# Recurrent Glioblastoma

Subjects: Oncology
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Glioblastoma (GBM) is the most aggressive central nervous system (CNS) primary malignancy in adults, with a median age at diagnosis of 65 years.

Keywords: glioblastoma ; MGMT

## 1. Introduction

The annual incidence of glioblastoma is approximately 3 per 100,000 per person year. The disease is more common in males and incidence increases with age [1][2]. The standard of care in newly diagnosed GBM includes maximal safe surgical resection, followed by radiotherapy and concurrent and adujvant temozolomide (TMZ) [3]. Median overall survival (OS) varies between 12–18 months [4][5] and the 5-year survival in GBM is below 7% [1][6]. In adults, younger age and a good performance status (Karnofsky performance score KPS > 70 or WHO score 0) at diagnosis are favorable prognostic factors [1][4].

After first line medical management, the tumour virtually always recurs and when it does prognosis is very poor (i.e., median PFS of 1.5–6 months and median OS of 2–9 months) [7][8][9]. Treatment options for recurrent GBM (rGBM) patiens are limited and the management remains a challenge. Loco-regional therapy may be evaluated in selected cases while traditional systemic therapy showed limited efficacy. In recent years, with greater knowledge of the underlying molecular characteristics, a multitude of new drugs and new combination regimens have been tested for efficacy in rGBM patients.

## 2. Molecular Characteristics of rGBM

### 2.1. MGMT Promoter Methylation in rGBM

It was first discovered over two decades ago that *MGMT* promoter methylation is associated with response to alkylating chemotherapy in GBM patients [10]. The predictive role of this biomarker was completed following confirmation in a randomized controlled clinical trial, and further strengthened in two trials in elderly GBM patients [11][12][13]. Perhaps somewhat less well known is the observation that *MGMT* promoter methylation is also prognostic: GBM patients with a methylated *MGMT* promoter have a longer survival, irrespective of treatment with alkylating chemotherapy.

Several studies have shown that *MGMT* promoter methylation is also prognostic at the time of recurrence in GBM patients. In general, post-progression survival is around 3–4 months longer in patients harbouring *MGMT*-promoter methylated v unmethylated tumors (10.9 v 7.2 months, 8.4 v 6.6 months, 12.5 v 7.9 months and 13.5 v 8.0 months in studies reported by the German Glioma Network, EORTC 1542 (GSAM), the DIRECTOR trial and the EORTC 26101 trial, respectively) [14][15][16][17]. Most of these studies defined *MGMT* promoter methylation using data from the primary tumor. This is possible since *MGMT* promoter methylation is relatively stable. At least three independent studies on paired primary-rGBM samples demonstrated that methylation status is maintained in approximately 70–90% of tumor samples [15][16][18]. Data therefore indicate that patients harbouring *MGMT*-promoter methylated rGBMs have a slightly better post-progression survival.

Evidence for a predictive effect of *MGMT* promoter methylation in response to alkylating chemotherapy in patients with relapsed or rGBM is quite scarce. One study reported improved outcomes in patients with *MGMT*-promoter methylated v. unmethylated tumors treated with fotemustine, where the opposite was observed when tumors were treated with bevacizumab [19]. As bevacizumab has limited clinical efficacy in GBMs, this study suggests that *MGMT*-promoter methylation is predictive of response to alkylating chemotherapy at tumor progression. However, other studies did not observe such differences between treatment and control (LOMUSTINE) arms in methylated v unmethylated tumors [20][21][22]. Establishing this potential predictive role, therefore, remains to be determined but is important to guide treatment decisions at tumor recurrence.

## 2.2. The Genomic Landscape of rGBMs

To understand what makes rGBMs unique, and thus expose potential treatment targets, one has to compare differences between tumors at diagnosis and at recurrence. For this review, we will only focus on tumors that were also diagnosed as GBMs (IDH-wildtype, if known) at initial diagnosis: lower grade gliomas (IDH-mutant) that evolve into secondary GBMs represent an entirely different tumor entity with unique evolutionary trajectories. Firstly, and perhaps slightly surprising, the number of mutations in known cancer genes does not appear to increase at tumor recurrence, at least for the majority of tumors [16][23][24][25] (though there is an increase in the overall mutational burden [25]). In line with the stability of the number of mutations in driver genes is the observation that many of them (on average ~80%) are retained in the recurrent tumor [16][24][25][26][27]. One study reported preferential gains of mutations in *LTBP4*, *MSH6*, *PRDM2* and *IGF1R* genes [24], though apart from the DNA mismatch repair gene *MSH6*, these have not been confirmed in other large cohort studies. No common larger chromosomal changes have been documented at tumor progression [16], but some individual gains and losses may show within tumor pairs [28]. Despite this apparent similarity in genetic makeup, there is evidence for gain of selective events in the majority (64%) of recurrent tumors and patients harbouring such tumors have worse outcomes [25].

