We work in the dark—
we do what we can—
we give what we have.
Our doubt is our passion,
and our passion is our task.
The rest is the madness of art.
Henry James

Someone once defined madness as doing the same thing over and over again, expecting a different result. Year after year we develop new technological methods (and new billing codes for these methods) that enable us to resect larger portions of a glioma more accurately. Despite these efforts, patients continue to die of recurrent disease. Over the past 40 years we have used the operating microscope, fluorescent fluorescence, ultrasonic imaging, image-guided surgery, volumetric stereotaxy, intraoperative computerized tomography (CT)–guided surgery and, more recently, interventional magnetic resonance (MR) imaging. The paper by Stadlbauer, et al., in this issue represents yet another technical advance. None of these past technical improvements has made a significant difference in the survival of patients with breast cancer that has already spread to regional lymph nodes and beyond. Modern surgical techniques simply result in a neurological deficit, and there is no assurance that the tumor will not recur anyway; we already know that 40 years ago. Nonetheless, our efforts seem similar to that of a general surgeon performing a “lumpectomy” in a patient with breast cancer that has already spread to regional lymph nodes and beyond. Modern surgical techniques simply allow us to make glioma lumpectomies bigger and safer. Nonetheless, I did not begin my neurosurgical life as a cynic and I am by no means a surgical nihilist.

I trained with Paul Bucy. He used to say to me, “Patrick, if we could totally remove a glioblastoma, we could cure it.” He frequently pointed out that gliomas grow by local extension and that the tumor will not recur anyway; we already know that 40 years ago. Nonetheless, our efforts seem similar to that of a general surgeon performing a “lumpectomy” in a patient with breast cancer that has already spread to regional lymph nodes and beyond. Modern surgical techniques simply allow us to make glioma lumpectomies bigger and safer. Nonetheless, I did not begin my neurosurgical life as a cynic and I am by no means a surgical nihilist.

Bucy was aggressive in the resection of these lesions. I once discussed with him the results of Scherer’s autopsy studies6 on gliomas published in 1940. The studies had shown widespread invasion of brain tissue far beyond the main glial tumor mass. Bucy looked at me as a father would regard a misguided child who was not terribly bright. Scherer’s patients, he told me, were people who died of advanced disease. His autopsy studies bore little relationship to the clinical situation. Bucy actually believed that he, in fact, had cured some, albeit a small number, of patients.7

Dr. Bucy’s concept of glial tumors was and is identical to that held by many neurosurgeons: that glial tumors truly grow as a mass by local extension and that there is, somewhere, a defined border at which the tumor ends and normal brain begins. This simple concept of a complex biology lends itself to a simplistic therapy: take it out! All we have to do is define the volume of a tumor and remove it. I must confess that at one time I actually believed this.

In the 1970s, I adapted some of Jean Talairach’s stereotactic resection techniques for epilepsy to the resection of gliomas. These procedures were based on the three-dimensional precise anatomical data set provided by CT scanning and MR imaging.8,9 In cases of glioblastoma multiforme (GBM) CT and MR imaging revealed a discrete contrast-enhancing mass surrounded by “edema.” The contrast-enhancing mass provided a convenient target for computer-assisted volumetric stereotactic resection. Postoperative imaging studies confirmed “gross-total resection” of these lesions. Did this high-tech, scientific, aggressive surgical approach followed by radiation and chemotherapy result in a cure? No, it did not. Tumors recurred in the margins of the “gross-total resection.” Patients died right on schedule (assuming that the pathological findings were correct). At best our procedures may have prolonged mean survival in patients with GBM from 37.5 to 50.5 weeks.2

Certainly, patients undergoing these radical resections lived longer than those who underwent biopsy alone. As a prognostic factor in malignant glioma, however, the extent of the surgical resection falls far behind factors over which a surgeon has no control: tumor grade, patient age, and Karnofsky Performance Scale score. In some studies, surgery does not even make it onto the radar screen of statistical significance.2

