Clinicians and Researchers Expand Options for Geriatric Cancer Patients
Dear Colleagues and Friends:

This is an exciting time for cancer care at Cleveland Clinic. Previously recognized as the top-ranked cancer program in Ohio, we have made significant strides in improving our services, earning a spot in the top 10 in the country in *U.S. News & World Report* “America’s Best Hospitals” survey in 2010. While we are proud of this acknowledgement, we are not resting on our laurels. We continue to seek innovative approaches that will improve outcomes and provide better care for our patients with cancer.

In this issue of *Cancer Consult*, I am pleased to share several of our initiatives aimed at treating the growing number of older adults with cancer. In 2009, we launched a new specialty clinic specifically for this vulnerable group of patients — Taussig Cancer Institute Oncology Program for Seniors (TOPS). This program focuses on new assessment tools, models for evaluating specific ethical issues and techniques for developing new treatment algorithms for older patients. We are excited about the growth and success of this program.

We continue to expand our access throughout the region, working closely with members of our team who are embedded in Cleveland Clinic regional hospitals and family health centers, bringing care closer to home for our patients. In addition, we have developed a specific outreach program focused on disparities of care and are leading the nation with creative approaches such as beauty and barbershop programs, cancer navigation and the evaluation of training programs.

Cleveland Clinic oncologists and scientists have a robust basic and clinical research program that continues to earn international attention. In the pages that follow, you’ll find several examples of our innovative work, as well as a small sample of articles authored by cancer program staff so far this year. We also recently released a new edition of our *Outcomes* book, available online, which provides data on our clinical outcomes and volumes, as well as our patients’ experiences throughout their continuum of care.

I hope you find this edition of *Cancer Consult* valuable, as it highlights new directions in our field and offers insight into our approach to treating cancer. I look forward to continued collaboration with you.

Sincerely,

Derek Raghavan, MD, PhD, FACP, FRACP
Chairman and Director, Taussig Cancer Institute
M. Frank & Margaret Domiter Rudy Distinguished Chair
The Taussig Oncology Program for Seniors (TOPS) in Cleveland Clinic’s Taussig Cancer Institute addresses the unique needs of patients 75 years of age and older who are diagnosed with cancer.

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TOPS, launched in July 2009, has a dual goal of improving clinical care for, and conducting research specific to elderly patients undergoing chemotherapy for solid tumors.

TOPS answers the need for the specialized treatment approach these patients require to achieve the best possible outcomes, says oncologist Dale Shepard, MD, PhD. He co-directs the geriatric oncology program with oncologist Abdo Haddad, MD. In addition to board certification in oncology, Dr. Shepard holds a PhD in pharmacology. He specializes in gastrointestinal and genitourinary tumors. Dr. Haddad, who is board-certified in medical oncology, geriatrics and palliative medicine, specializes in lung and breast tumors. They form the core of a multidisciplinary team that includes palliative medicine specialists, geriatric social workers, pharmacists, physical therapists, nutritionists, radiation oncologists and bioethicists.

Every patient in the geriatric oncology program undergoes a medical and functional assessment at the first visit that becomes a part of the patient’s electronic medical record (EMR). This comprehensive assessment for geriatric syndrome includes evaluation for polyphamacia, nutritional status, fall risk, mental status and multiple medical problems. The results of this assessment form the basis for referrals within the team and to other Cleveland Clinic specialists, and are essential to individualized treatment planning for that patient.

Integrating a comprehensive geriatric assessment like this into cancer treatment for the elderly is a new approach practiced at only a handful of cancer centers nationwide, says Dr. Haddad. He believes a pre-treatment assessment is essential to effectively treating this population.

“Underlying problems will affect how the patient will tolerate treatment and must be addressed prior to treatment to maximize the patient’s condition. If they are not addressed, problems will surface after the first cycle of chemotherapy,” he says. Untreated co-morbidities can contribute to treatment side effects and are a common cause of discontinuing treatment in older cancer patients after a single cycle, he adds.

To manage problems that are identified during the assessment, patients are referred to a specialist on the geriatric oncology team or to specialists in the Cleveland Clinic Center for Geriatric Medicine, if necessary. The EMR makes patient assessment results easily accessible to team members and physicians outside of the Geriatric Oncology program and facilitates collaborative intervention.

“There tends to be a fear of chemotoxicity in treating this population simply based on age that can lead to arbitrary chemotherapy dose reduction and potentially less than optimal results” he says. “Age is not a strong predictor of treatment success, and age alone should not be the criteria for chemotherapy dose reduction.”

To refer patients to TOPS, call 216.444.7923 or 866.223.8100.
The paucity of data about chemotherapy dosing in the elderly has motivated Drs. Shepard and Haddad to contribute to the body of knowledge in the field. Defining dosing based on age, functional status and co-morbidities has become a primary focus of the geriatric oncology program’s research. To this end, all patients are entered into a registry that captures liver, kidney and cardiac function data prior to, during and after therapy; tumor response; and adverse drug effects. The registry eventually will provide a rich source of data for clinical trials.

Although toxicities or adverse effects occasionally may require dose reduction when treating elderly patients, Drs. Shepard and Haddad prefer to optimize the patient’s condition prior to starting treatment and then to initiate full dose chemotherapy whenever possible in their patients. “Many patients will benefit from starting with full-dose therapy,” Dr. Shepard explains.

“Our team has the support and resources to resolve any problems that may result and adjust the dose if necessary,” he adds. “Every patient is treated with curative intent and the goal of prolonging survival.”

In addition to comprehensive cancer care, TOPS offers functional assessment and consultation services to referring physicians for patients over 75 years of age with gastrointestinal, genitourinary, lung and breast tumors.

