Treatment for posterior fossa dissemination of primary supratentorial glioma

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Object. This study was designed to assess the presentation, management, and outcome of cases involving patients who had a supratentorial glioma that subsequently progressed in the posterior fossa (PF).

Methods. The authors performed a retrospective chart review of adult patients treated between 1997 and 2005 for supratentorial gliomas that progressed in the PF. The 29 patients with PF progression in this study were relatively young (median age of 34 years at original presentation). Twenty of these patients presented with symptoms. The symptoms were typically nonspecific to this population, at times leading to delays in diagnosis. Overall, these symptoms resolved in eight patients (40%) and progressed or remained unchanged in 12 (60%). Patients treated with more than 5000 cGy of radiation administered to the PF were more likely to have symptom resolution than those who received any other form of treatment, including reduced doses of radiation (p = 0.004). The patients treated with higher doses also survived significantly longer after PF progression (univariate analysis, p = 0.01, and after adjusting for tumor grade, p = 0.04).

Conclusions. Patients with PF progression of supratentorial infiltrative gliomas may benefit from treatment, and the authors recommend more than 5000 cGy of radiation to the PF if prior radiotherapy ports and doses allow.

Key Words • glioma • progression • posterior fossa • external-beam radiation therapy • symptomatic outcome

Infiltrating gliomas remain a profound clinical challenge due to a propensity to recur despite aggressive treatment.7,21,22 Most recurrences develop within 2 cm of the original tumor and current therapies are primarily local (surgery) or regional (EBRT).7,22 It is extremely rare for infiltrative gliomas to metastasize to extracranial sites, and there have been only a limited number of reports on these patients.12,33,41,44 This distant intraneural recurrences have long been recognized, and they have been historically associated with a poor prognosis.2,4,6,9,15,27,29,32,35,37,41 With marked advances in neuroimaging and modest gains in the survival of patients as a result of improved therapies, the recognized occurrence of these lesions has increased.2,4,6,9,15,27,29,32,35,37,41

Systemic chemotherapy is the only standard treatment option that has the potential to treat metastatic neoplastic glial cells, but it does not always halt progression. Although repeated irradiation of recurrent tumors is rarely performed because of the increased risk of brain-tissue necrosis, the results of several recent studies have suggested that repeated irradiation is beneficial for patients with distant recurrent tumors if radiation ports permit and if it is directed far enough away from previously treated radiation fields.2,10

We examined a unique subset of patients who originally presented with supratentorial gliomas that subsequently progressed in the PF in order to determine optimal management of these cases. On the basis of our clinical experience, we hypothesized that symptoms resulting from PF progression may be effectively relieved by the administration of EBRT to the PF, if previously administered radiation doses and ports allow. We describe the clinical features of these patients, as well as their treatment and outcome, with particular attention to the role of repeated EBRT in symptom control.

Clinical Material and Methods

Patient Population and Clinical Data

Adult patients (≥ 17 years of age) with an original diagnosis of diffuse infiltrating supratentorial glioma (World
Patients who were used to estimate survival were measured from the time of treatment initiation. This study was approved by the UCSF Committee on Human Research.

Statistical Analysis

All statistical analyses were two-sided and were performed using SPSS version 11.5 (SSPS, Inc.), except for survival analyses, which were performed using StatXact (Statistical Solutions). A probability value less than 0.05 was considered statistically significant. Chi-square tests were used for comparisons of the distributions of categorical variables. For statistical analyses involving tumor grade, tumors were classified as either low-grade (Grade II) or high-grade (Grade III or IV) lesions. Patients who received EBRT for PF progression, but for whom the dose of this therapy could not be determined, were classified as having not received more than 5000 cGy of EBRT for statistical analyses. Patients who were asymptomatic at the time of PF progression diagnosis were excluded from all statistical assessments of symptom resolution. Because symptom resolution was noted up to 16 weeks after treatment, patients who had been followed up for less than 16 weeks after clinical diagnosis of PF progression and whose symptoms remained stable were excluded from statistical assessments of symptomatic outcome. Binary logistic regression analyses were performed to assess associations between continuous variables and symptomatic outcome, and the outcome variable was dichotomized to either symptom resolution or lack of symptom resolution.

