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CLINICAL STUDY—PATIENT STUDIES

Pattern of recurrence in paediatric malignant glioma: an institutional experience

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Abstract
Background: The purpose of this retrospective study was to investigate the pattern of recurrence in paediatric malignant gliomas.
Material and methods: We reviewed the notes, diagnostic imaging and treatment charts of 30 consecutive paediatric patients (age less than 18 years at diagnosis, range 0.5–17 years) presenting with a malignant glioma presenting to the paediatric oncology unit at the Royal Marsden Hospital over a 10-year period. The imaging at the time of first relapse was compared with the initial diagnostic scans to define a relapse as local, marginal or distant.
Results: Median follow-up was 13 months (range 1–99 months). Twenty-four of 30 patients (80%) showed evidence of progression with a median time to progression of 8.5 months (range 3–64 months). Thirteen out of 24 patients developed local or marginal recurrences while 11/24 patients recurred at distant sites as site of first relapse (46%).
Conclusion: Our series suggests that the pattern of relapses in paediatric malignant gliomas could be different from that reported in adult studies as we observed a significant incidence of distant relapses. Larger prospective series need to be conducted to investigate the clinico-biological characteristics of the population at high risk for leptomeningeal dissemination.

Keywords Malignant glioma · Dissemination · Metastases · Glioblastoma · Anaplastic astrocytoma · Recurrence

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Introduction

The prognosis of malignant gliomas (WHO III° and IV°) is poor and recurrence is usually due to failure to maintain local tumour control. It is rare for high-grade gliomas to present with dissemination at diagnosis both in adults and children and recent reports estimate this to occur in less than 3% of patients [4, 21]. In adult patients the incidence of metastatic spread at the time of tumour recurrence is reported as 2–14% of patients [1, 2, 21, 27].

To investigate the pattern of recurrence in paediatric malignant glioma we studied a consecutive series of patients referred to the paediatric oncology unit at the Royal Marsden Hospital from 1995 to 2005.

Patients and methods

All patients referred during the period 1995–2005 with an age less than 18 years and a histopathological confirmation of a malignant (high grade) glioma are included in this report. Treatment varied according to

unit protocols during this time. Patients were followed-up with a clinical examination on a three monthly basis for the first 2 years, four monthly in year 3, six monthly up to year 5 and annually thereafter. A baseline MRI scan was obtained 3-month post completion of therapy and subsequently if clinically indicated. Further imaging studies were obtained including imaging of the spine when clinical signs or symptoms indicated. Cerebrospinal fluid (CSF) examination at diagnosis or relapse was not routinely performed. To define the site of relapse, a neuro-radiologist in conjunction with a clinical oncologist compared the MRI scans at the time of recurrence with the initial diagnostic imaging and the radiotherapy planning films. Based on these findings, recurrences were defined as local (if occurred within the radiotherapy field), marginal (if adjacent but outside the radiotherapy field) or distant (if either spatially separated within the brain and spine or extra cranially). Only sites of first relapse were taken into account in this analysis.

Results

Thirty newly diagnosed patients with malignant glioma were seen in our institution in this 10-year period. Median age was 12 years (range: 6 months to 17 years). Fourteen patients were females and 16 males. All the patients had histologically proven high-grade glioma (WHO III° or IV°) on pathology review; glioblastoma multiforme ($n = 22$) and anaplastic astrocytoma ($n = 8$). The site of the primary tumour was; thalamic ($n = 16$), frontal ($n = 5$), parietal ($n = 4$), temporal ($n = 3$), cerebellar ($n = 1$) and spinal ($n = 1$) (Table 1). Two patients developed high-grade glioma as a second malignant neoplasm (SMN) after 7.5 and 4.5 years following previous cranial irradiation for a malignancy (leukaemia and primitive neuroectodermal tumour). No patient was clinically suspicious of having primary dissemination at the time of diagnosis.

Surgery consisted of a biopsy in 9 patients, partial to subtotal resection in 17 and complete macroscopic excision in 4 children. Two patients died before adjuvant therapy following surgery. One patient developed intracranial haemorrhage and one patient had tumour progression. Postoperative management consisted of; radiotherapy alone ($n = 10$), radiotherapy plus chemotherapy ($n = 16$) and chemotherapy alone ($n = 2$). Chemotherapy regimens used were; procabazine-CCNU-vincristine (PCV) ($n = 6$), temozolomide ($n = 5$), ifosfamide-cisplatin-etoposide (ICE) ($n = 5$), cisplatin-temozolomide ($n = 1$) and UKCCSG Baby Brain protocol ($n = 1$).