“Age is not a strong predictor of treatment success, and age alone should not be the criteria for chemotherapy reduction.”

Overcoming Disparities in Care: New Programs Offer Improved Outcomes

While Taussig Cancer Institute’s geriatric oncology program is tackling disparities in care for the elderly, several initiatives housed at main campus and at Huron Hospital on Cleveland’s near east side are breaking down barriers in minority populations. The efforts feature vigorous community outreach.

“What we have found is that it’s not enough to educate the community that they need to be screened. The most important mission of community outreach is to build trust in the community so that residents know they can come to us when they have health concerns,” says Kimberly Kreller, RN, BSN, Director of Community Outreach and Research. “We need to bring comprehensive cancer education to them. We have to give them access to necessary screenings, even providing transportation when needed. We can’t start outreach efforts when a patient walks in our door; we have to bring the community to the door.”

In 2009, Angela Bailey, Administrative Program Coordinator for Community Outreach, forged relationships with several local beauty salons and barbershops to provide cancer education and awareness. As part of the program, she trained beauticians and barbers, as well as nail technicians and other staff members, on how to discuss cancer prevention and screening with their clients. The program leverages the warm, trusting environment of a salon to offer cancer information in a non-threatening, natural way to a captive audience. She also equipped each salon with literature including information and the availability of free screenings in

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the area such as Mammogram Mondays at Huron Hospital. Ms. Bailey’s outreach efforts are closely tied to Taussig Cancer Institute’s Patient Navigation Program.

With a three-year, $100,000 grant from the Ralph Lauren Cancer Center for Preventative Care — one of five national grantees — the institute has developed the Patient Navigation Program at Huron Hospital, which has a large population of uninsured and under-insured patients. Stacey Booker, RN, MSN, Program Manager for Patient Navigation, has developed a program that includes a patient navigator. The role of the navigator is to assist any patient in the healthcare system who has an abnormal finding or cancer diagnosis. The navigator serves as a financial counselor who can help address insurance and other financial issues; and can connect patients with other social service agencies as needed. The program models the concept of Patient Navigation founded and pioneered by Harold P. Freeman, MD, in 1990 for the purpose of eliminating barriers to timely cancer screening, diagnosis, treatment and supportive care. This program hopes to see similar success. In its first 10 years, Dr. Freeman’s program changed the five-year survival rate of breast cancer patients from 39 percent to 70 percent.

To further enhance these efforts, Taussig Cancer Institute hosted a one-day symposium in April, “Churches and Hospitals Against Cancer,” in collaboration with the Cleveland Medical Association and the United Pastors in Mission. The event included political, community, and church leaders, along with physicians who discussed barriers to access, diagnosis and management of cancer in minority populations. The group worked together to uncover possible solutions. A task force identified during the event is now creating a cancer tool kit for pastors and community leaders to use to further advance their efforts to eliminate disparities in cancer care. Taussig Cancer Institute will be launching a mobile outreach initiative that will transport residents from churches and other community landmarks to cancer screening locations of their preferences in their geographic areas.
As a society, we have yet to form a consensus on the value of cancer care — what chance of success and degree of benefit justify the expenditure of limited resources.

This ethical and philosophical debate plays out everyday at Cleveland Clinic and other cancer centers around the country. All cancer patients ask themselves whether they should choose a treatment that is costly, but could prolong their lives for an undetermined amount of time. The trade-offs can be even more challenging for elderly patients diagnosed with cancer.

Even as the field of geriatric oncology grows, its goals are not uniformly stated. Some healthcare professionals assert that treatment of elderly cancer patients should aim to maintain or augment quality of life; others emphasize identifying effective treatments for the geriatric population as the goal, implying that any divergence from the approach taken with younger cancer patients reflects rationing or age-related bias.

Anne Lederman Flamm, JD, Associate Staff in Cleveland Clinic’s Department of Bioethics, hopes to shed new light on this ethical dilemma. She is proposing a research project that involves interviewing elderly cancer patients about whether and how their age and the cost of treatment influences their decision to pursue or reject chemotherapy.

Her aim is to increase the understanding of how elderly patients think about cost and age, allowing oncologists to feel more comfortable speaking with them about these issues. “Oncologists need to recognize the influence of cost on treatment decisions,” Ms. Flamm stresses.

Rising Population Group, Rising Cancer Rates

The influences of age and cost considerations have yet to be thoroughly investigated, but they are important because geriatric patients tend to be on fixed incomes, and they have comorbidities concurrently requiring medical treatment and other forms of supportive care.

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Ms. Flamm says her urgency to research these issues is based on U.S. Census Bureau projections that the number of people age 65 and older will double from 35 million to 70 million by 2030, comprising about 20 percent of the population. More than 5 percent of the population will be age 80 and older.

The incidence of cancer diagnosed in the elderly is also rising, she says.

She acknowledges there are empirical studies suggesting an age bias against treating geriatric cancer patients across treatment options — including surgery, chemotherapy and radiotherapy — despite evidence they tend to do as well as pediatric and young adult patients when stage-appropriate therapies are administered. “Age itself is not the kicker for whether a patient will or will not do well,” notes Ms. Flamm, adding other issues, such as performance status, renal function or a combination of factors, might be better predictors of success. “Just knowing a patient is 75 is proving not to tell you much.”

Yet, there is uncertainty and a lack of best evidence as to how to treat geriatric cancer patients. Physicians often reduce the standard dosage of a cancer-fighting drug because they are worried about greater side effects or greater impact of known side effects.

