Survival after stereotactic biopsy and irradiation of cerebral nonanaplastic, nonpilocytic astrocytoma

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The authors investigated the outcome of stereotactic biopsy and radiotherapy in 35 consecutive adult patients with nonanaplastic, nonpilocytic astrocytomas who were diagnosed between 1982 and 1992. The median patient age at presentation was 32 years. All received fractionated external-beam radiation therapy (median dose 56 Gy) as the initial management strategy. Additional treatment in two patients included intracavitary irradiation with colloidal phosphorus.6

Six patients (17%) had documented tumor progression during the follow-up interval and died. Three others died of causes unrelated to their tumor. Median survival after stereotactic biopsy and irradiation was 118 months (9.8 years). Median survival from the time of onset of neurological symptoms was 148 months (12.3 years). Only three patients required delayed cytoreductive surgery.

The outcome of brain astrocytomas, although improved because of earlier diagnosis and therapy, does not substantiate this tumor as having benign behavior; early recognition with neuroimaging, immediate histological diagnosis via stereotactic biopsy, and initial fractionated radiation therapy may provide the potential for longer survival for patients with low-grade astrocytomas. The majority of such surviving patients have a satisfactory quality of life, which is manifest by prolonged normal functional and employment status. The survival data reported in this prospective Phase I–II clinical trial suggest that stereotactic biopsy and radiation therapy are appropriate initial management strategies for astrocytomas.

KEY WORDS • astrocytoma • brain lesion • radiation therapy • stereotaxis

ONANAPLASTIC, nonpilocytic astrocytomas are tumors of young adults, with a peak incidence in the third decade of life.12 These lesions comprise approximately 15% of surgically diagnosed brain tumors.26 Because of their slower growth (with survival time far longer than that observed in anaplastic astrocytoma or glioblastoma multiforme) and their absence of histopathological features of malignancy, these tumors are considered benign. Because most patients with astrocytomas eventually die and only 20% to 30% of patients achieve long-term survival,21 the “benign” sobriquet is clearly erroneous. Although early diagnosis and treatment may enhance survival, with initial management options ranging from simple observation to radical surgical resection, no consensus on effectiveness of cytoreductive surgery or radiation therapy on survival has emerged.23 In 1982 the senior author (L.D.L.) initiated a prospective Phase I–II investigation to evaluate the role of adjuvant fractionated radiation after stereotactic histological diagnosis. Our study reports the long-term outcome of this treatment strategy.

Clinical Material and Methods

Patient Population

Thirty-five consecutive patients with a median age of 32 years (range 8 to 60 years) had histologically verified nonanaplastic, nonpilocytic astrocytomas. Table 1 details the clinical parameters of the study population. An onset of seizures in 22 individuals (62.8%) was the most frequent reason for presentation. Stereotactic biopsy was performed within 6 months of symptom onset in 27 patients (77.1%). Prolonged follow-up data ranging from 11 to 128 months (median 62 months) were available for all patients.

Total survival was recorded both as the interval after biopsy and the interval after onset of tumor-related neurological symptoms. Death or the latest follow-up evaluation was the end point. Survival curves were constructed using the Kaplan–Meier method.10 Although all individuals had evidence of local mass effect, none had evidence of increased intracranial pressure.
Diagnostic Technique

All patients underwent diagnostic biopsy using the Leksell stereotactic system. All stereotactic procedures were performed while the patient received local anesthesia. A dedicated intraoperative computerized tomography (CT) scanner, supplemented since 1987 by magnetic resonance (MR) imaging, was used for stereotactic target selection. Table 2 shows preoperative imaging characteristics in the series. The lesions were sampled at multiple points along a chosen trajectory. The mean tumor diameter was 3.5 cm (range 1.5 to 5.5 cm). Histological touch preparations were performed intraoperatively, after which the specimens were fixed for paraffin section analysis. An immediate postbiopsy CT scan was performed in the operating room to verify target accuracy and to assess possible complications.