The Kaplan–Meier method was used to estimate survival and the exact log-rank test was used to test for differences in survival time, where survival was measured from diagnosis of PF progression to death or the last date when the patient was known to be alive. Cox regression analyses were applied to assess for univariate association of treatment and patient characteristics with survival.

Results

Original Presentation

Twenty-nine patients (17 men and 12 women) were identified; their median age at presentation with the original tumor was 34 years (range 17–68 years). Seizure was the most common initial sign, identified in 16 patients (55%), followed by symptoms of raised intracranial pressure, identified in 14 patients (48%). More focal neurological deficits such as numbness, dysphasia, visual disturbance, and personality change were less common and were identified in six patients (21%). The median KPS score was 90 (range 70–100). Tumors included four Grade II (14%), nine Grade III (31%), and 16 Grade IV (55%) gliomas (Table 1). These tumors were most commonly located in the frontal (17 lesions, 59%), temporal (six lesions, 21%), and parietal (four lesions, 14%) lobes. Twenty-two tumors (79%) enhanced on MR images in response to intravenous administration of a contrast agent.

Management and Outcome of Original Tumors Prior to PF Progression

Management of the original tumor and treatment of recurrences prior to PF progression are summarized in Table 1. All patients underwent some form of surgical procedure after initial presentation to reduce the bulk of the tumor, establish a diagnosis, or both. Following surgery, 27 patients (93%) underwent EBRT, and 17 (59%) received systemic chemotherapy. Seventeen (59%) experienced at least one tumor recurrence prior to progression in the PF. Management of these recurrences included chemotherapy in 13 cases (76%), surgery in 10 (59%), stereotactic radiosurgery in five (29%), standard EBRT in three (18%), and brachytherapy in one (6%).

Presentation of PF Progression

The median time from initial tumor diagnosis to PF progression (defined as the time when abnormalities in the PF could be detected on follow-up MR images) was 16 months (range 5–226 months). Imaging findings predated the clinical diagnosis of PF progression in 12 patients (41%). The median duration of this delay in these patients was 4.5 months (range 2–25 months). Data on clinical status at time of PF progression diagnosis were available for 26 patients (90%). Among these patients, the most common symptoms at presentation were vertigo/imbalance, nausea/vomiting, and headache/neck pain, seen in 14 (54%), eight (31%), and six (23%), respectively (Table 2). In six cases (23%) the patients were asymptomatic and had progression noted on routine follow-up imaging. The median KPS score at the time of PF progression was 80 (range 40–90). Magnetic resonance imaging showed progression to be limited to the PF in 17 cases (59%) and to involve both the supratentorial and infratentorial regions in 12 (41%). Representative neuroimages obtained in two patients with PF progression following the diagnosis of a supratentorial infiltrative glioma are shown in Fig. 1. Of the 14 patients who had contrast-enhancing PF lesions, 12 (86%) had contrast-enhancing supratentorial lesions at initial diagnosis. Of the 15 patients who had nonenhancing PF lesions, 10 (67%) had enhancing supratentorial lesions at initial diagnosis (p = 0.22). Staging MR imaging studies of the spine were performed in eight patients (28%), and in two of these patients, CSF was obtained for cytological examination. None of these patients had evidence of spinal tumors or neoplastic cells in the CSF.

