Adult cerebellar medulloblastomas: the pathological, radiographic, and clinical disease spectrum

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The records of 34 patients over 16 years of age with cerebellar medulloblastoma were retrospectively reviewed. All patients were treated by surgery, and all surviving patients were given radiation therapy. The imaging characteristics of this rare entity were evaluated with regard to the tumor location in the cerebellum, and the prognostic effects of histological characteristics such as neuronal or glial differentiation and the presence of desmoplasia were investigated. Neither histological parameters nor tumor location (median, paramedian, or lateral cerebellar) affected patient survival. The desmoplastic variant was encountered in 38% of these adult medulloblastomas and occurred in all three cerebellar locations. The degree of surgical resection did not have a major effect on long-term survival; long-term survival was possible even in patients who had received only a biopsy. The extent of initial radiation therapy was positively correlated with recurrence-free survival; full neuraxis irradiation was associated with a 13% incidence of delayed spinal metastases, whereas 75% of patients treated with irradiation of only the posterior fossa and/or the whole brain developed spinal deposits. A similar local recurrence rate (12.5%) was noted in both irradiation groups. Chemotherapy resulted in palliation in some patients with metastatic disease.

KEY WORDS □9 brain neoplasm □9 medulloblastoma □9 primitive neuroectodermal tumor □9 radiation therapy □9 chemotherapy □9 posterior fossa tumor □9 immunocytoLOGY

MEDULLOBLASTOMAS represent 15% to 25% of primary central nervous system (CNS) tumors in children but only 1% or less of those in adults. The literature is replete with information on the disease spectrum in children, but few investigators have examined medulloblastomas specifically in adults. Most authors have considered patients of all ages together, and efforts to examine subpopulations by age are often inconclusive because of insufficient numbers.

Medulloblastomas in adults may present with a striking histological pattern of stromal reaction, the so-called “desmoplastic variant.” This histological feature was initially thought to carry a more favorable prognosis than the “classical” pattern, but this belief has subsequently been refuted. It has been shown that medulloblastomas have the potential in vitro and in vivo to differentiate along several cell lines, an observation consistent with the theory that the tumor arises from primitive or pluripotential cells. Rorke has stated that the medulloblastoma is simply one form of differentiation into one or more cell lines. She and her colleagues recently found that lack of such differentiation is associated with a more favorable prognosis in children with medulloblastoma. The clinicopathological features of 34 adult patients with medulloblastomas were reviewed to determine whether similar conclusions may be drawn regarding tumors in this age group.

Clinical Material and Methods

The case histories and pathological materials of 34 adult patients with medulloblastoma, all evaluated and treated at the Mayo Clinic between 1954 and 1984, were reviewed. Each tumor was examined for the presence or absence of light microscopically apparent cellular differentiation. The basic modalities consisted of routine histochemical stains including hematoxylin and eosin (H & E) and Gomori's reticulin method. The latter was used to evaluate the presence and extent of desmoplasia. Special attention was given to assessing the degree of mitotic activity, based upon the examination of 20 high-power fields; the results were ex-
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pressed on a three-point scale (1+ to 3+). When specimens from initial surgery and surgery for recurrence were available for the same patient, classification was performed on the initial specimen.

Immunostains for glial fibrillary acidic protein (GFAP)* at a 1:50 dilution and for the 48-, 150-, and 200-kD subunits of neurofilament protein (NF)† at a 1:80 dilution were also applied. In each instance, the technique was performed utilizing the avidin-biotin complex (ABC) method. A special effort was made to avoid considering as evidence of differentiation NF-reactive normal axons traversing the tumor and the GFAP-positive reactive astrocytes commonly observed either around the vessels or individually within the tumor or infiltrated parenchyma. In order to be considered neoplastic, isolated and clustered astrocytes were required to show nuclear features similar to or in transition from obvious tumor cells.

The tumors were classified histologically into two groups. Group I patients were those whose tumors, on H & E-stained sections, demonstrated either neuroblastic or glial differentiation. In each case special techniques were utilized to identify the presence of differentiation; these included 1) routine histochemical studies by the application of the Bodian method for axons and the phosphotungstic acid hematoxylin stain for glial fibrils, and 2) immunostains for NF and GFAP, respectively. These special techniques were not, however, used as sole diagnostic criteria in the absence of differentiation at the H & E level. Group II patients comprised those whose tumors exhibited no histological evidence of differentiation on H & E staining.