A nonpilocytic astrocytoma was identified in all patients; however, no feature of anaplasia, such as marked hypercellularity, nuclear pleomorphism, mitoses, necrosis, or endothelial proliferation, was observed. The astrocytoma grading system of Burger, et al., was used for tumor classification. Lesions in this study showed mild hypercellularity with cells fairly uniform and mature in appearance, occasionally exhibiting nuclear atypism or pleomorphism.

Outpatient Radiation Therapy Treatment

After diagnosis all patients had outpatient conventional fractionated external-beam radiation therapy. The radiation volume was based on CT or MR definition of the tumor volume plus a margin of 2 to 3 cm. The median radiotherapy dose was 56 Gy (range 45 to 60 Gy) and the median dose per fraction was 1.8 Gy. The median number of fractions was 31 (range 22 to 36), delivered over a median time of 5.5 weeks.

Because of subsequent neoplastic cyst formation, two patients also underwent intracavitary irradiation with a colloidal suspension of radioactive phosphorus-32. Cyst volumes were determined by volumetric calculations using standard stereotactic CT software. Phosphorus-32 was injected to provide a dose of 200 to 250 Gy to the cyst wall over five half-lives of the isotope (approximately 71 days). Intravenous chemotherapy was later administered to four patients who had delayed malignant tumor transformation.
Results

Clinical Response

Using anticonvulsant therapy, complete control of seizure activity was obtained in 20 of 22 patients who had presented with seizures. Two individuals continued to have intermittent partial seizures; control was achieved after treatment by appropriate anticonvulsant medications and was concomitant with the reduction in local tumor mass effect noted on serial posttreatment imaging studies (Fig. 1). Before biopsy, a good or excellent clinical neurological condition (Karnofsky Performance Scale score of 90 or 100) was noted in 91% of the patients (Table 3). Immediately after biopsy the same 91% maintained this score; two patients improved from a rating of 90 to a rating of 100, perhaps related to temporary oral corticosteroid administration. At last follow-up review (mean 49 months), 60% of the surviving patients had a Karnofsky Performance Scale rating of 90 or 100; four patients had a rating of less than 70. Four patients (11.4%) with deep-seated tumors developed hydrocephalus and received ventriculoperitoneal shunts. Functional levels in surviving patients are shown in Table 4. With a median follow-up period of 57 months, almost 70% of patients maintained a full working capacity.

Tumor Response

Serial imaging studies obtained at 6-month intervals for the first 3 years and yearly thereafter were reviewed in all patients. The low-attenuation area demonstrated by CT was used to assess tumor response after irradiation, whereas T2-weighted increased signal area was used in patients having MR follow-up studies. This MR imaging provided the most graphic images in multiple planes and proved to be the superior tool for serial imaging (Fig. 2). Tumor regression was noted in 16 of 35 patients (45.7%), tumor shrinkage occurred gradually over time, often within 2 years after irradiation (Fig. 3), and initial stabilization of the tumor volume was achieved in the remaining patients. Clinical response manifested by improved seizure control, resolution of headache, and improvement in neurological signs usually accompanied the improvement noted on serial imaging studies.

Subsequent Surgical Procedures

During the follow-up interval, three patients who had delayed tumor growth and developed increased mass effect coupled with new symptoms underwent craniotomy and cytoreductive surgery. The pathology at craniotomy showed a residual astrocytoma in one patient (56 months after biopsy), an anaplastic astrocytoma in a second patient (96 months after biopsy), and glioblastoma multiforme in a third patient (14 months after biopsy). A repeat tumor staging stereotactic biopsy was performed in two patients. One patient had increasing motor deficits and...
dysphasia 51 months after initial diagnosis; the repeat biopsy showed an anaplastic astrocytoma. The second patient had a midbrain tumor that developed central tumor necrosis 11 months after radiation therapy; a repeat stereotactic biopsy at this time showed an astrocytoma. Delayed transformation to a malignant glial neoplasm was suggested or confirmed in six patients (17%). Two patients had tumor progression confirmed after craniotomy and resection, and one had a repeat stereotactic biopsy. Three individuals had imaging evidence of tumor progression manifested by new marginal contrast enhancement and central necrosis in association with a deteriorating clinical condition. Because of progressive cyst formation within the tumor, two patients also had intracavitary irradiation with colloidal phosphorus-32. One patient with a lobar tumor diagnosed and treated with fractionated radiotherapy developed a large cyst 9 years later. The second patient had a cystic astrocytoma of the midbrain. The cyst persisted despite radiation therapy, but ceased to enlarge after intracavitary irradiation.

