

radiation and the induction of a radiation-induced phenotype in combination with the prodrug, there was a significant increase in cell death, with up to 80% of cells dead after 48 hours. Lee et al then performed real-time tracking of prodrug activation in cancer cell cultures. Twenty-four hours after treatment with radiation and prodrug, more than half of the doxorubicin had been activated and localized to the nucleus. Without radiation, the prodrug remained in the cytoplasm of the cells. Administration of a caspase inhibitor prevented this translocation of doxorubicin and prevented cell death.

The real beauty of RIATC is its use of a targeted inducer of the apoptotic phenotype, SRS, rather than diffuse radiation therapy. One of the many benefits of SRS is that it can provide an apoptosis-inducing radiation dose in a precise, accurate, and selective fashion and limit injury to surrounding tissues. Mice harboring a cancerous tumor in the body had their tumors treated with the Gamma Knife while also receiving the prodrug intravenously. This combination was significantly more effective at controlling tumor growth compared with SRS or prodrug alone. Moreover, the RIATC-treated mice demonstrated none of the systemic toxicity seen with the administration of an equivalent dose of doxorubicin. A real-time fluorescence assay of apoptosis via caspase-3 activity in the mouse tumors demonstrated that RIATC was much more effective at inducing apoptosis compared with the prodrug alone or radiation alone (Figure). Not surprisingly, this was prevented with coadministration of a caspase-3 inhibitor. Immunohistochemical testing of the RIATC tumor tissue triggered a significant increase in caspase-3-positive cells over the control treatments (Figure). Combined, these studies establish proof of the RIATC principle.

SRS has become an established treatment for brain metastases and is fast becoming the initial go-to strategy for the majority of patients. RIATC is an opportunity to create a synergy with SRS and potentially improve the already excellent tumor control rates experienced by patients with brain metastases by taking advantage of potential tumor homogenization brought about by SRS. In contrast to the use of radiation sensitizers and protectants that sensitize and protect both tumor and normal tissue, RIATC has the opportunity to synergize with the radiation administered by SRS only at the targeted sites. Its major limitation is that of most systemically administered therapies, an inability to achieve meaningful efficacy in the brain because the blood-brain barrier blocks agents out. As new systemic agents showing efficacy in

the brain come online, tremendous opportunities for synergy with SRS should be explored.

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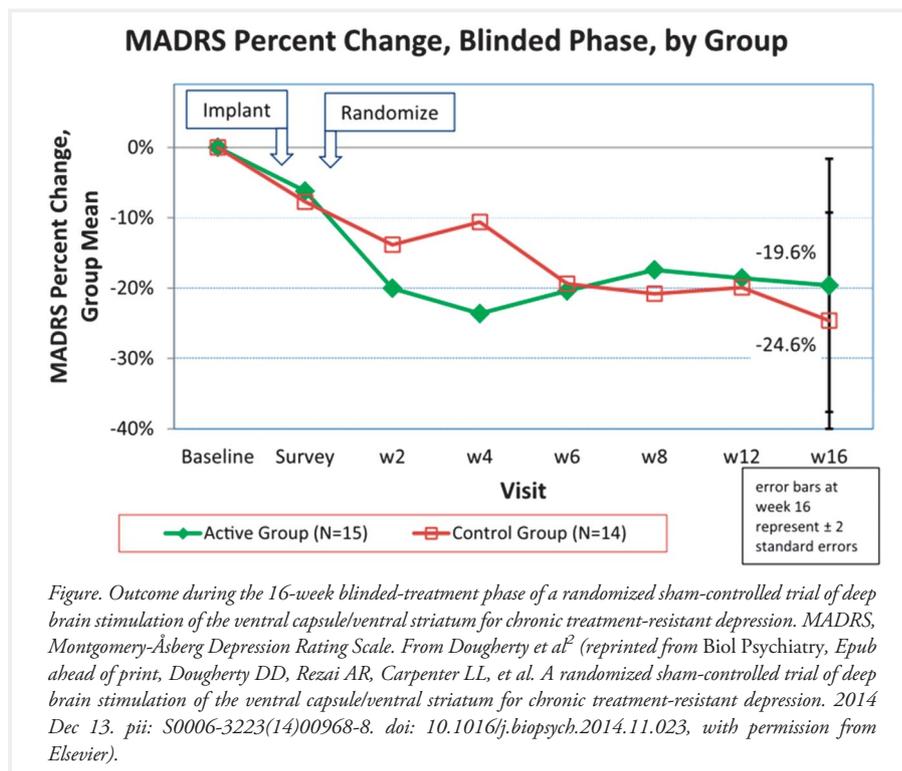
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Results of the First Randomized Controlled Trial of Deep Brain Stimulation in Treatment-Resistant Depression

The majority of open-label trials of deep brain stimulation (DBS) in the treatment of intractable major depressive disorder, commonly referred to as

treatment-resistant depression (TRD), have involved 2 brain targets: the ventral capsule/ventral striatum (VC/VS) and the subcallosal cingulate cortex and white matter. The broad nomenclature for these targets attests to the need to further understand the exact neural substrate that mediates the putative antidepressant effects of DBS observed in multiple open-label trials. This need is underscored further by the recent, long-awaited publication of the results of a randomized sham-controlled trial of DBS of the VC/VS for TRD, the first such trial of its kind, which began in 2009. This target was initially investigated after the incidental observation of improvement in depressive symptoms during studies of VC/VS DBS in patients with intractable obsessive-compulsive disorder.¹ Despite positive results in a subsequent open-label trial, however, Dougherty et al² recently reported negative results from the ensuing "pivotal" phase 2 trial, sponsored by the device manufacturer, Medtronic, Inc.