In an attempt to understand what was happening in the region surrounding the contrast-enhancing mass, we performed CT and MR imaging–directed stereotactic serial biopsies in many patients harboring high- and low-grade gliomas. In these studies, we sampled not only the contrast-enhancing regions of the neoplasm, but also regions demonstrating hypodensity (“edema”) on CT scans, prolongation of the T1 signal on MR images and perilesional regions that might be provided by recent-generation MR imaging units10,11 and 12. New insights into the biology of gliomas, however, have resulted in a neoplastic process. The problem with this thinking, of course, is that the tumor will ultimately die of their disease.

All the previous discussion has been based on our experiences with stereotactic biopsy and with conventional MR imaging. These are but one layer of the iceberg. The brain parenchyma above and below the contrast-enhancing mass is replete with isolated tumor cells. The clinical situation. Bucy actually believed that he, in fact, had cured some, albeit a small number, of patients.7

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applied normal on imaging studies. We found that the actual extension of the tumor is indicated neither by CT nor MR imaging. Examination of tissue obtained by stereotactic serial biopsies of the peritumoral "edema," which surrounds the contrast-enhancing mass in these lesions, demonstrated isolated tumor cells coexisting with intact normal parenchyma. In fact, tumor cells could be found far from any MR imaging-defined abnormality, at least as far away as 7 cm (which was as far away as we sampled). In essence, we confirmed in live patients what Scherer had found in dead patients.

Undoubtedly, the greatest numbers of tumor cells can be found within the MR imaging-defined abnormality. Perhaps resection of this entire abnormality (the site of Gd-enhancement plus the volume of T2 prolongation) will provide a significant cosmetic hit—a "greater log-kill"—to the neoplastic process. The problem of course is that these isolated tumor cells coexist with functional brain parenchyma. Removing anything but the contrast-enhancing mass is removing functioning brain tissue, possibly resulting in a neurological deficit, and there is no assurance that the tumor will not recur anyway. We already know that isolated tumor cells lurk in regions beyond the MR imaging-defined abnormality. Certainly, there are rare exceptions to this, namely tumors that display imaging abnormalities confined to a frontal or temporal pole, which can be treated with a generous lobectomy. In my own experience, however, these cases are very rare and, although the patients do, in fact, live longer when treated in this manner, they ultimately die of their disease.

All the previous discussion has been based on our experiences with stereotactic volumetric resections and serial stereotactic biopsies based on conventional CT and MR imaging. These are based on epiphenomena: the concentration of unbound water in the diseased brain compared with that in the healthy brain and/or the existence of neovascularization within solid tumor tissue defined by contrast enhancement. New insights into the biology of gliomas, however, may be provided by recent-generation MR imaging units with appropriate software capable of suppressing water proton resonance and observing the proton resonance of metabolic compounds in tissue.

Proton MR spectroscopy, the subject of the present paper, is based on the measured intensity of one or more metabolite groups. Proton MR spectroscopy supplies a biochemical profile of tissue contained in any defined voxel of the brain, which has been used to characterize the biochemical components of normal and abnormal tissue. Typically brain neoplasms demonstrate increased levels of choline-containing compounds (Cho, associated with cell membrane and myelin turnover), decreased levels of N-acetylaspartate (NAA, an indicator of healthy neurons), and decreased levels of creatinine (Cr) and phosphocreatine which produce inorganic phosphates for the production of adenosine triphosphate. These levels reflect cell membrane turnover, neuronal loss, and a reduction in energy production. The pattern of high Cho and low NAA and Cr in comparison with normal levels differentiates abnormal from normal brain tissue and, more specifically, tumor within a specific voxel. This information has been useful for diagnostic purposes, such as differentiating gliosis or radiation necrosis from active tumor. Can it provide an actual description of where "tumor" ends and "normal" brain begins?