Pediatric brain and spinal cord tumors pose a dilemma for physicians. Conventional radiation therapy, often combined with surgery and chemotherapy, can control and even cure several types of tumors. Yet while patient survival may be extended, quality of life can suffer dramatically because radiation can have long-term effects on a child’s growth and development. A critical advance, proton radiotherapy helps resolve this difficult problem. It delivers less radiation to healthy tissue surrounding the tumor, reducing long-term side effects for children receiving treatment. Preliminary studies have also shown a decreased rate of secondary tumors among patients treated with proton radiotherapy.

In proton radiotherapy, a cyclotron or synchrotron is used to generate and accelerate protons—the nuclei of hydrogen atoms without their electrons. The protons, which are positively charged particles, are then extracted from the machine and directed toward the tumor by a series of magnets. Protons deposit only a small amount of their energy when they enter the human body, and their remaining energy is released when they come to a sudden stop in the tumor. Unlike regular photon irradiation, the dose is distributed in a very limited space, so there is less damage to surrounding normal tissues.

The benefits of this approach are particularly pronounced for children with curable brain and spinal cord tumors. Today, most of these children go on to become long-term survivors. With conventional radiation therapy, however, the unintended consequence is often a lifetime of disabling side effects, such as intellectual impairment, hearing loss, stunted growth, glandular deficiencies and secondary malignancies. By reducing radiation damage to normal tissues, proton radiotherapy offers these children a brighter future, including greater success in school and an independent life as adults.
Proton Radiotherapy Offers Safer Treatment for Pediatric Brain and Spinal Cord Tumors

Key Points

• Conventional radiation therapy can treat several types of pediatric brain and spinal cord tumors. However, because healthy tissue is irradiated along with the tumor, survivors are often left with disabling long-term side effects.

• Proton radiotherapy achieves a similarly high rate of survival in pediatric brain and spinal cord patients. Yet the long-term side effects are significantly reduced, because the radiation is more precisely targeted and normal tissue surrounding the tumor can be avoided.

• Preliminary results from a trial of proton radiotherapy for pediatric medulloblastoma showed improved outcomes. Overall and progression-free survival were similar to reported rates for conventional radiation therapy, while long-term neurocognitive, audiological and endocrine outcomes were superior.

• The Mass General Cancer Center is one of only nine centers in the United States to offer proton radiation therapy.

the world. Preliminary results from a Mass General trial of proton radiotherapy for medulloblastoma were presented by Mass General Pediatric Radiation Oncology Director Torunn I. Yock, MD, MCH, at the June 2010 meeting of the American Society of Clinical Oncology.

Pediatric medulloblastoma—a rare tumor that arises in the brain and spreads to the spinal column—is commonly treated with a combination of surgery, radiation therapy and chemotherapy, typically in that order. Radiation therapy begins with craniospinal irradiation, or CSI, treating the whole brain and whole spine with a low dose of radiation. This is followed by “involved field” radiation, a higher boost of radiation to the tumor bed, in this case, the posterior fossa, the back part of the brain that holds the brainstem and cerebellum.

The Mass General proton radiotherapy study included 59 medulloblastoma patients, ages 3 through 22. Forty-five were classified as standard risk and 14 were considered high risk. After three years, 90 percent were still alive and 80 percent were free of tumor. These disease outcomes are similar to those reported elsewhere for conventional radiation therapy.

Neurocognitive Outcomes

The major benefit of proton radiotherapy is its improved safety profile. In the proton radiotherapy study, no decline was seen in full-scale IQ and most other measures of neurocognitive function after an average follow-up of two years. The only significant change found in this study was a drop in mental processing speed. In contrast, past studies using conventional radiation therapy to deliver CSI found significant declines in IQ and other neurocognitive test scores, which continued to decrease years after completion of treatment. Younger age at treatment and higher doses of CSI typically increase the magnitude of these deficits, so younger children are most apt to benefit from proton radiotherapy’s safety profile.

Audiological Outcomes

Audiological outcomes were also improved with proton radiotherapy, which reduces the amount of radiation that reaches the cochlea compared with conventional radiation therapy. After a two-year median follow-up, less than 20 percent of patients participating in the Mass General study had profound hearing loss. By comparison, past research using intensity-modulated radiotherapy (IMRT), the least ototoxic form of conventional radiation, found profound hearing loss in at least 25 percent of patients.

Cisplatin, the chemotherapy agent most commonly administered after radiotherapy for medulloblastoma, is also ototoxic. As a result, audiological testing is routinely performed before cisplatin treatment is initiated, and the dose is reduced for patients who already show signs of hearing loss. New evidence that cisplatin may have late ototoxic effects underscores the need to monitor these patients long term.

Endocrine Outcomes

In the short term, endocrine outcomes also improved with proton radiotherapy when compared with studies using conventional radiation. With conventional treatment, a significant amount of radiation reaches the hypothalamus, pituitary and thyroid...
glands, often causing deficiencies in the pituitary, thyroid, sex steroids and adrenal hormones. These deficiencies, in turn, may lead to problems with growth and puberty. Proton radiotherapy, in contrast, reduces radiation to the pituitary and hypothalamus, and it eliminates radiation to the thyroid.

In the study, 29 percent of patients receiving protons had hormonal deficiencies that required hormone replacement. That statistic compares favorably with previous studies of conventional radiation therapy, in which 50 to 70 percent of patients had hormonal deficiencies. However, endocrine side effects sometimes take years to manifest, so longer follow-up is needed before any firm conclusions can be drawn.