The overall survival for the 30 patients was 14% at 3 years with a median survival of 14 months. Twenty-four patients showed evidence of progression during follow-up. The median time of progression was 8.5 months (range 3–64 months). Four patients are alive without recurrence (all grade III tumours, all received chemotherapy). Of these children, three had debulking surgery and one complete macroscopic clearance. The median follow-up was 13 (range 1–99) months from the initial diagnosis. There is no loss to follow-up. Table 1 gives the characteristics of the 24 patients who have relapsed. One patient with GBM (patient 14) developed a local recurrence and metastasis to lung and vertebra. Figures 1, 2 and 3 show examples of distant relapses. Of the recurrences, 7 were local, 6 marginal and 11 distant (of which six were synchronously local and distant). There was no difference in any demographic characteristic between patients with local or distant recurrence. The median time to death after recurrence was 3.9 months (range 0.1–15.6). There was no significant difference in survival time for those with local or distant recurrence.

Chemotherapy was given at the time of relapse to 75% of patients (18 of 24) with six patients receiving more than one line of chemotherapy (seven patients were chemo naive). Regimes included temozolomide ($n = 9$), PCV ($n = 8$), liposomal daunorubicin ($n = 2$), oral cyclophosphamide + etoposide ($n = 2$), carboplatin + etoposide ($n = 1$) and thiotepa ($n = 1$).

Overall 11 of 30 children relapsed with distant metastasis (36.7%). The incidence of secondary dissemination was 46% of recurrent patients (11/24).

Discussion

High-grade gliomas of childhood are rare primary CNS tumours and only limited data on outcome and pattern of relapse are available. The aim of this retrospective study was to assess the pattern of relapses in consecutive childhood high-grade gliomas treated at the Royal Marsden Hospital over a 10-year period. In our patient population, it was possible to obtain complete surgical excision in only 4/30 patients. The CCG-945 study has demonstrated the survival benefit obtained with radical resection of tumours [28].

In the adult population high-grade gliomas constitute about 40% of all primary CNS tumours and their pattern of relapse has been extensively reported. The majority of recurrences are located in the primary tumour volume, defined as the tumour volume on T2-weigthed images plus a 2–3 cm margin. In agreement with the adult

Table 1 Age at diagnosis in years, Time to recurrence in months, Survival post recurrence in months

Patient	Gender	Age at diagnosis	Histology	Tumour site	Treatment	Recurrence	Site of recurrence	Time to recurrence	Survival after recurrence	Outcome
1	M	11.8	AA	Thalamus	B, R	Distant	IV ventricle, cerebellum, frontal lobe	7	1.4	Dead
2	F	3.8	GBM	Frontal lobe	D, R, C	Distant	Spinal cord	8	7.1	Dead
3	F	11.5	GBM	Cerebellum	D, R, C	Distant	Frontal lobe	7	1.5	Alive
4	F	13.3	GBM	Frontal lobe	D, R, C	Distant	Occipital lobe	14	1.8	Dead
5	F	17.0	GBM	Thalamus	D, R	Distant	Spinal cord	11	10.3	Dead
6	F	15.8	AA	Bithalamic	B, R, C	Local	Thalamus	13	2.6	Dead
7	F	6.7	AA	Bithalamic	B, R, C	Local	Thalamus	14	0.1	Dead
8	M	8.8	GBM	Frontal lobe	B, C	Local	Frontal lobe	6	3.9	Dead
9	F	10.3	AA	Parietal lobe	D, R	Local	Parietal lobe	22	15.6	Dead
10	F	14.3	GBM	Thalamus	D, R, C	Local	Thalamus	10	10.1	Dead
11	M	9.0	GBM	Thalamus	D, R	Local	Thalamus	19	1.8	Dead
12	F	12.0	GBM	Thalamus	D, R, C	Local	Thalamus	15	4.5	Dead
13	M	4.7	GBM	Thalamus	B, R, C	Local + Distant	Thalamus, brain stem	9	2.4	Dead
14	F	14.0	GBM	Parietal lobe	T, R, C	Local + Distant	Parietal lobe, lungs, vertebral bones	8	4.7	Dead
15	M	9.9	GBM	Thalamus	T, R	Local + Distant	Cerebellum	4	3.1	Dead
16	M	15.2	GBM	Parietal lobe	D, R, C	Local + Distant	Parietal & Frontal lobes, brain stem	8	5.8	Dead
17	F	11.0	GBM	Spine	D, R	Local + Distant	Lepto-meningeal brain & spine	5	6.5	Dead
18	M	12.4	GBM	Thalamus	D, R	Local + Distant	Thalamus, IV ventricle, cerebellum	8	0.8	Dead
19	M	9.6	GBM	Temporal lobe	B, R	Marginal	Fronto-temporal lobe	5	6.0	Dead
20	F	13.0	AA	Thalamus	B, R	Marginal	Frontal lobe, thalamus	9	5.3	Dead
21	M	13.9	GBM	Temporal lobe	T, R, C	Marginal	Corpus collosum	9	2.0	Dead
22	M	16.4	GBM	Frontal lobe	D, R, C	Marginal	Frontal Lobe	64	12.9	Alive
23	M	8.7	GBM	Thalamus	D, R, C	Marginal	Frontal lobe, thalamus	3	4.8	Alive
24	M	12.6	GBM	Temporal lobe	D, R	Marginal	Temporal lobe, basal ganglia	7	3.1	Dead

