

Intracranial ependymoma

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Object. An intracranial ependymoma is a relatively rare but very interesting variety of glioma. In this paper, the authors compiled a review of the pathological features, imaging characteristics, and treatment strategies related to this brain tumor.

Methods. A Medline search was conducted using the term "ependymoma." The bibliographies of papers obtained were also checked for articles and chapters that could provide additional understanding of this tumor. Malignant ependymomas and ependymomas of the spinal cord (including myxopapillary ependymomas) were excluded from this review.

Conclusions. The posterior fossa is the most frequent site for an intracranial ependymoma. Children are frequently affected. Most authors recommend resecting as much of the tumor as is safely possible. Microscopically, ependymal tumors show both epithelial and glial features. Glial fibrillary acidic protein immunohistochemistry, therefore, helps in identifying ependymomas. Because ependymomas often recur despite surgical intervention, radiotherapy and/or radiosurgery may also play an important role in their treatment. The use of chemotherapy in the treatment of these tumors, especially in the very young, is still being studied.

KEY WORDS • ependymoma • brain tumor • chemotherapy • cerebrospinal fluid • seeding • radiosurgery • radiotherapy

Ependymomas are derived from a neoplastic transformation of the ependymal cells, which line the ventricular system. They constitute 2 to 9% of all intracranial tumors and up to 12% of pediatric brain tumors.^{3,5,15,23,27} At least half of ependymomas present in the first two decades of life.²⁷ More than 70% of ependymomas occur infratentorially,²⁵ usually arising from the floor of the fourth ventricle in the midline. Approximately half of the supratentorial ependymomas arise from the wall of the ventricles, whereas the remainder seem to arise from the brain parenchyma itself.⁵ Ependymomas of the third ventricle are very rare. Although the ependymal surface area of the third ventricle is larger than that of the fourth ventricle,¹⁸ ependymomas are much more common in the posterior fossa.

According to one theory, ependymal tumors arise from ependymal cell "rests," which tend to accumulate where the ventricles are sharply angled.¹⁸ Such areas would include the anterior spur of the aqueduct of Sylvius, the area adjacent to the trigone of the lateral ventricle, the region near the foramen of Luschka, and in the terminal filum. Perhaps there is a paucity of such cell rests in the third

ventricle.¹⁸ Parenchymal ependymomas are believed to arise from rests of ependymal cells remaining within the brain parenchyma during embryological development.^{3,5}

In childhood, ependymomas frequently fill the entire fourth ventricle, insinuating themselves into the foramina of Luschka as well as out through the foramen of Magendie onto the posterior aspect of the spinal cord.¹³ They can also frequently extend into the CPA through a distended foramen of Luschka. As it spills out into the basal cisterns, the tumor can mingle with the lower cranial nerves.¹³ Unfortunately, aggressive resection of such lesions arising in the CPA can be associated with significant postoperative deficits.²⁶

PRESENTATION, DIAGNOSTIC IMAGING, AND CSF DISSEMINATION

Most tumors arising within the lateral ventricles are benign.²⁰ Because such tumors usually expand slowly and cause nonspecific symptoms, they may grow to a large size before detection.²⁰ The most consistent neurological problem associated with lateral ventricle tumors, including ependymomas, is cognitive impairment associated with hydrocephalus.²⁰ If the tumor is present at a critical site for CSF flow, acute obstructive hydrocephalus and sudden death may occur.²⁸ Supratentorial ependymomas

Abbreviations used in this paper: CPA = cerebellopontine angle; CSF = cerebrospinal fluid; Gd = gadolinium; MR = magnetic resonance.

may produce manifestations of increased intracranial pressure, including headache, nausea, vomiting, and bilateral papilledema. They may also cause focal deficits such as aphasia and motor impairment. Seizures have been reported to occur in one third of the cases.⁵ In cases of third ventricle ependymomas, patients may present with vertigo and Parinaud syndrome.¹⁸ The more common infratentorial tumors may produce nausea, vomiting (particularly when the area postrema is involved), and manifestations of cerebellar compression, mainly ataxia and nystagmus.^{5,15}