The patients ranged in age from 17 to 58 years, and included 19 women and 15 men. Based on surgical reports and radiographic data, the tumors were classified as median or vermian, paramedian (eccentric vermian extending into the hemisphere), or lateral (hemispheric) cerebellar tumors. The extent of surgical intervention was described as a biopsy, subtotal removal, or gross total removal. Radiographic data were available for 13 patients and were assessed in terms of tumor location as well as by computerized tomography (CT) and angiographic features. Postoperative radiation therapy was given to all survivors; treatment dosages were available on all but one patient. The majority (79%) of patients received their treatment at the Mayo Clinic. Many of the earlier patients in the series were median (vermian), 10 paramedian, and 11 lateral medulloblastomas. Table 1 indicates the tumor location relative to the histopathological classification. There was no significant difference in the distribution of medulloblastomas demonstrating cellular differentiation when compared to those without differentiation. Desmoplasia was found in all three cerebellar sites, but more frequently in the paramedian and lateral cerebellar locations. Patients with laterally placed hemispheric tumors did not show better survival periods than those with vermian lesions in this series of patients (Fig. 1), although death tended to occur earlier in patients with vermian tumors.

Pathological Findings

Desmoplasia. The tumors of 13 patients demonstrated a desmoplastic pattern of reticulin staining; the locations of these tumors within the cerebellum were median in two, paramedian in five, and lateral in six. There was no difference in survival times between desmoplastic and nondesmoplastic tumors, but the higher incidence of desmoplasia in lateral tumors with more favorable short-term survival should be noted. Simi-

* Glial fibrillary acidic protein supplied by DAKO, Santa Barbara, California.
† Neurofilament protein supplied by Behringer-Mannheim, Indianapolis, Indiana.

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**TABLE 1**

Clinical data correlated with histopathological classification*

<table>
<thead>
<tr>
<th>Factor</th>
<th>Group I</th>
<th>Group II</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of cases</td>
<td>16</td>
<td>18</td>
</tr>
<tr>
<td>% males</td>
<td>50</td>
<td>39</td>
</tr>
<tr>
<td>postoperative death</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>average survival time (yrs)†</td>
<td>4.6</td>
<td>4.8</td>
</tr>
<tr>
<td>no. alive</td>
<td>7</td>
<td>10</td>
</tr>
<tr>
<td>no. with recurrence/metastases</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>% receiving initial spinal axis</td>
<td>62.5</td>
<td>76.5</td>
</tr>
<tr>
<td>radiation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>tumor location</td>
<td></td>
<td></td>
</tr>
<tr>
<td>median (vermian)</td>
<td>7</td>
<td>6</td>
</tr>
<tr>
<td>paramedian</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>lateral</td>
<td>4</td>
<td>7</td>
</tr>
</tbody>
</table>

* Group I were patients with differentiated tumors and Group II had undifferentiated tumors; see text.
† Time from diagnosis, excluding postoperative deaths.

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Results

In the decade 1955 through 1964, four adults with medulloblastomas were diagnosed and treated; one died postoperatively and three eventually succumbed to their disease. Eleven patients were managed between 1965 and 1974; one died following the initial operation, one died after surgery for recurrent tumor, seven died of their disease, and two remain alive without apparent disease. Between 1975 and 1984, 19 patients were treated; four patients died of their disease and 15 remain alive without disease.

The most frequent symptoms on presentation included headache, nausea, vomiting, diplopia, and gait disturbance. Papilledema, nystagmus, and ataxia were usually noted on examination.

Tumor Location

The cerebellar tumors were distributed as follows: 13 were median (vermian), 10 paramedian, and 11 lateral medulloblastomas. Table 1 indicates the tumor location relative to the histopathological classification. There was no significant difference in the distribution of medulloblastomas demonstrating cellular differentiation when compared to those without differentiation. Desmoplasia was found in all three cerebellar sites, but more frequently in the paramedian and lateral cerebellar locations. Patients with laterally placed hemispheric tumors did not show better survival periods than those with vermian lesions in this series of patients (Fig. 1), although death tended to occur earlier in patients with vermian tumors.

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larly, the degree of mitotic activity had no effect on outcome.

