Journal of Neuro-Oncology (2021) 151:103–112
https://doi.org/10.1007/s11060-020-03671-w

TOPIC REVIEW

A contemporary update on glioblastoma: molecular biology, current management, and a vision towards bio-adaptable personalized care

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Received: 21 October 2020 / Accepted: 30 November 2020 / Published online: 4 January 2021

Abstract

Introduction Glioblastoma (GBM) is the most fatal brain tumor in adults. Current survival rates of GBM remain below 2 years due to GBM's aggressive cellular migration and genetically driven treatment escape pathways. Despite our rapidly increasing understanding of GBM biology, earlier diagnoses, and refined surgical techniques, only moderate survival benefits have been achieved. Nonetheless, the pressing need for better survival rates has brought forward a multitude of newer therapeutic approaches and opened the door for potential personalization of these modalities in the near future.
Methods We reviewed the published literature discussing the current state of knowledge regarding GBM biology and therapy and summarized the information that may point toward future personalized therapeutic strategies.
Results Several novel modalities such as oncolytic viruses, targeted immune, and molecular therapies, and tumor treating fields have been introduced. To date, there is no single treatment modality for GBM, but rather a wide spectrum of combined modalities that address intratumoral cellular and genetic variabilities. While the current state of GBM research and clinical trial landscape may hold promise, current literature lacks any fruitful progress towards personalized GBM therapy.
Conclusion In this review, we are discussing our recent knowledge of the GBM genetic biologic landscape and the current advances in therapy, as well as providing a blueprint for an envisioned GBM management paradigm that should be personalized and adaptable to accommodate each patient's diverse genetic variations and therapy response/escape patterns.

Keywords Glioblastoma · Biological · Organoid · Personalized

Introduction

Glioblastoma (GBM) is the most common and most fatal primary brain neoplasm in adults, representing almost half of all primary brain tumors [1]. Classified by the 2016 "WHO Classification of Tumors of the Central Nervous System" as a grade IV glioma, GBM has a current incidence of 3.1 per 100,000; a male predominance (1.6:1); and afflicts Caucasians more than African Americans (2:1) [1]. GBM is also a disease of the older population, with a peak incidence above 60 years [1]. Apart from a few genetically defined syndromes (e.g. familial glioma, Turcot Syndrome, Li-Fraumeni syndrome, and Neurofibromatosis type 1), risk factors for developing GBM remain poorly defined in the current literature [2].

Our knowledge of GBM has expanded dramatically, which leads in turn to moderately improve the median survival rates for GBM patients after receiving treatment [3]. Following surgical resection and chemoradiation, the median survival rate is 18 months, while survival for patients with only supportive treatment is 4 months [4]. Long term survivors represent 3–5% of patients surviving more than 3 years [5]. Age plays a significant role in predicting survival. Longer survival is inversely correlated with age: 5% of patients who are less than 65 years are alive 3 years following diagnosis, while only 2% of patients above 65 years old are alive after the same time period [1].

While surgical resection remains the main predictor of favorable survival outcome in GBM patients, multimodal treatment regimens are the standard of care [6]. Other factors may hinder further survival benefits; namely, the infiltrative

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nature of the GBM. Additionally, surgical resection is often limited by tumor proximity to eloquent regions, despite novel preoperative planning and surgical techniques. This may contribute to subtotal total resections [7]. Lastly, GBM employs numerous genetically-driven treatment escape pathways that suppress the immune response [8]. One of those pathways is the programmed cell death protein-1 ligand pathway (PD-L1); a potent immunosuppressive agent expressed in microglia which is highly expressed in normal brain tissue proximal to GBM [9]. PD-L1 acts as a suppressor of cytotoxic T-cells proliferation and induces apoptosis in this cell population [8]. Another immune evasion pathway is the activator of transcription 3 (STAT3) mediated pathway which is overexpressed in GBM leading to pro-inflammatory cytokine inhibition [10]. Moreover, this pathway plays an essential role in the inappropriate GBM vascularization and excessive O2 consumption by GBM cells [11]. Other factors: EGF, IL-6, and Metalloproteinases significantly mediate GBM invasion and migration [12].

