Multifocal glioblastoma

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Multifocal tumors are not multiple tumors; they originate from a unique cellular clone and grow multifocally in a single organ

see also multicentric glioma.

Cerebral gliomatosis (CG) is a diffuse infiltrating glial neoplasia which may affect any part of the central nervous system (CNS). Its diffuse infiltrating growth leads to difficulty with clinical suspicion and imaging technique diagnosis [1].

Multifocal glioblastoma has been defined as glioblastoma being found synchronously in multiple foci, and there is a presumed microscopic connection [2].

Multifocal glioblastoma is an uncommon and refractory subtype of high grade glioma since the burden of masses could not be eliminated simply by operation, and it is getting even harder to control if some deep structures, like thalamus and pineal region, are involved.

Molecular background

The analysis of a multifocal glioma revealed three main aspects:

1) the combined cytogenetic and molecular analysis of this subgroup of glioblastoma multiforme is a suitable tool to gain new perspectives in glioma development

2) the balanced translocation [t(1;15)(p3?6;q2?5)] might harbor a new genetic marker involved in glioma development

3) the pattern of p53 mutation suggests a role of p53 in the progression of malignancy, migration, and growth of this particular primary glioblastoma [3].

Outcome

Patients with newly diagnosed multifocal glioblastoma on presentation experience significantly worse survival than patients with solitary glioblastoma. Patients with multifocal tumors continue to pose a therapeutic challenge in the temozolomide era and magnify the challenges faced while treating patients with malignant gliomas [4]

Several studies showed significantly lower median survival about 7.6 to 12 months of patients with newly diagnosed multifocal or multicentric glioblastoma compared to solitary ones [5] [6] [7] , in spite of operation plus radio-chemotherapy being carried out.

While radiotherapy with concomitant and adjuvant temozolomide (6 cycles, 150 to 200 mg/m2/day) is the standard treatment after surgery in glioblastoma patients, several institutions have studied on

prolonged administration of temozolomide and show increased survival periods of these patients [8) 9) 10) 11)]

However, if the lesions affect deep-seated structures, like thalamus or post-third-ventricle structures, the operation is getting harder and patients often have even worse outcomes.

Case series

2015

A total of 30 patients with multifocal GBM were treated and had adequate follow-up for analysis; 21 patients (70%) were male, and 9 (30%) were female. Median age at diagnosis was 58 years. Regarding surgery, only 6 patients (20%) had subtotal tumor resection (STR), while 23 (77%) had biopsy. No patients had gross total resection (GTR), and one patient did not have resection or biopsy and was treated with RT. The O(6)-methylguanine-DNA methyltransferase (MGMT) gene was found to be methylated in 9 (30%) and unmethylated in 11 (37%) patients. MGMT gene methylation status was unknown for the remaining 10 (33%) patients. A total of patients (90%) had adjuvant RT; 14 patients (52%) were treated to a dose of 60 Gray (Gy), and 5 (19%) received 40–45 Gy. Three patients did not complete RT due to enrollment in hospice or death. Two patients had stereotactic RT as part of their primary RT. A total of 25 patients (83%) had CT: 23 had concurrent CT with RT, and 13 had adjuvant CT. Also, 26 patients had at least 6 months of follow-up after RT completion. Their overall MS was 10.1 months. MS was 16.6 months for patients who had STR and 5.5 months for patients who had biopsy.

Median survival of multifocal GBM is incredibly short, even compared with the already short median survival of single-lesion GBM. The majority of the patients had biopsy alone, likely due to the nature of multifocal GBM. This most likely contributes to a worse MS [12)].