Elderly patients are historically underrepresented in clinical trials compared with pediatric patients and younger adults. When they are offered participation, elderly patients don’t decline at any greater rates than other groups, but they are not offered the opportunity as much. Is that bias, uncertainty, or is it legitimated in some way by outcomes? “We don’t have the empirical piece definitively answered yet,” Ms. Flamm says. “But depending on what you read, there are people who find it to be age bias.”

There is a growing movement among some geriatric oncologists to focus clinical studies directly on elderly cancer patients. Another push is for a more comprehensive geriatric assessment before designing and recommending treatment options, though Ms. Flamm points out the present state of healthcare does not lend itself to compensate in terms of time and money for an assessment that can take two hours or longer. (One of the initiatives of Taussig Oncology Programs for Seniors is to develop a screening assessment to indicate whether a patient needs a full, comprehensive assessment.)

Is it Age Bias?

Ms. Flamm hopes her research illuminates whether and how geriatric cancer patients factor their age into the decision-making process; for example, whether and how often patients conclude, “I would choose this treatment if I was 70, but not at 90,” — and if so, what is their reasoning. Is it because they are satisfied with having lived a full life, they don’t want to experience treatment hardships for what they see is a limited payoff, or other considerations?

Is that attitude age bias? To the most objective and dispassionate person, the answer is yes. But is it age bias if the patient makes the decision for him or herself?

These questions have implications not just for individual patient encounters, but for societal policy as well. Few find age-based limitations a comfortable proposition to redress rising cancer care costs. “Should we weigh decisions in geriatric vs. non-geriatric settings differently?” Ms. Flamm says. “I would say we could avoid it by being just as explicit and comprehensive in weighing the benefits and costs of cancer treatments at every stage of life.”
For more than 30 years, the search for an effective breast cancer vaccine has eluded scientists throughout the world. However, a Cleveland Clinic researcher recently reported the development of a vaccine that provides safe and effective protection against the growth of breast tumors in mouse models. Remarkably, this protection occurs in the complete absence of any detectable side effects.

Scientists in the laboratory of Vincent Tuohy, PhD, Department of Immunology in the Lerner Research Institute, evaluated α-lactalbumin, a breast specific protein over-expressed in the majority of human breast tumors but expressed only during lactation in the normal breast.

The research involved vaccination of mice with recombinant mouse α-lactalbumin. The team then assessed responses in normal mice and in several mouse breast tumor models, including autochthonous tumors in MMTV-neu and MMTV-PyVT transgenic mice, as well as transplantable 4T1 tumors in BALB/c mice. The data show a significant treatment effect when mice with established breast tumors are vaccinated and also show a highly significant inhibition of tumor growth when vaccination occurs prior to the appearance of palpable autochthonous tumors and prior to inoculation of 4T1 breast tumors.

“We are hopeful that this vaccine strategy will someday be used to prevent breast cancer in adult women in the same way that vaccines prevent polio and measles in children,” Dr. Tuohy says.

Derek Raghavan, MD, PhD, Chairman of Taussig Cancer Institute, expressed cautious optimism over Dr. Tuohy’s findings.

“This work is intriguing and the science is impressive,” says Dr. Raghavan. “If Dr. Tuohy’s early research is validated in clinical studies, it could potentially reduce the incidence of breast cancer. We’re currently designing trials here at Cleveland Clinic to test the vaccine in humans, but we’re five to 10 years way from being able to offer it to women.”

Financial support is now needed to continue the processes involved in moving this from the lab to the research venue to the patient.

Dr. Tuohy’s research is published in Nature Medicine, June 2010, “A prophylactic, autoimmune-mediated vaccination strategy for breast cancer,” and can be found at www.nature.com/nm/index.html.
“Cancer-related fatigue is complex because it encompasses a variety of symptoms that develop over time,” says Mellar Davis, MD, Solid Tumor Oncology. “Yet, while fatigue is one of the most common unrelieved symptoms reported by patients, it is probably the least studied and most neglected.”

Current interventions, including growth factors, steroids and hemoglobin each have a niche in treating cancer-related fatigue. But nothing has been found to be universally effective.

Dr. Davis is engaged in research designed to correlate objective neuromuscular physiologic changes with fatigue. His team screened 29 advanced cancer patients and 16 healthy controls to clarify whether cancer-related fatigue was predominantly a centrally or peripherally mediated disorder.

Neuromuscular testing of the group involved a sustained submaximal elbow flexion contraction at 30 percent maximal level. Endurance time was measured from the beginning of flexion until the individual could no longer maintain the flexion. Both evoked twitch force (a measure of muscle fatigability) and compound action potential (an assessment of neuromuscular-junction transmission) were performed during the submaximal elbow flexion.

“What we found is that when patients with cancer can no longer continue a task, such as a sustained contraction, their ability to activate is significantly reduced relative to normal controls,” says Dr. Davis. “We noted changes in alpha, gamma and beta waves that occur, with a delay of recovery of the EEG signals after a task. There was a distinct difference between the participants in that cancer-

Research Under Way to Clarify Mechanisms of Cancer Related Fatigue

Cancer patients consistently report fatigue as the predominant factor affecting quality of life during and after treatment. But clinicians struggle to objectify fatigue. Advances in the management of cancer-related fatigue require better understanding of its underlying mechanisms.
related fatigue patients didn’t recover to normal patterns as quickly as the control group. There also is a loss of EEG/EMG coherence as fatigue occurs, and it was distinctly different in patients with cancer-related fatigue as compared to controls.” Together, the findings suggest that central fatigue plays a more prominent role in cancer-related fatigue than in normal individuals in tasks that require endurance.

