Long-term outcome of 89 low-grade brain-stem gliomas after interstitial radiation therapy

Fritz Mundinger, M.D., Dieter F. Braus, M.D., Joachim K. Krauss, M.D., and Walter Birg, Ph.D.

Department of Stereotaxy and Neuronuclear Medicine, Neurosurgical Hospital, Albert-Ludwigs University, Freiburg, Germany

Between 1974 and 1985, 89 patients suffering from histologically confirmed, nonresectable low-grade astrocytomas located in the brain stem were entered into a retrospective study. Iodine-125 (125I) was implanted in 29 patients and iridium-192 (192Ir) in 26 patients. Computerized tomography revealed that 78% of the tumors in these patients were located chiefly in the mesencephalic region, 70% were circumscribed, and 78% were contrast-enhanced. Thirty-four patients underwent biopsy without prior aggressive tumor-specific therapy such as chemotherapy or external beam irradiation. Among these, 70% of the tumors were located predominantly in the pons, 74% were diffuse, and 59% were hypodense or isodense after contrast enhancement. Long-term follow-up investigations indicated that life expectancy after interstitial radiation therapy with 125I implanted directly by catheter either permanently or temporarily showed a more favorable trend than that after treatment with 192Ir.

Interstitial radiation therapy with 125I appears to be an effective treatment for slowly proliferating, differentiated, well-delineated, nonresectable brain-stem gliomas. This technique makes it possible to achieve radiosurgical tumor control and, when carefully applied, represents the least traumatic treatment. Reduction of the tumor mass brings about improvement of the clinical symptoms. Further investigations on the biological behavior of brain-stem gliomas and prospective randomized long-term follow-up studies are necessary to evaluate the different kinds of treatment available for these patients.

Key Words • brain-stem neoplasm • astrocytoma • operative technique • radiation therapy • outcome

Brain-stem gliomas are common tumors, accounting for 14% to 28% of all infratentorial neoplasms. In the past, few patients with brain-stem gliomas lived longer than 3 years after diagnosis. Treatment was prescribed without the histology of the lesion being known, as though one were dealing with a homogeneous group of tumors. Thanks to modern diagnostic methods, we now know that brain-stem gliomas constitute a rather heterogeneous group encompassing significant differences with regard to their clinical incidence, appearance on computerized tomography (CT), microscopic features, and biological behavior. However, the majority of them are ultimately lethal, regardless of their initial histological classification.

The management of low-grade brain-stem gliomas thus remains a controversial subject. Surgery may be of value in cases of cervicomedullary cystic and exophytic tumors. Conventional fractionated radiation therapy may control tumor growth in endophytic brain-stem gliomas in 75% to 90% of patients; however, 5-year survival can be expected in only 25% to 43% of cases. In addition to external beam irradiation, interstitial radiation therapy with iridium-192 (192Ir) and iodine-125 (125I) has been proposed for histologically confirmed nonresectable low-grade brain-stem gliomas.

To determine the long-term benefit of this stereotactic therapy, we analyzed the data in 89 patients who were diagnosed and treated at our institution between 1974 and 1985. We later re-examined the survivors in December, 1988, and January, 1989. The long-term results of these patients with low-grade brain-stem astrocytomas after interstitial irradiation are presented and discussed.

Clinical Material and Methods

Study Population

Of 211 patients with brain-stem lesions who had undergone stereotactic biopsy in the period between 1965 and 1985, we reviewed 89 patients with low-grade
Interstitial radiation therapy in brain-stem gliomas

astrocytomas who had been consecutively diagnosed and treated in our department between 1974 (the beginning of the CT era) and 1985. There were 49 males (55%) and 40 females (45%), whose average age at diagnosis was 22.5 years (range 2 to 62 years) with a peak in the first two decades (Fig. 1). The brain stem was defined as including the midbrain, pons, and medulla oblongata.

The tumors in this study were low-grade brain-stem astrocytomas. In 54 cases (60.7%) they corresponded to Grade I and in 35 cases (39.3%) to Grade II of the World Health Organization (WHO) tumor classification system. 40,51 This included lesions that were histologically described as "protoplasmatic," "fibrillary," or "pilocytic astrocytomas." Excluded were all tumors with evidence of anaplasia, nuclear pleomorphism, or necrosis. 41,43,50,51

Stereotactic biopsy, aided by CT scanning, was performed in all 89 cases. In addition, 26 patients were treated interstitially with \(^{192}\)Ir and (since 1979) 29 patients with \(^{125}\)I. Interstitial radiation therapy was performed in patients with well- or relatively well-circumscribed tumors with a radius not exceeding 40 mm. Thirty-four patients underwent biopsy only. These patients received no tumor-specific therapy, either because the tumor was not well-delineated or because the patients refused to undergo any aggressive form of therapy. The most common additional treatments included a cerebrospinal fluid shunt (in 65% of cases) and catheter drainage of tumor cysts (in 15%). In six cases (11%) reimplantation of the radiation source was necessary due to tumor recurrence.

