The Role of Repeat Surgical Resection in the Management of Patients with Recurrent Glioblastoma

by

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ABSTRACT

The prognosis for patients with recurrent glioblastoma (GBM) is dismal, and the question of whether to offer repeat surgery at the time of recurrence is common. Re-operation in the management of these patients is controversial as there is no randomized evidence of benefit. The first component of this work was to evaluate the quality of the literature that addresses the question of whether repeat surgery for recurrent GBM provides a survival advantage. Multiple recent published systematic reviews were found, and we did not think that repeating another systematic review was necessary. However, all studies included in the systematic reviews were retrospective observational studies, and the answer regarding whether to re-operate remained unknown. All of the included studies suffered from the biases of observational studies, and the best management for recurrent GBM patients was unclear.

Because randomized controlled trials (RCT) are the gold standard to evaluate the effectiveness of an intervention, only an RCT can properly evaluate whether repeat surgical management leads to a meaningful survival advantage for patients with recurrent GBM. However, to justify an RCT, the neurosurgical community should be sufficiently uncertain about how to proceed in the care of these patients. In this second part of this work, we assayed the degree of community agreement regarding the management of patients with recurrent GBM. We performed a systematic review to ensure that such a study had not already been done. An inter-observer variability study was carried out and we found sufficient community uncertainty to justify the conduct of an RCT.

Finally, the third part of this work was to design and launch a pragmatic care trial that doctors can use to manage patients with recurrent GBM within an openly declared, transparent research context.

PREFACE

This thesis is an original work by Mukt N. Patel. The research project, of which this thesis is a part, received research ethics approval from the University of Alberta Research Ethics Board, Project Name "Repeat Resection in Recurrent Glioblastoma (3rGBM) Trial: a randomized care trial", HREBA.CC-21-0094, June 8, 2021.

Some of the research conducted for this thesis forms part of multi-institutional research collaboration, led by my supervisor Dr. Tim E. Darsaut at the University of Alberta with Dr. Jean Raymond at the Université de Montréal. The conceptualization of this project is original and was designed with collaborative inputs from T.D and J.R. The literature review mentioned throughout the thesis is my work with the search strategy guidance provided by Sandra Campbell of John W. Scott Health Sciences Library at the University of Alberta.

Chapter 2 of this thesis has been published as Patel, M., Au, K., Davis, F. G., Easaw, J. C., Mehta, V., Broad, R., Chow, M. M., Hockley, A., Kaderali, Z., Magro, E., Nataraj, A., Scholtes, F., Chagnon, M., Gevry, G., Raymond, J. & Darsaut, T. E. (2021). "Clinical Uncertainty and Equipoise in the Management of Recurrent Glioblastoma". American Journal of Clinical Oncology, 44 (6), 258-263. doi: 10.1097/COC.0000000000000812. I was responsible for methods, data collection, and manuscript composition. Contributing authors suggested manuscript edits and Chagnon, M provided statistical analysis. Gevry, G was responsible for formatting the portfolio for electronic distribution along with the final formatting of the manuscript for submission. Dr. Tim E. Darsaut was the supervising author and was involved with concept formation and manuscript composition.

Chapter 3 of this thesis represents ideas that were conceptualized by T.D and J.R. I was responsible for the composition of this chapter; the written work was revised by T.D and J.R. The ideas associated with this chapter will be translated into a manuscript and submitted to a journal for publication in the future.

Chapter 4 of this thesis was submitted to the Journal of Neurochirurgie on 08/02/2021 as Mukt Patel, Karolyn Au, Jacob C. Easaw, Faith Davis, Kelvin Young, Vivek Mehta, Greg N. Bowden, Michael B. Keough, Tejas Sankar, Felix Scholtes, Miguel Chagnon, Georges L'Espérance, Yan Yuan, Guylaine Gevry, Jean Raymond, Tim E. Darsaut "Repeat Resection in Recurrent Glioblastoma (3rGBM) Trial: a randomized care trial". This manuscript is currently under review. I was responsible for formulating the trial details and composing the manuscript, case report form (CRF) and the patient informed consent form (ICF). Contributing authors provided feedback related to the trial design and suggested manuscript edits. Dr. Tim E. Darsaut was the supervising author and was involved with the manuscript and accompanying material composition; the concept of the trial was formulated with collaborative efforts between myself, T.D, and J.R.

ACKNOWLEDGEMENTS

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I would like to thank my committee members Dr. Karolyn Au, Dr. Jacob C. Easaw, and Dr. Faith Davis for their helpful suggestions and encouragement. I would also like to thank my thesis defense external examiner who took the time to read and critique my work. A special thank you to Dr. Jean Raymond for providing feedback throughout the duration of my project. I also want to acknowledge Guylaine Gevry for her work related to formatting manuscripts and the patient portfolio for electronic distribution.

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Chapter 1: General Introduction to Glioblastoma Multiforme (GBM)

Background Information

1. General Introduction to Cancer

Cancer is the leading cause of death worldwide; it is estimated that there are approximately 9.6 million cancer-related deaths each year (Bray et al., 2018). About 18% of the cancer-related deaths are because of lung cancers; while brain and central nervous system (CNS) cancers are responsible for 2.5% of deaths each year (Bray et al., 2018).

1.1 Hallmarks of Cancer

Cancers can be classified as a dynamic disease that progresses via multistep processes which include evading growth suppressors, activating invasion and metastasis, enabling replicative immortality, inducing angiogenesis, resisting cell death, and sustaining proliferative signaling (Hanahan, D. & Weinberg, 2000). These six biological capabilities were the original hallmarks of cancer; however, four more properties were added to the list of hallmarks to better assist with the rationalization of this complex disease (**Figure 1.1**.). The four new proposed characteristics that allow cancers to survive and proliferate are deregulation of cellular energetics, evasion from immune system destruction, inherent genomic instability and mutations, and local tumor-promoting inflammation (Hanahan, Douglas & Weinberg, 2011).

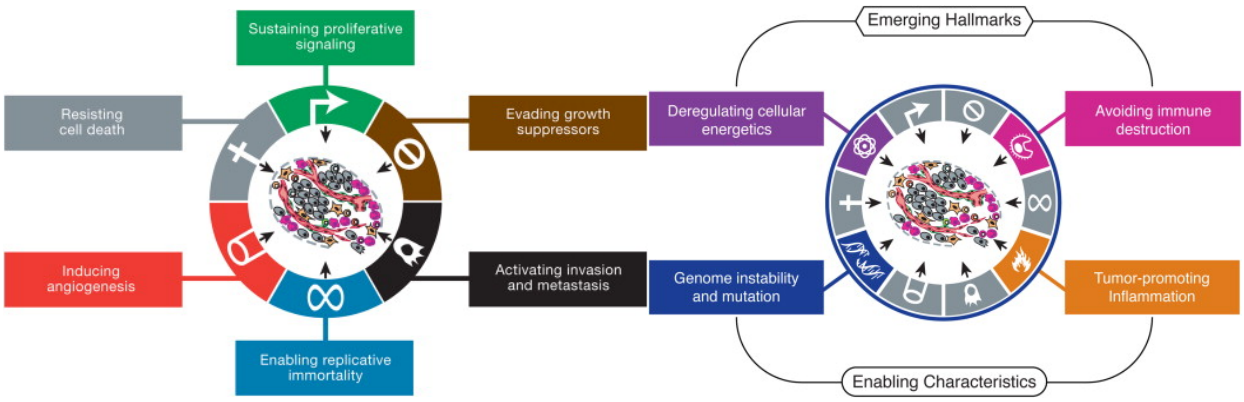

Figure 1.1. The original hallmarks of cancer (Hanahan, D. & Weinberg, 2000), along with emerging and enabling characteristics (Hanahan, Douglas & Weinberg, 2011).

Experiments from the early 1990s and onwards have repeatedly demonstrated that tumour formation is not an autonomous process but rather one in which there is crosstalk with the microenvironment and the tumorigenic cells (Balkwill & Capasso, 2012; Mueller & Fusenig, 2004).

Models have been created to describe the initiation and progression of cancers (Figure 1.2), throughout which cancerous cells of the growing tumour are dependent on the surrounding microenvironment for chemical, mechanical and physical cues (Lodish et al., 2000; Mueller & Fusenig, 2004). The first phase, known as the initiation phase, is characterized by the occurrence of genetic mutations. Initiators for this phase can include many DNA damaging substances such as chemicals, radiation, infections, hormones, and hypoxic environments (Nelson et al., 2004). The initial mutations commonly take place in proto-oncogenes or tumour suppressor genes (Downward, 2003; Finver et al., 1988). Generally, the development of cancer requires progressive accumulation of multiple mutations; however, certain mutations can lead to more rapid progression than others. Once the mutations have taken place, the cells can remain dormant or become proliferative (Lodish et al., 2000). As shown in Figure 1.2, the second step of cancer formation is

known as the promotion phase and is further characterized by 4 subphases: hyperplasia, dysplasia, in situ carcinoma, and invasive carcinoma (Lodish et al., 2000).

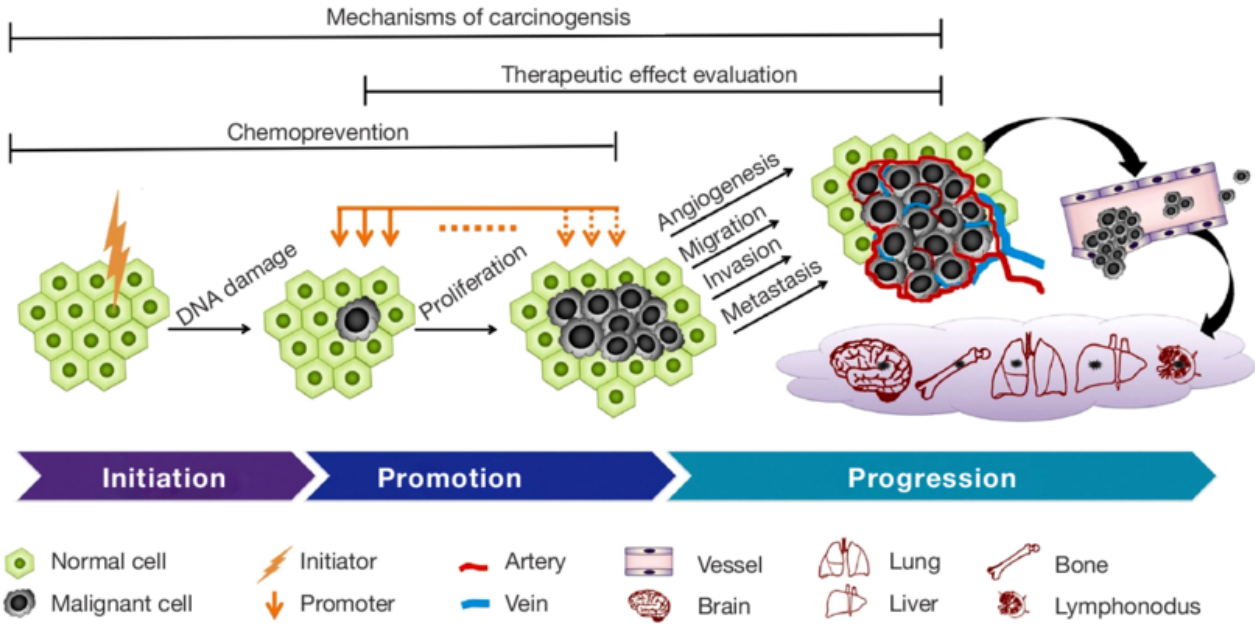

Figure 1.2. The progression of a tumour from healthy normal cells to metastasis (Liu et al., 2015).

1.2 Tumour Microenvironment

Cancers are not just a solid mass of cells but rather behave more like an organ that recruits and exploits other healthy cells from its surrounding. The intricate interaction between the transformed cells and the surrounding environment is termed tumour microenvironment (TME) (Balkwill & Capasso, 2012). The interaction with the microenvironment is responsible for many enabling characteristics as proliferating cells of the tumour rely heavily on the tumour-promoting effect creating by the non-malignant cells within the TME (Balkwill & Capasso, 2012).

The presence of a primary tumour is responsible for significant alterations to the microenvironment; some of the most common changes observed within the TME include increased concentrations of cytokines, growth factors, chemokines, and inflammatory enzymes (Balkwill & Capasso, 2012; Coussens & Werb, 2002; Hanahan, Douglas & Weinberg, 2011).

1.2.1 Targeting the Tumour Microenvironment

Due to the large dependence of the tumour on the TME, molecular targeting of regulatory mediators found within the microenvironment might provide therapeutic breakthroughs for certain types of cancers. There are pre-clinical and clinical studies underway which focus on targeting inflammatory signals as well as disrupting the cell-cell communication between the TME and the transformed cells (Dominiak, Chełstowska, Olejarz, & Nowicka, 2020; Hanahan, Douglas & Coussens, 2012).

Despite ongoing studies that focus on targeting the TME for growth suppression, the heterogeneity of the TME among cancers based on location represents a challenge of its own. The TME of certain central nervous system tumours and the composition of the microenvironment is poorly understood. Specifically for Glioblastoma (GBM), how the TME contributes to the increased heterogeneity, resistance to therapy and the aggressive nature of GBM remains elusive (de Gooijer, Navarro, Bernards, Wurdinger, & van Tellingen, 2018; Perrin et al., 2019). For highly infiltrative and progressive diseases such as GBM, the use of animal models are not sufficient to accurately characterize the heterogeneity and the complexity of the interaction between the tumour and microenvironment (Perrin et al., 2019). For tumours with high resistance to targeted therapy combined with chemotherapy and radiation therapy, maximal safe surgical removal of the tumour remains the best option to mitigate the symptoms.

2. Introduction to Gliomas

Primary brain tumours are responsible for approximately 2.5% of all cancer-related deaths in Europe and North America (Dolecek, Propp, Stroup, & Kruchko, 2012). Gliomas are the most common form of primary brain tumour and account for 32% of central nervous system (CNS) tumours and 80% of malignant CNS tumours (Agnihotri et al., 2013).

2.1 Types of Glial Cells

Glial cells are the most abundant cells found within the central nervous system (CNS); their main function is to provide support for surrounding neurons. When glial cells were first identified, in the early 19th century, it was thought their function was to act as a glue to anchor surrounding neural tissues; hence the name 'glial' which is derived from the Greek word for glue (Jäkel & Dimou, 2017). Within the CNS, there are four types of glial cells: astrocytes, oligodendrocytes, microglia, and ependymal cells **(Figure 1.3).** Astrocytes are the most abundant type of cells within the CNS and have a broad range of functionality; they provide structural and biochemical support to surrounding neurons. Additionally, astrocytes are involved in many essential functions including synaptic transmission and responding to brain trauma via reactive astrogliosis (Sofroniew & Vinters, 2010). Oligodendrocytes are responsible for modulating the propagation of action potentials via the myelination of neurons within the CNS (Jäkel & Dimou, 2017). Microglia are macrophages that respond to foreign materials within the CNS (Jäkel & Dimou, 2017). Ependymal cells line the ventricles of the brain and include ependomocytes, choroid plexus epithelial cells, and tanycytes. Ependymal cells play a key role in maintaining homeostasis within the brain and form a barrier between the cerebrospinal fluid and the blood.

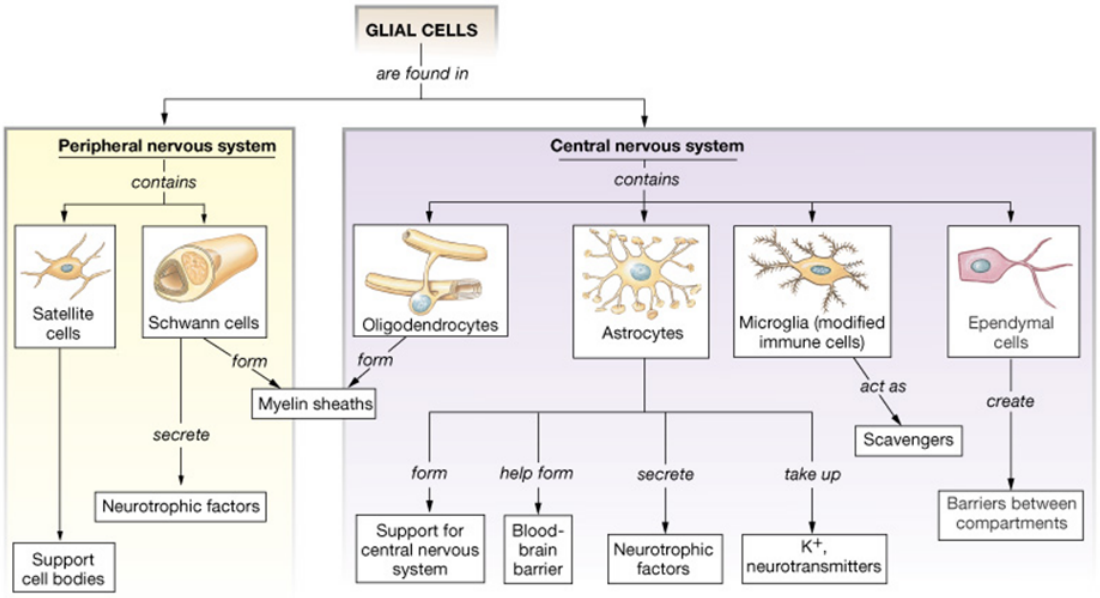

Figure 1.3. Types of glial cells and their function within the central and peripheral nervous systems. (Figure adapted from (Kolb & Whishaw, 2014)).

2.2 Classification and Grading of Gliomas

Primary brain tumours, such as gliomas, arise from cell lineages within the CNS; they can be classified as benign or malignant (Urbanska, Sokolowska, Szmidt, & Sysa, 2014). Historically, gliomas were classified according to the system designed by Bailey and Cushing where classification was based on the morphological appearance of the neoplasm and the normal glial development within the brain (Bailey & Cushing, 1928). As the glioma becomes more infiltrative and more aggressive, it loses the morphological resemblance to its precursor; however, due to the initial resemblance to its precursor cells, these tumours were historically termed astroblastomas (Friedmann-Morvinski, 2014).

Currently, human gliomas are diagnosed using histopathological features and follow a World Health Organization (WHO) classification system (Louis, Ohgaki, & Wiestler, 2007; Louis et al.,

2016). The WHO initially classified gliomas based on their respective glial cell lineage which they morphologically resemble; however, the new WHO classification of gliomas utilizes molecular parameters in combination with histological features (Louis et al., 2007; Louis et al., 2016). Of the various types of glioma, the most common are astrocytoma, which arises from the astrocytic lineage (Louis et al., 2007; Louis et al., 2016). Astrocytes play an important role in the blood-brain barrier and provide nutrients and biochemical support to neurons and epithelial cells. Histopathological features are used to determine glioma grade and aggressiveness. Grade I and II are considered low-grade benign tumours; whereas Grade III and IV tumours are considered to be high-grade malignant tumours with poor prognosis following diagnosis. Low-grade tumours are most common in young, otherwise healthy adults, whereas high-grade tumours are most common among the middle-aged and elderly (Stieber, 2001). Gliomas behave differently than other forms of cancers in that metastasis outside the CNS is extremely rare (Giese, Bjerkvig, Berens, & Westphal, 2003)

- WHO Grade I neoplasms proliferate slowly with no infiltrative components.
- WHO Grade II neoplasms proliferate slowly and have limited infiltrative properties. Some Grade II tumours have a tendency to recur and progress into higher grades of malignancy.
- WHO Grade III neoplasms proliferate rapidly and have histological evidence of malignancy.
- WHO Grade IV neoplasms (glioblastoma multiforme) are cytologically malignant and highly mitotically active; they also show microvascular proliferation and pseudopallisading necrosis (Louis et al., 2007; Louis et al., 2016).

Historically all astrocytic lesions were grouped together; however, the WHO now groups all diffusely infiltrating gliomas into a single grouping based on their shared growth pattern and IDH

1 and IDH 2 gene mutations (Louis et al., 2016). In the new classification diffuse gliomas include: WHO grade II and III astrocytic oligodendroglial tumours, WHO grade IV glioblastoma and other pediatric diffuse gliomas(Louis et al., 2016). IDH status is the key differentiating factor when characterizing gliomas thus diffuse gliomas fall into one of three categories: IDH- mutant, IDH-wildtype and Not Otherwise Specified (NOS) (Louis et al., 2016). **Figure 1.4** shows the WHO breakdown of diffuse gliomas based on histological and genetic features.

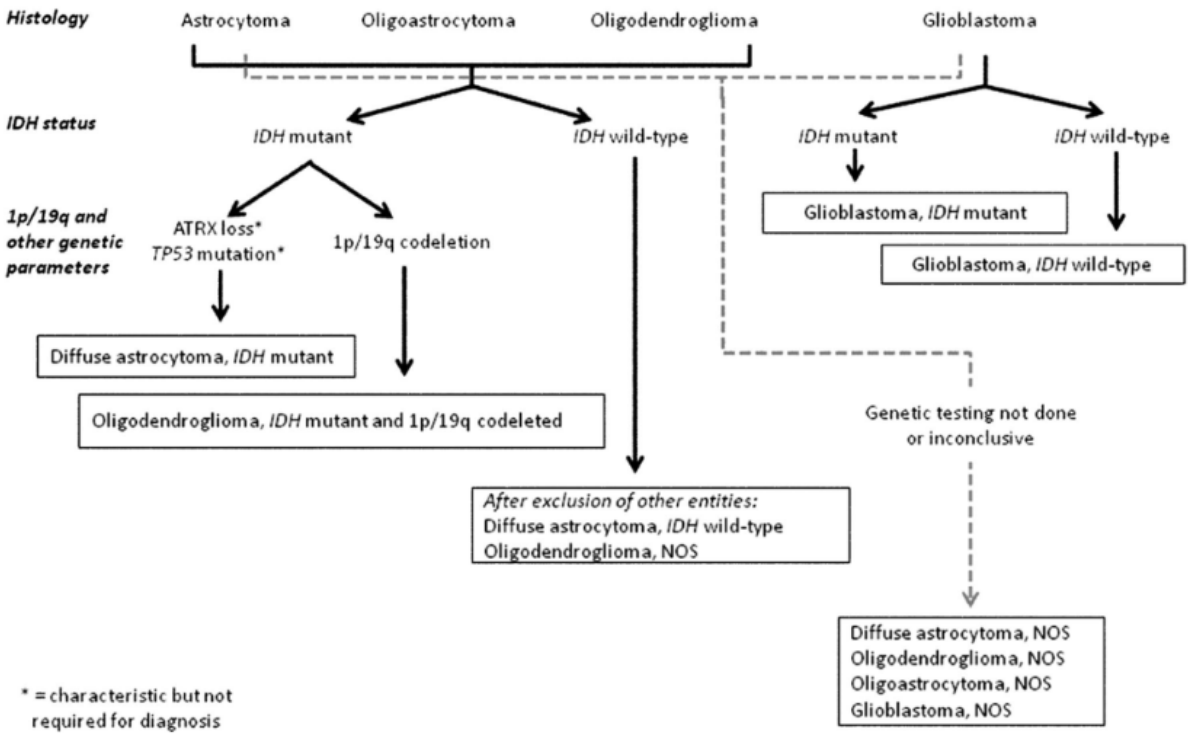

Figure 1.4. WHO classification of diffuse gliomas based on histological and genetic features. Figure adapted from (Louis et al., 2016)

2.2.1 Prognosis Based on WHO Classification

Grade I lesion have the highest chance of a cure following surgical resection alone (Louis et al., 2007). Grade II gliomas are most common in young adults and the average overall survival for patients diagnosed with WHO grade II gliomas is greater than 5 years. Patients diagnosed with WHO III tumours typically survive 2-3 years with a treatment combination of radiation/ chemotherapy and surgical resection (Louis et al., 2007; Louis et al., 2016). Though the overall survival for patients with WHO Grade IV does depend somewhat on the treatment regime and availability, the average survival after diagnosis is only usually 1-2 years (Kubben et al., 2011).

