Medulloblastoma in childhood: results of radical resection and low-dose neuraxis radiation therapy

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This review concerns 22 children who were treated from 1980 through 1983 for medulloblastoma in the posterior fossa. Treatment included attempts at radical resection of the tumor and postoperative craniospinal radiation therapy, with 5000 to 5500 rads directed to the posterior fossa and 2500 rads to the remaining craniospinal axis. This lower radiation dose to the neuraxis was used to avoid late adverse effects upon the growing central nervous system of the children. Gross confirmation of total resection was obtained in 13 patients (the "total resection group"); however, nine patients had a subtotal resection leaving a small portion of the tumor extending into the cerebellar peduncles or the cerebellopontine angle, or else encasing the posterior inferior cerebellar artery (the "subtotal resection group"). Six patients in the total resection group demonstrated tumor extension into the cerebellar peduncles, which was removed by means of a surgical carbon dioxide laser without neurological sequelae. Biopsy of the arachnoid membrane from the cisterna magna and cytological examination of the cerebrospinal fluid (CSF) prior to manipulation of the tumor were carried out in 12 patients. All but one showed dissemination of medulloblastoma cells. Myelography and CSF cytological study were undertaken 2 months after radiation therapy in 12 patients and were positive in two. There were no case mortalities in the total resection group during the 24- to 67-month follow-up period, whereas the 1-year survival rate in the "subtotal resection group" was only 44.4%. This study suggests that medulloblastoma can be controlled with a low radiation dose to the neuraxis, should a grossly confirmed total resection be achieved at craniotomy.

KEY WORDS □9 medulloblastoma □9 radiation therapy □9 radical resection □9 cerebellar extension □9 laser surgery □9 children

Because of the high incidence of local recurrence and the propensity for dissemination through the cerebrospinal fluid (CSF) pathways, patients with medulloblastoma require postoperative radiation therapy (RT). Our most recent data indicate that there is a high tendency for spontaneous seeding of medulloblastoma cells in the subarachnoid spaces. Dissemination of neoplastic cells is likely to be facilitated by surgical manipulation; thus, craniospinal RT is mandated to achieve a cure in patients with a medulloblastoma. However, recent literature has stressed the potential hazards of irradiation upon the growing central nervous system (CNS). Of particular concern are the radiation effects upon the intellectual and physical development of younger children. A previous study from our institution demonstrated that the great majority of children who received a high dose of RT (more than 4000 rads to the whole brain) had low intelligence quotients. Similar observations were reported by others. Intellectual impairment is more common in children treated at a younger age. Growth retardation due to irradiation to the growing spine and/or hypopituitarism secondary to irradiation to the hypothalamus-pituitary axis is another common consequence of craniospinal RT. These observations have prompted us for the past 5 years to lower the dosage of craniospinal RT to the current dose of 2500 rads to the entire neuraxis while delivering a higher dose (5000 to 5500 rads) to the posterior fossa.

This paper contains the results of this treatment protocol — radical resection of the tumor and postoperative low-dose craniospinal RT — for patients with medulloblastoma.

Clinical Material and Methods

Twenty-four children with cerebellar medulloblastomas were diagnosed and treated at the Children's Memorial Hospital from 1980 through 1983. Two patients were lost to follow-up review and the remaining 22 patients entered this study. There were 11 boys and 11

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girls, whose age at diagnosis ranged from 4 months to 14 years. The diagnosis of a cerebellar tumor was made by computerized tomography (CT) in all cases. Hydrocephaalus was present in 19 children, 16 of whom received a precraniotomy CSF shunt without complications. In these cases, the CSF from the lateral ventricle was sent for cytological study at the time of the shunt procedure. The remaining three were begun on dexamethasone therapy without shunt placement prior to posterior fossa craniotomy. Computerized tomography demonstrated a midline posterior fossa tumor in 18 patients and a laterally located tumor in four. No patient showed evidence of subarachnoid dissemination on CT scans with contrast enhancement before craniotomy.

A posterior fossa craniotomy was performed in all cases. Eleven patients underwent both arachnoid membrane biopsy from the cisterna magna and CSF aspiration for cytological study prior to the manipulation of the tumor. One patient had only arachnoid biopsy. Total resection of the medulloblastoma was attempted in all cases; however, in nine cases a small portion of the tumor extending into the cerebellar peduncles or into the cerebellopontine angle through the lateral recess, or encasing the posterior inferior cerebellar artery, was not removed ("subtotal resection group"). Gross confirmation of total resection was obtained in 13 cases ("total resection group"). In the total resection group, six patients had tumor involvement of the cerebellar peduncles, which was removed with the carbon dioxide laser. There was no surgical morbidity or mortality in either group.

