaceutical tilmanocept has confirmed its value as a mapping agent for use in sentinel lymph node biopsy.

Supportive Oncology Director **Elizabeth Weinstein, MD**, **MS**, is working on quality improvement from a different perspective. As one of the leads on UH Seidman Cancer Center's $4.7 million project funded by the Center for Medicare & Medicaid Innovation, she is testing an innovative payment model for advanced stage patients – a model that aims to make providing care coordination and early palliative care both feasible and sustainable.

Radiation oncologists **Mitchell Machtay, MD**, and **Simon Lo, MD, FACR**, are addressing quality improvement through technology. Dr. Machtay's work on PET scans in stage 3 non-small cell lung cancer has shown that PET-derived metrics can be used as valid prognostic indicators and as stratification variables in clinical trials. At the same time, Dr. Lo's work comparing the accuracy of treatment-planning algorithms for patients with spinal lesions indicates a clear winner – and reminds us to always keep highest-quality care as our goal.

These are just a few of the many quality improvement projects under way at UH Seidman Cancer Center. But they represent the best of what we offer to our patients as we continue to work for increasingly better outcomes.

Warm regards,
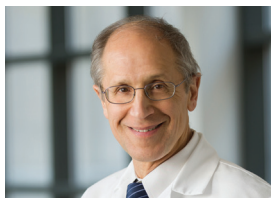
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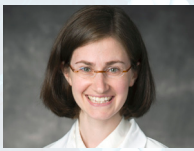
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Paradigm / Shift

Innovative payment model for complex cancer patients under study at UH Seidman Cancer Center

A $4.7 million Health Care Innovation Award will allow University Hospitals Seidman Cancer Center to empower its complex cancer patients with supportive services in a three-year project to measure the impact of early intervention on both quality of care and cost containment.

The U.S. Department of Health and Human Service's Health Care Innovation Awards have been given since 2012 to support public and private organizations in transforming health care delivery by improving outcomes while reducing total costs. The UH Seidman Cancer Center project, titled "Evidence-Conformant Oncology Care," is testing a unique model to enhance care of adult cancer patients with late-stage disease.

"We expect that this program will inform how UH Seidman and other cancer centers provide care coordination and supportive care services to some of the sickest patients," says Elizabeth Weinstein, MD, MS, Medical Director of Supportive Oncology for UH Seidman Cancer Center. "It is testing an innovative payment model that will hopefully allow us to make services like care coordination, early palliative care and ongoing discussions with patients about their goals of care both feasible and sustainable."

Initially, UH Seidman Cancer Center will automatically enroll patients with stage 3 or 4 solid tumors who have Medicare or Medicaid insurance. Eventually, a wider range of patients and payors will be introduced, involving patients with multiple comorbidities and high health care utilization who may benefit from early intervention. Over the course of the grant, the team expects to enroll more than 1,600 patients.

This broader array of services supports not only the patients but the physicians and clinical staff as well. Each patient sees a palliative care physician or nurse practitioner early in his or her treatment for proactive symptom management. Nurse care coordinators then develop a relationship with the patient and ensure that communication is improved throughout the patient's care team for as long as the patient is treated at University Hospitals. On a monthly basis, the team assesses each patient's emotional, social and physical well-being using a screening tool on an iPad that is linked to the electronic medical records (EMRs). These assessments facilitate discussions about each patient's goals of care and guide the development of the patient's personalized care plan. The enhanced communication is expected to result in a more informed, engaged patient who follows a care plan to improve his or her quality of life, and the additional documentation shared in the EMR can enhance the quality of care provided by physicians and staff.

These resources may also serve to keep patients on the proper care path – out of the emergency department and reducing unnecessary admissions.

"Medical care is so complicated these days and the medical system is so complex that it is the hope that these care coordinators will smooth things out for our patients," says Dr. Weinstein, who has received positive feedback on the project from staff and patients. "Our goal is always to provide treatment that matches with patient values, but this added resource will ensure that patients are receiving the full support of UH Seidman Cancer Center.

"Integration of these functions into our multidisciplinary model of care will ensure that our patient-centered care is truly aligned with both the clinical evidence and the personal values of each patient, yielding improved quality of care and contributing to the sustainability of the health care system."

