Infiltrative astrocytomas of the thalamus

HENDRIKUS G. J. KROUWER, M.D., AND MICHAEL D. PRADOS, M.D.

Neuro-Oncology Service of the Brain Tumor Research Center, Department of Neurological Surgery, School of Medicine, University of California, San Francisco, California

Clinical characteristics and outcome in 57 patients with infiltrative thalamic astrocytomas were analyzed retrospectively. The median patient age was 22 years (range 1 to 69 years). Fourteen patients had no surgery, 37 had biopsy, and six had subtotal resection. The histological diagnosis was astrocytoma in 14 patients, anaplastic astrocytoma in 25, and glioblastoma multiforme in two; two specimens were nondiagnostic. The initial treatment was conventional radiation therapy (RT) in 20 patients (one also received interstitial brachytherapy), RT followed by chemotherapy in 18, hyperfractionated RT in 17 (one also received chemotherapy), and chemotherapy alone in two. The median time to tumor progression was 47 weeks (range 5 to 388 weeks); median survival was 73 weeks (range 11 to 502 weeks). Actuarial 1-, 2-, 3-, and 5-year survival rates were 67%, 35%, 24%, and 20%, respectively. Tumor progression was usually treated with chemotherapy. The assessed treatment failure was within 2 months after RT in 12 patients in whom the findings of the neurological and radiological examinations did not correspond. This assessment showed false-negative diagnosis of radiation-induced changes in five patients (42%); false-positive diagnosis of tumor progression could not be ascertained. In univariate Cox proportional-hazards analysis, histological diagnosis of astrocytoma, age under 18 years, and open biopsy were prognostically favorable features; in multivariate analysis, only open biopsy was favorable. Infiltrative astrocytomas of the thalamus carry a dismal prognosis, regardless of the type of treatment. Hyperfractionated RT does not increase toxicity but its benefit over conventional RT remains unproven.

Key Words • infiltrative astrocytoma • thalamus • biopsy • chemotherapy • hyperfractionated radiation therapy

Clinical Material and Methods

Patient Selection

The database of the Neuro-Oncology Service at the University of California, San Francisco was reviewed to identify patients with primary thalamic glial tumors treated between August 1975 and November 1991. Patients were selected based on neuroimaging reports and histopathological diagnosis. Patients who did not complete RT and those with incomplete data on histological examination, treatment, serial imaging studies, and survival were excluded. Patients whose tumors arose primarily in surrounding structures (pineal region, hypothalamus/optic chiasm, brainstem, adjacent white matter of temporal/parietal/occipital lobes) were also excluded; however, those whose tumors involved the basal ganglia and extended into the thalamus were included.

Histopathological Criteria

The astrocytic tumors were classified as astrocytoma, anaplastic astrocytoma, or glioblastoma multiforme (Table 1). Juvenile pilocytic astrocytoma and tumors that were not, or not purely, astrocytic were excluded.
Clinical Review

The charts were reviewed to determine sex, age at diagnosis, Karnofsky Performance Scale (KPS) score, presenting symptoms and signs, and side and extension of the thalamic mass. The surgical procedure, including shunt placement, was determined from the operative report or from the charts. Also assessed were the type, extent, and dose of RT, type of chemotherapy, time to tumor progression, treatment for tumor progression, and complications of treatment.

Treatment With Radiation Therapy

All patients received conventional or hyperfractionated RT, usually postoperatively. The hyperfractionated RT protocol was similar to that used for brainstem tumors. Briefly, megavoltage radiation (4 to 18 MV) was given in fractions of 100 cGy twice daily (5 days/week) to the midplane of opposed lateral fields encompassing the tumor and a 1- to 2-cm margin, based on the tumor volume transferred from computerized tomography (CT) scan or magnetic resonance (MR) image to the simulation film. Chemotherapy (most often nitrosourea based) was given adjuvantly or at the time of tumor progression.

