Intracranial Ependymomas: Factors Influencing Prognosis*

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Our purpose in this paper is to analyze the case histories of a large number of patients with intracranial ependymomas in order to determine which clinical, pathological and therapeutic factors influence prognosis. Some of the general data on this group of patients have been reported elsewhere.10

Review of the Literature

Among large series of intracranial gliomas, the incidence of ependymomas has varied from approximately 2 per cent2 to 9 per cent.21 The average age of 126 patients with intracranial ependymomas reported by Mabon et al.13 was 23.4 years; thus emphasizing their predominance in early life. Indeed, the supratentorial ependymoma is considered by some to be the most common cerebral hemispheric glioma of children.17,24

Ependymomas usually grow slowly and, as with other relatively benign neoplasms, the prognosis is in a large part dependent upon the location of the tumor. In various series approximately 60 per cent of intracranial ependymomas have been infratentorial in location.5,8,17 Most of the tumors arise in the midline in the 4th ventricle, usually from the floor, but sometimes from the roof. They often fill the 4th ventricle and frequently project extraventricularly into the cisterna magna. Extension about the upper segments of the cervical cord is relatively common, while spread into the cerebellopontine angle, into the central canal of the spinal cord and into and through the aqueduct of Sylvius occurs less frequently. Ringertz and Reymond17 stated that only rarely do these tumors extend predominantly into the cerebellar vermis or hemispheres. Grossly these tumors usually are well defined, soft and somewhat lobulated.

Supratentorial ependymomas were found most commonly in the parietal lobe in one investigation2 but other reports have failed to disclose any characteristic location.19 The growth of these tumors often is by expansion toward the centrum semiovale rather than into the ventricular cavity.2 Ringertz and Reymond17 found that more than half of the supratentorial tumors in their series were unrelated visibly to the ventricles. Unlike infratentorial ependymomas, those in the cerebral hemispheres often are partly or extensively cystic.

Three histological forms of ependymoma—cellular, epithelial and papillary—have been defined by some authors.7 Although one architectural type may predominate, most frequently the cellular variety, many of these tumors contain representations of more than one type. In view of this, and because of the failure of other investigators18,17 and ourselves to find any correlation between the histological variations of ependymomas and their biological behavior, we have not classified our cases in this fashion.

There is controversy as to whether papilloma of the choroid plexus is a fourth type of ependymoma or a separate tumor. We recognize papillomas of the choroid plexus as neoplasms distinct from ependymomas; hence they are not included in this report.
**TABLE 1**

*Intracranial ependymomas (70 patients)*

<table>
<thead>
<tr>
<th>Age (Years)</th>
<th>No. of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Under 15</td>
<td>38</td>
</tr>
<tr>
<td>15–25</td>
<td>12</td>
</tr>
<tr>
<td>25–35</td>
<td>11</td>
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<td>35–45</td>
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<tr>
<td>45–55</td>
<td>1</td>
</tr>
<tr>
<td>Over 55</td>
<td>2</td>
</tr>
</tbody>
</table>

**Material**

A review of the records of surgical neuropathology of the Neurological Institute from 1943 to 1960 yielded 65 cases of intracranial ependymomas. Five additional patients seen between 1930 and 1943 were brought to our attention by virtue of autopsy records or recurrence of tumor in recent years. Pathological material was available for review in 63 cases; in the 7 remaining the original pathological report was used. Eighteen patients had supratentorial, and 52 infratentorial tumors. One was lost to follow-up immediately upon discharge from the hospital. The remaining 69 were followed either to the present time or to the patient’s death. All were followed for more than 3 years. Fifty-nine patients were available for a follow-up of longer than 5 years. Of these, 45 had infratentorial tumors while 14 had supratentorial tumors. Forty-six were followed for 10 years, and 12 for more than 20 years.

**Age**

The average age of all patients when first seen was 16.4 years, with a range of 4 months to 66 years. Patients with supratentorial tumors had an average age of 18.8 years, while the average age of those with infratentorial tumors was 15.4 years. Table 1 shows the distribution of ages of these patients. Customarily, 15 years of age is taken as the dividing line between children and adults; thus 54 per cent of the ependymomas occurred in the pediatric age group.