Management and Outcome After PF Progression

Management of PF progression is summarized in Table 2. Most cases were managed without any further surgical intervention. Of the five patients who underwent subsequent surgery, two had a PF lesion with a grade and histological subtype similar to the original supratentorial tumor (Table 3). The prior radiotherapy dose administered to the PF was the primary factor determining whether or not patients received more than 5000 cGy of EBRT in this series. Based on available dosing information, all patients who were eligible to receive more than 5000 cGy of EBRT to the PF did so (Table 2). One patient (Case 4) was lost to follow-up after identification of PF progression. Of the remaining 28 patients, 15 (54%) received EBRT to the PF.
Based on radiation dosing in 12 of these patients, six received more than 5000 cGy of EBRT to the PF and six received a reduced dose (< 5000 cGy). Four patients (14%) were treated with Gamma Knife or CyberKnife surgery, and 10 (36%) did not receive any form of radiation therapy. Fourteen (50%) received some form of systemic chemotherapy (temozolomide, carmustine, lomustine, etoposide, irinotecan, tamoxifen, thalidomide, and/or PTK787). Of the patients receiving more than 5000 cGy of EBRT, three (50%) also received some form of chemotherapy. Five patients (18%) received supportive care only.

Symptoms attributed to PF progression subsequently resolved in eight (40%) of the 20 patients who presented with symptoms and progressed or remained unchanged in 12 (60%) of these patients (Table 2, Fig. 2). To confirm our initial hypothesis, we first assessed the association between symptom resolution and treatment with more than 5000 cGy of EBRT to the PF. Symptom resolution was significantly more common among symptomatic patients who were treated with more than 5000 cGy of EBRT delivered to the PF compared with patients who received any other form of treatment, including reduced or unknown doses of EBRT (p = 0.004). In contrast to patients treated with reduced doses of EBRT (< 5000 cGy), all symptomatic patients treated with more than 5000 cGy of EBRT had symptom resolution. The median time to symptom resolution in those whose condition improved after they had received more than 5000 cGy of EBRT was 6 weeks (range 3–16 weeks).

In subsequent exploratory univariate analyses, we did
not find any significant association between resolution of symptoms and patient age at initial diagnosis, grade of the supratentorial tumor at initial diagnosis, whether the patient received treatment for PF progression, KPS score at the time of PF progression diagnosis, or evidence of supratentorial tumor progression at the time PF tumor progression was diagnosed.

**Clinical Follow Up and Patient Survival**

Overall, 69% of the patients in our study population had died by the time of this writing. For the patients who died, the median duration of survival from the time of initial tumor diagnosis was 40 months (95% CI 10–70 months), and the median duration of survival after PF progression was 9 months (95% CI 7–11 months). In the group of patients who remained alive, the median duration of follow up from the time of PF progression diagnosis was 18 months (range 2–55 months). Most patients who had Grade IV tumors had died (81%) as of this writing, and approximately one half of the patients who had Grade II and Grade III tumors had died (50 and 56%, respectively). In the group of patients with Grade IV tumors, the median survival from the time of initial diagnosis was 16 months (95% CI 14–18 months), and median survival from the time of PF progression was 7 months (95% CI 4–10 months).

Based on the strong association between administration of more than 5000 cGy of EBRT to the PF and symptom resolution, we hypothesized that this treatment may also be associated with longer duration of survival from the time of

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**TABLE 2**

*Management of PF lesions and effect on presenting symptoms for 37 patients with supratentorial glioma and progression in the PF*  

