Recurrent Medulloblastoma in Children

Shunji NISHIO, Masashi FUKUI, Iwao TAKESHITA, Hiroyuki NAKAGAKI, Katsutoshi KITAMURA and Kenichi JINGU*

Department of Neurosurgery, Neurological Institute, and *Department of Radiology, Faculty of Medicine, Kyushu University, Fukuoka

Abstract

Treatment and outcome in 31 cases of recurrent medulloblastoma arising in childhood are described. As initial treatment, all patients underwent some degree of tumor resection, and 28 patients received radiation therapy postoperatively. The younger children tended to have recurrence earlier after the initial treatment and to die sooner after recurrence than the older children. Early recurrences (within the first 2 postoperative years) often took the form of spinal subarachnoid dissemination, whereas late recurrences (after more than 2 years postoperatively) most often involved intracranial regrowth. Patients who underwent extensive tumor resection and received higher doses of radiation to the entire neuraxis generally had longer remission than those who had less extensive tumor removal and lower doses of radiation. Two of four patients who received intrathecal chemotherapy with methotrexate, cytosine arabinoside, and hydrocortisone as part of the initial treatment had remission lasting more than 3 years. The usual treatment for recurrent medulloblastoma was reirradiation, which generally improved survival time. Tumor removal plus intrathecal chemotherapy in selected cases of recurrence also provided abatement of symptoms. Early recurrence was usually difficult to control, whereas treatment for late recurrence was generally palliative but not curative. Average survival was 4.3 months after early recurrence, and 21.9 months following late recurrence. Two of the nine patients subjected to autopsy had no local recurrence but had extensive spinal subarachnoid dissemination. At the time of initial extensive tumor resection, irradiation or intrathecal chemotherapy, or both, should be added to prevent regrowth of the tumor and subarachnoid dissemination.

Key words: medulloblastoma, recurrence, CSF dissemination, treatment, childhood

Introduction

The results of surgery alone for cerebellar medulloblastoma have been discouraging. The development of such therapy as whole neuraxis irradiation has significantly improved the 5-year survival to 33% to 73%, as reported in some series. However, 40% to 60% of patients have recurrence within 5 years after initial treatment. The poor results of treatment are thought to be due to the tumor's infiltrative growth into the brain stem and its great tendency to disseminate to the cerebrospinal fluid (CSF). No therapeutic regimen available at present can cure recurrent growth, and thus the management of medulloblastoma remains a perplexing problem.

In the hope of contributing to advances in the treatment of medulloblastoma in children, we studied 31 patients who had recurrence, including nine on whom autopsies were performed. Our clinical and pathological observations mainly concerned recurrence and its treatment.

Patients and Methods

From June, 1959 through December, 1984, 54 children were treated for medulloblastoma at this institution. The diagnosis of medulloblastoma was confirmed histologically in all cases. We studied the 31 evaluable children who survived for more than 3 months after initial therapy and developed recurrence. The time of recurrence was defined as the point at which regrowth or metastasis was detected.
by physical and neurological examinations in conjunction with computed tomography, vertebral angiography, myelography, CSF cytology, or biopsy. The patients were followed until death; follow-up of long-term survivors ranged from 4.2 to 7.9 years after the initial diagnosis. Autopsies were performed on nine patients who had been retreated for recurrence.

Results

The patients ranged in age from 6 months to 15 years, with an average of 7.6 years and a median of 8 years, at the time of diagnosis. Twenty-two were boys and nine were girls. The primary tumors were all located in the posterior cranial fossa. Of the 31 patients, 27 died before December, 1984.

I. Clinical features of recurrent disease

The length of remission after initial treatment (postoperative period without signs of recurrence) ranged from 1.5 to 61 months, averaging 18.8 months (median, 15 months) (Fig. 1).