For more information about this project, contact Dr. Weinstein at Elizabeth.Weinstein@UHhospitals.org.
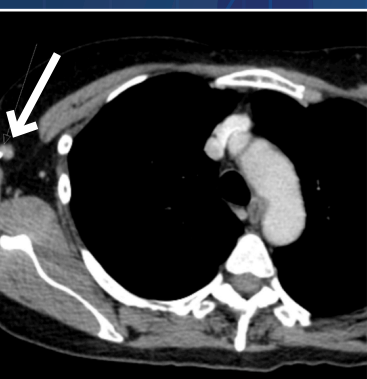
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on **the** W**I**RE

Figure 1: Patient with history of invasive ductal carcinoma, status post preoperative chemotherapy, and right axillary lymph node surgery. Axial CT scan image done after surgery demonstrates right axillary lymph node clip remaining after surgery (white arrow).
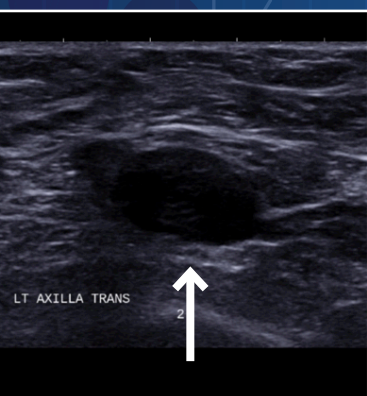
Figure 2 (a): Ultrasound of metastatic abnormal axillary lymph node with loss of the normal fatty hilum and cortical thickening (white arrow).
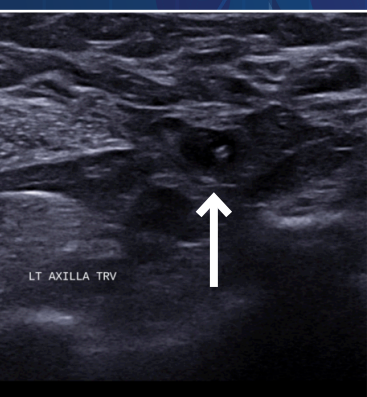
Figure 2 (b): Ultrasound of the same lymph node after six months of chemotherapy. The lymph node is not visualized, only the remaining clip is detectable for needle localization (white arrow).

Study suggests wire localization may expand pool for SLNB, decrease unnecessary axillary dissections

Neoadjuvant chemotherapy is increasingly being used in women with invasive breast cancer, especially among women with larger tumors and positive axillary lymph nodes.

"It has several advantages, but the most important one is that it can reduce the size of large primary tumors, increasing the chances for a lumpectomy," says Donna Plecha, MD, Director of Breast Imaging at University Hospitals Seidman Cancer Center.

With the success of neoadjuvant therapy, however, has come an interesting new problem. The chemotherapeutic agents shrink metastatic lymph nodes so much that they are extremely difficult to detect afterward, both during a clinical exam and during sentinel lymph node biopsy (SLNB).

"The nodes can fibrose down so that they don't pick up the dye from the SLNB procedure," says Robert Shenk, MD, a breast surgeon and Medical Director of the Breast Center at UH Seidman Cancer Center. "Because of this, the standard of care has been to remove all the lymph nodes after neoadjuvant therapy to be on the safe side. SLNB hasn't really been the standard for these patients." In fact, the false-negative rate for SLNB in a recent American College of Surgeons Oncology Group (ACOSOG) trial, measured against axillary lymph node dissection (ALND), was 12.6 percent.

To address this issue, Drs. Plecha, Shenk and their colleagues at UH Seidman Cancer Center now use ultrasound-guided wire localization to 'flag' biopsy-proven metastatic axillary lymph nodes. They place the wire about an hour before SLNB or ALND surgery, guided by the 'clip' in the node placed during the core needle biopsy.

Research shows that this approach yields good results. In a retrospective study of 107 breast cancer patients at UH Seidman Cancer Center, Drs. Plecha and Shenk found that wire localization improved success in removing metastatic axillary lymph nodes from just under 80 percent (without wire localization) to just over 97 percent (with wire localization). For those women undergoing neoadjuvant chemotherapy, the results were similar. For those undergoing SLNB, successful lymph node removal improved from just under 86 percent (without wire localization) to 100 percent (with wire localization). The team published its results recently in the

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Study Confirms Value of New Agent for Lymphatic Mapping in SLNB

The radiopharmaceutical tilmanocept (Lymphoseek®) received approval from the U.S. Food and Drug Administration in 2014 as the first FDA-approved mapping agent to guide sentinel lymph node biopsy (SLNB). "Our group at University Hospitals played a significant role in the clinical trials that led to the approval of this agent," says Julian Kim, MD, Division Chief of Surgical Oncology and Chief Medical Officer at UH Seidman Cancer Center.