**Significance of Differentiation.** There were 16 patients in Group I (those whose tumors showed differentiation on H & E staining). The tumors of 11 patients demonstrated neuroblastic differentiation, whereas only one showed neuronal and three showed glial differentiation. Only one example disclosed the presence of maturation along both cell lines. Correlation with immunocytological methods in 12 tumors showed NF immunoreactivity in only eight with H & E evidence of neuroblastic or neuronal differentiation; GFAP reactivity was noted in two of three tumors showing light microscopic evidence of glial differentiation.

There were 18 Group II patients (those who had tumors without apparent H & E evidence of differentiation). This group included three cases in which some NF immunoreactivity was seen and one with GFAP immunoreactivity; however, none of these four showed light microscopic evidence of differentiation. The survival curves for Group I and II patients were similar (Fig. 2).

**Morphology Correlated with Subsequent Therapy and Dissemination.** Tumor samples obtained before and after radiation therapy were available in seven patients: five at repeat operation and two at postmortem examination. The tumors of four patients initially de-

monstrated either neuroblastic differentiation in the form of Homer Wright rosettes or an astrocytic component. On repeat examination, no differentiation was noted except in the tumor of one patient who survived 11.5 years, of whom autopsy tissues showed evidence of some astrocytic differentiation. In the remaining cases, the recurrent tumors consisted entirely of undifferentiated cells. These changes may result from the effects of therapy, the effects of the milieu of a disseminated tumor sample, or simply the passage of time.

**Radiographic Imaging**

Fourteen preoperative CT scans were available on 13 patients. Nine were obtained with and without administration of contrast material and five were with contrast enhancement only. The CT characteristics are shown in Table 2.

The midline vermis tumors averaged 2.75 cm in diameter, the paramedian tumors averaged 3.1 cm, and the diffuse cerebellar hemispheric tumors averaged 4.5 cm. The CT appearance of the vermis tumors in adults closely resembled that of medulloblastomas in childhood. These tumors were usually round with fairly clear margination. They were isodense or hyperdense on precontrast scans with generally homogeneous postcontrast enhancement; ring-like enhancement was not seen. Angiographically, these tumors were hypovascular. The fourth ventricle was compressed, displaced, or obliterated, with associated obstructive hydrocephalus in all four vermis tumors. Paramedian medulloblastomas, extending from the vermis into one cerebellar hemisphere, resembled the midline vermis tumors in density and contrast enhancement pattern, but were less likely to obstruct the ventricular system despite their larger size.

Tumors located in the lateral cerebellar hemispheres had a different, yet distinctive appearance. Two were faintly hyperdense on noncontrast CT scans and all five
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demonstrated slight contrast enhancement (Fig. 3). The increased density of the tumor seemed to blend in with the hyperdense tentorium making it difficult to determine whether the tumor was intra- or extra-axial in origin. An infratentorial meningioma was suggested in the differential diagnosis of three of the five cerebellar tumors. These lesions, however, were uniformly hypovascular on angiography. Coronal CT scans and magnetic resonance images were more helpful in defining the intra-axial location of the cerebellar medulloblastoma than were axial CT slices.

Magnetic resonance imaging was performed on two patients. The location of the tumor within the vermis or cerebellar hemisphere was well demonstrated on the sagittal and coronal images (Fig. 4). Both tumors exhibited prolonged $T_1$ and $T_2$ relaxation times, characteristic of most glial neoplasms.

**Surgical Treatment**

"Total" extirpation of the tumor was achieved in seven of 34 patients. Biopsy only was performed in five patients, three of whom also required cerebrospinal fluid (CSF) shunt placement. In the remainder, subtotal removal was accomplished, usually described as leaving a "capsule" behind. The influence of the degree of surgical removal on survival time is shown in Fig. 5. In seven of the medially located tumors, extension into the fourth ventricle was noted, but this had no adverse effect on patient survival.

**Radiation Therapy**

All surviving patients received postoperative radiation therapy. Prior to 1970, most were given treatment to the posterior fossa with or without whole-brain irradiation. After 1970, the majority of patients were treated with 50 to 55 Gy to the posterior fossa, 35 to 55 Gy to the whole brain, and 25 to 45 Gy to the spinal cord. There were no complications from this treatment except for one case in which radiation-induced myelopathy was clinically suspected. The likelihood of disease-free survival was improved with full neuraxis radiation therapy (Fig. 6). Six of eight patients who received only posterior fossa/whole-brain radiation developed metastatic deposits in the spinal cord, compared to three of 23 who received full neuraxis radiation.