AA anaplastic astrocytoma, *GBM* glioblastoma multiforme, *B* biopsy, *R*: radiotherapy, *C* chemotherapy, *D* debulking surgery, *T* total surgical excision

experience, several paediatric studies have reported local failure as the primary site of relapse [8]. In the CCG protocol 945 conducted between 1986 and 1992, most relapses were local, with 94 of 110 (85%) documented relapses within or contiguous to the primary tumour site [12]. Contrasting with these observations, Heideman reported the St. Jude experience showing a 30% incidence of distant seeding in his series of 41 patients

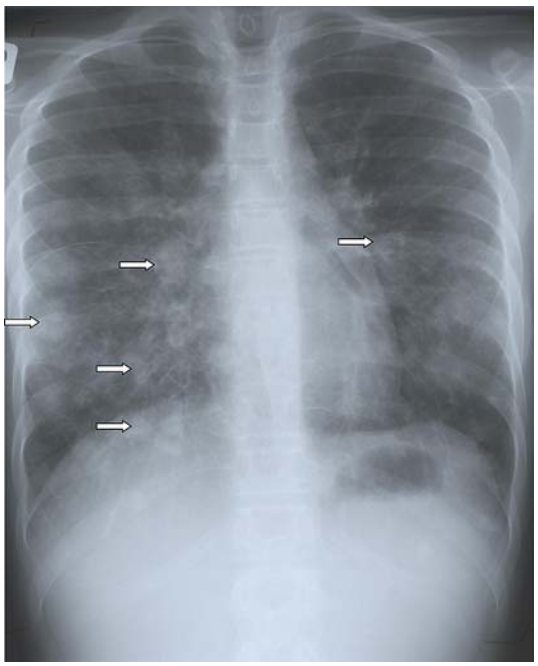

Fig. 1 Chest X-ray of a patient with GBM. *Arrows* show a few of the lung metastases

treated over a 10-year period [17]. Another single institution series from Pittsburgh also showed a 33% rate of CSF dissemination at recurrence [15].

Similar results are being reported in paediatric brain stem gliomas. A study from New York University Medical Centre has reported leptomeningeal dissemination in nearly 30% children within 1 month of progressive disease [7]. A recent study from Duke's University has reported 17% incidence of neuraxis metastasis in children with diffuse pontine gliomas [16].

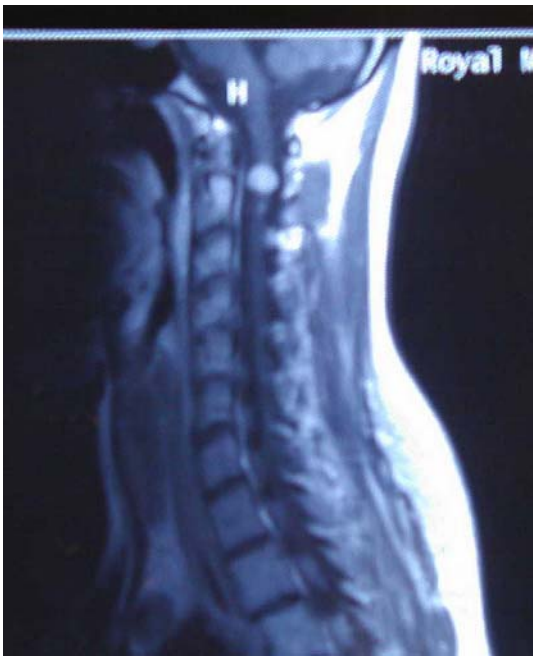

Fig. 2 Sagittal T1 weighted scan with Gadolinium [TR/TE,400/15] demonstrates an avidly enhancing metastasis within the sub-arachnoid space in the cervical spine

