

UPMC Cancer Centers cancerinsights



Hillman Cancer Center is the academic hub of the UPMC Cancer Centers network. The state-of-the-art facility offers cutting-edge cancer care and is also home to the research activities of the University of Pittsburgh Cancer Institute (UPCI). UPMC Cancer Centers and UPCI are the only center in western Pennsylvania with the elite Comprehensive Cancer Center designation from the National Cancer Institute.

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It was a tremendous pleasure to assume leadership of the University of Pittsburgh Cancer Institute (UPCI) and University of Pittsburgh Cancer Centers on February 1, 2009. As only the second director of this institution,

I am honored to follow in the footsteps of Ronald B. Herberman, MD, who founded UPCI in 1985 and was instrumental in its progression to one of the top centers for cancer research and care in the country.

This is a most exciting time to work in the field of cancer. We have seen significant declines in incidence of and mortality from this devastating disease thanks to advances in scientific discovery, improved screening, more active prevention efforts, and development of new therapies. But we're not done.

In 2010, it is anticipated that cancer will surpass heart disease as the number one killer in the United States. The need to translate scientific discovery to clinical practice is greater than ever — and we at UPCI and UPMC Cancer Centers are uniquely poised to do this.

In this issue of Cancer Insights, we highlight a number of Phase I trials that are translating what we have learned at the bench to clinical application. Our ultimate goal is to personalize cancer therapy by developing treatments that target cancer cells

specifically, thereby resulting in increased efficacy, fewer side effects, and ultimately better quality of life for our patients.

From vaccines targeting cancer at its earliest stages, to new applications of radiation techniques that reduce toxicity, to minimally invasive surgical options that lead to shorter recovery times for patients, we are building on our scientific strengths to develop new therapies that are changing the standards of treatment for many types of cancer. And together, we will reduce morbidity and mortality from cancer.

To learn more about clinical research or patient care opportunities at the University of Pittsburgh Cancer Institute, and UPMC Cancer Centers please call 412-647-2811 or visit our website at www.UPMCCancerCenters.com.

Sincerely,

Nancy E. Davidson, MD

Director, University of Pittsburgh Cancer Institute and UPMC Cancer Centers

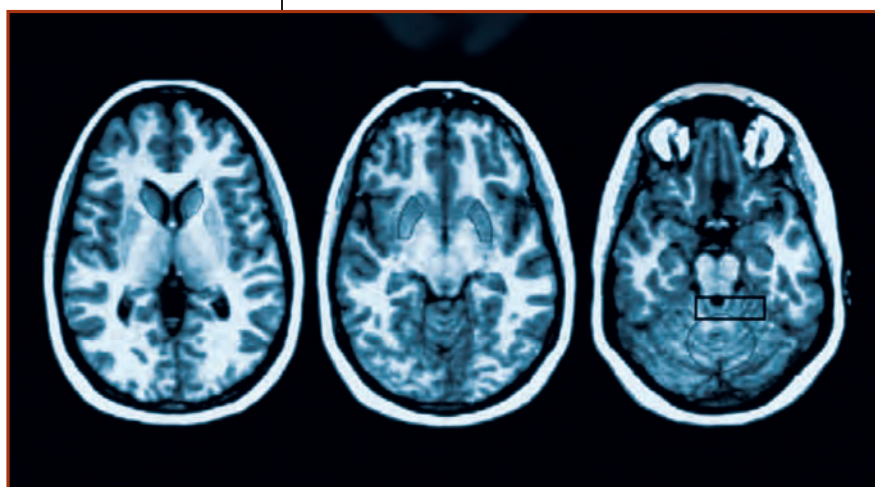
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medical oncology

Vaccine trial offers options for rare brain tumor

Patients with low grade gliomas may have a new option for treatment through a new Phase I vaccine trial being conducted at the University of Pittsburgh Cancer Institute (UPCI) and Wake Forest University.



Vaccine enhances immunity to slow or prevent the growth of new tumor cells.

