Prognostic significance of intracranial dissemination of glioblastoma multiforme in adults

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Object. The clinical outcome and treatment of adult patients with disseminated intracranial glioblastoma multiforme (GBM) is unclear. The objective in the present study was to assess the prognostic significance of disseminated intracranial GBM in adults at presentation and at the time of tumor progression.

Methods. Clinical data from 1491 patients older than 17 years and harboring a GBM that had been diagnosed between 1988 and 1998 at the University of California at San Francisco neurooncology clinic were retrospectively reviewed. Dissemination of the GBM (126 patients) was determined based on Gd-enhanced magnetic resonance images. Classification of dissemination was as follows: Type I, single lesion with subependymal or subarachnoid spread; Type II, multifocal lesions without subependymal or subarachnoid spread; and Type III, multifocal lesions with subependymal or subarachnoid spread. Subgroups of patients were compared using Kaplan–Meier curves that depicted survival probability.

The median postprogression survival (PPS), defined according to neuroimaging demonstrated dissemination, was 37 weeks for Type I (23 patients), 25 weeks for Type II (50 patients), and 10 weeks for Type III spread (19 patients). Patients with dissemination at first tumor progression (52 patients) overall had a shorter PPS than those in a control group with local progression, after adjusting for age, Karnofsky Performance Scale score, and time from tumor diagnosis to its progression (311 patients). When analyzed according to tumor dissemination type, PPS was significantly shorter in patients with Type II (33 patients, p < 0.01) and Type III spread (11 patients, p < 0.01) but not in those with Type I spread (eight patients, p = 0.18).

Conclusions. Apparently, the presence of intracranial tumor dissemination on initial diagnosis does not in itself preclude aggressive treatment if a patient is otherwise well. A single focus of GBM that later demonstrates Type I dissemination on progression does not have a worse prognosis than a lesion that exhibits only local recurrence.

Key Words • tumor dissemination • multifocal lesion • glioblastoma multiforme • glioma • survival

Glioblastoma multiforme typically presents as a single lesion that recurs locally after treatment. Although these lesions usually recur close to the primary tumor site, dissemination can occur throughout the central nervous system. The prognostic significance of various clinical parameters for patients harboring GBMs at the time of diagnosis—including patient age, KPS score, and the extent of tumor resection—have been well characterized. In contrast, the prognostic significance of intracranial tumor dissemination is unclear. In this report we focused on intracranial dissemination as defined by contrast-enhancing T1-weighted MR imaging. Three categories of dissemination were neuroimaging defined: Type I, single focus of GBM with subependymal or subarachnoid spread; Type II, multifocal GBM without subependymal or subarachnoid spread; and Type III, multifocal GBM with subependymal or subarachnoid spread (Fig. 1).

Dissemination of GBM can occur intracranially or throughout the spinal axis. In one of the first studies in which GBM dissemination was systematically examined, Erlich and Davis performed autopsies in 25 patients over a span of 7 years. Spinal cords were analyzed in 20 patients and five demonstrated spinal leptomeningeal metastases. Data from this 1978 study confirmed the prior anecdotal experience of several clinicians. Subsequently, many investigators have corroborated the observations of Erlich and Davis through various means, including postmortem studies and prospective radiographic or cytological evaluations. The advent of high-resolution MR imaging has facilitated documentation of dissemination with relative ease, and new techniques are evolving to optimize detection even further.

Authors who document tumor dissemination raise important questions regarding the biological features of glioma as well as the clinical repercussions of therapies aimed at preventing only local recurrence. The goal of the present study...
was to determine the prognostic significance of intracranial dissemination through a retrospective analysis of patients with GBM who had undergone treatment at our institution. As we develop more effective therapies for local disease, the prognostic significance of disseminated GBM becomes increasingly relevant.

Clinical Material and Methods

Study Design

This study was a retrospective, single-institution analysis in which patients with documented GBMs were evaluated for neuroimaging demonstrated evidence of tumor dissemination. Various clinical parameters were recorded (see Clinical Data Acquisition) and used to facilitate a comparison of patients with and those without tumor dissemination. Data collection for this study was approved by the Committee on Human Research at UCSF.