The pressing need for better survival rates for patients with GBM has brought forward a multitude of different therapeutic approaches. Substantial efforts have focused on creating effective biological therapeutic modalities for GBM, including vaccines and immuno-targeted therapies [13]. Although initial survival improvements are modest, these novel therapies carry significant potential, newer techniques, and advances in personalized medicine that may hold promise and excitement for the future of GBM therapeutic management.

Genetics and cellular biology of GBM

The genetic profile of GBM and the impact on treatment

GBM is one of the most genetically studied tumors and the first cancer systematically analyzed by the Cancer Genome Atlas Research Network [14]. Of the highly diverse genetic landscape of GBM, some genes have a significant effect on the clinical course of GBM. The DNA repair protein O6-Methylguanine-DNA methyltransferase (MGMT) is a universally expressed protein in human tissues and is predominantly epigenetically regulated in high-grade gliomas [15]. MGMT encodes a DNA repair protein that naturally inhibits the effect of alkylating agents, by removing the alkyl group rendering chemotherapy ineffective [16]. In a study by Hegi et al. in 2005, they reported that epigenetic silencing of the MGMT DNA-repair gene by methylation is associated with longer survival in GBM patients who receive the alkylating agent Temozolomide [16]. Currently, MGMT methylation status is one of the most important biomarkers to predict tumor response to standard of care Temozolomide [16]. One of the hallmark gene mutations that led to a clinically relevant classification in adult glioma is the IDH status [17]. The relevance of the NADP (+)-dependent isocitrate dehydrogenases protein encoded by IDH1 and IDH2 genes was first described by Yan et al. in 2009 [18]. In their study, the authors sequenced 445 central nervous system (CNS) tumors and 494 non-CNS tumors in which they compared the enzymatic activity of the proteins produced by normal and mutant IDH1 and IDH2 Genes. They concluded that IDH1 mutations are present in more than 70% of WHO grade II and III astrocytomas, oligodendrogliomas, and GBMs that developed from low-grade gliomas. The authors also described that tumors without IDH1 mutations often manifest a corresponding IDH2 gene. The data from this study, as well as subsequently published data, confirmed that adults diagnosed with IDH wild-type GBM uniformly have a poor prognosis. Currently, the (MGMT) methylation status and mutation in NADP (+)-dependent isocitrate dehydrogenases encoded by IDH1 and IDH2 genes are the most impactful factors on the clinical course of GBM [19]. Moreover, another factor that could be implicated in the GBM overall survival is sex difference [20]. Yang et al. recently investigated sex differences in GBM patients using quantitative imaging-based analysis, transcriptome, and survival data. They have concluded that standard GBM therapy is more effective in female patients [21].

From Glioma stem cells (GSCs) to the tumor microenvironment

GBM is characterized by heterogeneity on both a gross and microscopic level. At the gross level, an area of central hypoxia and necrosis is surrounded by a pseudo-palisading, proliferative edge with a highly vascular stroma [22]. The outer, contrast-enhancing rim, is a region of tumor growth with increased cellular atypia and pleomorphism. In contrast, the inner core of the tumor has a high hypoxic gradient and harbors a high concentration of GSCs residing in perivascular niches. GSCs, with a widely diverse cellular hierarchy structure, are believed to be the cellular origin of GBM [23]. These cells have a fast growth rate, the ability of self-renewal, and a very long lifespan; consequently, they accumulate chance genetic mutations leading to treatment resistance [24]. GSC can produce histopathologically similar tumors in orthotopic mouse models and proliferate indefinitely in vitro. In the lab, these cell populations display more resistance to chemotherapy and radiation. Thus, GBM pathogenesis, recurrence, and heterogeneity are believed to be, in part, orchestrated by GSCs which are highly heterogeneous [25]. They are categorized into two groups based on the hypothesized cellular origin: proneural (PN) and mesenchymal (MES) GSCs. PN GSCs share similarities with fetal neuronal stem cells and can often be found in lower-grade gliomas and secondary GBM [26]. In contrast, MES GSCs more closely resemble adult neuronal stem cells and display more aggressive behavior, invasiveness, and treatment resistance. Within tumors, GSCs are often polygenic with different groups of stem cells having different genetic drivers, effects on growth, and treatment resistance [27]. Along the same lines, Wang et al. recently identified lineage-specific subtypes in murine and human-derived GBM models with specific transcriptomic profiles that harbor potential therapeutic targets [28]. This intra- and inter-tumoral heterogeneity makes understanding GSCs challenging. GSCs express a set of defining biomarkers and stem cell-associated genes (e.g. *Nestin, Sox2, P53, NF2, PTEN, Rb, (RTK)/Ras/PI3K,* etc.) [29]. This suggests that despite the intense genetic heterogeneity, these cells all contain intrinsic stem cell features that are potentially targetable.