Follow-Up Review

The response to treatment was assessed by neurological examination and neuroimaging studies performed 2 to 8 weeks after completion of RT and every 6 to 12 weeks thereafter. Any decrease in tumor size on imaging studies was considered a response. Stable disease was defined as no significant change in tumor size, provided the patient was neurologically stable and receiving a fixed or decreasing dose of steroids. Tumor progression was defined as any tumor enlargement on neuroimaging studies. Assessment of tumor progression was also based on neurological findings. In patients with radiographic (areas of new enhancement or increase in tumor size) and neurological deterioration, tumor progression was thought to have occurred. However, increased intensity of contrast enhancement without increased mass effect on CT scans, or increased abnormal signal intensity on T2-weighted MR images only, was considered to be radiation induced, regardless of the neurological findings. Tumor progression was considered to be local if tumor enlargement was seen within 2 cm of the primary site; distant tumor progression was defined as appearance of tumor more than 2 cm beyond the primary site.

Data Analysis

Time to tumor progression (documented by CT scans or MR images or by histological examination of tissue obtained at reoperation) and survival time (Kaplan–Meier method) were measured from the first operation or from the time of diagnosis based on imaging studies. Prognostic factors were evaluated by univariate and multivariate Cox proportional-hazards models.

Results

Clinical Characteristics

Fifty-seven patients met the entry criteria. The clinical characteristics are summarized in Table 2. There were 30 males and 27 females, with a median age of 22 years at diagnosis; 24 were under 18 years of age. The median KPS score was 90%. A representative tumor is shown in Fig. 1.

The presenting symptoms and signs are summarized in Table 1.
Table 3. The most common symptoms were those related to increased intracranial pressure (60%). The most frequent sign was hemiparesis/hemiplegia (53%).

Histopathological Findings

A histopathological diagnosis was obtained in 41 patients. Fourteen patients had astrocytomas, 25 had anaplastic astrocytomas, and two had glioblastomas multiforme. Tissue diagnosis was not available for 16 patients at the start of treatment (no operation in 14, surgical specimen insufficient for diagnosis in two). Glioblastoma multiforme was diagnosed at autopsy in three patients.

At reoperation, performed 11 times in nine patients, malignant transformation was a possibility in one case in which the first stereotactic biopsy showed an anaplastic astrocytoma and the second, 2 months later, showed glioblastoma multiforme.

Initial Treatment

The initial treatment is summarized in Table 4. Forty-three patients underwent a surgical procedure. A cerebrospinal fluid shunt was placed in 33 patients. In two patients, an Ommaya reservoir was placed in the cystic portion of the tumor. Fifty-five patients received RT, and two received chemotherapy only.

Assessment of Treatment Failure

At the first follow-up examination after completion of RT, 26 of the 57 patients had deteriorated; in two of the 26 patients, information on imaging studies was not available. In 12 of the remaining 24 patients, neuroimaging studies showed increased abnormalities and the neurological examination showed deterioration; the imaging changes were considered to be radiation induced in one patient and due to tumor progression in 11. In 12 patients, the clinical and radiological findings did not correspond: six patients had clinical deterioration without corresponding changes on CT scans or MR images and six had increased neuroimaging abnormalities without signs of clinical deterioration. In seven of these 12 patients, the neuroimaging findings proved correct (either tumor progression or radiation changes), as shown by the clinical course. In five patients, the interpretation of imaging studies proved incorrect (false-negative); radiation-induced changes were suspected and treatment with corticosteroids was started or intensified, but further progression was documented, both clinically and radiologically, at the next follow-up visit.

Radiographic Location of Initial Tumor Progression

Computerized tomography scans or MR images showed first tumor progression (or radiation-induced changes) in 48 patients (Table 5). The tumor progression was local in 39 (89%) of the 44 patients who could be evaluated, and nonlocal in five (11%).