2014

Between August 2000 and May 2010, 161 patients with GBM were treated with modern radiotherapy techniques. Of this group, 33 were considered to have multiple lesion GBM (25 multifocal and 8 multicentric). Patterns of failure, time to progression and overall survival were compared based on whether the tumor was considered a single focus or multiple lesion GBM. Genomic groupings and methylation status were also investigated as a possible predictor of multifocality in a cohort of 41 patients with available tissue for analysis. There was no statistically significant difference in overall survival ($p < 0.3$) between the multiple lesion tumors (8.2 months) and single focus GBM (11 months). Progression free survival was superior in the single focus tumors (7.1 months) as compared to multi-focal (5.6 months, $p = 0.02$). For patients with single focus, multifocal and multicentric GBM, 81, 76 and 88 % of treatment failures occurred in the 60 Gy volume ($p < 0.5$), while 54, 72, and 38 % of treatment failures occurred in the 46 Gy volume ($p < 0.4$). Out of field failures were rare in both single focus and multiple foci GBM (7 vs 3 %). Genomic groupings and methylation status were not found to predict for multifocality. Patterns of failure, survival and genomic signatures for multiple lesion GBM do not appreciably differ when compared to single focus tumors [13)].

2013

Forty-one patients were accrued over 12 months; 39 had a full set of MRI scans available for evaluation. Assessment for best radiographic responses was as follows: partial responses in 24.4%, stable disease in 68.3%, and progressive disease in 2.4%. Treatment-related toxicities included seven grade 4 toxicities and one grade 5 toxicity (myocardial infarction). From this study, it was concluded that an upfront regimen of TMZ and BV for unresectable glioblastoma was well tolerated and provided a significant level of disease stabilization. Therapeutic toxicities were consistent with those seen in the adjuvant setting using these agents. The upfront approach to treatment of glioblastoma in the unresectable population warrants further investigation in randomized controlled phase III trials [14)].

2011

In a retrospective analysis of data prospectively collected between 1993 and 2008 in 20 patients with multifocal or multicentric glioblastomas (Group A) who underwent resection of all lesions via multiple craniotomies during a single surgical session. Twenty patients who underwent resection of solitary glioblastoma (Group B) were selected to match Group A with respect to the preoperative Karnofsky Performance Scale (KPS) score, tumor functional grade, extent of resection, age at time of surgery, and year of surgery. Clinical and neurosurgical outcomes were evaluated.

In Group A, the median age was 52 years (range 32-78 years); 70% of patients were male; the median preoperative KPS score was 80 (range 50-100); and 9 patients had multicentric glioblastomas and 11 had multifocal glioblastomas. Aggressive resection of all lesions in Group A was achieved via multiple craniotomies in the same session, with a median extent of resection of 100%. Groups A and B were comparable with respect to all the matching variables as well as the amount of tumor necrosis, number of cysts, and the use of intraoperative navigation. The overall median survival duration was 9.7 months in Group A and 10.5 months in Group B ($p = 0.34$). Group A and Group B (single craniotomy) had complication rates of 30% and 35% and 30-day mortality rates of 5% (1 patient) and 0%, respectively.

Aggressive resection of all lesions in selected patients with multifocal or multicentric glioblastomas resulted in a survival duration comparable with that of patients undergoing surgery for a single lesion, without an associated increase in postoperative morbidity. This finding may indicate that conventional wisdom of a minimal role for surgical treatment in glioblastoma should at least be questioned [15)].

2007

The records of 50 patients with multifocal glioblastoma multiforme treated with RT were reviewed. Univariate analyses were performed using survival methods and the Cox proportional hazards regression method. Multivariate analyses were performed using the Cox proportional hazards regression method.

The mean age was 61 years, and 71% had a Karnofsky performance status (KPS) score of > or =70. Of the 50 patients, 32% underwent WBRT and 68%, three-dimensional conformal RT. Progression was local in all evaluable patients, as determined by imaging in 38 patients and early neurologic progression in 12. The median time to progression (TTP) was 3.1 months, and the median survival time (MST) was 8.1 months. The significant independent predictors of TTP on multivariate analysis were a KPS score <70 ($p = 0.001$), the extent of surgery ($p = 0.040$), a radiation dose <60 Gy ($p =$

0.027), and the lack of chemotherapy (p = 0.001). The significant independent predictors of a reduced MST were a KPS score <70 (p = 0.022) and the absence of salvage surgery (p = 0.011) and salvage chemotherapy (p = 0.003).