**Sex**

While the total group of tumors was almost equally divided between males and females, 36 and 34 respectively, 12 of the 18 supratentorial tumors were present in females; 30 of the 52 infratentorial tumors occurred in males.

**Symptoms**

The average duration of symptoms associated with supratentorial ependymomas prior to diagnosis was 7 months with a range of 2 weeks to 8 years. Symptoms were dependent primarily upon the location of the lesion and usually consisted of headache, seizures and visual disturbance. Patients with infratentorial tumors presented most frequently symptoms of increased intracranial pressure such as vomiting, headache or decreased visual acuity. However, nearly one-fifth had complaints of either vertigo or loss of balance. The average duration of symptoms in the infratentorial group was 9 months with a range of 2 weeks to 2 years. Of interest is the fact that patients with infratentorial tumors that were found to be grossly invasive at operation had symptoms for an average of 5.4 months, whereas patients with tumors that were not grossly invasive had an average duration of symptoms of 11.0 months.

**Locus and Growth**

Twelve supratentorial tumors were solid, while 6 were cystic. The neoplastic masses varied in size from 3 cm. to 10 cm. There did not seem to be any favored ventricular site of origin, except for a slight predilection for the 3rd ventricle (Fig. 1). Ependymomas of
the 3rd ventricle may be more common than is apparent from these figures, for tumors in this location frequently are treated by a ventricular shunt and radiation rather than by a direct surgical attack on the tumor. All the neoplasms were related grossly to the ventricular system, but the major growth of 10 was into the cerebral white matter rather than towards the ventricular cavity. Eight tumors remained primarily intraventricular. Four of these grew extensively enough to spread by continuity through the foramen of Monro from either above or below. In only 1 case seen at autopsy was there seeding at a distance from the primary tumor. In this instance, implants from an ependymoma of the left lateral ventricle were found in the right lateral ventricle, 3rd ventricle and 4th ventricle. The spinal cord was free of any disease.

The 52 infratentorial tumors comprised 74 per cent of the cases in this series. This high proportion of infratentorial ependy-
omas has been noted by others. All the tumors arose in the 4th ventricle. Only 4 tumors were limited to the 4th ventricle at the time of initial exploration; 36 had grown into the cisterna magna. Of these 16 extended below the foramen magnum into the cervical subarachnoid space; 3 had also grown into the cerebellopontine cisterns. Eighteen tu-
mors appeared invasive grossly, as noted by the surgeon; 13 had invaded the cerebellar vermis and/or hemispheres and 5 had in-
vaded the brain stem.

The frequency of seeding from intracranial ependymomas to the spinal subarachnoid space has not been clarified completely. This point has considerable therapeutic significance. Russell and Rubinstein considered such spread to be a rare event. Svien et al. in a study of spinal cords from 19 patients with intracranial ependymomas, found sub-
arachnoid implants in 6. None of these had given clinical evidence of their presence. However, others have recorded occasional cases of compression of the spinal cord from such implants. Seeding usually has resulted from infratentorial tumors that had pro-
jected into the cisterna magna. While seeding often has followed operation, this is by no means a necessary precursor. Extracranial spread to the calvarium, soft tissues of the neck, lymph nodes and internal organs rarely has been reported following opera-
tion. In this series metastases to the spinal cord were suspected clinically in only 1 patient. In a 17-year-old boy a Brown-Séquard syn-
drome developed at T8 level 6 years after treatment of his primary tumor of the 4th ventricle. His initial treatment consisted of a partial resection followed by 2000 r in 13 days to the bed of the tumor and 2600 r in 34 days to the entire spinal cord. No autopsy was performed.

Twelve spinal cords from patients who had intracranial ependymomas were ex-
aminied. In no case was a metastasis from the primary ependymoma found, although 1 patient did have leptomeningeal implants from a metastasizing carcinoma of the lung.