Fourteen patients had 23 episodes of tumor progression after the first one; all but one were local. One was accompanied by leptomeningeal–subependymal spread. Leptomeningeal–subependymal dissemination occurred in four patients (8%) after a mean interval of 39 weeks (range 19 to 79 weeks). Nine patients (21%) have shown...
Infiltrative thalamic astrocytomas

Initial treatment in 57 patients with infiltrative thalamic astrocytomas

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No.</th>
<th>Percent</th>
</tr>
</thead>
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<td></td>
</tr>
<tr>
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<td>14</td>
<td>25</td>
</tr>
<tr>
<td>stereotactic biopsy</td>
<td>20</td>
<td>35</td>
</tr>
<tr>
<td>open biopsy</td>
<td>17</td>
<td>30</td>
</tr>
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<td>subtotal resection</td>
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<tr>
<td>radiation therapy</td>
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</tr>
<tr>
<td>conventional</td>
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</tr>
<tr>
<td>median dose 5960 cGy</td>
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<td>35</td>
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<td></td>
</tr>
<tr>
<td>hyperfractionated RT</td>
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<td></td>
</tr>
<tr>
<td>median dose 7600 cGy</td>
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<td>33</td>
</tr>
<tr>
<td>(range 7200–7800 cGy)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>chemotherapy</td>
<td>2</td>
<td>33</td>
</tr>
</tbody>
</table>

* Whole-brain RT in 11 patients (tumor boost in six) and focal in nine; one received conventional RT combined with 131I interstitial brachytherapy.
† Whole-brain radiation therapy (RT) in six patients (tumor boost in two) and focal in 12.
‡ The chemotherapeutic regimens included: BCNU (carmustine) (five patients); CCNU (lomustine), procarbazine, vincristine (five, two patients also received bromodeoxyuridine as a radiosensitizer); 6-thioguanine, BCNU (one); 6-thioguanine, procarbazine, dibromodulcitol, CCNU, vincristine (six); 6-thioguanine, procarbazine, dibromodulcitol, CCNU, 5-fluorouracil, hydroxyurea (one); 6-thioguanine, 5-fluorouracil, hydroxyurea (one); cyclophosphamide, procarbazine, vincristine, prednisone (one).
§ One patient received hyperfractionated RT combined with nitrosourea-based chemotherapy (6-thioguanine, procarbazine, dibromodulcitol, CCNU, vincristine).
∥ One patient was a 10-year-old child; the other had a low-grade glioma.

no signs of tumor progression on clinical neurological examination or imaging studies.

Treatment for Tumor Progression

The first episode of tumor progression was not treated in 18 of 48 patients. The remaining 30 patients received surgery, RT, chemotherapy, or combinations thereof. Two patients had their first operation (stereotactic biopsy) after the initial treatment (chemotherapy) failed. Of 14 patients who had a second recurrence, seven received no further therapy and seven received chemotherapy. Chemotherapy at recurrence is summarized in Table 6. Eleven reoperations (three stereotactic biopsies, one stereotactic biopsy with implantation of 131I, one biopsy with cyst aspiration, four subtotal resections, one attempted subtotal resection, one laminectomy) were performed in nine patients.

Complications of Treatment

Operative morbidity after initial surgery was seen in three (7%) of the 44 patients who could be evaluated: one had new hemiparesis after a subtotal resection; one had increase of a preoperative hemiparesis after open biopsy, and one had an unspecified decrease in performance status after a stereotactic biopsy. Reoperation in two patients (both subtotal resections) led to decreased performance status in one patient; in the other, perioperative cerebral edema resulted in coma and death. This was the only operative death.

One patient treated with hyperfractionated RT had a 75% hearing loss on the left side after 27 months. No other events could be related unequivocally to RT. Two patients who received chemotherapy developed severe, prolonged bone marrow suppression: one also had sepsis from a urinary tract infection. One patient had vincristine-induced neurotoxicity after the third cycle of chemotherapy. Serious behavioral and memory disturbances were found in four patients; two also had endocrinological abnormalities (diabetes insipidus and deficiencies of thy-

<p>| TABLE 4 |
| Initial treatment in 57 patients with infiltrative thalamic astrocytomas |</p>
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<tr>
<td>chemotherapy</td>
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<td>33</td>
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</table>

