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E ven 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
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.4,9,39

Whereas medical innovation is traditionally restricted to well-regulated clinical trials, surgical innovation is part of the daily life of surgery.4 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.4 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 ethically 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.29 Many writers have also questioned the difficult ethical requirements of so-called sham-surgery placebos, which are not true placebos but rather surgical procedures that do not carry out the intended operation, and blinding surgeons to their patient’s treatment is nearly always impossible.21,32,42 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.5,36,40,41

Furthermore, surgical practice is generally more dependent on emerging technologies than medical treatment.4 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.39

Although surgical innovation is ubiquitous, there are clearly different types, and defining what is and what is not appropriate has been historically difficult.4,9,13,40,41 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.15 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-

neuroses in California purposely inoculated bacteria into the tumor resection cavity of several patients on whom he had operated for recurrent GBM.28,29 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.10,11,25,37 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.

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It is clear from the above discussion that surgical inno-
vation differs significantly from medical innovation, and that the vast ethical discussion on medical innovation and compassionate use cannot necessarily be applied directly to surgical innovation. Already, many writers have discussed the relative difficulties for meeting the high ethical and regulatory standards for medical treatments in a surgical setting, where innovation is constantly occurring in small and incremental ways. Moving from these arguments, many have made the claim that access to surgical innovation aligns with patient autonomy, and should be permitted in certain circumstances.

Autonomy is a fundamental principle of biomedical ethics that maintains the right of all patients to make decisions regarding their own care and treatment, free from interference by others. Philosophically based on the human right to self-determination and now legally codified in many countries, autonomy has become an essential part of modern medical practice. Autonomy is the ethical and philosophical justification for both shared decision making and informed consent, and permits patients to have significant control over their treatment course.

Autonomy extends even to extreme cases. Ethicists have repeatedly reaffirmed the right of a patient to refuse treatment, even in cases when it will certainly cause her or his harm or death. This principle has typically been referred to as the “right to die.” In the same way, many ethicists have argued that patients nearing the end of life should have a “right to life,” which would allow them to choose high-risk, innovative, or unproven treatment strategies as a final effort at extending life. Although the existing literature has focused mainly on medical innovation, some bioethicists have also argued that these rights should extend to access to innovative surgical procedures, when such procedures may extend life or palliate symptoms.

For recurrent GBM, these innovative surgical procedures might include, for example, the use of 5-aminolevulinic acid (5-ALA) for fluorescence and photodynamic therapy, a procedure for which evidence has recently been mounting. Whereas such innovations have been reported to improve outcomes, few have been subjected to the high standard of true RCTs.

In light of the potential risks, why should patients participate in medical or surgical innovation at all? Classically, patients participate in clinical trials for 2 primary reasons. First, they hope, despite frequently low chances and the nature of randomized study designs, that participating in a clinical trial may improve the course of their disease and result in prolonged survival. Second, patients near the end of life often wish to take ownership of their disease and contribute in any small way to the development of generalizable knowledge that may improve outcomes for future patients with the same disease. Patients seeking innovative neurosurgical care near the end of life often have similar interests. The informed consent and oversight processes that currently exist allow patients to participate in clinical trials based on their right to autonomy, even at some risk to themselves, and some have argued that this right to assume reasonable risk should be extended to surgical innovation as well.

**Limitation of the Right to Access Surgical Innovation**

Although autonomy is a fundamental human right, many bioethicists have acknowledged that few rights are absolute, and that the right to access innovative treatments near the end of life is one that can justifiably be infringed. Autonomy, although crucial to biomedical ethics, is just one of many fundamental rights that must be weighed when deciding the appropriateness of an intervention, and other factors, like beneficence and non-maleficence, must also be considered.

Allowing access to innovative treatments near the end of life may subvert important knowledge-generation structures, which are closely related to but distinct from regulatory structures. Allowing access to surgical innovations at the end of life outside the structures of these trials may exclude patients from participation in existing RCTs or cloud the results of well-designed studies, thus harming future patients who could benefit from a complete and rigorous analysis. Allowing access to innovative surgery could result in fewer patients participating in RCTs, thereby depriving the public of essential scientific knowledge that may have gone on to benefit future patients. As previously discussed, conducting surgical RCTs for recurrent GBM is already difficult. Policies that allow easier access to surgical innovation outside of RCTs may make conducting such studies nearly impossible.