Shifting the paradigm in GBM classification

While a firm understanding of GSCs remains elusive, significant progress has been made over the last decade in understanding the microenvironment of GBM. With the advent of large-scale genomic analyses, Phillips et al. in 2006 initially separated high-grade gliomas, including GBM, into three distinct subtypes (proneural, proliferative, and mesenchymal); these subtypes differ in survival rates and gene expression [30]. Subsequently, in 2010, Verhaak et al. separated GBM into four subtypes based on molecular markers, chromosomal deletions, and tumor microenvironment: Proneural, Mesenchymal, Neural, and Classical [26]. While GBM subtypes were thought of as more rigid entities and were thought to guide future clinical trials, it now appears that the tumor microenvironment quickly evolves in a niche-specific fashion and rapidly adapts to endogenous and exogenous stressors (e.g. hypoxia, immune system, radiation, and chemotherapy), making it currently rather thought to be a dynamic process [31]. Along that line, Suva et al. [32] recently thought to redefine GBM subtypes based on single-cell expression profiling. Suva et al. demonstrated the putative cellular hierarchies of three classes of glioma (IDH-mutant glioma, H3K27M glioma, and IDH-wildtype Glioma). For IDH-mutant glioma, they demonstrated that ~50% of the cellular hierarchy is non-proliferating oligodendrocytes like [OC], ~30% are non-proliferating astrocytes-like [AC], and both originate from neural progenitor cells [NPC] which represent ~10%. For the IDH wild-type GBM, they proposed that the GBM cellular hierarchy is comprised of 4 interchangeable subgroups of cells: proliferating oligodendrocyte-progenitor cells [OPC-like], proliferating neural progenitor cells [NPC-like], proliferating astrocytes -like cells [AC-like], and proliferating mesenchymal-like cells [MES-like]. This latter model system adds insight and significantly enhances the prior more rigid subclassification model [26]. It becomes apparent now that the formerly described GBM subclasses are perhaps more a snapshot of any given time when the whole-genome analysis was performed and that they may transform, even class-switch, over time as cancer evolves. Thus, every single GBM carries a mix of the above mentioned Suva subpopulations of cells [32]. This is a possible explanation of why none of the GBM subclasses have yielded a clear prognostic or therapeutic implication thus far [33].

GBM stem cells molecular pathways, potential therapeutic targets?

Venkatesh et al. recently discovered that the PI3K-mTOR pathway may regulate high-grade gliomas growth through neuronal precursors. In their study, the authors found that soluble synaptic protein neuroligin-3 (NLGN3) was responsible for exerting a mitogenic effect on neuronal and oligodentritic precursor cells, leading to robust high-grade glioma proliferation. Feedforward expression of NLGN3 expression was driven, in turn, by the PI3K-mTOR pathway, which is targetable with FDA approved medications. NLGN3 expression levels in human HGG negatively correlated with patient overall survival [34]. Likewise, Tao et al. [35] proposed that secreted synaptic proteins, carbonic anhydrase-related proteins 11 and 10 (CA11 and CA10), negatively regulate neuronal activity-dependent growth of gliomas via the Akt signaling pathway. The authors found that the gene encoding CA11 is part of a gene signature associated with favorable radiotherapy response and overall better prognosis in gliomas. Future studies investigating neuronal pathways and their interactions with glioma stem cells as a potential target in GBM therapy are promising.