Local progression was observed in all patients. On multivariate analysis, no significant difference was found in the TTP or MST between three-dimensional conformal radiotherapy and WBRT. The KPS was a consistent independent predictor of both TTP and MST. On the basis of the progression pattern, we do not recommend WBRT as a mandatory component of the treatment of multifocal glioblastoma multiforme [16].

Case reports

2015

A 30-year-old male with multifocal glioblastoma affected his right thalamus, left lateral ventricle, and pineal region. Clinical manifestations include operation, concurrent radiochemotherapy, and a 12-cycle adjuvant temozolomide administration. The masses of this patient nearly disappeared after 15 months from the primary diagnosis, and no severe adverse event or neurological sequel occurred.

Long-term temozolomide might be an optimal choice for patients with multifocal glioblastoma, especially with deep-seated structure involvement [17].

2013

A 69-year-old woman presented with recurring episodes of vertigo, headache, and progressive weight loss. Three multifocal cerebellar and brainstem lesions highly suspicious for metastases were identified by magnetic resonance imaging (MRI). Workup for malignancy elsewhere in the body was negative.

The patient underwent craniotomy with successful resection of the tumor in the cerebellar vermis with an excellent outcome and uneventful postsurgical course. Histopathology of the tumor revealed features consistent with the diagnosis of GBM and ruled out metastatic lesions. Workup for molecular genetics characterized this tumor as a primary GBM. The patient initially responded to treatment with radiation therapy and temozolomide but died after 10 months with a tumor relapse.

Multifocal primary GBMs in the posterior fossa, although rare, they should be considered in the differential diagnosis of cerebellar tumors, which stresses the importance of a surgical treatment to establish a histological diagnosis because there are no reliable radiographic criteria for distinguishing multifocal infratentorial gliomas from multiple metastases and other tumor entities. The differentiation between a primary and secondary cerebellar GBM did not lead to any change of the treatment strategy in this case [18].

2012

Pediatric GBM is a rare entity, and a multifocal development in a pediatric GBM is much rarer.

Cugati et al report one such rare case of pediatric multifocal GBM in a 5-year-old child who developed

rapidly increasing multiple lesions after radiotherapy. More studies are required to study the genetic analysis, tumor behavior, management and outcome of these rare tumors [19].

2009

A 63-year-old man presented with focal seizures and mental impairment. Computed tomography (CT) scan revealed a left frontoparietal mass. He underwent a gross total removal of the tumor. The tissue diagnosis was that of a GBM. Seven months later, the patient developed a left scapular subcutaneous mass. Fine-needle aspiration cytology (FNAC) was performed and the cytological findings disclosed again a GBM. One month later, after clinical deterioration, a repeat magnetic resonance imaging (MRI) scan was carried out which demonstrated two new distinct lesions in the opposite hemisphere, as in a multifocal GBM. Both lesions were biopsed under stereotactic guidance and the recurrence of GBM was confirmed. The patient died ten months after the primary diagnosis of the intracranial GBM.

Improved diagnostic modalities and prolonged survival have increased the likelihood of detection of extracranial mestastases from GBM. This potential may be greater in multifocal GBM. FNA is a valuable method for the definite diagnosis of metastatic GBMs. Although several theories have been postulated, the route of remote cutaneous dissemination and the mechanism of multifocal recurrence remain to be elucidated [20].

2008

A 65 year old man who presented with left hemiparesis, and was found to have multiple, discrete, peripherally enhancing, hemorrhagic intra-axial masses in the right hemisphere of the brain. Workup for malignancy elsewhere in the body was negative, and biopsy confirmed glioblastoma multiforme. The patient responded clinically to treatment with radiation therapy and temozolomide [21].

1989

A patient with two intracerebral glioblastomas of differing histology with metastases to the liver in the absence of surgery is reported. The gliomatous nature of the lesions was confirmed by staining for glial fibrillary acidic protein. Histological and immunohistochemical evidence suggests that the metastases arose from the more poorly differentiated of the intracerebral tumors. One of the intracerebral tumors had enhanced expression of the ras p21 oncogene as compared to the other tumors and as compared to nonmalignant brain tissue from this patient [22].

1986

A 60-year-old patient is described with two independently located foci of glioblastoma multiforme in both frontal lobes [23].

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