All patients were examined neurologically before and 3 days and 6 months after surgery. The follow-up review through December 31, 1988, comprised examination of patient records, pathology reports, surgical records, radiation therapy reports, CT scans, and either a personal examination or contact with the patients, their families, or their physicians. The Karnofsky Performance Scale score 22 was used to measure the quality of life and the Kaplan-Meier analysis 21 was employed to determine life expectancy. Three subgroups were defined to include those receiving "biopsy only," \(^{125}\)I, or \(^{192}\)Ir. Special attention was directed to the exact location of the tumor in the brain stem, because there seems to be a difference in mean survival periods between the groups with tumors in the midbrain and those with tumors in the pons. 29,46

Stereotactic Biopsy

The Riechert/Mundinger stereotactic device originally developed in 1956 40 and modified by Mundinger and Birg 8,33 to be computer-compatible was used for the stereotactic biopsy and interstitial implantation of radioactive isotopes. Stereotactic biopsy was performed under local anesthesia, except in children younger than 15 years of age. In the same session the same 7-mm diameter burr hole, the puncture track for biopsy and radionuclide implantation was made using the transcerebral or transcerebellar approach. The localizing accuracy was better than 1 mm. 32-34

In neoplasms with a homogeneous tissue architecture, a stereotactic sample volume of 1 cm is sufficient for diagnostic evaluation. 4,23 but this requires careful targeting of the biopsy site. 4,25,33 The intraoperative rapid smear preparation makes it possible to recognize tumor borders immediately and this can be used to guide the removal of samples for paraffin embedding. This makes it mandatory for the neuropathologist to be present at the operation. 22 A diagnostic accuracy of between 91% and 95% can then be reached. 4

Radioactive Isotopes and Radiation Dose

The radioactive isotopes \(^{125}\)I and \(^{192}\)Ir are used to produce tumor radionecroses. The half-life of \(^{192}\)Ir is 74.2 days. This isotope emits gamma rays ranging in energy from 300 to 610 keV. The specific dose-rate factor used for dosimetry is 4.55 cGy/hr and mCi at 1 cm in tissue. The peripheral tumor accumulation dose (at the tumor surface) should be 120 Gy. Iodine-125 has a slightly shorter half-life of 60.2 days and a much lower photon energy spectrum, ranging between 27 and 35 keV. The specific dose-rate constant is 1.32 cGy/hr and mCi at 1 cm in tissue. 30,34 The peripheral tumor accumulation dose was 100 Gy. The dose fall-off is more rapid in \(^{125}\)I than in \(^{192}\)Ir.

Results

Life Expectancy and Tumor Grading

All patients were subjected to a statistical study to determine the relationship between life expectancy and tumor grade. The tumors comprised 54 Grade I and 35 Grade II brain-stem astrocytomas according to WHO

J. Neurosurg. / Volume 75 / November, 1991
grading. The log-rank test, which weighs the long-term course, could demonstrate no significant difference with regard to life expectancy between Grade I and Grade II brain-stem gliomas (p = 0.3, Fig. 2). Thus, in this study, as in other studies,11,13,18,19,43-46 the astrocytomas were not subclassified into Grades I and II for the evaluation of results of the therapeutic subgroups.

Clinical Symptoms and Karnofsky Scores

The three therapeutic subgroups "192Ir," "125I," and "biopsy only" were checked for comparability with respect to prognostic factors. Mean age was comparable in all groups; the age distribution shows that the vast majority of the patients in all groups were younger than 20 years at the time of diagnosis. The main clinical symptoms upon admission in all subgroups included headache and vomiting (79.5%), cranial nerve palsies (62%), ataxia (54.1%), and pyramidal tract signs (33.9%) (Table 1). The mean Karnofsky score22-47 on admission in all subgroups ranged from 67% to 69% (Table 1). The mean Karnofsky score of the survivors on admission was 71% (range 60% to 90%); on January 1, 1989, their mean Karnofsky score was 87% (range 60% to 100%).