On computerized tomography scanning, ependymomas are usually demonstrated as low density masses, often accompanied by hydrocephalus.¹⁴ With the administration of contrast material, the tumors usually enhance strongly and homogeneously.¹⁹ Calcifications and cystic components may also be seen.¹⁹ Magnetic resonance imaging without and with contrast is the preferred neuroimaging modality for both diagnosis and surgical planning because it provides greater soft-tissue detail, especially for infratentorial lesions. On T_1 -weighted MR images a hypointense contrast-enhancing mass is demonstrated that typically fills and expands a ventricle. Often, the MR imaging appearance is heterogeneous.¹⁹ The administration of contrast may be necessary to distinguish the tumor margins from surrounding edema. Ependymomas are usually hyperintense on T_2 -weighted sequences. Images of a posterior fossa ependymoma are provided in Fig. 1, and



Fig. 1. Imaging studies obtained in a 34-year-old man with an ependymoma of the posterior fossa. *Upper Left:* Axial computerized tomography scan revealing a large, fairly homogeneous mass filling (and expanding) fourth ventricle. *Upper Right:* Sagittal T_1 -weighted MR image (without Gd) demonstrating flow voids that indicate blood vessels. *Lower Left:* Axial T_1 -weighted MR image after Gd infusion. *Lower Right:* Coronal T_1 -weighted MR image also demonstrating enlarged ventricles.

images of a supratentorial intraventricular ependymoma are given in Fig. 2.

As with the more malignant medulloblastomas, ependymomas can spread extensively throughout the CSF pathways. Among 754 patients with intracranial ependymomas reported before 1983, evidence of CSF seeding was observed in 94 (12%).²⁵ Because of this, in the past there was a tendency to include diagnostic myelography in the workup of patients with posterior fossa ependymomas. This has shed light on the incidence of seeding. Salazar²⁵ found that CSF seeding of intracranial ependymoma is: 1) more common in infratentorial tumors; 2) more likely to occur in the spinal subarachnoid space than over the cerebral hemispheres; and 3) more frequent with higher-grade tumors. Rezai, et al.,²² reported on a series of 52 patients with intracranial ependymomas treated with surgery between 1986 and 1994. In five patients (9.6%) CSF seeding was demonstrated. Several predisposing factors for dissemination were found: 1) younger age; 2) inability to achieve gross-total resection; 3) higher proliferative indices; and 4) higher-grade tumors.²² The incidence of symptomatic seeding in patients with ependymoma has been reported to be lower (< 5%).²⁵ Because of this, preoperative MR imaging of the whole spine (without and with Gd administration) is recommended in patients in whom ependymoma is suspected.

PATHOLOGICAL FEATURES OF EPENDYMOMAS

In the World Health Organization classification of ependymal tumors, the lesions are divided into four types: 1) ependymoma (the focus of this paper); 2) anaplastic ependymoma; 3) myxopapillary ependymoma; and 4) subependymoma.^{2,10,24} Microscopically, ependymal tumors show both epithelial and glial features. The epithelial features include the lining up of cuboidal cells into linear tubules, which in cross-section appear as rosettes; hence, the name "ependymal rosettes." Ependymal tumors exhib-

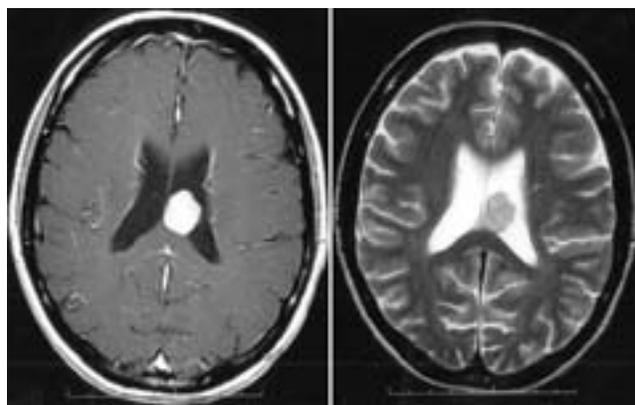


Fig. 2. Imaging obtained in a 47-year old woman with a supratentorial intraventricular ependymoma. *Left:* Axial T_1 -weighted MR image after Gd infusion revealing homogeneous enhancement. Preinfusion images had demonstrated a tumor isointense to gray matter. *Right:* Axial T_2 -weighted MR image demonstrating lobulations and attachment to the ventricular wall.