Pathological Material

A number of laboratories utilize the grading system for ependymomas based upon histological features devised by Kernohan. Correlations have been made between such grades and the postoperative life expectancy of the patients. In this study 71 surgical biopsies from 63 patients with intracranial ependymomas were reviewed and graded prior to learning the duration of postopera-
tive survival, response to radiation, or the gross characteristics of the tumor. Nine supratentorial ependymomas were Grades I and II, and 4 were Grades III and IV. Two contained elements of oligodendroglia. Twenty-six infratentorial tumors were Grades I and II, and 15 were Grades III and IV. Seven contained elements of astrocy-
toma. Our data suggest that those tumors, whether supratentorial or infratentorial, that contain histological features of increased biologic activity, such as frequent mitoses and pleomorphism, necrosis and vascular proliferation (Grades III and IV), in general are more apt to have a poorer prognosis than the more benign-appearing tumors (Grades I and II). However, in many instances, the
grades correlated very poorly with the subsequent course of the disease and even patients with tumors that were essentially similar had vastly different survivals. For example, we could see no essential microscopic differences between the ependymoma of the 4th ventricle in 1 patient who survived for 24 years following operation and only 900 r of roentgen-ray therapy, and those from a similar location in other patients who survived less than 3 years. In addition, there was no correlation between grade of tumor and invasiveness of infratentorial tumors as seen grossly at operation, or between grade of tumor and duration of symptoms before diagnosis (Table 2). Consequently, we feel that in most cases the histological appearance of the tumor is of less importance in estimating prognosis than other factors to be detailed subsequently.

Russell and Rubinstein\(^\text{18}\) pointed out that cytologically malignant forms are uncommon, even in recurrent tumors. This is in accord with our experience, for we found only 1 case that seemed to fit the criteria for Kernohan’s Grade IV. The admixture of ependymoma with astrocytoma or oligodendroglioma occurs occasionally. In our series the former event was noted 7 times and the latter twice. Seventeen of 71 biopsies contained microscopic foci of calcium deposits, but in only 1 instance was the amount striking.

Twenty autopsies were performed on patients with intracranial ependymomas. Six of these were supratentorial. Two of the 6 afforded an opportunity to compare the histology of the surgical biopsy and the tumor as sampled more widely at autopsy. In both cases, the pathological grade assigned was similar. In 9 cases of infratentorial tumors a similar comparison was made. In 6 instances, the biopsy and autopsy grades were similar. In the remaining 3 cases, in 2 of which the patients had lived for many years following operation, the tumor at autopsy showed slightly greater evidence of biological activity than did the biopsy specimen. In 6 cases examined at various times after roentgen-ray therapy, there was no evidence of radiation necrosis outside the borders of the tumor. These patients had received from 2000 to 4000 r in from 3 to 4 weeks.

**Method of Treatment**

Operation was performed on 65 patients. The surgical procedure usually consisted of a partial resection of tumor with removal of from 10 to 90 per cent of the neoplastic mass. When this did not relieve the cerebrospinal-fluid block, a shunt was performed. In no instance did the surgeon believe that he had accomplished a total removal of the tumor. In a few instances the patient’s condition dictated a more limited procedure. Surgery in these patients was limited to a biopsy and shunting procedure. Twelve had more than 1 operation; in 8 the secondary procedure was revision of a shunt. Four had a second partial removal of tumor from 1 to 10 years following initial operation.

All but 1 of the patients who did not die in the postoperative period were treated by radiation. Treatment was started as soon as the operative wound was healed, usually 5 to 10 days after operation.

Prior to 1953 the method of treatment was basically that formulated by Dyke.\(^\text{5}\) This consisted of 2 to 3 short courses of orthovoltage radiation spaced 1 to 4 months apart. The usual treatment delivered an estimated tumor dose of 3600 r over a period of 4 months.