Many also argue that physicians have a fundamental obligation to protect their patients from unethical treatments. This argument can most aptly be summarized by stating that a physician’s obligation to her or his patients should be based on an assessment of the current evidence base, and that the use of innovative yet unproven treatments outside of investigative structures may be unethical because such a treatment could be harmful to the patient or to others who might benefit from any generalizable knowledge that is being sacrificed.

Innovations outside traditional regulatory structures may truly be dangerous, and it is the duty of physicians to steer their patients away from situations in which they may be vulnerable to false promises or harmful treatments.

Last, from an ethical perspective, many who argue that the right to innovative treatment can justifiably be infringed point out that whereas the so-called right to die is a negative right, the right to innovative treatment would be a positive right. Positive rights, unlike negative rights, yield power to the right-holder that she or he can wield over others. Particularly from the perspective of a medical professional, asserting that a patient should have the right to receive surgical treatment may infringe on the rights of surgeons to refuse to perform such operations.

**Ethical Evaluation of Surgical Innovations for Recurrent GBM**

If one respects patient autonomy, there must be certain circumstances in which surgical innovation can be carried out ethically, and in which patients can consent to innovative procedures. Based on this fundamental ethical principle, the right to innovative treatment should be presumed, and must only be ruled out under special circumstances. Below are 4 different conditions that should be met for surgical innovation to be considered ethical, each of which also highlights the ways in which surgical innovation differs from medical innovation on ethical grounds. If any
of these conditions are not met and surgical innovation is deemed unethical, a patient’s right to innovative surgical treatments can be justifiably infringed.

Informed Consent and Vulnerable Patients

Informed consent is a fundamental principle of ethical clinical research that depends significantly on acknowledging the right of a patient to autonomy.1,3,5–7,9,30,34 When a patient undergoes an innovative surgical procedure, informed consent requires a higher standard than in the course of normal clinical care, due to the lower quality of evidence in favor of the intervention and the unique nature of experimentation in the surgical patient.9

First, surgeons performing the innovative procedure must disclose to the patient the exact nature of the innovation, specifically stating that the strategy being used is not part of the standard treatment for the patient’s disease.38 The treatment team must also disclose alternative treatment options to the patient, including the relative risks and benefits of each option.30

For patients with recurrent GBM, informed consent takes on considerably more importance due to the increased vulnerability of this population.3,12,34,48 This vulnerability occurs partially because they may not be able to protect their own interests, and because they have not voluntarily chosen their status of having a terminal illness.15 Although there has been some debate about this issue, patients with terminal illnesses are generally considered to be more willing to assume risks and choose treatments with lower chances of potential benefits.20,48 In these cases, the informed consent process must be considerably more formal and require a lengthy, face-to-face discussion, with attention paid specifically to the unique situation of the terminally ill patient.1,6,20,30

Additionally, patients with recurrent GBM may not have the capacity to make decisions about their medical care, due specifically to the nature of their disease. Near the end of life, patients must meet at least 4 criteria that determine capacity: 1) that the patient is able to communicate a choice; 2) that they understand the information relevant to that choice; 3) that they appreciate the situation and its consequences; and 4) that they can reason through the options being presented to them.1 Patients who have neurocognitive deficits or the psychiatric illnesses that are frequently present in patients with recurrent GBM, including depression, may not be deemed to have the capacity to make decisions about their care; such patients cannot ethically receive innovative surgical treatments without involving surrogate decision makers or local ethics committees.9

Oversight and Regulation

Because surgical innovation is not generally considered to be human-subject research, it often does not fall under the regulatory structure of an institutional review board (IRB).30,36,46,47 Nevertheless, surgical innovation does fall under the auspices of the IRB if certain conditions are met.9 These include cases in which a surgeon is testing a formal hypothesis and attempting to produce generalizable knowledge, or if a surgeon plans to perform an innovative procedure repeatedly, on multiple patients.4,9,40,41 Many surgical innovations occur outside these conditions, however, and these innovations should not go without any oversight or regulation.