3. Glioblastoma Multiforme Overview

Glioblastoma multiforme (GBM) is the most common and most lethal form of primary brain tumour (Dolecek et al., 2012). The incidence rate is slightly higher in Caucasian men. (Verdecchia et al., 2002). Though there have been reports of GBM in neonates and children, they are much more common in the middle-aged and elderly population and the mean age of diagnosis is 64 years (Dolecek et al., 2012; Mahvash, Hugo, Maslehaty, Mehdorn, & Stark, 2011; Winters, Wilson, & Davis, 2001). In the most recent report (2019) of the Central Brain Tumour Registry of the United States (CBTRUS), GBM accounted for 14.6% of all central nervous system (CNS) tumours, and was the most common malignant brain tumour (48.3% of all malignant CNS tumours, and 57.3% of all gliomas (Ostrom et al., 2019). Within Canada, GBM accounts for 17% of all primary brain tumours and it is estimated that in 2021 there will be 1785 patients diagnosed with GBM (Smith T, Yuan Y, Walker EV, Davis FG., 2019a). 5-year survival following diagnosis of GBM is 7 % (95%CI:0.06-0.08) (Smith T, Yuan Y, Walker EV, Davis FG., 2019b). Despite treatment advances over the past three decades, the prognosis of GBM remains poor. (Gallego, 2015).

GBMs are classified as either primary or secondary. Primary GBMs develop spontaneously *de novo*, usually among the older population; these tumours have no clinical or histological evidence of arising from lower grade gliomas (Ohgaki & Kleihues, 2013). Approximately 90% of all GBM are primary gliomas that arise from normal glial cells (Urbanska et al., 2014). The remaining 10% of GBMs are secondary gliomas that progress from low-grade diffuse astrocytoma or anaplastic astrocytomas and are much more commonly observed among the younger demographic (Ohgaki & Kleihues, 2013). As demonstrated in **Figure 1.5**, primary and secondary GBMs share similar histological appearances; however, they vary in their origin and prognosis (Ohgaki & Kleihues,

2013). Genetic pathways of primary and secondary GBMs will be discussed in section 3.4 (Pathological and Molecular Features).

The most common initial treatment involves surgical management to acquire a tissue diagnosis with or without cytoreduction, followed by radiotherapy and chemotherapy (Gallego, 2015). Even after aggressive initial surgical and oncologic management, symptomatic recurrence from this tumour approaches 100% (Dolecek et al., 2012; Ostrom et al., 2019)

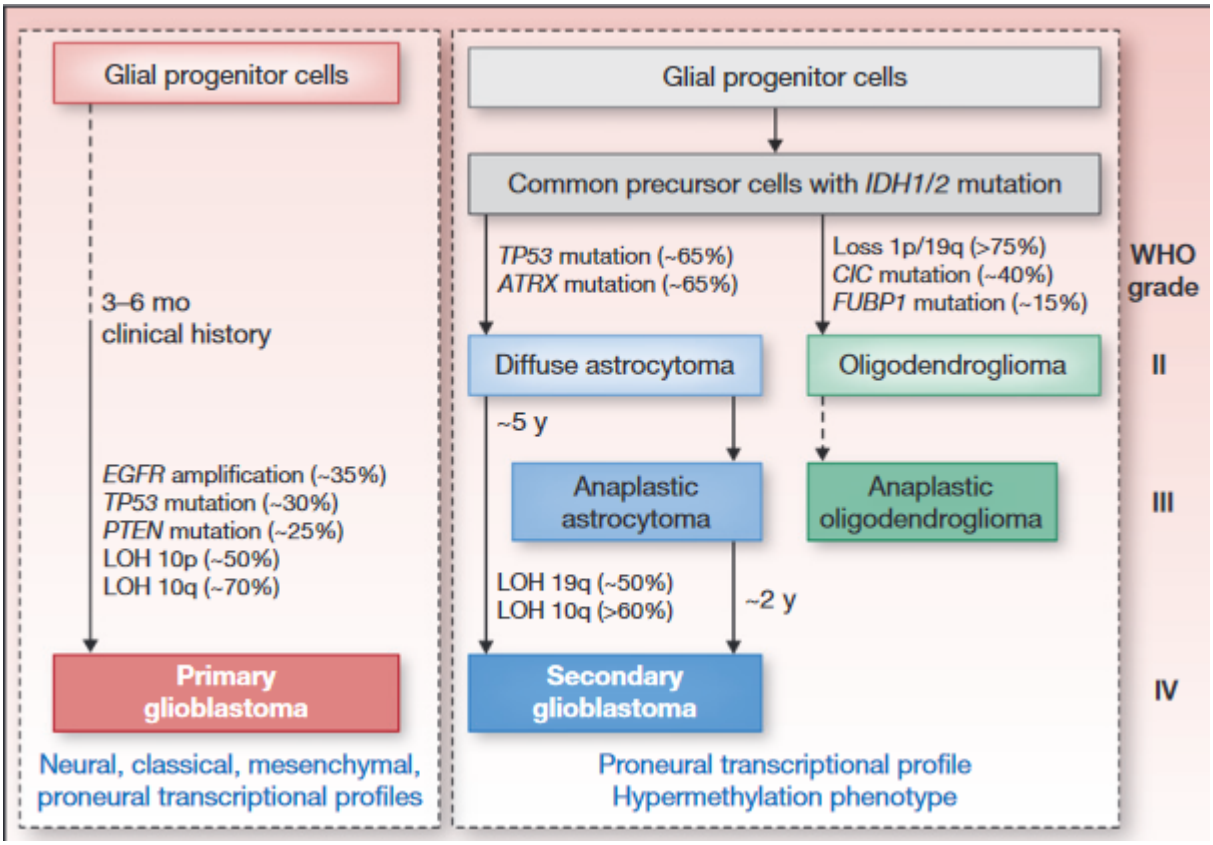

Figure 1.5. Most common mutations and genetic pathways that lead to the development or progression to primary or secondary GBM (Ohgaki & Kleihues, 2013)

3.2 Etiology

The etiological features of GBM are not fully understood. Individuals with genetic diseases such as tuberous sclerosis, Turcot syndrome, multiple endocrine neoplasia, and neurofibromatosis are at a greater risk of being diagnosed with GBM (Broekman, Risselada, Engelen-Lee, Spliet, & Verweij, 2009; Grips et al., 2002; Padmalatha, Harruff, Ganick, & Hafez, 1980; Sanchez-Ortiga, Boix Carreno, Moreno-Perez, & Pico Alfonso, 2009). Certain viruses such as human cytomegalovirus (HCMV) are also thought to be related to the development of glioblastoma (Agnihotri et al., 2013).

Some environmental factors have been proposed to increase the risk for glioblastoma; however, most reports are based on poor quality correlational studies. It was previously thought that prolonged use of cell phones may be a contributing factor to GBM; however, recent studies have shown that mobile phone usage is not correlated with increased risk of glioblastoma (Spinelli et al., 2010). Environmental exposure to pesticides, polycyclic aromatic compounds, certain types of metals, and electromagnetic fields are also thought to increase the risk of GBM (Spinelli et al., 2010). Individuals working in the petrochemical and rubber manufacturing industry face the highest environmental risks of developing GBM (Houben, van Duijn, Coebergh, & Tijssen, 2005). Prior therapeutic ionizing radiation is also considered an additional factor for developing glioblastoma (Houben et al., 2005).

3.3 Anatomical Characteristics

One of the main reasons for the poor prognosis of GBM is because they are invasive, with indistinct tumour boundaries which make total resection nearly impossible (Cha, J. & Kim, 2017; Stummer et al., 2006). It is common for GBM lesions to arise from the cerebrum and to develop near the stem cell-concentrated ventricles (Lim et al., 2007). Systematic metastasis of GBM is extremely rare and the tumour cells are usually confined within the boundaries of the CNS (Holland, 2000).

The anatomical features of GBM have been extensively studied and as with other tumours, GBM is characterized as a heterogenous bundle compromised of tumour cells forming a microenvironment with the surrounding cellular and noncellular components (Cha, J. & Kim, 2017; Hambardzumyan, Gutmann, & Kettenmann, 2016). Pro-migratory and pro-invasive factors facilitated by the microenvironment aid in GBM progression and further contribute to its invasiveness (Cha, J. & Kim, 2017; Quail & Joyce, 2017).

GBM cell migration has been proposed to occur via structures first identified by Hans Scherer in 1938. These so-called Scherer's Structures are white matter tracts and capillaries compromised of bundled axons (Cha, J. & Kim, 2017; Scherer, 1938). Histopathological analysis has identified another substructure in the tumour core which is characterized as pseudopalisading necrosis; this arises because of the hypoxic environment at the core (Rong, Durden, Van Meir, & Brat, 2006). The hypoxic core of the lesion is infiltrated with a stem-cell-like subpopulation of cells that are more resistant to therapy compared to other cellular subpopulations (Mamun et al., 2009). A common feature of GBM is a center core of necrosis that is surrounded by a proliferative cellular rim of the tumour (Giese et al., 2003).

3.4 Pathological and Molecular Features

In the past decade, there have been many studies aiming to determine the molecular biomarkers that can guide the management of GBM and ultimately improve the estimate of prognosis (Huang et al., 2000; Sallinen et al., 2000). Specifically, in response to chemotherapy, some molecular signatures have already been shown to influence the length of overall survival. Due to the heterogeneity of GBM, sampling from different sites of the same tumour can present varying subtypes altogether (Sottoriva et al., 2013).

Advances in molecular profiling allow GBMs to be subdivided into different categories based on their isocitrate dehydrogenase (IDH) gene profile (Louis et al., 2016). IDH wild type corresponds with primary GBM, whereas IDH mutant corresponds most closely to secondary GBM (D'Alessio, Proietti, Sica, & Scicchitano, 2019; Louis et al., 2016). IDH-mutant and IDH wildtype subtypes of GBM have varying clinical outcomes with overall survival being 7.8 months and 4.7 months, respectively ($P = 0.003$) (Ohgaki & Kleihues, 2013)

Another important gene is the O6-methylguanine-DNA-methylatransferase (MGMT) gene; which predicts how a patient will respond to temozolomide (a DNA alkylating chemotherapeutic drug). The MGMT gene codes for a DNA-repair enzyme that ultimately reverses DNA damage caused by alkylating agents (Pegg, 2000). The MGMT enzyme is responsible for catalyzing the removal of the alkyl group from the O6 position (Pegg, 2000). The description of how MGMT enzymes disrupt treatment with temozolomide is discussed in section 7.1 (MGMT Methylation).

3.4.1 Subtypes of GBM

3.4.2 Molecular Features of Primary (de novo) GBM

Mutations to the tumour suppressor genes such as TP53 are uncommon in primary GBMs (Nobusawa, Watanabe, Kleihues, & Ohgaki, 2009; Ohgaki & Kleihues, 2013). For primary GBMs it is very common to have overexpression of epidermal growth factor receptor (EGFR) and the complete loss of chromosome 10 (Ohgaki & Kleihues, 2013). As shown in **Figure 1.5,** patients diagnosed with primary GBM will have a short history of symptoms due to the rapid growth of the tumour.

3.4.3 Molecular Features of Secondary GBM

The most common mutations observed in secondary GBM include alteration in the promoter of telomerase reverse transcriptase (TERT), loss of tumour suppressor genes such as Tp53 and RB1, and alteration within chromosome 1, 7, 10 and 19 (Ohgaki & Kleihues, 2013). Almost all secondary GBMs will have isocitrate dehydrogenase 1 (IDH1) mutations; for patients who are lacking this mutation, there will be reduced amounts of TP53 mutation and they generally have a short clinical history (Ohgaki & Kleihues, 2013). Secondary GBMs with IDH mutations have progressed from WHO Grade II gliomas; whereas those which are lacking the IDH mutation have progressed from WHO grade III gliomas (Nobusawa et al., 2009; Ohgaki & Kleihues, 2013). The clinical implications of Isocitrate Dehydrogenase (IDH) 1 and 2 mutations will be discussed in section 7.2 (Isocitrate Dehydrogenase (IDH) 1 and 2).

Management of GBM at Time of Initial Diagnosis

4. Diagnosis

4.1 Clinically Relevant Symptoms

Patients can present with a wide array of symptoms depending on the size and location of the lesion as well the local mass effect created by the tumour. Most common symptoms include seizures, persistent headaches, personality changes, aphasia, memory loss, and other location-specific neurological deficits (Demir, Hakan, Akinci, & Berkman, 2005). Approximately one-third of GBM patients will experience at least one episode of a generalized seizure (Louis et al., 2007; Louis et al., 2016).

4.2 Clinical Diagnosis

The occurrence of symptoms and signs suggestive of CNS dysfunction is initially investigated with a computed tomography (CT) scan, followed by contrast-enhanced magnetic resonance imaging (MRI) of the brain. However, histopathological analysis is the only way to confirm the diagnosis of GBM, as several other entities, such as lower-grade gliomas, metastatic tumours, and occasionally intracranial abscesses can give similar imaging appearances (Shukla et al., 2017).

Compared with other imaging modalities, MRI can best determine the location of the tumour (Agnihotri et al., 2013). In cases where surgical removal of the tumour is judged not safe, a stereotactic biopsy is performed to retrieve a sample of the tumour for histopathological analysis.

T1-weighted (T1w), T1-weighted contrast-enhanced (T1CE), T2-weighted (T2w), and T2-fluid-attenuated inversion recovery (T2-FLAIR) sequences are typically ordered for MRI imaging (Shukla et al., 2017). T1 highlights normal anatomy, whereas T2w and T2-FLAIR is used to show

tissues with the greatest water content, which highlight pathological processes **(Figure 1.6)**. The contrasting enhancing agent used for T1CE is generally gadolinium; it primarily acts to increase the signal intensity on T1 imaging (Smirniotopoulos, Murphy, Rushing, Rees, & Schroeder, 2007).

On an MRI, GBM will typically appear as a heterogeneous mass with a central necrotic region contained within an infiltrative, nonuniform border (Smirniotopoulos et al., 2007). The necrotic center of the mass is not contrast enhancing but is often surrounded by a highly vascularised enhancing rim, indicating blood-brain barrier disruption (Smirniotopoulos et al., 2007).

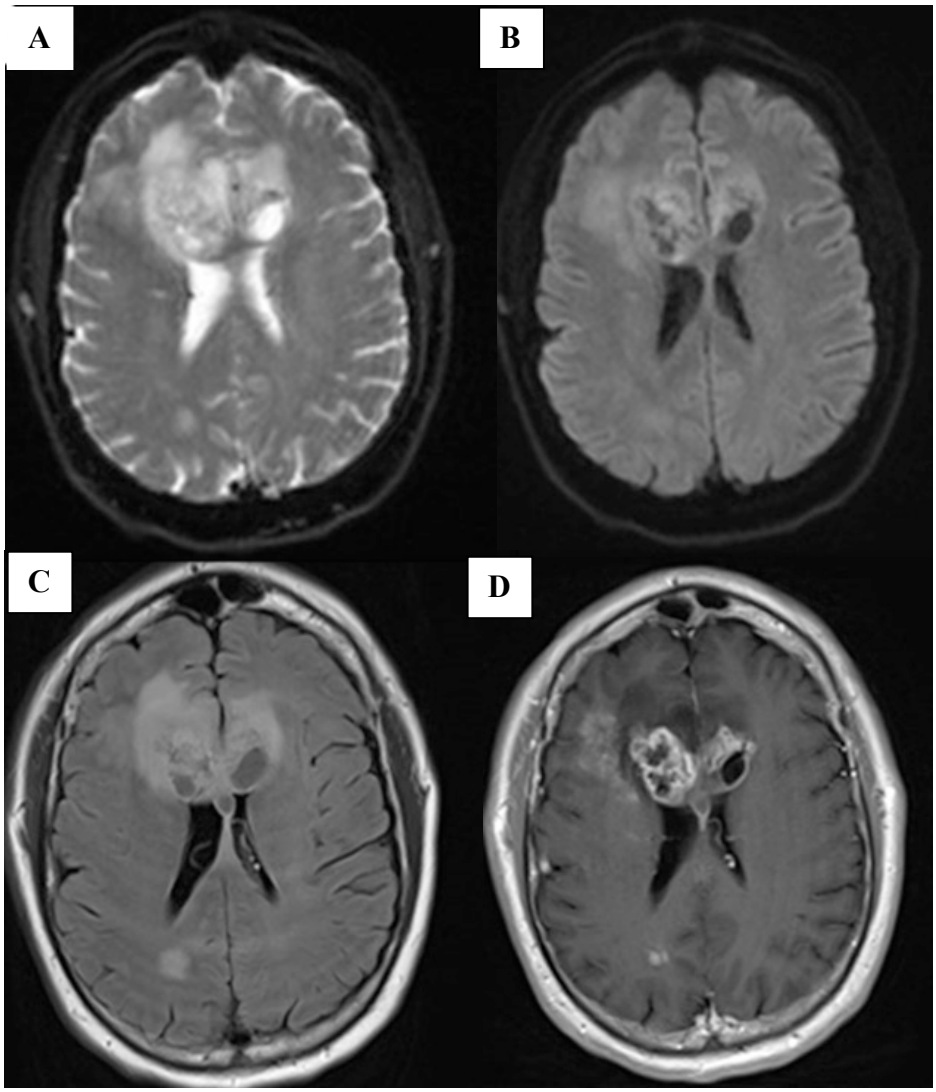

Figure 1.6. Butterfly glioblastoma imaged with varying MRI sequences. A) T2- weighted, B) T2 -weighted FLAIR, C). T1- weighted, D) T1-weighted contrast enhanced sequences.

5. Standard Management of Glioblastoma

Over the last three decades, there has been little change with regards to managing patients with GBM, although many novel approaches have been tried. Depending on the location and stage of the disease, conventional management often includes surgical resection followed by second line adjuvant therapy.

5.1 Surgical Operative Management

The most common initial treatment of suspected GBM involves surgical management to acquire tissue for diagnosis with or without cytoreduction, followed by radiotherapy and chemotherapy (Gallego, 2015). Surgical debulking of as much of the tumour as safely possible can also mitigate symptoms due to increased intracranial pressure, decrease tumour-associated edema and steroid requirements, improve the efficacy of adjuvant therapies, and perhaps also prolong survival, although this has not been shown in a randomized trial (Dejaegher & De Vleeschouwer, 2017).

When managing patients with glioblastoma, surgeons attempt to balance maximal safe resection with minimization of new permanent neurological deficits due to the resection. A retrospective study conducted in 2002 suggested that an extent of resection (EOR) of greater than 98% could lead to survival benefits (Lacroix et al., 2001). Other studies suggest survival benefits for surgical resection with an EOR as low 78%, but all studies are hampered by a number of methodological shortcomings, including measurement of EOR, which has not been tested with interobserver variability methods.

The relationship between tumour resectability based on location, associated surgical risk and EOR need to be carefully considered. Newly acquired neurological deficits following debulking surgery pose a significant risk for patients with GBM (ref McGirt et al., 2009

Neurosurgery. 2009 Sep; 65(3):463-9; discussion 469-70). It is estimated that 15-20% of patients develop new neurological deficits after initial resection (Gulati, Jakola, Nerland, Weber, & Solheim, 2011). Recognized peri-operative complications include new neurological deficits, infections, hematomas, and seizures; which, if they occur may also decrease the likelihood of those patients receiving adjuvant chemotherapy and radiation (Gulati et al., 2011). Chemotherapy and radiation have been suggested to be independent predictors of overall survival; therefore, peri-operative complications may not only decrease quality of life but also exclude subsequent treatments and impact survival.

5.2 Radiation Therapy

Radiotherapy is used as a treatment modality for over 50% of all cancer patients (Chinot et al., 2014). Radiotherapy consists of targeted gamma-irradiation to induce cell death via DNA damage. Cancer cells are vulnerable to damaged DNA and will reduce mitotic activity in response to radiation. Radiation therapy generates free radicals which ultimately are responsible for inducing cell death. Radiation can eradicate large amounts of cancerous cells; however, this treatment can also damage healthy surrounding tissue adjacent to the target site causing further neurological deficits. This is especially detrimental for patients with severe neurological impairments prior to treatment initiation (Epstein, Robertson, Emerton, Phillips, & Stevenson-Moore, 2001).

The efficacy of post-surgical radiotherapy for GBM patients was first demonstrated by a randomized control trial in 1978. Patients were randomly allocated to four different groups: 1,3-bis(2-chloroethyl)-1-nitrosourea (BCNU) alone, whole brain radiation therapy (WBRT) alone, WBRT with BCNU, and observation alone (Walker et al., 1978). They demonstrated that the use of WBRT with or without the combination of BCNU resulted in improved overall survival by 3

months compared to conventional GBM management at the time of the study (Walker et al., 1978). WBRT was used for a long period of time; however, due to growing concerns over toxic effects and large cognitive impairments, there is currently a shift towards using localized fields of radiation therapy (Fabian et al., 2019; Giese et al., 2003).

5.3 Chemotherapy

Over the last decade, many new chemotherapeutic drugs have been introduced to the market that has changed the management of glioblastoma (Stewart, 2002). Initially, the most common chemotherapeutic agents used for GBM were procarbazine, vincristine, and lomustine (Stewart, 2002). Despite being used commonly, these drugs did not improve the overall survival and were often coupled with additional toxicities (Stewart, 2002).

Currently, temozolomide (TMZ) is the most commonly used chemotherapeutic agent. TMZ is an oral DNA-alkylating agent that sensitizes cells to radiation; this drug was initially tested in mice during the late 1990s where it showed promising results (Plowman et al., 1994). In a randomized clinical trial 573 histologically confirmed glioblastoma patients were divided into two groups: a combination of radiotherapy plus temozolomide (n=287) and radiotherapy alone (n=268). They noted that the median survival for patients treated with temozolomide and radiotherapy was 14.6 (95%CI:13.2-16.8) months compared to 12.1 (95%CI:11.2-13.0) months for the radiotherapy alone group (Stupp et al., 2005). In the trial, they also reported that the two-year survival rate for the radiotherapy plus temozolomide group was 26.5% (95%CI:21.2-31.7) compared to only 10.4% (95%CI:6.8-14.1) for the radiotherapy alone group (Stupp et al., 2005). Patients treated with both temozolomide and radiotherapy had the greatest survival advantages compared to patients treated with radiotherapy alone (Hegi, Monika E. et al., 2005). With the

introduction of TMZ the overall survival in patients with newly diagnosed GBM has increased from 8.1 months in 2000-2003 to 9.7 months in 2005 – 2008 (Hegi, M. E. et al., 2004).

O6-methyguanine-DNA-methyltransferase (MGMT) promoter methylation has been found to be the strongest predictor of how the patient will respond to temozolomide chemotherapy (Hegi, M. E. et al., 2004). The role of MGMT promoter status will be discussed in greater detail in the prognosis section under 7.1 (MGMT methylation).

6. Experimental Treatments of GBM

Many experimental treatments have been attempted to halt the progression of GBM; however, all have failed to convincingly show improved benefits. Stereotactic radiosurgery, gross total resection using multiple methods, and countless other chemotherapeutic drugs have also failed to show significant improvements in the prognosis of the disease (Giese et al., 2003). The extent of resection and aggressive surgical management of GBM have been studied in the past; however, they only suggested modest effects in prolonging overall survival. Some older studies indicate that stereotactic biopsy followed by external-beam radiation may provide the same survival benefits as surgical removal of the rumour. A study in 1993 compared 58 patients who received stereotactic biopsy followed by external beam radiation with 57 patients who were treated with surgical resection followed by external beam radiation; they found no differences between the two groups in terms of mean overall survival. (Kreth, Warnke, Scheremet, & Ostertag, 1993).

6.1 Intraoperative Techniques

6.1.1 Fluorescence Guided surgery

For studies that focus on the extent of resection, there have been reports of modest possible improvements in overall survival (Stummer et al., 2006). Intraoperative techniques that target a greater extent of resection are widely being used currently. The most common intraoperative guided surgeries utilize fluorescence-guided 5-aminolevulinic acid (ALA) or intraoperative magnetic resonance imaging (iMRI). A phase III clinical trial by Stummer et al., 2006 randomly allocated 260 patients to either conventional neuronavigation or 5-ALA aided surgery (Stummer et al., 2006). They demonstrated that 5-ALA aided surgery resulted in a greater extent of resection compared to conventional neuronavigation (Stummer et al., 2006). It was also reported that the six-month progression-free survival for patients operated using 5-ALA was significantly higher than with conventional neuronavigation (41% vs. 21.1%) (Stummer et al., 2006). To date, there are no phase III randomized clinical trials examining gross total resection and using iMRI and improved overall survival.

Prognostic Factors in GBM

7. GBM Prognostic Factors

Multiple factors influence the prognosis of GBM. Studies have suggested age, tumour size and location, performance status, and the extent of resection to be important prognostic factors (Ahmadloo et al., 2013; Ewelt et al., 2011). Recently, the molecular characteristics of glioblastoma have been recognized to impact the response to adjuvant treatment and thus survival.
We will here discuss in more depth the two most common markers: MGMT promoter methylation, and IDH 1 and 2.