Grading and Tumor Localization

Histomorphologically, 65.5% of the 125I subgroup and 65.4% of the 192Ir subgroup were classified as having Grade I tumors, as opposed to only 53% in the biopsy-only subgroup (Table 1). According to the CT findings, in the biopsy group 70% of the tumors were located predominantly in the pons, 74% were diffuse, and 59% were hypodense or isodense after CT contrast enhancement. In the radiation therapy groups, 78% of the tumors were located chiefly in the mesencephalic region, 70% were circumscribed, and 78% were contrast-enhanced (Table 2). The approximate mean tumor volume according to CT measurement was 9 to 11.6 cu cm. Thus, the 192Ir and 125I subgroups were approximately homogeneous with respect to mean age, clinical symptoms, appearance on CT scan, tumor volume, and histological grading, whereas the biopsy subgroup was not comparable with the other two.

Mortality and Morbidity

The mortality rate in all patients with tumors in the brain stem with and without radiation therapy was

---

**TABLE 1**

Clinical summary of 89 patients with low-grade brain-stem astrocytoma by treatment group*

<table>
<thead>
<tr>
<th>Feature</th>
<th>125I</th>
<th>192Ir</th>
<th>Biopsy Only</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of cases</td>
<td>29</td>
<td>26</td>
<td>34</td>
<td>89</td>
</tr>
<tr>
<td>age on admission</td>
<td>25.3</td>
<td>23.7</td>
<td>18.5</td>
<td>22.5</td>
</tr>
<tr>
<td>mean age (yrs)</td>
<td>2.6-8</td>
<td>3.5-9</td>
<td>3-53</td>
<td>2-62</td>
</tr>
<tr>
<td>age range (yrs)</td>
<td>22/7</td>
<td>11/15</td>
<td>16/18</td>
<td>49/40</td>
</tr>
<tr>
<td>male/female</td>
<td>6</td>
<td>4</td>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td>clinical symptoms</td>
<td>24</td>
<td>24</td>
<td>21</td>
<td>69</td>
</tr>
<tr>
<td>headache</td>
<td>20</td>
<td>17</td>
<td>18</td>
<td>55</td>
</tr>
<tr>
<td>cranial nerve palsy</td>
<td>14</td>
<td>12</td>
<td>23</td>
<td>49</td>
</tr>
<tr>
<td>ataxia</td>
<td>8</td>
<td>9</td>
<td>14</td>
<td>31</td>
</tr>
<tr>
<td>pyramidal tract signs</td>
<td>6</td>
<td>4</td>
<td>2</td>
<td>12</td>
</tr>
<tr>
<td>visual disorder</td>
<td>67</td>
<td>67</td>
<td>69</td>
<td>68</td>
</tr>
<tr>
<td>mean KPS score (%)</td>
<td>60-90</td>
<td>60-90</td>
<td>60-90</td>
<td></td>
</tr>
<tr>
<td>KPS score range (%)</td>
<td>60-90</td>
<td>60-90</td>
<td>60-90</td>
<td></td>
</tr>
<tr>
<td>Grade I tumor</td>
<td>19</td>
<td>17</td>
<td>18</td>
<td>54</td>
</tr>
<tr>
<td>Grade II tumor</td>
<td>10</td>
<td>9</td>
<td>16</td>
<td>35</td>
</tr>
</tbody>
</table>

* 125I = treatment by iodine-125 implant; 192Ir = treatment by iridium-192 implant. KPS = Karnofsky Performance Scale.22 Tumor grading according to the World Health Organization classification.30,31

**TABLE 2**

Appearance on CT and tumor location in 89 patients with low-grade brain-stem astrocytoma by treatment group*

<table>
<thead>
<tr>
<th>Feature</th>
<th>125I</th>
<th>192Ir</th>
<th>Biopsy Only</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of cases</td>
<td>29</td>
<td>26</td>
<td>34</td>
<td>89</td>
</tr>
<tr>
<td>appearance on CT</td>
<td>21</td>
<td>23</td>
<td>59</td>
<td>34</td>
</tr>
<tr>
<td>hypodense/isodense</td>
<td>79</td>
<td>77</td>
<td>41</td>
<td>66</td>
</tr>
<tr>
<td>hyperdense</td>
<td>72</td>
<td>68</td>
<td>26</td>
<td>55</td>
</tr>
<tr>
<td>circumscribed</td>
<td>28</td>
<td>32</td>
<td>74</td>
<td>45</td>
</tr>
<tr>
<td>predominant location</td>
<td>83</td>
<td>73</td>
<td>24</td>
<td>60</td>
</tr>
<tr>
<td>midbrain</td>
<td>14</td>
<td>23</td>
<td>70</td>
<td>36</td>
</tr>
<tr>
<td>pons</td>
<td>3</td>
<td>4</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>pontomedullary</td>
<td>9.0 ± 6.5</td>
<td>11.6 ± 11.9</td>
<td>11.5 ± 8.8</td>
<td>10.7</td>
</tr>
</tbody>
</table>