**Proton Radiotherapy Treatment**

The Francis H. Burr Proton Therapy Center at the Mass General Cancer Center—one of only nine such centers in the United States—treats both children and adults from across the country and around the world. Proton radiotherapy is appropriate for brain and spinal cord tumors that respond well to precisely targeted radiation. In addition to medulloblastomas, other types of tumors that fall into this category include astrocytomas, ependymomas and craniopharyngiomas. Proton radiotherapy is also increasingly being used to treat tumors in other parts of the body.

Prior to treatment, patients are fitted with an immobilization device, which ensures that the patient’s body will be in exactly the same position for each treatment session. For brain tumor patients, the device consists of a mask and head cup that conforms to the patient’s head. Once the immobilization device is created, patients undergo CT and MRI scans to define the boundaries of the tumor for radiation planning purposes.

The number of treatment sessions and total radiation dose depend on the tumor type and location. For pediatric medulloblastoma, for example, the treatment goal might be a total radiation dose of 54 GyE (gray equivalent dose), with outpatient treatment sessions scheduled five days a week over the course of six weeks. Children ages 6 and younger usually require general anesthesia to prevent them from moving during treatment, but the therapy is painless even for unanesthetized older patients.

Each treatment session takes 20 to 60 minutes, depending on the complexity of the treatment and whether anesthesia is required. Immediate side effects—such as fatigue, skin reddening, nausea and vomiting—are generally mild and manageable.

Proton radiotherapy is a major advance in the precise delivery of radiation therapy. The younger the patients are, the more significant that advantage becomes. For many children with brain and spinal cord tumors, conventional radiation therapy and proton radiotherapy have similar rates of disease control. But proton radiotherapy improves the odds that they will also be able to learn in school and later obtain employment and live on their own. In addition to saving their lives, it also helps safeguard their futures.

**Selected References**


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International Researcher Heightens Cancer Center Focus on Early-Phase Clinical Research

José Baselga, MD, PhD, the new chief of hematology oncology and associate director of the Massachusetts General Hospital Cancer Center, is as much an architect as he is a physician-researcher. In his new role, Dr. Baselga will build upon the center’s continued efforts to integrate early-phase clinical and translational research with the advanced, personalized patient care provided at the Mass General Cancer Center.

Reinforcing Targeted Therapy Research Efforts

Dr. Baselga was previously chairman of the medical oncology service and the founding director of the Vall d’Hebron Institute of Oncology in Barcelona, Spain. He is an internationally renowned clinical scientist with extensive experience in the development of cancer therapies targeting growth factor receptors and downstream molecules. Dr. Baselga’s research has focused on the development of numerous targeted cancer drugs, particularly for human epidermal growth factor receptor 2 (HER2) positive breast cancer. Drugs he helped bring into clinical testing include cetuximab, trastuzumab, lapatinib, pertuzumab, insulin-like growth factor receptor (IGFR) inhibitors and a variety of antiangiogenic agents.

Dr. Baselga’s focus on targeted therapies complements the extensive work already conducted by the Mass General Cancer Center in this area, including some of the world’s first studies to understand mutations of epidermal growth factor receptor (EGFR) and anaplastic lymphoma receptor tyrosine kinase (ALK) proteins in lung cancer patients, as well as the protein BRAF in patients with melanoma. (See related article on page 8.)

Dr. Baselga is responsible for leading the development of new and targeted agents, as well as novel treatments for cancers that are resistant to current therapies. Under his leadership, the Cancer Center has established a Center for Targeted Therapeutics, which will develop a portfolio of early clinical trials across disease centers and focus intensively on identifying predictive biomarkers.

Bispecific Antibody Research: Targeting Drug Resistance

One of Dr. Baselga’s research priorities is the development of bispecific antibodies that can be used in combination to break down a tumor’s defense mechanisms. As part of this effort, he and a team of several physician–researchers are testing a new anti-EGFR/HER3 monoclonal antibody called MEHD7945A in advanced epithelial tumors. This “two-in-one” antibody targets both EGFR (also known as HER1) and HER3, which play key roles in regulating tumor growth.

The theory underlying this work is that an agent blocking more than one receptor may more successfully halt drug resistance in patients. Early research suggests that bispecific therapy may also be more effective than monospecific antibodies against HER-driven carcinomas of the head and neck, lung, colon and pancreas. Dr. Baselga will lead this research as the principal investigator.

Expanding Studies of Anti-mTOR Agents

Another growing research area under Dr. Baselga’s direction is the development of agents that interrupt the mammalian target of the rapamycin (mTOR) pathway. Currently, Dr. Baselga is the global principal investigator for a phase 2 trial of a dual-targeted therapy, ridaforolimus and mTOR, which interact with the PI3K pathway.

Targeting Key Pathways: IGFR-1, PI3K and mTOR

Dr. Baselga leads a global phase 2 trial investigating a bi-specific agent that combines dalotuzumab and ridaforolimus to target IGFR-1 and mTOR, which interact with the PI3K pathway.

Key Points

- Internationally renowned clinical scientist José Baselga, MD, PhD, will lead the Cancer Center’s development of new and targeted agents, as well as novel treatments for cancers resistant to current therapies.

- Researchers at the Cancer Center will be testing a new anti-EGFR/HER3 monoclonal antibody called MEHD7945A in advanced epithelial tumors. This “two-in-one” antibody has been designed to target EGFR and HER3, which play key roles in regulating tumor growth.

- Dr. Baselga is the global principal investigator for a phase 2 trial of a dual-targeted therapy against the mTOR and IGFR-1 pathways, using ridaforolimus and dalotuzumab, with patient enrollment continuing in 2011. The international study will compare this combination agent to exemestane in estrogen-receptor-positive breast cancer patients.