Now, a new, three-year follow-up study at UH Seidman Cancer Center confirms the value of the new agent (NCT00671918). Among 57 clinically node-negative breast cancer patients who underwent SLNB with use of tilmanocept, 100 percent were free of regionally recurrent disease three years later. In addition, the false-negative rate for SLNB among these patients was zero. Thirteen patients were correctly identified as node-positive with the SLNB; 44 patients were correctly identified as node-negative.

Among 32 melanoma patients, 93 percent were cancer-free after three years. Four patients were correctly identified as node-positive with SLNB; 27 were correctly identified as node-negative and one patient was falsely identified as negative, yielding a false-negative rate of 20 percent.

Dr. Kim and his colleague James O'Donnell, MD, Division Chief of Nuclear Medicine at UH Case Medical Center and Professor of Radiology at Case Western Reserve University School of Medicine, presented these findings at the recent meeting of the Society of Surgical Oncology. "The long-term follow-up on the use of this agent is very promising and positive," Dr. Kim says.

Previous studies of tilmanocept have shown an SLNB localization rate of more than 98 percent, as well as a failed detection rate of less than 2 percent – performance significantly better than the sulphur colloid that has traditionally been used in lymphatic mapping.

"The unique aspect of tilmanocept is that it has a very small particle size, which binds to receptors of macrophages in the lymph node," Dr. Kim says. "With sulphur colloid, it is less predictable in how it moves from the breast to the lymph nodes. Some particles can move out of the first node and into the other nodes, which is a disadvantage. You want to remove only the initial lymph nodes that the agent is getting to, not the second and third ones down the line."

Annals of Surgical Oncology (Plecha, et al, 2015; DOI 10.1245/s10434-015-4527-y).

Somewhat surprisingly, ultrasound-guided wire localization also increased the successful removal of metastatic nodes in ALND. Without it, the success rate was just under 78 percent, but with it, the success rate was more than 96 percent.

"People may think they're being very thorough by doing a full lymph node dissection, but you can miss positive nodes that way, too," Dr. Shenk says. "The extra step of wire localization really adds value."

For Drs. Plecha and Shenk, the hope is that this quality improvement will result in more accurate staging of breast cancer patients and therefore more appropriate treatment. Ultimately, they hope it will also allow more breast cancer patients to be candidates for SLNB after neoadjuvant chemotherapy.

"With some of the newer neoadjuvant chemotherapeutic agents, between 30 and 60 percent of breast cancer patients have a pathologic complete response," Dr. Shenk says. "Accurate SLNB with wire localization would result in these patients avoiding ALND and the increased risk of lymphedema and other associated morbidities, such as pain, numbness and decreased arm mobility. In simple terms, we may be saving a large group of women from axillary dissections they don't need."

Dr. Plecha concurs. "Accurate SLNB would allow it to become standard treatment after neoadjuvant therapy," she says. "With it, we can be much more targeted with our surgery. Less is better."

For more information about this study, please contact Dr. Plecha or Dr. Shenk at Donna.Plecha@UHhospitals.org or Robert.Shenk@UHhospitals.org.

New study validates prognostic value of PET scans in stage 3 non-small cell lung cancer

Stage 3 non-small cell lung cancer remains one of radiation oncology's most intractable challenges. Surgery is usually not an option, leaving definitive chemoradiation as the standard of care.

"Some of these people can be cured with well-designed chemotherapy and radiation together. But while there have been some advances in radiation technology, the overall treatment unfortunately hasn't changed much in more than 10 years," says Mitchell Machtay, MD, Chairman of the Department of Radiation Oncology at University Hospitals Seidman Cancer Center.

Prognostic factors for the disease, too, have been hard to come by.

"In stage 3 non-small cell lung cancer, other than the age and general health of the patient, there has never been a truly validated prognostic factor," Dr. Machtay says.

That changed somewhat two years ago, when the first results of a large trial examining the prognostic value of pre- and post-treatment PET scans were published in the Journal of Clinical Oncology (Machtay, et al, 2013; DOI 10.1200/JCO.2012.47.5947). The research group, led by Dr. Machtay, found that patients with elevated uptake of F-fluorodeoxyglucose (FDG), as shown on the post-treatment PET scan, tended to have poorer survival than other patients.

"We hypothesized that the PET scan you use for radiation planning could also give you valuable information about prognosis, and that proved to be the case," Dr. Machtay says.