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Presentation at PF Progression</th>
<th>Location of PF Lesion</th>
<th>ST Lesion Progression†</th>
<th>KPS Score†</th>
<th>Radiation to PF (cGy)</th>
<th>Chemo</th>
<th>Sx</th>
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<tr>
<td>1</td>
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<td>UK</td>
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<td>2</td>
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<td>3</td>
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<td>none</td>
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<td>prog</td>
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<td>5</td>
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<tr>
<td>6</td>
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<td>no</td>
<td>90</td>
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<td>res</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>asymptomatic cerebellar peduncle</td>
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<td>80</td>
<td>none</td>
<td>yes</td>
<td>prog</td>
<td>prog</td>
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<td>prog</td>
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<td>60</td>
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<td>no</td>
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<td>prog</td>
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<td>60</td>
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<td>prog</td>
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<td>14</td>
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<td>prog</td>
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<td>90</td>
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<td>80</td>
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<td>res</td>
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<td>EBRT (dose UK)</td>
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<td>res</td>
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<td>20</td>
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<td>70</td>
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<td>yes</td>
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<td>70</td>
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<td>prog</td>
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<td>22</td>
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<td>yes</td>
<td>prog</td>
<td>prog</td>
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<td>40</td>
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<td>no</td>
<td>prog</td>
<td>prog</td>
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<tr>
<td>24</td>
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<td>80</td>
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<td>res</td>
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</tr>
<tr>
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<td>no</td>
<td>90</td>
<td>EBRT (dose UK)</td>
<td>no</td>
<td>res</td>
<td></td>
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<td>80</td>
<td>EBRT (dose UK)</td>
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<td>res</td>
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<td>27</td>
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<td>no</td>
<td>70</td>
<td>EBRT (dose UK)</td>
<td>no</td>
<td>res</td>
<td></td>
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<tr>
<td>28</td>
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<td>80</td>
<td>none</td>
<td>no</td>
<td>prog</td>
<td>prog</td>
</tr>
<tr>
<td>29</td>
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<td>yes</td>
<td>90</td>
<td>GKS (dose UK)</td>
<td>no</td>
<td>res</td>
<td></td>
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<tr>
<td>30</td>
<td>nausea/vomiting 4th ventricle, cerebellar hemispheres</td>
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<td>90</td>
<td>UK</td>
<td>EBRT (dose UK)</td>
<td>no</td>
<td>res</td>
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<td>31</td>
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<td>yes</td>
<td>90</td>
<td>UK</td>
<td>EBRT (dose UK)</td>
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<td>res</td>
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<td>90</td>
<td>UK</td>
<td>EBRT (dose UK)</td>
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<td>res</td>
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<td>33</td>
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<td>yes</td>
<td>90</td>
<td>UK</td>
<td>EBRT (dose UK)</td>
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<td>34</td>
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<td>90</td>
<td>UK</td>
<td>EBRT (dose UK)</td>
<td>no</td>
<td>res</td>
</tr>
<tr>
<td>35</td>
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<td>yes</td>
<td>90</td>
<td>UK</td>
<td>EBRT (dose UK)</td>
<td>no</td>
<td>res</td>
</tr>
<tr>
<td>36</td>
<td>nausea/vomiting 4th ventricle</td>
<td>yes</td>
<td>90</td>
<td>UK</td>
<td>EBRT (dose UK)</td>
<td>no</td>
<td>res</td>
</tr>
<tr>
<td>37</td>
<td>nausea/vomiting 4th ventricle</td>
<td>yes</td>
<td>90</td>
<td>UK</td>
<td>EBRT (dose UK)</td>
<td>no</td>
<td>res</td>
</tr>
</tbody>
</table>

* CN = cranial nerve; prog = progressed; res = resolved; ST = supratentorial; Sx = symptoms; UK = unknown.
† At the time of PF progression diagnosis.
‡ Due to worsening of symptoms, EBRT was not completed.

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PF progression diagnosis. Patients whose PF progression was treated with more than 5000 cGy of EBRT survived significantly longer than all other patients in this study (Fig. 3, p = 0.01), even after adjusting for the effects of tumor grade (p = 0.04), but patients who also had primary lesion progression when PF progression was diagnosed were significantly less likely to receive more than 5000 cGy of EBRT to the PF (p = 0.017). Although there was a trend for patients who had lower KPS scores at the time of the diagnosis of PF progression to be less likely to receive any treatment (EBRT, chemotherapy, and/or radiosurgery) for the PF lesion, this association was not statistically significant (p = 0.075). The presence of concurrent primary lesion progression at the time of diagnosis of PF progression was not significantly associated with whether the patient received any treatment (p = 0.62).

In addition, we hypothesized that histological grade of the supratentorial tumor at initial diagnosis, despite the advanced disease state of this entire population, may be associated with duration of survival following the diagnosis of PF progression. Indeed, patients with low-grade supratentorial tumors did demonstrate significantly longer survival following PF dissemination in comparison with patients with high-grade lesions (p = 0.020). On subsequent exploratory univariate analyses, patient age and KPS score at diagnosis of PF progression were not significantly associated with duration of survival following PF progression. Patients with evidence of supratentorial tumor progression at the time of PF progression did demonstrate a shorter overall duration of survival following diagnosis of PF progression (p = 0.043).