- Dr. Baselga is also leading the Cancer Center’s research on phosphatidylinositol 3-kinase (PI3K) inhibitors. Some of the agents being tested include the PI3K inhibitor known as BKM120 and an agent called BEZ235, which is being used in combination with exemestane, for estrogen receptor–positive breast cancer. In addition, a highly potent and specific inhibitor called BYL719 will be studied in a phase 1 trial of tumors with PI3K mutations.
Early results of the combination have been promising. At the 2010 meeting of the American Society of Clinical Oncology (ASCO), Dr. Baselga and colleagues from Vall d’Hebron presented results from a phase 1 study of ridaforolimus and dalotuzumab in patients with advanced cancer. Patients who failed standard therapy received ridaforolimus at escalating doses five times a week combined with dalotuzumab every other week. The study found that the combination of ridaforolimus and dalotuzumab is well-tolerated and has positive anti-tumor activity in heavily pretreated advanced cancer, particularly in estrogen receptor-positive/high-proliferation breast cancer. In this challenging subset of patients, there was evidence of clinical activity in more than 40 percent of patients, who came into the study after extensive pretreatment.

**Additional PI3K Inhibitor Trials Under Way**

Another key area of early clinical research at the Cancer Center is ongoing work with phosphatidylinositol 3-kinase (PI3K) inhibitors. The PI3K pathway is the most aberrantly hyperactivated pathway in cancer. Researchers suspect that PI3K pathway inhibition will have a significant impact on tumor survival and proliferation.

At the ASCO annual meeting last spring, Dr. Baselga also presented the results of his work with the PI3K inhibitor called BKM120. This agent is a potent and highly specific, oral, pan-class 1 PI3K inhibitor. Unlike other inhibitors, it does not inhibit the related kinases, mTOR and VPS34. The ASCO data showed that the maximum tolerated daily oral dose produced a favorable pharmacokinetic profile, consistent pharmacodynamic changes and clear signs of clinical activity.

In addition, Cancer Center researchers are studying other PI3K inhibitors, including a highly potent and specific inhibitor called BYL719. Dr. Baselga will lead this phase 1 trial in patients with advanced solid tumors with PI3K mutations.

Moving forward, Dr. Baselga has also begun work with Steven Jay Isakoff, MD, PhD, also of the Gillette Center, on a randomized, phase 2 trial of BEZ235, a dual PI3K and mTOR inhibitor, used in combination with exemestane for estrogen-receptor-positive breast cancer. The agent specifically inhibits PI3K in the PI3K/AKT kinase (or protein kinase B) signaling pathway, which may trigger apoptotic cell death through Bax, a member of the proapoptotic Bcl-2 family of proteins. This work is being funded by a grant from the Stand Up To Cancer organization.

Other work with Dr. Isakoff includes an upcoming randomized phase 2 trial of an anti-MET monoclonal antibody (MetMAb), with paclitaxel and bevacizumab for triple-negative breast cancer, as well as a phase 1/2 trial of the PI3K inhibitor XL147 combined with letrozole for metastatic breast cancer.

**Genotyping, Imaging Make Advanced Research Possible**

Critical research capabilities support the development of targeted therapeutics at the Cancer Center. The Translational Research Laboratory, one of the few such hospital-based molecular diagnostics laboratories in the United States, performs broad-based tumor genotyping. The Center for Molecular Therapeutics conducts cell-line screening to identify which tumor types are the most sensitive to specific agents. The Cancer Center’s strong biomarker program will help accelerate the study of these agents in a relevant clinical setting.

Other key resources include the Cancer Center’s circulating tumor cell platform (supported by Stand Up To Cancer), allowing for the serial monitoring of tumor genotypes during the course of therapy, and a collaboration with Cancer investigators José Baselga, MD, PhD, brings an internationally recognized clinical research portfolio with him to the Cancer Center.

Massachusetts General Hospital nuclear medicine researchers to develop dynamic positron emission tomography (PET) imaging, which will allow much earlier detection of treatment effectiveness.

With Dr. Baselga now leading translational and early-phase clinical research, the Cancer Center is prepared to aggressively advance the search for targeted anti-cancer agents and identify new therapies for treatment-resistant cancers.●

**Selected References**


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Cancer investigator José Baselga, MD, PhD, brings an internationally recognized clinical research portfolio with him to the Cancer Center.
Landmark Study Links Palliative Care with Survival Benefit for Lung Cancer Patients

A landmark study published in the New England Journal of Medicine has provided the first evidence that early palliative care can lengthen the survival of lung cancer patients. Published last August, “Early Palliative Care for Patients with Metastatic Non-Small-Cell Lung Cancer” reported the results of a clinical trial conducted by a team of researchers at the Massachusetts General Hospital Cancer Center.

Study Documents Survival Benefit

Metastatic non-small-cell lung cancer (NSCLC) is the leading cause of cancer death in the United States. In their study, Mass General Cancer Center investigators found that patients who received early palliative care along with standard-of-care oncologic treatment lived on average 2.7 months longer than patients who received standard cancer treatment alone. Researchers consider that extension significant, as most patients with metastatic NSCLC survive less than a year, with a high symptom burden and poor quality of life.

Medical oncologist Jennifer S. Temel, MD, clinical director of the Center for Thoracic Cancers at the Cancer Center, was the study’s lead author. Dr. Temel designed the study in which newly diagnosed metastatic NSCLC patients, with their full consent and after complete disclosure of the study details, agreed to participate and were randomly assigned to receive either standard-of-care cancer treatment or standard cancer care plus early palliative care.

Patients with metastatic NSCLC receiving standard care are typically referred for palliative care as part of their inpatient treatment close to the end of life, often within the last few days of life. Those patients receiving “early palliative care” in Dr. Temel’s study started seeing palliative care providers on an outpatient basis shortly after they were diagnosed with advanced disease. They each continued to meet with a palliative care provider at least monthly over the course of their illness. The primary endpoint of the study was quality of life; overall survival was a secondary endpoint.

