Surgical management of brain-stem tumors in children: results and statistical analysis of 75 cases

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A study was made of 75 children treated between 1970 and 1990, with partial, subtotal, or total removal of three intrinsic and 72 exophytic or surface brain-stem tumors. In all cases, the goal of surgery was to remove as much tumor as possible. Extent of removal was defined according to data obtained from postoperative computerized tomography or magnetic resonance imaging, and was considered partial when only a small amount of tumor was removed, subtotal when a few cubic millimeters of tumor was left, and total when no residual tumor was seen on postoperative radiological investigations. An ultrasonic aspirator was used for the 43 most recent operations. Among tumor removals without the aspirator, 24 (75%) were partial, eight (25%) subtotal, and none total; with the use of the aspirator, the number of partial removals decreased to 44.5% while that of subtotal and total removals increased to 32% and 23.5%, respectively. There were 69 gliomas (92%) and 47 benign tumors (62.6%). Forty-nine patients were irradiated postoperatively, and 14 of the 23 patients whose benign tumors were removed totally or subtotally did not undergo irradiation.

This study showed that: 1) the overall prognosis of patients with malignant tumors was poor and was not improved by surgery; 2) the survival rate of those with benign tumors was significantly (p < 0.01) lower after partial removal than after total or subtotal removal (52% and 94%, respectively, at 5 years); 3) comparison of means and proportions (Student's and chi-squared tests) between benign and malignant tumors showed a significant difference relating to patient age (p < 0.03), peritumoral hypodensity (p < 0.001), and preoperative duration of symptoms (p < 0.001); 4) stepwise logistic regression analysis confirmed that two of these three variables were related to malignancy: namely, patient age at surgery (p < 0.03) and presence of peritumoral hypodensity (p < 0.001); and 5) routine postoperative irradiation was contraindicated after total or subtotal removal of benign tumors.

KEY WORDS • brain-stem tumor • tumor removal • prognosis • children

Clinical Material and Methods

Case Material

From 1970 to June, 1990, 81 patients with brain-stem lesions were operated on at Hôpital Necker-Enfants Malades in Paris. Six vascular lesions were excluded from this study, leaving 75 tumors that constitute this series. The patients included 44 boys and 31 girls. At surgery, patient age ranged from 3 months to 19 years (median age 6.2 years, mean age 6.7 years). Eleven children (14.7%) were under 2 years of age.

The tumors originated in the mesencephalon, pons, or medulla. Some were contained within the limits of the brain stem; others extended to the cervical spinal cord or the cerebellar peduncles. Tumors that only
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FIG. 1. Computerized tomography scans without (left pair) and with (right pair) contrast enhancement showing a cystic, apparently well circumscribed, enhancing brain-stem tumor in the pons and the right cerebral peduncle.

FIG. 2. Sagittal T1-weighted magnetic resonance image showing heterogeneous contrast enhancement of a tumor arising from the pons and medulla. The lesion is exophytic, fills the cisterna magna and part of the fourth ventricle, and extends downward to the C-2 vertebral level. Note enhancement of the subarachnoid spaces anterior to the medulla and pons.

inserted on the floor of the fourth ventricle, such as the majority of ependymomas and many medulloblastomas, were not considered brain-stem tumors and therefore were excluded from this study.

Exophytic and surface tumors were distinguished in the analyses from intrinsic tumors. "Exophytic tumors" were defined as lesions bulging into the fourth ventricle or the subarachnoid spaces surrounding the brain stem, "surface tumors" were lesions reaching the pial or ependymal boundaries of the brain stem, and "intrinsic tumors" were lesions separated from the surface of the brain stem by a layer of apparently normal nervous tissue. In this series, 72 tumors (96%) were exophytic or surface, and three (4%) were intrinsic. This ratio reflects an early decision to operate on only exophytic and surface tumors.

Surgical Indications

Five tumors were operated on before 1975, prior to the availability of the computerized tomography (CT) scanner. In these cases surgery was performed because pneumoencephalography or ventriculography showed that, although the lesions arose from the brain stem, they bulged into the fourth ventricle or the cisterna magna.

The remaining 70 cases were operated on using data obtained by CT or magnetic resonance (MR) imaging. Surgery was indicated if two criteria were fulfilled (Figs. 1 and 2). First, the tumor had to reach the surface of the brain stem at some point, allowing the surgeon to enter the lesion without injuring overlying functional brain-stem tissue. Early in the study, three patients with tumors that did not reach the surface underwent surgery. The patients did badly and would not now be considered for surgery. Second, tumors had to be focal on radiological investigation. A focal tumor was defined as one that was circumscribed, with a sharp margin, and apparently compressing rather than invading the remaining normal brain stem at the level involved. However, tumor size, location, and behavior following injection of contrast material did not contraindicate surgery. Similarly, the presence of peritumoral hypodensity on CT (Fig. 3) or hypointensity on MR imaging was not considered an a priori contraindication to surgery. Diffuse tumors as shown in Fig. 4 were not operated on and therefore were excluded from this series.