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it their glial heritage in the form of cell processes packed with glial fibrillary acidic protein–immunoreactive filaments, which are aligned around blood vessels.²⁴ These are called “perivascular pseudorosettes,”^{24,25} and they contain a perivascular eosinophilic zone, together with the perivascular nuclei. Both ependymal rosettes and perivascular pseudorosettes are striking and their presence is diagnostic. When the ependymal cells are present in low density and these processes are abundant, the lesion can resemble a well-differentiated astrocytoma.⁵

Ependymomas can be further subdivided into the cellular, papillary, clear-cell, and tanyctic varieties.² On histological examination, cellular ependymomas are hypercellular, with narrow perivascular pseudorosettes, a benign cellular appearance, and little proliferative activity. An example of a cellular ependymoma is shown in Fig. 3. In contrast, the papillary ependymoma subtype contains a predominantly tubulovillous architecture. This variety is exceedingly rare. Clear-cell ependymomas possess tumor cells characterized by an oligodendrocyte-like clear cytoplasm. They may mimic to perfection both the oligodendroglioma and the neurocytoma on routine histological inspection.^{17,24} The differential diagnosis of a clear-cell ependymoma includes glioneurocytoma. Tanyctic ependymomas, on the other hand, with their elongated cells and less conspicuous pseudorosettes, may resemble astrocytomas.²

SURGERY, RADIATION THERAPY, AND CHEMOTHERAPY

Treatment of intracranial ependymomas may include surgery, radiation therapy, and chemotherapy. Surgery is the mainstay of therapy, and total resection is recommended if possible.^{7,8,15,27,30,31} Preoperative placement of a CSF shunt is often required.¹³ In children with large posterior fossa tumors, however, upward herniation resulting in death has followed ventriculoperitoneal shunt placement.³¹ At the time of craniotomy, the patient, especially if a child, is usually placed in the prone position. The sitting position has also been used, despite its higher risk of air embolism.¹³ As with other intracranial tumors, periop-

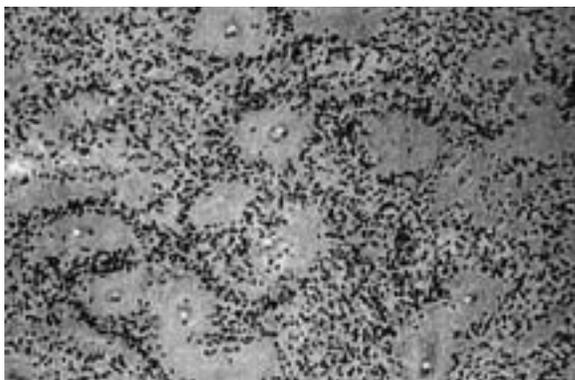


Fig. 3. Photomicrographs of H & E–stained sections demonstrating the histological features of a cellular ependymoma. Note the round- to oval-shaped nuclei and perivascular pseudorosettes. Original magnification $\times 400$.

erative steroid agents are very useful.⁵ In their study of 22 infants and children with posterior fossa ependymomas, Tomita, et al.,³¹ found that incomplete tumor resection almost invariably led to recurrence; hence, they recommended that an attempt should be made to excise posterior ependymomas totally at the initial craniotomy. The completeness of resection is confirmed by postoperative MR imaging.²⁷