Palliative Care Patients Report Better Mood and Quality of Life

At enrollment and after 12 weeks in the study, the two groups completed the Functional Assessment of Cancer Therapy—Lung (FACT-L) scale to assess each patient’s quality of life. On a scale of 0 to 136, higher FACT-L scores reflect better quality of life. At 12 weeks, the mean FACT-L score for palliative care patients was 98, compared with 91.5 for standard care patients, a statistically significant difference. While the standard care group reported worsening quality of life, the palliative care patients showed improvement from baseline.

Perhaps most significant were mood scores, assessed by the Hospital Anxiety and Depression Scale (HADS). About 16 percent of patients in palliative care were depressed, compared with 38 percent in standard care, with antidepressant use similar across the two groups.

The authors attribute the survival benefit among the palliative care patients, at least in part, to these positive changes in quality of life and mood.

Palliative care was also associated with what is widely considered more appropriate use of medical services at the end of life. Patients who received only standard care were more likely to undergo chemotherapy within 14 days of their death and less likely to be referred to hospice either at all or close to the time of death, compared with patients in the standard care plus palliative care group. While patients with early palliative care had less aggressive care at the end of life, they still experienced a survival benefit: they lived on average 2.7 months longer.

Overcoming Barriers to Expand Palliative Care

Misconceptions about palliative care remain prevalent among physicians and patients. Many confuse palliative care with hospice care. Such misconceptions

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Key Points

- In the New England Journal of Medicine, researchers from the Massachusetts General Hospital Cancer Center recently reported that patients with metastatic non-small-cell lung cancer (NSCLC) who received early palliative care along with standard-of-care cancer treatment lived on average more than two months longer than patients who received standard cancer care only.

- Patients receiving palliative care lived longer and experienced improved mood and quality of life. The presence of depression was about half of that reported in the standard-of-care group at 12 weeks, although rates of antidepressant use in the two groups were similar.

- Palliative care was associated with more appropriate end-of-life care. More than half of the standard-of-care patients received chemotherapy within 14 days of death or were not referred to hospice at all or close to the time of death, compared with only one-third of the palliative care group.
make both parties reluctant to discuss the ways in which palliative care can help patients manage their symptoms and the concerns that may surface after being diagnosed with advanced cancer. This confusion is one reason why cancer patients traditionally receive palliative care late in their disease. However, research conducted a few years ago by Cancer Center investigators concluded that providing palliative care earlier in the course of disease was feasible. These results were published in 2007 in the *Journal of Clinical Oncology*.

Dr. Temel and her colleagues hope their 2010 study demonstrating that palliative care may offer a survival benefit and better quality of life will help change clinical practice, so that more patients receive palliative care earlier. In their view, the integration of palliative approaches with standard cancer care may offer the optimal treatment for certain cancer patients. Referral to a palliative care team soon after receiving a diagnosis of advanced disease may enable patients to better manage their symptoms, stabilize the disease and live longer. Dr. Temel adds that she will soon lead a new study to test this hypothesis in patients with lung cancer and advanced gastrointestinal cancers. The development of best practice guidelines for outpatient palliative care is one of the study goals.

When more research becomes available, both physicians and the public may have a clearer picture of the potential impact that early palliative care can have on the quality of life and survival of cancer patients.

**An Integrated Model at Mass General**

At the Massachusetts General Hospital Cancer Center, the Palliative Care Program includes physicians, nurses, social workers and chaplains who manage patients’ symptoms, such as pain and shortness of breath, while helping them cope with the psychological and spiritual issues that arise during a terminal diagnosis. The team is led by Vicki A. Jackson, MD, MPH, acting director of the Palliative Care Program. Palliative care providers see cancer patients in both outpatient and inpatient settings, with a tendency now to see them in the outpatient setting earlier in the course of their illness, before their symptoms become debilitating.

Palliative care consultations at the Cancer Center typically last about an hour and may cover symptom management; goals of care; psychological support; and care coordination with other services. While often separate from outpatient oncology at other cancer centers, palliative care has been integrated into outpatient oncology at the Mass General Cancer Center for more than a decade. Oncologists and palliative care providers work in the same location, side by side, often seeing patients in joint or consecutive appointments. When providers are unable to consult face-to-face, they use the Cancer Center’s electronic medical records system to coordinate care and discuss issues such as symptom management. The integrated care model has also supported clinical investigations like the *New England Journal of Medicine* study, as oncologists and palliative care providers share the same research platform.

By providing access to clinical trials and advanced treatments as well as palliative care services, experts at the Cancer Center are presenting patients with options that may improve their quality of life—and even extend it.

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Targeted Therapy Advances Treatment Options for Metastatic Melanoma

Targeted therapies are changing the outlook for some melanoma patients, and the Massachusetts General Hospital Cancer Center is playing a key role in this research.

With the incidence rising by 3 to 5 percent a year and few therapeutic options available, metastatic melanoma has been a particularly frustrating disease for patients, clinicians and scientists. Surgical excision is usually successful in treating early-stage melanoma. Once it has metastasized, however, traditional therapeutic approaches—chemotherapy, radiation and immunotherapy—have not proven reliably effective against this aggressive malignancy. High-dose interleukin-2 and dacarbazine, the only two agents approved by the Food and Drug Administration for treating disseminated melanoma, yield response rates of only 10 to 20 percent and, even then, do not appear to improve survival. The vast majority of patients diagnosed with late-stage melanoma succumb to the disease today, just as they did 10, 20 and 100 years ago.