Early and late recurrence: Early recurrence was defined as that which developed within 2 years following surgery, and late recurrence as that which developed more than 2 years postoperatively (Table 1). The average age was younger for early and older for late recurrences. All 19 patients with early recurrence died within 3 years after the initial diagnosis and within 13 months (average, 4.3 months) after recurrence. The 12 patients with late recurrence survived an average of 21.9 months (range, 2 to 53 months) after recurrence; 10 survived more than 3 years after the initial diagnosis.

Site of recurrence: The principal sites of the initial recurrence are shown in Fig. 2. Of the 19 children with early recurrence, seven had local intracranial regrowth, nine had spinal subarachnoid dissemination, and three had both. Late recurrence was observed in the posterior cranial fossa in nine patients, in both the posterior cranial fossa and the spinal subarachnoid space in two, and in the spinal subarachnoid space in one. Eighty percent of subarachnoid dissemination occurred within 2 years after the initial operation.

The relationship between the site of recurrence and the survival period after recurrence is shown in Fig. 3. Patients with intracranial recurrence generally lived longer after the recurrence (average survival, 17.5 months) than those with spinal metastases (average survival, 4.5 months).

II. Treatment

Initial treatment and recurrence: The extent of initial surgery was clearly related to the duration of remission; patients who underwent extensive tumor resection tended to have longer remission (Table 1). Radiation therapy, if included in the treatment plan, was given after surgery. Of the 31 patients we studied, eight were treated between 1959 and 1968 and 23 were treated after 1969. Between 1959 and 1968, only the posterior cranial fossa was irradiated. Since 1969, whole neuraxis irradiation has usually been given. Twenty patients received whole neuraxis irradiation, but three received radiation only to the whole brain and posterior cranial fossa because of their poor conditions. The radiation plan was to give 3,000 rads to the whole brain, an additional 2,000 rads to the posterior cranial fossa, and 3,000 rads to the whole spine, over 10 to 11 weeks. However, about three fourths of the patients could not tolerate the full dose of spinal irradiation because of leukopenia or thrombocytopenia.

*Of the total of 54 children treated, 23 were excluded from our consideration, 18 because of inadequate follow-up or early death (within 1 month after initial surgery) and five because they had no recurrence. These five patients have survived without recurrence for over 10 years postoperatively, and all have surpassed the risk period of Collins et al.7)
Table 1 Initial treatment

<table>
<thead>
<tr>
<th>Group</th>
<th>No. of patients</th>
<th>Age at diagnosis (years)</th>
<th>Extent of tumor removal</th>
<th>Average radiation doses (rads)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Average</td>
<td>Range</td>
<td>Partial</td>
</tr>
<tr>
<td>Early recurrence*</td>
<td>19</td>
<td>6.8</td>
<td>2-13</td>
<td>7</td>
</tr>
<tr>
<td>Late recurrence**</td>
<td>12</td>
<td>8.8</td>
<td>0-15</td>
<td>1</td>
</tr>
</tbody>
</table>

*Within 2 years postoperatively, **after more than 2 years postoperatively.

Fig. 2 Sites of recurrence. *Within 2 years postoperatively, **after more than 2 years postoperatively. I: intracranial recurrence, S: spinal subarachnoid dissemination.

Of the 20 patients who received radiation to the whole neuraxis, seven developed spinal subarachnoid dissemination, 10 had local regrowth, and three had both spinal subarachnoid dissemination and intracranial regrowth at the time that recurrence was discovered. Of the 11 patients who had no radiation to the spine, six developed spinal subarachnoid dissemination.

Of the 19 patients who had early recurrence, 16 had received radiation therapy. All the patients who had late recurrence had received radiation therapy. The average doses of radiation were smaller in the early recurrence group than in the late recurrence group, though the difference was not significant (Table 1). Intrathecal chemotherapy with methotrexate, cytosine arabinoside, and hydrocortisone was administered in four recent cases. The total doses varied among the patients, but a usual dosage was 60 mg/m² of methotrexate, 120 mg/m² of cytosine arabinoside, and 80 mg/m² of hydrocortisone, given in four lumbar punctures within 2 weeks following surgery. Three of the four patients who received intrathecal chemotherapy and whole spine irradiation did not develop spinal subarachnoid dissemination, whereas nine of the 16 who received irradiation to the spine without intrathecal chemotherapy developed spinal subarachnoid dissemination as the initial recurrence.