In 63 (84%) of the 75 patients, surgery was the primary treatment. In nine (12%), it was decided to operate after previous therapy had failed. In the three remaining patients (4%), surgery was performed during the course of radiotherapy. In these three cases, surgery was indicated because the tumors, which were apparently intrinsic and/or diffuse before radiotherapy, looked exophytic and circumscribed after irradiation with 20 to 25 Gy (Fig. 5). These three lesions were malignant.

Surgical Procedure

The choice of surgical route was based on tumor localization: a midline vermian incision in 70 cases (93.3%) for tumors bulging posteriorly into the fourth ventricle, a retromastoid approach in three cases in which the tumor filled the cerebellopontine angle, a
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FIG. 4. Magnetic resonance images, sagittal (left) and axial (right) slices, demonstrating the presence of a large, diffuse, and slightly enhancing pontine lesion that is typically non-operable.

FIG. 3. Computerized tomography scan after administration of contrast material showing an apparently well-circumscribed tumor in the pons on the left side. The lesion is heterogeneous and grossly hypodense with a peripheral ring enhancement. The whole pons around the lesion is itself hypodense.

FIG. 5. Sagittal T1-weighted magnetic resonance images after contrast enhancement showing that the pontine tumor, intrinsic before irradiation (left), is extrinsic after being irradiated at a dose of 20 Gy (right).

FIG. 6. Computerized tomography scans with contrast enhancement. Left: Before surgery. Right: After subtotal removal with only a few cubic millimeters of tumor (arrow) left in contact with the remaining healthy brain stem.

combined supra- and infratentorial approach to one of the lesions that involved the three levels of the brain stem, and a subtemporal approach for one case in which the neoplasm involved only the cerebral peduncle. This last case was operated on with the patient in the lateral decubitus position, whereas all the others were in the sitting position. The Cavitron ultrasonic aspirator (CUSA)* was introduced to our institution in January, 1985, and was used for the 43 operations (57.3%) performed since that date.

The exophytic or surface lesions were incised at the point where they were immediately apparent and were generally debulked and removed until, in some cases, normal parenchyma was encountered. The goal of surgery was radical excision of the tumor, but this was frequently not possible. When there were cardiovascular reactions, surgery was interrupted at least in the area that had induced the response. Surgery was also interrupted in the following situations: 1) when the narrowness of the operative field limited visibility; 2) when introduction of the CUSA handpiece was impossible; and 3) when cranial nerves known to be functional preoperatively were seen emerging from the tumor (mainly observed in pontine lesions protruding into the cerebellopontine angle).

Extent of removal was defined as partial, subtotal, or total according to intraoperative observations and data obtained from postoperative CT scans or MR images. Partial removal was defined as removal of only a small amount of tumor. Removal was termed subtotal when only a few cubic millimeters of tumor was left (Fig. 6) and total when no residual tumor was visible on postoperative radiological investigations (Figs. 7 and 8).

Pathology records and tissue blocks were reviewed for this study. Glial tumors were classified according to Kernohan's four grades.13 Grade I and II tumors were considered benign and included pilocytic astrocytomas. Complementary radiotherapy (45 to 50 Gy to the tumor bed) was delivered to all patients whose tumors were

* Cavitron ultrasonic aspirator manufactured by Cavitron (Valleylab, Inc.), Boulder, Colorado.
either malignant or benign but were partially removed. Fourteen (61%) of 23 patients whose tumors were both benign and totally or subtotally removed did not undergo irradiation. The mean follow-up period for the series was 2.6 years (range 1 month to 19.5 years).