Now, Dr. Machtay and his group have expanded on this work. In a paper recently published in the Journal of the National Cancer Institute, they report that metabolic tumor volume (MTV) before treatment, as measured on FDG-PET scan, predicts clinical outcomes for stage 3 non-small cell lung cancer patients treated with chemoradiotherapy (Ohri, et al, 2015; DOI 10.1093/jnci/djv004). Specifically, they found that patients with higher pretreatment MTV were more likely to experience treatment failure. Median survival for those in the lowest third for MTV was 29.7 months, 21.2 months for the middle third of MTV and 13.6 months for those with the greatest MTV. For its determinations of tumor edges and other PET metrics, the research group used "PET Edge" and other software from MIMVista, developed by former University Hospitals biophysicist Dennis Nelson, PhD.

The prospective, multicenter study included 214 patients with stage 3 non-small cell lung cancer – one of the largest prospective PET-scan trials in this population to date. It included academic medical centers like UH Seidman Cancer Center, but also community hospitals and international sites in Canada and South Korea.

For Dr. Machtay, the findings of this study point toward a more effective method of stratifying stage 3 non-small cell lung cancer patients for future clinical trials. "Right now, patients are stratified by age, stage and performance status. This new information about MTV really tells us something about the biology of the tumor.

"We hypothesize that selectively intensifying therapy may benefit those patients with high-volume disease, who are at increased risk for early local disease progression," he adds. Dr. Machtay is currently one of the national leaders of a clinical trial evaluating intensified radiation therapy, based on findings from patients' mid-treatment PET scans. This study, and several other stage 3 non-small cell lung cancer clinical trials, are available at UH.

For more information on the thoracic oncology program at UH Seidman Cancer Center or to refer a patient, contact Dr. Machtay at **Mitchell.Machtay@UHhospitals.org**.

PET
PROGNOSIS

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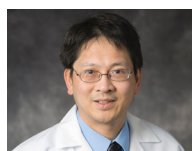
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Computation Conundrum

First-of-its-kind study comparing SBRT-planning algorithms in thoracic spinal tumors has a clear winner

The accuracy of treatment-planning algorithms is an emerging issue in stereotactic body radiation therapy (SBRT). In patients with lung cancer, research has shown that the Ray Tracing algorithm provides less accurate dose calculations than the more labor-intensive Monte Carlo algorithm.

"What's been shown is that if you use the Ray Tracing planning algorithm to create the treatment plan, you may be overestimating the actual dose to the lung tumor," says Simon Lo, MD, FACR, a radiation oncologist at University Hospitals Seidman Cancer Center. "There is literature showing that this could result in inferior tumor control."

In a first-of-its-kind study, Dr. Lo, UH radiation oncology resident Christian C. Okoye, MD, and other UH Seidman Cancer Center colleagues have examined this issue in patients with thoracic spine lesions treated with CyberKnife®-based SBRT. They've found that the discrepancies between the two treatment-planning algorithms also occur in patients with thoracic spinal tumors.

"We found that treatment plans generated through Ray Tracing calculation methods generally overestimate target dose and coverage," Dr. Lo says. "What is more disturbing, though, is that in a significant portion of patients, the Ray Tracing algorithm underestimates the radiation dose to at-risk structures, including the spinal cord." The group published its findings recently in the journal Technology in Cancer Research & Treatment (Okoye, et al, 2015; DOI: 10.1177/1533034614568026).

Dr. Lo attributes some of the discrepancies seen in the study to the unique aspects of thoracic anatomy.

"The spine is very dense, but lung tissue is a small fraction of its electron density," he says. "In situations where you have one kind of tissue abutting another, there is a possibility that if you're using a suboptimal algorithm, you may be underestimating or overestimating the dose to certain structures."

For the study, Dr. Lo, Dr. Okoye, and UH Seidman Cancer Center colleagues compared the calculations generated for 37 patients with thoracic spine lesions. Parameters compared the radiation dose to 90 percent of the target volume (D90), the volume receiving the prescribed radiation dose (VP) and the maximum radiation doses to the spinal cord, esophagus and skin. Specifically, results show that the Ray Tracing algorithm overestimated D90 by 10 percent or more, when compared with Monte Carlo estimates, in 27 percent of cases and overestimated VP by 10 percent or more in 35 percent of SBRT plans.

"It is plausible that this degree of change in calculated dose and coverage could lead to in-field and marginal treatment failures," Dr. Lo says. "This is particularly relevant because these patients often have so few salvage options when disease control is compromised."