* Several patients received more than one chemotherapeutic regimen.
† BCNU = carmustine; DFM0 = difluoromethylornithine; 6-TG = 6-thioguanine; 5-FU = 5-fluorouracil; CCNU = lomustine; PCB = procarbazine; HU = hydroxyurea; 6-MP = 6-mercaptopurine; MTX = methotrexate; AraC = cytarabine; it = intrathecally; DBD = dibromodulcitol; VCR = vincristine; PCNU = 1-(2-chloroethyl)-3-(2,6-dioxo-3-piperidyl)-1-nitrosourea; MGBG = methylbisguanyldihydrazine; CBDCA = carboplatin; VP-16 = etoposide; LPAM = L-phenylalanine mustard.

<p>| TABLE 6 |
| Chemotherapeutic regimens given at recurrence in 20 patients without reoperation and four with reoperation* |</p>
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<th>Chemotherapeutic Regimens†</th>
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<td>BCNU/DFMO</td>
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</tr>
<tr>
<td>BCNU/6-TG</td>
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</tr>
<tr>
<td>BCNU/5-FU/CCNU/PCB/HU/6-MP</td>
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</tr>
<tr>
<td>BCNU/5-FU/MTX/PCB + AraC/thetaite, it</td>
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</tr>
<tr>
<td>CCNU/5-FU/6-MP/HU</td>
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<tr>
<td>CCNU/6-TG/PCB/BDB/VCR</td>
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<tr>
<td>PCB</td>
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<td>DFM0/MGBG</td>
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<tr>
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<td>1</td>
</tr>
<tr>
<td>CBDCA</td>
<td>1</td>
</tr>
<tr>
<td>VP-16</td>
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</tr>
<tr>
<td>thiopeta</td>
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</tr>
<tr>
<td>LPAM</td>
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* CT = computerized tomography; MR = magnetic resonance.
† Data on pattern of progression were available for 44 patients.

<p>| TABLE 5 |
| Radiographic pattern of first tumor progression in 57 patients with infiltrative thalamic astrocytomas |</p>
<table>
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<th>CT/MR Pattern*</th>
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<th>Percent</th>
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<td>16</td>
</tr>
<tr>
<td>first progression</td>
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<td>84</td>
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<tr>
<td>local only</td>
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<td>89</td>
</tr>
<tr>
<td>local + distant</td>
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<td>11</td>
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<tr>
<td>local + leptomeningeal/subependymal</td>
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</tr>
<tr>
<td>local + distant + leptomeningeal</td>
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<td>2</td>
</tr>
<tr>
<td>subependymal + extraneural</td>
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<td>2</td>
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<td>7</td>
</tr>
<tr>
<td>subependymal only</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

* CT = computerized tomography; MR = magnetic resonance.
† Data on pattern of progression were available for 44 patients.
roid, growth, and adrenocorticotropic hormones). It could not be ascertained whether these phenomena were related to the tumor or the treatment.

**Time to Tumor Progression and Survival**

The median time to tumor progression in all 57 patients was 47 weeks (range 3 to 388 weeks) and the median survival was 73 weeks (range 11 to 502 weeks) (Fig. 2). Eleven patients (19%) are still alive at a median of 267 weeks (range 95 to 388 weeks); nine were 18 years of age or younger at diagnosis. Forty-six patients (81%) have died after a median interval of 59 weeks (range 11 to 502 weeks). Actuarial 1-, 2-, 3-, and 5-year survival rates were 67% (95% confidence interval (CI), 53% to 77%), 35%
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FIG. 4. Graphs showing Kaplan–Meier curves. Time to tumor progression (upper left) and survival (upper right) for patients who had no surgery, stereotactic biopsy, open biopsy, and subtotal resection. Time to tumor progression (lower left) and survival (lower right) for patients treated with radiation therapy, radiation therapy with nitrosourea-based chemotherapy, and hyperfractionated radiation therapy.