Statistical Methods

Comparison of means and proportions was made using Student's and chi-squared tests, respectively. The level of significance was p less than 0.05. Survival function was estimated by the Kaplan-Meier method and survival curves were compared using the generalized Wilcoxon test (Breslow). Seven parameters were entered into a stepwise logistic regression to identify factors that could predict the benign or malignant grade of the tumors: 1) patient age at operation; 2) symptomatology; 3) duration of symptoms prior to diagnosis; 4) topography of the tumors; 5) presence of peri- or intratumoral cyst; 6) presence of peritumoral hypodensity; and 7) presence of a tumor ring enhancement. The last three criteria were determined from the data obtained by CT. All analyses were made using BMDP statistical software.†

Results

Symptoms

Following the study of Epstein and McCleary, we separated the patients into two subgroups: Group 1 included those in whom symptomatology was typical of a brain-stem tumor (multiple and bilateral cranial nerve palsies, spasticity, and ataxia, but showing no sign of hydrocephalus), and Group 2 included those in whom symptomatology was atypical (increased intracranial pressure, but minimal spasticity or ataxia, and no more than one cranial nerve palsy). Twenty-eight patients (37.3%) had typical and 47 (62.7%) atypical symptomatology. The mean interval (± standard deviation) between the first symptom and treatment was 21 ± 36 months for the whole series (median 5.9 months, range 1 day to 14 years).

As shown in Table 1, 34 tumors (45.3%) originated in one of the three levels of the brain stem, most often from the medulla (19 cases, 25.4%). Of these, 25 cases (33.3%) originated from two levels, and 16 (21.3%) from all three levels.

Therapy and Surgery

The number of patients operated on in a 5-year period increased after 1975 when CT became available.

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† BMDP statistical software supplied by the University of California, Berkeley, California.

<table>
<thead>
<tr>
<th>Location of Tumor</th>
<th>No. of Cases</th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>medulla</td>
<td>19</td>
<td>25.4</td>
</tr>
<tr>
<td>pons/medulla</td>
<td>18</td>
<td>24</td>
</tr>
<tr>
<td>pons</td>
<td>10</td>
<td>13.4</td>
</tr>
<tr>
<td>pons/peduncle</td>
<td>7</td>
<td>9.3</td>
</tr>
<tr>
<td>peduncle</td>
<td>5</td>
<td>6.6</td>
</tr>
<tr>
<td>medulla/pons/peduncle</td>
<td>16</td>
<td>21.3</td>
</tr>
</tbody>
</table>

Table 1
Tumor location in 75 patients

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in our hospital, and even more underwent surgery after 1985 following the acquisition of a CUSA: five patients (6.6%) were operated on before 1975, 13 (17.3%) between 1975 and 1980, 14 (18.7%) between 1980 and 1985, and 43 (57.3%) after 1985. Before 1985 and the availability of the CUSA, 24 removals (75%) were partial, eight (25%) subtotal, and none total. Since 1985, with the CUSA, the number of partial removals decreased to 19 cases (44.5%), while that of subtotal removals increased to 14 (32%) and total removals increased to 10 (23.5%). For the whole series, 43 tumors (57.3%), were partially removed, 22 (29.3%) subtotally, and 10 (13.3%) totally.

Pathology
Of the 75 tumors, 69 (92%) were glial: 58 astrocytomas and 11 oligodendrogliomas. The other six tumors included one ganglioglioma, two ependymomas, two primitive neuroectodermal tumors, and one of an undetermined type. The tumors were benign in 47 patients (63%) and malignant in 22 (29%). The histological grade was uncertain in the remaining six patients (8%).

Operative Mortality
Twelve (16%) of the 75 patients died; these included eight (25%) of the 32 operated on without the CUSA and four of the 43 (9.3%) with the CUSA. It is noteworthy that these last four patients died after several days of normal consciousness, breathing without assistance, and oral feeding. On the theory that these deaths might be due to anoxia or increased intracranial pressure, the next 29 patients were maintained under assisted ventilation and external cerebrospinal fluid (CSF) drainage for 1 week after surgery. All 29 patients survived surgery. This protocol is now routine for all brain-stem surgery.

Survival Time
The survival rates for the 63 patients who survived surgery were 55% at 3 and 5 years and 49% at 10 years (Fig. 9). Figure 10 shows that these rates were significantly higher (p < 0.0001) in benign tumors (74% at 3 years) than in malignant tumors (22% at 3 years). Among patients with malignant tumors, three were alive more than 2 years postoperatively, at 25, 26, and 43 months, respectively: two had a medulloblastoma and one an ependymoma. In the group with benign tumors (Fig. 11), the 3- and 5-year survival rates were also significantly higher (p < 0.01) after total or subtotal removal (94%) than after partial removal (52%). No recurrence was observed among the 14 patients with benign tumors removed totally or subtotally and not irradiated postoperatively. In this subgroup the median
TABLE 2
Comparison of means and proportions of seven variables between benign and malignant tumors*