* CT = computerized tomography. 125I = treatment by iodine-125 implant; 192Ir = treatment by iridium-192 implant.
† Expressed ± standard deviation.
Interstitial radiation therapy in brain-stem gliomas

2.4%. Thirteen (6.2%) of the total 211 patients with brain-stem lesions suffered complications, five (2.4%) being hemorrhage with hemipareses and cranial nerve palsy.

Life Expectancy

On December 31, 1988, the average catamnestic period (± standard deviation) of all 89 patients with low-grade brain-stem astrocytomas was 40.8 ± 40.1 months (range 1 to 167 months). Seven patients (8%) had been lost to follow-up review. Thirty patients (34%) were alive: 19 (65.5%) of the 29 patients treated with 125I, six (26.1%) of the 26 patients treated with 192Ir, and five (14.7%) of the 34 patients with biopsy only. The actual survival at 5 years after diagnosis was 54.8% in the 125I group, 26.9% in the 192Ir group, and 14.7% in the biopsy group. The life expectancy curve (Kaplan-Meier method) showed a marginal level of statistically significant difference between the 125I group and the 192Ir group (log rank, p = 0.0301, Fig. 3). A comparison of life expectancy in patients with midbrain tumors (the vast majority) (Fig. 4) revealed the same trend (p = 0.09). Thus, the results are only suggestive of a difference but are not statistically significant.

Discussion

Neuroradiological Studies

Modern neuroimaging and histopathological methods have revealed that, contrary to what was once believed, low-grade brain-stem astrocytomas do not represent a homogeneous group of lesions. There are differences in the appearance of these lesions on CT scans. They can show diffuse and circumscribed spread, and in 66% of the study population they were contrast-enhanced (Table 2). The mechanism of contrast enhancement has not been clearly elucidated: it has been suggested that it may be due to vascular proliferation or angiogenic activity of gliomas. This may correspond to a disruption of the blood-brain barrier or to increased vascular permeability.

Histological Characteristics

Histopathologically, there are also considerable differences in the microscopic features of these heterogeneous tumors. Besides fibrillary, protoplasmic, gemistocytic, and pilocytic astrocytomas, there are mixed histological types which complicate the WHO classification of astrocytomas.

Stereotactic Biopsy

The advent of low-risk neuroimaging stereotactic brain biopsy has been a major advance and the procedure has become routine, even in the brain-stem region, before any invasive therapy is initiated. On the basis of biopsy, the neoplasm can be confirmed, the tumor type identified and graded, and unnecessary invasive therapy in cases of brain-stem encephalitis or demyelinating disease can be avoided.

Therapeutic Approach

Just as the CT appearance and histomorphology of deep-seated, nonresectable brain-stem gliomas vary, the therapeutic attitudes toward these lesions also differ widely. Suggested treatments include radiation therapy or chemotherapy and irradiation, hyperfractionated external beam therapy, photoradiation therapy, boron-neutron capture therapy, and interstitial radiation therapy with 192Ir and 125I.

Interstitial Radiation Therapy

The major advantage of stereotactic interstitial radiation therapy is that it can be carried out directly.
following the neuroimaging-guided stereotactic biopsy, and during the same operation. Ostertag and coworkers, on the basis of experimental data, and Mundinger, et al., on the basis of clinical data, showed that the local radionecrosis caused by these radionuclides achieves a kinetically significant reduction of the tumor cellular burden. Thus, the mass effect of the tumor can be reduced, which can be demonstrated by CT (Fig. 5) and by the improvement in clinical symptoms. In contrast to external beam irradiation, an interstitially implanted radioisotope delivers radiation continuously at very low dose rates. The therapeutic ratio is enhanced as a result of the rapid dose fall-off in tissue (within millimeters). Unwanted side effects, mainly from overdosage (vasogenic edema or radiation damage of functionally critical structures), can be avoided with careful dosimetry, cortisone protection, and temporary implantation by catheter. Nausea, vomiting, somnolence syndrome, and hair loss, commonly seen after external cranial irradiation, are not observed after interstitial radiotherapy. Furthermore, the procedure can be repeated if the tumor recurs.