There was no morbidity or mortality related to either the initial stereotactic biopsy or to subsequent surgical management. No patient developed clinical or imaging evidence of cerebral radiation necrosis, although one (discussed above) had evidence of extensive tumor necrosis. No patient or their family reported significant memory loss or cognitive impairment after radiation therapy, although detailed neuropsychological testing was not performed in most patients.

Survival Rates

Kaplan–Meier survival curves are provided in Fig. 4. Survival was stratified according to various clinical parameters. In this series of 35 patients, we identified no survival differences among the following stratification variables: tumor size greater than 3 cm versus less than or equal to 3 cm (p = 0.34), brainstem versus lobar tumor location (p = 0.57), fractionated radiotherapy dose less than 56 Gy or greater than 56 Gy (p = 0.99), and patient age (p = 0.84).

At the time of completion of this study, nine patients had died: six from tumor progression and three from other illnesses (diabetes mellitus, congestive heart failure, and sepsis). These three patients were excluded from survival analysis because they were in stable neurological condition. The median survival after stereotactic biopsy was 118 months (88.4% ± 6.5% at 5 years, and 47.2% ± 20.9% at 10 years). The median survival time after symptom onset was 148 months (88.4% ± 6.5% at 5 years, and 64.3% ± 16.3% at 10 years) (Table 5).

Discussion

Morbidity and Mortality After Biopsy or Craniotomy

The long-term outcome of patients with cerebral astrocytomas has improved over the past 60 years, in part related to earlier diagnosis, advances in neuroimaging, and the availability of corticosteroids. The roles of radiation therapy and surgical cytoreductive surgery remain controversial. Further improvements in surgical outcomes are still required since operative morbidity and mortality continue to be reported.

Literature Review

In 1988, Fadul, et al. described 104 patients who underwent surgery for supratentorial gliomas. They found a combined medical plus neurological morbidity after surgery of 31.7%, with significant postoperative neurological deterioration in 20%. Thirteen percent of patients who were normal preoperatively developed new postoperative neurological deficits. These authors reported that the risk for development of a significant neurological deficit after attempted total resection was approximately 20%. McCormack, et al. found that 5.6% of 53 patients who were neurologically intact before surgery developed mild postoperative deficits, two patients developed bone flap infections, and one developed cerebrospinal fluid leakage. Sixty years before McCormack, Cushing reported an
Astrocytoma results after biopsy and radiotherapy

TABLE 5
Survival statistics of 35 patients with anaplastic, nonpilocytic astrocytomas who underwent stereotactic biopsy and radiation therapy*

<table>
<thead>
<tr>
<th>Survival</th>
<th>5 Yrs (%)</th>
<th>10 Yrs (%)</th>
<th>Median (mos)</th>
</tr>
</thead>
<tbody>
<tr>
<td>from date of biopsy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>disease-specific</td>
<td>88.4 ± 6.5</td>
<td>47.2 ± 20.9</td>
<td>118</td>
</tr>
<tr>
<td>overall survival</td>
<td>81.6 ± 7.5</td>
<td>36.3 ± 17.3</td>
<td>118</td>
</tr>
<tr>
<td>from symptom onset</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>disease-specific</td>
<td>88.4 ± 6.5</td>
<td>64.3 ± 16.3</td>
<td>148</td>
</tr>
<tr>
<td>overall survival</td>
<td>81.4 ± 7.6</td>
<td>51.8 ± 15.2</td>
<td>148</td>
</tr>
</tbody>
</table>

* Values are mean ± standard error of the mean; disease-specific refers to death from brain tumor; overall survival refers to death from any cause.

operative mortality of 11% for intracranial gliomas. In 1955, MacCarty17 noted a mortality of 7.9%. Reports in 1987, 1990, and 199342–26 found a mortality rate of 3.3% to 6.5% after resection of low-grade astrocytomas.