**Recurrence/Metastatic Disease**

Local recurrences developed in 12.5% of patients in

![Fig. 4. Midline medulloblastoma: computerized tomography scan with contrast enhancement (left), and magnetic resonance images in the axial (center) and sagittal (right) projections.](image)

![Fig. 5. Survival data related to extent of tumor removal in 34 patients.](image)

<table>
<thead>
<tr>
<th>TABLE 2</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Radiographic findings in 13 adult medulloblastomas</strong></td>
</tr>
<tr>
<td><strong>Factor</strong></td>
</tr>
<tr>
<td>no. of cases</td>
</tr>
<tr>
<td>diameter (cm)</td>
</tr>
<tr>
<td>average</td>
</tr>
<tr>
<td>range</td>
</tr>
<tr>
<td>computerized tomographic density</td>
</tr>
<tr>
<td>without contrast</td>
</tr>
<tr>
<td>without contrast</td>
</tr>
<tr>
<td>angiographic vascularity</td>
</tr>
<tr>
<td>calcification</td>
</tr>
<tr>
<td>obstructive hydrocephalus</td>
</tr>
<tr>
<td>rim of edema</td>
</tr>
</tbody>
</table>

* Hyper = hyperdense; iso = isodense; hypo = hypovascular.
each of the two irradiation groups. Metastases to the
brain or spinal cord occurred in 10 (29%) of the 34
patients. The mean time from diagnosis to local recur-
rence presentation was 4.4 years (range 2.5 to 6.5 years),
and the median time from diagnosis to development of
metastasis was 2.5 years (range 1.3 to 10.5 years). One
patient developed extraneural metastases to her femur,
and another developed a retro-orbital metastasis after
gross total removal of a midline undifferentiated me-
dulloblastoma followed by complete neuraxis irradia-
tion. A majority of the neural metastases were intra-
medullary, often with diffuse subarachnoid seeding.

Adjunctive chemotherapy with DAG (dianhydroga-
lactitol), TZT (triazothrotinate), and VP-16 (epipodo-
phyllotoxin) was used in three patients with metastatic
disease and produced some palliative benefit. One pa-
tient in particular had nearly total resolution of a
medulloblastoma as a distinct histological entity in 1925, experience

Discussion

Since Bailey and Cushing3 established medulloblas-
toma as a distinct histological entity in 1925, experience
with this tumor has been widely reported.11,20,27,43,44 Because 75% to 80% of medulloblastomas occur in child-
hood (age ≤ 16 years), most reviews have emphasized
the pediatric experience.1,8 Whereas 80% of adult cases
occur between the ages of 21 and 40 years, by 1983
only 13 cases had been reported presenting after 50
years of age.23 In adult cases, men usually outnumber
women in a ratio of 2:1.1,1,2,3,11,26,29

In our series, the male:female ratio was almost 1:1,
with 70% presenting between 20 and 40 years of age.
Nearly equal incidences of median, paramedian, and
lateral tumor locations were found as well as an equal
distribution by sex, in agreement with others.40 This
contrasts with several reports in adults which showed a
higher incidence of lateral hemisphere tumors,8,11,12,27,29
especially among males.2,26,34 In addition, tumor loca-
tion and presence or absence of desmoplasia had no
influence on long-term survival. These findings are in
agreement with those of Müller, et al.,29 Miles and
Bhandari,27 Cushing,11 Ingraham, et al.,40 Spitz, et al.,44
and Rubinstein and Northfield.41 The effect of tumor
location and desmoplasia is not addressed in the large
series of 79 adults reported by Arseni and Ciurea.2 The
majority of other studies either are too small or do not
give sufficient information from which to draw conclu-
sions about the adult population.1,5,8,12,19,23,34

Significance of Location and Desmoplasia

Correlations between survival and such factors as
tumor location and histological appearance have been
made. Marty-Double and Barneon8 found prolonged
survival in patients with laterally placed cerebellar me-
dulloblastomas as compared to those with midline tu-
mors. Chatty and Earle,7 in their retrospective review
of 201 cases of medulloblastoma (of which 105 were
evaluable), found improved survival in patients of any
age whose tumors showed the presence of desmoplasia.
Müller, et al.,29 on the other hand, found no difference
in survival times between classical and desmoplasic
tumors in adults. Finally, in their large literature review,
Choux, et al.,9 concluded that histological variations
had no major impact on the survival time in any age
group.