7.1 MGMT Methylation

MGMT codes for a DNA repair protein that is involved in removing alkyl groups from damaged DNA.

7.1.1 Mechanism of Action

The cytotoxic effects of temozolomide are largely due to the introduction of alkyl groups at multiple sites along the DNA backbone (Shah et al., 2011). The most damaging to cellular replication is the alkylation of the guanine at the O6 position (O6-MeG) (Shah et al., 2011). This prevents DNA strand elongation by a persistent mismatch of O6-MeG to thymine rather than cystine. Mismatch repair results in a persistent O6-MeG in the template strand and which ultimately leads to a stoppage of cell replication and tumour cell death.

In healthy cells, multiple DNA repair proteins detect and repair cellular damage to ensure proper replication. One such protein responsible for DNA repair is the O6-alkylguanine DNA

alkyltransferase (AGT). The primary role of AGT is to remove alkyl groups from the O6 position of guanine and the O4 position of thymine to restore proper DNA base pairing (Shah et al., 2011). Ultimately, when there is an abundance of AGT, the cytotoxic effects of TMZ will be reduced and the tumour cells will continue to replicate.

The AGT protein is encoded by MGMT gene; thus tumours that express the MGMT will respond poorly to TMZ (Hart, Garside, Rogers, Stein, & Grant, 2013; Zhang, J., FG Stevens, & D Bradshaw, 2012). The MGMT gene can be silenced when there is methylation of the cytosine nucleotides at the promoter region of the gene (Shah et al., 2011)

7.1.2 Detection of MGMT methylation status

Several methods can be employed to determine MGMT status (mRNA levels, protein levels by immunohistochemistry (IHC), and promoter methylation; however, in a clinical setting only MGMT protein expression and promoter methylation are typically assessed (Hart et al., 2013; Zhang, J. et al., 2012).

7.1.3 Clinical relevance

Methylation of the MGMT promoter occurs in approximately 45% of newly diagnosed GBM patients and is prognostic for a more robust response to TMZ treatment. MGMT promoter methylation is associated with prolonged overall survival; at 18 months the survival for patients with MGMT methylation was 62% compared to 8% for patients whose MGMT was not methylated (Hegi, Monika E. et al., 2005; Hegi, M. E. et al., 2004).

7.2 Isocitrate Dehydrogenase (IDH) 1 and 2

Until the discovery of IDH-1 as a molecular marker, primary and secondary GBMs were classified based on clinical observational history only; GBMs were considered secondary if there was imaging or histological evidence of having arisen from lower-grade gliomas (Ohgaki & Kleihues, 2013). Now GBMs are distinguished based on the presence or absence of IDH1/2 mutations as they are only seen among secondary GBMs. If a GBM has IDH 1/2 mutation then it will be classified as a secondary GBM.

7.2.1 Mechanism of Action

The IDH1 and IDH2 enzymes catalyze the oxidative decarboxylation of isocitrate, producing α-ketoglutarate (α-KG) and regenerating NADPH as part of the tricarboxylic (TCA) cycle. For both enzymes, arginines in the catalytic pocket are mutated. IDH mutations will lead to increased cytoplasmic concentration of 2-hydroxyglutarate (2-HG) and the depletion of NADPH (Turkalp, Karamchandani, & Das, 2014). 2-HG can bind to α-KG dependent enzymes and prevent normal DNA demethylation. Ultimately, the hypermethylation of DNA by IDH1 alters cellular differentiation and leads to the accumulation of premature cells that contribute to oncogenesis and tumour growth (Turkalp et al., 2014).

7.2.2 Detection of IDH Type

IDH status is most commonly obtained by performing immunohistochemistry analysis of the tissue obtained during surgical resection (Louis et al., 2016). The most common mutation, in approximately 90% of mutants, occurs at the arginine (R) 132 site; it is a missense mutation in which the R is replaced by histidine (Louis et al., 2016).

7.2.3 Clinical Relevance

More aggressive tumours have wild-type IDH, whereas when these genes are mutated, the tumours are less aggressive, and survival is improved. A majority of low-grade gliomas carry mutations of IDH-1 or IDH-2, and de-differentiated lower-grade gliomas (secondary GBMs) have a greater proportion of mutant IDH proteins than primary GBM (Prensner & Chinnaiyan, 2011; Zhang, C., Moore, Li, Yung, & Zhang, 2013).

Management of Recurrent Glioblastoma

Studies that have used the combination of surgical resection and chemoradiation suggest only a slight increase in overall survival compared to no treatment (Gallego, 2015). The recurrence of GBM is detected based on imaging surveillance or when the patient reports new or reoccurring symptoms **(Figure 1.7)** (Hou, Veeravagu, Hsu, & Victor, 2006). Once the recurrence of GBM has been confirmed with imaging, management is often determined based on the patients' Karnofsky Performance Score (KSP), age, location, and whether the recurrent GBM is focal or diffuse (Hou et al., 2006).

8. Challenges Associated with Treatment of Glioblastoma

Many features of glioblastoma multiforme make it a very challenging disease to treat with conventional therapies. It is hypothesized that gross total resection may result in increased overall survival; however, the invasive nature of GBM renders complete surgical removal of these tumours nearly impossible (Giese et al., 2003; Lacroix et al., 2001). GBM shows extensive infiltration of the healthy brain, which makes complete surgical removal of the tumour nearly impossible (Giese et al., 2003). After initial surgical resection, GBM will recur in more than 95% of patients within 2-3 centimeters of the resected cavity (Burger et al., 1983). Though only found in approximately 1- 10% of the patients, there have been reports of recurrence of lesions in the contralateral hemisphere of the initial resection cavity (Barnard & Geddes, 1987; Batzdorf & Malamud, 1963).

8.1 Heterogeneity

As indicated by the name Glioblastoma Multiforme, this is morphologically a very heterogeneous tumour (Friedmann-Morvinski, 2014) thus rendering the development of targeted therapies extremely difficult. GBM shows heterogeneity at cytopathological, transcriptional, and genomic levels (Friedmann-Morvinski, 2014). Though there are differences in the latency periods between primary and secondary GBMs, they are morphologically and clinically identical (Friedmann-Morvinski, 2014; Urbanska et al., 2014). Over the last decade, genetic profiling has shown that there are large differences in genetic alteration between the GBM subtypes which makes designing a treatment paradigm difficult (Cancer Genome Atlas Research Network, 2008). The heterogeneity is also hypothesized to contribute to drug resistance and tumour recurrence (Bhatia, Frangioni, Hoffman, Iafrate, & Polyak, 2012).

8.2 Invasiveness

The invasive nature and infiltrative properties within the parenchyma pose additional challenges to the management of GBM (Giese et al., 2003). In many cases, the tumour is located in areas where the blood-brain barrier is intact, which makes delivery of drugs difficult (Blacklock et al., 1986; Cristante, Siepmann, Westphal, Hagel, & Hermann, 1992). In recent years there have been many failed attempts to improve prognosis with targeted drug delivery methods (Le Rhun et al., 2019).

9. Role of Reoperation

Currently, the optimal first-line of treatment for patients with recurrent GBM is unknown and is often dependent on the treating physician (Hou et al., 2006). Despite the lack of clinical evidence of benefit, repeat surgical resection is performed in over 25% of patients with recurrent GBM (Gallego, 2015).

Cha et al., 2000 suggested that age and preoperative performance scores were significant positive predictive factors for repeat resection (Cha, S. et al., 2000). Other studies have shown that repeat resection provided an improved response to chemotherapeutic treatments with temozolomide (Barker et al., 1998). A tumour size of less than 10 centimeter3 has been suggested to have greater responsiveness to temozolomide (Keles, Lamborn, Chang, Prados, & Berger, 2004). Individuals with tumour located in non-critical areas, high pre-operative performance scores, and severe local mass effect may benefit from repeat surgical resection (Hou et al., 2006).

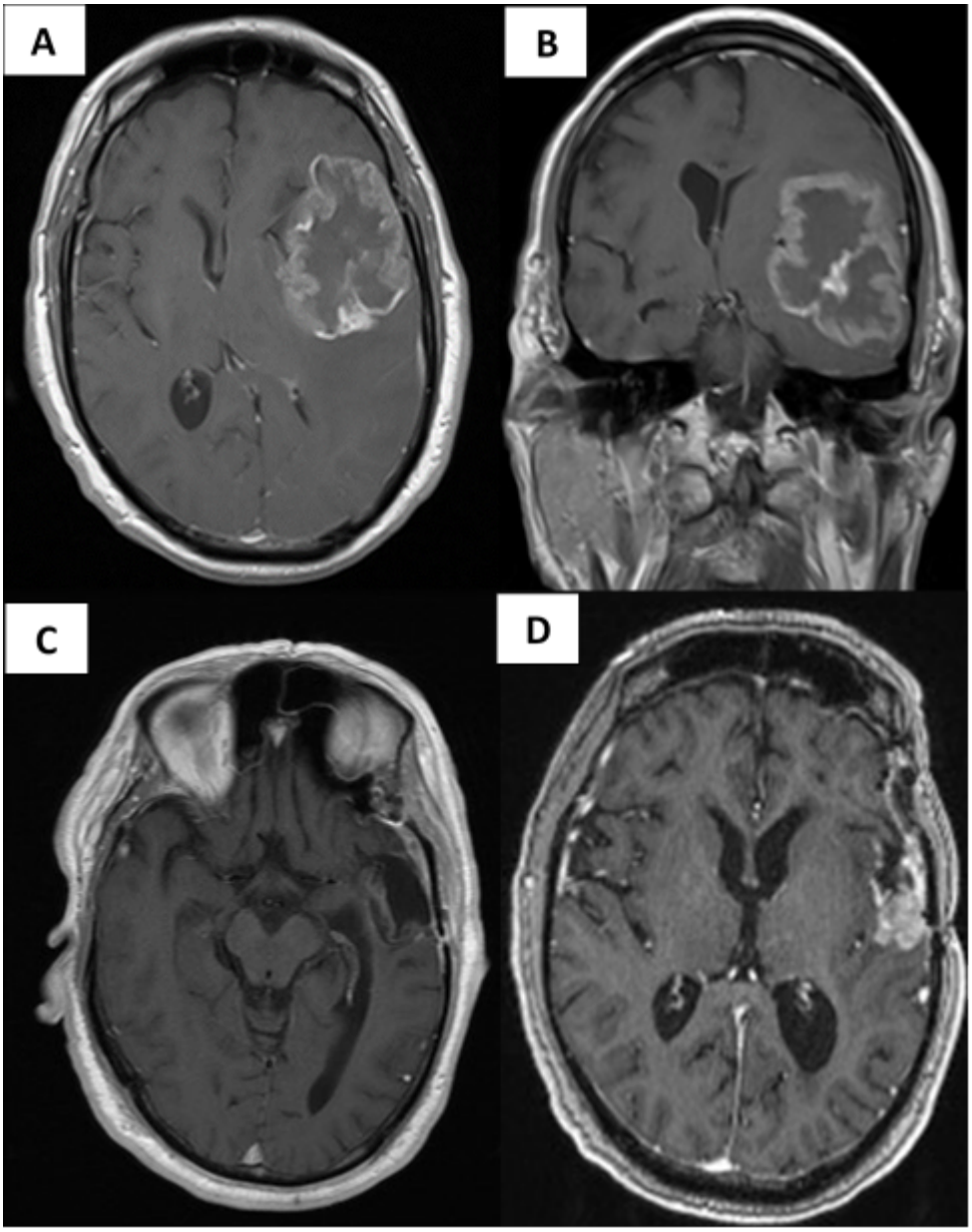

Figure 1.7. MRI images of local recurrent glioblastoma. **A and B.)** Axial and coronal MRIs at the initial diagnosis of GBM, respectively. **C.)** MRI scan showing the surgical cavity following initial resection. **D.)** MRI acquired at the time of symptomatic recurrence, 7 months after initial surgery.

Chapter 2: Clinical Uncertainty and Equipoise in the Management of Recurrent Glioblastoma

2.1 Introduction

Recurrence of the GBM becomes a problem as a result of progressive neurological deterioration, or can remain asymptomatic, with growth discovered on serial imaging. If the prognosis of GBM at initial diagnosis is grim, it is worse at time of recurrence, and how to best manage patients with recurrent GBM remains uncertain. In many centers, general neurosurgeons are frequently called on to manage or provide an opinion on these cases, and a wide range of conducts are considered acceptable. On one end of the spectrum, some neurosurgeons do not offer repeat resection given the dismal prognosis. On the other end, others are more aggressive, using cytoreduction and symptom control as justification. Many clinicians between these extremes attempt to select candidates case-by-case for repeat resection according to resectability, past experience, or for other reasons.(Helseth et al., 2010; Sonabend et al., 2017). Although the clinical context commonly calls for action such as repeat resection, the potential benefits of reoperation compared with other management options has yet to be shown in a randomized clinical trial (RCT) (Archavlis, Tselis, Birn, Ulrich, & Zamboglou, 2014; Clarke et al., 2011; Michaelsen et al., 2013; Ryken, Kalkanis, Buatti, & Olson, 2014; Suchorska et al., 2016; Yong et al., 2014).

Randomized trials of neurosurgical treatments remain difficult to conduct (Mansouri, Cooper, Shin, & Kondziolka, 2016; Walid, Robinson III, & Robinson, 2012). A common conception regarding the propriety of randomly allocating treatment options is that there should be sufficient disagreement, uncertainty, or “equipoise” in the expert community regarding how best to proceed in order to justify a trial (Fahed, 2019; Freedman, 2017). Methods to measure such uncertainty have recently been described (Fahed, 2019; Fahed, Darsaut, Farzin, Chagnon, &

Raymond, 2020). The goal of the this study was to measure the degree of clinical uncertainty or equipoise among general and neuro-oncology trained neurosurgeons by testing the repeatability of decisions to reoperate versus other management options for a series of diverse patients with recurrent GBM.

2.2 Methods

A systematic review was first carried out using the Cochrane, EMBASE, and Medline databases to search for previously conducted studies on interobserver agreement, uncertainty, variability, or equipoise concerning the management of recurrent GBM. Details of the search strategy are available in the Appendix section of this thesis.

We then designed and conducted an interobserver study to measure clinical uncertainty and equipoise according to a published framework, which presupposes that a dilemma concerning the use of at least 2 management options exists (Fahed et al., 2020). The general method is that a sufficient number of diverse individual patients sharing a similar clinical problem and covering a wide spectrum of clinical presentations be assembled into a portfolio that is then submitted to a variety of clinicians who routinely manage patients with the clinical problem. These clinicians are then asked to independently choose one of the predefined management options selected from those that would be compared within a randomized trial that would address the clinical dilemma. The idea is not to discover the "right treatment" by tabulating the most frequently proposed option for each patient, but to measure whether sufficient uncertainty exists to design and justify a trial (Fahed et al., 2020).

2.2.1 Portfolio of Patients

The number of clinicians and cases necessary to provide meaningful results in a measurement of equipoise study was estimated to be >10 clinicians evaluating 30 to 50 patients.(Donner & Rotondi, 2010; Fahed et al., 2020). An electronic portfolio composed of select magnetic resonance images acquired from 37 anonymized patients with pathology-confirmed GBM, at time of follow-up imaging or symptomatic recurrence at least 3 months from time of initial resection was assembled (**Figure. 2.1**). Patients were selected from a database of tumor patients managed at the University of Alberta between January 2002 to January 2019. For each case, at least 2 representative postgadolinium magnetic resonance images were presented along with some pertinent clinical data: age, sex, Karnofsky Performance Score (KPS), and the number of months since initial resection. To ensure that the portfolio (and the study of the repeatability of the clinical judgments) would include a wide variety of patients covering the entire clinical spectrum, and to minimize paradoxes known to occur with κ statistics (Cicchetti & Feinstein, 1990; Feinstein & Cicchetti, 1990), one third of cases were selected because they were estimated to be favorable for repeat resection, 1/3 not favorable for repeat resection, and 1/3 “gray zone” cases, according to the judgment of the senior neurosurgical author (T.E.D.), based on the following criteria: age, performance status, and tumor location (eloquence of involved brain). Fifteen of the 37 included patients (41%) actually underwent repeat resection.

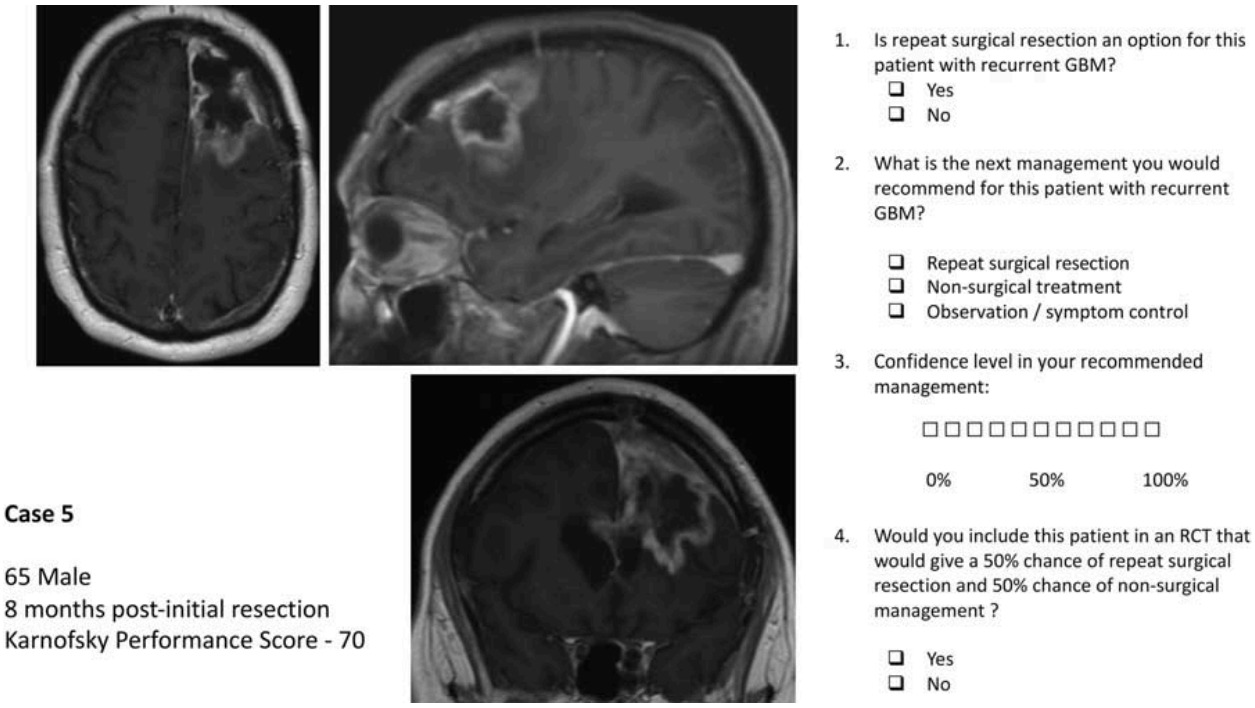

Figure 2.1. Typical case included in the portfolio of pathology-confirmed recurrent glioblastoma patients.

For each patient, clinicians were asked the following questions: (1) Is repeat surgical resection an option for this patient with recurrent GBM, Y/N? (2) What is the next management option you would recommend for this patient with recurrent GBM? (Responders chose from: Repeat surgical resection, Nonsurgical treatment, or Observation/Symptom control.) (3) Confidence level in your recommended management: (0% to 100%). (4) Would you include this patient in an RCT that would give a 50% chance of repeat surgery and a 50% chance of nonsurgical management Y/N?

2.2.2 Clinicians

Because the question concerns whether or not general neurosurgeons should reoperate, the portfolio was circulated to a wide diversity of practicing neurosurgeons (n=44) from different countries, with or without neuro-oncology training, and with varying years of experience. All of the neurosurgeons surveyed manage patients with GBM, have previously responded to requests for assessment of interobserver variability, and are considered to be prospective trial participants for an RCT addressing the clinical dilemma. Anonymity was assured but some demographic information was collected. Each responder had to complete the survey independently. Ten clinicians who responded to the first request in a timely fashion were asked to complete the survey a second time, with case order permutated, at least 4 weeks apart for the intraobserver portion of the study.

2.2.3 Statistical Analysis

Agreement on best next management was analyzed for all 3 choices, and then in a dichotomized manner (repeat surgery vs. other nonsurgical management), using Fleiss κ statistics with 95%CIs. κ scores were interpreted according to Landis and Koch (0 to 0.2, slight; 0.21 to 0.4, fair; 0.41 to 0.6, moderate; 0.61 to 0.8, substantial; 0.81 to 1.0 perfect agreement) (Landis & Koch, 1977). Differences between point estimates, or between κ values were considered to exist when CIs did not overlap. Confidence in decision-making (scale of 0 to 10) was analyzed with analysis of variance and differences between proportions with Fisher exact tests. All analyses were conducted by a statistician (M.C.) using STATA Version 16 and SPSS Version 25 and a significance level of 5%.

2.3 Results

The systematic review did not yield any previous interobserver variability studies on best management of recurrent GBM. The search strategy yielded 132 titles, 122 of which were rejected by reading the titles, 3 further were rejected after reading the abstracts. A total of 7 articles were given full-text review; however, none were identified as being an agreement or interobserver variability study on the management of recurrent GBM. The entire search strategy is available in the Appendix.The characteristics of patients included in the portfolio and responder demographics are presented in **Table 2.1**. Twenty-six of the 44 neurosurgeons (59%) responded to the survey. Responders had the following experience in managing patients with GBM: 0 to 5 years (n=5), 6 to 10 years (n=5), and ≥11 years (n=16). Five neurosurgeons (5/26 [19%]) had fellowship training in neuro-oncology, 4 of whom had 11 or more years of experience.

Table 2.1. Characteristics of Patients Included in the Portfolio and Surgeon Responder Demographics.

Patient Characteristics	Number of Patients, n (%)	Responder Demographics	Number of Responders, n (%)
Total	37	Total	26
Male	21 (57)	Practice location	
Tumor location		North America	18
Left hemisphere	19 (51)	Europe	8
Right hemisphere	15 (41)	Neuro-oncology Fellowship Training	
Bilateral involvement	3 (8)	Yes	5 (19)
Patient age (y)		No	21 (81)
≤50	9 (24)	Experience managing GBM	
51-60	15 (41)	0-5 y	5 (19)
≥61	13 (35)	6-10 y	5 (19)
Karnofsky Performance Score (KPS) at time of consideration for reoperation		11 or more years	16 (62)
≤70	21 (57)		
≥80	16 (43)		
Actually underwent repeat resection			
Yes	15 (41)		
No	22 (59)		

For each case, at least 1 responder considered repeat surgical resection to be an option. Each of the 37 cases was evaluated by 26 responders, yielding 962 responses. Repeat surgical resection (429/962 [44.6%,95%CI: 0.41-0.48]) and nonsurgical treatment choices were chosen with almost equal frequency (424/962 [44.1%,95%CI:0.41-0.47]), followed by observation/symptom control (109/962 [11.3%,95%CI:0.09-0.13]). There was a wide disparity between the number of cases each neurosurgeon would elect to reoperate: individual choices for repeat surgery ranged from 3/37 cases (8%) by a senior North American neurosurgeon (>11 y experience) to 33/37 (89%) by a North American neurosurgeon with 6 to 10 years experience. Repeat surgery was chosen overall a mean of 18.2±2.6 times/37 cases, or 49% of the time by the 26 surgeons. Number of votes for reoperation according to patient characteristics and surgeon-related factors are presented in **Table 2.2**. Surgeons from North America and from Europe were not significantly different in the number of times they recommended reoperation for GBM. Having a neuro-oncology fellowship training background, or having different years' experience did not significantly increase the likelihood of recommending reoperation. Patient characteristics such as age, KPS, and tumor location in the right versus left hemisphere did not significantly change recommendations, with the exception of having bilateral recurrence, for which surgeons were significantly less likely to choose reoperation: Yes to repeat surgery was chosen 18.9% (95%CI: 11%-29%) of the time for bilateral recurrence compared with 43.6% (95%CI: 39%-48%) for left and 50.3% (95%CI: 46%-56%) Yes votes for right hemisphere recurrences.

Table 2.2. Number of Votes for Re-operation and Inter-rater Agreement Regarding Best Next Management Choice.