Morbidity and Mortality Rates After Biopsy

The morbidity and mortality of biopsy procedures were high in the years before CT became widely available; however, technical advances in imaging and stereotactic surgical techniques have reduced the risks associated with biopsy of intrinsic brain tumors, regardless of their location. In our overall experience in more than 700 patients with brain tumors undergoing stereotactic biopsy, surgical morbidity remains less than 1% and no individual has died as a complication of the procedure. The typical findings of a low-density, noncontrast-enhancing tumor on CT scan or a high signal lesion on long-TR MR imaging without short-TR tumor enhancement do not always indicate the diagnosis of astrocytoma.13 We believe that stereotactic biopsy is necessary to make a specific diagnosis. Although stereotactic sampling can err (infrequently, we think) in providing a lower grade diagnosis when a tumor is really anaplastic, in this series no patient developed early tumor progression and then had histologically confirmed malignancy at craniotomy.

Fractionated Radiotherapy in Tumor Management

Some physicians withhold fractionated radiotherapy as initial management for a suspected or confirmed low-grade astrocytoma. They argue that as yet no prospective randomized series has been performed to prove a survival benefit with irradiation and that the potential delayed morbidity of brain irradiation is significant.29 In a study of patients who survived longer than 2 years after receiving 20 Gy prophylactic whole-brain irradiation for small-cell lung cancer, Lishner, et al.,16 reported that nine patients (18%) developed clinical sequelae thought to be related to radiotherapy.

We advocate fractionated radiotherapy consisting of 1.8 Gy per fraction (total tumor dose 55 to 60 Gy), targeted to the entire image-defined tumor volume plus a margin of 2 to 3 cm. If such a fractionation regimen is used, the risk for new neurological deficits is low. In this series, we did not observe cognitive impairment or brain radiation injury. We also do not support the concept of withholding radiation therapy in patients whose median survival may be as low as 5 to 7 years.14,31

Biopsy Versus Resection

Because astrocytoma infiltration is not limited to regions of contrast enhancement and can extend beyond the area of low-attenuation CT or the increased T2-weighted signal changes seen by MR imagery, the actual extent of tumor infiltration is often difficult to quantify.23 Serial stereotactic sampling in regions thought to represent only white-matter edema have confirmed that these peritumoral areas frequently contain tumor cells.23 The concept of gross total or even radical resection of astrocytomas is tenious at best; because astrocytomas often contain 3 to 6 × 106 tumor cells at presentation, a 99% surgical resection still leaves as many as 105 tumor cells remaining.40 Current radiation therapy protocols directed at astrocytomas include an area of several centimeters of brain surrounding the imaging abnormality.

The benefit of radical surgical resection on the survival of patients with astrocytomas remains controversial.7,14,20,24,26,34 Salcman28 found in his literature review that patients who had only resection (and no postoperative adjuvant therapy) survived for the longest time with extensive resection, an intermediate time with partial resection, and the shortest period with biopsy only. However, this analysis included pilocytic astrocytomas: a tumor may be more amenable to complete resection and afterward generally has a significantly improved survival.