**Discussion**

Diffuse infiltrating glioma typically presents as a single lesion that recurs locally after treatment. Although these lesions usually recur in the area of the primary tumor site, dissemination can occur throughout the central nervous system. Based on limited case series and retrospective reviews, the erroneous bias of many clinicians may cause

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**TABLE 3**

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Primary Lesion</th>
<th>PF Progression</th>
<th>Op for PF Lesion</th>
<th>Total FU (mos)</th>
<th>Status</th>
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<tbody>
<tr>
<td>16</td>
<td>Grade II OA</td>
<td>Grade II A</td>
<td>biopsy only</td>
<td>101/alive</td>
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<tr>
<td>17</td>
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<td>18</td>
<td>Grade III A</td>
<td>Grade III A</td>
<td>STR</td>
<td>27/dead</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>GBM</td>
<td>GBM</td>
<td>STR</td>
<td>53/alive</td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>Grade III A</td>
<td>Grade II A</td>
<td>biopsy only</td>
<td>205/alive</td>
<td></td>
</tr>
</tbody>
</table>

* FU = follow up.
them to refrain from treating these patients because of their advanced disease.\cite{1,3,8,11–13,17,19,25,26,29–31,36} The appropriate management of such cases is becoming increasingly relevant as more effective modalities for controlling primary disease are developed,\cite{5} allowing more patients to survive long enough to develop disseminated disease. Through this study, we sought to better understand the presentation, management, and outcome of a specific subgroup of these cases—those involving a supratentorial glioma that progressed in the PF.

Most of the 29 patients in this study were symptomatic at the time of presentation of PF dissemination. Among the most common presenting symptoms were vertigo/imbalance, nausea/vomiting, and headache/neck pain. The relatively nonspecific nature of these symptoms probably contributed to the delay in diagnosis (mean 4.5 months) that we observed in these cases.

It is clear that patients who received more than 5000 cGy of EBRT to the PF had an improved symptomatic outcome compared with patients who were treated with other approaches, including low-dose EBRT to the PF. Importantly, we cannot exclude a potential confounding effect of chemotherapy, because three of the six patients who received more than 5000 cGy of EBRT to the PF also received some form of systemic chemotherapy. Based on the symptomatic improvement seen with this treatment, we recommend treatment with more than 5000 cGy of EBRT to the PF in all eligible patients. Any other form of radiation therapy (radiosurgery or fractionated therapy < 5000 cGy) did not appear to be helpful. Chemotherapy may be considered as a treatment option, as it normally would be for any patient with a recurrent glioma, but based on our data it does not appear to lead to symptom relief in this population.

The authors\cite{8,10} of two recent reports have also noted the radiosensitivity of infiltrative glioma that has disseminated to the PF. Cohen and colleagues\cite{8} reported on three patients with intractable vomiting resulting from GBM that had metastasized to the fourth ventricle. Each of these patients experienced complete resolution of vomiting within 10 days of receiving additional EBRT to the PF at doses of 2100, 3000, or 4500 cGy. Fujimura and associates\cite{32} reported on five patients with supratentorial high-grade astrocytoma who developed intractable vomiting as a result of tumor dissemination to the fourth ventricle. Two of the five patients were treated with radiosurgery, and in one of these two cases subsequent imaging demonstrated resolution of the PF lesion. The reason for the relative radiosensitivity of tumor deposits in the PF remains unclear, but it has been hypothesized to be related to their small size, good vascular supply, and absence of necrosis relative to the primary lesion.\cite{5,10,18,23,28,37}

The median survival after PF progression was 9 months in our study population, including all patients, even those who received no therapy, suggesting that the presence of PF tumor dissemination should not preclude aggressive treatment. This finding is consistent with the recent report of Parsa et al.,\cite{32} who studied the prognostic significance of disseminated intracranial GBM in adults at presentation and at the time of tumor progression. They demonstrated that patients with a single focus of GBM that later demonstrated subependymal or subarachnoid dissemination of tumor at the time of progression did not have a worse prognosis than patients with a lesion that exhibited only local recurrence.