Perhaps more striking, however, were the study's findings on maximum radiation dose to the spinal cord. Results showed that the Ray Tracing algorithm underestimated the Monte Carlo-derived dose by between 5 and 10 percent in almost 14 percent of treatment plans.

"When we do radiosurgery for spinal metastases, the most feared complication is injury to the spinal cord," Dr. Lo says. "We limit the spinal cord to an acceptable dose. If the estimation of the dose to the spinal cord is not accurate, it defeats the purpose.

Just a small miscalculation can paralyze the patient."

At UH Seidman Cancer Center, treatment for all thoracic spinal lesions is planned using the Monte Carlo algorithm, and has been for some time. However, the Ray Tracing algorithm is still widely used at various academic medical centers globally.

"The Ray Tracing method has remained popular because it has been perceived to be quicker, more straightforward and less costly," Dr. Lo says. "In the past, the computer capacity was more limited such that a plan could not be generated within a reasonable amount of time. Back 10 years ago, a Monte Carlo calculation could take several hours."

However, for Dr. Lo, advances in computing power and emerging research on the superiority of the Monte Carlo algorithm argue for moving in a new direction. He's made it a point to share the new UH Seidman Cancer Center research with the manufacturer of CyberKnife and other sites doing CyberKnife-based SBRT.

"This paper shows that if a suboptimal treatment planning algorithm is used for SBRT treatment planning for thoracic spinal tumors, the consequences could be detrimental," he says. "We hope that by getting these findings out, more centers will use Monte Carlo planning algorithm when they are planning SBRT for spinal tumors in the thoracic region."

For more information on CyberKnife-based SBRT at UH Seidman Cancer Center, contact Dr. Lo at Simon.Lo@UHhospitals.org.

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NATIONAL CANCER INSTITUTE HEAD VISITS UH SEIDMAN CANCER CENTER

THIRD ANNUAL SCIENTIFIC SYMPOSIUM

THE HARRINGTON PROJECT FOR DISCOVERY & DEVELOPMENT

The Acting Director of the National Cancer Institute, Douglas Lowy, MD, visited University Hospitals Seidman Cancer Center in late May and met with a team of physician-scientist leaders.

While in Cleveland, Dr. Lowy received The Harrington Prize for Innovation in Medicine at the Harrington Discovery Institute at University Hospitals in Cleveland, Ohio – part of The Harrington Project for Discovery & Development – 3rd Annual Scientific Symposium. Dr. Lowy's research helped pave the way for the human papillomavirus (HPV) vaccine, which was developed in cooperation with Merck and GlaxoSmithKline and approved by the U.S. Food and Drug Administration (FDA) in 2006.

Dr. Lowy has donated his prize money from the Harrington Discovery Institute to the Foundation for the National Institutes of Health.

CASE COMPREHENSIVE CANCER CENTER ELECTED TO NCCN

The Case Comprehensive Cancer Center at Case Western Reserve University, which includes University Hospitals Seidman Cancer Center, has been elected to institutional membership of the National Comprehensive Cancer Network (NCCN). NCCN includes only 26 member institutions in the United States.

"Case Comprehensive Cancer Center brings to NCCN unique and valuable attributes, including a robust genomics program and clinical research operational infrastructure, that indeed will enhance the already extraordinary collaboration of the alliance," says Robert W. Carlson, MD, Chief Executive Officer of NCCN. "We look forward to working with their renowned experts and leadership to further the NCCN mission, support and enhance evidence-based decision-making, and promote the importance of continuous process improvement."

FIVE STAR SENSATION EVENT RAISES $2.25 MILLION FOR UH SEIDMAN CANCER CENTER

Cleveland's most celebrated benefit – Five Star Sensation – raised $2.25 million for programs and research at UH Seidman Cancer Center in late June. Led by Cleveland native and renowned "Iron Chef" Michael Symon, the event attracted more than 2,500 guests with its festive atmosphere and gourmet fare.

Five Star Sensation has raised more than $16 million for UH Seidman Cancer Center since its inception in 1987. Funds from the benefit support UH Seidman Cancer Center physician-scientists' innovative work to identify promising new therapies, as well as community cancer screenings, cancer information service and many public education programs.

"I was thrilled to participate in this culinary extravaganza in my hometown benefiting University Hospitals Seidman Cancer Center," says Michael Symon. "It raised vital funds for such an important cause and was truly a sensational evening."

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University Hospitals Case Medical Center and Case Western Reserve University School of Medicine are consistently recognized as two of the premiere institutions in the nation, according to U.S. News & World Report.

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