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Clinical commentary

Frontal glioblastoma multiforme may be biologically distinct from non-frontal and multilobar tumors

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ABSTRACT

Glioblastoma multiforme (GBM) is the most common primary brain tumor in adults and carries a grim prognosis. Lobar GBM, notably those localized to the frontal lobe, are generally more amenable to complete surgical resection, and may carry a better prognosis. The biology of differently localized GBM has been reported scarcely in terms of prognostic markers, including isocitrate dehydrogenase 1 (IDH1) mutation and O(6)-methylguanine-methyltransferase (MGMT) methylation. To our knowledge, there has been no evaluation in the literature of different proliferation indexes in different GBM locations in the brain. We performed a retrospective evaluation of our prospectively collected database to assess the rate of IDH1 positivity, MGMT methylation and Ki67 index for GBM located in the frontal lobes alone, lobar GBM in other supra-tentorial lobes and multilobar GBM. IDH1 mutated tumors were localized in the frontal lobes in 50.0%, whereas only 20.3% of IDH1 wild-type tumors were localized in the frontal lobe ($p = 0.006$); MGMT methylated tumors were localized in the frontal lobe in 32.0% of the cases. Only 13.75% of the MGMT unmethylated tumors were localized to the frontal lobe ($p = 0.005$); Tumors with higher Ki67 proliferation index were more likely to be localized in the frontal lobe (40.6% vs. 19.5%, $p = 0.019$). This is the largest cohort of GBM assessed for these purposes in the literature. Frontal lobe GBMs may be intrinsically biologically distinct from GBM in other lobes and from multilobar tumors.

1. Introduction

Glioblastoma multiforme (GBM) is the most common primary brain tumor in adults, and carries a grim prognosis [1–3]. Several advances have been made in GBM care and management, leading to improved prognosis [4–7]. Treatment of GBM currently includes maximal safe surgical resection and a combination of chemotherapy and radiation [1,3,8]. One aspect of management which has received significant attention, is the extent of surgical resection. Several adjuncts to maximal safe resection are now routinely employed, including neuronavigation, intraoperative imaging and intraoperative fluorescence [9–12]. Extent of resection (EOR) has been shown to correlate with outcome, and the threshold above which a survival benefit is shown has been reported between 70–90% in different series [8,11,13–15].

However, the correlation between EOR and prognosis may not represent a simple causative effect. It has been suggested that resectability may be a surrogate marker of tumor aggressiveness [16]. In simple terms, more completely resectable tumors may be intrinsically biologically favorable, and differently located tumors may be biologically different [14].

Among other factors, tumor location has been shown to correlate with outcome, independent of EOR [16]. It has been shown that periventricular tumors carry a worse prognosis as compared to other locations [13], that tumors that involve the corpus callosum also have a worse outcome than tumors that don't [17,18], and that GBMs located in the frontal lobe carry a better prognosis than tumors in other locations [19–21].

The location of glial tumors has been shown to correlate with genetic anomalies [22,23] and, lately, with the likelihood of other markers of tumor progression and aggressiveness [24]. This has been shown for low grade, and for high grade gliomas [25,26].

Isocitrate dehydrogenase 1 (IDH1) is an enzyme involved in glucose metabolism as part of the tricarboxylic acid cycle. It is also involved in mitigation of mitochondrial and extramitochondrial oxidative damage [27]. Mutations in the IDH1 gene are common in GBM, and have been shown to cause diffuse changes in methylation of DNA [2,27,28]. Clinically, presence of an IDH1 mutation

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has been shown to infer a survival benefit in GBM when compared to tumors in which the IDH1 gene is not mutated [4,27,29–32].

O(6)-methylguanine-methyltransferase (MGMT) is a DNA repair protein, which is presumed to protect GBM from the effect of alkylating agents, mainly temozolomide (TMZ) [2–4,21]. When the gene is silenced by methylation, the tumor is more susceptible to TMZ effect. MGMT methylation has also been shown to improve overall prognosis compared to MGMT unmethylated tumors [2–4,21].

Ki67 is a nuclear protein, with function related to cellular proliferation. In many tumor specimens, including GBM, it is used to calculate a proliferation index, which has been shown to correlate with tumor aggressiveness and, ultimately, prognosis [20,33].

In this article we sought to assess the correlation between IDH1 mutation, MGMT methylation and Ki67 positivity, with the location of GBM within the brain.

2. Materials and methods

The prospectively collected brain tumor database of The Royal Melbourne Hospital Department of Neurosurgery was retrospectively reviewed, to identify all those patients who have undergone resection or a biopsy of a GBM. This is a prospectively maintained Central Nervous System (CNS) Tumor Database at the co-located Royal Melbourne Hospital and Melbourne Private Hospital in Victoria, Australia. Patient data are entered into the CNS Tumor Database prospectively by neurosurgical residents, neurosurgeons and medical oncologists and newly entered data are reviewed weekly for accuracy, by a neurosurgeon.

