Medical Xpress

Gene mutation defines brain tumors that benefit from aggressive surgery

February 3 2014

Astrocytomas are the most common malignant brain tumors. While most patients' tumors prove to be quite aggressive, outcomes overall can vary widely, with some patients surviving for many years. Now a new study has found that malignant astrocytoma patients whose tumors carry a specific genetic mutation benefit greatly from surgical removal of the largest possible amount of tumor. Preliminary results of the study were reported at the 2012 American Society of Clinical Oncology meeting, and the team's full report appears in the January issue of the journal *Neuro-Oncology*. A type of glioma, astrocytomas include the highly aggressive glioblastoma and the less aggressive but still dangerous anaplastic astrocytoma.

"We found that the benefit of surgery and how aggressively the surgery should be done depend, in large part, on whether or not patients' tumors have the mutated form of the IDH1 gene," says Daniel Cahill, MD, PhD, of the Pappas Center for Neuro-Oncology in the Massachusetts General Hospital (MGH) Cancer Center, who led the study. "Under the prior system of categorization, these tumors were considered the same diagnosis and were treated the same way; but we have found that this mutation identifies a completely different subclass of glioma that probably should be treated differently." Now an assistant professor of Neurosurgery at Harvard Medical School, Cahill was at the University of Texas MD Anderson Cancer Center when the study was initiated, and all study participants were treated at MD Anderson.

Ian McCutcheon, MD, professor of Neurosurgery at MD Anderson

Cancer Center, who co-led the study with Cahill, adds, "We have long wondered why some patients with malignant glioma live much longer than others despite having been treated with similar approaches." In 2008 a comprehensive genetic analysis of glioblastomas found IDH1 mutations in more than 10 percent of patients' tumors, and subsequent studies have found similar mutations in from 50 to 70 percent of anaplastic astrocytomas. Significant clinical differences between IDH1-mutant tumors and those without that mutation have been identified previously; patients with mutant tumors tend to be younger and survive longer, and the tumors are more likely to be located in the frontal lobe.

The current study was designed to investigate whether the presence or absence of the IDH1 mutation might help determine the optimal treatment strategy – in particular, how extensive surgery should be. Traditionally, how much of a brain tumor is removed depends on its location and whether that tissue can be safely removed. A key question has been whether to take out only the most actively growing part of the tumor – what is called "enhancing disease" – or also to remove the non-enhancing edge of the tumor that infiltrates adjacent tissue.

To determine whether IDH1 status made a difference, the research team examined data on 335 patients – 128 with anaplastic astrocytoma, 67 percent of which were IDH1 mutated, and 207 with glioblastoma, 13 percent of which had the mutation – treated at MD Anderson from June 1993 to April 2009. The analysis revealed that more than 90 percent of tumors with IDH1 mutation had been completely removed, compared with 67 percent of the nonmutant tumors. More importantly, while removal beyond the enhancing disease of nonmutated tumors did not substantially improve patient survival, more complete removal of IDH1 mutant tumors had a remarkable association with survival. The average survival of all patients with mutant tumors was 13.5 years, compared with less than 1.5 years for those with nonmutant tumors, but almost all

of those with mutant tumors who received aggressive surgery are still alive, some nearly 20 years after surgery.

McCutcheon says, "This study shows that aggressive surgical removal of tumor leads to long survival when tumors carry a particular molecular signature – in this case the IDH1 mutation – but not when that mutation is absent. In current surgical planning, tumor location drives how aggressive a removal we obtain. Our results suggest that we should take the risk of maximum tumor removal not in all patients but in those whose tumor mutation status suggests they will benefit most.

"The way we classify a tumor determines how we treat it and how successful that treatment will probably be," McCutcheon explains. "Therefore, classifying malignant gliomas by IDH1 mutation status allows us not only to tailor our surgical treatments better but also to predict better who will survive longer after that treatment. As such, this paper carries the subversive general message that classifying tumors from a molecular genetic perspective may be superior to older methods of diagnosis that rely only on histology – the way a tumor appears under a microscope."

Cahill adds, "These findings can help us tailor our surgery for patients who will benefit from the more aggressive approach. If it's an IDH mutant glioma and complete removal might cause a temporary deficit, like the weakening of an arm or leg, that might be worthwhile if the associated benefit would be an additional 5 or 10 years of survival. I think many patients would be willing to make that tradeoff."

He also notes, "While a number of other studies have identified mutations that confer the benefit of drugs targeted against those mutations, this is the first study that identifies patients who will benefit from aggressive surgery as a therapeutic intervention. We have tools – such as intraoperative MRI scanners – that can safely guide these

aggressive resections, including removal of tumor tissue that looks normal to the naked eye. In our continuing collaboration, this information is being used to identify candidates for MRI-guided surgery both here at MGH and at MD Anderson."

Provided by Massachusetts General Hospital