All patients received craniospinal RT. The total dose of irradiation was 5000 to 5560 rads to the posterior fossa, 2406 to 2570 rads to the whole brain, and 2300 to 2570 rads to the spine. Two patients who had late recurrences (20 to 30 months) received repeat irradiation to the craniospinal axis (2000 rads to the whole brain and 3000 rads to the spine in one; 3050 rads to the brain and 2450 rads to the spine in the other). Chemotherapy was not used primarily, but four patients received chemotherapy for recurrent tumors.

All patients were closely followed in our Tumor Clinic. Computerized tomography scans of the head with and without administration of contrast material were obtained before RT, at the completion of RT, and subsequently every 3 months during the 1st year. After that, scans were obtained at 6-month intervals. The last 12 patients underwent metrizamide myelography along with CSF cytological study 2 months after completion of RT. In another four patients, myelography and/or CSF cytological examination were undertaken during various periods thereafter.

Results

Table 1 shows the results and outcome of the 22 patients with medulloblastoma. Thirteen underwent total resection and nine had subtotal resection. Analysis of tumor staging according to the system of Chang, et al.,4 on the basis of CT findings and surgical observations, indicated that 19 tumors were T2 or T3a. However, in three cases the system was not applicable because the tumor extended from the cerebellar hemisphere into the cerebellopontine angle (Cases 5 and 14) and to the middle cranial fossa through the tentorium cerebri (Case 17).

Of 12 arachnoid biopsies from the cisterna magna, eight (66.7%) showed islands of medulloblastoma cells. Cytological studies of the CSF for neoplastic cells in the cisterna magna were conducted in 11 cases, and were positive in eight and questionably positive in one. Only one patient (8.3%) had negative results for both arachnoid biopsy and CSF cytology of the cisterna magna. All ventricular fluid obtained at the shunt insertion was negative on cytological study. One patient (Case 10) underwent ventricular cannulation without a preoperative shunt during a posterior fossa craniotomy in the prone position. The ventricular fluid prior to tumor resection was cytologically negative, whereas fluid obtained at the end of craniotomy contained tumor cells.

Myelography and CSF cytological studies were performed 2 months after RT in 12 patients, and showed that only one patient (Case 22) had positive results for both. Another patient (Case 8) had positive CSF cytology, with negative myelographic findings. A CT scan in Case 22 also showed diffuse enhancement of cranial subarachnoid spaces after contrast administration. In Cases 16 and 20, diffuse enhancement of the cranial subarachnoid space was noted on CT scanning 10 and 8 months after craniotomy, respectively, when a lumbar puncture produced CSF that tested positive for medulloblastoma cells. In Case 15, a local recurrence was noted 30 months after surgery, and myelography and CSF cytological results were positive. This patient was also found to have metastatic lesions in the liver and bone at that time. In Case 19, recurrence in the posterior fossa and basal cistern was found 20 months after craniotomy, when myelography and CSF cytology were both positive. In Case 7, long-bone metastatic lesions developed 15 months postoperatively, but there was no evidence of CNS recurrence on CT, myelography, or CSF cytology. Case 8 received a chemotherapy regimen of intrathecal methotrexate and intravenous vincristine and BCNU (1,3-bis(2-chloroethyl)-1-nitrosourea) after a positive CSF cytological finding 2 months post-RT. Serial myelography and CSF cytology have been negative for the subsequent 12 months. One patient (Case 21) underwent myelography twice, 1 and 2 months after RT. Both were negative, but CSF cytological studies for medulloblastoma cells were positive at the first study and negative at the second study.

During the follow-up period, ranging from 24 months to 67 months, six patients died and 16 were alive. All 13 patients who underwent total resection were alive without CNS recurrence. One patient (Case 7) showed
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* M = midline; L = lateral; P.F. = posterior fossa; CSF = cerebrospinal fluid; IQ = intelligence quotient; NA = not applicable; + = positive findings; - = negative findings.

† Tumor staging according to the system of Chang, et al. 4

‡ Myelography was performed 2 months after radiation therapy.

§ + = alive; NED = no evidence of disease; mets = metastases; local = local recurrence; cord = spinal cord metastases; diffuse = diffuse subarachnoid dissemination; CSF = positive CSF cytology.

