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.1,2,26,45 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
ticing 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.10,11,12,37 These reports suggested that bacte-
rial 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 suffer-
ing 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 treat-
ments 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 fun-
damental right to access innovative, unproven surgical
treatments, even if these treatments may pose risk of seri-
ous injury?

The current literature on this issue centers around 2
opposing arguments: on the one hand, that patients near-
ingen the end of life have a right to innovative treatment
for reasons of protecting patient autonomy and compassion-
ate 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 ar-
guements specifically in the context of surgical innovation
for patients with recurrent GBM, which is fundamentally
different from medical innovation, and has not been dis-
cussed 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 “exception-
”al status of surgery, which distinguishes both regula-
tion 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 sur-
geons 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 al-
together. In nearly all cases, these innovations are not sub-
ject to the traditional regulatory structures of a random-
ized, 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 evalu-
ates 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 be-
ing 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 ethi-
cal manner requires equipoise—the reasonable belief that
patients in neither treatment group have a significant ad-
antage over the other—a circumstance that is extremely
rare in surgical innovation.38 Many writers have also ques-
tioned 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 treat-
ment is nearly always impossible.7,21,32,42 Although these
differences have precluded the use of RCTs for most surgi-
cal 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 re-
current GBM.5,36,40,41

Furthermore, surgical practice is generally more depend-
don emerging technologies than medical treatment.4 If
all surgical procedures using new technologies were to re-
quire 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 re-
wards 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 doz-
eens or hundreds of times and are undergoing only small
modification; others are entirely new and radically differ-
ent from the standard of care. The respective views of neu-
rosurgeons and ethicists on these procedures differ based
on personal experience, and excellent surgeons often dis-
agree on what should or should not be considered inno-
vative. Minor modifications to a procedure or the use of
slightly different equipment is part of the day-to-day real-
ity of surgery, but radical changes to surgical procedures,
or new procedures entirely, are generally not.13 In the
context of the ethical discussion presented here, we will larg-
ely 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-
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. 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 might 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 investigational 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.

Limitation of the Right to Access Surgical Innovation

Although autonomy is a fundamental human right, and 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.

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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. 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.

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. The treatment team must also disclose alternative treatment options to the patient, including the relative risks and benefits of each option.

For patients with recurrent GBM, informed consent takes on considerably more importance due to the increased vulnerability of this population. 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. 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. 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.

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. 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.

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). Nevertheless, surgical innovation does fall under the auspices of the IRB if certain conditions are met. 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. 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. 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. 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. 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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