Surgery often results in subtotal removal because many ependymomas have insinuated into critical structures such as the brainstem and/or into cranial nerves in the CPA and the associated vasculature. Because of this, a complete resection is not feasible in approximately 50% of patients.¹² Thus, ependymal tumors show a high recurrence rate. Foreman, et al.,⁸ concluded that the role of complete resection, possibly including a second-look surgery, needs further evaluation. Postoperative complications are related to tumor location and have been reported to include cranial nerve palsies, increased ataxia, mutism, and (rarely) death.^{4,12,15,21,25,26,31} It is interesting to mention that a possible postoperative resection-related complication of a posterior fossa ependymoma is mutism, a state in which a patient is conscious but unwilling or unable to speak. This has been reported to occur, especially when the lesion involves the vermis, often weeks after surgery.²¹ Although cerebellar mutism is an infrequent complication, neurosurgeons should be aware that it might occur and that it generally resolves over a period of months.^{3,12}

Intracranial ependymal tumors are considered to be relatively radiosensitive. Radiation therapy seems to increase the survival period and delay recurrence for several years.^{6,27,31} In an informative study of 10 adults recently reported by Donahue and Steinfeld,⁶ it was concluded that postoperative radiation therapy is effective in preventing regrowth of intracranial ependymoma following subtotal resection. Radiation ranging from 3500 to 7200 cGy doses have been given over 5 to 6 weeks.^{5,6,16} Treatment fields should cover the initial tumor bed with a 1- to 2-cm margin to avoid causing long-term radiation damage.⁶ For tumors in the posterior fossa, the recommended dose is 5400 cGy. Craniospinal-axis fields are used only when spinal seeding is radiologically or pathologically evident.¹⁶ In young children (< 5 years of age) with brain tumors, the provision of radiation therapy is usually avoided, if possible. Because of the severity of this disease, however, even young children with intracranial ependymomas usually require chemo- and radiation therapy.⁷

Radiosurgery has also been reported to be an option in patients with ependymomas.^{11,27} In a study by Grabb, et al.,¹¹ which included 25 children with a variety of surgically incurable brain tumors of glial origin, it was concluded that radiosurgery has a role in the adjuvant management of unresectable glial neoplasms of childhood, including ependymomas.¹¹ Based on a study conducted by the Pediatric Oncology Group in which 48 children younger than 3 years of age with intracranial ependymomas were treated with prolonged postoperative chemotherapy and delayed radiation therapy, future radiation treatment trials should emphasize maximum resection and a delay in radiation therapy of no more than 1 year.⁷

To date, chemotherapy has not yielded a significant improvement in survival for patients with ependymal tumors. Children with subtotally resected ependymomas, however, have been treated with chemotherapy in attempts to avoid radiation therapy. In very young children with brain tumors, primary chemotherapy, omitting radiation therapy, has been reported to improve neurodevelopmental outcome and survival.¹ Ater, et al.,¹ reported on 17 consecutive children (< 3 years of age) treated between 1976 and 1988 in whom either medulloblastoma or ependymoma was diagnosed. The patients received MOPP (mechlo-retchamine, vincristine [oncovine], procarbazine, and prednisone) as a primary therapy following excision or biopsy sampling of the tumor. Ten of the 17 patients survived without evidence of disease; median survival time in two with ependymoma was 13 and 16 years, respectively, and in eight with medulloblastoma median survival was 10.6 years. Two of the 10 harbored ependymomas (five total) (the other eight were medulloblastoma).¹ Additionally, preliminary data have suggested that in children with incompletely resected tumors, chemotherapy may be of benefit as an adjunct to second-look surgery.²⁹

For chemotherapy of ependymomas, the platinum compounds, cisplatin and carboplatin, may be the most effective agents discovered to date.⁹ Treatments with other agents such as cyclophosphamide, ifosfamide, methotrexate, vincristine, procarbazine and nitroreureas (often in combination, with up to eight drugs) have been attempted but have shown limited benefit.⁹ Limited studies of additional agents have also been conducted, and future studies are being planned.²⁹ Tomita, et al.,³¹ concluded that, according to their experience, recurrent tumors are resistant to chemotherapy. At this point, the data are not sufficient to justify the use of chemotherapy in patients with ependymomas, except in younger children (in whom radiation therapy is not recommended) or patients in whom surgery and radiation therapy have failed to control tumor growth.