**Case Study Tests Objective Measures**

Dr. Davis says that several cohort and phase two studies have demonstrated that methylphenidate improves fatigue and cognitive function while decreasing pain and depression in cancer patients. He and his colleagues combined objective and subjective outcomes in a single case study of methylphenidate in a female patient with severe cancer-related fatigue. They found that improvements in her Brief Fatigue Inventory score were associated with normalization of her neurophysiologic tests.

These results give impetus to understanding the correlation of physiology with subjective responses to methylphenidate in the treatment of cancer-related fatigue and may give clinicians an objective methodology to study other cancer-related fatigue interventions.

“We are continuing to analyze our data,” says Dr. Davis. “If we can isolate the mechanisms involved in cancer-related fatigue, we may be able to successfully intervene. Certainly, new drug development can be based on these mechanisms.”

Charis Eng, MD, PhD, Chair and Founding Director of Cleveland Clinic’s Genomic Medicine Institute, earned the American Cancer Society’s coveted Clinical Research Professor Award. Offered annually to a limited number of established investigators, the award recognizes those who have changed the direction of health policy or clinical, psychosocial, behavioral, or epidemiologic cancer research.

Dr. Eng’s professorship project focuses on PTEN Hamartoma Tumor Syndrome (PHTS) – which confers increased cancer risk – to impact personalized healthcare; facilitate clinical diagnosis, screening, treatment and prevention by increasing the ability to accurately diagnose inheritable cancers; predictively test family members; and assess and manage cancer risk.

Dr. Eng received her undergraduate and medical degrees at the University of Chicago. She completed her residency in Internal Medicine at Beth Israel Deaconess Medical Center in Boston.

Dr. Eng has published more than 260 peer-reviewed original papers in some of the world’s most prominent journals. She has received numerous awards and honors including election to the American Society for Clinical Investigation, to the Association of American Physicians, and as Fellow of the American Association for the Advancement of Science. She received the Doris Duke Distinguished Clinical Scientist Award.

Dr. Eng was the recipient of the American Cancer Society’s 2006 John Peter Minton, MD, PhD, Hero of Hope Research Medal of Honor. Recently, she was appointed to the US Department of Health and Human Services Secretary’s Advisory Committee on Genetics, Health, and Society.
Myelodysplastic syndromes (MDS) are a heterogeneous group of progressive bone marrow neoplastic disorders associated with increased risk for transformation to acute myeloid leukemia (AML). MDS symptoms include peripheral blood cytopenias (especially anemia) and dysplastic changes in one or more hematopoietic lineages. MDS primarily develops in older adults, with the median age of diagnosis 71 years.

MDS is a diagnosis that has only been tracked since 2001. The age-adjusted annual incidence rate is 3.4 per 100,000 people, which translates to 10,000 to 15,000 new cases annually and an estimated 30,000 to 60,000 Americans living with this disease.

MDS can be primary or secondary (resulting from cancer treatment with radiation or chemotherapy) and is divided into two categories: lower-risk disease, which has a low risk of transformation to AML and a median survival range of three to seven years; and higher-risk disease, which has a pathobiology similar to AML. Patients with higher-risk MDS either develop AML or die from complications of the disease, on average within 1.5 years. Approximately 25 percent of newly diagnosed patients and 15 percent to 20 percent of established patients have higher-risk disease.

The wide variation in the clinical presentation of MDS has frustrated treatment strategies and hindered the development of new therapies. Stem cell transplant is the only cure for MDS, but the majority of patients are not eligible due to older age and other medical problems. In recent years, three drugs — azacitidine, decitabine and lenalidomide — have been approved by the U.S. Food and Drug Administration for the treatment of MDS or one of its subtypes.

Azacitidine and decitabine, which work through DNA methyltrasferase inhibition and direct cytotoxicity, are effective in 40 to 50 percent of higher-risk patients. The mechanism of action of lenalidomide has not been definitively determined, says Cleveland Clinic Leukemia Program Director Mikkael Sekeres, MD, MS, but it purportedly works by blocking the effect of cytokines that cause premature death of cells in bone marrow and by direct cytotoxic action on the 5q deletion cytogenetic abnormality found in some patients. Lenalidomide is commonly used to treat lower-risk MDS.

The results of the first Phase I trial combining two FDA-approved drugs for myelodysplastic syndromes offers new promise for treating higher-risk patients with this newly recognized and intractable blood marrow disorder.
Combination therapy with azacitidine and lenalidomide was chosen for Cleveland Clinic’s Phase I trial of higher-risk MDS patients based on the “assumption that the cells in higher-risk disease retain qualities of lower-risk disease in the bone marrow microenvironment,” says Dr. Sekeres. Thus, the complementary mechanisms of the two agents might yield additive benefit. The goals of the study were to investigate the safety, tolerance and response rates of combination therapy.

The multicenter, single-arm, open-label study evaluated 18 higher-risk patients with a median age of 68 and a median interval from diagnosis of five weeks. Their International Prognostic Scoring System (IPSS) classifications were: Int-1 (2 patients), Int-2 (10 patients) and High (6 patients).

Patients were grouped into four dosing cohorts and received up to seven cycles of therapy, each lasting 28 days, and were followed for seven months. Reported side effects included hemorrhage and neutropenic fever. Myelosuppression, which was a concern in combining the two drugs, was not a major side effect.

The overall response rate was 67 percent: eight patients (44 percent) had a complete response (CR); three (17 percent) hematologic improvement; and one (6 percent) a marrow CR. Patients who achieved CR were more likely to have normal cytogenetics and lower methylation levels. No dose-limiting toxicities occurred and a maximum tolerated dose was not reached.