Retreatment: Twenty of the 31 children were retreated for recurrence by irradiation and/or intrathecal and systemic chemotherapy, and some of them were also reoperated (Table 2). Eleven received no retreatment. Patients who were retreated lived for an average of 15.1 months thereafter, and five survived longer than 2 years after the retreatment. Patients who were not retreated lived for an average of 4.2 months and all died within 9 months after recurrence. Among the patients with early recurrence, retreatment did not affect the length of survival (Fig. 3). Eleven patients with late recurrence were

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retreated and survived for an average of 23.4 months. One patient who was not retreated died 6 months after late recurrence.

Patients with intracranial local recurrence who were retreated survived for an average of 22.5 months after recurrence; in the non-retreated group, the average survival period was 5.0 months. Retreated patients with spinal subarachnoid dissemination survived for an average of 4.8 months after recurrence, and non-retreated patients for 4.1 months.

The tumor was re-excised in four patients with intracranial local regrowth. The second operation benefited all four, and three survived for an average of 14.7 months after surgery.

A second course of radiation therapy was administered to 14 patients who had recurrence. For intracranial regrowths, 1,800 to 5,900 rads were administered to the whole brain or to the posterior cranial fossa. Spinal metastases were irradiated with 1,000 to 3,000 rads. The average post-recurrence survival of the 14 reirradiated patients was 17 months (median, 10 months), whereas that of the non-reirradiated patients was 6.3 months (median, 3 months). Reirradiation was generally beneficial, and radiological evidence of two patients' metastatic tumor disappeared. One patient was irradiated for metastasis in the right humerus.

Intrahecal chemotherapy was administered to five patients with recurrence, three of whom also received additional irradiation. The chemotherapy was effective in two cases but was ineffective in three cases of advanced subarachnoid dissemination. The post-recurrence survival of these patients ranged from 3 to 52 months, averaging 17.5 months (median, 11 months).

III. Autopsy findings

The locations of the tumors, as determined by autopsy, were in the primary site, the subarachnoid space, and/or the ventricular wall.

In the nine autopsied cases, seven had macroscopic regrowth of the tumor at the primary site. Two had no tumor regrowth at the primary site, but showed extensive spinal subarachnoid dissemination.

Intracranial subarachnoid dissemination was discovered in eight cases and was most extensive at the base of the brain. Supratentorial subarachnoid dissemination was also found in five cases. Six had slight to moderate lateral ventricular seeding.

Spinal subarachnoid seeding was found in eight cases. The subarachnoid growth was characteristically thicker on the dorsal aspect of the cord, but otherwise did not predominate at any particular site. The extent of seeding varied at each level of the cord. Secondary changes, such as myelomalacia, secondary syringomyelia,21) and deformity due to tumor compression, were found within the spinal cord. Tumor cells had infiltrated into the cord in some cases. Necrosis of the cauda equina, conceivably related to intrathecal chemotherapy, was noted in a patient with extensive subarachnoid dissemination. In one case, extracranial metastases were detected in the lymph nodes and bones.

Discussion

In comparing children who had early recurrence of medulloblastoma (within 2 years of initial surgery) with those who had late recurrence (more than 2 years postoperatively), we found differences in the age at initial diagnosis, the site of recurrence, the initial operative procedure, the radiation dose and the length of survival after recurrence.