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of Tumors</th>
<th>Cases With Benign Tumors</th>
<th>Cases With Malignant Tumors</th>
<th>Statistical Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>no. of cases</td>
<td>69</td>
<td>47</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>patient age at surgery</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean</td>
<td>7.5 ± 5 yrs</td>
<td>5 ± 4 yrs</td>
<td></td>
<td>p &lt; 0.03</td>
</tr>
<tr>
<td>range</td>
<td>7 mos-19 yrs</td>
<td>4 mos-14 yrs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>symptomatic: typical</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>time to evolution</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean</td>
<td>30 ± 42 mos</td>
<td>6 ± 11 mos</td>
<td></td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>median</td>
<td>13 mos</td>
<td>3 mos</td>
<td></td>
<td></td>
</tr>
<tr>
<td>range</td>
<td>3 days-14 yrs</td>
<td>15 days-4.5 yrs</td>
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<td></td>
</tr>
<tr>
<td>tumor location</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>medulla</td>
<td>17</td>
<td>14</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>pons/medulla</td>
<td>16</td>
<td>12</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>pons</td>
<td>10</td>
<td>5</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>pons/peduncle</td>
<td>6</td>
<td>6</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>peduncle</td>
<td>5</td>
<td>4</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>medulla/pons/peduncle</td>
<td>15</td>
<td>6</td>
<td>9</td>
<td></td>
</tr>
<tr>
<td>hypodensity</td>
<td>8.5%</td>
<td>60%</td>
<td></td>
<td>p &lt; 0.001</td>
</tr>
<tr>
<td>cyst present</td>
<td>55%</td>
<td>76%</td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>ring enhancement</td>
<td>8%</td>
<td>28.5%</td>
<td></td>
<td>NS</td>
</tr>
</tbody>
</table>

*Comparisons were performed using univariate analysis. Means are expressed ± standard deviation. NS = not significant.

Follow-up period was 24 months (range 15 to 95 months).

Morbidity

Of the 39 surviving patients who were operated on with the aid of a CUSA, 31 (79.5%) either improved or remained symptomatic postoperatively and eight (20.5%) worsened. Of these eight patients, one deteriorated due to acute postoperative hydrocephalus and seven showed cranial nerve palsies that did not exist before surgery (mainly at the level of the sixth, seventh, and lower cranial nerves). In two of these seven patients the obex had to be split; in five, the tumor, located laterally in the pons, bulged into the cerebellopontine angle. Palsies of the sixth and seventh nerves did not improve in any patients, but all patients recovered from their initial postoperative swallowing or respiratory problems.

The postoperative intelligence quotient (IQ) was evaluated in seven patients operated on without and in 15 with the CUSA. The mean IQ was 76 in the first group (range 37 to 97) and 84 (range 42 to 100) in the second. Among the 43 children operated on since 1985, 28 attend school and 16 (57%) have normal grades.

Comparisons Between Malignant and Benign Tumors

The comparison of means or proportions indicated that three of the seven variables studied differed significantly between benign and malignant tumors (Table 2). In the 22 patients with malignant tumors the mean age at operation was lower (p < 0.03); six (85.7%) of the seven infants below 2 years of age had malignant tumors, whereas most (75.5%) of the older patients had benign tumors. Duration of preoperative symptoms was shorter in malignant tumors (p < 0.001 with t-test and Mann-Whitney test); however, in three cases, there was a long interval between the first symptoms and diagnosis (4.5 years, 11 months, and 8 months). Peritumoral hypodensity was also far more frequent in malignant tumors (p < 0.001). In this series of tumors, which were exophytic or surface and in addition apparently well circumscribed, the topography of the lesions did not significantly differ in benign and malignant tumors, despite a great predominance of benign lesions at the level of the medulla (82.3%).

Stepwise logistic regression analysis showed at the final step that only two parameters were significantly related to the benign or malignant grade of the tumors: patient age (p < 0.03) and peritumoral hypodensity (p < 0.001). Moreover, among the seven children aged under 2 years, the tumors in six were malignant: all three tumors with peritumoral hypodensity and three of four without hypodensity.

Discussion

This study concerns a subgroup of brain-stem tumors with a radiological appearance of circumscribed and superficial lesions. The 75 tumors analyzed here were referred to the neurosurgical service by pediatric neurologists, so a selection was made before assessment by a neurosurgeon. Tumors that were large, hypodense, and diffuse were not considered for surgery. Only tumors that were apparently well circumscribed and reached the surface were considered technically operable and included in the series. Thus, a high percentage of benign tumors in the total series has no epidemiological value. Nevertheless, using these selection criteria, 62.6% of the tumors were benign, suggesting that radiographically focal tumors reaching the surface are more likely to be benign than malignant. This is in agreement with the finding of Barkovich, et al., that focal tumors had a significantly better outcome.