The CR rate was higher than that reported in other MDS studies. “We were concerned that the two drugs wouldn’t be more effective together than they are alone. We were pleasantly surprised by the results. This finding is a major advance in the treatment of MDS,” says Dr. Sekeres.

The Phase II trial is currently under way using the dose (azacitidine: 75/mgm2 daily for 5 days and lenalidomide: 10mg daily for 21 days) that achieved the highest rate of CR without any serious non-hematologic adverse events. The trial will address the duration of combination therapy and whether this regimen would be more tolerable with better efficacy if administered sequentially, and whether it is best suited to higher-risk patients with the 5q (del) cytogenetic abnormality.

“The goals of the study were to investigate the safety, tolerance and response rates of combination therapy.”
“For many years, oncologists considered brain metastasis as a uniformly fatal condition, and treatments were limited to palliative brain radiation,” says Gene Barnett, MD, Director of the Brain Tumor and Neuro-Oncology Center at Cleveland Clinic’s Neurological Institute. “Over the last two decades, however, approaches that are more aggressive and accurate have been developed that may lead to a local cure or a sustained control of the disease in some patients.”

Nevertheless, Dr. Barnett believes cancer patients with systemic cancers are poorly informed about the risks of developing brain metastasis, its early warning signs and modern therapeutic options available beyond the traditional treatment of whole brain radiation.

Moreover, we have found there are some physicians who may not be mindful of new treatment options, or may still be of the mindset that brain metastasis is a uniformly fatal turn in patients with systemic cancers,” Dr. Barnett observes.

B-Aware program launches

To address this issue, the Brain Tumor and Neuro-Oncology Center has launched the B-Aware™ program to educate and empower patients with information on the risks, symptoms and treatment options that may increase their life-spans and improve quality of life.

“At the same time, we are actively engaged in developing physician awareness,” says Dr. Barnett. “To that end, we officially announced the B-Aware initiative before physicians who attended the International Symposium on Long-Term Control of Secondary Central Nervous System Malignancies held last spring in Cleveland.”

The Brain Tumor and Neuro-Oncology Center is collaborating with the American Cancer Society to promote the B-Aware program on its website.

“The B-Aware program is unique because it is believed to be the first initiative of its kind to directly educate cancer patients about the health issues of brain metastasis,” Dr. Barnett says.

Understanding the symptoms

In addition to the risks, cancer patients also should know about the common symptoms that may indicate brain metastasis. Many of the symptoms are similar to those of an acute stroke. However, the symptoms for brain metastasis typically manifest gradually as opposed to suddenly during a stroke. Common symptoms include problems with vision, numbness, weakness, difficulty with balance, speaking or memory problems, headaches that are generally progressive and seizures.

“When patients experience the onset of any of these symptoms, particularly when the symptoms begin to become more frequent, prolonged or become worse, they should see their oncologist immediately,” Dr. Barnett says. “Aggressive therapies may improve outcomes when brain metastasis is diagnosed in its early stages.”

At Cleveland Clinic, a multidisciplinary team of physicians evaluates each patient and recommends an individualized course of treatment that is most likely to produce an optimal outcome.

“Traditional treatments such as whole brain radiation and glucocorticoids still play important roles in the treatment of brain metastasis,” says Dr. Barnett. “However, for many patients, whole brain radiation is inadequate to achieve sustained control and quality. In fact, it may be best reserved
for later use as opposed to being used as a first line of treatment in some cases."

**Aggressive treatments work**

Alternatively, research has shown that aggressive treatments such as minimal access surgery and radiosurgery can help an appreciable number of patients to survive up to five years, and in some cases, up to 10 years.

At the Brain Tumor and Neuro-Oncology Center, for example, neurosurgeons commonly utilize aggressive therapies such as minimal access procedures to extract metastatic tumors. For patients with new or recurrent metastatic tumors following radiotherapy, surgery in conjunction with the placement of carmustine wafers in the tumor cavity or radiosurgery to the tumor cavity may preclude local recurrence.

In addition, the Brain Tumor and Neuro-Oncology Center’s Gamma Knife uses state-of-the-art stereotactic radiosurgery to treat metastatic tumors. Lesions are typically small (<3 cm at presentation) and spherical, which displace rather than infiltrate the brain. Results from radiosurgery appear comparable to those achieved by surgery with radiotherapy, and allow for effective treatment even for surgically inaccessible secondary brain tumors.

A recent multi-centered randomized trial showed that radiosurgery in addition to whole-brain radiotherapy led to improved survival or enhanced quality of life for patients with one or more metastatic brain tumors, respectively. In addition, radiosurgery may reduce the chance of leptomeningeal spread as a result of surgery for certain types of tumors.

**Other treatment options**

In some cases, chemotherapy may be a treatment option. For example, patients who have systemic breast cancer and brain metastases with lesions that are estrogen-receptor positive may respond to high doses of Tamoxifen, which can compensate for the medication’s limited penetration to the brain. What’s more, temozolomide – an orally administered methylation agent – effectively penetrates the brain and may be considered for selected patients.

“Often times, by applying a combination of these aggressive therapies, we are able to control brain metastasis for an extended period of time for patients and improve their quality of life,” concludes Dr. Barnett.

To learn more about the B-Aware program, please visit, [http://my.clevelandclinic.org/b-aware](http://my.clevelandclinic.org/b-aware).

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To refer patients, please call 216.636.5860 or 800.553.5056.

For pediatric patients, ask for the chief of pediatric neurological resident on call.
Over the past several years, research has focused on uncovering biomarkers, specifically genetic mutations in lung tumors themselves, which could lead to targeted treatment. Investigational treatments focused on two such mutations, the epidermal growth factor receptor (EGFR) and the fusion gene echinoderm microtubule associated protein like 4 – anaplastic lymphoma kinase (EML4-ALK), are showing promising results.