PROGNOSIS AND SURVIVAL

Generally, the 5-year survival rate for patients (age > 5 years) with intracranial ependymomas is approximately 50 to 60% and the 10-year survival is approximately 40 to 50%.²⁷ In general, survival times have improved in the more recent series.⁸ Prognosis is poor because of the difficulty of total excision and because of CSF dissemination.¹⁹ The occurrence of leptomeningeal disease in very young children may be a factor in their poor outcome.⁷ The best results have been achieved by debulking the tumor as much as possible and then administering radiation therapy.^{5,7,23} The following clinical variables seem to favor long-term survival: 1) adult age; 2) tumors located within the cerebral hemisphere; 3) more benign histological appearance; and 4) total resection. Unfavorable prognostic factors include: 1) younger age; 2) posterior fossa location; 3) anaplastic disease; and 4) subtotal resection.²⁷

In a review of 30 patients harboring histologically confirmed posterior fossa ependymomas who underwent surgery at the Mayo Clinic (age range 1–69 years), the following factors were found: 1) younger (≤ 5 years) age was associated with a poorer prognosis; 2) there was a trend toward a better 5-year survival rate with a gross-total

resection; 3) tumors recur at the primary intracranial site; and 4) symptomatic spinal seeding does not occur frequently.²⁹ In another retrospective study of 31 children presenting with intracranial ependymomas between 1976 and 1993, it was found that failure at the primary site was the major obstacle to improved cure rates.^{16,23} This study confirmed the prevailing impression that local disease control is the major factor in predicting ependymoma recurrence.²³

CONCLUSIONS

Intracranial ependymomas are relatively rare gliomas, the treatment for which is primarily surgical but may also include radiation therapy or radiosurgery for residual or recurrent tumor. Histologically, ependymomas have characteristic ependymal rosettes and perivascular pseudorosettes. The role of chemotherapy appears limited but has been attempted, especially in the very young, in order to avoid the deleterious effect of radiation therapy. In the future, advances in surgical technique and/or in the development of new therapies (for instance, based on monoclonal antibodies) may improve the outlook for patients with these tumors.

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References

1. Ater JL, van Eys J, Woo SY, et al: MOPP chemotherapy without irradiation as primary postsurgical therapy for brain tumors in infants and young children. *J Neurooncol* **32**:243–252, 1997
2. Burger PC, Scheithauer BW, Vogel FS: *Surgical Pathology of the Nervous System and Its Coverings*, ed 3. New York: Churchill Livingstone, 1991, pp 271–286
3. Coons SW, Johnson PC: Pathology of primary intracranial malignant neoplasms, in Morantz RA, Walsh JW (eds): *Brain Tumors: A Comprehensive Text*. New York: Marcel Dekker, 1994, 45–108
4. Crutchfield JS, Sawaya R, Meyers CA, et al: Postoperative mutism in neurosurgery. Report of two cases. *J Neurosurg* **81**: 115–121, 1994
5. Dohrmann GJ: Ependymomas, in Wilkins RH, Rengachary SS, (eds): *Neurosurgery*, ed 2. New York: McGraw-Hill Companies, 1996, Vol 1, pp 1195–1200
6. Donahue B, Steinfeld A: Intracranial ependymoma in the adult patient: successful treatment with surgery and radiotherapy. *J Neurooncol* **37**:131–133, 1998
7. Duffner PK, Krischer JP, Sanford RA, et al: Prognostic factors in infants and very young children with intracranial ependymomas. *Pediatr Neurosurg* **28**:215–222, 1998
8. Foreman NK, Love S, Thorne R: Intracranial ependymomas: analysis of prognostic factors in a population-based series. *Pediatr Neurosurg* **24**:119–125, 1996
9. Freeman AI: Chemotherapy of Pediatric Brain Tumors, in Morantz RA, Walsh JW (eds): *Brain Tumors: A Comprehensive Text*. Marcel Dekker, 1994, pp 745–762
10. Fuller GN, Burger PC: Gliomas: Pathology, in Wilkins RH, Rengachary SS (eds): *Neurosurgery*, ed 2. New York: McGraw-Hill Companies, 1996, Vol 1, pp 735–747
11. Grabb PA, Lunsford LD, Albright AL, et al: Stereotactic radiosurgery for glial neoplasms of childhood. *Neurosurgery* **38**: 696–702, 1996