Patient Population

Patients with evidence of tumor dissemination were selected from a database of adult patients (> 17 years old) harboring GBMs, whose KPS scores were at least 60 and who had been evaluated and treated in the neurooncology clinic at UCSF. Because the criteria for neuroimaging dissemination required that Gd-enhanced MR images be obtained, our database search was limited to the years from 1988 to 1998. Patients with dissemination at recurrence and without MR images documenting the absence of dissemination at initial diagnosis were excluded. A pathological diagnosis of intracranial GBM was confirmed in all patients by neuropathologists at UCSF. All patients had undergone diagnostic surgery together with various extents of resection; thereafter, all received standard external-beam radiation therapy. The extent of resection was defined as "biopsy" (< 10% resected), "subtotal" (10–90% resected), and "gross-total" or "near-total" (> 90% resected) on the basis of the surgeon’s intraoperative impression in conjunction with postoperative imaging results. Cases classified by the original surgeon as “total” and in which the postoperative image demonstrated less than a 90% resection were classified as “subtotal.” In patients who had undergone treatment at outside institutions, all relevant records and radiographic images were obtained and reviewed (see Clinical Data Acquisition).

Neuroradiological Evaluations

Conventional T1-weighted MR images with contrast enhancement were used to detect tumor dissemination. In some cases these images had been obtained at UCSF, whereas in other cases they had been obtained at outside facilities. The quality of outside images was evaluated independently, and patients without MR sequences of suitable quality were excluded from the study. Three subtypes of neuroimaging abnormalities were considered evidence of intracranial tumor dissemination: a single focus of GBM with subependymal or subarachnoid spread at sites distant from the primary tumor location (Type I), multifocal GBM without subependymal or subarachnoid spread, or Type II dissemination, and multifocal GBM with subependymal or subarachnoid spread at sites distant from the primary tumor location (Type III).
Clinical Data Acquisition

Clinical charts, hospital records, and neuroimaging studies were reviewed for each patient. We recorded patient age at diagnosis, sex, tumor location, extent of initial resection, postoperative KPS score, pathological diagnosis, type of radiation therapy, other adjuvant therapy, and time to first progression following dissemination. The extent of resection was scored as 1, 2, or 3, according to whether the surgery was a biopsy (10% resected), subtotal (10–90% resected), or total resection (90% resected), respectively. Adjuvant therapy included carmustine, procarbazine, and temozolomide as well as combination therapy in some cases. Time to tumor dissemination was measured in weeks from the date of diagnostic surgery to the date of the neuroimaging study revealing evidence of spread. The patient’s KPS score on dissemination and subsequent therapy were recorded, as were the number of tumor progressions that had preceded dissemination. All patients had undergone regular follow-up examinations and MR imaging studies at intervals of 1 to 2 months following the diagnosis of dissemination. All treatment decisions had been made by UCSF neurooncologists after consulting with patients and, in some cases, with the UCSF tumor board. Survival times were measured in weeks from the date of documented dissemination to the date of death and from the date of diagnosis to the date of death. For patients still living, the date of the last clinical follow up was used to calculate follow-up times.

Statistical Analysis and Clinical Comparisons

To evaluate survival trends, the patients were divided into two groups based on the timing of tumor dissemination: patients with dissemination at the time of tumor diagnosis and patients with dissemination at the time of tumor progression. Survival time after tumor spread was measured in these two groups. Within each group, survival times were also figured for the three radiographic subtypes of tumor dissemination described previously. Median survival times were estimated from Kaplan–Meier curves depicting survival probability for each subgroup. Confidence intervals of 95% were calculated using the Greenwood formula.

The subgroup of patients with radiographic evidence of GBM spread at diagnosis was small. Accordingly, they were individually matched to control groups with local GBMs at diagnosis while accounting for the following prognostic criteria: patient age (± 5 years), extent of initial tumor resection, and initial KPS score. Each patient with disseminated disease was matched to as many control volunteers with local tumors as possible. Survival times were compared using a two-tailed stratified log-rank test. Statistical significance was defined at a probability value less than 0.05.