Since 1953 the method of treatment has consisted of a single protracted course of orthovoltage therapy. The plan of treatment is to deliver a tumor dose of 4000 r in 4 weeks or 5000 r in 6 weeks. Children are treated with a modification of Richmond’s schedule.\(^\text{16}\) Patients were retreated as the need arose. A detailed discussion of the methods used and
the value of radiation therapy is the subject of another report.\textsuperscript{10}

Some authors\textsuperscript{5, 9, 11, 14} recommend that epen-
dymomas be treated in the same manner as medulloblastomas, i.e., radiation therapy to the entire axis of the central nervous system. Bouchard and Peirce\textsuperscript{1} did not advocate prophylactic treatment of the spinal cord. Only 4 of our patients were so treated. Interestingly enough, 1 of these patients was the only one in the series to have a spinal-cord implant from his primary disease.

\textbf{Results of Treatment}

Ringertz and Reymond\textsuperscript{17} reported a follow-up of 54 patients with intracranial ependymomas (21 supratentorial and 33 infratentorial) who were treated by operation alone. The supratentorial group had local recurrence in 7 of 21 patients. The 5-year survival rate was 15 per cent, and the average survival was less than 2 years. The infratentorial group had a 50 per cent operative mortality. The remaining 15 patients had 6 local recurrences. The over-all 5-year survival rate was 17.5 per cent, or 35 per cent of those surviving operation. The average survival was 13 months.

Mabon et al.\textsuperscript{18} reported 57 patients with intracranial ependymomas that had survived operation by more than 1 month. The postoperative survival was compared with the histologic grading of the tumor. Patients with Grade I tumors had an average postoperative survival of 77 months, those with Grade II tumors had an average survival of 37.7 months, and those with Grade III tumors had an average survival of 10.1 months.

Bouchard and Peirce\textsuperscript{4} reported 12 ependymomas that were treated by operation and radiation therapy. Seventy-five per cent of these patients were alive after 3 years, 58 per cent were alive after 5 years and 50 per cent after 10 years.

In our series 4 patients died before any type of treatment could be started, and 13 died postoperatively. Six postoperative deaths occurred in patients with supratentorial tumors; 4 of these had explorations for tumors of the 3rd ventricle. We have considered any death occurring within 1 month of surgery as a postoperative death. Thirty-six patients succumbed to local recurrence of tumor. One died of spread to the thoracic spinal cord, and 1 died of bronchogenic carcinoma. Fourteen patients are still alive at the time of this report.

The average survival from time of diagnosis was 5.2 years with a range of 1 month to 26 years. Patients with supratentorial tumors survived an average of 2.8 years, whereas those with infratentorial tumors survived an average of 6 years. If one eliminates postoperative deaths, the average survival is 3.7 years and 7 years respectively.

Fifty-nine patients were available for a 5-year follow-up from the time of diagnosis. Seventeen, or 28 per cent, were alive at the end of that time. If postoperative deaths and untreated patients are eliminated the 5-year survival is 41 per cent. Thirty-three per cent of patients with infratentorial tumors and 14 per cent with supratentorial tumors survived more than 5 years. Eliminating postoperative deaths, the per cent surviving increases to 45 per cent and 33 per cent respectively.

Of the 36 children in this report, only 9, or 25 per cent, survived longer than 3 years. Fifteen of 38 adults, or 45 per cent, survived longer than 3 years.

It is of interest that 7 patients who survived for more than 10 years died subsequently of local recurrence of tumor. One patient was asymptomatic for 24 years following initial operation and minimal radiation (900 r) only to die of local recurrence of posterior-fossa tumor.

Survival of itself is of little value. It is only worth while if the patient is a useful individual. The functional state of patients surviving for more than 1 year following treatment was evaluated carefully and the patients were divided into 4 groups: (1) Excellent. Patient asymptomatic. Neurological findings normal or only minimal deficit elicited by the examiner. (2) Good. Mild neurological deficit, but patient functions well. (3) Fair. Moderate neurological deficit.
Patient's activities are curtailed, but he can do limited work and is capable of partial self-care. (4) Poor. Severe neurological deficit. Needs care of others. The functional state of patients surviving more than 1 year is shown in Table 3. As can be seen, patients with infratentorial tumors were considerably more intact than patients with supratentorial disease.