	Total Number of Yes Surgery Votes (%, 95% CI)	Point Estimate CI Overlap	Dichotomized κ (95% CI)	κCI Overlap
Surgeon responders (n = 26)	413/962 (42.9, 39.8-46.1)	NA	0.198 (0.133-0.276)	NA
Training background				
Neuro-oncology fellowship training	93/185 (50.2, 43.1-57.4)	Yes	0.167 (0.055-0.314)	No
None	342/777 (44.0, 40.6-47.5)		0.601 (0.556-0.646)	
Years of experience				
0-5 y of experience	76/185 (41.0, 34.2-48.3)	Yes	0.090 (0.027-0.178)	Yes
6-10 y of experience	89/185 (48.1, 41.0-55.3)		0.211 (0.069-0.393)	
11+ years of experience	248/592 (41.9, 38.0-45.9)		0.181 (0.112-0.269)	
Practice location				
North America	319/666 (47.9, 44.1-51.7)	Yes	0.528 (0.488-0.563)	No
Europe	127/296 (42.9, 37.4-48.6)		0.436 (0.394-0.478)	
Portfolio cases (n = 37)				
Patient age (y)				
≤50	113/229 (49.4, 42.9-55.8)	Yes	0.428 (0.388-0.473)	No for ≤50 vs. ≥61
51-60	162/387 (41.8, 37.1-46.8)		0.488 (0.407-0.523)	
≥61	152/346 (43.8, 38.8-49.2)		0.554 (0.511-0.634)	
Tumor location				
Left hemisphere	217/498 (43.6, 39.3-48.0)	No for left vs. bilateral	0.338 (0.295-0.393)	No for left vs. right hemispheres, no for left vs. bilateral
Right hemisphere	196/390 (50.3, 45.6-55.5)	No for right vs. bilateral	0.415 (0.395-0.474)	
Bilateral involvement	14/74 (18.9, 11.3-28.6)		0.573 (0.418-0.622)	
Karnofsky Performance Score				
≤70	227/491 (46.2, 41.9-50.7)	Yes	0.484 (0.428-0.517)	Yes
≥80	199/471 (42.2, 37.9-46.8)		0.469 (0.413-0.526)	

CI indicates confidence interval; NA, not applicable.

The case with the greatest number of Yes votes for reoperation (22/26, 84.6%) was a 49-year-old male (case 25) with recurrent GBM in the left temporal lobe and a KPS of 70. The case with the fewest number of Yes responses (1/26, 3.8%) was a 35-year-old male (case 13) with a bilateral GBM in the pineal region, and a KPS of 70 (**Figure. 2.2**).

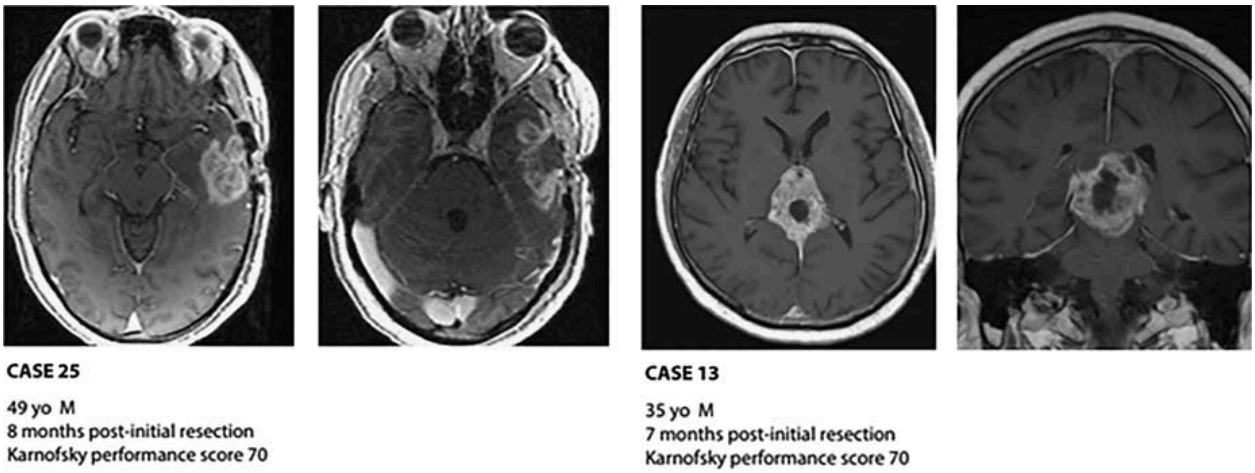

Figure 2.2. Cases with the highest (22/26, 84.6%) and lowest (1/26, 3.8%) number of Yes votes for repeat resection.

Overall agreement regarding the next best management option was slight (according to Landis and Koch) for patients with recurrent GBM (κ[95%CI]:0.148[0.102-0.209]) (nondichotomized data and percent agreement are available in **Table A2.4** within the Appendix. Agreement remained slight when responses were dichotomized into surgical management vs. the other management options (κ [95%CI]=0.198[0.133-0.276]). Agreement between surgeons was not better when location of practice, or years' experience were considered (**Table 2.2**). Those with additional expertise in neuro-oncology disagreed with each other about which cases they would reoperate even more (κ=0.167 [0.055-0.314]) than those without neuro-oncology fellowship training (κ=0.601 [0.556-0.646]).Responders were no more likely to agree on management of recurrent GBM in the right compared with the left hemisphere. KPSs greater or less than 70 did not influence agreement, but surgeons were more likely to agree on the management of patients older than 60 compared with patients less than 50 years of age (**Table 2.2**).Seven of 10 requested surgeons responded to the portfolio twice (**Table 2.3**). Intra-observer agreement remained poor

and below substantial (<0.61) for all responders except 1: an experienced (≥11 y) North American surgeon without neuro-oncology fellowship training.

Table. 2.3. Inter-rater Agreement Regarding Best Next Management Choice for Recurrent Glioblastoma

	Nondichotomized κ for All Cases (n = 37)	Dichotomized κ (Surgery vs. All Others)	Interpretation*
Rater 1	0.140 (–0.130, 0.490)	0.130 (–0.212, 0.473)	Slight
Rater 2	0.720 (0.498-0.929)	0.668 (0.402-0.934)	Substantial
Rater 3	0.300 (0.048-0.568)	0.308 (0.002-0.613)	Fair
Rater 4	0.459 (0.165-0.723)	0.532 (0.255-0.809)	Moderate
Rater 5	0.080 (–0.229, 0.391)	0.081 (–0.229, 0.391)	Slight
Rater 6	0.295 (0.025-0.581)	0.228 (–0.062, 0.518)	Fair
Rater 7	0.220 (0.025-0.407)	0.164 (–0.242, 0.570)	Slight

*According to Landis and Koch.[20]

Overall, the self-assessed surgeon's confidence that the selected management was best on an 11-point scale (11 categories from 0% to 100%) was 8.7/11 (95%CI:8.3-9.2). European surgeons expressed slightly less confidence in their recommendations (North America: 8.9/11 [95% CI:8.4-9.1], Europe: 7.4/11 [95%CI:7.2-7.9]). Having fellowship training in neuro-oncology was also associated with lower confidence (7.3/11 [95%CI:7.1-7.5]), compared with not having such training (8.5/11 [95%CI:8.2-8.7]). After the first 5 years of practice, surgeons expressed more confidence in their recommendations: 0 to 5 y (5.8/11 [95%CI:5.6–6.1]), compared with 6 to 10 years (7.7/11 [95%CI:7.3–8.1]), and 11 or more years (7.6/11 [95%CI:7.4–7.7]). The mean confidence score of the 7 responders that answered the portfolio twice (7.6/11 [95%CI:6.6-8.6]) was comparable to that of the 19 raters that only responded once (6.6/11 [95%CI:5.7-7.5]).

Surgeons agreed to randomized trial inclusion 657/962 times (68.3%, 95%CI:0.65-0.71). For 26/37 (69%) cases, a majority (51%) of responders were willing to include the patient in a randomized trial comparing repeat surgery to any other management. When surgeons agreed to

include the patient in a randomized trial, they also had less confidence in their recommended management (confidence scores of 6.8/11 [Yes to RCT] vs. 8.5/11 [No to RCT], P<0.01).

2.4 Discussion

While patients commonly seek "second opinions," the reliability of medical recommendations is infrequently tested in real-world practice. We did not find any previous interobserver reliability studies on management recommendations for recurrent GBM in our systematic review. Unlike surveys which look for a majority opinion (Sonabend et al., 2017), regarding generic or theoretical case scenarios, this novel type of study follows the principles and methods of interobserver reliability studies on the repeatability of clinical judgments made on individual patients. The degree of clinical uncertainty or equipoise within the surgical community is measured by testing the likelihood of receiving the same response when the same patient is presented to a different surgeon or to the same surgeon twice (Fahed, 2019; Fahed et al., 2020).

The clinical dilemma we wanted to test in this study concerns the propriety of performing repeat surgery for recurrent GBM patients in routine practice. This type of dilemma calls for a different type of clinical trial than most clinical research which aims to verify the promising benefit of a therapeutic innovation (Raymond, Darsaut, & Altman, 2014). An agreement study can be done before the conduct of a pragmatic trial to ensure that sufficient community equipoise about the options exists. We found little agreement among surgeons regarding whether or not to offer reoperation to patients presenting with recurrent GBM. Clinicians' characteristics, such as sharing a country of practice, having more years of experience, or background specialty training in neuro-

oncology did not change the level of agreement. The lack of agreement existed even though clinicians were typically confident in their individual decisions.

The uncertainty we documented may not be surprising, for the lack of reliable knowledge of how best to proceed with these patients is well-documented in the literature (Robin, Lee, & Kalkanis, 2017), with opinions and recommendations for (Archavlis et al., 2014; Michaelsen et al., 2013; Suchorska et al., 2016; Yong et al., 2014), and against reoperation (Clarke et al., 2011; Gorlia et al., 2012). However, the level of uncertainty is particularly high here, for most clinicians questioned twice on the best management of the same patients did not agree with themselves (Fahed et al., 2020).

This suboptimal situation, in which no one really knows how to best care for individual patients, does have an upside: with clinical community uncertainty measured to be substantial (k=0.198), the potential for recruitment in a randomized trial is high (Fahed et al., 2020). This study supports the need for a trial that examines the question of whether or not reoperating on recurrent GBM patients is worthwhile. The fact that a majority of clinicians were willing to offer, to a majority of patients, participation in a randomized trial is a step in the right direction. One such trial is underway (Schucht P, 2020).

Limitations of this study include the relatively small number of responders, and the artificial nature of the context of the survey. A different set of cases, or different responders may have led to different results. Our choice of a heterogeneous case and responder mix does however improve the generalizability of results to routine practitioners. Cases of radiation injury, which can

sometimes mimic tumor recurrence, may have been present in the portfolio, as not all cases were re-confirmed with pathology. We limited the amount of clinical information provided for each case to minimize disagreements based on various interpretations. How much information should be included in such studies is a difficult methodological question (Fahed et al., 2020). While clinicians may commonly look for "reasons" to decide one way or another in order to manage the uncertainty, additional information also increases the risk of clinicians disagreeing for extraneous reasons. Details of molecular profiles, chemotherapeutics, or time since last radiation treatment were not included, as these details could have influenced decision-making to a different degree. Similarly, the commonly proposed indications for repeat resection (raised intracranial pressure, progressive neurological deficits, and recurrent seizures) (Helseth et al., 2010), were not included. These details were not provided, because the purpose of our study was not to identify all the potential reasons clinicians might disagree on a particular case, but rather to measure the clinical uncertainty that remains even when reasons for potential disagreement are minimized.

In the spirit of pragmatic clinical research (Schwartz & Lellouch, 1967), we did not restrict our evaluation to neuro-oncology experts from academic or research centers. Such a selection would have affected generalizability of results, for the clinical dilemma commonly confronts general neurosurgeons that are regularly called upon to decide whether or not to reoperate on such patients. They are the clinicians that would participate in a pragmatic RCT on this clinical dilemma. It is interesting to notice that neuro-oncology surgical experts themselves showed even more uncertainty in the management of these patients.

Finally, answering a survey and seeing a real patient in clinic are very different things. One can only hope that surgeon responders took the time and care in answering the survey questions that they would normally devote to a clinical interaction.

Participation in studies that reveal clinical uncertainty may be a humbling experience, but one that can help modify the way we practice. It is promising that a significant proportion of responding surgeons were willing to include a majority of patients in a randomized trial. Physicians and patients' perceptions regarding the role of randomized trials in medical care may have to be modified if we are to practice outcome-based medical care (Raymond, Jean et al., 2014; Raymond, Darsaut, & Roy, 2019; Raymond, J., Magro, & Darsaut, 2018). In the meantime, while we still do not know how best to manage patients with recurrent GBM, the results presented here may promote participation in an RCT that properly addresses the dilemma.

2.5 Conclusion

The best management of patients with recurrent GBM remains uncertain. Neurosurgical decision-making for these patients is characterized by much uncertainty and poor agreement, regardless of patients' or clinicians' characteristics, including years of experience or having a neuro-oncology background. This demonstration of community uncertainty and equipoise supports the need for a randomized trial.

Chapter 3: Understanding the Differences Between Explanatory and Pragmatic Trials

Introduction

Randomized controlled trials (RCTs) are widely considered to be the gold standard for measuring the safety and efficacy of an intervention. RCTs are prospective, quantitative, and comparative in nature, and can be conducted on a large scale. The results of RCTs are recognized as essential to guide clinical care in all medical and surgical disciplines, including neurosurgery.

A multitude of published systematic reviews conclude the same way: there is a pervasive lack of good quality evidence, specifically in the form of randomized clinical trials, to guide clinical decision-making in almost all fields of medicine. One of the recommendations for conducting a trial is that a new trial protocol be registered and publicly available to ensure that the eventual published trial result matches pre-specified hypotheses and statistical analyses, and to prevent needless duplication of effort (Chan, Hrobjartsson, Jorgensen, Gotzsche, & Altman, 2008; Greenberg, Jairath, Pearse, & Kahan, 2018). It is encouraging that on average, more than 350 new clinical trial protocols are registered with the largest such website (ClinicalTrials.gov) each week, but many trials are at risk of termination as a result of improper trial design and conduct, in addition to the poor recruitment (Califf et al., 2012; Califf & Sugarman, 2015). Issues surrounding trial design ought to be at the forefront of medical education, and high-quality, ethical trials promoted at every level, but the large majority of physicians and surgeons do not receive formal training in how to properly design randomized trials.

This chapter will contrast the differences between pragmatic and explanatory research ideologies and discuss how a recently described new type of trial known as a care trial can be used to guide clinical practice under uncertainty. We will briefly review some of the classical teaching on different trial designs that prospective designers invariably must choose from when they set out to design a trial. We will conclude that the desire for "randomized information" to guide *future*

decision-making to help *future* patients should not be the main consideration when designing a trial. Instead, the ethical care of *current* patients that are being proposed trial participation must take primacy (as it does in normal clinical care), and that benefits following from gain of information, if any, must be secondary.

3.1 Explanatory trials mimic laboratory experiments

The explanatory attitude in the design of clinical trials is inspired from the laboratory. The goal of scientific experiments conducted in a laboratory is to reveal phenomena or mechanisms that would otherwise go unnoticed under normal non-laboratory circumstances. The main laboratory strategies used to detect a causal signal, and the relation to explanatory trials are reviewed in **Table 3.1.**

Table 3.1. The relationship between laboratory research and explanatory trials.

Goal	In the laboratory	Explanatory trials	Caveat
Reliably produce an outcome (a phenomenon)	Select an experimental model	Select patients more likely to have the outcome	Too hard or too easy a model and both treatments may fail or both may succeed; nothing is shown
Reliably show an effect of treatment	Select the model that responds to the treatment	Select patients more likely to respond or be compliant	May not apply to most patients
Isolate the signal	Compare with sham (everything other than 'the cause' being equal)	Placebo controlled or sham-controlled RCT	Ethically problematic if treatments exist
Reduce noise from variations between individuals	Same animals, same litter	Narrow patient selection criteria to reduce standard errors (and sample size)	Chosen target may be the wrong one (Nobody really knows in whom the treatment works)
Reduce potential confounding effects	Healthy animals kept in the controlled environment of the lab (same diet, same activity etc…)	Exclude patients with any confounding disease or factor	May not apply to real patients who almost always have confounding factors
Reduce noise from variations between experiments	Rigid protocols in a controlled environment (lab)	Rigid treatment protocols performed in few expert centers	Treatments and results may become impossible to reproduce in real world practice
Increase or multiply the signal	Look for microscopic or molecular signals	Surrogate outcomes or biomarkers	May not be pertinent to patients
Other strategies	Exclude stray results	Per-protocol analyses	Inappropriate to a science of medical practice
Increase representativity by random selection of subjects	Almost never done in the laboratory	Almost never done in clinical trials	Inappropriate to a science of medical practice
Minimize bias in the evaluation of results	Masking of treatment groups	Blinding and masking of treatment groups	Crucial whenever possible in all scientific studies
Randomized allocation to treatment groups	Rarely done in the laboratory (but should be done)	Randomized allocation of treatment options	Should always be done

The idea is to tightly control all variables, including the variable of interest. When this isolated variable is modified or manipulated in one group of subjects as compared to another, all other things being equal, the consequence of that manipulation can be determined. This approach can then be applied one variable at a time, for all the known or hypothesized variables.

The effects of systematically manipulating one variable at a time are recorded, and the information thus obtained can be used to try to *explain* the phenomenon under investigation; HOW it works. Emphasis is placed on "*explain*" because this is the approach used in explanatory trials. Emphasis is also placed on HOW, because this approach is decidedly better suited to understanding the mechanisms of diseases or of treatments, rather than to study whether or not the treatment that will subsequently be proposed actually accomplishes what it is supposed to accomplish in practice.

3.1.1 Explanatory aspects of a randomized trial

An RCT is said to be "explanatory" when clinical variables are tightly controlled (**Table 3.1**). Explanatory research aims to 'understand' a theory, a mechanism, or a proof-of-principle. For example, a trial designer could choose to strictly limit selection criteria to only a certain type of patient and circumstance, chosen to best reveal 'a causal signal' (ie: patients and circumstances best suited to show that a treatment effect exists). To use a neuro-oncology example, an explanatory trial strategy would be to limit inclusion within a GBM repeat resection trial to only patients under 50 years of age with good Karnofsky performance scores, and gliomas located in non-eloquent brain regions. Designers could also choose to include only elite, neuro-oncology trained surgeons, and they could request proof that each participating surgeon had performed a minimum number of repeat resections performed (say 50 GBM patients, in the last 2 years, with

an acceptable morbidity rate). This selection is used to ensure that potential treatment effects are not diluted or diminished by less-than-optimal surgical expertise or performance. Explanatory trials sometimes include "run-in" phases to try to ensure patients (and surgeons) will be compliant with treatment protocols, and that they react and respond in the expected fashion. Explanatory trials often require additional tests to rule out the influence of other clinical entities which could "contaminate" the trial results. They can also reveal effects on disease markers that do not necessarily translate into better clinical outcomes, such as a mandatory post-op MRI of the brain to ensure a protocol-mandated acceptable extent of resection (EOR) has really been achieved. All these 'explanatory' elements are geared towards 'understanding' abstract theory. Explanatory trials are usually strictly monitored, and research-specific staff are tasked with ensuring adherence to the study protocol. The aforementioned requirements are justified by the ultimate goal of the enterprise: Can treatment work under idealized circumstances, designed to show any signal of an effect?

As we will discuss in more detail, and as shown in **Figure 3.1**, if a highly controlled (explanatory) trial does manage to provide positive results, they are not generalizable to the larger population. Using the neuro-oncology example, if an explanatory RCT showed that repeat resection in highly selected (young, otherwise healthy patients with right frontal tumours) and elite surgeons led to better outcomes, the explanatory trial design would ensure that the results would not be applicable to the much larger proportion of recurrent GBM patients. This is because most GBM patients are older than 60, have tumours located in brain areas that are not necessarily amenable to aggressive repeat resection, and most will be managed by general neurosurgeons. In fact, strictly speaking, the only thing that a highly explanatory trial like this could ever actually show is that recurrent GBMs should never be re-operated.

Table 3.2. Design distinctions between explanatory and pragmatic randomized clinical trials.

	Explanatory	Pragmatic
Question	Can the treatment work under ideal controlled conditions?	Does the treatment work in normal clinical conditions?
Patient Eligibility	Very selective, limited to the ideal and compliant patients	All patients with target disorder
Physicians	Select only the best physician with high level of experience and expertise	Normal expertise
Treatments	Closely monitored specifications	Standard care
Follow-up test and Intensity	Frequent visits and special tests to assess the biological responses	Routine practice
Outcomes	Restricted to biological mechanistic outcomes	Clinical outcomes

* Table modified from (Sackett, 2006)

3.2 Pragmatic trials

In a pragmatic trial, the emphasis is not on theory, or proof of principle. The main goal of a pragmatic trial is to find out whether the theorized intervention actually works in practice (**Table 3.2**). To mimic the real world more closely, fewer (or no) controls are placed on known "variables". Loose inclusion criteria, to permit the inclusion of all or almost all routine patients, no explanatory "run-in" phases to demonstrate patient and surgeon compliance, and acceptance of the heterogeneity of clinical circumstances and surgical skills and technologies that are in current routine use in the real world. In this context, with a positive pragmatic trial, results can immediately change practice: they can immediately be applied to the real world, because the results were obtained under real-world circumstances.

3.2.1 Interpretation of the results of a randomized trial

What clinicians need are positive pragmatic trials to guide practice. What they most often get are positive explanatory trials that are being passed off as pragmatic trials.

	Conclusion From this Trial	
	Positive Results	**Negative Results**
Explanatory Trials	Ambiguous results	Clearly sensible to abandon this treatment
Pragmatic Trials	Clearly worthwhile to adopt this treatment	Ambiguous results

Figure 3.1. Conclusions that can be drawn from pragmatic and explanatory trials. This figure is one of the most important, and unfortunately least respected, determinants of how a trial should be designed to inform clinical practice.
* Figure modified from (Sackett, 2006)

Explanatory Trial Designs Should have Almost no Place in Clinical Medicine

The classic teaching is that both explanatory and pragmatic trials hold scientific value, and that the onus is on investigators to choose the proper trial design best suited to answer their question of interest. An example of an explanatory trial would be a Phase 1 study, conducted by a pharmaceutical company trying to understand the metabolism of a new drug. Conditions of such studies are strictly controlled; patients are highly selected and tested to minimize the chances of unwanted events, the study protocol is carefully monitored, and adherence assured. It is almost certain that the results will not be applicable to someone who has comorbidities such as diabetes or hypertension, or who doesn't take their prescribed medicines.

There is an acceptable context for these kinds of experiments to be conducted, but these explanatory trials are clearly unsuitable for clinical medicine. In fact, the ethical distinction between explanatory and pragmatic trials was clearly delineated more than 50 years ago by Schwartz and Lellouch: 'Fundamental research aimed at the verification of a biological hypothesis is done on a …population which is ultimately treated as means rather than as an end…Normally, explanatory work must be done on animals, therapeutic trials on human subjects being limited to pragmatic experiments' (Schwartz & Lellouch, 1967); This paper has been cited over 1400 times.

3.3 How to Evaluate Where a Trial Falls on the Explanatory-Pragmatic Continuum

Nonetheless, it remains true that many all-too explanatory trials are published; in 2003, a group examined the number of RCTs identified on Pubmed from 1976-2002, and found 168 000 RCTs, only 95 of which were pragmatic trials (Treweek & Zwarenstein, 2009; Vallve, 2003). We will discuss some of the unfortunate reasons that explanatory trials are more common in section

3.4 (Forces that promote "explanatory" features in trial design). From the perspective of a practising clinician reading the published literature, they must decide whether or not a newly published trial should impact their clinical practice. In other words, readers require a measure of how explanatory or pragmatic the published trial is, with the former having only a minimal clinical impact (if any), while a well-done positive pragmatic trial should trigger a change in practice.

To help readers differentiate explanatory from pragmatic trials, the Pragmatic Explanatory Continuum Indicator Summary tool (PRECIS) was introduced in 2008 (Thorpe et al., 2009), and then refined in 2015 (PRECIS-2) (Loudon, Treweek, Donnan, Thorpe, & Zwarenstein, 2015). PRECIS-2 evaluates trials along 9 domains, each of which are given a score from 1 (very explanatory) to 5 (very pragmatic): Eligibility, Recruitment, Setting, Organization, Flexibility (in delivery), Flexibility (in adherence), Follow-up, Primary outcome, and Primary Analysis. PRECIS-2 results are presented as wheels, with spokes of different lengths (**Figure 3.2**).