Recently, however, researchers at the Mass General Cancer Center have unraveled some of the complicated biology of melanoma as they seek to identify molecular targets for individualized therapy. In the August 26, 2010 issue of the New England Journal of Medicine, Cancer Center Director of Developmental Therapeutics Keith T. Flaherty, MD, and colleagues reported that a new targeted therapy was effective in 81 percent of metastatic melanoma patients whose tumors had a particular genetic mutation.

Interrupting the MAPK Signaling Pathway

The target was a mutation in the BRAF protein, which is found in the chain of proteins known as the mitogen-activated protein kinase (MAPK) pathway. MAPK relays growth signals from outside the cells to the nucleus and has been implicated as an important contributor in the proliferation of many types of cancers. The mutated, activated BRAF continually stimulates cell division downstream, leading to uncontrolled tumor growth. Its presence in human cancers—and notably high prevalence in melanomas—was first reported in 2002.

The clinical trial, for which Dr. Flaherty served as principal investigator, showed that the orally available investigational drug PLX4032 (co-developed by Plexxikon and Roche) could induce rapid tumor regression by targeting the BRAF mutation, which occurs in 40 to 60 percent of melanomas and 7 to 8 percent of other common cancers. An initial dose escalation phase of the trial established a recommended dose of 960 mg twice daily; higher doses were limited by side effects such as rash, fatigue and arthralgia. Of the 32 patients in the second phase of the trial, all of whom had metastatic melanoma with the BRAF mutation, 24 had a partial response to PLX4032 (tumor shrinkage of 30 percent or more) and two had complete tumor regression. Symptomatic patients experienced reduced pain and symptoms shortly after starting treatment, and imaging studies showed regression of tumors at sites throughout the body.

Targeted therapies are changing the outlook for some melanoma patients, and the Massachusetts General Hospital Cancer Center is playing a key role in this research.

This pre-treatment lung CT scan from a patient with metastatic melanoma shows multiple metastatic foci (arrows).

Two months into treatment with BRAF inhibitor PLX4032, the same patient’s scan indicates substantial clinical response—more than 30 percent, a partial response by standard response criteria.
the body, including the liver, other visceral organs and bone.

PLX4032 has a remarkably high degree of selectivity. It blocks mutated, hyperactive BRAF, halting the MAPK signaling that melanoma cells rely on. Normal cells are largely left untouched: researchers have discovered that they do not depend on mutant BRAF the way melanoma cells do. The relative lack of toxicity to healthy cells enhances the ability to maintain treatment at an optimal or close-to-optimal dose.

In spite of the impressive early response, however, most tumors eventually developed resistance to PLX4032 and resumed growing. At the time the trial's results were published, progression-free survival (the median duration until tumor growth) was estimated to be about seven months. The larger question of overall survival benefit remains unanswered, but a multicenter phase 3 trial is under way that will compare survival in patients receiving PLX4032 or the chemotherapeutic agent dacarbazine.

The New Goal: Individualized Therapy

Tailoring treatment to the genetic fingerprint of an individual patient's tumor is emerging as a new paradigm in melanoma therapy, and one that owes much to the unique resources at Mass General. It is one of the few hospitals in the country now conducting broad-based tumor genotyping through routine biopsies. Today, the Translational Research Laboratory screens for 130 known genetic mutations in key cancer driver genes. Without this capability, the clinical research on targeted drugs like PLX4032 could not have easily moved forward.

The laboratory is now supporting a national clinical trial of targeted therapy against another genetic abnormality seen in 5 percent or fewer of melanoma cases, the C-KIT mutation. Led by Donald P. Lawrence, MD, clinical director of the Cancer Center's Melanoma Center, the trial will evaluate the efficacy of dasatinib (a kinase inhibitor) in treating these uncommon melanomas that arise on palms, on soles and in mucosal tissue.

Understanding the precise genetic profile of tumors is expected to greatly speed up the development of targeted therapies. Even if such therapies do not provide a cure, researchers believe they may help patients achieve remission, prolong survival and provide a window of opportunity for adjuvant therapy.

Promise of Targeted Therapies Shapes Future Research

Under the leadership of Director David E. Fisher, MD, PhD, the Cancer Center’s Melanoma Center is playing a leading role in both the basic science and clinical aspects of melanoma research.

Key Points

- Incidence of melanoma is increasing at the rate of 3 to 5 percent a year, and metastatic melanoma has become a leading cause of cancer deaths. The American Cancer Society estimated there would be 68,000 new cases and 8,700 deaths from melanoma in the United States in 2010.
- Surgical treatment is usually successful in treating early-stage melanoma, but until now, there have been no viable treatment options for metastatic melanoma.
- Approximately 50 percent of metastatic melanoma tumors have a mutation in the BRAF gene, which drives tumor cell growth. A recent clinical trial found that targeted therapy with PLX4032 was successful in more than 80 percent of melanoma patients with this mutation, halting or regressing disease for an estimated median of more than seven months.
- Continuing research on the genetic mutations in melanoma, the mechanisms of tumor resistance, and the development of sequential or multi-agent treatment strategies to target that resistance will advance the development of individualized therapy options for metastatic melanoma.
targeted therapy advances treatment options for metastatic melanoma

resistance, biopsies are routinely taken at the Mass General Cancer Center before a melanoma patient starts treatment, during treatment and at the point that resistance develops.

Researchers are also keen to develop and test sequential and combination therapies, which may be critically important strategies for turning the temporary response of a targeted therapy into a more lasting response. Strategies to combine PLX4032 and immunotherapy now being piloted will explore this possibility. This work is based on new evidence that oncogenic BRAF helps the tumor evade recognition by the immune system and that treatment with a selective BRAF inhibitor improves tumor cell antigen recognition.