The population of patients who harbor EGFR mutations is distinct from those who test positive for the EML4-ALK fusion gene. Therefore, treatments must be optimized for the individual patient based on unique characteristics of each cancer, targeting the specific tumor’s vulnerability.

Cleveland Clinic oncologists are participating in a Phase III trial of a newly developed ALK inhibitor, crizotinib, which has demonstrated impressive activity in an earlier small trial. The degree of activity was strong, including tumor shrinkage in 90 percent of patients and a 72 percent probability of remaining progression-free at six months. Although EML4-ALK-positive tumors represent only about 5 percent of NSCLC, this translates into about 10,000 patients annually in the United States.

These findings come on the heels of FDA-approval of erlotinib (Tarveca®), an oral small molecule inhibitor of EGFR, for patients with advanced or metastatic NSCLC who have failed first- or second-line chemotherapy. When the mutation is present, 70 percent or more of patients will respond to erlotinib, and the average survival rate tends to be twice as long as in patients without the EGFR mutations.

“Given the effectiveness of erlotinib in advanced NSCLC patient with the EGFR mutation, it makes sense to investigate the drug in the adjuvant setting,” says Nathan Pennell, MD, PhD, Solid Tumor Oncology. “We are participating in a phase II trial of erlotinib in stage I – IIIA patients with the mutation. Patients can still receive standard adjuvant chemotherapy after surgery prior to starting erlotinib, and are eligible for enrollment if they are within six months of surgery.” The goal of the study is to show an improvement in the number of patients who are alive and free of recurrence two years after surgery.

“This work demonstrates a need for tumor tissue typing in all NSCLCs for drug selection,” says Dr. Pennell. “It also is exciting because it shows that once we isolate the molecular mechanisms of a cancer type, it is possible to quickly develop effective targeted therapy.”

Both EGFR and EML4-ALK are detected more frequently in NSCLC patients who were never, or light (<10 pack-years) cigarette smokers. Dr. Pennell says these patients represent the rising face of lung cancer, which includes young people, mostly women, who have never smoked.

“Worldwide, non-smokers represent 25 percent of lung cancers,” says Dr. Pennell. “But research funding for this disease has been hampered by the common misperception that lung cancer could be avoided by eliminating smoking. I am optimistic that new targeted therapies will have a significant impact on outcomes for patients with this disease.”
Patients with clinical stage 1 nonseminomatous germ cell testicular cancer (CS1 NSGCT) and their doctors must weigh three primary options (surgery, chemotherapy and surveillance) and the potential consequences of those options when making therapeutic decisions. The complexity of this challenge is amplified by the absence of level-one evidence that would identify an option with maximum survival benefits and minimal side effects.

For instance, patients unfamiliar with the rigors and consequences of chemotherapy can find it difficult to properly imagine and balance the potential of extended life against the possibility of late toxicity, secondary malignant neoplasms and cardiovascular disease that may not appear for decades.

Investigators at Cleveland Clinic’s Taussig Cancer Institute and Glickman Urological & Kidney Institute, Department of Quantitative Health Science, have created and evaluated a decision model for CS1 NSGCT that for the first time offers reasonable estimates of quality adjusted survival (QAS) for each of the disease’s three initial therapies — retroperitoneal lymph node dissection (RPLND), primary chemotherapy and surveillance.

The model is believed to be the first that weighs both quantity and quality of life. It is designed to offer physicians a means of formulating a course of therapy for individual patients and offer patients a mechanism that allows them to evaluate therapies in terms of survival and side effects. Although the patient, with the help of the physician, must still choose a therapeutic option, the model puts that decision on a much sounder clinical foundation.

Each of the three initial therapies — surveillance, RPLND and chemotherapy — is associated with excellent long-term survival probabilities and acceptable short- and long-term adverse effects. Because the outcomes are similar, treatment recommendations and subsequent patient decisions have historically been based on physician bias. The decision tree created by our team offers patients a grasp of the probabilities of specific clinical events, the opportunity to see both the decisions they may have to consider in the future and the long-term potential outcomes associated with each of the three initial therapies.

To create the decision tree, the investigators developed a model that incorporates literature-derived estimates of survival, treatment-related morbidity, and patient utilities for each of the health states that might be a consequence of each of the three initial treatments. Patient utilities (a measure of an individual’s preference for a state of health under conditions of uncertainty) were derived from 24 healthy volunteers with no history of cancer. The utilities incorporated in the model included living with untreated cancer.
small bowel obstruction, infertility, cardiovascular disease, second malignant neoplasm, peripheral neuropathy and ototoxicity. The volunteers were asked two questions to ascertain their attitudes toward the conditions in regard to death and their acceptance of the risk of death versus definitive treatment.

Noting that the risk of relapse in NSGCT can be predicted with reasonable confidence using the histology of the primary tumor and computed tomography staging, the rating scale analysis showed that all patients except those at high risk of relapse, preferred surveillance as the primary treatment. Active treatment with RPLND or chemotherapy became the clearly preferred treatment when the risk of relapse exceeded 46 percent to 54 percent. These findings are consistent with treatment guidelines that recommend surveillance for those patients at low risk for relapse. The QAS differences among the three treatment options are small, and the physician and patient, when evaluating the merits of a therapy, should base decisions on QAS conditions that are clinically relevant to the individual patient.
The initial benefit derived from this effort is the identification of a range of factors found to be strongly associated with the risk of recurrence following nephrectomy. Such findings hold the promise of offering more accurate prognoses, and as with all studies that identify factors associated with pathology, they lay the foundation for a deeper understanding of disease mechanisms and create avenues for new therapeutic strategies designed to meet specific risks.