(95% CI, 23% to 47%), 24% (95% CI, 14% to 36%), and 20% (95% CI, 10% to 31%), respectively.

The influence of age, histopathological diagnosis, extent of surgery, and type of adjuvant treatment on time to tumor progression and on survival is shown in Table 7 and Figs. 3 and 4. Univariate analysis showed that both tumor progression and survival were significantly influenced by age, histopathological diagnosis, and extent of surgery. Multivariate analysis showed that the extent of resection was the most important prognostic factor, both for tumor progression and for survival.

Because of their small numbers, glioblastoma multiforme, subtotal resection, and leptomeningeal–subependymal dissemination were not included in the statistical analysis. The mean time to tumor progression in the five patients with glioblastoma multiforme was 37.8 weeks, and the mean survival time was 102.2 weeks. Three of six patients who had subtotal resection (two anaplastic astrocytoma, one astrocytoma) had tumor progression after 12, 40, and 54 weeks, respectively, and survival times of 22, 56, and 59 weeks, respectively; the other three (two with anaplastic astrocytoma and one with glioblastoma multiforme) have not had tumor progression after subtotal resection and are alive after 95, 288, and 303 weeks, respectively. Finally, the mean survival from initial diagnosis in the five patients with leptomeningeal–subependymal dissemination was 52 weeks (range 27 to 83 weeks).

Discussion

Epidemiological and Clinical Characteristics

The incidence of thalamic tumors is difficult to ascertain. In many series, these lesions are collectively called “central” or “nonlobar” tumors and are grouped with tumors of other deep-seated regions, such as the corpus callosum, hypothalamus, midbrain, pons, medulla oblongata, or even cerebellum. The incidence of “pure” thalamic lesions in various institutional series is approximately 1% to 5%. A preponderance of children and adolescents has been reported by several authors, and thalamic tumors may account for up to 10% of pediatric brain tumors. Twenty-four (42%) of our patients were younger than 18 years old.

The presenting signs and symptoms in our series (Table 3) were similar to those previously reported: signs of increased intracranial pressure, focal motor and sensory findings, neuropsychological symptoms, and occasionally seizures. The reported frequencies of
these presenting symptoms have varied considerably. Finally, as reported previously,\textsuperscript{2,8,39,45,47} the "classic" thalamic syndrome of Dejerine and Roussy\textsuperscript{13} is rarely seen in patients with thalamic tumors: only two of our patients (3.5\%) had spontaneous painful sensation in the arm or leg contralateral to the lesion.

Tumor-Related Characteristics

Tumor histology was a significant prognostic factor for both tumor progression and survival in a univariate Cox proportional-hazard analysis in our study (Table 7 and Fig. 3). Older reports on thalamic tumors either do not attempt to correlate duration of survival with degree of anaplasia in gliomas\textsuperscript{2,8,47} or do not have sufficient data to do so.\textsuperscript{21,24–27,39} In some recent reports, in which surgical specimens were more often available for histopathological examination, the survival rates for patients with malignant lesions were fairly similar to ours. In one series of 60 patients with thalamic tumors, mean survival was 1.1 years in 20 patients with malignant thalamic neoplasms (13 malignant astrocytomas and five glioblastoma multiforme, but also two primitive neuroectodermal tumors; Kernohan classification\textsuperscript{33}) after either no surgery (diagnosis at autopsy), biopsy, or resection, and followed by RT in 18 of these patients (two received no further therapy after biopsy); the mean survival of 19 patients with histopathologically unverified tumors was 6.9 to 8.7 years.\textsuperscript{6} In contrast to our series, mean survival among our 16 patients with histologically unverified tumors was only 84 weeks. However, all of our patients had CT or MR imaging, which would reduce the likelihood of misdiagnosing nonneoplastic lesions as tumors.\textsuperscript{44} In a recent series of 72 patients with histologically verified thalamic tumors, mean survival times were 91, 54.4, and 21.4 weeks after stereotactic biopsy for patients with Kernohan Grade 2, 3, or 4 astrocytomas, respectively, and 62 weeks after stereotactic resection for patients with Grade 4 astrocytomas.\textsuperscript{32}