Significance of Differentiation

Medulloblastoma, the principal member of the em-
bryonal group of CNS neoplasms, has long been con-
sidered to be bipotential (that is, capable of both glial
and neuronal differentiation). Evidence of the latter has
been sought by routine light microscopy, immunohis-
tochemical methods, and electron microscopy — ap-
proaches that vary markedly in their sensitivities. Un-
derstandably, authors applying such diverse methods
and studying differing patient subgroups have reported
conflicting conclusions regarding tumor morphology,
the frequency of cellular differentiation, and the clinical
implications of such differentiation (Tables 3, 4, and 5).
At the routine histochemical level, the most obvious
manifestation of neuroblastic differentiation is the for-
mation of Homer Wright rosettes; unassociated with
rosette formation, neuroblasts are usually recognized
only on silver stains, preferably applied to frozen sec-
tions. Recognition of neuronal maturation, a rare event,
usually poses no diagnostic problem. The identifi-
cation of glial differentiation is significantly hampered
by the inability even of experienced observers to distin-
guish neoplastic from reactive astrocytes (Table 3).

The introduction of immunohistochemistry has con-
tributed greatly to our understanding of the histo-
genesis of poorly differentiated neoplasms of the CNS
but, as can be seen in Table 4, there is considerable
subjectivity regarding the interpretation of these stains.
There are also differing specificities of the varied anti-
sera utilized. Electron microscopic studies generally suf-

Fig. 6. Recurrence-free survival curves related to radiation
therapy for patients surviving to complete their initial courses of
irradiation.
TABLE 3

Differentiation in medulloblastoma detected by routine light microscopic studies*

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>No. of Cases</th>
<th>Age Group</th>
<th>Desmoplastic</th>
<th>No. of Cases with Differentiation</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chatty &amp; Earle, 1971</td>
<td>201</td>
<td>all ages</td>
<td>42</td>
<td>None 150 Neuroblastic 38 Neuronal 2 Glial 11 Both 0</td>
<td>improved survival in desmoplastic variant; no prognostic effect of differentiation</td>
</tr>
<tr>
<td>Marty-Double &amp; Barneon, 1974</td>
<td>17</td>
<td>adults</td>
<td>6</td>
<td>None 12 Neuroblastic 1 Neuronal 0 Glial 2 Both 2</td>
<td></td>
</tr>
<tr>
<td>Müller, et al., 1982</td>
<td>303</td>
<td>all ages</td>
<td>46</td>
<td>NS NS NS NS NS NS</td>
<td></td>
</tr>
<tr>
<td>Packer, et al., 1984</td>
<td>38</td>
<td>children</td>
<td>NS</td>
<td>None 20 Neuroblastic 0 Neuronal 18 Glial 1 Both 0</td>
<td>poorer survival with differentiation</td>
</tr>
<tr>
<td>Hubbard, et al., 1989</td>
<td>34</td>
<td>adults</td>
<td>13</td>
<td>None 18 Neuroblastic 11 Neuronal 1 Glial 3 Both 1</td>
<td>survival unaffected by differentiation</td>
</tr>
</tbody>
</table>

*NS = not stated.