Because melanomas are characterized by hundreds of genetic changes, exploring how numerous genetic and signal transduction alterations together give rise to melanoma is another important endeavor. Currently, Mass General is participating in a clinical trial to assess the efficacy of two signaling inhibitors from GlaxoSmithKline, a BRAF inhibitor and a MAP extracellular signal-regulated kinase (MEK) inhibitor, that appear to complement each other.

The substantial effect seen in Dr. Flaherty’s clinical study indicates the power of a single point of intervention—in this case, the targeting of the mutant BRAF gene. With metastatic melanoma, historically one of the most treatment-resistant of all cancers, exhibiting significant response when the right drug is directed at the right mutation, researchers believe they have important new evidence demonstrating the potential of the targeted therapy paradigm.

continued from the previous page

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Gastric cancer is the fourth most common type of cancer and the second highest cause of cancer deaths worldwide. Until the 1930s, gastric cancer was the leading cause of cancer-related deaths in the United States, but it has been on the decline in this country since that time. Currently, an estimated 21,000 new cases of gastric cancer are diagnosed each year in this country, with 10,570 related deaths.

**A Leader in Gastric Cancer Care**

With gastric cancer rates declining in the United States, centers that provide experienced treatment for these cancers are vital. Facilities treating fewer numbers of gastric cancer cases report significantly higher morbidity and mortality rates than those at high-volume institutions. Unfortunately, about 80 percent of all gastric cancer cases in the United States are treated at low-volume facilities, which are defined as treating fewer than 15 gastric cancer cases each year.

The Tucker Gosnell Center for Gastrointestinal Cancers at the Massachusetts General Hospital Cancer Center has one of the largest and most experienced gastric cancer programs in New England, treating more than 100 gastric cancer patients annually. The Center offers innovative treatment of all types of gastric cancers.

The vast majority of gastric cancers are not hereditary. Between 1 and 3 percent, however, stem from an inherited gastric cancer syndrome and are commonly of the diffuse type—that is, they are composed of discohesive single cells that infiltrate the submucosa of the stomach. This type of cancer is commonly referred to as hereditary diffuse gastric cancer (HDGC).

At the Gosnell Center, surgical oncologists Sam S. Yoon, MD, and John T. Mullen, MD, along with gastroenterologist Daniel C. Chung, MD, and pathologist Gregory Y. Lauwers, MD, provide nationally recognized expertise in the diagnosis and treatment of HDGC.

**The CDH1 Germline Mutation Link**

HDGC has been linked to germline mutations of the CDH1 gene, which encodes for E-cadherin, a membrane-expressed cell adhesion protein. This mutation is estimated to account for 25 to 30 percent of HDGC cases. In patients with the mutation, E-cadherin is often missing or nonfunctional. This causes a failure of cell adhesion; hence, the “diffuse” nature of this cancer. HDGC signet ring cells, so-called due to their appearance (see page 12), do not stick to one another and, therefore, tend to spread. For men and women with the CDH1 mutation, the estimated risk of developing HDGC is more than 80 percent. The current view is that other cases of HDGC are related to genetic causes that have not yet been identified.

The CDH1 gene mutation is also closely linked to lobular breast cancer, increasing the risk for breast cancer by 60 percent for women with the mutation. A link to colon cancer has also been established, although more research is needed to determine the relative risk.

HDGC is characterized by microscopic precursor lesions that often develop in normal-appearing mucosa, making early detection extremely difficult. Endoscopic biopsy has been found inadequate to identify such early lesions. Indeed, superficial endoscopic biopsies are often falsely negative.

Of those patients found to have lesions, just 10 percent are identified in the early stages of disease. Once the cancer becomes clinically apparent, it has often metastasized; the mortality rate for metastatic gastric cancer is more than 95 percent.

It is therefore imperative that individuals with the CDH1 gene mutation are identified and treated proactively. The only definitive treatment for individuals with the CDH1 mutation is total prophylactic gastrectomy. The physician who suspects that a patient may have the mutation should refer the individual for genetic testing. Consultation with HDGC experts on the referral criteria is key. Timing and the choice of an expert treatment center like the Mass General Cancer Center are also paramount.

**Experts in Diagnosis, Treatment of Rare Hereditary Gastric Cancer**

Mass General is at the forefront of care for HDGC patients. In addition to providing treatment for the rare disease, physicians at the Mass General Cancer Center have published some of the most extensive data and findings on HDGC to date in the United States. They also serve as experts in international groups to set diagnosis and treatment standards.

Dr. Chung, clinical director of Gastrointestinal Cancer Genetics at the Mass General Cancer Center, is a member of the International Gastric Cancer Linkage Consortium, which has set HDGC diagnosis criteria. Those criteria include individuals who have:

- Two or more documented cases of diffuse gastric cancer in first- or second-degree relatives, with at least one diagnosed before age 50; or
- Three or more cases of diffuse gastric cancer in first- or second-degree relatives, regardless of age of onset.

continued on the next page
Mass General Cancer Center Surgeons Perform Rare Surgery

The Mass General Cancer Center is among the few centers in the United States that perform total prophylactic gastrectomy. Its surgical teams have performed 10 total prophylactic gastrectomies—one of the largest series by any single institution in the United States. To date, fewer than 100 total prophylactic gastrectomies have been performed worldwide.

Mass General gastric cancer specialists also offer close surveillance of many other patients whose HDGC diagnosis is not definitive or who have not yet decided to undergo surgery. This may include annual endoscopy to ensure that there is no evidence of clinically significant lesions, with the understanding that current endoscopic techniques in general are inadequate to identify all lesions.

