Ethical difficulties in the innovative surgical treatment of patients with recurrent glioblastoma multiforme

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Even with aggressive treatment, glioblastoma multiforme (GBM) nearly always recurs, yet there is currently no consensus on how best to manage recurrence. As a result of this uncertainty, surgical innovation in the treatment of recurrent GBM remains energetic. A thorough ethical discussion of these innovative treatment options for recurrent GBM is of paramount importance, yet little has been published on the topic in the literature. On the one hand there are those who argue that patient autonomy must permit access to innovative surgical procedures. On the other hand there are those who argue for restriction of the right to autonomy, pointing out that patients with recurrent GBM may be vulnerable to unethical experimentation, and that surgical innovation may endanger patient safety and undermine knowledge-generation structures. Patients with recurrent GBM should have some rights to innovative surgical treatments, because this aligns with the fundamental ethical principle of autonomy. This right is not absolute, however, and reasonable and appropriate measures should be taken to ensure adequate protection of these vulnerable patients. Specifically, these measures include: 1) a high standard of truly informed consent; 2) oversight and regulation of the innovative surgical treatment; 3) adequate evidence that the innovative surgical treatment will be successful, either in the form of animal model studies or in the application of closely related procedures in humans; and 4) no risk of harm to others. If these standards are not met, a patient’s right to innovative surgical treatment can be justifiably infringed.

Outcomes for patients with recurrent GBM remain poor, and many patients opt for palliative care over aggressive intervention at the time of recurrence.1,26,45 Innovative treatment for GBM is desperately needed, and dozens of clinical trials around the world are investigating new treatment options for this disease.21,22,27,29 Even with the most aggressive treatment possible in a patient diagnosed early with GBM, which includes some combination of neurosurgery, radiotherapy, and systemic chemotherapy, mean survival time is short and tumor recurrence almost always occurs.21,26,29,50 Surgical innovation in the care of these patients is also robust, with current investigations examining the use of fluorescent agents, intratumoral infusion of oncolytic viruses, stem cell transplants, implantable chemotherapeutic agents, and other surgical adjuncts.22,24,54

It was in this milieu that in 2013 a neurosurgeon prac-
ticing in California purposely inoculated bacteria into the tumor resection cavity of several patients on whom he had operated for recurrent GBM. He did so in the hopes of extending survival, basing the treatment on scattered case reports that showed prolonged survival in patients who developed postoperative infections after resection of CNS malignancies. These reports suggested that bacterial infection in patients treated for GBM could provoke an immune response in the area of the tumor that may lead to improved survival.

This case provides an example of the ethical difficulties that may arise when patients with GBM, who are suffering from a terminal illness with little hope of long-term survival, approach the end of life. Many of these patients seek innovative surgical procedures or innovative treatments through surgery that may improve their prognosis, but are far from proven. In these cases, a conflict can arise between the duty of surgeons to provide ethically correct care and the fundamental bioethical principle of patient autonomy. Do patients with terminal illnesses have a fundamental right to access innovative, unproven surgical treatments, even if these treatments may pose risk of serious injury?

The current literature on this issue centers around 2 opposing arguments: on the one hand, that patients nearing the end of life have a right to innovative treatment for reasons of protecting patient autonomy and compassionate use; on the other, that access to innovative treatment near the end of life frequently subverts regulation, risks undermining knowledge-generation structures, and poses a serious ethical risk. This paper will evaluate these arguments specifically in the context of surgical innovation for patients with recurrent GBM, which is fundamentally different from medical innovation, and has not been discussed as extensively in the current literature.

Surgical Innovation

Discussion of the ethics of surgical innovation in the case of recurrent GBM first requires sufficient background on the broad realities of surgical innovation in clinical practice, and an understanding of the ethical issues at hand. Surgical innovation has historically received less focus in ethical discussions than medical innovation, for a variety of reasons. Many of these relate to the “exceptional” status of surgery, which distinguishes both regulation of and innovation in surgical procedures from those of medical treatments.

Whereas medical innovation is traditionally restricted to well-regulated clinical trials, surgical innovation is part of the daily life of surgery. Each surgical case is slightly different from the one preceding it, and 2 excellent surgeons may approach the same problem from completely different perspectives. Slight modifications of surgical procedures frequently produce distinct procedures, to the point that these could possibly be called new operations altogether. In nearly all cases, these innovations are not subject to the traditional regulatory structures of a randomized, controlled clinical trial (RCT), largely because RCTs are often impractical in the case of surgical innovation.

Unlike surgical procedures, determining the efficacy of a medical treatment is largely accomplished through RCTs, which depend on a rigid structure that first evaluates the safety of the drug, followed later by an evaluation of its efficacy. In most cases, the effects of a new drug are compared with the current standard of care, or a placebo. Physicians that are part of the care team are often blinded to the patient’s arm in the trial. In surgical innovation, this design is nearly impossible, but other trial designs are being increasingly recognized as legitimate. To carry out a Phase I–like trial of a surgical innovation, one would need to find a population of volunteers willing to undergo a surgical procedure from which they might not benefit, to demonstrate its relative safety. Furthermore, comparing innovations to the standard of care or to placebo in an ethical manner requires equipoise—the reasonable belief that patients in neither treatment group have a significant advantage over the other—a circumstance that is extremely rare in surgical innovation. Many writers have also questioned the difficult ethical requirements of so-called sham-surgery placebos, which are not true placebos but rather are surgical procedures that do not carry out the intended operation, and blinding surgeons to their patient’s treatment is nearly always impossible. Although these differences have precluded the use of RCTs for most surgical interventions, resulting in an overall lower quality of evidence, surgery is frequently considered the standard of care for a wide variety of disease processes, including recurrent GBM.

Furthermore, surgical practice is generally more dependent on emerging technologies than medical treatment. If all surgical procedures using new technologies were to require carefully performed animal model studies and RCTs before regular use in humans, surgical innovation would grind to a halt, and many patients would be denied truly safe treatment options that may be more effective than the current standard of care. There are massive potential rewards to surgical innovation, so it is imperative that future regulation does not overly burden the practice to the extent that it risks stifling growth.

Although surgical innovation is ubiquitous, there are clearly different types, and defining what is and what is not appropriate has been historically difficult. One of the major difficulties in assessing innovative therapies of any kind is defining exactly what types of procedures require assessment. Most surgical procedures exist along a spectrum of innovation: some have been performed dozens or hundreds of times and are undergoing only small modification; others are entirely new and radically different from the standard of care. The respective views of neurosurgeons and ethicists on these procedures differ based on personal experience, and excellent surgeons often disagree on what should or should not be considered innovative. Minor modifications to a procedure or the use of slightly different equipment is part of the day-to-day reality of surgery, but radical changes to surgical procedures, or new procedures entirely, are generally not.

In the context of the ethical discussion presented here, we will largely be considering innovation in the latter categories, which seeks to shift the treatment paradigm for recurrent GBM through radical innovation.

Patient Autonomy and the Right to Surgical Innovation

It is clear from the above discussion that surgical inno-