Glioblastoma clinical course and conventional management paradigm

Treatment of newly diagnosed GBM requires a multi-disciplinary approach. The first step is to obtain a histopathological diagnosis and surgical resection if deemed feasible. The role of surgery in the management of GBM has been a subject of debate about whether it is safer to perform tumor debulking vs. maximal resection with negative margins. Although the available data in the published literature depicting the causal relationship between the extent of resection and overall survival, along with progression-free survival, is of retrospective nature, the results of such studies show an overwhelming consistency of the positive linear relationship between gross total resection and longer overall survival (OS) and progression-free survival (PFS) when compared to subtotal resection and surgical biopsy. Brown et al. [36], in their meta-analysis, investigated the relationship between the extent of resection and survival in GBM between January 1, 1966, and December 1, 2015; they concluded that gross total resection (GTR) increases the likelihood of one-year survival when compared with subtotal resection (STR) by 61% and increases the likelihood of 2-year survival by about 19%. Twelve-month progression-free survival is more likely after GTR [37, 38]. Furthermore, Lacroix et al. in their multivariate analysis of 416 GBM patients who underwent surgical resection, concluded that the median survival for GBM patients with resection of 98% or more was 13 months vs. 8.8 months for patients with less than 98% resection ($P < 0.0001$) [37]. Currently, maximal gross total resection, including removal of the non-contrast-enhancing tumor, has the largest improvement on the survival of any treatment regardless of IDH status [39].

Due to the invasive nature of GBM, even with GTR, a course of concurrent chemoradiation with maintenance temozolomide improves survival. Temozolomide is an oral alkylating agent and second-generation Imidazotetrazine derivative that can cross the blood–brain barrier. It exerts its cytotoxic effect through alkylating DNA sites, which are less able to be repaired in GBMs with methylated silencing of the DNA repair protein, MGMT. Temozolomide also sensitizes GBM to the effects of radiation. The National Cancer Institute of Canada Clinical Trials Group (NCIC) and The European Organization for Research and Treatment of Cancer (EORTC) published the results of their randomized, open-label, phase 3 trial in 2016, and they showed that administering temozolomide adjuvantly and concurrently with radiation therapy provided a significant survival benefit in patients with GBM. The reported median survival was 14.6 months with radiation therapy plus temozolomide and 12.1 months with radiation therapy alone, with respective 2-year survival rates of 27% and 10%. MGMT methylation improved survival by 8 months. The 2-year survival rate improved from 10.4% for RT alone to 26.5% in the RT plus temozolomide group. Second- and third-line therapies are less well-validated.

Advances in glioblastoma therapeutics

Tumor treating fields for GBM treatment

Tumor treating fields (TTF) are alternating low-intensity electric fields that are administered through a special wearable head device. These low-intensity electrical fields have been demonstrated to halt the mitotic activity within GBMs, and consequently, they arrest the cell cycle and tumor progression [40]. (TTF) technology was first introduced by the company Novocure as a first-in-human study to treating GBM in 2003 and was followed by the EF-07 GBM pilot trial [41].

The Food and Drug Administration (FDA) approved the NovoTTF-100 device in 2011 as a result of the EF-11 trial that showed a superior survival benefit for TTF compared to chemotherapy for recurrent GBM [42]. The interim results from the subsequent trial EF-14, published by Stupp et al. in 2015, showed a significant increase in overall survival (OS) and progression-free survival (PFS) in newly diagnosed GBM patients who completed the standard chemoradiation treatment course with added TTF therapy (Table 1) [43]. The final results from the EF-14 trial were published by the same group in 2017, and they concluded that patients with newly diagnosed GBM who had received standard chemoradiation therapy plus TTF vs. maintenance temozolomide alone, in their results they demonstrated statistically significant improvement in PFS (6.7 months vs. 4.0 months, $P < 0.001$) and OS. (20.9 months vs. 16.0 months, $P < 0.001$) [44]. The final EF-14 trial results were consistent with the previous interim results. [43, 44] Currently, the Optune® system (Novocure Ltd., Haifa, Israel) is the FDA-approved TTF portable device that is available commercially for patients [45]. The reported side effects of TTF are mainly scalp skin toxicities and dermatitis, without any major side effects [46].

Table 1 Summary of the tumor treating filed EF-11 and EF-14 Trails

Trial	Population	# Patients	Therapeutic intervention	PFS		OS	
				Median (mo)	*P*-value	Median (mo)	*P*-value
EF-14 *NCT00916409*	Newly diagnosed GBM	466	TT Fields and TMZ	6.7[a]	< 0.01	20.9	0.0004
		229	Maintenance TMZ	4.0[a]		16.0	
EF-11 *NCT00379470*	Recurrent GBM	120	TT Fields	2.2	0.13	6.6[a]	0.27
		117	Chemotherapy[b]	2.1		6.0[a]	

mo months, *yr* year, *TMZ* temozolomide, *TTFields* tumor treating fields, *EF* electrical fields, *GBM* glioblastoma