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12. Hahn YS, Ciro E: Family and the child with a posterior fossa tumor, in Raimondi AJ, Choux M, DiRocco C (eds): **Posterior Fossa Tumors**. New York: Springer-Verlag, 1993, pp 201–210
13. Hoffman HJ: Tumors of the fourth ventricle: technical considerations in tumor surgery. **Clin Neurosurg** **34**:523–545, 1988
14. Holt RM, Maravilla KR: Supratentorial gliomas: Imaging, in Wilkins RH, Rengachary SS (eds): **Neurosurgery**, ed 2. New York: McGraw-Hill Companies, 1996, Vol 1, pp 753–775
15. Lyons MK, Kelly PJ: Posterior fossa ependymomas: report of 30 cases and review of the literature. **Neurosurgery** **28**:659–665, 1991
16. McLaughlin MP, Marcus RB, Buatti JM, et al: Ependymoma: results, prognostic factors and treatment recommendations. **Int J Radiat Oncol Biol Phys** **40**:845–850, 1998
17. Min KW, Scheithauer BW: Clear cell ependymoma: a mimic of oligodendroglioma: clinicopathologic and ultrastructural considerations. **Am J Surg Pathol** **21**:820–826, 1997
18. Oppenheim JS, Strauss RC, Mormino J, et al: Ependymomas of the third ventricle. **Neurosurgery** **34**:350–353, 1994
19. Peretti-Viton P, Perez-Castillo AM, Martini P, et al: [Supratentorial ependymomas. Neuroradiological study.] **J Neuroradiol** **18**:201–209, 1991
20. Piepmeier JM: Tumors and approaches to the lateral ventricles. Introduction and overview. **J Neurooncol** **30**:267–274, 1996
21. Pollack IF, Polinko P, Albright AL, et al: Mutism and pseudobulbar symptoms after resection of posterior fossa tumors in children: incidence and pathophysiology. **Neurosurgery** **37**:885–893, 1995
22. Rezaei AR, Woo HH, Lee M, et al: Disseminated ependymomas of the central nervous system. **J Neurosurg** **85**:618–624, 1996
23. Robertson PL, Zeltzer PM, Boyett JM, et al: Survival and prognostic factors following radiation therapy and chemotherapy for ependymomas in children: a report of the Children's Cancer Group. **J Neurosurg** **88**:695–703, 1998
24. Rosenblum MK: Ependymal tumors: a review of their diagnostic surgical pathology. **Pediatr Neurosurg** **28**:160–165, 1998
25. Salazar OM: A better understanding of CNS seeding and a brighter outlook for postoperatively irradiated patients with ependymomas. **Int J Radiat Oncol Biol Phys** **9**:1231–1234, 1983
26. Sanford RA, Kun LE, Heideman RL, et al: Cerebellar pontine angle ependymoma in infants. **Pediatr Neurosurg** **27**:84–91, 1997
27. Sanford RA, Gajjar A: Ependymomas. **Clin Neurosurg** **44**:559–570, 1997
28. Shemie S, Jay V, Rutka J, et al: Acute obstructive hydrocephalus and sudden death in children. **Ann Emerg Med** **29**:524–528, 1997
29. Souweidane MM, Bouffet E, Finlay J: The role of chemotherapy in newly diagnosed ependymoma of childhood. **Pediatr Neurosurg** **28**:273–278, 1998
30. Sutton LN, Goldwein J, Perilongo G, et al: Prognostic factors in childhood ependymomas. **Pediatr Neurosurg** **16**:57–65, 1990–1
31. Tomita T, McLone DG, Das L, et al: Benign ependymomas of the posterior fossa in childhood. **Pediatr Neurosci** **14**:277–285, 1988

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