Genetic Counseling Plays Key Role in Diagnosis, Treatment

Genetic counseling is a key aspect of treating patients with HDGC. Many patients are referred each year to the Mass General Center for Cancer Risk Assessment for CDH1 germline mutation testing. Genetic testing can confirm the presence of the CDH1 mutation and enable physicians to make the diagnosis of HDGC syndrome. The patient diagnosed with HDGC has an increased risk of diffuse gastric cancer and also lobular breast cancer.

Dr. Chung was part of a worldwide group of gastric cancer experts that published new HDGC genetic testing guidelines in the Journal of Medical Genetics in July 2010. They expanded the list of those who should be tested for the CDH1 germline mutation to include individuals who:

- Have one family member with diffuse gastric cancer
- Develop diffuse gastric cancer before age 40 without a family history of the disease
- Have any family history of both diffuse gastric cancer and lobular breast cancer

Although prophylactic gastrectomy is recommended for all patients identified with the CDH1 mutation, timing of the surgery is debatable. There have been rare reported cases of HDGC in patients during their teen years. However, most individuals with the CDH1 mutation develop the cancer in their late 30s or 40s. Once presence of the mutation has been confirmed, the physician and patient must determine when to proceed so that the stomach is removed before the cancer begins to grow.

Counseling Enhances Patient Preparation for Side Effects

Prophylactic gastrectomy is a major endeavor that includes lifelong consequences. In addition to typical surgical risks, total gastrectomy has significant nutritional consequences. On average, patients lose 10 to 20 percent of their total body weight within the first six months following surgery. Patients must eat and drink small amounts of food and liquid continuously throughout the day until they are able to transition to small meals and snacks.

Patients must also receive a monthly intramuscular vitamin B12 and daily oral multivitamin for life. Despite compliance with this regimen, some patients have difficulty maintaining adequate nutrition levels and must work closely with gastroenterologists and nutritionists on a long-term basis.

Given the side effects that can be anticipated, it is important for patients to be physically and mentally prepared...
to manage the gastrectomy, both in terms of the procedure itself, as well as life after surgery. Genetic counseling assists patients through this difficult process. **Multidisciplinary Team Ensures Optimal Outcomes**

Mass General’s multi-disciplinary HDGC team includes geneticists, gastroenterologists, oncologists, surgeons, pathologists and nutritionists. They help determine the diagnosis, educate and counsel patients regarding treatment and help rehabilitate and transition patients back into their daily lives following the life-changing surgery. Multidisciplinary education and counseling are also critical to screen for the related risk for lobular breast cancer. Both breast mammograms and breast MRI scans are recommended for women ages 35 and older who have the mutation. While prophylactic gastrectomy is the definitive treatment for individuals with the CDH1 mutation to prevent gastric cancer, the procedure does not alter one’s risk of developing lobular breast cancer. Mutation-positive patients at risk for lobular breast cancer should be counseled about the role of prophylactic bilateral mastectomy.

**Mass General-Led Research: Data to Inform Patient Decision-Making**

Because HDGC is such a rare syndrome, analysis of every case is essential for further understanding of the disease and its treatment. Mass General Cancer Center physician-researchers continue to pursue important research regarding HDGC. Director of Surgical Pathology Gregory Y. Lauwers, MD, has been analyzing CDH1 precursor lesions to better understand the progressive changes in the gastric lining that characterize the disease.

Working with Dr. Chung, Dr. Lauwers has also conducted a comprehensive analysis of biopsy results for HDGC, given that it is not uncommon for patients diagnosed with HDGC to have had previous negative results on multiple biopsies. The lack of clinical evidence can complicate patient decision-making on whether to undergo a total prophylactic gastrectomy.

To gauge how many biopsies would be required to ensure even a 50 percent detection rate, Dr. Chung and Dr. Lauwers analyzed the entire resected stomach from each one of Mass General’s prophylactic gastrectomy cases. They searched for the precancerous lesions that often are embedded in the submucosa and elude standard endoscopy.

Conducting the first study designed to estimate the number of biopsies needed for positive diagnosis of HDGC, the researchers found that it would take an average of 1,800 biopsies per patient to yield even a 50 percent detection rate. Their analysis has clarified the need for improved screening methods that are both feasible and definitive. The study results were recently presented at Digestive Disease Week, an international gathering of gastrointestinal physicians and researchers—and are currently submitted for publication.

**Implications for the Future**

Research regarding the diagnosis and treatment of HDGC is still in its infancy. The link to the CDH1 gene mutation was discovered slightly more than a decade ago. Physician-researchers at the Mass General Cancer Center are committed to advancing our understanding of this largely unknown cancer, as they continue to provide lifesaving diagnosis and treatment to families with this rare genetic mutation.

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**Selected References**


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Dr. Zietman said “perverse” incentives in the last decade have affected the entire practice of medicine and that radiation oncology has not been spared.

The result, he said, is an excess number of procedures performed without basis in medical efficacy. He emphasized that integration of evidence-based principles into radiation oncology practice is crucial to preserving the field’s credibility.

To that end, Dr. Zietman highlighted the need for more rigorous professional and institutional standards to ensure continued public trust in the quality and safety of radiation treatment centers.

In testimony to Congress, Dr. Zietman called for greater regulatory oversight, stricter standards and passage of the CARE Act to establish national accreditation and staffing requirements. He noted that only 10 percent of radiation oncology treatment centers nationally undergo such external review. That’s changing, he said, as institutions recognize the need to address patients’ safety concerns and ensure continued confidence in radiation oncology treatment.