Discussion

The 5-year survival rate in this series is better than that reported by Ringertz and Reymond\(^\text{17}\) in their group of patients who were treated by operation alone. Furthermore, the high operative mortality in their infratentorial group (50 per cent) may have eliminated many advanced cases which would have lowered further their survival figures.

There seems to be a great variation in the response of ependymomas to irradiation. Some patients were aided remarkably by roentgen-ray therapy; others did not receive any apparent benefit. The reasons for this are unknown. We could find no histological or clinical criteria which would allow one to predict which ependymoma will respond to radiation therapy and which will not. Therefore, we believe that all patients with intracranial ependymomas should have post-operative therapy to the site of the tumor. It is our belief that patients whose tumors have shown a good response to initial treatment should be retreated with a tumor dose of from 1500 to 2000 r whenever symptoms warrant. The danger inherent in the re-growth of tumor is far greater than that of damage to the normal brain from repeated irradiation.

In this study none of the 12 spinal cords examined at autopsy showed any evidence of a metastatic implant. This is in marked contrast to the group of Svien et al.\(^\text{20}\) wherein 6 of 19 spinal cords showed metastatic deposits. Only 1 patient in our series of 70 cases had clinical findings suggestive of a spinal-cord metastasis from an intracranial ependymoma. None of Svien et al.'s\(^\text{20}\) 19 patients had any clinical findings to suggest disease of the spinal cord.

Although there is room for argument regarding the true frequency of spinal-cord implants, there seems to be no question that clinically significant spread is quite rare. Thus, we see no reason for treating the entire axis of the central nervous system as a prophylaxis for possible spinal-cord metastases.

The prognosis of a patient with a slowly growing supratentorial tumor such as an ependymoma is to a large degree influenced by the location of the tumor. The duration of symptoms as well as the resectability of the tumor vary greatly depending upon the site of the lesion. Thus, an attempt to correlate survival with duration of symptoms, size of tumor or pathological features seems to be subject to considerable error.

Infratentorial ependymomas, on the other hand, all arise in a common location, the 4th ventricle. Therefore, the relative prognosis of patients with these tumors often is a function of the rate of growth of the tumor and the influence of treatment upon it. The duration of symptoms prior to seeking medical aid probably reflects, in large part, both the rate of growth of the tumor and its invasiveness. There is a good correlation between length of symptoms and survival of patients with infratentorial ependymomas. Generally, the longer the duration of symptoms prior to diagnosis, the longer the survival. In addition, patients with infratentorial tumors which were invasive grossly at operation had an average period of symptoms approximately one-half that of patients whose tumors were not invasive. On the other hand, there was no discernible correlation between pathologic grading of these tumors and the length of symptoms or invasiveness of tumor.

<table>
<thead>
<tr>
<th></th>
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<tbody>
<tr>
<td>Excellent</td>
<td>13</td>
<td>3</td>
</tr>
<tr>
<td>Good</td>
<td>14</td>
<td>2</td>
</tr>
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<td>Fair</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Poor</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

TABLE 3
Functional state of patients surviving more than 1 year from time of diagnosis
Intracranial Ependymomas

The rate of cure of many tumors outside the nervous system has been related to clinical or operative staging based primarily upon the local extent or invasiveness of the tumor. In most cases clinical staging has been shown to be superior to histological grading as a means of predicting survival.3 Clinical staging is not applicable to the vast majority of intracranial tumors, because the site of origin varies and frequently is an important determinant of symptoms and cure. Furthermore, accurate clinical or surgical determination of extent frequently is impossible. The infratentorial ependymoma is the only glioma to have a relatively constant site of origin. Furthermore, the extent of the tumor usually is visible to the surgeon. Thus, it has been possible for us to divide these tumors into groups representing the extent of the neoplasm. The classification of infratentorial ependymomas in this way offers a more reliable estimate of prognosis than any clinical or pathologic criteria. We propose that these tumors be classified in the following manner.

T1: Tumor is limited to the 4th ventricle.
T2: Tumor that has extended beyond the 4th ventricle into, but not beyond, the cisterna magna.
T3: Tumor has extended beyond the cisterna magna. This usually is to the cervical subarachnoid space, but may be to the cerebellopontine cisterns.
T4: There is gross invasion of the cerebellum or brain stem regardless of the size of the tumor.
M: Distant metastases throughout the central nervous system or beyond the central nervous system.