Clear cell renal cell cancer is the most common form of the highly-aggressive malignancy, appearing in 3 percent to 4 percent of all new cancers in the United States, or more than 51,000 cancers annually. It presents two- to three-times more frequently in men and seems to be more common in African Americans than Caucasians. Surgical intervention in early stage disease (pT1-2) produces very good results with five-year survival rates ranging from 71 percent to 97 percent following nephrectomy. Despite efforts to devise post-nephrectomy preventive strategies, 20 percent to 30 percent of these patients will relapse. Their expected five-year survival is 10 percent. Moreover, the incidence of this disease has been increasing for the past 50 years. Identifying factors associated with recurrence could have a substantial impact on survival.

Cleveland Clinic researchers, in coordination with Genomic Health, Inc. of Redwood City, Calif, have completed the largest known genomic study of localized clear cell renal cell carcinoma (cc RCC).

“Identifying factors associated with recurrence could have a substantial impact on survival.”

Genes Associated with Renal Cancer Recurrence Identified:
Prognostic Algorithm to Be Designed

By Brian I. Rini, MD

Dr. Rini is a member of the Department of Solid Tumor Oncology. For more information or to refer a patient call 216.444.9567 or email rini2@ccf.org.
To identify genes associated with recurrence, a team of Taussig Cancer Institute researchers reviewed the records of patients who had undergone nephrectomy between 1985 and 2003 and selected those for whom paraffin-embedded tissue samples were available. Patients with inherited RCC, those who had undergone neoadjuvant systemic therapy, and those with less than six months of follow-up were excluded from the study.

Some 931 patients with complete clinical/pathological data and tissue samples were identified. Although Cleveland Clinic is a tertiary hospital, the demographics of the cohort paralleled those seen among RCC patients in the population. The majority (63 percent) of the patients were male, with a median age of 61. Stage I disease was dominant, appearing in 68 percent of the cohort; stage II appeared in 10 percent; and stage III made up 22 percent. The clinical/pathological covariates associated with the patients’ recurrence-free interval (RFI) included microscopic necrosis, Fuhrman grade, stage, tumor size and lymph node involvement.

RNA was extracted from 6 x 10 μm tissue sections and screened for 732 genes, five of which were used as reference. Researchers identified 300 genes that were significantly associated with four or more of the five covariates (p<0.05, unadj., Cox models) and 448 genes that were significantly (p<0.05) associated with RFI. Multivariate analysis winnowed these numbers to 16 genes that remained strongly associated with RFI after covariate and false discovery adjustments. Of those, four genes were strongly associated with a lower risk of recurrence. These were the angiogenesis-associated genes EMCN and NOS3 and the immune-related genes CCL5 and CXCL9. The ECMC gene codes for endomucin, and the NOS3 for nitric oxide. CCL5 is a cytokine that is chemotactic for T cells, eosinophils, and basophils. CXCL9 is a cytokine that attracts T cells.

The magnitude of hazard ratios (HRs) associated with these four genes is comparable to that seen with the breast cancer marker genes ER (estrogen receptor) and HER2 (human epidermal growth factor receptor 2).

This research serves as the foundation for the development of a multi-gene algorithm that should bring prognoses for ccRCC recurrence into sharper focus and help with post-nephrectomy decision-making. Work on that algorithm is under way.
Several Taussig Cancer Institute physicians were recently awarded “top” rankings from two independent national sources.

**Aplastic Anemia**
- Jaroslaw Maciejewski, MD, PhD
  - Castle Connolly “Top Doctors”
  - Cleveland Magazine Best Doctors
- Mikkael Sekeres, MD, MS
  - Castle Connolly “Top Doctors”
  - Cleveland Magazine Best Doctors

**Benign Hematology**
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  - Castle Connolly “Top Doctors”
  - Cleveland Magazine Best Doctors
- Jaroslaw Maciejewski, MD, PhD
  - Castle Connolly “Top Doctors”
  - Cleveland Magazine Best Doctors
- Roy Silverstein, MD
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- Jorge Garcia, MD
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- Brian Rini, MD
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- Brad Pohlman, MD
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- John Suh, MD
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  - Cleveland Magazine Best Doctors
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  - Castle Connolly “Top Doctors”
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  - Castle Connolly “Top Doctors”
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  - Cleveland Magazine Best Doctors
- Derek Raghavan, MD, PhD
  - Castle Connolly “Top Doctors”
  - Cleveland Magazine Best Doctors
- Brian Rini, MD
  - Castle Connolly “Top Doctors”
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  - Cleveland Magazine Best Doctors

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  - Cleveland Magazine Best Doctors
- Gary Schnur, MD
  - Cleveland Magazine Best Doctors
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Fairview Hospital
18101 Lorain Ave.
Cleveland, OH 44111
216.476.7000

Hillcrest Hospital
6780 Mayfield Road
Mayfield Heights, OH 44124
440.312.4500

Huron Hospital
13951 Terrace Road
East Cleveland, OH 44112
Phone: 216-761-4258

Beachwood
Family Health and Surgery Center
26900 Cedar Road
Beachwood, OH 44122
216.839.3000 or 800.801.2233

Independence
Cancer Center
6100 Westcreek Road
Ste. 15 & 16
Independence, OH 44131
216.524.7979, Medical Oncology
216.524.9747, Radiation Oncology

Lorain
Family Health and Surgery Center
5700 Cooper Foster Park Road
Lorain, OH 44053
440.204.7400 or 800.272.2676

Parma
Cancer Center
6525 Powers Blvd.
Parma, OH 44129
440.743.4747

Strongsville
Family Health and Surgery Center
16761 SouthPark Center
Strongsville, OH 44136
440.878.2500 or 800.239.1098

Twinsburg
Medical Offices
22365 Edison Blvd., Suite 100
Twinsburg, OH 44087
330.888.4000

Willoughby Hills
Family Health Center
2570 SOM Center Road
Willoughby Hills, OH 44094
440.943.2500 or 800.807.2888

Wooster
Specialty Center
721 East Milltown Road
Wooster, OH 44691
330.287.45000 or 800.451.9870
Taussig Cancer Institute has been awarded more than $2 million from the American Recovery and Reinvestment Act (ARRA) for the renovation and expansion of its translational cancer research facilities.