No long-term results of cases of low-grade brainstem gliomas treated with $^{125}$I and $^{192}$Ir have been published. The objective of the present retrospective study was to follow the patients treated between 1974 and 1985 to see whether there were any differences in results between the two radionuclides used. A comparison was made of the prognostic factors such as mean age at diagnosis, histological grading at diagnosis (Table 1), mean tumor volume after CT measurement (Table 2), and preoperative Karnofsky score (Table 1). Because of their prognostic relevance, special attention was paid to the exact location of the tumor and CT density (Table 2).

Tumor Location and CT Density

More recent investigations have shown that tumors appearing hypodense on CT scans and tumors involving the entire brain stem correlate with a significantly decreased survival time. Tumors predominantly located in the midbrain or medulla oblongata are less malignant than those located in the pons. Among our patients, 60% of the tumors were in the midbrain region, 4% were in the pontomedullary region, and 36% were in the pons. There were no major differences with regard to location between the $^{125}$Ir and $^{192}$Ir groups. In the biopsy-only group the incidence of tumors located in the pons was markedly higher than in the other groups, which made a comparison of this group with the other two impossible.

Analysis of Results

Our results show that interstitial radiation therapy with $^{125}$I lengthens the actual survival time and improves the quality of life and life expectancy in well-delineated, nonresectable low-grade brain-stem gliomas compared with $^{192}$Ir (Figs. 3 and 4). The statistical tests indicate a difference, but not a significant one.

These results differ from those obtained after interstitial irradiation of low-grade astrocytomas in other locations. The most likely reason for this discrepancy seems to be that the high-energy gamma ray emitter $^{192}$Ir, with its less rapid dose fall-off, has a greater tendency to have side effects in the brain stem, where functionally critical structures are located just millimeters from the tumor, than the low-energy emitter.
Interstitial radiation therapy in brain-stem gliomas

This is consistent with experiments on dogs, which have demonstrated that implants produce sharply delineated necrosis with only a slight perifocal zone of demyelination, gliosis, and vasogenic edema. This zone is considerably smaller than 192 Ir-induced necrosis; however, in interpreting the results, the fact that the 192 Ir and 125 I groups were treated during different time periods might also have had an influence on survival.

Our results also show that in the long term there are no major differences with regard to life expectancy between patients with Grade I and II brain-stem gliomas (Fig. 2). This could be explained by a slow change in biological behavior of the tumor during the course of time.31,41

The poorer prognosis in the group of patients undergoing biopsy only is probably due to the fact that the most frequent tumor found in this group was a diffuse, hypodense glioma located in the pons. This seems to be a more unfavorable site in terms of prognosis than the hyperdense glioma located in the midbrain. For the diffuse hypodense tumor in the pons, neither resection11 nor interstitial implantation12 can be performed. In such cases, hyperfractionated radiotherapy with delivery of larger numbers of smaller fractions of radiation is perhaps a way to increase tumor control without increasing neurological toxicity.10,12

In view of the aforementioned aspects of heterogeneity, it is very difficult to compare our results with those of other treatments such as external beam radiation therapy. Furthermore, other reports are not restricted to well-circumscribed, low-grade gliomas predominantly located in the midbrain region. Thus, only a trend can be recognized in the long term. In our patients the 5-year survival rate after 125 I implantation was 54.8%, which is better than that after external beam irradiation (25% to 43%).26

Conclusions

Our results show that stereotactic radiation therapy with interstitial 125 I for nonresectable, circumscribed gliomas of the brain stem is an appropriate and effective treatment associated with a trend of improved life expectancy in comparison with treatment by 192 Ir implantation. The special advantages of this method are that diagnosis and treatment can be performed in one intervention, that additional therapeutic measures (external beam irradiation, hyperfractionated radiotherapy, or chemotherapy) are not influenced by local irradiation, and that the radiation therapy can be repeated. Further efforts must be made to elucidate the basic biology of low-grade astrocytomas in the brainstem region. Special attention should be paid to the exact location of the tumor and its CT density. Such knowledge may provide a more scientific rationale for the different therapeutic possibilities. Furthermore, prospective randomized long-term therapy studies are necessary to improve the prognosis of patients with these common tumors.

Acknowledgments

The authors thank Professor Dr. B. Volk and Professor Dr. K. Schwechheimer of the Neuropathological Institute, University of Freiburg, for histopathological diagnosis of the stereotactic biopsy material.

References

18. Hoshino T: A commentary on the biology and growth
41. Russell DS, Rubinstein L: Pathology of Tumours of the Nervous System, ed 5, Baltimore: Williams & Wilkins, 1989, pp 95–161