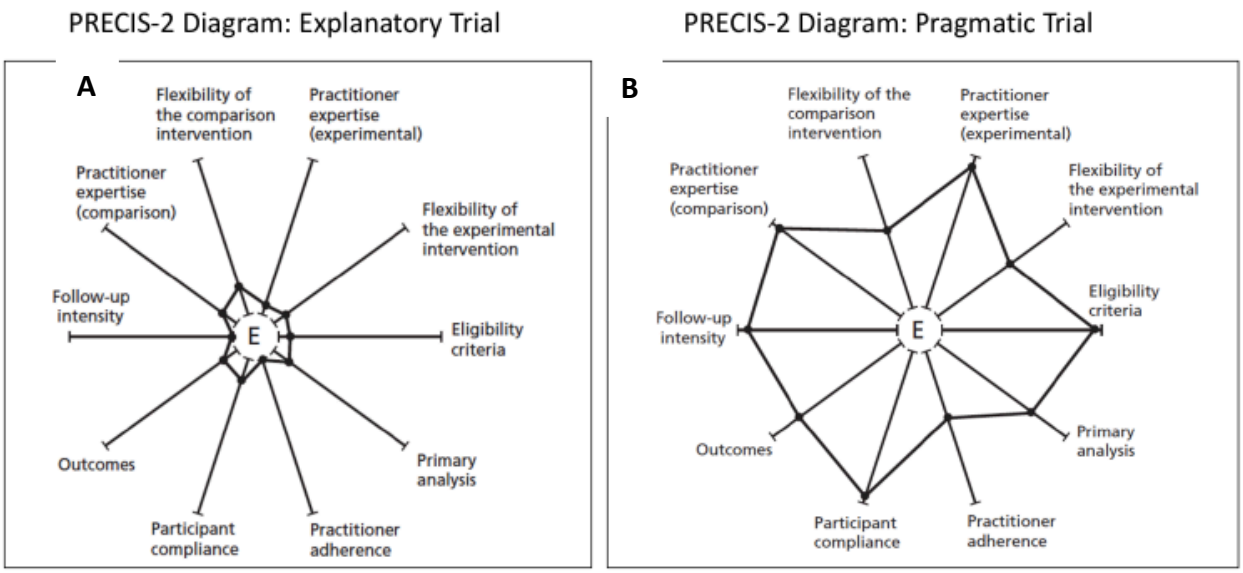

Figure 3.2. Results of PRECIS-2 tool to determine to which extent a trial should influence clinical practice. Panel A) represents an explanatory trial with small surface area, while Panel B) represents a pragmatic trial with larger surface area.

3.4 Forces that promote "explanatory" features in trial design

In the real world, within as well as outside the scientific realm, there are many forces that can influence the design of scientific studies. Because RCTs are widely recognized to be the gold standard for evaluating the safety and efficacy of a drug or intervention, a positive trial result is a potentially 'powerful' result, which can create or open up major markets. Many scientific endeavours are not truly interested in discovering the real-world truth about a matter, rather most trials are attempts to try to obtain a pre-determined result. Research means big business; in 2019 for example, the pharmaceutical industry spent $83B on research and development (Congressional Budget Office, 2021). Of the 245 999 clinical trials registered with ClinicalTrials.gov between 2000 and 2019, 48 668 (36%) of them were funded by industry (Gresham, Meinert, Gresham, & Meinert, 2020). It is understandable that a powerful company, for example, might want to ensure

that a 10-year investment in a product would be accompanied by a "positive" trial result, and they would want to design a trial accordingly. To show their product in a good light, they will make sure only the right types of patients receive their products. Another reason is tied to the prevalent views (influenced by industry, no doubt) of regulatory bodies such as the Food and Drug Administration (FDA). The FDA associates explanatory trial design with well conducted, replicable, and reliable science; therefore, in doing so they favour trials that are inapplicable to decision-making in normal practice (Treweek & Zwarenstein, 2009).

For those with more limited funding, such as most academics, cost considerations also have a strong influence on trial design choices. One trick believed to decrease the sample size and thus render trial completion supposedly faster and less expensive, is to make a trial as explanatory as credibly possible, and then try to pass it off as applicable at a large scale, as if it had been pragmatic. To accomplish this feat, trial designers attempt to control those important patient demographics and circumstances of those included in the trial so that those who are randomly allocated to receive the desired treatment T will almost certainly have a good result, while those included patients who do not receive T will have a bad result. This requires strict selection criteria, and a willingness to withhold what is strongly suspected to be good for a patient from 50% of patients in the name of science. That sort of explanatory trial does not require very many patients and has a strong likelihood of obtaining a positive result. The ethics of such conduct has been questioned (Raymond, Darsaut, & Roy, 2019). The *coup de grace* then occurs when the scientific community fails to recognize the trial as explanatory, and inappropriately promotes the treatment T, as if the trial had been pragmatic (Raymond et al., 2019).

3.5 Explanatory trials, "informativeness", and the ethics of trials

The idea that trials are primarily designed to gain information has untoward effects (Zarin, Goodman, & Kimmelman, 2019). The best way to ensure trials will be 'informative' is to limit trials to (explanatory) research questions that are more simple to answer, but that may not necessarily be pertinent or generalizable to practice. Research agencies and Industry want information for their money. The pressure to deliver 'information' promotes explanatory trials, with the selection of patients, centers and outcomes most likely to maximize the 'signal to noise ratio', even though this design is not appropriate to inform practice.

The priority on gaining knowledge also leads to the trap of trial 'feasibility' often listed as a 'necessary condition of informative trials' (Zarin et al., 2019). Trials that examine common surgical practices are already difficult to conduct, but they are rendered even more difficult when deprived of the authority and financial support of Research or Regulatory Agencies or Industry, which too readily label them difficult, at risk, or 'unfeasible'. This, of course, then becomes a self-fulfilling prophecy. How are we in neurosurgery, without all the "knowledge" that would come from so-called unfeasible trials, to define what is "good medical practice"? How can we find out what is best for our patients, if it is not by doing trials?

Trials are not optional and should not be conditioned on gaining knowledge or on their feasibility. Trials can be designed to regulate unvalidated care long before knowledge becomes available. The idea that patients primarily participate in trials to help advance medical science, and that 'uninformative trials' should be rejected because 'preventable uninformativeness is a serious breach of trust and a violation of research ethics' that is not supported by reality. Clinical trials proposed by clinicians should focus on a more important primary goal: to minimize harm related to uncertainty and guide care interventions in real time. Clinicians design and participate in trials,

not primarily to advance science, but because they have to provide optimal care even when no one really knows what to do.

Designing Pragmatic Care Trials to Practice Outcome-Based Medical Care

Rather than designing a trial for knowledge, care trials are designed to help clinical practice in the presence of uncertainty (**Figure 3.1.**) (Raymond, Darsaut, & Altman, 2014). In order to justify trial participation for all patients, every element of the care trial design is chosen to be in the best interest for the participating patient. To understand how Care Research is different from the prevailing research enterprises requires an explanation of the differences between validated and unvalidated care. Validated care is care that is known (read: positive pragmatic trial) to lead to better patient outcomes. Unvalidated care consists of experimental treatments that are promising but that have yet to be shown as beneficial. To protect all patients, unvalidated care should only be offered within an explicitly avowed, transparent research trial setting. Care trials are designed to protect patients from unvalidated care (Darsaut & Raymond, 2016). Care research is appropriate for situations where there is hope that patients might benefit, but reliable knowledge regarding the best management choice is lacking. From a clinician's perspective, when no one knows which choice is best (and either management could be randomly allocated within the trial), the clinician must be confident that trial participation is in the patient's best interests. But not any trial design will do. Care trials have been carefully designed to always place the *current participating* patient's interests first, so that clinicians can be comfortable knowing they are delivering best care by participating in a 1:1 allocation randomized trial. Other than the randomized management choice, there are no other differences from normal care. As might be expected, a

care trial is located at the pragmatic pole of the explanatory-pragmatic continuum. A suggested PRECIS-2 diagram is presented in **Figure 3.3.**

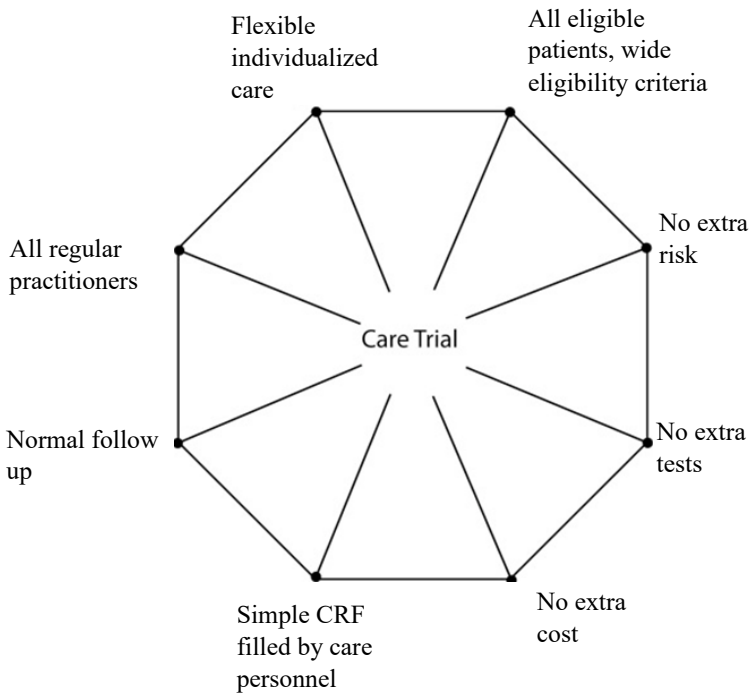

Figure 3.3. The PRECIS-2 diagram for a care trial, adapted from (Raymond et al., 2014).

3.6 Design Characteristics of Care Trials

Care trials have no additional risks, tests, or interventions other than what a routine patient would encounter in normal clinical care (Raymond et al., 2014). Inclusion criteria are as wide as possible, and exclusion criteria kept to an absolute minimum; all patients who are considered for the treatment (while uncertainty exists) should be offered trial participation. Randomized allocation is 1:1 to protect patients from an intervention that may turn out to be needless or harmful. Patients have an equal 50% chance of receiving the promising but unproven care option. Care trials examine "hard" (resistant to bias) clinical outcomes that are meaningful and relevant to

patients and physicians. There are no additional research-specific risks, tests, or questionnaires. Other than the decision of whether to receive the validated or the promising but unvalidated option (which is 1:1 randomly allocated), clinicians are given the flexibility to deliver the care as they see fit, without protocol-driven constraints.

3.7 Designing a Care Trial Protocol

3.7.1 Background and Purpose:

The background and purpose section of the protocol should include a full discussion of the prevailing uncertainty in the community, preferably with a systematic review of the literature, and an inter and intra-observer variability study demonstrating community uncertainty. Risks and potential benefits associated with both management choices that could be allocated should be discussed.

3.7.2 Design and Methods:

In a care trial, the focus is placed on ensuring that all elements of the trial design are chosen to be in the *current* patient's best interests. The hypothesis must place the burden of the proof on the more morbid option: it does not make sense to build a hypothesis that states "We suspect treatment T is bad for you but we want to prove it". The hypothesis must be of the sort "We suspect that promising treatment T may be better for you, but we are not certain". Primary and secondary outcomes should be easy to measure, meaningful to patients and clinicians alike, and as 'hard' (resistant to bias or interpretation) as possible, such as death or major morbidity (Raymond et al., 2014). Follow-up consists only of what a normal patient would encounter in routine clinical care.

3.7.3 Participants:

Eligibility criteria need to be as broad as possible; all patients who are considered for the promising but unproven intervention should be offered trial participation. Exclusion criteria should be kept to an absolute minimum.

3.7.4 Interventions

Care trials compare at least two management options (Raymond et al., 2014). The promising but unvalidated treatment is compared to whatever care is already validated; if there is none, a placebo may be appropriate.

3.7.5 Randomization

Randomized allocation ratio of 1:1 balances the risks associated with each intervention, and prevents patient from being subject to decision-making based on belief or fashion (Raymond et al., 2014).

3.7.6 Implementation and Multicenter Collaboration

The simplicity of the trial obviates the need for study-specific nurses or administrators, and because there is no exchange of money, there is also no need for (long delays and bureaucratic hurdles that accompany) contracts between institutions. The protocol, case report forms (CRFs), and a template informed consent form (ICF) can be made available for free online, and individual centers worldwide can apply to their local ethics boards for approval. This should facilitate world-wide collaboration and trial completion.

Why a Care Trial is Needed for Patients with Recurrent GBM

In routine clinical practice, neurosurgeons often receive requests from their neuro-oncology colleagues regarding patient eligibility for repeat surgery at the time of GBM recurrence. Generally, the patient still has an acceptable clinical status, despite their poor initial prognosis, and now has encountered a new neurological deficit or has imaging recurrence.

Choosing the next best management in this context is not always straightforward. The decision to reoperate may ultimately come down to the neurosurgeon's discretion, or the degree of insistence of the patient and family. Many factors, including the surgeon's enthusiasm for a repeat operation may influence whether the patient will be offered repeat resection. Patient optimism may increase the desire for repeat resection; after all, it is only human to want to do more, fight harder and live longer. However, although there may be satisfaction at "having done everything we could", there are also circumstances where repeat operation leads to premature death or disability. This raises the question of whether surgeons are actually doing these unfortunate patients any good by having them submit to another major cranial operation, especially when their life expectancy is already so short.

In this context, we have demonstrated the pervasive uncertainty among neurosurgeons regarding whether or not to reoperate: an inter-observer variability study showed that agreement regarding re-operation was slight (kappa of 0.198) (Landis & Koch, 1977).

What does the literature say? The literature offers conflicting views. Two recent systematic meta-analyses of case series gave opposing conclusions about the merit of re-operation (Lu, Jue, McDonald, & Rovin, 2018; Zhao et al., 2019). Repeat surgical treatment has been suggested to be more favorable with younger age (<60 years), and a preoperative Karnofsky performance status (KPS) of at least 70 (Barbagallo, Jenkinson, & Brodbelt, 2008). On the other hand, some studies

report that re-operation leads to no improvement in terms of survival or quality of life (Chaichana et al., 2013; Franceschi et al., 2015). Of course, all reports suffer from the limitations of retrospective observational studies, the most obvious being selection bias (Chen, Morsy, Liang, & Ng, 2016).

3.8 The RESURGE Trial, a trial with many explanatory features

When we set out to examine the question, we found one ongoing randomized clinical trial that was designed to address this dilemma (Schucht P, 2020). Randomized Controlled Comparative Phase II Trial on Surgery for Glioblastoma Recurrence (RESURGE) has many features that we considered to be too explanatory in design. First, the selection criteria for patients were quite narrow. For patients to be included into the trial, the treating neurosurgeon needs to believe that complete resection is possible, patients need to have a good functional status (KPS $\geq$ 70), there cannot be tumour involvement of the sylvian fissure or the vital motor and speech centers. Patients are excluded if they have received more than 1st line chemotherapy after the initial operation. Participating surgeons were tasked with completing research-specific procedures to ensure that only 'appropriate' patients were included. MRI images had to be sent to Germany for the study investigators to agree that complete resectability was possible, before they would 'approve' inclusion into the trial.

Finally, the treatment allocation ratio in RESURGE can be seen as unethical, or at least suboptimal. RESURGE has a 2:1 re-operation: conservative allocation ratio, perhaps because trial designers feared that physicians and clinicians would not want to participate in the trial unless they had a high chance of performing (or receiving) repeat craniotomy. When there is no supporting evidence to suggest that the benefits of repeat surgical resection outweigh the risks, why give a patient a 67% chance of being allocated a treatment that may be useless or harmful? A 2:1

allocation also sends the message that the (physician) trial designers believe repeat resection to be a better option.

3.9 Design of a Care trial for patients with Recurrent GBM

To address the pervasive uncertainty head-on, and to avoid the explanatory shortcomings of the RESURGE trial, the Repeat Resection for Recurrent GBM (3rGBM) trial was designed. 3rGBM is a simple, inexpensive, multicenter international care trial that can be easily integrated into routine neurosurgical practice (Details discussed in Chapter 4). Our goal is to provide a declared research context for neurosurgeons to manage patients with recurrent GBM, given the lack of reliable clinical outcome data associated with repeat resection. The primary outcome is overall survival, with an accompanying measure of quality of life, measured in days of survival spent outside a care facility.

<u>Chapter 4:</u> Repeat Resection in Recurrent Glioblastoma (3rGBM) Trial: a randomized care trial.

Introduction

Recurrence after the initial resection, which can be symptomatic or discovered on surveillance MRI imaging, occurs in nearly all patients, often within 8-9 months, even when the initial management is aggressive (Djamel-Eddine, De Witte, Mélot, & Lefranc, 2019). There is no standard way to care for recurrent GBM patients and there is community uncertainty regarding the next best management option for patients experiencing recurrence (Patel et al., 2021). Repeat surgical management carries a greater risk of wound infection and cerebrospinal fluid leak than the initial surgery, especially in patients who received radiation treatment (Gempt et al., 2013; Hoover et al., 2013). When maximal resection is attempted at the time of the initial procedure, the second surgery also carries a greater risk of causing additional neurological injury (D'Amico et al., 2015).

In the absence of randomized evidence of benefit, re-operation is considered an experimental intervention, one that needs to be offered within a research context. This chapter will discuss the design of a simple pragmatic care trial, to offer patients a chance at a promising but unproven therapeutic option (repeat surgical resection). The trial will include hard primary endpoint that is meaningful for patients and clinicians. The primary goal of our trial design is to provide a care trial context to help neurosurgeons and patients manage the uncertainty regarding the surgical treatment of recurrent GBM. The study will test the hypothesis that repeat resection can improve median overall survival and increase the number of days patients will spend outside of a hospital/nursing/palliative care facility.

Methods

Trial Design

The Repeat Resection for Recurrent GBM (3rGBM) trial is a simple, all-inclusive, prospective, multicenter, randomized care trial (Darsaut & Raymond, 2021) that allocates in a 1:1 ratio re-operation plus standard care vs. standard care without re-operation to patients with recurrent glioblastoma. The primary outcome for this trial will be overall survival (OS). Secondary outcomes include standard peri-operative safety outcomes, and the notion of 'quality survival', or survival at home, measured by counting days of survival from trial inclusion, minus days in a hospital/nursing home/palliative care setting.

Primary Hypothesis

Patients with recurrent glioblastoma, at the time they are considered for repeat resection (time of inclusion) who undergo repeat resection for the GBM, will experience an increase in median overall survival from 6 to 9 months (80% power at a 0.05 significance level to detect a hazard ratio of 0.65 when the control group median survival time is 6.0 months; 250 patients to account for 25% losses and cross-overs).

Selection Criteria

In the spirit of a care trial (Darsaut & Raymond, 2021), inclusion criteria will be broad and exclusions few. The main criterion for including the patient in the trial is that the treating physician considers that re-operation may improve quality survival for the patient. Other criteria include age ≥ 18, and previous pathology-confirmed, surgically resected GBM (needle biopsies alone do not

count as a resection). When informed consent cannot be obtained from the patient or their representative, patients will be excluded.

Patients allocated to receive a second operation within the 3rGBM trial context may undergo additional (third or even fourth) resections; this is necessary for those patients for whom the surgeon continues to believe that additional resection is in the patients' best interest, but the merits of this choice will not be examined in this trial. The number of repeat operations performed for each patient will be recorded.

Patient Allocation

The randomization process will be completed using a secure web-based program available 24 hours a day. 3rGBM will ensure concealment of treatment allocation with a 1:1 randomisation algorithm, with the following minimization criteria to ensure a balanced number of patients: Karnofsky Perfomance Score (≥70 vs less than 70), age (<60 vs ≥60), MGMT methylation status (non-methylated (<9%) + unknown vs methylated (≥9%)), and IDH-1 status (wild-type + unknown vs mutant).

Outcome Measures

The primary outcome is time to death from any cause, starting from the time of inclusion. Secondary outcomes include standard safety outcomes such as incidence of peri-operative non-neurological complications (wound infection, CSF leak, systemic deterioration) and incidence of new significant neurological deficits after surgery (defined as new or substantially worsened aphasia, or new weakness (Medical Research Council (MRC) power ≤3 in one or more limbs).

The incidence of additional operative procedures required following hospitalization for repeat resection will be recorded, along with the total length of hospitalization in days and discharge location.

Involvement of Individual Centers and the Role of the Steering Committee

All centers who have obtained approval by local ethics boards are invited to participate. There is no financial compensation for participating centres, and there will be no contracts between institutions. Necessary materials for the trial (full study protocol, a template informed consent document in English and/or French, and the CRF (case report form)) will be made available on the website; the mentioned material can be found on the Appendix section (Chapter 4 Appendix) of this thesis. Local investigators can report their own local data, but we propose that all participating centers share the same DSMC to monitor the progress of the trial. The SC assumes responsibility to transparently report the aggregate results of local investigators, who have shown their willingness to share anonymized randomized data by using the web-based platform, but all participating surgeons will be invited to co-author the trial reports.

Monitoring

The trial will be monitored by an independent Data Safety Monitoring Committee (DSMC), who will make recommendations regarding whether the trial should be interrupted, or whether recruitment should continue. Masked data will be provided to the DSMC after the first 100 patients have reached the primary outcome, or 2 years of follow-up, whichever applies. The Steering Committee is responsible for the final decision regarding continuation of the study. The DSMC charter will in the Appendix section (Chapter 4 Appendix) of this thesis.

Planned Statistical Analysis

The statistical method for the primary outcome will be the Cox proportional hazards model for the two allocated management groups, with 95% confidence intervals. Kaplan-Meier curves will be presented for visual comparison. Means, standard deviations, and ranges will be presented for quantitative variables and frequency tables for categorical variables. Secondary outcomes will be compared between groups using independent t-tests with 95% confidence intervals (95%CI) for quantitative variables and χ^2 tests with odds ratios and 95%CI for categorical variables. All tests will be interpreted with a 0.05 level of significance. Results will be analyzed and presented as intent-to-treat and as-treated.

Duration of the Trial

Patients will be followed until they reach the primary outcome, or they are censored from further continuation in the trial. We plan a 5-year recruitment phase; the trial should be completed within 7 years.

Regulatory and Ethical Considerations

The Health Research Ethics board of Alberta (HREBA) approved the study protocol on June 8, 2021 (HREBA.CC-21-0094), and the protocol is currently before other institutional review boards at other centers. Participants will be made fully aware of the study purposes and procedures. When signing the study consent form, they will be informed that participation is voluntary, and that they may withdraw from the trial at any point. Patient enrollment in this trial will comply with the principles enunciated in the Declaration of Helsinki. All collected information will be anonymized and kept confidential. Trial management will be transparent,

independent and will aim to preserve the scientific integrity of the research and the wellbeing of the participants. The SC will not have access to the unmasked data before completion or interruption of the trial. The DSMC will follow the progress of the trial, with masked results and events, but with the possibility of unmasking if necessary.

Discussion

As clinicians, our first duty is to properly manage these unfortunate patients, even while best treatment remains unknown. This pragmatic care trial approach differs from other, more explanatory designs (Schwartz & Lellouch, 1967). There is currently one other RCT ongoing, the RESURGE trial (Schucht P, 2020) that also addresses the question of whether or not repeat resection leads to better overall survival. The explanatory features of the RESURGE trial become evident when using the results of the PRECIS-2 tool to determine the extent of which it should influence clinical practice (**Figure 4.1**). Explanatory design aspects of RESURGE unfortunately lead to the exclusion of many recurrent GBM patients, and also render participation difficult for centers and surgeons. For example, patients are excluded if they have recurred within 3 months of initial resection, or if they have already received second-line chemotherapy. Central imaging review by a study eligibility committee is required to ensure that "Complete removal of contrast-enhancing lesion is considered feasible without significant risk of permanent speech or motor function according to MRI, and that there is no midline shift, or contrast enhancement encroaching on A1 or M1 vessels." Other explanatory elements include a mandatory post-op MRI, and an array of additional outcome questionnaires for patients to complete. One final problem with RESURGE is the 2:1 allocation ratio re-operation: no re-operation, which presupposes the benefits of surgery, and implicitly sends the message that experts believe surgery is better. This is problematic if repeat

resection proves useless or harmful, as each patient will have been exposed to twice the risks of the 'experimental treatment', as compared to the 1:1 allocation we propose that better balances risks for individuals, and better matches the documented neurosurgical uncertainty ((Patel et al., 2021).