Tumor progression was local in the majority of our patients, as in other studies of malignant gliomas.\textsuperscript{9} Eight of 44 patients (18\%; excluding those with leptomeningeal–subependymal spread) had distant tumor progression documented by CT scan or MR images. This high percentage may be explained by our selected population and probably also by the use of MR images. Five patients (11\%) had stable disease at the primary site, but had distant tumor progression or leptomeningeal–subependymal dissemination. In contrast to a previous report,\textsuperscript{48} no relationship was found between leptomeningeal–subependymal dissemination and younger age at presentation or longer survival in our series.

Therapeutic Considerations

Surgery. The surgical approach to thalamic tumors has evolved from initiation of RT without prior tissue diagnosis\textsuperscript{8,30,39,47} to open biopsy or partial resection\textsuperscript{1,6} and, more recently, CT-guided stereotactic biopsy.\textsuperscript{4,19} The latest approach to the resection of thalamic tumors is based on computer-assisted stereotactic open microsurgical techniques\textsuperscript{32,38} or computer- and robot-assisted techniques.\textsuperscript{15} These techniques have been applied to both low-grade (including juvenile pilocytic and some fibrillary astrocytomas) and high-grade gliomas. They may hold promise for the former group of slow-growing, discrete tumors, but longer follow-up periods will be needed to assess the benefits of extensive resections.\textsuperscript{15,32} For patients with high-grade gliomas, however, there seems little to be gained from these techniques. Kelly\textsuperscript{32} reported on seven patients with Grade 4 astrocytomas who were deteriorating neurologically at the time of surgery; three improved postoperatively, one stabilized, and three continued to

\begin{table}
\centering
\caption{Prognostic variables for outcome in 57 patients with infiltrative thalamic astrocytomas*}
\begin{tabular}{lccccccc}
\hline
Characteristic & No. of Patients & Tumor Progression/Recurrence & & & Survival & & \\
& & HR & 95\% CI & p Value$^\dagger$ & Median Time (wks) & HR & 95\% CI & p Value & Median Time (wks) \\
\hline
age & & & & & & & & & \\
$<18$ yrs & 24 & -- & -- & -- & 60 & -- & -- & -- & 90 \\
$\geq 18$ yrs & 33 & 1.9 & (1.0, 3.4) & <0.05 & 43 & 2.3 & (1.2, 4.4) & 0.01 & 70 \\
histology$^\ddagger$ & & & & & & & & & \\
unknown & 16 & 5.6 & (2.1, 14.4) & <0.001 & 40 & 4.1 & (1.6, 10.4) & 0.003 & 73 \\
astrocytoma & 14 & -- & -- & -- & 180 & -- & -- & -- & 198 \\
AA & 22 & 3.3 & (1.5, 7.3) & 0.004 & 29 & 4.7 & (1.9, 11.5) & <0.001 & 54 \\
extent of surgery$^\S$ & & & & & & & & & \\
none & 14 & 2.5 & (1.1, 5.5) & 0.02 & 40 & 2.0 & (0.9, 4.5) & 0.08 & 67 \\
stereotactic biopsy & 20 & 1.5 & (0.7, 3.1) & 0.25 & 35 & 1.6 & (0.7, 3.3) & 0.24 & 60 \\
biopsy & 17 & -- & -- & -- & 77 & -- & -- & -- & 97 \\
adjuvant treatment & & & & & & & & & \\
RT & 19 & 1.9 & (0.9, 4.1) & 0.08 & 57 & 1.5 & (0.7, 3.1) & 0.33 & 83 \\
RT-NU & 18 & -- & -- & -- & 60 & -- & -- & -- & 73 \\
hyperfractionated RT & 16 & 1.5 & (0.7, 3.3) & 0.28 & 35 & 1.5 & (0.7, 3.4) & 0.30 & 60 \\
\hline
\end{tabular}
\footnotesize{* HR = hazard ratio; CI = confidence interval; AA = anaplastic astrocytoma; RT = radiation therapy; NU = nitrosourea-based chemotherapy.
$\dagger$ Based on univariate analysis.
$^\ddagger$ Glioblastoma multiforme not included in analysis.
$^\S$ Subtotal resection not included in analysis.
\end{table}