The study will evaluate the safety and immune response of a novel, peptide-based vaccine, in combination with Poly-ICLC, which is able to target multiple glioma-associated antigens at different stages of tumor development. Most vaccine trials to date target high grade (late stage) glioma cells. By targeting tumors at earlier stages of tumor development, researchers hope to induce effective protective immunity and prevent or slow the growth of new tumor cells.

According to principal investigator, Hideho Okada, MD, PhD, Brain Tumor Program, UPCI, the trial is exciting because to date there have been very few clinical trials for patients diagnosed with low grade gliomas. This is due to a number of factors: patients tend to do well for a period of time because the tumors are slow-growing; and they are also extremely rare. Only 1,800 new cases are reported annually in the United States.

“Because of the low frequency, the slow progression of the disease, and the observation period that is needed to determine clinical outcomes, investigators have not felt encouraged,” explains Dr. Okada.

The current standard-of-care for patients with low grade gliomas is to manage the symptoms and to remove or reduce the tumor. “Deciding when to offer treatment to these patients has been controversial,” says Dr. Okada. “Although radiation therapy has been shown to prolong a patient’s progression-free survival, there is no established standard as to when treatment should be offered.”

Dr. Okada and his team chose to study patients with low grade gliomas because of the lack of effective therapy and slower growth rate of the tumors.

“These patients have a better quality of life for a longer period of time,” says Dr. Okada. “Their immune system is much healthier because they do not require radiation therapy or chemotherapy, giving us sufficient time to measure healthy immune response.”

Because the vaccine will be completely synthetic, it improves applicability and convenience factors by eliminating logistical problems associated with older methods of creating individualized vaccines.

The study is restricted to high-risk patients with supratentorial WHO grade II astrocytomas or oligoastrocytoma who are HLA-A2 positive. Patients will receive eight vaccinations and will be followed for up to two years. Patients with a favorable response may be eligible for a booster vaccination.

For more information on eligibility criteria or for patient referrals, contact Dr. Okada at okadah@upmc.edu.

Drug trial targets BRCA-related cancers

UPCI will launch a Phase I clinical trial of ABT-888, a drug previously shown to improve chemotherapy's effectiveness by lowering cancer cell resistance to treatment. This trial will, for the first time, examine ABT-888 as a single agent for patients with cancers related to a BRCA 1 or 2 genetic mutation.

According to the study's principal investigator, Shannon Puhalla, MD, breast oncologist, Magee-Womens Cancer Program of UPMC Cancer Centers, the trial is the first to target patients with a BRCA 1 or 2 gene mutation who are at higher risk for both breast and ovarian cancers with chronic dosing and without the addition of chemotherapy.

ABT-888 targets the polymerase (PARP) family of enzymes responsible for a wide variety of cellular processes in the body. Cancer cells have been shown to have increased levels of PARP, which are believed to cause resistance to chemotherapies and other cancer treatments. ABT-888 inhibits this resistance, which means cancer cells become more sensitive to chemotherapy. In patients with BRCA mutations, tumor cells are particularly reliant on the mechanism of DNA repair that is inhibited by the PARP inhibitor, and early data suggest that patients with BRCA mutations are particularly sensitive to this drug.

"This drug is intriguing because it is essentially tailored therapy that specifically targets the cancers caused by BRCA mutations. Unlike chemotherapy, which affects all cells, this drug only affects the tumor cells with the mutation," says Dr. Puhalla. "Patients aren't going to lose their hair with this drug, or become nauseous. They can have a better quality of life while on the trial. Additionally we have data to suggest that certain types of breast and ovarian cancers in patients without BRCA mutations

may be sensitive to this drug as well, so this has the potential to be an option for many patients."

The study will primarily be open to breast and ovarian cancer patients with a BRCA 1 or 2 genetic mutation, but patients with other subtypes of breast cancer may be eligible.

For more information about eligibility criteria or for patient referrals, contact Dr. Puhalla at puhallasl@upmc.edu.