The PPS times in patients with dissemination at the time of first tumor progression were compared with those in patients harboring local disease at first progression by using a proportional hazards model that accounted for age, time from diagnosis to progression, and KPS score. Chemotherapy following recurrence was not used in the experimental model given that no prospectively randomized study data have indicated a major benefit. Control groups with nondisseminated GBMs were selected from the UCSF neu-

| TABLE 1 |
| Summary of characteristics in 109 patients with GBMs |
| Characteristic | All | At Diagnosis | At Progression |
| total no. of patients | 109 | 17 | 92 |
| male | 72 | 10 | 62 |
| female | 37 | 7 | 30 |
| median age at diagnosis in yrs (range) | 52 (22–76) | 56 (24–71) | 51 (22–76) |
| primary tumor location | | | |
| supratentorial | 107 | 17 | 90 |
| rt | 65 | 10 | 55 |
| lt | 38 | 7 | 31 |
| bifrontal | 3 | 0 | 3 |
| bithalamic | 1 | 0 | 1 |
| infratentorial | 2 | 0 | 2 |
| cerebellar | 2 | 0 | 2 |
| KPS score at tumor dissemination | | | |
| 60 | 15 | 2 | 13 |
| 70 | 36 | 4 | 32 |
| 80 | 13 | 2 | 11 |
| 90 | 42 | 9 | 33 |
| 100 | 3 | 0 | 3 |
| initial surgical management | | | |
| biopsy | 14 | 9 | 5 |
| subtotal resection | 74 | 8 | 66 |
| gross-total resection | 21 | 0 | 21 |
| type of radiographic dissemination | | | |
| I | 24 | 1 | 23 |
| II | 66 | 16 | 50 |
| III | 19 | 0 | 19 |


FIG. 2. Graph of survival curve for patients with tumor dissemination at diagnosis. This Kaplan–Meier survival curve depicts the survival probability in all 17 patients with dissemination at the time of initial diagnosis.
Prognostic significance of intracranial dissemination of GBM

Neurooncology database of patients treated in clinical trials at the time of first tumor relapse. The proportional hazards model for comparing survival time among patients with different radiographic dissemination criteria was the same as that for comparing the dissemination groups with controls. Again, a probability value less than 0.05 was considered statistically significant.

Results

Patient Characteristics

Among the 1491 adult patients with GBMs who had been entered into the UCSF neurooncology database between 1988 and 1998, 126 (8%) had neuroimaging evidence of intracranial tumor dissemination. Seventeen patients did not meet the study inclusion criteria: seven because they had computerized tomography scans instead of MR imaging, nine with KPS scores less than 60 at the time of tumor dissemination, and one who had received nonconventional radiation therapy. The 109 remaining patients (72 male and 37 female patients) were included in the survival analysis and their demographic, tumor, and treatment characteristics are featured in Table 1. Dissemination can appear at presentation or subsequent progresses. Seventeen patients presented with neuroimaging evidence of dissemination, whereas 52 patients had dissemination at first progression, 25 at second progression, and 15 at a subsequent progression (that is, third relapse or later).

Patients With Tumor Dissemination on Initial Diagnosis

All 17 patients with tumor dissemination at the time of diagnosis harbored supratentorial lesions. Sixteen patients demonstrated radiographic evidence of Type II dissemination, whereas one patient had Type I. On conclusion of the study, 16 patients had died; one patient was alive with myelofibrosis disease 99 weeks after initial diagnosis. The patient with Type I dissemination survived 88 weeks, whereas the median survival in patients with Type II dissemination was 42 weeks (95% CI 18–59 weeks). A Kaplan–Meier curve in Fig. 2 depicts the survival probability for patients with tumor dissemination at the time of initial diagnosis. The prognostic significance of tumor dissemination on initial diagnosis was determined by comparing the survival of patients who had presented with Type II dissemination with suitable control groups who had presented without dissemination. Fourteen of the 16 patients had suitable matches from the database of controls based on age and KPS score, with the number of matches ranging from two to 28. Survival times in patients with tumor dissemination compared with those in suitably matched controls were not significantly different (p = 0.25). Of the 16 patients with Type II dissemination, only two had received adjuvant chemotherapy compared with approximately 50% of the control population. Adjuvant chemotherapy therefore did not account for the survival results.