The National Center for Research Resources, part of the National Institutes of Health, awarded the grant, which will create 17 new jobs.

The project involves the renovation of the original 3,600 square feet of laboratory space built on Cleveland Clinic’s main campus in 1928. The historic space was last renovated in the 1950s, and its use has diminished in recent decades due to the availability of new, more state-of-the-art facilities.

The renovation will include modernizing the space to meet current research laboratory standards, creating a shared instrumentation room that will free up an additional 500 square feet to allow for more bench research, and installing major, fixed research equipment. The expanded lab area also will allow for the recruitment of up to four new independent researchers, along with 12 new technical support positions and one administrative assistant position.

“The expansion of our translational cancer research capabilities is essential to the mission of the Taussig Cancer Institute,” says Chairman Derek Raghavan, MD, PhD “This award will allow us to continue to bring the latest research straight from the lab to the bedside to aid in the diagnosis and treatment of patients.”

Currently, 42 scientists and technicians along with six administrative staff members occupy the available laboratory space in the Taussig Cancer Institute, which is at capacity.
A Sampling of 2010 Journal Publications


Subramanian S, Thayanithy V, West RB, Lee CH, Beck AH,


Critical to Taussig Cancer Institute’s success is the complete partnership established with Cleveland Clinic’s nationally recognized teams of cancer care specialists.

Leading surgeons from other Cleveland Clinic institutes collaborate with Taussig staff to provide the most advanced care to our patients:

- Cole Eye Institute
- Dermatology & Plastic Surgery Institute
- Digestive Disease Institute
- Endocrinology & Metabolism Institute
- Glickman Urological & Kidney Institute
- Head & Neck Institute
- Miller Family Heart & Vascular Institute
- Neurological Institute
- Ob/Gyn & Women’s Health Institute
- Orthopaedic & Rheumatologic Institute
- Respiratory Institute
- Pediatric Institute & Children’s Hospital
Supporting and caring for patients is the number one priority at Taussig Cancer Institute. In addition to clinical and research expertise, Taussig provides a variety of programs and services to assist patients and their caregivers with the challenges of their cancer experience.

**Support Groups** provide patients, families and friends an opportunity to have their concerns, fears, and hopes reaffirmed by others who are experiencing similar life challenges. Support groups are led by our oncology social workers, oncology nurses and psychologists who are specialists in providing reliable and helpful information in an atmosphere of encouragement.

**Reflections Wellness Program** offers a variety of complementary and aesthetic services to Cleveland Clinic cancer patients. All treatments are designed to reduce anxiety and promote healing while patients are undergoing cancer treatments and leave them feeling their best.

**Late Effects Clinic** provides follow-up with cancer survivors years after successful treatment to stave off or detect minor or serious side effects as early as possible.

**Fertility Preservation** offers options prior to treatment for cancer patients who hope to eventually become parents.

**Scott Hamilton CARES Initiative**, created by the champion figure skater after successful treatment at Cleveland Clinic Taussig Cancer Institute, promotes cancer awareness, education and research.

**Chemocare.com**, developed jointly by Taussig Cancer Institute and Scott CARES, is a website that takes the mystery out of chemotherapy.

**4th Angel Mentoring Program** matches newly diagnosed patients with trained volunteers who are cancer survivors.

**Helen Meyers McClarine Patient Resource Center** provides print and online information on everything from treatment overviews to support groups. The Center is staffed by clinical nurse specialists and is open from 8 a.m. to 4:30 p.m., Monday through Friday.

**Cancer Answer Line** is a convenient resource for your cancer-related questions. Call 216.444.7923 or toll-free 866.223.8100, Monday through Friday from 8 a.m. to 4:30 p.m., for answers or to schedule an appointment.

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Cancer Consult provides information from Cleveland Clinic Taussig Cancer Institute specialists about innovative research and diagnostic and management techniques.

Please direct correspondence to
Taussig Cancer Institute/R35
Cleveland Clinic
9500 Euclid Avenue
Cleveland, OH 44195

Cleveland Clinic Taussig Cancer Institute annually serves more than 26,000 cancer patients. More than 250 cancer specialists are committed to researching and applying the latest, most effective techniques for diagnosis and treatment to achieve long-term survival and improved quality of life for all cancer patients. Taussig Cancer Institute is part of Cleveland Clinic, an independent, not-for-profit, multispecialty academic medical center.

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Online medical second opinions from Cleveland Clinic’s MyConsult are particularly valuable for patients who wish to avoid the time and expense of travel. Visit clevelandclinic.org/myconsult, email eclevelandclinic@ccf.org or call 800.223.2273, ext 43223.

Outcomes Data Available View the latest clinical Outcomes book from many Cleveland Clinic institutes at clevelandclinic.org/quality/outcomes.

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216.445.5600 or 800.223.2273, ext. 55600

Bone Marrow Failure Clinic Appointments/Referrals
216.445.5962 or 800.223.2273, ext. 55962

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