Prostate cancer screenings don't cut death rates

According to a new report published in the *New England Journal of Medicine*, annual screenings for prostate cancer lead to more diagnoses of the disease, but no fewer prostate cancer deaths. These results were released as part of the NCI-sponsored Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial of which UPCI was one of ten investigation sites. The U.S. Preventive Services Task Force, whose recommendations are considered the gold standard for clinical preventive services, recently concluded that there is insufficient evidence to assess the balance of benefits and harms of prostate cancer screening in men younger than 75 and recommended against prostate cancer screening in men ages 75 and older.



radiation oncology

Trial validates SBRT for treatment of head and neck cancer

Each year approximately 500,000 cases of squamous cell carcinoma of the head and neck are diagnosed worldwide. Although treatment for the disease has improved with advances in surgery, radiation, and chemotherapy, more than half will die from recurrent disease.



SBRT offers patients with inoperable head and neck cancer a new option for treatment.

According to Dwight E. Heron, MD, FACRO, director, Radiation Oncology Services, UPMC Cancer Centers, treatment options for patients with recurrent disease are limited. For many patients, surgery may not be an option because the tumor is unresectable. Chemotherapy can offer patients meaningful palliation, but has not been shown to prolong survival. And while reirradiation may be beneficial in select cases, nearby critical structures pose a significant treatment challenge even with highly conformal techniques such as IMRT.

An alternative for this high risk population is the use of stereotactic body radiotherapy techniques (SBRT). “In a previous study we were able to demonstrate that SBRT is feasible, well-tolerated, and provided adequate palliation,” says Dr. Heron. “Building on the success of that study, we designed a Phase I dose-escalation trial to determine the optimal dose and fractionation to maximize local control among patients while maintaining a low rate of treatment-related toxicity.”

Results from the latest study, recently published in the *International Journal of Radiation Oncology, Biology, Physics*, showed that a maximum tolerated dose, as well as dose limiting toxicities, were not seen in the trial. This data appears to validate SBRT as a potential alternative treatment approach for patients with recurrent unresectable head and neck cancers that is safe, convenient, and efficacious.

SBRT is a relatively new technique that uses CyberKnife® technology to deliver high doses of radiation with more precision than conventional techniques. In the trial 31 patients with recurrent, inoperable head and neck cancer were treated in five dose tiers up to 44Gy, administered in five fractions over a two-week period.

Because head and neck cancers frequently result in changes in tissues, which may include scarring, the diagnosis of recurrence may be challenging, particularly when SBRT is to be used for salvage treatment. As part of the study, PET-CT is used in SBRT to develop an individualized treatment plan for each patient. By using PET-CT, radiation oncologists have a better definition of the tumor allowing them to more accurately target the cancer while sparing healthy tissue.

“Ultimately, SBRT gives patients a better quality of life. Instead of having to go through six or seven weeks of treatment with a lot of toxicity and side effects, you can do a more conformal treatment plan over a shorter course and still get the same outcomes compared to traditional approaches to reirradiation,” says Dr. Heron.

Based on the results of this trial, a Phase II trial has been initiated incorporating concurrent cetuximab with SBRT.

To learn more about the trial or for patient referrals, contact Dr. Heron at herond2@upmc.edu

Medicare HMO costs may prevent clinical trial participation

In today's economy, many Americans are forgoing necessary medical treatments because they cannot afford the additional health care expenses. For cancer patients these expenses can be significant. Patients are dealing with costs for doctor visits, lab work, and other specialty care. Even with health insurance, the out-of-pocket expenses of health care services can strain any budget.

According to a study at the University of Pittsburgh Cancer Institute (UPCI), concerns about treatment-related costs may also hinder senior citizen participation in clinical trials. Newly diagnosed cancer patients who are enrolled in Medicare's Health Maintenance Organization (HMO) plans may be unlikely to participate in clinical trials because of prohibitive costs. Under these HMO plans, which cover people age 65 and older, patients are required to pay 20 percent of the treatment cost. As a result, access to state-of-the-art care is limited for some of society's most vulnerable members.

Chyongchiou Lin, PhD, lead author of the study and associate professor of health economics in UPCI's Department of Radiation Oncology, says that two-thirds of cancer patients are age 65 or older, with 60 percent of new cancers — and 70 percent of cancer-related deaths — occurring in this age group. Yet, less than one-third of clinical trial enrollees fall into this age group. Patients often cite cost and insurance coverage as barriers to their participation. Because the Medicare HMO payment policy requires significant out-of-pocket expense, Dr. Lin and her team believe the disparity in clinical trials representation and the payment policy are likely related.