[a]Primary trial endpoint

[b]Treating physician choice of chemotherapy (variable)

Vaccine-based immunotherapeutics

A vaccine is a biological agent administered to a human or an animal with the intent of generating a long-term immunity against a specific pathological agent via inducing the subject adaptive immunity. Typically, vaccines work by preventing disease; however, experimental GBM vaccines are designed to provide the subject immune system the ability to recognize and eradicate the tumor cells. Antigenic components used in such vaccines could be peptide in origin (e.g. Epidermal Growth Factor Receptor Variant Type III—EGFRvIII), heat shock proteins, or cell-based vaccine (dendritic cell vaccines) [47]. Despite the promising results of the EGFRvIII vaccine in phase I/II, the preliminary results from phase III demonstrate that the EGFRvIII vaccine does not seem to have any survival benefits in patients with newly diagnosed EGFRvIII-positive GBM [48]. More recently, promising phase I trials are underway for a personalized GBM vaccine. Hilf et al. introduced the first-in-human trial of a personalized peptide vaccine for newly diagnosed GBM (GAPVAC) (NCT02149225) [49]. Their proposed vaccine is composed of 2 components (APVAC1&2) and is based on whole-exome sequencing and human leukocyte antigen (HLA)-ligandome analyses. The GAPVAC phase-I results showed that APVAC1 elicited sustained central memory CD8+ T-cells while APVAC2 induced CD4+ T-cell response of T-1 helper against GBM specific-Neoepitopes. Furthermore, Keskin et al. introduced a tumour-specific protein (neoantigen) vaccine that is able to generate an intratumoral T cell response [50].

While increasing evidence shows that the current experimental vaccines are capable of inducing an immune response against GBM cells, no evidence currently supports that GBM vaccines can induce an adequate anti-tumoral response that leads to a survival benefit [51].

Oncolytic viral therapy

Oncolytic viruses are a promising therapeutic approach to treating GBM. These viruses are genetically engineered viral particles able to selectively infect and kill tumor cells without inflicting damage to the surrounding normal tissue. Viruses were first introduced as a means of treating cancer in 1912 when the rabies virus was used to treat cervical cancer. In 1991, the first genetically engineered virus was introduced and the field of viral oncolytic therapy was born [52]. In 1998, the first trial in the US for Oncolytic HSV-1, G207 as a treatment for glioma commenced [53].

Since 1998, a wide spectrum of clinical trials using numerous viruses has been developed to investigate new therapeutic approaches for treating GBM [54]. Multiple strains of viruses have been used including Adenoviridae (DNX-2440, DNX-2401, CRad-S-pk7); Herpesvirales (C134, M032, rQNestin 34.5, G207); Vaccinia virus; Measles Virus _MV-CEA; and Poliovirus_PVSRIPO), Toca 511)) (Table 2) [55]. These viruses induce targeted malignant cell death through different necrotic mechanisms including damage-associated molecular pattern (DAMPs) and tumor-associated antigen (TAAs), apoptosis, and autophagic cell death via DAMPs [56].

DNX-2401 (Delta-24-RGD) is a promising example of a modified adenovirus therapy for recurrent GBM [57]. Recently published data from the Delta-24-RGD phase I trial showed a slight increase in the overall survival of patients to 13 months. Seven patients reached long-term survival over 24 months [57]. Currently, Delta-24-RGD is being investigated in phase I and II trials as a combination therapy with Interferon Gamma *NCT02197169* and Pembrolizumab *NCT02798406*. Similarly, the recombinant non-pathogenic polio-rhinovirus chimera (PVSRIPO) works by recognizing the poliovirus receptor CD155, which is widely expressed in the GBM tumor microenvironment. A phase one trial showed an increase in long term survivors at 24 and 36 months compared to historical controls [58].

Although oncolytic viral therapy may represent a promising therapeutic approach to treating GBM, the current results from early trials favor oncolytic viruses to be an adjunct therapy rather than a sole therapeutic agent [59]. With the current advancement of genetic engineering technology, larger controlled trials are needed to provide more efficient viral GBM therapies that are based on optimized viral construction to reduce clinical toxicity and maximize the efficiency of administration.