TABLE 4

Differentiation in medulloblastomas detected by immunocytological studies*

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>No. of Cases</th>
<th>Age Group</th>
<th>Desmoplastic</th>
<th>Immunostaining Results</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Palmer et al., 1981</td>
<td>13</td>
<td>all ages</td>
<td>NS</td>
<td>GFAP 11 immunoreactive</td>
<td>medulloblastomas: multipotential stem-cell tumors</td>
</tr>
<tr>
<td>Mannoji, et al., 1981</td>
<td>25</td>
<td>all ages</td>
<td>1</td>
<td>NF 18 immunoreactive (3 definite tumoral)</td>
<td>majority of GFAP-positive cells non-neoplastic</td>
</tr>
<tr>
<td>Roessman, et al., 1983</td>
<td>47</td>
<td>NS</td>
<td>NS</td>
<td>NSE 24 (6 positive for both GFAP &amp; NF) 12</td>
<td>majority of GFAP-positive cells non-neoplastic</td>
</tr>
<tr>
<td>Schindler &amp; Gollotta, 1983</td>
<td>50</td>
<td>all ages</td>
<td>40%</td>
<td>GFAP 33 immunoreactive (5 definite tumoral, 28 reactive astrocytes)</td>
<td>majority of GFAP-positive cells non-neoplastic</td>
</tr>
<tr>
<td>Pasquier, et al., 1983</td>
<td>17</td>
<td>NS</td>
<td>?</td>
<td>GFAP 15 immunoreactive (1 definite tumoral, 10 intermediate cells, 4 reactive astrocytes)</td>
<td>—</td>
</tr>
<tr>
<td>Coffin, et al., 1983</td>
<td>20</td>
<td>all ages</td>
<td>3</td>
<td>GFAP 5 immunoreactive (1 definite tumoral, 4 reactive astrocytes)</td>
<td>no reactivity in seven recurrent or metastatic tumors; glial differentiation rare; GFAP reactivity often nontumoral high frequency of glial differentiation in desmoplastic variant high frequency of neuroblastic differentiation histology &amp; immunoreactivity may not correlate</td>
</tr>
<tr>
<td>Herpers &amp; Budka, 1985</td>
<td>17</td>
<td>all ages</td>
<td>17</td>
<td>GFAP 8 immunoreactive (all tumoral astrocytes)</td>
<td></td>
</tr>
<tr>
<td>Velasco, et al., 1985</td>
<td>27</td>
<td>NS</td>
<td>NS</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Hubbard, et al., 1989</td>
<td>34</td>
<td>adults</td>
<td>13</td>
<td>GFAP 3 (1 undiff on H &amp; E) 10 (3 undiff on H &amp; E)</td>
<td></td>
</tr>
</tbody>
</table>

*NS = not stated; GFAP = glial fibrillary acidic protein; NF = neurofilament; NSE = neuron-specific enolase; undiff = undifferentiated; H & E = hematoxylin and eosin staining.

TABLE 5

Differentiation in medulloblastomas detected by electron microscopic studies

<table>
<thead>
<tr>
<th>Authors &amp; Year</th>
<th>No. of Cases</th>
<th>Age Group</th>
<th>Desmoplastic</th>
<th>Ultrastructural Differentiation</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Camins, et al., 1980</td>
<td>20</td>
<td>all ages</td>
<td>4</td>
<td>Neuroblastic/Neuronal 7 2 10 1</td>
<td>astrocytic differentiation somewhat improves survival</td>
</tr>
<tr>
<td>Moss, 1983</td>
<td>5</td>
<td>children</td>
<td>0</td>
<td>Neuroblastic 7 2 10 1</td>
<td>medulloblastomas have bipotential differentiating capacity</td>
</tr>
</tbody>
</table>

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fer from the small number of patients involved, from the limited scope of the examination (often based on the study of only several hundred cells), and from the difficulties inherent in differentiating between neoplastic and reactive cells at the ultrastructural level. Despite some lack of agreement, the consensus is that medulloblastomas are bipotential tumors which far more frequently demonstrate neuroblastic than glial differentiation (Table 5).

The question of prognosis and its relationship to differentiation is unsettled. No consensus has been reached regarding the method by which the latter should be assessed. Clearly, to be applicable, the methods should be simple and standardized. At present, given the disparate conclusions reached by the application of sophisticated techniques, it would appear that routine light microscopy and histochemistry might serve as sufficient indices. Indeed, Packer, et al., reported significant differences in survival times based solely upon these simple methods. They applied the system of classifying primitive neuroectodermal tumors described by Rorke to lesions in 38 children and found markedly improved survival times in patients with undifferentiated medulloblastomas.

Neuroblastic differentiation in the form of Homer Wright rosettes has also been described in the majority of cases. As a correlate, neuron-specific enolase staining has been said to be present in 100% of cases. On the other hand, NF has been reported in only 25% to 33% of medulloblastomas. In our series, such immunoreactivity was noted in 10 patients (30%), seven of whom showed convincing neuroblastic or neuronal differentiation on H & E staining.

Astroglial differentiation, evidenced by GFAP immunoreactivity, has been reported to occur in 10% to 60% or more of medulloblastomas. Some investigators, including ourselves, believe that GFAP positivity in the majority of medulloblastomas is related to staining of invaded normal and reactive brain parenchyma rather than being an expression of tumoral differentiation. In our study, tumoral GFAP positivity was observed in three patients (9%), only two of whom had light microscopic evidence of glial differentiation on H & E staining. Staining of incorporated normal and reactive parenchyma was far more often encountered than was definitive staining within the tumor. In contrast to the study of Herpers and Budka, no relationship was noted between the occurrence of GFAP positivity and the presence or absence of desmplasia.