Although this relatively large concordance in the genetic makeup between primary and rGBM is true for the majority of tumors, there are some notable exceptions. Firstly, mutation retention is lower in the case of a distant recurrence [26], though distant recurrences are quite rare. Second, despite a generally high mutation retention rate in driver mutations, there are some marked differences between individual genes. For example, mutations in the *TERT* promoter show the highest mutation retention rate (~90%), whereas mutations in the *EGFR* gene is at the other end of the spectrum with a retention rate of approximately 50% [16][25][29]. Of note, there can be ‘driver switches’ where the same gene (such as *EGFR*) is affected in primary and recurrent gliomas, but the mutation differs [16][24]. Hypermutated tumors are the third main exception to the relatively stable genotype ‘rule’. These are detailed in a separate section of this review.

Cataloguing the retention rate is important for clinicians when designing molecular targeted therapy trials. This is because trials at tumor recurrence are usually based on molecular data from the primary tumor (repeat surgeries are not often performed) and potential loss of a mutation should therefore be taken into account. To give an example, when an objective response rate of ~40% is considered positive, the number of patients to be included in a trial is 41 (assuming a power of 80% and a one-sided alpha of 0.025). However, when the genetic change is lost in 20% of samples, the number of patients to achieve similar power is almost doubled ($n$ = 80) [16].

Similarities between primary and rGBM are also apparent at RNA level, where unsupervised analysis highlighted a significant overlap between primary and rGBM [30]. Expression-based molecular subtypes are also relatively stable during tumor progression [31][32]. Some changes are however noticeable when looking at the expression of individual genes, for example, in stemness-related genes [33][34]. Methylation classes are also stable at progression in ~85% of cases [31]. This contrasts IDH-mutant low-grade gliomas which, at recurrence, often exhibit lower overall DNA methylation levels, an increase in the frequency of poorer prognostic subclasses and worse outcomes for patients at progression [35][36].

Despite this similarity between primary and recurrent glioblastomas, there is evidence for considerable intratumoral heterogeneity in both. For example, spatially separated samples taken from the same resection may differ with respect to their genetic makeup [27][37]. Even if most studies on intratumoral heterogeneity have been performed on primary tumor samples it is therefore likely such heterogeneity also exist in recurrent glioblastomas and may affect treatment response [38]. In summary, recurrent gliomas generally retain the genetic and epi-genetic makeup of the primary tumor and, as such, are likely to require similar treatment regimens.

## 2.3. Hypermutated GBMs

A subset of temozolomide-treated GBMs gain inactivating mutations in DNA damage repair genes, such as *MSH6*, *MSH2* and *MLH1,* as first described in 2006 by the Sanger institute [39]. Because of their impaired DNA repair pathways, these tumors fail to correctly repair the damage inflicted by the alkylating agent and as a consequence, acquire an exceptionally large number of mutations (often > 10 mutations per megabase) [40]. Temozolomide-induced hypermutated tumors are characterized by G:C > T:A transitions within a specific genetic context (COSMIC mutational signature 11) [41][42]. Hypermutated tumors may also arise de novo, which occurs in the context of germline mutations in DNA mismatch repair genes [40][43][44]. Such tumors have mutational signatures associated with mismatch repair pathways [40]. Although hypermutation is common in recurrent (IDH-mutant) low grade gliomas, it is quite rare in rGBMs, with frequencies generally reported in the order of less than 10% (6/89 [24]), 14/186 [16], 16/99 [25] and 0/29 [26]). Hypermutation appears to occur more often in *MGMT*-methylated GBMs (23%) compared to *MGMT*-unmethylated tumors (5.6%) [40].

Despite the large difference in the genetic makeup of hypermutated tumors, it is unclear whether patients with such tumors have a different clinical course. One report suggested a longer survival [24], although other studies noted no survival differences [16][25][45][46] or even a trend towards poorer survival in IDH-wt rGBMs [40]. There is scarce evidence on the efficacy of treatment of hypermutated GBMs. The effect of alkylating chemotherapy seems limited: a retrospective analysis found highly similar survival between hypermutated and non-hypermutated tumors treated with alkylating chemotherapy [25] and preclinical evidence suggested hypermutated tumors are resistant to temozolomide [40]. Because of their increased mutational burden, it has been speculated that hypermutated tumors may be more susceptible to immune checkpoint inhibition. Initial anecdotal evidence supported this notion [44][47], although a later retrospective analysis of gliomas with high mutational burden found no evidence for this, with no increased immune infiltration [40]. However, evidence in larger trials is thus-far lacking and to date, there are no specific treatment options for hypermutated GBMs [48].

# 3. Management of rGBM

## 3.1. Diagnosis of rGBM

The diagnosis of rGBM relies on clinical status and MRI findings, according to Response Assessment in Neuro-Oncology (RANO) criteria and medical history [49]. MRI features of rGBM are heterogeneously described [50]. GBM may recur: (i) at the initial tumor site—most frequently <2 cm from lesion—in about 80% of cases [50] and/or, (ii) distant, with unifocal/multifocal parenchymal lesions or leptomeningeal spread [51]. Surprisingly, among different localizations, cortical GBMs seem more prone to multifocal recurrence [52].