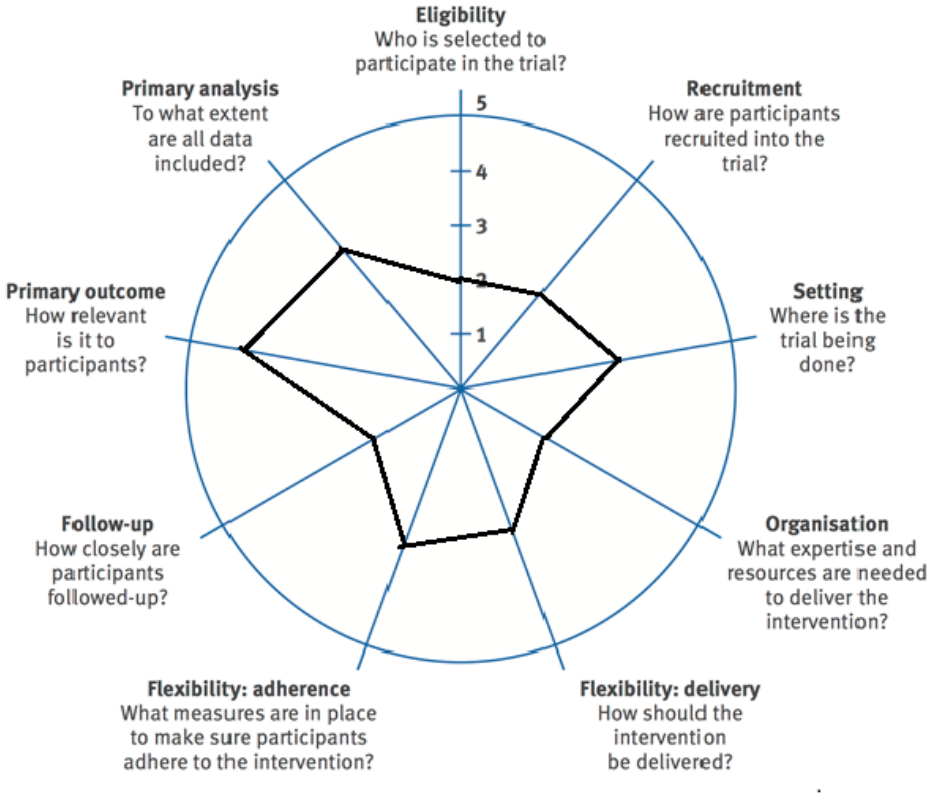

Figure 4.1. Application of PRECIS-2 tool to determine the degree of explanatory vs. pragmatic nature of the RESURGE trial.

In a pragmatic trial, the overall outcome is what is relevant. While explanatory features may help explain *why* the observed outcomes occurred, or to formulate hypotheses for future trials, in a pragmatic trial the focus is on the primary outcome. Overall survival is a hard (unambiguous) outcome, simple to measure (time from study inclusion to death), and clinically meaningful to patients and clinicians. However, because increased survival in a debilitated state, recovering from

morbid surgery is unlikely to be perceived by patients as beneficial, we have included another simple-to-measure outcome, the number of days spent in a care facility between time of study inclusion and death, which can readily be recorded. Other pragmatic design choices that ensure as many patients are able to participate include the very inclusive selection criteria and the non-directive protocols which allow flexibility in post-operative and non-surgical care; standardized surgical or oncological treatments are not imposed. Surgeons may use any adjuncts they would like, including intra-operative MRI or 5-ALA guided resections, but these will not be mandated by protocol. If from an explanatory perspective these choices may be criticized, this is because we do not want centers to opt-out because the protocol is not consistent with local practices. We recognize that undergoing repeat craniotomy (as opposed to conservative management) may bias oncologists' decisions about subsequent oncologic treatment decisions. If an explanatory trial attempts to dissect the effects of surgery from the effects of subsequent treatments, in a pragmatic trial what is important is the final patient outcome. Similarly, an explanatory trial could seek an association between a good outcome and extent of resection (EOR) obtained at time of second craniotomy. But this post-hoc explanation of an outcome that cannot be changed (unless a third craniotomy is proposed). We have not required an assessment of EOR on post-operative MRIs, but we do request that surgeons record the extent of resection obtained (biopsy only/subtotal re-resection, gross-total re-resection) on the case report form. Other concerns which have been raised include the problem of pseudo-progression, pathological sampling errors, and disagreements in diagnosis (Holdhoff et al., 2019). We expect these problems to occur equally among groups due to 1:1 randomization.

The 3rGBM trial is primarily designed to offer a treatment that has yet to be validated as beneficial within a transparent care research context. Eventually learning which treatment is best, or gaining knowledge, is a secondary goal, in the spirit of care trials (Raymond, Darsaut, & Molyneux, 2011). Every trial design choice is conceived in the best medical interest of the patient, and there are no additional pertinent-to-research-only risks, tests, or visits. The trial is designed to impose as little disruption in patient lives, and in routine clinical care as possible, and yet still eventually serve a useful research purpose (**Figure 4.2**). The design provides patients a 50% chance to offer a potentially promising treatment but controlled by an equal 50% chance of avoiding what may be a risky, potentially harmful or even useless re-operation.

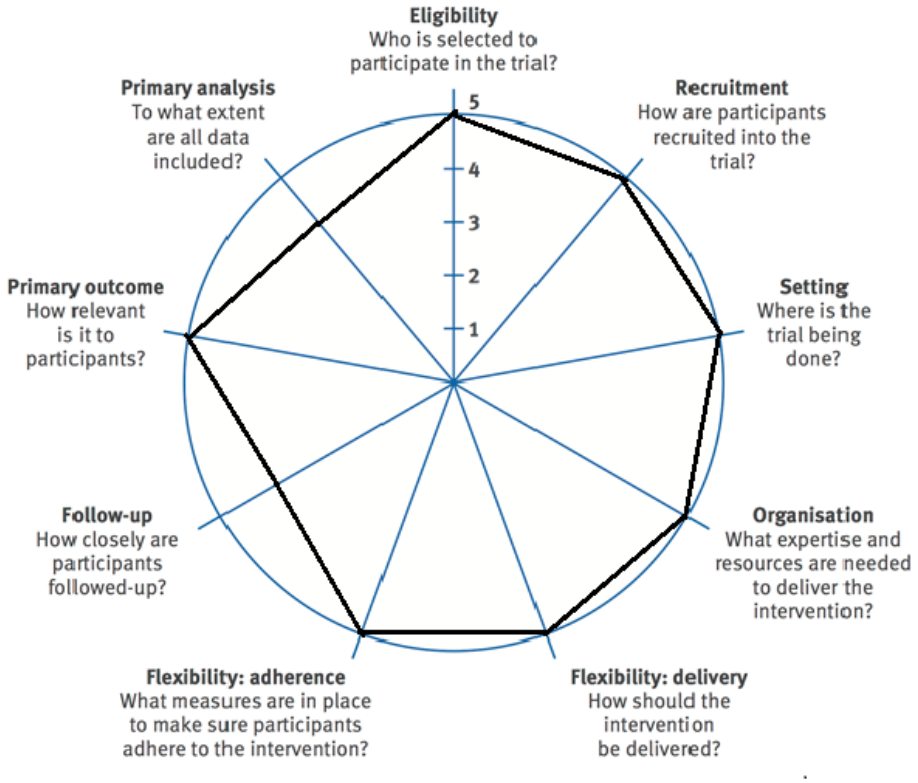

Figure 4.2. Application of PRECIS-2 tool to determine the degree of explanatory vs. pragmatic nature of the 3rGBM Trial.

The idea that unvalidated care should only be offered within the context of a transparent care trial means that trial availability should not be conditioned on winning competitions for financial support. Competing with other research endeavours often leads to the introduction of 'scientifically interesting' explanatory features into trial design, which necessitates extra work for care personnel and clinicians, and increases the research burden for cancer patients. Randomized surgical trials remain difficult to conduct (Horton, 1996). In the classic paradigm, once (and only if) financial compensation to centers is secured, organization is rendered even more complex by the requirements for legal contracts between institutions and harmonized between countries. We here propose to bypass all these difficulties and delays and to minimize bureaucratic hurdles by not requiring financial compensation for centers. The care research context departs from the usual assumption that the trial is primarily conceived to gain knowledge; in this case, the trial is primarily conceived to offer optimal care despite the uncertainty. Thus, conducting the trial cannot be conditioned on securing research grants. The yet to be validated treatment (here repeat resection) can be offered, but in the absence of convincing evidence, only within the context of the trial (Raymond et al., 2011). This choice automatically requires the research burden for patients and clinicians to be minimized.

Interested local investigators are invited to freely download study documents (protocol, CRF, and a template of the informed consent form) from the web, and submit the project as their own local investigator-led trial to their authorities. After obtaining IRB approval, each center can use the common web-based randomization platform and electronic case report forms. Data collection will be kept to the absolute minimum to obtain a meaningful answer to the study question. Centers will be responsible to maintain the integrity of their own local data. Participating

centers agree to have their local trials monitored by the same DSMC. Data will be shared and analyzed by the Steering Committee when recruitment targets are met. This very pragmatic, more "grassroots" approach will ensure that the trial will be conducted and hopefully facilitate trial completion (Raymond, Darsaut, & Roy, 2019).

Conclusion

The pervasive uncertainty regarding how surgeons ought to manage patients presenting for possible craniotomy for repeat resection of known glioblastoma requires a pragmatic care trial. We have designed a simple pragmatic care trial that has no additional risks, tests or interventions and can easily be integrated into normal clinical practice.

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Chapter 1

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Chapter 2

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Appendix

Appendix A: Additional Material for Chapter 2

Table 2.4A: Votes for re-operation, non-dichotomized and dichotomized inter-rater and percent agreement regarding best next management choice.

	Total Number ofYes Surgery Votes	95% CI for Yes Surgery Votes	Non-Dichotomized Kappa (95% CI)	Dichotomized Kappa(95% CI)	Percent Agreement (95%CI)
Surgeon Responders (n=26)	413/962 (42.9%)	39.8 - 46.1	0.148 (0.102 - 0.209)	0.198 (0.133 - 0.276)	60.4 (56.8 - 64.0)
Training Background					
Neuro-oncology fellowship training	93/185 (50.2%)	43.1 - 57.4	0.183 (0.074 - 0.316)	0.167 (0.055 - 0.314)	59.7 (44.5 – 75.0)
None	342/777 (44.0%)	40.6 - 47.5	0.135 (0.088 - 0.193)	0.601 (0.556 - 0.646)	60.1 (55.6 - 64.6)
Years of Experience					
0-5 years of experience	76/185 (41.0%)	34.2 - 48.3	0.045 (0.002 - 0.104)	0.090 (0.027 - 0.178)	58.0 (46.9 - 69.1)
6-10 years of experience	89/185 (48.1%)	41.0 - 55.3	0.120 (0.019 - 0.243)	0.211 (0.069 - 0.393)	60.5 (43.8 - 77.3)
11+ years of experience	248/592 (41.9%)	38.0 - 45.9	0.140 (0.081 - 0.213)	0.181 (0.112 - 0.269)	59.4 (55.3 - 63.4)
Practice Location					
North America	319/666 (47.9%)	44.1 - 51.7	0.389 (0.365 - 0.401)	0.528 (0.488 - 0.563)	60.2 (57.8 - 62.4)
Europe	127/296 (42.9%)	37.4 - 48.6	0.244 (0.217 - 0.654)	0.436 (0.394 - 0.478)	59.3 (56.9 - 61.8)
Portfolio Cases (n=37)					
Patient Age (Years)					
≤ 50	113/229 (49.4%)	42.9 - 55.8	0.201 (0.188 - 0.216)	0.428 (0.388 - 0.473)	61.5 (58.9 - 64.3)
51-60	162/387 (41.8%)	37.1 - 46.8	0.176 (0.154 - 0.203)	0.488 (0.407 - 0.523)	61.3 (59.1 - 63.0)
≥61	152/346 (43.8%)	38.8 - 49.2	0.318 (0.303 - 0.341)	0.554 (0.511 - 0.634)	57.6 (55.3 - 60.1)
Tumour Location					
Left hemisphere	217/498 (43.6%)	39.3 - 48.0	0.136 (0.119 - 0.163)	0.338 (0.295 - 0.393)	62.4 (60.2 - 65.1)
Right hemisphere	196/390 (50.3%)	45.6 - 55.5	0.264 (0.248 - 0.285)	0.415 (0.395 - 0.474)	59.5 (56.4 – 61.8)
Bilateral involvement	14/74 (18.9%)	11.3 - 28.6	0.395 (0.375 - 0.413)	0.573 (0.418 - 0.622)	61.6 (59.8 - 63.7)
Karnofsky Performance Score					
≤ 70	227/491 (46.2%)	41.9 - 50.7	0.159 (0.106 - 0.233)	0.484 (0.428 - 0.517)	61.8 (58.0 - 65.7)

Search MEDLINE (OvidSP Interface) up to Feb 15th, 2019		
Step	**Question**	**Results**
S1	Glioblastoma /	24838
S2	Astrocytoma /	36246
S3	(High grade glioma or high grade astrocytoma).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	3159
S4	glioblastoma multiforme.mp./	10638
S5	(oligodendroglioma or glioma).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]/	61587
S6	Or/1-5	88774
S7	observer variability.mp.	2706
S8	(agreement study or agreement).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	266864
S9	Observer Variation/	42147
S10	(interobserver or intraobserver or intra rater or inter rater).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	30154
S11	or/7-10	308495
S12	management.mp.	1257648
S13	(surgery or repeat surgery).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	2615324
S14	or/12-13	3613113
S15	**6 AND 11 AND 14**	**148**

Search EMBASE (OvidSP Interface) up to Feb 15th, 2019		
Step	**Question**	**Results**
S1	Glioblastoma /	66483
S2	Astrocytoma /	82403
S3	(High grade glioma or high grade astrocytoma).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	5721
S4	glioblastoma multiforme.mp./	15572
S5	(oligodendroglioma or glioma).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]/	92810
S6	Or/1-5	143699
S7	observer variability.mp.	4904
S8	(agreement study or agreement).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	315293
S9	Observer Variation/	19907
S10	(interobserver or intraobserver or intra rater or inter rater).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	41086
S11	or/7-10	350474
S12	management.mp.	2411613
S13	(surgery or repeat surgery).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	3494645
S14	or/12-13	5435562
S15	**6 AND 11 AND 14**	**322**

Search Cochrane Library up to Feb 15th, 2019		
Step	**Question**	**Results**
S1	(Glioblastoma):ti,ab,kw	1897
S2	Astrocytoma	512
S3	High grade glioma or high grade astrocytoma	559
S4	glioblastoma multiforme	518
S5	oligodendroglioma or glioma	1531
S6	#1or#2or#3or#4or#5	3084
S7	observer variability	963
S8	agreement study or agreement	12576
S9	Observer Variation	2749
S10	interobserver or intraobserver or intra rater or inter rater	3325
S11	#7or#8or#9or#10	16086
S12	management	122430
S13	surgery or repeat surgery	228454
S14	#12or#13	325061
S15	**#6AND#11AND#14**	**41**

Clinical Uncertainty and Equipoise in the Management of Recurrent Glioblastoma

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Background: A significant proportion of glioblastoma (GBM) patients are considered for repeat resection, but evidence regarding best management remains elusive. Our aim was to measure the degree of clinical uncertainty regarding reoperation for patients with recurrent GBM.

Methods: We first performed a systematic review of agreement studies examining the question of repeat resection for recurrent GBM. An electronic portfolio of 37 pathologically confirmed recurrent GBM patients including pertinent magnetic resonance images and clinical information was assembled. To measure clinical uncertainty, 26 neurosurgeons from various countries, training backgrounds, and years' experience were asked to select best management (repeat surgery, other nonsurgical management, or conservative), confidence in recommended management, and whether they would include the patient in a randomized trial comparing surgery with nonsurgical options. Agreement was evaluated using κ statistics.

Results: The literature review did not reveal previous agreement studies examining the question. In our study, agreement regarding best management of recurrent GBM was slight, even when management options were dichotomized (repeat surgery vs. other options; $\kappa = 0.198$ [95% confidence interval: 0.133-0.276]). Country of practice, years' experience, and training background did not change results. Disagreement and clinical uncertainty were more pronounced within clinicians with ($\kappa = 0.167$ [0.055-0.314]) than clinicians without neuro-oncology fellowship training ($\kappa = 0.601$ [0.556-0.646]). A majority (51%) of responders were willing to include the patient in a randomized trial comparing repeat surgery with nonsurgical alternatives in 26/37 (69%) of cases.

Conclusion: There is sufficient uncertainty and equipoise regarding the question of reoperation for patients with recurrent glioblastoma to support the need for a randomized controlled trial.

Key Words: glioblastoma, recurrence, resection, agreement, interobserver variability, equipoise

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Glioblastoma (GBM) is the most common and lethal primary malignant brain tumor.[1] Despite multiple treatment advances, prognosis remains grim, with 5-year survival rates of 21.9% (95% confidence interval [CI]: 21.0%-22.8%) if diagnosed between the age of 20 to 44 years, decreasing to 5.9% (95% CI: 5.6%-6.2%) for the most commonly affected ages (55 to 64 y).[1] Initial treatment typically involves surgery to reduce tumor burden and secure pathologic diagnosis, followed by radiotherapy and chemotherapy.[2]

Recurrence of the GBM becomes a problem as a result progressive neurological deterioration, or can remain asymptomatic, with growth discovered on serial imaging. If the prognosis of GBM at initial diagnosis is grim, it is worse at time of recurrence, and how to best manage patients with recurrent GBM remains uncertain. In many centers, general neurosurgeons are frequently called on to manage or provide an opinion on these cases, and a wide range of conducts are considered acceptable. On one end of the spectrum, some neurosurgeons do not offer repeat resection given the dismal prognosis. On the other end, others are more aggressive, using cytoreduction and symptom control as justification. Many clinicians between these extremes attempt to select candidates case-by-case for repeat resection according to resectability, past experience, or for other reasons.[3,4] Although the clinical context commonly calls for action such as repeat resection, the potential benefits of reoperation compared with other management options has yet to be shown in a randomized clinical trial (RCT).[5–10]

Randomized trials of neurosurgical treatments remain difficult to conduct.[11,12] A common conception regarding the propriety of randomly allocating treatment options is that there should be sufficient disagreement, uncertainty, or "equipoise" in the expert community regarding how best to proceed in order to justify a trial.[13,14] Methods to measure such uncertainty have recently been described.[13,15] The goal of the present study was to measure the degree of clinical uncertainty or equipoise among general and neuro-oncology trained neurosurgeons by testing the repeatability of decisions to reoperate versus other management options for a series of diverse patients with recurrent GBM.

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METHODS

A systematic review was first carried out using the Cochrane, EMBASE, and Medline databases to search for previously conducted studies on interobserver agreement, uncertainty, variability, or equipoise concerning the management of recurrent GBM. Details of the search strategy are available in the Appendix, Supplemental Digital Content 1 (http://links.lww.com/AJCO/A368).

We then designed and conducted an interobserver study to measure clinical uncertainty and equipoise according to a published framework, which presupposes that a dilemma concerning the use of at least 2 management options exists.[15] The general method is that a sufficient number of diverse individual patients sharing a similar clinical problem and covering a wide spectrum of clinical presentations be assembled into a portfolio that is then submitted to a variety of clinicians who routinely manage patients with the clinical problem. These clinicians are then asked to independently choose one of the predefined management options selected from those that would be compared within a randomized trial that would address the clinical dilemma. The idea is not to discover the "right treatment" by tabulating the most frequently proposed option for each patient, but to measure whether sufficient uncertainty exists to design and justify a trial.[15]

This report was written according to the Guidelines for Reporting Reliability and Agreement Studies (GRRAS).[16] Ethics approval was deemed by the local IRB to not be required as all images and survey responses were anonymous.

Portfolio of Patients

The number of clinicians and cases necessary to provide meaningful results in a measurement of equipoise study was estimated to be >10 clinicians evaluating 30 to 50 patients.[15,17] An electronic portfolio composed of select magnetic resonance images acquired from 37 anonymized patients with pathology-confirmed GBM, at time of follow-up imaging or symptomatic recurrence at least 3 months from time of initial resection was assembled (Fig. 1). Patients were selected from a database of tumor patients managed at the University of Alberta between January 2002 to January 2019. For each case, at least 2 representative postgadolinium magnetic resonance images were presented along with some pertinent clinical data: age, sex, Karnofsky Performance Score (KPS), and the number of months since initial resection. To ensure that the portfolio (and the study of the repeatability of the clinical judgments) would include a wide variety of patients covering the entire clinical spectrum, and to minimize paradoxes known to occur with κ statistics,[18,19] one third of cases were selected because they were estimated to be favorable for repeat resection, 1/3 not favorable for repeat resection, and 1/3 "gray zone" cases, according to the judgment of the senior neurosurgical author (T.E.D.), based on the following criteria: age, performance status, and tumor location (eloquence of involved brain). Fifteen of the 37 included patients (41%) actually underwent repeat resection.

For each patient, clinicians were asked the following questions: (1) Is repeat surgical resection an option for this patient with recurrent GBM, Y/N? (2) What is the next management option you would recommend for this patient with recurrent GBM? (Responders chose from: Repeat surgical resection, Nonsurgical treatment, or Observation/Symptom control.) (3) Confidence level in your recommended management: (0% to 100%). (4) Would you include this patient in an RCT that would give a 50% chance of repeat surgery and a 50% chance of nonsurgical management Y/N? The portfolio is available in the Appendix, Supplemental Digital Content 1 (http://links.lww.com/AJCO/A368).

Clinicians

Because the question concerns whether or not general neurosurgeons should reoperate, the portfolio was circulated to a wide diversity of practicing neurosurgeons ($n=44$) from different countries, with or without neuro-oncology training, and with varying years of experience. All of the neurosurgeons surveyed manage patients with GBM, have previously responded to requests for assessment of interobserver variability, and are considered to be prospective trial participants for an RCT addressing the clinical dilemma. Anonymity was assured but some demographic information was collected. Each responder had to complete the survey independently. Ten clinicians who responded to the first request in a timely fashion were asked to complete the survey a second time, with case order permutated, at least 4 weeks apart for the intraobserver portion of the study.

Statistical Analysis

Agreement on best next management was analyzed for all 3 choices, and then in a dichotomized manner (repeat surgery vs. other nonsurgical management), using Fleiss κ statistics with 95% CIs. κ scores were interpreted according to Landis and Koch (0 to 0.2, slight; 0.21 to 0.4, fair; 0.41 to 0.6, moderate; 0.61 to 0.8, substantial; 0.81 to 1.0 perfect agreement).[20] Differences between point estimates, or between κ values were considered to exist when CIs did not overlap. Confidence in decision-making (scale of 0 to 10) was analyzed with analysis of variance and differences between proportions with Fisher exact tests. All analyses were conducted by a statistician (M.C.) using STATA Version 16 and SPSS Version 25 and a significance level of 5%.

RESULTS

The systematic review did not yield any previous interobserver variability studies on best management of recurrent GBM. The search strategy yielded 132 titles, 122 of which were rejected by reading the titles, 3 further were rejected after reading the abstracts. A total of 7 articles were given full-text review; however, none were identified as being an agreement or interobserver variability study on the management of recurrent GBM. The entire search strategy is available in the Appendix.

The characteristics of patients included in the portfolio and responder demographics are presented in Table 1. Twenty-six of the 44 neurosurgeons (59%) responded to the survey. Responders had the following experience in managing patients with GBM: 0 to 5 years ($n=5$), 6 to 10 years ($n=5$), and ≥ 11 years ($n=16$). Five neurosurgeons (5/26 [19%]) had fellowship training in neuro-oncology, 4 of whom had 11 or more years of experience.