Silverman and Simpson29) concluded that there is no correlation between survival and age. Many authors,2,12,24,25) however, have reported lower survival rates in younger than in older individuals. In our series, the younger children had recurrences sooner after initial treatment than did the older
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Since 1969, the initial treatment in our institution has been gross total removal of the tumor followed by whole neuraxis irradiation. Some authors have been unable to demonstrate any significant correlation between the extent of surgical resection and outcome. However, others have noted a better outcome following subtotal or total gross removal than following less extensive surgical procedures. Although the patients whose tumors were only partially removed might have had very extensive tumors, our data showed a clear relationship between the extent of tumor resection and the length of initial remission. Only two of our patients who underwent partial excision as the initial treatment survived significantly beyond the risk period of Collins. The extent of surgical excision may not be the only factor in determining the length of remission. Nonetheless, at present it appears advantageous to strive for maximum tumor removal. Although several authors have cast doubt upon the effectiveness of reoperation for late intracranial recurrence, selected patients in our series benefited from surgical reexcision.

Since the introduction of improved whole neuraxis radiation therapy, increased survival rates have been reported. Recurrence of medulloblastoma is considered by some to be related most closely to the postoperative radiation dose. In our series, children with late recurrence received, as initial treatment, a larger dose to the central nervous system than those with early recurrence. Recommended doses of irradiation are 5,000 to 5,500 rads to the posterior fossa, 3,000 to 3,500 rads to the whole brain, and 3,000 to 4,000 rads to the spinal cord.

The usual treatment for local intracranial regrowth or spinal subarachnoid dissemination was, in our series, reirradiation. This approach to recurrence generally gives good symptomatic palliation. Although patient selection should be taken into account in the evaluation of results, the average survival of reirradiated patients was longer than that of non-reirradiated patients. Some patients have survived for more than 5 years after reirradiation.

Intrathecal chemotherapy has been reported to be effective against subarachnoid spread of leukemia, lymphoma, and carcinoma. Its use for prophylaxis and treatment of CSF dissemination of medulloblastoma is currently under investigation. In our series, two of the four patients who received intrathecal methotrexate, cytosine arabinoside, and hydrocortisone as part of the initial treatment had good health for more than 3 years after the initial treatment. Furthermore, the initial recurrences of these patients were intracranial local regrowth. Intrathecal chemotherapy, though not always effective, may be useful in suppressing the residual tumor and preventing CSF dissemination of medulloblastoma. Although intrathecal chemotherapy did not eradicate the tumors in our series, it appeared beneficial in terms of preventing CSF dissemination.

For treatment of recurrence, polychemotherapy with intravenous CCNU, vincristine, procarbazine, and dexamethasone, as well as intrathecal or intraventricular methotrexate, have been recommended. Although we have only limited experience with intrathecal chemotherapy for recurrent lesions, this approach was apparently effective in two of five patients. It should be kept in mind, however, that intrathecal and intraventricular administration of methotrexate can be seriously neurotoxic, particularly when CSF stasis is present. Such other untoward effects as meningeal irritation, paraplegia, necrotizing leukoencephalopathy, and seizures have also been reported.

Although the number of patients in our series was too small for statistical significance, our limited experience suggests that the initial treatment for medulloblastoma is most crucial to the outcome. Treatment for recurrence is not curative at present, but is sometimes rewarding. Although a high percentage of deaths is due to local recurrence, patients with intracranial local recurrence often respond to retreatment and some have a second remission. On the other hand, once the patient develops spinal subarachnoid dissemination, the prognosis is decidedly poor. In our series, no patients with spinal subarachnoid dissemination survived for more than 1 year after recurrence. Two of the nine
autopsied cases in our series had extensive spinal subarachnoid dissemination without gross intracranial local recurrence. At the time of initial treatment, whole neuraxis irradiation in sufficient doses and intrathecal chemotherapy should be added to prevent regrowth of the tumor and spinal subarachnoid dissemination.

References

14) King GA, Sagerman RH: Late recurrence in medulloblastoma. Amer J Roentgen 123: 7-12, 1975
30) Smith B: Brain damage after intrathecal methotrexate. J Neurol Neurosurg Psychiatry 38: 810-815, 1975

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Address reprint requests to: M. Fukui, M.D., Department of Neurosurgery, Neurological Institute, Faculty of Medicine, Kyushu University, 3-1-1 Maidashi, Higashi-ku, Fukuoka 812, Japan.