Previous writers have described the formation of a Surgical Innovations Committee (SIC), a committee similar to an IRB that is tasked with reviewing surgical innovations that do not fall under the auspices of the IRB itself and are not part of the innovative nature of surgery.9 These cases include operations that differ significantly from the standard of care or that have not been rigorously studied or previously reported. The SIC would independently monitor surgical innovations submitted for review, assess the relevant risks and benefits in the context of the current standard of care, ensure informed consent and a reasonable chance of success, and approve or deny submissions on a case-by-case basis. Postoperatively, the SIC would ensure adequate follow-up of patients undergoing innovative procedures, and mandate the reporting of outcomes and adverse events. The development of SICs at investigative medical centers nationwide would allow for ethical surgical innovation without damaging the current culture of innovation crucial to the success and future development of surgical specialties.

Efficacy of the Innovative Neurosurgical Treatment

For a surgical innovation to be ethical, there must be a reasonable belief that it could be as successful as or more successful than the current standard of care.5,30,41 This principle depends primarily on the idea of nonmaleficence, and relates to the previous discussion of equipoise. In this sense, the ethical evaluation of surgical treatments is no different from the ethical evaluation of medical treatments. If a surgeon believed that a patient could benefit from the standard of care, but subjected that patient to an innovative, unproven treatment that did not have a reasonable chance at success, this practitioner would be committing an ethical violation, even if the patient were to provide truly informed consent.

Unfortunately, determining the relative efficacy of a surgical innovation is extremely difficult or even impossible preoperatively, and drawing the line between treatments that are completely unproven and those that may have a reasonable chance at success is difficult. Predicting success depends both on the medical community’s knowledge of disease processes and pathophysiology, which is incomplete, and on predictions of the relative merits of the innovation, which would undoubtedly be tenuous in a procedure being performed for the first time. Thus the evaluation of a surgical innovation’s efficacy should not be determined solely by the performing surgeon, but rather should be summarized and presented by that surgeon to an independent SIC or some similar alternative, which could then evaluate the innovative procedure in the context of the current standard of care. Alternatives to formal SICs include peer review by a surgeon’s local, national, or international colleagues, a dedicated form of IRB, the input of an external institution, or review by the surgeon-in-chief.13 Surgical innovations that place an unreasonable burden on the patient, pose a serious risk of morbidity or mortality, or do not have sufficient evidence in animal models (if applicable) should be deemed unethical until more information is made available.
Harm to Others

A key argument against compassionate use in the context of medical treatments is the subversion of knowledge-generation structures, as previously mentioned. In surgical innovation, this is generally not an issue, because so few surgical procedures are subject to the rigid structure of RCTs in the first place. In fact, surgical procedures are often driven forward by technical case reports of a single individual or a handful of patients, which can sometimes revolutionize surgical care.

As such, harm to others is a less relevant but still important consideration in ethical surgical innovation. Surgical innovations for patients with recurrent GBM could directly harm the patients involved if the preoperative discussion and evaluation of possible risks is inadequate. Additionally, patients seeking surgical innovations for recurrent GBM may harm current knowledge-generation structures (e.g., medical clinical trials for this disease) if these innovations were attempted prior to participation in clinical trials and later resulted in exclusion of patients from participation, or they may harm family and loved ones, who play a crucial role in supporting patients with recurrent GBM through a difficult treatment course. Truly innovative surgical treatments for patients approaching the end of life should generally be carried out only after exhausting other reasonable options.

Conclusions

Patients with recurrent GBM should have a right 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. These measures include the following: 1) a high standard of truly informed consent, with attention given specifically to the vulnerability of the patient, the innovative aspects of the procedure, and the capacity of the patient to consent; 2) substantial oversight and regulation of the innovative treatment, preferably in the form of an SIC or, when appropriate, an IRB; 3) adequate evidence that the innovative treatment will be successful, either in the form of animal model studies or prior use 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.

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References

52. Tsou A: Ethical considerations when counseling patients about stem cell tourism. Continuum (Minneap Minn) 21 (1 Spinal Cord Disorders):201–205, 2015

Disclosures

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