Discussion

All patients in this series received a relatively uniform treatment protocol, including a posterior fossa craniotomy with maximum tumor resection and postoperative craniospinal RT with low-dose radiation to the spine and brain. The total resection and subtotal resection groups showed no difference in incidence of spontaneous seeding in the cisterna magna or in tumor staging scores. However, a follow-up study demonstrated a marked contrast in the incidence of CNS recurrence and survival between these two groups. No CNS recurrences developed in the total resection group, but seven of nine patients in the subtotal resection group had recurrences (p = 0.0003). There was no case mortality in the total resection group, while the 1-year survival rate was 44.4% in the subtotal resection group. As the age and sex distribution of the patients and the incidence of hydrocephalus showed no difference between these two groups, the extent of radical resection of medulloblastoma appears to be the sole clinical factor contributing to the patients' outcome. Further long-term follow-up review is necessary to identify late-onset recurrences after use of the present protocol.
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A surgical laser enabled us to resect the portion of the tumor extending into the cerebellar peduncles. The six patients who underwent that procedure did not show any postoperative neurological sequelae, and a visibly apparent total resection of the medulloblastoma was possible. Retrospectively, it might have been possible to totally resect the tumor in the majority of cases in the subtotal resection group if a surgical laser had been used. The literature concurs that the extent of surgical resection does influence the patients’ outcome. Those who underwent radical (total) resection of the medulloblastoma enjoyed a longer survival than their counterparts with partial (subtotal) resection. Total resection of a medulloblastoma enhances efficacy of RT.

Our preliminary data and the present study indicate that, even after complete resection is achieved, in a great majority of cases medulloblastoma cells seed spontaneously and microscopically in the subarachnoid space, although they rarely cause symptoms before detection of primary intracranial tumors. This justifies treating the entire neuraxis postoperatively in patients with medulloblastoma. Various authors have reported the influence of radiation dosage on survival of medulloblastoma patients and the importance of delivering at least 5000 or 5200 rads to the posterior fossa. Jereb, et al., reported that none of their patients who received less than 3400 rads to the entire neuraxis survived, nor did any of those who received less than 5000 rads to the posterior fossa. In his recent remarks on medulloblastomas in children, Bloom recommended postoperative megavoltage RT with a minimum dose of 3500 to 4000 rads to the brain, 3000 to 3500 rads to the spinal cord, and 5000 to 5500 rads to the posterior fossa.

Safe effective radiation doses to the brain and spinal cord, however, are not yet known. More attention is being paid to the adverse effects on the development of intelligence and the performance of children after cranial irradiation. Soni, et al., reported that prophylactic cranial or craniospinal RT with 2400 rads in leukemic children caused no noteworthy neurological or psychological differences between subjects and controls. Based on our present data, low-dose (2500 rads) irradiation to the neuraxis can prevent recurrence or at least prolong remission without intellectual impairment should the tumor be removed totally. Development of a CNS recurrence remote from the primary site in the subtotal resection group of this series occasionally occurred and could be detected as early as a few months after completion of RT, or 2 years later. Bloom stated that “providing the entire cerebro-spinal axis is included in the irradiated volume, any recurrence in the supra-tentorial region or along the spinal cord is likely to have arisen from persistent disease at the original primary site.”

The presence of spontaneous seeding prior to the tumor resection is not a factor that affects patient outcome. Subclinical cerebral and spinal tumor at the time of presentation appears to be potentially curable by irradiation, and the microscopic volume of tumor cells is probably eradicated by RT at doses as low as 2500 rads. In three of our patients, however, diffuse dissemination of tumor cells in the subarachnoid space (giving the spinal cord a “bamboo stick” appearance) was found at autopsy performed 6 to 10 months after surgery. It is important to evaluate the entire neuraxis with high-resolution CT scanning, myelography, and CSF cytology to detect evidence of CNS recurrence in the early stages.

The prognostic value of a tumor staging system for medulloblastoma patients has been verified by some authors but not by others. In this series all tumors were more than 3 cm in size. None directly invaded the floor of the fourth ventricle or the spinal cord, but 11 showed tumor extension to the cerebellar peduncles. Moreover, we conducted prospective cisterna magna examinations in 12 patients and found that 91.7% had metastases from the primary tumor. Consequently, we submit that a tumor staging system is of no value in predicting the patients’ outcome; surgical resectability and the extent of surgical resection of the medulloblastoma may be the major factors influencing the prognosis.

Postoperative myelography has been recommended by several authors. A 36% to 43% incidence of positive findings on myelography has been reported before initiation of RT. This contrasts with our results, in which only 8.3% of patients showed positive myelographic results after RT. This discrepancy may be the result of response to the irradiation, but it may also be due to the postsurgical changes (presence of subarachnoid blood or segmental arachnoiditis) demonstrated on myelography in the early postoperative period.

Conclusions

Medulloblastomas in childhood should be resected totally whenever possible. If the amount of irradiation to the developing CNS can be reduced to the doses used in the present protocol, long-term adverse effects of craniospinal irradiation may be avoided. Patients in whom total resection of the medulloblastoma is not achieved should be considered a high-risk group and should be treated with higher doses of radiation and adjuvant chemotherapy.

References


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