* HR = hazard ratio; CI = confidence interval; AA = anaplastic astrocytoma; RT = radiation therapy; NU = nitrosourea-based chemotherapy.
$\dagger$ Based on univariate analysis.
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$^\S$ Subtotal resection not included in analysis.
\| Reference category.
Infiltrative thalamic astrocytomas

deteriorate. The mean duration of survival after subsequent conventional RT for these seven patients was 62 weeks. Although this was significantly longer than for patients with Grade 4 astrocytomas undergoing stereotactic biopsy and RT (21.4 weeks), the operative morbidity was also substantially higher (43% vs. 0%). Operative morbidity in our series (7% in 43 patients who initially underwent surgery and 9% in nine patients who underwent 11 reoperations) seems acceptable. Operative mortality was also low (0% for initial operation, 9% for reoperation). Owing to the small numbers, no clear relationship between type of surgery and either morbidity or mortality can be established; however, three of 11 subtotal resections (six as initial treatment, five for recurrence) led to complications or death.

In our multivariate analysis, open biopsy was associated with a longer time to tumor progression and longer survival. However, because our study was retrospective, there may have been selection bias favoring certain types of surgery or no surgery at all. Therefore, we conclude that the most rational surgical approach to a thalamic mass lesion is a biopsy, either open or stereotactic, to obtain a tissue diagnosis and rule out a nonneoplastic lesion. More extensive and possibly radical resection using computer-assisted techniques should be considered for low-grade gliomas, but the value of this approach for anaplastic glioma awaits further evaluation in a prospective study.

Radiation Therapy. Several recent studies have addressed the possible benefits of RT in patients with thalamic lesions. Five-year survival rates of 20% to nearly 73% after RT have been reported. There is some evidence that tumors in children younger than 18 years of age respond better to RT than tumors in adults. However, the results of these studies are difficult to interpret because of insufficient histopathological data and/or clustering of tumor locations (thalamic with midbrain, third ventricular and hypothalamic tumors). Our results with conventional RT (Table 7) are generally similar to those in patients with high-grade gliomas, in which mean survival times after open or stereotactic biopsy and conventional RT were approximately 57 weeks and 55 to 62 weeks, respectively.

In our study, no clear differences in time to tumor progression or survival were found between 16 patients treated with hyperfractionated RT only, and those treated with conventional RT, with or without adjuvant chemotherapy. The late sequelae of either type of RT, which have been extensively described and were also noted in some of our patients, could not be attributed unequivocally to the treatment(s), as similar clinical symptoms and signs could well be associated with the tumor itself. Hyperfractionated RT did not appear to be more toxic than conventional RT, but because of the small sample size, we cannot determine if it was more effective.

Chemotherapy. No definitive conclusion about the usefulness of chemotherapy can be made based on the 20 patients in our study who initially received this treatment. Chemotherapy for recurrent malignant thalamic astrocytomas is feasible, but the responses are usually brief; median survival after the start of chemotherapy is only 25 weeks (range 5 to 133 weeks). The toxicity of chemotherapy in both settings seems acceptable. One previous report found no definitive benefit from various forms of chemotherapy in four patients who did not respond to RT.