Specifically addressing the issue of differentiation in adult medulloblastomas, it is of note that Marty-Double and Barneon reported glial or neuronal differentiation in 29% of 17 adult patients, whereas Camins, et al., reported a 50% incidence in six adult subjects. The overall 47% frequency noted in our 34 patients is therefore similar. Although most investigators of immunocytochemical markers in medulloblastomas have primarily studied tissues from a pediatric population, our findings suggest that a similar incidence of tumor differentiation occurs in adults. One cannot, therefore, consider the incidence of tumor differentiation to be the basis for the more favorable survival times observed in adults. Statistically, in our study only the extent of initial radiation therapy influenced long-term survival in adults, and histological features were not of prognostic significance. In any event, it appears that the biological aggressiveness of medulloblastomas decreased somewhat with increasing patient age.

The importance of radiation therapy is well supported in the literature both for adults and for children with medulloblastomas. Dhellemmes, et al., found a higher incidence of spinal metastases in their patients who received only posterior fossa radiation compared to those who received full neuraxis treatment. This is confirmed in the extensive review by Choux, et al., who concluded that “irradiation of the spine must be systematic and total.” Since maturation of neural tissue is complete in adults, a higher radiation dosage may be delivered without the adverse sequelae noted in children. The optimal dosage recommended is 52 to 55 Gy to the posterior fossa and 25 to 35 Gy to the rest of the neuraxis. Some investigators believe that no further benefit is gained by exceeding a dose of 25 Gy to the rest of the neuraxis. Others have found a linear correlation between improved survival times and increasing radiation dosage to the posterior fossa. One of our patients suffered a retro-orbital metastasis after whole-brain and spinal radiation. This has been reported by others, and likely represents a “geographic miss” of the radiation due to measures taken to protect the eye.

Opinions regarding the influence of the extent of surgical removal on survival times are divided. The extent of surgical resection had no major bearing on long-term survival in our series, although the majority of patients were treated with subtotal resections. Some of the laterally placed tumors were so infiltrative that complete removal would have required cerebellar hemispherectomy with damage to the cerebellar nuclei. We continue to recommend a complete removal if it is possible to accomplish it without jeopardizing the integrity of the brain stem. Limited resection is nevertheless compatible with long survival.

The success rate of treatment for recurrent disease is usually dismal; methods are generally limited to chemotherapy and occasionally to reoperation for localized posterior fossa tumor. Surgery for metastatic disease to the spine is usually futile because of leptomeningeal seeding and nodular infiltration of the spinal cord and nerve roots. Chemotherapy as a primary adjunctive modality in children has not been shown to improve survival times; however, stabilization and improvement in neurological function have been reported with a number of chemotherapeutic agents in children and adults, offering reasonable palliation. This study demonstrates that metastases may occur up to 10 years after treatment in an apparently stable patient.

Extraneural metastases occur with medulloblastomas
Adult cerebellar medulloblastomas

perhaps more frequently than with any other primary CNS tumor. The common secondary sites (in approximately decreasing frequency) include bone, lymph nodes, lung, pleura, liver, and breast. Most metastases occur within 2 years of tumor diagnosis; Hoffman and Duffner believed that the presence of a CSF shunt increased this risk even with a millipore filter in line. Extraneural metastases occurred in just one of our patients, who did not have a shunt in place.

Common and uncommon imaging features of medulloblastomas have been reviewed previously. Other investigators have not stressed the unique features of the laterally placed cerebellar tumors, which may mimic meningiomas on CT scans but have a lower incidence of associated obstructive hydrocephalus. These tumors, however, are avascular on angiography. Magnetic resonance imaging has proved helpful in distinguishing a vermian medulloblastoma from an intrinsic brain-stem glioma, and should be even more useful in distinguishing intrinsic cerebellar hemisphere tumors from extraxial meningiomas, both by the lack of cerebellar compression and by the longer T2 signal as compared to meningiomas. The combination of an unenhanced CT scan and a magnetic resonance image may prove diagnostic for medulloblastomas in adults.

Based on this review, it would appear that future advances in the treatment of medulloblastomas in adults must lie with chemotherapy and immunotherapy, especially for those patients presenting with disseminated disease. This combined with early detection, tumor identification and surgical removal, and aggressive neuraxis radiation offers the hope of long-term and good-quality survival. It is fascinating that a tumor which may be of embryonic origin can remain latent and become manifest many years later, suggesting differences in biology involving the tumor itself or the host.

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