The present series demonstrates that removal of ex-

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ophytic or surface brain-stem tumors is feasible and that the risks of surgery are now low when the following precautions are taken. First, avoid excessive mobilization of the normal brain stem during removal of the tumor. This can be achieved by using the CUSA. In our experience, this tool was essential in reducing mortality and allowing more complete tumor removal. Second, avoid the onset of postoperative anoxia and waves of increased intracranial pressure. It is noteworthy that there were no postoperative deaths among the 29 patients who were routinely maintained under controlled ventilation and CSF external drainage for approximately 1 week after surgery. This was also the case for the 28 patients operated on consecutively since 1990 and therefore not included in this study.

Removal of intrinsic tumors is, on the contrary, a major undertaking that involves high functional and vital risks. In the three cases in which we split the normal floor of a fourth ventricle to reach the tumor, the operation either had to be stopped or was followed by severe complications. Perhaps the laser could be useful, as it is in spinal cord surgery. However, at the level of the brain stem and for strictly intrinsic tumors, we doubt that a laser would permit cutting with preservation of the highly functional nervous tissue that covers the tumor.

This pediatric series and other recent reports demonstrate that removal of brain-stem tumors is only beneficial to children with benign tumors and that long-term survival is the rule. It is now clear that surgery does not improve the prognosis of malignant tumors, where survival time almost never exceeds 18 months. In this series, three patients with malignant tumors are alive 2 years after surgery. These survival periods are probably the consequence of the radiosensitivity of the tumors, two of which were medulloblastomas and one an ependymoma.

One question remains: is surgical removal preferable to irradiation? It is difficult to give a definite answer since many benign tumors in this series were both operated on and irradiated. However, three arguments lead to an affirmative answer. 1) The more radical tumor excisions led to longer survival. Among our patients, the 3-year actuarial survival rate increased from 52% after partial removal (same rate as reported by Litman, et al. after biopsy) to 94% after total or subtotal removal. 2) This rate of 94% was much higher than the best rates (54.8% at 5 years) obtained by irradiation of low-grade gliomas. 3) No recurrence was observed among the 14 patients who did not undergo irradiation after total or subtotal removal of a benign tumor. This last finding agrees with the report by Stronk, et al., that systematic postoperative radiotherapy should not be recommended after almost total excision of benign tumors, if these patients' regular follow-up evaluations include repeated CT or MR imaging.

Since surgery is indicated only for benign tumors, it is of utmost importance to know, or to accurately forecast, the grade of the tumor before determining treatment. This, however, is far from easy because stereotactic biopsies are sometimes dangerous and often unreliable since brain-stem tumors are frequently heterogeneous; in addition, there is controversy over the value of some factors that have been said to reflect the prognosis or the grade of a tumor. In our study, age at operation and presence of peritumoral hypodensity were the two variables related to malignancy in both univariate and multivariate statistical analysis. Concerning preoperative duration of symptoms, the difference between benign and malignant tumors was significant in the univariate analysis, but not apparent in the multivariate analysis.

In this series, tumor topography was not related to grade. Despite a great majority of benign tumors at the level of the medulla (14 of 17), many of the tumors involving the pons were benign as well, including five (50%) of the 10 involving only the pons and 18 (81.8%) of the 22 involving both the pons and one or two of its adjacent levels. Of the 21 nonmedullary tumors, 15 (71.4%) were benign. This apparently contradicts the experience of Epstein and McCleary in which most pontine tumors were malignant. However, the difference between the two series stems from the fact that patient selection was not the same. While radiographically diffuse and unlimited pontine tumors were included by Epstein and McCleary, they were excluded from ours. We agree with the general opinion that the overwhelming majority of tumors affecting the medulla are benign, and that most pontine tumors are infiltrating and malignant; however, contrary to Epstein and McCleary's statement, we think that if a pontine tumor has the clinical and radiological presentation of a benign tumor and if it is superficial or exophytic, it should be removed rather than irradiated.

Conclusions

Removal of focal and exophytic or surface brain-stem tumors now carries low vital and functional risks. This surgery is indicated only for benign tumors. In such cases removal must be as total as possible, since the higher the tumor resection, the longer the survival. Indications for immediate postoperative irradiation are restricted to tumors that are malignant or to those that are benign but impossible to remove more than partially. Youth of the patients, short duration of the preoperative symptoms, and presence of peritumoral hypodensity on CT scans are factors that may indicate malignant tumors.

References


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