New Technique May Improve Brain Tumor Margin Imaging Resections

By Mike Fillon

Virtually every neurosurgeon wishes for a new and better method, preferably noninvasive, to rapidly and accurately see residual malignancy during surgery to remove a tumor. A new study by researchers in the Department of Biomedical Engineering at Stony Brook University in Stony Brook, N.Y., might someday grant this wish.

Researchers combined a new brain tumor–targeting contrast agent that differentiates between normal and cancerous cells in conjunction with a high-powered microscopy system that may lead to more precise neurosurgery for brain tumors.

Currently, histopathology of biopsied tissue samples is the most accurate way to assess malignancy. However, this analysis is rarely performed at the tumor margins during surgery because of the time required to prepare frozen sections for interpretation by a pathologist. And histopathology is expensive and invasive, requiring the removal of brain tissue.

Senior author Jonathan T. C. Liu, Ph.D., an assistant professor of biomedical engineering at Stony Brook, said that accurate demarcation of tumor margins is critical at the final stages in the surgical treatment of brain tumors and is associated with extent of resection and improved patient outcomes. “Real-time, high-resolution imaging with the aid of a tumor-targeting fluorescent contrast agent has the potential to enable intraoperative differentiation of tumor versus normal tissues with accuracy approaching the current ‘gold standard’ of histopathology,” Liu said.

The main idea behind this technique is that selectively tagging tumor tissue with fluorescent dyes enables surgeons to visually tell apart normal and tumor tissues and remove as much tumor tissue as possible. The researchers conjugated a monoclonal antibody targeting VEGFR-1 (vascular endothelial growth factor receptor 1) to fluorophores and evaluated it as a tumor-contrast agent in a transgenic mouse model of medulloblastoma, the most common malignant brain tumor in children.

The team administered the probe topically and tested its value as an imaging agent in vitro by using flow cytometry, as well as ex vivo on fixed and fresh tissues through immunohistochemistry and dual-axis confocal microscopy, respectively. The researchers used a handheld DAC (dual-axis confocal) microscope they developed for intraoperative optical biopsy at the tumor margins. “The DAC architecture allows for relatively deep optical sectioning within tissues,” said Liu.

The probe was drawn more to tumor than to normal tissue, suggesting that a topically applied VEGFR-1 probe could be used with real-time intraoperative optical sectioning microscopy to guide brain tumor removal.

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The Stony Brook team isn’t the first to use a fluorescent contrast agent in neurosurgery. In vivo use of fluorescence in brain tumors dates back to 1948. It resurfaced about 12 years ago when neurosurgeons in Germany and Japan took advantage of aminolevulinic acid (ALA)-induced photosensitizer protoporphyrin IX (PpIX) fluorescence and fluorescein fluorescence–guided removal of brain tumors.

Earlier studies found that fluorescence–guided neurosurgery is especially important for removing some cancerous tumors where the tumor and normal tissue have similar appearance and texture, and complete removal is essential for patient outcomes. Therefore, researchers are using several different biomarkers and biochemical agents and are investigating several technological approaches.

William A. Friedman, M.D., professor and chairman of the Department of Neurosurgery at the University of Florida in Gainesville, said that the neurosurgical group at Dartmouth has probably done the most with this technology in the U.S. In a May 2010 review article in the IEEE Journal of Selected Topics in Quantum Electronics, Dartmouth researchers wrote that the systems and biomarkers available are “a complicated matchup.” Senior author of the review was Keith D. Paulsen, Ph.D., codirector of the Cancer Imaging and Radiobiology Research Program in the Norris Cotton Cancer Center at Dartmouth’s Geisel School of Medicine in Hanover, N.H.