Final remarks and future perspective

Our understanding of the pathogenesis and treatment of GBM has greatly expanded over the past 50 years. Despite the established survival benefits of Temozolomide plus concomitant radiation therapy for GBM patients, over the past decade, no profound additional therapy mediated survival advantage has been realized [44]. This is likely due to GBM developing resistance to treatment and to significant intra and inter-tumoral heterogeneity, as well as the rapidly evolving and heterogeneous cellular cancer landscape. Many molecular therapeutic targets have been described in recent literature. To our knowledge, we do not commonly use upfront, targeted GBM therapy [60]. Although GBM prognosis remains bleak, several new avenues of treatment modalities, ranging from oncolytic viruses to targeted immunotherapy, hold promise to change the disease course of GBM. There likely is no single agent cure for GBM but rather a series of treatments based on intratumoral niche-based genetics. Furthermore, GBM therapy should be highly personalized and

Table 2 Summary of the recent major oncolytic viral therapy trials fro high-grade gliomas including glioblastomas

NCT#	Status	Condition(s)	Enrolled	Interventions	Phase	Outcomes[b]	Completion[a]
NCT03294486	Recruiting	Glioblastoma	78	Combination of TG6002 and 5-flucytosine	Phase 1 Phase 2	6-month PFS	September 2021
NCT03714334	Recruiting	Glioblastoma, Adult	24	DNX-2440	Phase 1	Overall Survival at 12 months (OS12) Overall response rate (ORR)	October 16, 2022
NCT04479241	Not yet recruiting	Recurrent Glioblastoma Supratentorial Glioblastoma	10	PVSRIPO pembrolizumab	Phase 1	Incidence of objective radiographic response Disease control rate	March 2023
NCT01956734	Completed	Glioblastoma Recurrent Glioblastoma	31	DNX2401 and Temozolomide	Phase 1	Tumor response	March 2017
NCT03072134	Completed	Anaplastic Astrocytoma Anaplastic Oligodendroglioma Anaplastic Oligoastrocytoma Glioblastoma Astrocytoma, Grade III Astrocytoma, Grade IV	13	Neural stem cells loaded with an oncolytic adenovirus	Phase 1	Tumor response	April 6, 2020
NCT03896568	Recruiting	DH1 wt Allele Recurrent Anaplastic Astrocytoma Recurrent Glioblastoma	36	Oncolytic Adenovirus Ad5-DNX-2401 Conventional Surgery	Phase 1	Maximum-tolerated dose (MTD) Incidence of adverse events (AEs) Tumor response	February 28, 2020
NCT03152318	Recruiting	Malignant Glioma Astrocytoma	108	rQNestin Cyclophosphamide Stereotactic biopsy	Phase 1	Maximum Tolerated Dose MRI Changes in Permeability MRI Changes in Volume	July 2022
NCT03657576	Recruiting	Glioblastoma Anaplastic Astrocytoma Gliosarcoma	24	C134	Phase 1	OS PFS	September 2024
NCT01301430	Completed	Glioblastoma	61	PVSRIPO	Phase	Safety and tolerability	May 2015

OS overall survival, *PFS* progression-free survival

[a]Study completion

[b]Only relevant outcomes mentioned

adaptable. This prospective therapy should be trainable and flexible to accommodate the diverse genetic variations and the different demographic factors of each patient. We envision a patient-derived 3D in-vitro cancer model system recapitulating each patient's GBM, as well as serving as a bio-factory used to test and train different therapeutic agents (e.g. oncolytic viruses) in a rapid and cost-efficient co-clinical trial fashion (Fig. 1). This model may serve as a bio-adaptable training avatar that continuously evolves to address the ever-changing cancer genetic landscape under therapy stress. Future research efforts should in part focus not only on the technical aspects of the current conventional management paradigm but also on constructing and validating personalized in-vitro and ex-vivo based high throughput 3D tumor models for each patient. Although we are hopeful that a groundbreaking, personalized molecular therapy for GBM will be available in the near future, we are also realistic in recognizing the challenges that