For each case, at least 1 responder considered repeat surgical resection to be an option. Each of the 37 cases was evaluated by 26 responders, yielding 962 responses. Repeat surgical resection (429/962 [44.6%, 95% CI: 0.41-0.48]) and nonsurgical treatment choices were chosen with almost equal frequency (424/962 [44.1%, 95% CI: 0.41-0.47]), followed by observation/symptom control (109/962 [11.3%, 95% CI: 0.09-0.13]). There was a wide disparity between the number of cases each neurosurgeon would elect to reoperate: individual choices for repeat surgery ranged from 3/37 cases (8%) by a senior North American neurosurgeon (>11 y experience) to 33/37 (89%) by a North American neurosurgeon with 6 to 10 years experience. Repeat surgery was chosen overall a mean of

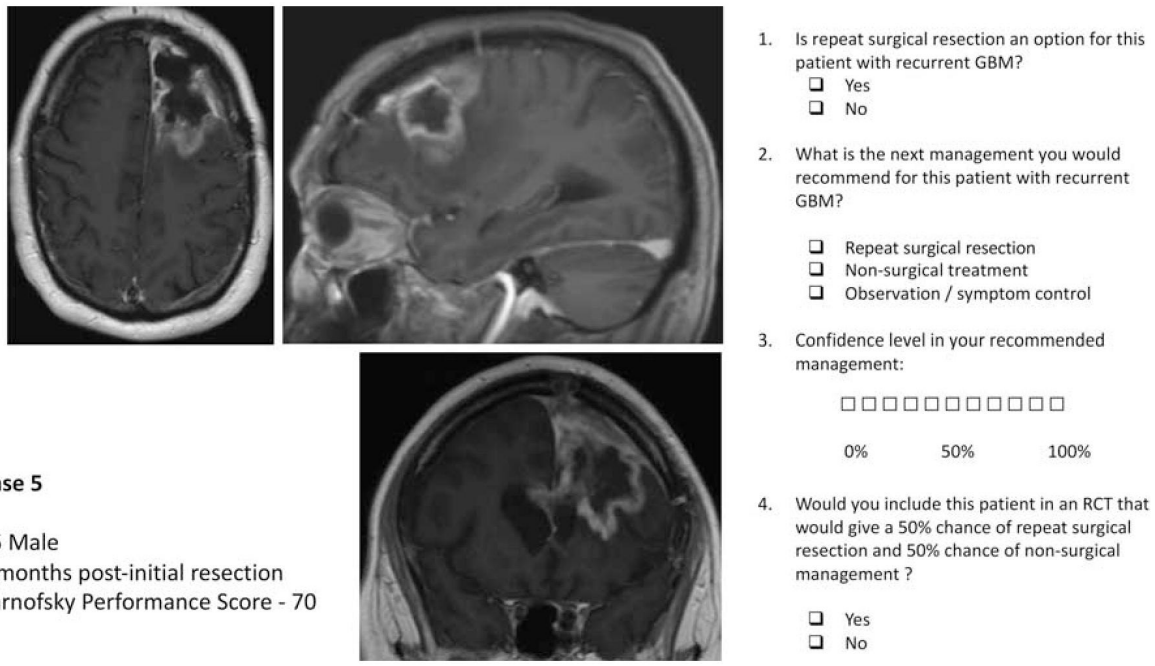

FIGURE 1. Typical case included in the portfolio of pathology-confirmed recurrent glioblastoma patients.

18.2 ± 2.6 times/37 cases, or 49% of the time by the 26 surgeons. Number of votes for reoperation according to patient characteristics and surgeon-related factors are presented in Table 2. Surgeons from North America and from Europe were not significantly different in the number of times they recommended reoperation for GBM. Having a neuro-oncology fellowship training background, or having different years' experience did not significantly increase the likelihood of recommending reoperation. Patient characteristics such as age, KPS, and tumor location in the right versus left hemisphere did not significantly change recommendations, with the exception of having bilateral recurrence, for which surgeons were significantly less likely to choose reoperation: Yes to repeat surgery was chosen 18.9% (95% CI: 11%-29%) of the time for bilateral recurrence compared with 43.6% (95% CI: 39%-48%) for left and 50.3% (95% CI: 46%-56%) Yes votes for right hemisphere recurrences.

The case with the greatest number of Yes votes for reoperation (22/26, 84.6%) was a 49-year-old male (case 25) with recurrent GBM in the left temporal lobe and a KPS of 70. The case with the fewest number of Yes responses (1/26, 3.8%) was a 35-year-old male (case 13) with a bilateral GBM in the pineal region, and a KPS of 70 (Fig. 2).

Overall agreement regarding the next best management option was slight (according to Landis and Koch) for patients with recurrent GBM (κ [95% CI]: 0.148 [0.102-0.209]) (non-dichotomized data and percent agreement are available in Table 4 Appendix, Supplemental Digital Content 1 (http://links.lww.com/AJCO/A368). Agreement remained slight when responses were dichotomized into surgical management vs. the

TABLE 1. Characteristics of Patients Included in the Portfolio and Surgeon Responder Demographics

Patient Characteristics	Number of Patients, n (%)	Responder Demographics	Number of Responders, n (%)
Total	37	Total	26
Male	21 (57)	Practice location	
Tumor location		North America	18
Left hemisphere	19 (51)	Europe	8
Right hemisphere	15 (41)	Neuro-oncology Fellowship Training	
Bilateral involvement	3 (8)	Yes	5 (19)
Patient age (y)		No	21 (81)
≤ 50	9 (24)	Experience managing GBM	
51-60	15 (41)	0-5 y	5 (19)
≥ 61	13 (35)	6-10 y	5 (19)
Karnofsky Performance Score (KPS) at time of consideration for reoperation		11 or more years	16 (62)
≤ 70	21 (57)		
≥ 80	16 (43)		
Actually underwent repeat resection			
Yes	15 (41)		
No	22 (59)		

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TABLE 2. Number of Votes for Re-operation and Inter-rater Agreement Regarding Best Next Management Choice

	Total Number of Yes Surgery Votes (%, 95% CI)	Point Estimate CI Overlap	Dichotomized κ (95% CI)	κCI Overlap
Surgeon responders (n = 26)	413/962 (42.9, 39.8-46.1)	NA	0.198 (0.133-0.276)	NA
Training background				
Neuro-oncology fellowship training	93/185 (50.2, 43.1-57.4)	Yes	0.167 (0.055-0.314)	No
None	342/777 (44.0, 40.6-47.5)		0.601 (0.556-0.646)	
Years of experience				
0-5 y of experience	76/185 (41.0, 34.2-48.3)	Yes	0.090 (0.027-0.178)	Yes
6-10 y of experience	89/185 (48.1, 41.0-55.3)		0.211 (0.069-0.393)	
11+ years of experience	248/592 (41.9, 38.0-45.9)		0.181 (0.112-0.269)	
Practice location				
North America	319/666 (47.9, 44.1-51.7)	Yes	0.528 (0.488-0.563)	No
Europe	127/296 (42.9, 37.4-48.6)		0.436 (0.394-0.478)	
Portfolio cases (n = 37)				
Patient age (y)				
≤ 50	113/229 (49.4, 42.9-55.8)	Yes	0.428 (0.388-0.473)	No for ≤ 50 vs. ≥ 61
51-60	162/387 (41.8, 37.1-46.8)		0.488 (0.407-0.523)	
≥ 61	152/346 (43.8, 38.8-49.2)		0.554 (0.511-0.634)	
Tumor location				
Left hemisphere	217/498 (43.6, 39.3-48.0)	No for left vs. bilateral	0.338 (0.295-0.393)	No for left vs. right hemispheres, no for left vs. bilateral
Right hemisphere	196/390 (50.3, 45.6-55.5)	No for right vs. bilateral	0.415 (0.395-0.474)	
Bilateral involvement	14/74 (18.9, 11.3-28.6)		0.573 (0.418-0.622)	
Karnofsky Performance Score				
≤ 70	227/491 (46.2, 41.9-50.7)	Yes	0.484 (0.428-0.517)	Yes
≥ 80	199/471 (42.2, 37.9-46.8)		0.469 (0.413-0.526)	

CI indicates confidence interval; NA, not applicable.

other management options (κ [95% CI] = 0.198 [0.133-0.276]). Agreement between surgeons was not better when location of practice, or years' experience were considered (Table 2). Those with additional expertise in neuro-oncology disagreed with each other about which cases they would reoperate even more (κ = 0.167 [0.055-0.314]) than those without neuro-oncology fellowship training (κ = 0.601 [0.556-0.646]).

Responders were no more likely to agree on management of recurrent GBM in the right compared with the left hemisphere. KPSs greater or less than 70 did not influence agreement, but surgeons were more likely to agree on the management of patients older than 60 compared with patients less than 50 years of age (Table 2).

Seven of 10 requested surgeons responded to the portfolio twice (Table 3). Intraobserver agreement remained poor and below substantial (< 0.61) for all responders except 1: an experienced (≥ 11 y) North American surgeon without neuro-oncology fellowship training.

Overall, the self-assessed surgeon's confidence that the selected management was best on an 11 point scale (11 categories from 0% to 100%) was 8.7/11 (95% CI: 8.3-9.2). European surgeons expressed slightly less confidence in their recommendations (North America: 8.9/11 [95% CI: 8.4-9.1], Europe: 7.4/11 [95% CI: 7.2-7.9]). Having fellowship training in neuro-oncology was also associated with lower confidence (7.3/11 [95% CI: 7.1-7.5]), compared with not having such training (8.5/11 [95%CI:8.2-8.7]). After the first 5 years of practice, surgeons expressed more confidence in their recommendations: 0 to 5 y (5.8/11 [95%CI:5.6–6.1]), compared with 6 to 10 years (7.7/11 [95%CI:7.3–8.1]), and 11 or more years

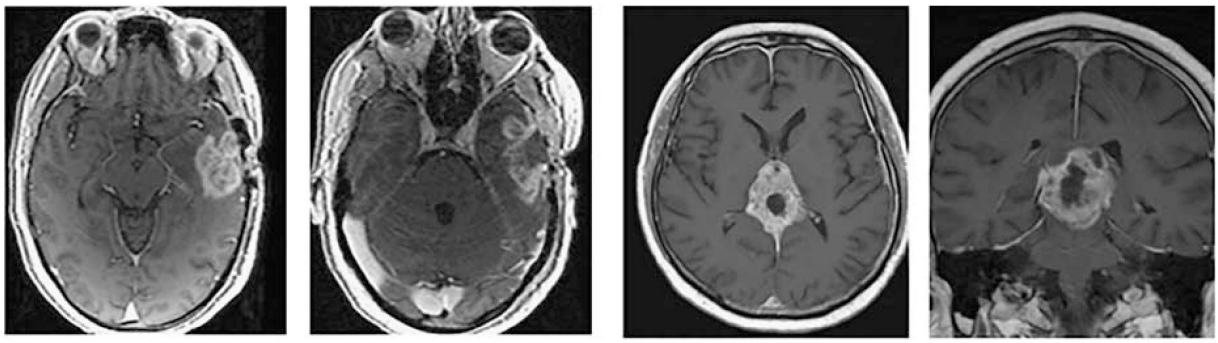

FIGURE 2. Cases with the highest (22/26, 84.6%) and lowest (1/26, 3.8%) number of Yes votes for repeat resection.

(7.6/11 [95%CI:7.4–7.7]). The mean confidence score of the 7 responders that answered the portfolio twice (7.6/11 [95% CI:6.6-8.6]) was comparable to that of the 19 raters that only responded once (6.6/11 [95%CI:5.7-7.5]).

Surgeons agreed to randomized trial inclusion 657/962 times (68.3%, 95%CI:0.65-0.71). For 26/37 (69%) cases, a majority (51%) of responders were willing to include the patient in a randomized trial comparing repeat surgery to any other management. When surgeons agreed to include the patient in a randomized trial, they also had less confidence in their recommended management (confidence scores of 6.8/11 [Yes to RCT] vs. 8.5/11 [No to RCT], $P < 0.01$).

DISCUSSION

While patients commonly seek "second opinions," the reliability of medical recommendations is infrequently tested in real-world practice. We did not find any previous interobserver reliability studies on management recommendations for recurrent GBM in our systematic review. Unlike surveys which look for a majority opinion[3] regarding generic or theoretical case scenarios, this novel type of study follows the principles and methods of interobserver reliability studies on the repeatability of clinical judgments made on individual patients. The degree of clinical uncertainty or equipoise within the surgical community is measured by testing the likelihood of receiving the same response when the same patient is presented to a different surgeon or to the same surgeon twice.[13,15]

The clinical dilemma we wanted to test in this study concerns the propriety of performing repeat surgery for recurrent GBM patients in routine practice. This type of dilemma calls for a different type of clinical trial than most clinical research which aims to verify the promising benefit of a therapeutic innovation.[21] An agreement study can be done before the conduct of a pragmatic trial to ensure that sufficient community equipoise about the options exists. We found little agreement among surgeons regarding whether or not to offer reoperation to patients presenting with recurrent GBM. Clinicians' characteristics, such as sharing a country of practice, having more years of experience, or background specialty training in neuro-oncology did not change the level of agreement. The lack of agreement existed even though clinicians were typically confident in their individual decisions.

The uncertainty we documented may not be surprising, for the lack of reliable knowledge of how best to proceed with these patients is well-documented in the literature,[22] with opinions and recommendations for[6,8–10] and against reoperation.[7,23] However, the level of uncertainty is particularly high here, for most clinicians questioned twice on the best management of the same patients did not agree with themselves.[15]

This suboptimal situation, in which no one really knows how to best care for individual patients, does have an upside: with clinical community uncertainty measured to be substantial ($k = 0.198$), the potential for recruitment in a randomized trial is high.[15] This study supports the need for a trial that examines the question of whether or not reoperating on recurrent GBM patients is worthwhile. The fact that a majority of clinicians were willing to offer, to a majority of patients, participation in a randomized trial is a step in the right direction. One such trial is underway.[24]

Limitations of this study include the relatively small number of responders, and the artificial nature of the context of the survey. A different set of cases, or different responders may have led to different results. Our choice of a heterogeneous case and responder mix does however improve the generalizability of results to routine practitioners. Cases of radiation injury, which can sometimes mimic tumor recurrence, may have been present in the portfolio, as not all cases were re-confirmed with pathology. We limited the amount of clinical information provided for each case to minimize disagreements based on various interpretations. How much information should be included in such studies is a difficult methodological question.[15] While clinicians may commonly look for "reasons" to decide one way or another in order to manage the uncertainty, additional information also increases the risk of clinicians disagreeing for extraneous reasons. Details of molecular profiles, chemotherapeutics, or time since last radiation treatment were not included, as these details could have influenced decision-making to a different degree. Similarly, the commonly proposed indications for repeat resection (raised intracranial pressure, progressive neurological deficits, and recurrent seizures),[4] were not included. These details were not provided, because the purpose of our study was not to identify all the potential reasons clinicians might disagree on a particular case, but rather to measure the clinical uncertainty that remains even when reasons for potential disagreement are minimized.

In the spirit of pragmatic clinical research,[25] we did not restrict our evaluation to neuro-oncology experts from academic or research centers. Such a selection would have affected generalizability of results, for the clinical dilemma commonly confronts general neurosurgeons that are regularly called upon to decide whether or not to reoperate on such patients. They are the clinicians that would participate in a pragmatic RCT on this clinical dilemma. It is interesting to notice that neuro-oncology surgical experts themselves showed even more uncertainty in the management of these patients.

Finally, answering a survey and seeing a real patient in clinic are very different things. One can only hope that surgeon responders took the time and care in answering the survey questions that they would normally devote to a clinical interaction.

TABLE 3. Intrarater Agreement Regarding Best Next Management Choice for Recurrent Glioblastoma

	Nondichotomized κ for All Cases (n = 37)	Dichotomized κ (Surgery vs. All Others)	Interpretation*
Rater 1	0.140 (–0.130, 0.490)	0.130 (–0.212, 0.473)	Slight
Rater 2	0.720 (0.498-0.929)	0.668 (0.402-0.934)	Substantial
Rater 3	0.300 (0.048-0.568)	0.308 (0.002-0.613)	Fair
Rater 4	0.459 (0.165-0.723)	0.532 (0.255-0.809)	Moderate
Rater 5	0.080 (–0.229, 0.391)	0.081 (–0.229, 0.391)	Slight
Rater 6	0.295 (0.025-0.581)	0.228 (–0.062, 0.518)	Fair
Rater 7	0.220 (0.025-0.407)	0.164 (–0.242, 0.570)	Slight

*According to Landis and Koch.[20]

Participation in studies that reveal clinical uncertainty may be a humbling experience, but one that can help modify the way we practice. It is promising that a significant proportion of responding surgeons were willing to include a majority of patients in a randomized trial. Physicians and patients' perceptions regarding the role of randomized trials in medical care may have to be modified if we are to practice outcome-based medical care.[21,26,27] In the meantime, while we still do not know how best to manage patients with recurrent GBM, the results presented here may promote participation in an RCT that properly addresses the dilemma.

CONCLUSION

The best management of patients with recurrent GBM remains uncertain. Neurosurgical decision-making for these patients is characterized by much uncertainty and poor agreement, regardless of patients' or clinicians' characteristics, including years of experience or having a neuro-oncology background. This demonstration of community uncertainty and equipoise supports the need for a randomized trial.

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Appendix B: Chapter 4 – Trial Related Material

Case Report Form (CRF)

Form A - Registration and Randomization

Registration

1. Date of enrollment (dd/mmm/yyyy) ☐

2. Patient initials or Identification # (Last, Middle, First) ☐

3. Date of Birth (dd/mmm/yyyy) ☐

4. Gender **Male** ☐ **Female** ☐

5. **Eligibility Criteria**

Inclusion Criteria (**Must All be Yes)**

Age ≥ 18 **Yes** ☐ **No** ☐

Previously histologically confirmed and surgically resected glioblastoma **Yes** ☐ **No** ☐

Previous craniotomy for open tumor resection
(needle biopsies alone do not count as resection) **Yes** ☐ **No** ☐

The attending surgeon considers re-operation may improve quality survival **Yes** ☐ **No** ☐

Neurological Status

6. Clinically significant neurological deficit?

   a. **Aphasia** (disabling) **Yes** ☐ **No** ☐

   b. **Motor score ≤ 3/5 in any limb** **Yes** ☐ **No** ☐

   c. **Other** (please explain) **Yes** ☐ **No** ☐

7. Karnofsky Performance Status (KPS) at time of study enrolment ☐ < 70 ☐ ≥ 70

Medical History

8. Date of initial GBM resection (dd/mmm/yyyy) ☐

9. MGMT promoter methylation Yes ☐ No ☐ Unknown ☐

10. IDH-1 status IDH-wildtype ☐ IDH-mutant ☐ Unknown ☐

11. Previous chemotherapy? **Yes** ☐ **No** ☐

12. Previous radiation therapy? **Yes** ☐ **No** ☐

Recurrent GBM Characteristics

13. Type of recurrence Symptomatic ☐ Imaging only ☐

14. Location (check all that apply)

☐ Left Frontal
☐ Left Parietal
☐ Left Occipital
☐ Left Temporal

☐ Right Frontal
☐ Right Parietal
☐ Right Occipital
☐ Right Temporal

☐ Cerebellar +/- brainstem

☐ Deep gray structure involvement

☐ Other, please detail

Save for Randomized Allocation

Form B – Patient Consent

1. Allocated management

AUTO POPULATED

2. Is the management plan accepted by both patient and treating physician?

Yes ☐ No ☐

2.a If No, new management

☐ Standard care without repeat resection

☐ Repeat resection

2.b Reason for cross-over

☐ Patient choice
☐ Physician choice
☐ Other, please explain

3. Has the patient/ representative signed the consent form? **Yes** ☐ **No** ☐

Form C – Repeat Resection and Discharge (complete as many times as needed)

1. Date of Hospital Admission (dd/mmm/yyyy) ☐
2. Date of repeat surgical resection ☐

3. Surgical complications?

☐ None

☐ Cerebrospinal fluid leak

☐ Wound Infection

☐ Neurological deterioration (if so please detail) ☐

☐ Systemic deterioration

☐ Additional operation required (in addition to re-resection; ie: hematoma evacuation, VP shunt). If so, please detail)

☐

Discharge

4. Date of discharge (dd/mmm/yyyy) ☐
5. Length of hospitalization (days) AUTO-Populated
6. Discharge destination

Home ☐ Other hospital ☐ Rehabilitation center ☐

Death during this hospitalization ☐

Form D – Follow up form (complete as many times as needed)

1. Date of enrollment (dd/mmm/yyyy) AUTO- populate from Form A
2. Date of this follow-up (dd/mmm/yyyy)

3. Disease progression since last follow-up **Yes** ☐ **No** ☐

   If yes, ☐ **symptomatic ?** **or** ☐ **imaging only ?**

   Please explain:

4. Patients' current location

   ☐ Home

   ☐ Hospital
   ☐ Rehabilitation center
   ☐ Long-term care facility
   ☐ Deceased (please fill form F)

5. If applicable, date of admission into hospital, nursing home, or palliative care facility. (dd/mmm/yyyy)

6. If applicable, date of discharge from the hospital, nursing home, or palliative care facility. (dd/mmm/yyyy)

Form F – Mortality Report

1. Date form completed (dd/mmm/yyyy)

2. Date of enrollment (dd/mmm/yyyy) Auto-populate from Form A

3. Date of death (dd/mmm/yyyy)

   Enrollment to death (days) Date Difference (AUTO)

4. Cause of death

   - ☐ Surgery related complication
   - ☐ GBM progression
   - ☐ other (please specify)

5. Additional comments (optional)

DSMC Charter

Table of Contents

Abbreviations

AE	Adverse Event
DSMC	Data Safety and Monitoring Committee
SAE	Serious Adverse Event
SC	Steering Committee
3rGBM	Role of Repeat Resection for Recurrent Glioblastoma

Data Safety and Monitoring Committee Members

Georges L'Esperance, MD – Chair (neurosurgery)
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Yan Yuan, PhD (statistics)
Edmonton, Alberta Canada
E-mail: yyuan@ualberta.ca

SECTION 1 PREAMBLE

This document constitutes the Charter for the Data Safety and Monitoring Committee (DSMC) for the Role of Repeat Resection in Recurrent Glioblastoma (3rGBM) study. The Charter describes the governing principles as well as the operational details pertaining to the safety monitoring and interim safety analysis for 3rGBM. The membership, organization, roles, and primary responsibilities of the independent DSMC are detailed, as are the responsibilities of other parties involved in the preparation of safety and interim data.

SECTION 2 Functions of the DSMC

The function of the DSMC is to ensure, to the extent possible, the safety of all patients in the 4rGBM study through periodic review of relevant study-related data captured during the course of the clinical trial. To accomplish this task, the DSMC will:

2.1 Review all Serious Adverse Events (SAE), sorted by site but without attribution of causality. Review of SAE will occur at intervals specified by the Chair who will receive a periodic update on all AEs. The Chair and the DSMC members will be blinded to treatment allocation as much as possible (certain treatment-specific SAEs do not lend themselves to true blinding).

2.2 Review all safety data at planned interim analyses when a specified number of patients have been enrolled and have completed their first evaluation following the planned intervention. Each trial interim safety analysis will occur when 100 patients have been recruited and follow-up is complete.

Data utilized in the periodic safety data reviews will be the best available data at the time of the data cut-off date for the review, regardless of whether the data have been fully cleaned and finalized. Based upon interim findings, the DSMC may change the frequency and the number of reviews at any time.

2.3 Provide recommendations to the Steering Committee (SC), including protocol modifications and whether or not to continue patient enrolment into this trial.

SECTION 3 Roles and Responsibilities

3.1 DSMC Members

3.1.1 All members will sign a copy of the approved DSMC Charter prior to the first review of SAE data.

3.1.2 The DSMC will approve recommendations only after unanimous agreement between the members.

3.2 DSMC Chair

3.2.1 The Chair reviews all Serious Adverse Events (SAEs).

3.2.2 The Chair shares information about SAE with other members of the DSMC at a frequency determined by number and severity of SAEs. The Chair may call for the expertise of the trial statistician, if needed. Based on feedback from the trial statistician, the Chair may call for a meeting.

3.2.3 The Chair ensures that appropriate records of each meeting of the DSMC are established and maintained.

3.2.4 The Chair communicates DSMC recommendations to the SC through the Principal Investigator.

3.2.5 The Chair is responsible for calling emergency meetings of the DSMC, if required.

3.3 4rGBM Steering Committee

3.3.1 The SC is responsible for all aspects of conducting the trial.

3.3.2 The SC provides timely notice of DSMC and SC recommendations and decisions to all 4rGBM investigators and other organizations involved in conducting the trial.

3.4 Trial Coordinator

3.4.1 The trial coordinator is responsible for preparing the SAEs report sorted by site for ongoing safety review and interim analyses.

3.4.2 The trial coordinator is responsible for timely entry and resolution of queries of the clinical data so that the data are available for transfer to the DSMC.

3.4.3 The trial coordinator is responsible for collecting all source documents from investigative sites for appropriate review of SAEs.