Patients With Tumor Dissemination on Progression

Among this group, 23, 50, and 19 patients demonstrated Types I, II, and III neuroimaging results, respectively. The time from diagnosis to tumor dissemination varied with the different dissemination types (p = 0.04, Kruskal–Wallis). The median times from diagnosis to dissemination were 54 weeks (Type I), 37 weeks (Type II), and 52 weeks (Type III). In patients with spread at the time of progression, 86 (93%) of 92 patients had died on conclusion of the study, with a median PPS of 23 weeks (95% CI 19–30 weeks). The PPS for each tumor dissemination type was also analyzed. Patients with Type I dissemination had the longest interval of PPS (37 weeks, 23 patients) compared with those demonstrating Types II (25 weeks, 50 patients) and III (10 weeks, 19 patients). These patterns of survival are reflected in the Kaplan–Meier curves shown in Fig. 3, demonstrating an increased duration of survival in patients with Type I dissemination compared with those with Type II or III dissemination. These differences are statistically significant based on a stratified log-rank test (p < 0.001). Paired comparisons were made among the three groups by using a proportional hazards model, including age at diagnosis, KPS score, and time from diagnosis to tumor dissemination. Patients with Type I dissemination survived longer than those with Types II and III (p = 0.01 and p < 0.001, respectively). Those who demonstrated Type II dissemination survived longer than those who demonstrated Type III (p = 0.003).

Patients With Dissemination on First Progression

Among the patients with dissemination on tumor progression, we identified a subset of 52 patients who had dissemination on first progression. In these patients the time between initial diagnosis and relapse was calculated and analyzed with respect to tumor dissemination type. As
shown in Table 2, patients with Type I dissemination relapsed later than those with Type II or III, although the difference was not statistically significant (p = 0.18). When measured as a function of dissemination type, median PPS was 78 weeks in patients who demonstrated Type I (eight patients, 95% CI 25–123 weeks), 27 weeks in those with Type II (33 patients, 95% CI 19–33 weeks), and 8 weeks in those with Type III (11 patients, 95% CI 5–20 weeks). Using a stratified log-rank test, we determined that these groups differed (p < 0.001). A pairwise comparison of the three groups was done using the proportional hazards model, including age at diagnosis, KPS score, and time from diagnosis to dissemination. Patients who demonstrated Type I dissemination survived significantly longer than those with Type II or III (p ≤ 0.01). The difference between patients with Type II and those with Type III dissemination was marginally significant (p = 0.08), favoring the patients with Type II.

To assess the relative effect of dissemination on overall survival, patients with disseminated GBMs on first progression were compared with a control group with local recurrence on first relapse (311 patients). After combining all types of dissemination, we found that patients with dissemination on first progression (52 patients) had significantly shorter survival times than those in the control group (hazard ratio 1.8, p < 0.001; Fig. 4 upper). When evaluated based on classification of dissemination, however, patients with Type I showed no significant survival difference when compared with controls (hazard ratio 0.6, p = 0.18; Fig. 4 lower).

Discussion

The question of how to treat a patient with intracranial tumor dissemination is increasingly relevant. The advent of effective experimental modalities for controlling local disease will result in more patients with dissemination at progression. Furthermore, the intuitive bias of many clinicians not to treat patients with disseminated intracranial GBMs at presentation may be erroneously based on limited case series and retrospective reviews. To date there has been no report in which the authors formally evaluate the prognostic significance of intracranial GBM dissemination.