In an address titled “Conscience-Based Medicine in the Age of Temptation,” Dr. Zietman focused the conference on the separate but related themes of treatment efficacy and treatment safety. Keynote speakers included Sir Michael Rawlins, chairman of the National Institute of Health and Clinical Excellence for the National Health Service in Great Britain, and Massachusetts General Hospital Chief of Radiology James H. Thrall, MD, both vigorous advocates of practicing evidence-based medicine.

In his address, Dr. Zietman discussed the clinical and scientific aspects of the current field and the need to change what he termed “perverse” incentives that have affected the practice of medicine. Drawing on his role as president of the American Society for Radiation Oncology (ASTRO), Mass General Cancer Center radiation oncologist and genitourinary cancers expert Anthony L. Zietman, MD, directed plans for ASTRO’s 52nd annual meeting in San Diego last fall, which drew an estimated 12,000 radiation oncology professionals. With the new year, he has assumed the role of ASTRO chair.

Society for Translational Oncology Convenes 2010 Conference in Boston

Hosted by Massachusetts General Hospital Cancer Center, the Society for Translational Oncology (STO) drew medical oncologists, translational researchers and pharmaceutical industry representatives from across the globe to its 2010 conference in November, “Collaboration in Cancer Drug Trials: Targets, Biomarkers and Drugs.”

Meeting Chairman Bruce A. Chabner, MD, director of clinical research at the Mass General Cancer Center, moderated discussion about development of targeted therapies focused on the PI3K and PARP pathways, and agents that continued on page 16
New Physicians Join the Cancer Center

Twenty-two new physicians joined the Cancer Center staff this fall. In addition to new Chief of Hematology Oncology and Cancer Center Associate Director José Baselga, MD, PhD, they include:

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Redesigned, More Effective Circulating Tumor Cell (CTC) Chip Provides Additional Information About CTCs

The CTC Chip, the microchip-based device for capturing circulating tumor cells that was developed at Massachusetts General Hospital, has been redesigned so that it provides more comprehensive and more easily accessible data from the rare cells. Called the HB-(herringbone) Chip, the new device also facilitates the increased production needed to conduct larger clinical studies. Mass General researchers reported on the second-generation device in a Proceedings of the National Academy of Sciences paper that received online release in October 2010.

Co-lead author of the paper, Shannon Stott, PhD, of the Mass General Center for BioMicroElectroMechanical Systems (BioMEMS), says the new device also captures "small clusters of CTCs, the significance of which we need to study."

No previous method for capturing CTCs has ever found such clumps of tumor cells.

“These clusters may have broken off from the original tumor or they might represent proliferation of CTCs within the circulation,” says BioMEMS Center Director Mehmet Toner, PhD, senior author of the PNAS paper. He adds that “further study of these clusters could provide valuable insight into the metastatic process.”

Toner co-leads the CTC Chip project with Daniel A. Haber, MD, PhD, director of the Mass General Cancer Center, who says the new technology “will enable increasingly sophisticated analyses of metastasis and support clinical research in targeted cancer therapies.”

Image: Mass General Center for BioMicroElectroMechanical Systems (BioMEMS)

Photo (above): The new HB-(herringbone) Chip, so-called due to the herringbone-like grooves inside the device. The twisting grooves cause the blood to churn, resulting in greater capture of individual circulating tumor cells (CTCs), as well as CTC clusters.

Inset (left): A cluster of CTCs captured on the herringbone surface. Current CTC isolation technologies have never before detected such CTC clusters.
Massachusetts General Hospital/Harvard Medical School
Stem Cell Scientist David T. Scadden, MD, Wins American Society of Hematology Award

Massachusetts General Hospital Cancer Center Chief of Hematologic Malignancies David T. Scadden, MD, co-director of the Harvard Stem Cell Institute and the Gerald and Darlene Jordan Professor of Medicine at Harvard Medical School, was honored this year by the American Society of Hematology (ASH) at its annual winter meeting in Orlando, Florida.

At the meeting, Dr. Scadden, who is also director of the Massachusetts General Hospital Center for Regenerative Medicine, was awarded the 2010 Dameshek Prize for his contributions to stem cell biology. The Dameshek Prize is awarded annually to an individual who has made an important contribution in hematology during the preceding years. He was one of six scientists ASH chose to recognize this year.

The Scadden laboratory focuses on regulation of hematopoietic stem cells— the multipotent stem cells that give rise to all the blood cell types—by the stem cell micro-environment or niche. Based on its prior work to understand the mechanisms governing normal stem cells in their normal environment, the Scadden team has now investigated the role of the niche in disease. Their research has demonstrated the primary role the micro-environment can play in disordered tissue homeostasis and the emergence of malignancy.

In a finding supporting the idea of niche-induced oncogenesis, the Scadden team reported in the March 2010 issue of Nature that deletion of the DICER1 gene in bone precursor cells induced bone marrow dysfunction and myelodysplasia, a blood disorder that has a high risk of evolving into leukemia. The study offered new insight into how abnormal signals from the stem cell micro-environment might be potential novel therapeutic targets in cancer.

Scadden’s work on cell-niche interactions, including stem cell proliferation, homing and engraftment, has also contributed to the development of stem cell therapeutics and, specifically, improving stem cell transplantation.

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Society for Translational Oncology Convenes 2010 Conference in Boston

inhibit the BRAF and the ALK mutations. In discussing biomarkers, speakers highlighted the use of molecular profiling and circulating tumor cell analysis; biomarkers as a tool for tracking resistance to disease; and the use of emerging genomic technologies to predict tumor response and drug resistance.

Other conference topics included the use of animal models in the development of targeted therapies, and drug development for rare cancers, including myeloma, adenoid cystic carcinoma and neuroblastoma.

For more information about the STO and a record of the proceedings, go to theoncologistcommunity.com.