The material in this study demonstrates a good correlation between the surgical stage of infratentorial ependymomas and average survival. Patients with T1 and T2 tumors survived an average of about 11 years. Patients with T3 tumors survived an average of 5.5 years; patients with T4 disease survived an average of 2.3 years. There were no M lesions in this series (Table 4). Analysis of the number of patients in each group who survived a given number of years leads to similar results (Table 5). Postoperative deaths were excluded from the average survival data; however, they are included in parentheses in Table 5 in order to show that operative mortality also may be related to the extent of the disease.

The patients with the worst prognosis were those with invasive ependymomas. These patients also had a shorter average duration of symptoms than the noninvasive group. It was not possible to compare the surgeon's impression of invasiveness of the tumor with that seen at autopsy, for in those patients who died soon after operation the tumor had been removed extensively; while in those patients who survived operation by many months, the invasiveness seen at autopsy could well have been a function of continued growth of the tumor.

Conclusions and Summary

Seventy case records of intracranial ependymoma have been reviewed. This tumor occurs most frequently in young people; slightly more than one-half of the patients in this series were children.

The prognosis seems to be poorer in children than in adults. Patients with supra-

### TABLE 4
**Surgical stage and survival of infratentorial ependymomas**

<table>
<thead>
<tr>
<th>Surgical Stage</th>
<th>No. Pts.</th>
<th>Average Survival</th>
<th>Per Cent Survived 3 Yrs. from Diagnosis</th>
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<tbody>
<tr>
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<td></td>
<td>from Symptoms (Yrs.)</td>
<td>from Diagnosis (Yrs.)</td>
</tr>
<tr>
<td>T1</td>
<td>4</td>
<td>11.0</td>
<td>10.1</td>
</tr>
<tr>
<td>T2</td>
<td>10</td>
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</tr>
<tr>
<td>T4</td>
<td>14</td>
<td>2.3</td>
<td>1.8</td>
</tr>
</tbody>
</table>

### TABLE 5
**Surgical stage of infratentorial ependymomas and survival from time of diagnosis**

<table>
<thead>
<tr>
<th>Surgical Stage</th>
<th>No. Pts.</th>
<th>Survival of Patients</th>
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</thead>
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<tr>
<td></td>
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<td>1-3 Yrs.</td>
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<tr>
<td>T1</td>
<td>4</td>
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<tr>
<td>T2</td>
<td>11 (1)</td>
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<tr>
<td>T3</td>
<td>14 (2)</td>
<td>12</td>
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<tr>
<td>T4</td>
<td>18 (4)</td>
<td>9</td>
</tr>
</tbody>
</table>

Number of operative deaths are noted in parentheses.
tentorial tumors have a worse prognosis and generally have greater neurological deficit than do patients with infratentorial ependymomas.

Surgery followed by radiation therapy to the site of the tumor offers a greater chance of cure than surgery alone. Retreatment of a recurrent primary tumor may add many useful years to the patient's life. There is no valid reason to subject the entire axis of the central nervous system to prophylactic radiation.

There appears to be a direct relationship between the length of symptoms prior to operation and the survival of patients with infratentorial ependymomas. This would suggest that the rate of growth of the tumor or its invasiveness greatly influences survival. Surgical staging of infratentorial ependymomas based on their extent and invasion of surrounding brain is the most valuable prognostic criterion available. We propose that all posterior-fossa ependymomas be classified in this manner.

Histological grading of the tumor does not appear to offer as much information in this regard. However, there is a tendency for patients with tumors having histologic features of increased biologic activity to have a shorter course than patients with more benign-appearing tumors. Histological grading has not been of value in predicting invasiveness or radioresponsiveness. In our hands the correlation of histological features with survival has not been nearly as good as with duration of symptoms or tumor stage.

References


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19. Sherbanuuk, R. W., and Suni, T. K. Metasta-