The Dartmouth researchers also said that neurosurgical guidance of tumor removal is a key area where fluorescence imaging appears to have immediate impact.
“Part of this is due to the fact that brain tumors have such poor prognosis in general, and any tools to help improve the resection can have immediate short-term benefit on patients’ lives. . . . A substantial benefit for brain tumor patients will probably come in improved systems to track weak fluorescence signals in areas not well resected using current systems, and in tumor subtypes that do not present well with ALA-PpIX fluorescence or vascular marking fluorescence such as fluorescein or indocyanine green.”

Liu said that the combination of the distinctive contrasting agent and the microscopic device sets his group’s research apart. “It’s very important to use the two together,” said Liu. “There are a lot of contrast agents being developed, and there are other types of imaging devices. We took those two worlds and brought them together, showing that by using advanced microscopy technique, you can see the tumor cells and differentiate them from the normal cells with the use of this contrast agent.”

The Stony Brook researchers believe that the combination of intraoperative confocal microscopy with molecularly targeted contrast agents could complement current image-guided surgery approaches, such as those with magnetic resonance imaging or computed tomography, to surgically remove brain tumors and other forms of cancer.

Nader Sanai, M.D., director of the Division of Neurosurgical Oncology and Barrow Brain Tumor Research Center at St. Joseph’s Hospital in Phoenix, said he believes that the study is an important advance. “I think it is a clever way of using the tumor’s molecular biology to tell you where you are at with respect to the margins of the tumor. Plus, your naked eye is only going to tell you so much.”

Sanai said that although microscopes are already in the operating room, they offer only magnification, not cellular resolution. “This device,” he said, “in combination with intelligently selected probes, gives you an entirely different dimension of understanding of what you’re looking at, where the tumor cells are, and how much you’ve actually done in removing them.”

Friedman has a mixed reaction to the research and this study in particular. “Most of the studies published so far do suggest that the completeness of the resection is enhanced by using this technique,” Friedman said. “So that’s the good news. The bad news is that the fluorescence is only on the surface, meaning it’s limited. You can’t see anything that’s going on under the surface, since the light doesn’t penetrate more than a couple of millimeters. This means that no matter how good your resection is, you’re never going to completely cure these tumors with surgery.”

Preventing Graft-Versus-Host Disease: Transplanters Glimpse Hope Beyond Immunosuppressants

By Caroline McNeil

In the early 2000s, sirolimus (Rapamune) looked promising to prevent graft-versus-host disease (GVHD) in leukemia patients with bone marrow transplants. More than a decade later, a Dana–Farber Cancer Institute researcher stood before the December 2012 meeting of the American Society of Hematology with disappointing news: In phase III trials, the drug proved no better than placebo.

Corey Cutler, M.D., and colleagues were hardly the first to face the problem of GVHD. Ever since hematopoietic stem cell transplants emerged as a lifesaving treatment for leukemia and other hematologic diseases 40 years ago, patients and physicians have had to balance its benefits against serious risks.

Transplants restore stem cells destroyed by high doses of chemotherapy and/or total-body irradiation (TBI), the conditioning regimens that prepare patients for infusions of cancer-free, and cancer-fighting, stem cells. GVHD, which develops when donor T cells attack patient cells they see as foreign, is a life-threatening condition affecting the skin, liver, intestines, and other organs. The mortality rate for chronic GVHD is 40%.

GVHD also profoundly affects quality of life. “It completely interrupts normal life,” said Susanne Liewer, Pharm.D., pharmacy coordinator at the University of Nebraska’s Blood and Marrow Transplant Service.

The longstanding preventive agents are immunosuppressive drugs—cyclosporine, tacrolimus, and methotrexate—given immediately after transplant. Despite these, 60% of patients still develop acute GVHD in the first 100 days, and up to half develop chronic disease. The rates have changed little for decades.

But last year brought news of successful trials with new drugs and other approaches to prevention. In February, at the combined meetings of the American Society for Blood and Marrow Transplantation and the Center for International Blood and Marrow Transplant Research—the large, annual tandem meetings of the transplant world—speakers highlighted strategies for trials that go beyond immunosuppression.