"Clinical trials are the cornerstone to finding better, more effective cancer treatments," said Dr. Lin. "The National Cancer Institute (NCI) has made clinical trial participation a national priority, yet current Medicare reimbursement policies present a participation barrier for a large number of patients, cutting them off from these leading-edge treatment options. The current policy should be re-examined to be consistent with NCI initiatives."

The study was conducted through the Radiation Oncology Community Outreach Group (ROCOG), an NCI-supported program based at UPMC McKeesport which focuses on improving access and outcomes for underserved populations with cancer. Preliminary data

presented at the annual American Society for Therapeutic Radiology and Oncology (ASTRO) meeting showed that the overall proportion of newly diagnosed cancer patients who had consultations and were insured by Medicare HMOs increased from 21 percent in 2003 to 27 percent in 2007. The research team found that patients eligible for innovative clinical trials often opted out of enrolling in a "Medicare Qualifying" clinical trial due to the financial burden of participating.

Early this year Senators Edward M. Kennedy and Kay Bailey Hutchinson introduced the 21st Century Cancer Access to Life-Saving Early detection, Research and Treatment Cancer (ALERT). The legislation addresses the need to increase enrollment in clinical research by increasing access and removing barriers to patients' participation in clinical trials. Contact your U.S. Senators to voice your support of the ALERT Act.

Residency program receives recognition

The Radiation Oncology Residency and Training Program at the University of Pittsburgh was recently ranked one of the top programs in the country for radiation oncology research. According to a paper published in the *International Journal of Radiation Oncology, Biology, Physics*, Pitt's program ranked 7th out of the 81 training facilities reviewed based on the number of articles and abstracts accepted for publication or presented at scientific meetings by radiation oncology residents. Pitt's program was started in 2001 and requires residents to complete nine months of research during their four years of training compared to an average of three to six months at other institutions. Other accolades received by Pitt residents include the Resident Clinical/Basic Science Research Award and the Resident/Fellow in Radiation Oncology Research Seed Grant, both awarded by American Society for Therapeutic Radiology and Oncology.

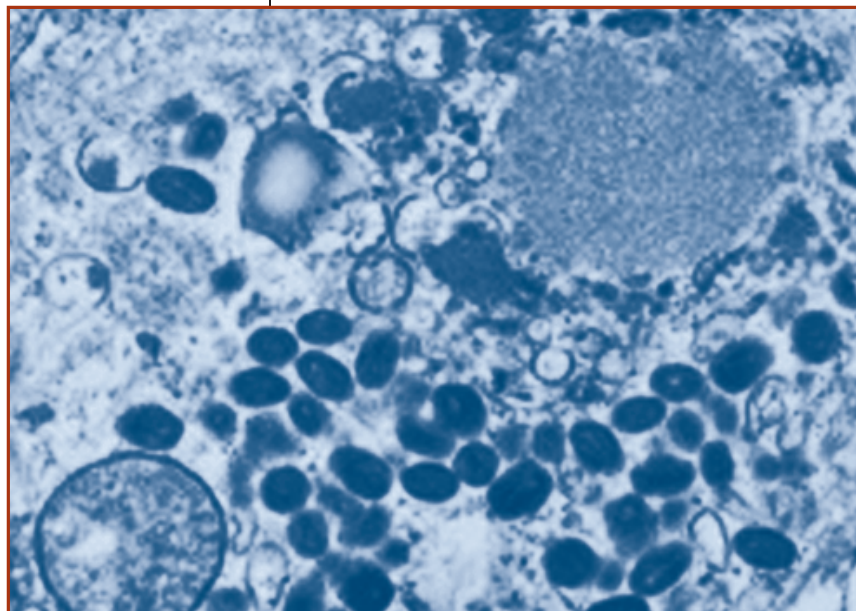


surgical oncology

Vaccinia virus coded for tumor destruction

A Phase I trial at the University of Pittsburgh Cancer Institute (UPCI) is building on the success of a well-known virus to develop a novel agent for tumor destruction.