Cases in which more than one operation had been performed were considered once, even if GBM was the pathological diagnosis in more than one operation. Cases with pathology other than GBM were excluded. We also excluded cases in which staining or immunohistochemistry (IHC) for IDH1 mutation, MGMT methylation or Ki67 was not undertaken.

All preoperative images were reviewed by a neurosurgeon (KJD) at the time of insertion to our computerized database. The main bulk of the tumor was defined as frontal, temporal, parietal, occipital, cerebellar, brainstem, thalamus or basal ganglia. In order to create larger, clinically relevant groups, we grouped all tumors into four groups: Frontal, supratentorial non-frontal (SNF), multilobar and other areas (including brainstem, limited basal ganglia or thalamus, and cerebellar tumors). SNF tumors were those that were limited in location to one supratentorial lobe other than the frontal lobe. Multilobar tumors were all those tumors that were located in more than one area — either more than one lobe (for example, temporal and occipital, frontal and parietal), or involving deep and lobar structures (for example, frontal-basal ganglia, thalamic-temporal).

Testing for all three markers is done in our center with IHC staining. Positive IHC staining for MGMT is presumed to represent an unmethylated tumor, and tumors with negative staining are considered methylated tumors, with a 15% staining cutoff as reported in the literature [34,35]. Manual counting at high power is performed for Ki67 proliferation index.

The data were statistically analyzed with GraphPad Prism 5 for Windows (GraphPad Software, Inc., La Jolla, CA, USA). Contingency Table analysis and chi-squared tests were used to investigate the correlation between the location of the tumors and the positivity, or negativity of IDH1 and MGMT, and the Fisher's exact test was used when relevant. Ki67 staining index results were dichotomized into above and below 30%, based on preliminary analysis. Contingency table analysis and chi-squared test, were used for the correlation between dichotomized Ki67 staining results and tumor location. $p < 0.05$ was considered a statistically significant difference.

3. Results

Review of our database yielded 268 patients who were operated for a GBM. Of these, 45 were excluded because IHC for none of the markers was undertaken. There was no significant difference in terms of tumor location between those patients with no IHC and those who had IHC for at least one of the markers (data not shown). 223 patients were operated between June 2009 and November 2015, for which at least one of the markers was available. The locations found in the entire cohort were 51 frontal, 78 SNF and 89 multilobar. Five other patients had tumors in other locations: two isolated in the thalamus or in the basal ganglia, one isolated in the corpus callosum, one isolated in the midbrain and one was multifocal in the posterior fossa. Due to the small number, these five patients were not included in our analysis, leaving three groups only: Frontal, SNF and multilobar.

After removal of these five patients, 180 patients had MGMT methylation status in our files. 204 had IDH1 status and 165 had Ki67 results.

3.1. IDH1 mutation

Of the 204 patients for whom IDH1 status was available, 22 were mutated and 182 were IDH1 wild type. The rate of IDH1 positivity in our GBM cohort was thus 10.8%. The rate of IDH1 positivity in GBM varies widely in the literature, from 1.4% to 20% [29,30,36,37].

IDH1 wild type tumors were localized to the frontal lobe in 37 of the cases (20.3%), to the SNF lobes in 71 (39%), and were multilobar in 74 cases (40.7%).

Of the 22 IDH1 mutated tumors, 11 were in the frontal lobe (50.0%), and two were in the SNF region (9.1%). Nine of the IDH1 mutated tumors were multilobar (40.9%). These results are presented in Figure 1.

The difference between the groups was statistically significant, $p = 0.002$. Frontal lobe versus other location: $p = 0.006$.

3.2. MGMT methylation

Data for MGMT methylation was available for 180 patients. Of these, 100 were methylated and 80 were unmethylated.

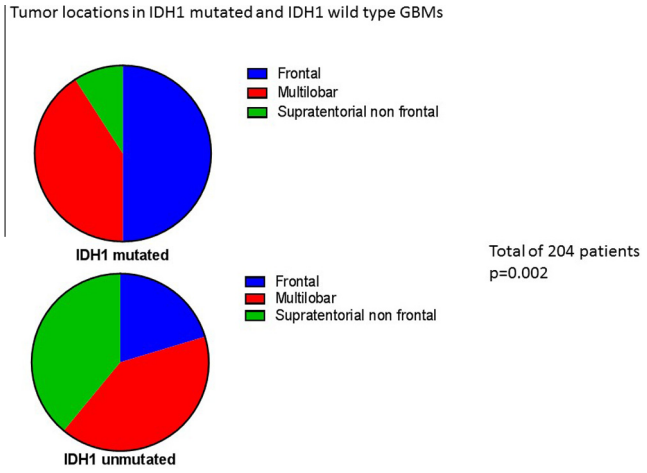

Fig. 1. Tumor locations in isocitrate dehydrogenase 1 (IDH1) mutated and IDH1 wild type glioblastoma multiforme (GBM).