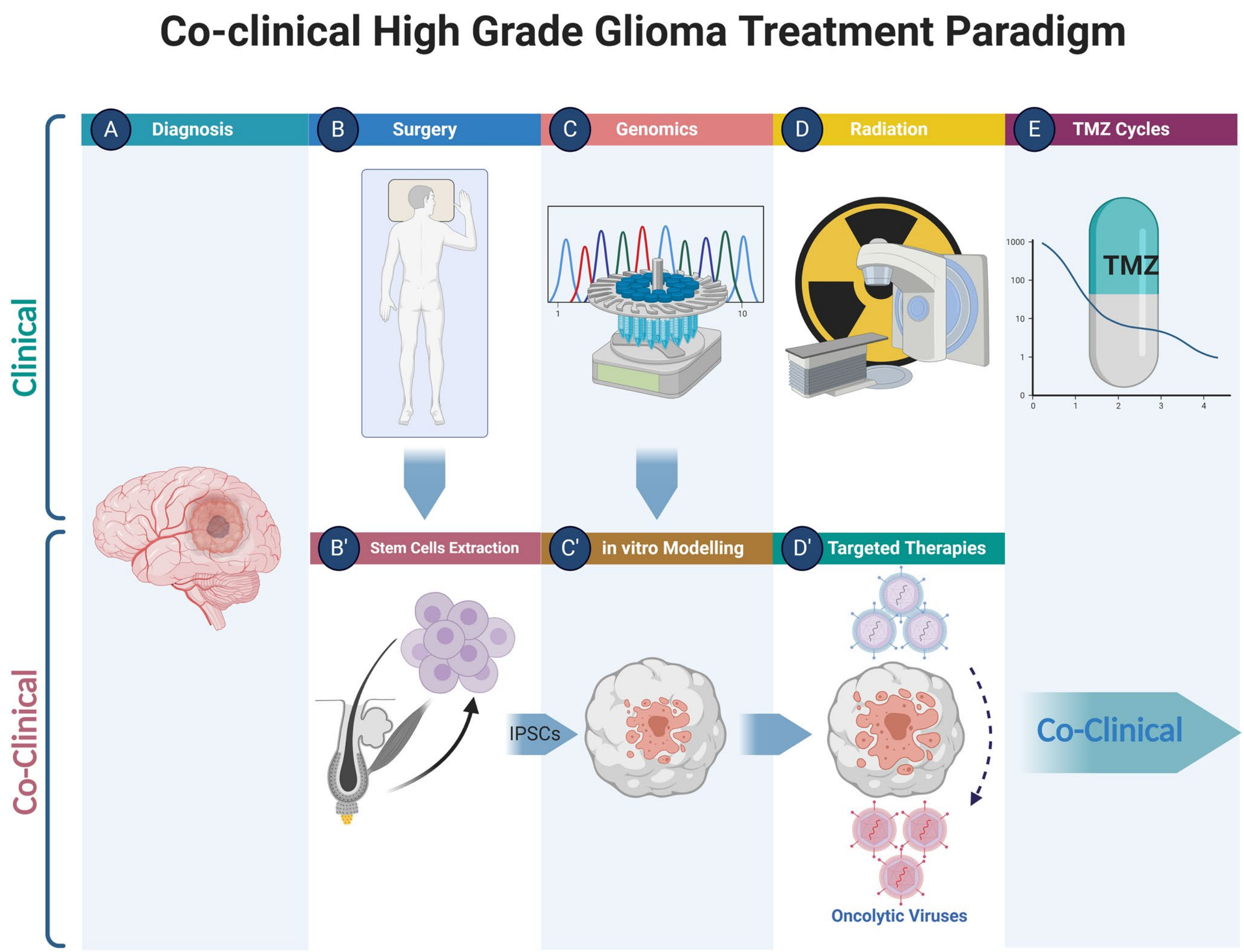

Fig. 1 An envisioned co-clinal management construct based on a patient-derived 3D in-vitro cancer model (e.g. cancer-based cerebral organoid). This in-vitro 3D model should serve as a testing ground for therapeutic modalities (e.g. oncolytic viruses) in a clinical trial fashion going parallel with the conventional treatment course. This model should also address each patient GBM genetic landscape and should serve as an adaptable trainable model that continuously evolves with each patient. Created with BioRender.com

ought to be overcome to disrupt current treatment paradigms towards making GBM a chronic disease.

Author contributions Conception and design: POZ. Interpretation of data: POZ and AH. Drafted the manuscript: AH. Approved the final version to be published: POZ. Agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: POZ and AH.

Funding UPMC University of Pittsburgh medical center startup funds.

Compliance with ethical standards

Conflict of interest All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest in the subject matter or materials discussed in this manuscript.

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