The vaccinia virus, more commonly known for its use as the modern small pox vaccine, was first used in the 1930s to inoculate millions of people against small pox.



**UPCI
researchers
capitalize
on vaccinia's
natural ability
to replicate
and kill cells
to destroy
tumors.**

Since then, much attention has been given to using the virus to fight cancer, but with limited success. Previous trials utilized a non-replicating strain of the vaccinia virus as a vaccine; these trials primarily focused on the ability of the virus to promote the patient's immune system to attack the tumor. UPCI researchers have taken a very different approach, instead capitalizing on the virus' natural ability to replicate and kill cells to destroy tumors.

"The vaccinia virus has many advantages as a targeted oncolytic therapeutic," explains Herbert J. Zeh, MD, principal investigator of the trial. "Vaccinia is able to spread rapidly from cell-to-cell and efficiently destroys

infected cells. We have shown in the laboratory that vaccinia demonstrates significant antitumor properties against virtually all human cancer cell lines."

To harness vaccinia's ability to selectively destroy tumor cells, UPCI researchers genetically re-engineered the virus, eliminating the thymidine kinase (TK) and vaccinia growth factor (VGF) genes. These genes are important for the virus to divide in normal cells. Tumor cells have genes that function similar to VGF and TK, so the virus doesn't need them to divide. Deleting these genes significantly attenuates the virus' ability to infect and divide in normal cells, without decreasing replication in tumors.

Preclinical studies in animals have shown that the double-deleted virus behaves as predicted, eradicating tumors with minimal side effects. UPCI researchers hope that modified vaccinia will lead to a radical new approach to cancer therapy.

"The mechanism of action of the virus is unlike any other anti-cancer agents currently being utilized," says Dr. Zeh. "For a patient who has exhausted all of their options for treatment, oncolytic viral therapy may offer renewed hope."

The study, which is only available at Hillman Cancer Center, will evaluate the safety and ability of the virus to kill cells after it has been injected into a tumor. Eligibility is restricted to patients with a histologically-confirmed injectable cancer mass that has progressed despite standard therapy. Subjects will be stratified into two groups, patients previously vaccinated with vaccinia and those who have not been vaccinated. Each participant will receive the double-deleted vaccinia virus at one of five dose levels and will be evaluated for adverse events and tumor response.

For more information on eligibility criteria or for patient referrals, contact Dr. Zeh at zehh@upmc.edu.

Minimally invasive esophagectomy improves patient outcomes

The incidence of esophageal cancer has increased dramatically over the past three decades, with an estimated 16,470 people diagnosed in 2008 according to the American Cancer Society. Despite treatment advances, more than half are expected to lose their battle with the disease. Researchers agree that newer, more effective therapies are needed to improve long-term survival for these patients.

According to James D. Luketich, MD, Henry T. Bahnson Professor of Cardiothoracic Surgery, director, Heart, Lung, and Esophageal Surgery Institute, UPMC, and co-director, Lung and Esophageal Cancer Program, University of Pittsburgh Cancer Institute (UPCI), one of the main reasons esophageal cancers are hard to treat is because they are being diagnosed too late.

“Esophageal cancer is a silent disease,” explains Dr. Luketich. “Often we find the cancer after it has already metastasized and we are unable to contain it. When we are able to identify the cancer very early, recent advances in minimally invasive surgery leads to a cure in a high percentage of patients with a mortality of only one to two percent, and a very good quality of life. When the disease has progressed to include local lymph node involvement, combinations of surgery, chemotherapy, and radiotherapy may still lead to a cure in some cases.”

UPCI, a recognized leader in the surgical treatment of esophageal cancer, demonstrated that minimally invasive esophagectomy (MIE) significantly lowers postoperative morbidity and mortality rates and shortens hospital stay compared to traditional open surgical procedures. MIE is a video-assisted surgical procedure that utilizes instruments introduced into the body through very small incisions and a laparoscope.