At many centers, stereotactic surgery is reserved for patients with deep-seated lesions or those who are elderly or in poor neurological or medical condition. Such features alone may account for the poor outcomes when results after biopsies are compared in an uncontrolled fashion to results after attempted cytoreductive surgery. North, et al.,24 found that patients who underwent radical or subtotal surgery fared significantly better than those who had a biopsy alone. However, individuals selected for radical resection tended to have tumors that were easily accessible, appeared less invasive on imaging, and were smaller in size. Laws, et al.,14 also noted that resection tended to be performed for tumors that were smaller and more superficial. It is not surprising that their study found that 5-year survival depended on whether the patient underwent biopsy (32%), subtotal resection (44%), or radical removal (61%). When appropriate stratification variables such as age, tumor volume, radiation technique, and tumor location are used, the possible benefit of surgical cytoreductive surgery may be less convincing. McCormack, et al.,20 stated that it was their bias that radical surgery was indicated although data to support this philosophy were not compelling. The majority of patients in their series had subtotal (64%) or gross total (19%) resection; biopsy (17%) was reserved for patients with deep-seated tumor or tumor located in critical brain regions. Patients with deep tumors had a median survival time of less than 2 years.

Soffietti, et al.,22 reported a 5-year survival rate of 51%, 23.5%, and 0% when total, subtotal, or partial removal was used. North, et al.,24 found an overall actuarial survival at 5 and 10 years of 55% and 43%, respectively.
McCormack and colleagues noted a median survival of 7.5 years with a 5-year survival of 64%. Vertosick and associates reported their survival data for 25 patients with astrocytomas: 20 had a biopsy alone (16 stereotactic, four open), and median survival for the entire group was 8.2 years. In our experience, stereotactic biopsy followed by radiation therapy was associated with a median survival of 9.8 years. During this interval only three of 35 patients required delayed cytoreductive surgery because of increasing tumor size.

Surgical cytoreduction has also been advocated in the belief that tumor cells are at risk to dedifferentiate; a reduction in tumor cell burden may reduce the risk of subsequent malignant transformation. Because no surgical procedure can completely remove an astrocytoma, the validity of this hypothesis is difficult to test.

Role of Radiation Therapy

The role of astrocytoma radiation therapy also remains controversial, despite overwhelming evidence that radiation therapy significantly improves patient survival. Laws, et al., stated that radiation therapy was not strongly associated with survival, although patients who received doses above 40 Gy generally fared better than those who received lesser doses. A subsequent reanalysis of the Mayo Clinic experience by Shaw and colleagues showed a benefit to radiation therapy. Medbery, et al., indicated that doses above 50 Gy were associated with better outcomes than lower doses. Most radiation oncologists now administer 50 to 60 Gy at 1.8 Gy per fraction in a regimen of 5 to 7 weeks. Higher doses may exceed brain tolerance and may actually reduce both the length and quality of patient survival.

Before high-resolution neuroimaging was available, whole-brain irradiation often was advocated because of the difficulty in defining the tumor volume. Our recommendation is to provide a total radiation dose between 55 and 60 Gy to the MR image–defined tumor mass plus a 2 to 3 cm margin.

Prognostic Factors in Astrocytoma

In larger series of patients with astrocytomas, prognostic factors such as age at time of diagnosis, tumor location, and tumor volume, have been identified that affect patient survival. In the present series of 35 patients, we were not able to detect any difference in survival based on these factors. The failure to detect such a difference may be related to the small number of patients, or to the fact that all patients had uniform low-grade histology and all received fractionated radiation therapy shortly after the onset of their symptoms.

The longer survival of patients with astrocytomas reported in this series may in part be related to earlier detection. In this series median survival after the onset of symptoms was more than 12 years. The ability of CT and MR imaging to detect and define the extent of an astrocytoma facilitates both surgical and radiation therapy localization. Image-guided stereotactic surgery provided a histological diagnosis in all patients in this series without surgical morbidity.

Conclusions

We believe that every patient with a clinically suspected diagnosis of astrocytoma should be offered early diagnosis and treatment. Patients who present without significant mass effect do not require cytoreductive surgery. In the future, it is anticipated that molecular biological techniques may help define astrocytomas that are at high risk for malignant degeneration. In such patients even more aggressive therapy may be indicated.

Only three individuals in our series subsequently required surgical tumor debulking because of increased mass effect. Final resolution of the controversy on potential treatment strategies (observation, biopsy, cytoreductive surgery, and radiation) as the initial management of brain astrocytomas will require a multiinstitutional, long-term, properly stratified Phase III clinical trial.

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