The distinction between disease recurrence and treatment-related complications is challenging and needs specific attention. The main treatment-related complications are pseudoprogression (PsP) and radionecrosis [7]. PsP, more common in *MGMT* methylated GBM, is seen in up to 30% of patients treated with standard of care [53][54]. Usually, PsP is characterized by tumor volume increase within 3 months post-chemoradiation therapy, but delayed cases have been reported [5][55]. This phenomenon is also seen after immunotherapies with a longer time frame leading to the development of dedicated assessment tools: iRANO [54][57][56][58]. Radiation necrosis is another complication seen later in GBM patients treated with both radio and chemotherapy [7][55]. It usually appears between 3-12 months after radiotherapy [55]. In both situations, RANO and iRANO criteria suggest: (i) careful selection of reference imaging, (ii) close clinical and radiological follow-up and, (iii) avoidance of premature discontinuation of a potentially efficient treatment in the absence of worsening symptoms [7][54][58]. Multimodal imaging including spectroscopy MR, dynamic susceptibility MR perfusion and nuclear imaging can help reach a final diagnosis [5][7][50]. The importance of multimodal imaging is even more apparent with blood-brain barrier permeability modifiers, such as antiangiogenic drugs [55].

Moreover, functional molecular imaging such as positron emission tomography (PET) using amino acid tracers emerged as a promising investigational strategy in the setting of diagnosis, biopsy, resection and response assessment [59]. Histological proof remains the best approach to get molecular features of rGBM for potential molecular targeted therapies. However, a limited number of rGBM patients are eligible for second biopsy or resection due to their frailty. Therefore, in this setting, multimodal approach including PET and MRI appear an interesting alternative [5].

## 3.2. Prognostic Factors in rGBM

Older age at diagnosis and a decreased performance score (KPS or WHO) at recurrence have been associated with a poor outcome in multiple cohorts of rGBM patients [4][9]. In the same line, localization of recurrence (i.e., contact with SVZ and/or ventricle) and ependymal spread on MRI have been linked to a poor outcome [52][61][62]. In contrast, cortical localization, volume of FLAIR hyperintensities on MRI do not significantly impact outcome [4][61][63]. rGBM localization in eloquent areas and tumor volume [60] time to first recurrence [4] and RTOG-RPA class [9] were also proposed as prognostic indicators, but data are conflicting and warrant further investigations. As described previously, the *MGMT* promoter methylation status can represent an important factor correlating with survival in rGBM patients.

## 3.3. Treatment of rGBM

Less than 50% of rGBM patients are eligible for second surgery (12–48%) [63][64][65]. When feasible, surgical resection is associated with increased OS (i.e., 5–11 months) and preserved neurological status (i.e., >90% of patients) [4][63][64][65][66][67]. In these studies, an age of less than 65 years, a good performance status, radical surgery, tumor location and chemotherapy treatment before recurrence were founded predictors of re-surgery benefits; in the presence of these clinical and surgical parameters, second surgery at the time of GBM recurrence could be considered as a therapeutic

strategy in selected patients. However, the observed increased survival should be taken with extreme caution due to a selection bias of prognostically favorable patients for second surgery. The impact of surgery in rGBM was never assessed in a prospective manner, nor compared to medical treatments.

Reirradiation (re-RT) can be a therapeutic option in rGBM. A secondary analysis of the Radiation Therapy Oncology Group (RTOG) 0525 trial demonstrated a modest clinical benefit of re-RT compared to best supportive care alone in rGBM patients (HR 0.74, 95% CI, 0.43–1.28). This survival benefit is amplified when re-RT is combined with systemic therapies (HR 0.44, 95% CI, 0.30–0.63) [68]. A systematic review and a metanalysis of 50 studies support the benefit of re-RT with a PFS6 of 43% (95% CI, 35–50%, $I^2$ = 82%) [69]. However, the lack of prospective trials, the heterogeneity of studies for patients and the radiotherapy regimen limit the drawing of robust conclusions in rGBM [69][70]. Re-RT can only be proposed after careful consideration of the risk of radionecrosis [55]. A phase III trial has currently been withdrawn due to funding issues (NCT01830101). Stereotactic radiosurgery has been shown to be associated with a better PFS6 (47%). It has the theoretical advantage of sparing normal tissue but is restricted to small tumors with well-defined borders - a rare condition in rGBM [7][69].

With regard to systemic treatments in rGBM, multiple therapeutic options may be considered: (i) temozolomide rechallenging [71], (ii) lomustine or bevacizumab or both [14], and (iii) tumor-treating fields [72], but most agents proved to be limited or had no efficacy in randomized trial settings (median PFS of 2–3 months and PFS6 rate below 15% [6][7]). Thus, due to a lack of validated standard of care, the National Comprehensive Cancer Network (NCCN) recommends clinical trials as the preferred option for eligible patients [5][70].

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