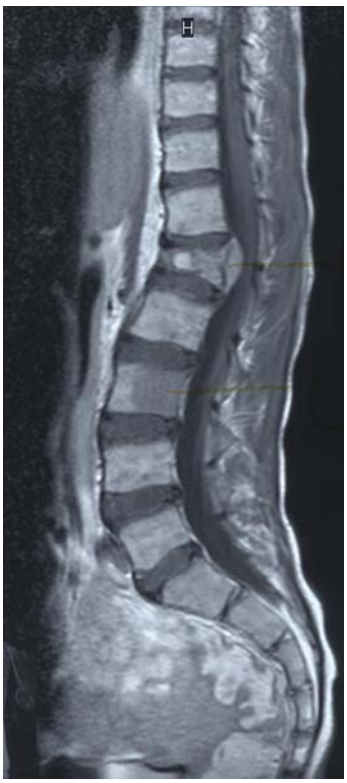

Fig. 3 Sagittal T1-weighted image [TR/TE,400/15] of the lumbar spine demonstrates metastatic collapse of the first lumbar vertebra with narrowing of the spinal canal. An area of hypo-intensity in the body of L3 identifies a second metastasis

The results of our study with a 46% secondary dissemination rate confirm further the high frequency of metastatic disease in paediatric malignant glioma. Single institution series may benefit from higher detection rates of metastatic disease due to more robust and consistent investigations at the time of relapse compared to reports of multi-institutional trials. Our study still has limitations, the first of which is the small number of patients. In addition most patients had no systematic imaging of the craniospinal axis if only local relapse was suspected at the time of progression. CSF examination was not routinely performed either. This might suggest that our findings in keeping with other published series may underestimate the exact incidence of distant metastasis in high-grade glioma of childhood.

Yet local failure remains the main cause of death and further efforts to improve local tumour control with more aggressive surgical resection and augmentation of radiotherapy (e.g. radiosensitisation) remain

important. However, the high incidence of distant relapse within the neuroaxis and extracranially suggests that systemic therapy could form an essential part of initial management strategy for malignant gliomas of childhood. One could also consider the use of whole brain radiotherapy or indeed craniospinal radiotherapy. However, many previous studies and one meta-analysis have demonstrated that neither technique improves local, marginal or distant control over and above focal radiotherapy [3, 14, 18, 23]. In the St. Jude experience, nine patients were treated with craniospinal radiation [17]. The choice of craniospinal radiation was related to the presence of leptomeningeal dissemination at the time of diagnosis in two patients, progression on chemotherapy in four patients and was part of the initial treatment in three patients. Despite this, 33% (3/9 patients) subsequently developed neuraxis dissemination in keeping with our experience of using focal radiotherapy only.

The use of adjuvant chemotherapy, at least theoretically, might not only provide increased local tumour control but also some prophylaxis against distant tumour spread. Until recently no large randomised study had demonstrated a survival advantage of adjuvant chemotherapy against radiotherapy alone in adults with malignant gliomas [20]. However, the combination of Temozolomide and radiotherapy has now been shown to offer a significant survival benefit for adults with GBM and is perceived as new gold standard in the management of adult high-grade gliomas [26]. Although there has only been one randomised study in children demonstrating the survival benefit of chemotherapy [25] there have been several single arm studies suggesting some effectiveness of adjuvant chemotherapy with differing regimens [9–12, 19, 30]. In our own study the use of chemotherapy at presentation did not appear to improve time to progression or prevent metastatic disease at relapse compared to published data, although large scale prospective studies are needed to draw any firm conclusions. Also, previous studies have shown that for children with high grade glioma, survival using high dose chemotherapy is no better than that reported with conventional studies [5, 6]. Based on our series it appears that CSF dissemination is a major cause of failure. The use of intrathecal chemotherapy may seem an attractive therapeutic approach. Several agents have been used in this setting with varying results [13, 24, 29].

The question arises why is there such a discrepancy between the rates of secondary dissemination between paediatric and adult patients with malignant glioma? Of course there may be biological differences explaining the increased predisposition in the young. Recent studies have confirmed that malignant gliomas in children and in adults have different molecular defects and this may translate in a different behaviour [22]. However, it may simply reflect the natural history of malignant gliomas with dissemination generally occurring only as a late event and therefore reflecting the known longer survival of younger patients.

In conclusion, this series confirms previous observations of poor outcome in children with primary high-grade gliomas. In addition it suggests a significant incidence of distant relapses. Given the rarity of the disease in childhood multinational prospective studies should be conducted to determine the clinico-biological characteristics of the population at risk for leptomeningeal dissemination. New therapeutic avenues have to be considered given the persisting dismal outcome of these patients.

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