Assessment of Tumor Progression

Early after RT, there is a risk of both false-positive and false-negative diagnosis of tumor progression when the imaging results do not correspond to the findings of the neurological examination. Radiation-induced changes misdiagnosed as tumor progression (false-positive diagnosis) may occur in up to 20% of cases of brainstem gliomas, especially after hyperfractionated RT. This may also have occurred in our series but cannot be confirmed because a tissue diagnosis was not obtained in these cases. The risk of a false-negative diagnosis also appears to be substantial: in five of 12 patients, changes in the results of the clinical examination or imaging studies 2 to 8 weeks after completion of RT proved to be early signs of tumor progression, rather than radiation-induced effects as first suspected. Both pitfalls may be circumvented to a great extent by the use of functional brain imaging techniques such as positron emission tomography (PET), dual-isotope, single-photon emission computerized tomography (SPECT) with 99mTc and 99mTc-HMPAO or MR spectroscopy, all of which reportedly help to differentiate between tumor progression and radiation necrosis.

Prognostic Variables

Statistical analysis to assess the importance of several prognostic variables in patients with thalamic astrocytomas has been done by one other group, although the grouping of these lesions together with brainstem tumors by these authors makes interpretation of their findings less reliable. In a univariate analysis, they found age to be prognostically significant. In a multivariate analysis of thalamic and brainstem tumor combined, the total dose of radiation, race, duration of symptoms, and subtotal resection were prognostically important, whereas the primary site (thalamus vs. brainstem) was not. There were too few patients for statistical analysis of tumor histology. In our study, these factors either could not be assessed (race, because of missing data; subtotal resection, because of too few patients; total dose of radiation, because of standardized doses) or were not significant (duration of symptoms). The median survival time in our study group (73 weeks) is similar to or somewhat better than that in patients with brainstem gliomas treated with hyperfractionated RT. Infiltrative astrocytomas of the thalamus, although supratentorial, may therefore be grouped with brainstem gliomas on the basis of biological behavior. One may perhaps conclude that the biological behavior of an infiltrative astrocytoma of the thalamus is “one grade more aggressive” than tumors of similar histology in other supratentorial sites. Whether this is mainly or exclusively the result of relative surgical inaccessibility may be demonstrated in the future when more experience with stereotactic resection has been accrued.

Conclusions and Future Directions

Our study confirms the dismal prognosis for patients with infiltrative astrocytomas of the thalamus; the median
time to tumor progression was 47 weeks in our patients and the median survival was only 73 weeks. Unknown histology or more malignant tumor type and age over 18 years were prognostically unfavorable factors in the univariate analysis, and more extensive surgery (open biopsy) was prognostically favorable in both the univariate and the multivariate analysis. However, because of the retrospective nature of our study and the small numbers of patients in some subgroups, no strong conclusions or recommendations can be based on these findings. Hyperfractionated RT was not more toxic than conventional RT, but did not appear to increase time to tumor progression or duration of survival. Adjuvant chemotherapy after conventional RT did not have any beneficial effect. Treatment at the time of tumor progression may be worthwhile, but its benefits are usually short-lived.

In future studies, stereotactic, computer-assisted resection of thalamic astrocytomas should be evaluated. Likewise, new dose fractionation schedules for conventional external RT, novel radiation techniques such as stereotactic radiosurgery with megavoltage x-radiation from a linear accelerator or with 60Co gamma radiation, and application of three-dimensional treatment planning techniques using CT and MR data merit further investigation. Hyperfractionated RT should be evaluated in a prospective, randomized study. These studies should also include radiobiological data about tumor dimensions, quantitative information about dose and fractionation schedules, and strict criteria for assessment of treatment-related complications. In this respect, functional brain imaging techniques (PET, dual-isotope SPECT, MR spectroscopy) should be included in these studies to differentiate between radiation-induced changes and tumor progression. Finally, recent experimental research, such as intrasional administration of immunotoxins and in vivo gene transfer using retroviral vector to introduce tumor cell–specific vulnerability, may hold promise for treating patients with these deep-seated lesions.

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Manuscript received July 7, 1993. Accepted in final form June 10, 1994. Address for Dr. Krouwer: University Hospital Utrecht, Utrecht, The Netherlands. Address reprint requests to: Michael D. Prados, M.D., Department of Neurological Surgery, c/o The Editorial Office, 1360 Ninth Avenue, Suite 210, San Francisco, California 94122.