SECTION 4 Confidentiality

All trial data reviewed by the DSMC will be held in the strictest of confidence. These data will not be shared with any person involved in the conduct of the 4rGBM study until after patient enrolment in the trial has ceased, all enrolled patients have completed the trial and final data lock has occurred, or if the trial is terminated for other (administrative) reasons.

SECTION 5 Conflict of Interest Disclosure

The members of the DSMC must not have a direct interest, financial or otherwise, in the outcome of this trial. Members of the DSMC will be responsible for advising the Principal Investigator of any changes in their status of conflict of interest throughout the trial. Members of the DSMC who develop significant or potentially significant conflicts of interest as determined by the SC will be required to resign from the DSMC.

SECTION 6 Duration and Changes of DSMC Membership

6.1 The length of DSMC membership will cover the duration of the trial. If a Committee member resigns from the DSMC and a replacement is deemed necessary by the SC and the DSMC, the SC will be responsible for recommending a replacement.

6.2 Should the DSMC require additional expertise for data evaluation, external consultants may be added to the DSMC. The DSMC Minutes should reflect the Committee's consensus that additional expertise was needed, as well as the special requirements of the new (or temporary) Member(s) and a list of recommended candidates. The DSMC Chair will relay this information to the Principal Investigator. This information shall include a recommendation from the DSMC of the name and

credentials of appropriate additional candidate(s) to be added to the DSMC.

SECTION 7 DSMC Meetings and Voting

7.1 Minutes must be taken at all DSMC meetings. These Minutes will include a summary of the discussion, recommendations, and the rationale for those recommendations. At the conclusion of the trial, a complete file of Minutes from each meeting will be provided to the SC by the DSMC chairperson.

7.2 The DSMC will approve recommendations unanimously.

7.3 The trial coordinator is responsible for the scheduling and logistics of the initial face-to-face organizational meeting for the DSMC members, as well as providing appropriate protocol information. DSMC members are expected to review this information before the initial organizational meeting.

SECTION 8 Planned Interim Analyses

The planned interim analyses are summarized as follows:

8.1 **Safety Analysis:** One interim safety analysis is planned during patient enrolment, when 100 randomized patients have completed their follow-up. The timing of the interim safety analyses may be adjusted based upon the rate of AE reporting by investigators for the trial.

8.2 The primary purpose of the interim safety analysis is to ensure that SAEs are within expected confidence intervals for each management option.

8.3 **Efficacy Analysis:** No interim efficacy analyses are planned.

8.4 **Pre-specified Stopping Rules:** The Steering Committee cannot foresee what findings would require trial stoppage, given that all patients are expected to have mortality within 2 years. Because surgery is standard treatment, there is no need to monitor unexpected events, as with experimental therapy.

SECTION 9 Safety Monitoring Procedures and Unscheduled DSMC Meetings

9.1 Ongoing monitoring of all SAEs for this trial will be conducted by the trial coordinator.

9.2 The trial coordinator will forward SAE case summaries to the DSMC Chair on a periodic basis.

9.3 The DSMC Chair will forward SAE summaries to other members of the DSMC at intervals depending on the frequency and severity of SAEs.

9.4 If requested by the Chair, the trial statistician will perform a formal evaluation of summaries to check for any persistent trend across successive reviews.

9.5 The DSMC Chair has the authority to convene the DSMC if safety issues are identified during the reviews.

SECTION 10 Steering Committee Actions

10.1 The Principal Investigator is responsible for documenting the receipt of a DSMC recommendation. If an internal review is necessary, the Principal Investigator is responsible for maintaining a list of personnel involved in the review and a description of what subset of data, if not all the data, were shared.

10.2 The decision that the SC makes of whether to implement or decline a DSMC recommendation must be communicated to the DSMC Chair by the Principal Investigator. If a disagreement arises between the DSMC recommendation and SC action, a meeting between the DSMC and SC will be convened. Action taken on all

DSMC recommendations must be documented.

SECTION 11 Documentation

11.1 **Safety Reports on all SAEs** : SAE case summaries will be prepared by the trial coordinator based upon the SAE and other case report forms or source documents. Case summaries will be forwarded to the DSMC Chair.

11.2 **Interim Analysis (100 enrolled patients):** Number of enrolled patients, number of evaluable patients, reasons for excluding from analysis; reason for early termination or withdrawal during the trial; tabular safety data will be provided to the DSMC according to the following format :

	Group 1	**Group 2**
Primary Outcome		
Death		
Time to Death (days)		
Serious adverse events within 31 days of treatment		
Number of days hospitalized / nursing home / palliative care /		

Appendix I: Signatures for the Charter

I confirm that I have read the DSMC Charter for the 4rGBM study, I understand it, and I will work according to this Charter and to the ethical principles stated in the latest version of the Declaration of Helsinki and the applicable guidelines for Good Clinical Practices.

_____ _____

Georges L'Esperance, MD Date

_____ _____

Yan Yuan, PhD Date

Patient Informed Consent Form

Informed Consent Form for Participation in a Research Study

Study title: **Repeat Resection in Recurrent Glioblastoma (3rGBM) Trial: a randomized care trial for patients with recurrent GBM**

[Is another brain operation beneficial for patients with recurrent glioblastoma or not?]

Protocol ID: HREBA.CC- 21-0094

Principal Investigator: Tim Darsaut, MD FRCPC
Department of Surgery
University of Alberta
2D1.02 WMC
8440 112 Street
Edmonton, AB, T6G 2B7
Phone: (780) 407-1440

Co- Investigators:
Dr. Karolyn Au (407-1776)
Dr. Vivek Mehta (407-8346)
Dr. Aaron Hockley (407-7179)
Dr. Cian O'Kelly (407-1440)
Dr. Richard Fox (407-3558)
Dr. Jenny Souster (407-6870)
Dr. Tejas Sankar (407-6869)
Dr. Michael. Chow (407-1428)
Dr. Andrew Nataraj (407-7179)
Dr. Robert Broad (407-8296)
Dr. Greg Bowden (407-1776)
Dr. Matt Wheatley (407-6869)
Dr. Max Findlay (407-3548)
Dr. Andrew Jack (407-1428)

Sponsor: University of Alberta

Emergency Contact Number (24 hours / 7 days a week): 780-407-6324.

Non-Emergency contact numbers are noted at the end of this document under the section heading "WHO DO I CONTACT FOR QUESTIONS?".

For assistance with terminology within this consent form, please refer to the Canadian Cancer Society Glossary of Terms at http://info.cancer.ca/e/glossary/glossary.html

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WHY AM I BEING ASKED TO TAKE PART IN THIS RESEARCH STUDY?

You are being invited to participate in a research study because your brain tumor (glioblastoma) has recurred.

This consent form provides detailed information about the study to assist you with making an informed decision. Please read this document carefully and ask any questions you may have. All questions should be answered to your satisfaction before you decide whether to participate.

The study staff will tell you about timelines for making your decision. You may find it helpful to discuss the study with family and friends so that you can make the best possible decision within the given timelines.

Taking part in this study is voluntary. You may choose not to take part or, if you choose to participate, you may leave the study at any time without giving a reason. Deciding not to take part or deciding to leave the study will not result in any penalty or any loss of medical or health-related benefits to which you are entitled.

The study doctor, who is one of the researchers, will discuss this study with you and will answer any questions you may have. If you do consent to participate in this study, you will need to sign and date this consent form. You will receive a copy of the signed form.

WHAT IS THE BACKGROUND INFORMATION FOR THIS STUDY?

The term glioblastoma refers to a tumour of the brain. Reoccurrence of glioblastoma almost inevitably happens and the question of the benefit to you of a repeat surgical procedure arises. Alternatively, you could be treated by other standard of care methods such as chemotherapy or radiotherapy, without repeat surgery. Also, these treatments can be given after surgery.

The two standard of care treatment concepts that are applied worldwide in accordance with internationally recognized treatment guidelines to treat a recurrent glioblastoma are:

I. Re-operation for further resection of the known glioblastoma

II. Non-surgical treatment methods that include radiotherapy and/or second line chemotherapy

Although both surgical and non-surgical options can help combat the glioblastoma, whether there is any additional benefit of repeat surgery is unclear. While surgery might prolong survival, there are additional risks and discomforts with re-operation.

Furthermore, following surgery, chemotherapy or radiotherapy is delayed due to the necessary healing time required after the surgery. Immediate second-line treatment with chemotherapy/ radiotherapy without surgery means that more tumour is present at the time that is started which may be less sensitive to the treatment..

The Health Research Ethics Board of Alberta – Cancer Committee (HREBA-CC), which oversees the ethical acceptability of research involving humans, has reviewed and granted ethics approval for this study.

WHY IS THIS STUDY BEING DONE?

We would like to see if repeat surgery for recurrent glioblastoma improves the amount and quality of life compared to standard of care non-surgical treatments.

Up to now it is unknown which of the two treatment concepts offers greater benefits to you as a patient. The objective of this clinical trial is to examine the benefits and risks which these two treatment concepts for patients with recurrent glioblastoma.

WHAT ARE OTHER OPTIONS IF I DECIDE NOT TO PARTICIPATE IN THIS STUDY?

You do not have to take part in this study, in order to receive continued care. Standard care may include:

- Repeat surgery
- Radiation therapy
- Chemotherapy
- Combination of radiotherapy and chemotherapy
- Continuing regular observation and routine follow-up care e.g., symptom management

Please talk to the study doctor or your care doctor about the known benefits and risks of these other options before you decide to take part in this study. Your study or care doctor can also discuss with you what will happen if you decide not to undertake any treatment at this time

HOW MANY PEOPLE WILL TAKE PART IN THIS STUDY?

About 250 participants will be take part into this study in Canada. We plan to enroll up to 100 participants at the University of Alberta hospital.

WHAT WILL HAPPEN DURING THIS STUDY?

ASSIGNMENT TO A GROUP

If you decide to participate then your treatment will be randomly allocated, to one of the groups described below. Randomization means that your treatment is decided by chance (like flipping a coin).There is no way to predict which group you will be assigned to. You will have an equal chance of being placed in either group. Neither you, the study staff, nor the study doctor can choose what group you will be in.

I. **Surgical group -** Repeat surgery for additional tumour removal, followed by additional radiotherapy or chemotherapy as per standard of care

II. **Non-surgical group -** Standard of care treatment (radiotherapy or chemotherapy as decided by your neurooncologist) without having another cranial surgery

STUDY INTERVENTION

I. Group 1 (Surgical group): If you are randomly allocated to receive surgery, your doctors will decide on a date for surgery.

II. Group 2 (Non-Surgical group): If you are randomly allocated to receive non-surgical care, your doctors will discuss other standard of care non-surgical treatment possibilities with you (chemotherapy or radiotherapy).

STUDY PROCEDURES

1. Established Procedures

After you consent to participate in the trial, we will ask you a few questions about yourself and your medical history and carry out a neurological examination. These data and investigations are routinely recorded and carried out, whether you participate in the trial or not.

The following established procedures will be done as part of this study before assigning you to a group:

- questions about personal details – same as standard of care
- questions about medical history and medication: Same as standard of care
- neurological examination: Same as standard of care. The neurological examination is used to detect the frequency and type of neurological deficits (for example, speech disorders, motor disorders of the arms and legs, vision or memory impairment). It will be done as per standard of care treatment
- magnetic resonance imaging (MRI) scan - You have most likely already had several of these studies already as part of your care. MRI uses a strong magnet to produce pictures of areas inside the body such as organs and other tissue, and inside of bones. MRI scans often involve injecting a dye into your vein. Although the dye is relatively safe, occasionally side effects or allergic reactions can occur. These may be mild such as skin rash or hives to severe including difficulty breathing, shock and very rarely may result in death. We will use the same MRI data that would have been done as a part of your standard of care treatment.

2. Experimental Procedures

Randomization:

After the initial standard procedure, you will be randomly allocated to receive either of surgical or non-surgical management.

If you are assigned to the surgical group, your doctors will decide on a date for surgery. After you have had your surgery and are discharged from the hospital, you will be referred to your treating neurooncologist for additional second-line treatment (chemotherapy or radiotherapy) as soon as your condition after surgery permits.

If you are assigned to the non-surgical group, your doctors will discuss the possibility of second-line treatment (chemotherapy or radiotherapy) with you and you will be referred to your treating neurooncologist. In this case, second-line treatment can be started without delay.

If you are assigned to the surgical group, an MRI of the head will be obtained after the operation and a further neurological examination will be carried out before you are discharged from the hospital. The radiological examinations (MRI) are carried out in order to determine whether the glioblastoma has been completely removed (after surgery) or whether it has grown again (follow-up examinations). MRI examinations are carried out routinely with all patients with glioblastoma and will likely be carried out if you receive second line treatment.

FOLLOW UP

There are no research specific visits or follow ups involved. All follow-ups will be conducted as part of your standard of care. We will collect data from your routine clinic appointments.

If you are assigned to the surgical group, after surgery you have to be in the hospital until your treating physician discharges you. There will be a routine post-surgery neurological assessment prior to your discharge which will take approximately 10 minutes. After discharge, you will be referred to your treating neuro-oncologist to start your second line treatment (chemo or radiotherapy) soon as your condition after surgery permits. It would take approximately 1 month to start your second line treatment. If you are in the non-surgical group, your second line treatment can be started immediately.

WHAT ARE THE BENEFITS OF PARTICIPATING IN THIS STUDY?

Both approaches – repeat surgery followed by second-line treatment as well as the immediate second-line treatment comply with treatment guidelines applied worldwide. Participation in the clinical trial will not provide you with any additional benefit. Findings from this trial, however, may be important for others who develop a recurrent glioblastoma, and can help us to improve treatment in the future.

WHAT ARE THE POTENTIAL SIDE EFFECTS FROM PARTICIPATING IN THIS STUDY?

If you are assigned to the group having re-operation, you will be subjected to the risks associated with surgery.

The main risks of repeat surgery are:

- Brain injuries with corresponding disability, depending on which part of the brain is injured (for example, speech disorders, motor disorders of the arms and legs, vision or memory impairment or even death). The risks of brain injury are thought to be slightly greater than after the initial surgical operation.
- Bleeding in the brain, around the meninges or below the skin
- Wound healing problems, including infections

Your surgeon will inform you about the nature and extent of the risks in your particular case.

After surgery, you first need to recover before second-line chemotherapy or radiation treatment can be started. Thus, the second-line treatment is delayed, which means that growth of unremoved tumor cells is possible.

If you are assigned to the group that does not undergo renewed surgery, no operation will be performed, and the risks associated with surgery do not exist. The main part of the tumor visible in the MRI remains. However, second-line treatment can be started immediately.

WHAT ARE MY RESPONSIBILITIES AS A STUDY PARTICIPANT?

As a participant in a care trial you will receive standard care and standard followup:

- to follow the medical instructions of the study doctor as you would normally.

• to inform the study doctor about the progression of the disease and to report any new symptoms, new disorders or changes to your condition, as you would normally.

HOW LONG WILL I BE PARTICIPATING IN THIS STUDY?

For both groups, there will be follow up visits according to normal routine, and for up to 5 years. There will be no additional follow-up visits other than your routine clinical appointments, there will be no additional tests and they will not require additional time.

CAN I CHOOSE TO LEAVE THIS STUDY EARLY?

You can choose to end your participation in this research (called early withdrawal) at any time without having to provide a reason. If you choose to withdraw early from the study without finishing the intervention, procedure, or follow-up, you are encouraged to contact the study doctor or study staff. Information that was collected before you withdrew will be used by the researchers for the purposes of the study, but no additional information will be collected or sent to the sponsor after you withdraw your permission. We would request to record data from the chart regarding survival times unless you choose to completely withdraw your consent.

CAN MY PARTICIPATION IN THIS STUDY END EARLY?

In addition to you being able to stop the study at any time, the study doctor or the sponsor may withdraw you from this study at any time for the following reasons:

- if there are changes in the internationally recognized treatment guidelines for recurrent glioblastomas which do not justify a continuation,
- if further surgery proves to be a significantly better or worse form of therapy
- If the investigator in charge of the study thinks it is in your best interest
- If there are administrative reasons to abandon the study.

If you are removed from the study, the study doctor will discuss the reasons with you and plans will be made for your continued care outside of the study.

HOW WILL MY PERSONAL INFORMATION BE KEPT CONFIDENTIAL?

If you decide to participate in this study, the study doctor and study staff will only collect the information they need for this study.

Records identifying you, including information collect from your medical files/records, such as your Electronic Medical Records (EMR), Netcare, charts, etc., will be kept confidential to the extent permitted by the applicable laws, will not be disclosed or made publicly available, except as described in this consent document. A unique study ID will be assigned to you and all your personal identifiable information (name, DOB etc.) will be removed from the research documents before sharing with other study collaborators. Only research team members will have access to your medical charts and to your personal identifiable information.

Authorized representatives of the following organizations may look at your identifiable medical/clinical study records at the site where these records are held for quality assurance

purposes and/or to verify that the information collected for the study is correct and follows proper laws and guidelines:

- Members of the Regulatory/Audit team at University of Alberta for quality assurance purposes.
- The Health Research Ethics Board of Alberta – Cancer Committee, which oversees the ethical conduct of this study;

Authorized representatives of the above organizations may **receive** information related to the study from your medical/clinical study records that will be kept confidential in a secure location and may be used in current or future relevant health research. Your name or other information that may identify you will not be provided (i.e., the information will be de-identified). The records received by these organizations will be coded with a number. The key that indicates what number you have been assigned will be kept secure by the researchers directly involved with your study and will not be released.

The de-identified study data (i.e., All personal identifying information will be removed and replaced with a unique study ID) may be shared with study collaborators at various sites around the world.

Any disclosure of your identifiable health information will be done in accordance with federal and provincial laws including the Alberta Health Information Act (HIA). The organizations listed above are required to have organizational policies and procedures to protect the information they see or receive about you, except where disclosure may be required by law. The study doctor will ensure that any personal health information collected for this study is kept in a secure and confidential location at University of Alberta, Edmonton as also required by law.

If the results of this study are published, your identity will remain confidential. It is expected that the information collected during the study will be used in analyses and will be published/presented to the scientific community at meetings and in journals.

Even though the likelihood that someone may identify you from the study data is very small, it can never be completely eliminated. Every effort will be made to keep your identifiable information confidential, and to follow the ethical and legal rules about collecting, using and disclosing this information.

Any study-related data sent outside of Canadian borders may increase the risk of disclosure of information because the laws in those countries dealing with protection of information may not be as strict as in Canada. However, all study data transferred outside of Canada will be coded (this means it will not contain your personal identifying information such as your name, address, medical health number or contact information). Any information will be transferred in compliance with all relevant Canadian privacy laws. By signing this consent form, you are consenting to the disclosure of your coded information to organizations located outside of Canada.

A copy of the consent form that you sign to enter the study will be included in your health record/hospital chart.

WILL MY HEALTHCARE PROVIDER(S) BE INFORMED OF MY PARTICIPATION IN THIS STUDY?

Your family doctor/health care provider will be informed that you are taking part in a study so that you can be provided with appropriate medical care. If you do not want your family doctor/health care provider to be informed, please discuss with your study team to find out your options.

WILL THERE BE COSTS INVOLVED WITH PARTICIPATING IN THIS STUDY?

There would be no extra costs involved in participating in this study.

WILL I BE COMPENSATED FOR PARTICIPATING IN THIS STUDY?

You will not be paid for taking part in this study. Although no funds have been set aside to compensate you in the event of injury or illness related to the study treatment or procedures, you do not give up any of your legal rights for compensation by signing this form.

WHAT ARE MY RIGHTS AS A PARTICIPANT IN THIS STUDY?

You will be told, in a timely manner, about new information that may be relevant to your willingness to stay in this study.

You have the right to be informed of the results of this study once the entire study is complete. If you would like to be informed of these results, please contact the study doctor.

Your rights to privacy are legally protected by federal and provincial laws that require safeguards to ensure that your privacy is respected.

By signing this form, you do not give up any of your legal rights against the hospital, researchers, sponsor, institutions or their agents involved for compensation, nor does this form relieve these parties from their legal and professional responsibilities

IS THERE ANY CONFLICT OF INTEREST RELATED TO THIS STUDY?

There are no conflicts of interest related to this study.

WHERE CAN I FIND ONLINE INFORMATION ABOUT THIS STUDY?

A description of this clinical trial will be available on http://www.clinicaltrials.gov (Registration # NCT04838782). This website will not include information that can identify you. You can search for this website at any time.

WHO DO I CONTACT FOR QUESTIONS RELATED TO THIS STUDY?

If you have questions about taking part in this study you should talk to the researcher, co-investigator or study nurse. These person(s) are:

Dr. Tim Darsaut (Principal Investigator) Phone: (780) 407-1440

If you have questions about your rights as a participant or about ethical issues related to this study and you would like to talk to someone who is not involved in the conduct of the study, please contact the Office of the Health Research Ethics Board of Alberta.

Telephone: 780-423-5727, Toll Free: 1-877-423-5727

UNDERSTANDING AND SIGNATURES PAGE

Part 1 –**PARTICIPANT ACKNOWLEDGEMENT** (to be completed by the potential participant)

	Yes	No
Do you understand that you have been asked to take part in a research study?	☐	☐
Do you understand why this study is being done?	☐	☐
Do you understand the potential benefits and risks/discomforts of taking part in this study?	☐	☐
Do you understand what you will be asked to do should you decide to take part in this study?	☐	☐
Do you understand that you are free to leave the study at any time, without out having to give reason or without penalty?	☐	☐
Do you understand that we will be collecting information about you for use in this study only?	☐	☐
Do you understand that by signing this consent form you are allowing the study team to collect, use and disclose information about you from your personal medical records?	☐	☐
Do you understand who can potentially see your medical /study records, including those that identify you?	☐	☐
Do you understand that by signing this consent form that you do not give up any of your legal rights?	☐	☐
Do you understand that your family doctor/health care provider will/may be informed of your participation in this study?	☐	☐
Have you had enough opportunity to ask questions and discuss this study?	☐	☐

If a potential participant has answered "no" to any question above, please make sure to go over the relevant information with them until they do understand it. ***Only once they are comfortable with all the information can you accept their decision to participate in the study***

By signing this form, I agree to participate in this study.

_____	_____	_____
Signature of Participant	**Printed Name**	**Date**

Part 2 - **STUDY TEAM ACKNOWLEDGEMENT**

To be completed by the study doctor or designee who conducted the informed consent discussion. Only compete this section if the potential participant has **agreed** to participate
I believe the person signing this form understands what is involved in this research study and has freely decided to participate.

Signature of Person Conducting the Consent Discussion	Printed Name	Date

Part 3 - **TRANSLATOR/INTERPRETER ACKNOWLEDGEMENT**
To be completed only if the participant is unable to read or requires assistance of an oral translator/interpreter.

- The informed consent form was accurately explained to, and apparently understood by the participant.
- Informed consent was freely given by the participant.

Signature of Impartial Witness/Interpreter	Printed Name	Date

****You will be given a copy of this signed and dated consent form prior to participating in this optional research ****

Neurochirurgie

Repeat Resection in Recurrent Glioblastoma (3rGBM) Trial: a randomized care trial.

--Manuscript Draft--

Manuscript Number:	
Article Type:	Original Article
Section/Category:	Submission for a regular issue / Article scientifique pour un numéro normal
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Abstract:	Background : The prognosis for patients with recurrent glioblastoma (GBM) is dismal, and the question of repeat surgery at time of recurrence is common. Re-operation in the management of these patients remains controversial, as there is no randomized evidence of benefit. An all-inclusive pragmatic care trial is needed to evaluate the role of repeat resection. Methods : 3rGBM is a multicenter, pragmatic, prospective, parallel-group randomized care trial, with 1:1 allocation to repeat resection or standard care with no repeat resection. To test the hypothesis that repeat resection can improve overall survival by at least 3 months (from 6 to 9 months), 250 adult patients with prior resection of pathology-proven glioblastoma for whom the attending surgeon believes repeat resection may improve quality survival will be enrolled. A surrogate measure of quality of life, the number of days outside of hospital/nursing/palliative care facility, will also be compared. Centers are invited to participate without financial compensation and without contracts. Clinicians may apply to local authorities to approve an investigator-led in-house trial, using a common protocol, web-based randomization platform, and simple standardized case report forms. Discussion : The 3rGBM trial is a modern transparent care research framework with no additional risks, tests, or visits other than what patients would encounter in normal

	care. The burden of proof remains on repeat surgical management of recurrent GBM, because this management has yet to be shown beneficial. The trial is designed to help patients and surgeons manage the uncertainty regarding optimal care.