Results from previous trials led surgeons at UPMC Cancer Centers to develop an Eastern Cooperative Oncology Group (ECOG)-sponsored Phase II, multicenter study to further evaluate the safety and efficacy of MIE (ECOG 2202). As part of the 16-institution trial, participating surgeons were credentialed at the University of Pittsburgh.

The ECOG study included 106 patients, 99 of whom underwent MIE for histologically-confirmed esophageal cancer. The results, which are being presented this year at the American Society of Clinical Oncology annual meeting,

found that MIE is safe and feasible in a multi-institution setting, with low perioperative mortality rates and morbidity. Complications included an overall 30-day mortality rate of less than 2 percent. This compares favorably to operative mortality rates after open esophagectomy, which have been reported in previous studies to be as high as 8 to 23 percent, depending on whether the esophagectomy was performed in a high volume or a low volume center.

Treatment of esophageal cancer is more effective when the cancer is detected at an early stage. With endoscopic surveillance programs for Barrett's esophagus, more patients with high grade dysplasia and early stage lesions are being detected. In the ECOG study, more than one third of patients in the series underwent MIE for early stage lesions. Esophagectomy performed through minimally invasive techniques offers a less invasive and more effective option in these patients.

“We are encouraged by the results of this study,” says Arjun Pennathur, MD, co-investigator, UPCI. “The ideal procedure for treating esophageal cancer is one that can improve patient outcomes without compromising accepted standards of care.”

Another Phase II study by the research team, recently published in the *Annals of Thoracic Surgery*, found that offering patients with locally-advanced esophageal cancer neoadjuvant chemotherapy followed by esophagectomy improves long-term survival. To accurately stage the cancer, each patient was evaluated with a CT scan, endoscopic ultrasound, and laparoscopy. During long-term follow-up with a median of 79 months, 14 of the 63 patients showed no evidence of recurrence. Further studies on the management of esophageal cancer are ongoing at the University of Pittsburgh.

Sentinel lymph node mapping technology

A recent Phase II trial at Magee-Womens Hospital of UPMC is improving quality of life for patients with cervical cancer by combining cutting-edge minimally invasive surgical options with sentinel lymph node (SLN) mapping technology. Using preoperative and intraoperative diagnostics, surgeons identified and removed the SLN, the first node in the basin that receives drainage from the primary tumor. If histology revealed no metastasis in the SLN, then no further nodes were removed. Results from the study, published in *Gynecologic Oncology*, showed that the technique was both reliable and accurate. By confirming the feasibility of SLN biopsy, patients who are node negative at the time of surgery can avoid major surgery, preventing potentially debilitating postoperative, comorbid conditions.

upcoming events

UPMC Cancer Centers

UPMC Cancer Centers and
University of Pittsburgh
Cancer Institute

Nancy E. Davidson, MD
Director

UPMC Cancer Pavilion
5150 Centre Ave.
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UPMC has consistently received national recognition from *U.S. News & World Report* magazine for offering one of America's top cancer programs. For more information about UPMC Cancer Centers' clinical services, or University of Pittsburgh Cancer Institute research, call 1-800-533-UPMC or visit www.UPMCCancerCenters.com.

2009 ASCO Conference

Physician researchers from UPMC Cancer Centers and the University of Pittsburgh Cancer Institute (UPCI) will present findings from numerous studies at the annual American Society of Clinical Oncology (ASCO) Meeting, May 29 to June 2, 2009, in Orlando, Fla. UPMC Cancer Centers experts will be available at booth 101 in the ASCO Exhibit Hall to discuss these and other presentations.

Brain

- Clival chordoma molecular subtypes and clinical behavior
- Post-therapeutic changes in the molecular profile of glioblastomas

Breast

- Changes in body composition in women with breast cancer on aromatase inhibitors: a two-year trial
- Long-term treatment with intravenous bisphosphonates in metastatic breast cancer (MBC)

Esophageal

- Minimally invasive esophagectomy: results of a Phase II multicenter Eastern Cooperative Oncology Group Study (E2202)

Gastrointestinal

- Effect of proton pump inhibitor comedication on imatinib disposition—a healthy volunteer study