In this study we have proposed a classification system for disseminated intracranial GBMs based on lesion appearance on conventional T₁-weighted MR imaging with contrast. Among patients with dissemination on initial diagnosis, survival time for patients who demonstrated Type II dissemination was not significantly different from suitably matched patients who presented with focal GBMs. Although adjuvant chemotherapy was not matched for in the

<table>
<thead>
<tr>
<th>Dissemination Type</th>
<th>No. of Patients</th>
<th>Median Time (wks)</th>
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<tbody>
<tr>
<td>all patients</td>
<td>52</td>
<td>29</td>
</tr>
<tr>
<td>Type I</td>
<td>8</td>
<td>46</td>
</tr>
<tr>
<td>Type II</td>
<td>33</td>
<td>29</td>
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<tr>
<td>Type III</td>
<td>11</td>
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TABLE 2
Timing of tumor dissemination in 52 patients on first progression

Fig. 4. Graphs depicting survival in patients with dissemination on first progression. Upper: This Kaplan–Meier survival curve depicts survival probability in patients with dissemination at first progression as compared with appropriately matched controls. Dashed line represents patients with dissemination; solid line, controls. Lower: This Kaplan–Meier survival curve depicts survival probability in patients after dissemination on first tumor progression, as stratified by type. — — — represents Type I; dashed line, Type II; and — — —, Type III.
control group—because the majority of the patients with Type II dissemination had not received adjuvant therapy—these results cannot be explained by a positive impact of chemotherapy. Accordingly, these patients should be considered for aggressive therapies based on other factors such as age and KPS score. Our results are encouraging but by no means definitive given the small sample size. A single focus of GBM that later demonstrated Type I dissemination on first progression did not appear to have a worse prognosis than a local recurrence.

Data in this study provide some insight into the appropriate treatment of patients harboring GBMs with atypical radiographic patterns on presentation or recurrence. Nonetheless, the limitations of this study deserve consideration. The subgroup of patients with neuroimaging evidence of GBM dissemination on diagnosis was small. They were individually matched to control groups harboring local GBMs at diagnosis on the basis of the following criteria: age (± 5 years), extent of initial resection, and initial KPS score. In some cases only a few adequately matched controls could be found for patients with dissemination. Adjuvant chemotherapy was not used as a factor in the matching of controls. Given that only a minority of newly diagnosed Type II cases had been treated using chemotherapy, we can conclude that this treatment probably does not contribute to the similar survival results in the control group. Nevertheless, further testing with larger sample sizes is needed to validate our findings definitively.

Because of the retrospective nature of this study, patients with dissemination on progression were not treated in a homogeneous manner and the control volunteers were treated in various prospective clinical trials at the time of tumor progression. These factors could serve as confounders for outcome measures such as the time to subsequent progression and survival. There was not a major difference in chemotherapy treatment among the various dissemination types at the time of progression. Given that no controlled study at the progression of GBM has demonstrated a survival advantage for any specific chemotherapy, this particular method of treatment probably does not account for the survival results. Finally, the general applicability of our proposed classification system to some extent may be compromised because patients seen in a tertiary referral center may have different presentations from those seen in a tertiary referral center. The ability of this system to accurately reflect those seen in the community.

Despite these limitations, the classification system we have constructed has potentially wide application for practitioners. Conventional T-weighted MR imaging with contrast is a standard method for evaluating patients with GBMs preoperatively and after treatment. We are currently evaluating the prognostic utility of the classification system in patients with intracranial GBMs treated in prospective clinical trials. In addition to clinical applications, this classification system may serve as a future platform for investigating molecular profiles of GBM cells that contribute to dissemination.

Conclusions

Intracranial tumor dissemination can occur at presentation or progression in patients harboring GBMs. At the time of diagnosis, Type II tumor dissemination may not be a worse prognostic factor than local presentation. If dissemination occurs at progression, there is a significant difference in outcome depending on the type of dissemination. This fact may be useful in terms of selecting patients for clinical trials. At tumor progression, patients with Type I dissemination have a survival similar to patients with local recurrence. Despite anecdotal and historical biases that indicate otherwise, these patients in particular deserve aggressive treatment if they have an adequate KPS score.

Acknowledgments

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References


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