In our study population, treatment with more than 5000 cGy of EBRT administered to the PF was also associated with improved survival on univariate analysis; however, patients who did not receive more than 5000 cGy of EBRT to the PF were significantly more likely to have concurrent progression of the primary lesion compared with those who received more than 5000 cGy of EBRT to the PF. Any other form of radiation therapy (radiosurgery or fractionated therapy < 5000 cGy) did not appear to be helpful. Chemotherapy may be considered as a treatment option, as it normally would be for any patient with a recurrent glioma, but based on our data it does not appear to lead to symptom relief in this population.

The authors\cite{8,10} of two recent reports have also noted the radiosensitivity of infiltrative glioma that has disseminated to the PF. Cohen and colleagues\cite{8} reported on three patients with intractable vomiting resulting from GBM that had metastasized to the fourth ventricle. Each of these patients experienced complete resolution of vomiting within 10 days of receiving additional EBRT to the PF at doses of 2100, 3000, or 4500 cGy. Fujimura and associates\cite{32} reported on five patients with supratentorial high-grade astrocytoma who developed intractable vomiting as a result of tumor dissemination to the fourth ventricle. Two of the five patients were treated with radiosurgery, and in one of these two cases subsequent imaging demonstrated resolution of the PF lesion. The reason for the relative radiosensitivity of tumor deposits in the PF remains unclear, but it has been hypothesized to be related to their small size, good vascular supply, and absence of necrosis relative to the primary lesion.\cite{5,10,18,23,28,37}
did receive more than 5000 cGy of EBRT, and patients with concurrent progression of the primary lesion had shorter survival. Conclusive statements are limited in this study by the relatively small number of patients.

Although staging for disease spread to the spinal cord (MR imaging or CSF cytological studies) was performed only in a minority of our patients, the results of staging studies were uniformly negative. According to the available follow-up data, no patient who did not undergo spinal staging subsequently developed symptoms of spinal disease. Therefore, we believe that spinal staging is unnecessary in the absence of symptoms of spinal cord compromise in patients with PF progression of supratentorial diffuse gliomas.

The patients in this study were relatively young (median age 34 years), which did not seem to correspond simply to an increased number of patients with low-grade gliomas, but rather seemed to reflect younger ages across all grades. The majority (55%) of patients in this study initially presented with seizures, including 67% of patients with Grade III and 44% with Grade IV tumors.

Youth is a good prognostic indicator, and the patients in this study might simply have lived long enough to develop PF progressions. Alternatively, PF progression might reflect some aspect of tumor biology that is unique to these patients. For example, young age and presentation with seizures are associated with an increased likelihood of p53 tumor suppressor gene mutation and decreased likelihood of epidermal growth factor receptor oncogene amplification or overactivity in these tumors, although this was not assessed in the present study. Interestingly, two PF biopsies demonstrated lower tumor grade than the original tumors, and two PF biopsies demonstrated a different histological subtype compared with the original tumor. This may simply reflect the limitations of a single biopsy to lead to the correct diagnosis of these lesions; however, other potential explanations cannot be ruled out. For example, these PF lesions could be new tumors arising in patients at high risk of developing diffuse infiltrating gliomas. Alternatively, they may represent dissemination of low-grade portions of the original tumors.

Conclusions

Overall, in our study population—including all patients, even those who received no therapy—median survival after PF progression was 9 months, suggesting that the presence of PF tumor dissemination should not preclude aggressive treatment. Patients treated with more than 5000 cGy of EBRT administered to the PF had significantly improved symptomatic outcomes compared with those who received any other form of treatment, including reduced doses of radiation. Based on our findings, we recommend treatment with more than 5000 cGy of EBRT to the PF in this patient population if prior radiotherapy ports and doses allow.

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