The goal of this trial, a collaboration between the psychiatry and neurosurgery departments at 5 institutions, was to demonstrate that active stimulation was better than no stimulation. The primary outcome



measure was defined as a $\geq 50\%$ improvement in the Montgomery-Åsberg Depression Rating Scale from baseline to the end of a 16-week blinded phase. Electrodes were implanted bilaterally in the VC/VS on the basis of anatomic imaging, with a requirement that the 2 distal-most contacts be placed within stereotactically defined boundaries (5-mm range in each plane). Although the trial was originally intended to enroll 208 subjects, Medtronic stopped enrollment after analysis of the blinded-treatment phase data from the initial 30 subjects. These results failed to demonstrate the efficacy of VC/VS DBS for TRD, and the active group did not achieve the level of response seen in previous open-label studies (Figure). At 16 weeks, 3 of 15 subjects in the active group were responders compared with 2 of 14 subjects in the control group. At 24 months, 7 subjects met response criteria, 6 of whom met remission criteria. During the 16-week blinded-treatment phase, psychiatric adverse events were more common in the active stimulation group, which included worsening depression, insomnia, irritability, suicidal ideation, hypomania, disinhibition, and mania. In addition, there was a statistically significant negative effect of DBS on performance of a response inhibition task requiring mental flexibility, suggesting that VC/VS DBS may result in unwanted cognitive side effects. Although these results are disappointing, important caveats also emerged. For example, at 24 months, the mean improvement in Montgomery-Åsberg Depression Rating Scale scores was 40%, which could represent clinically significant improvement in this severely ill sample. Indeed, 26 of 30 subjects elected to continue to receive DBS after the 24-month study period had ended.

The study investigators offered some reasonable explanations for the lack of efficacy in this trial. First, it may be that the VC/VS region, at least as implanted in this study, simply is not an effective surgical target for the treatment of TRD. The authors point out that, given emerging evidence for the importance of activating specific white matter pathways in the treatment of TRD,³ it is also possible that DBS to the VC/VS region may be efficacious only if adjacent white matter pathways are adequately stimulated. Indeed, optimal lead placement may require the prospective application of fiber pathway activation data rather than reliance on anatomic coordinates. In this trial, although only 1 lead revision was required as a result of initial implantation outside the predetermined target area, the

range for acceptable implantation (ie, 5-mm range in each plane) may have resulted in a more functionally heterogeneous distribution of leads than intended. The authors also point out that the blinded phase may not have been long enough to differentiate the active from the sham group, given that a single-center trial showed that the response rate to DBS of the subcallosal cingulate white matter more than doubled between years 1 and 2.⁴ Although the primary end point was not met, the quality of the reported psychiatric adverse events supports the importance of VC/VS for mood regulation.

These results indicate the need for more precise selection of brain targets for DBS for neuropsychiatric syndromes. In addition, despite the use of precise diagnostic procedures, we encourage subgroup analysis of the characteristics of responders to this study and earlier open-label trials. Characteristics that may further define responders compared with nonresponders include the severity and pattern of neurovegetative symptoms; response to prior treatments, in particular electroconvulsive therapy or transcranial magnetic stimulation; and systematic differences in the electrode positioning. Further development of neurophysiological measures for identifying the optimal site for stimulation and for monitoring the expected biological response may also significantly improve chances for success in future studies.

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Dual Intraoperative Visualization Approach Surgery: A Novel Technique Enhances Intraoperative Glioma Visualization

Residual tumor on postoperative magnetic resonance imaging (MRI) in glioma patients represents a negative prognostic factor, and the extent of tumor resection affects the disease course.^{1,2} Recent innovations have enhanced the ability of neurosurgeons to safely increase the degree of tumor resection, including intraoperative MRI guidance and 5-aminolevulinic acid (5-ALA).^{2,3} Both tools provide intraoperative feedback, allowing the surgeon to proceed with further resection when prudent. Similar to these novel intraoperative methods of tumor visualization, the authors of a recent article in *Nature Scientific Reports* propose an alternative use of a familiar technology, indocyanine green (ICG).⁴

ICG has been used for many years in ophthalmology to assess retinal microvasculature. It requires special optics, specifically near-infrared light incorporated into the surgical microscope.⁵ ICG angiography is widely used in aneurysm surgery and other open neurovascular procedures.^{5,6} Eyupoglu and colleagues⁴ report its ability to show hypervascular areas of tumor that are not visible under either light microscopy or 5-ALA-enhanced visualization in what is called the vascular dual intraoperative visualization approach (DIVA). The group presents 3 illustrative cases in which this novel use of ICG angiography is verified by intraoperative imaging and histology.

In each of the 3 cases, patients underwent resection of supratentorial glioblastomas. Preoperative planning included both functional MRI and diffusion tensor imaging to determine the anatomic relationship of the tumor to eloquent brain and white matter tracts. Intraoperatively, tumor resection was performed with light microscopy. When no visible tumor remained, residual tumor was visualized and resected with the use of 5-ALA signaling. After the 5-ALA signal was undetectable, ICG was administered intravenously, and the tissue cavity was re-examined. ICG-enhanced tissues were resected and subsequently confirmed to contain tumor cell infiltration by an experienced neuropathologist. Further histological analysis