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Ependymomas in Adults

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Abstract Ependymomas are rare primary central nervous system tumors in adults. They occur most commonly in the spinal cord, where histopathologic evaluation is critical to differentiate the grade I myxopapillary ependymoma from the grade II ependymoma or grade III anaplastic ependymoma. Brain ependymomas are either grade II or III. Treatment for all grades and types includes maximum surgical resection. For myxopapillary ependymoma, complete removal while maintaining capsule integrity may be curative. Some grade II ependymomas may be observed carefully after imaging confirms complete resection, but grade III tumors require adjuvant radiation treatment. Radiation commonly is given to the region of tumor, except in cases in which there is imaging or cerebrospinal fluid evidence of tumor dissemination. Chemotherapy has not been studied extensively, although most reports suggest only modest benefit. Ongoing laboratory studies have uncovered important signal transduction pathways that may be better therapeutic targets, leading to the development of clinical trials using targeted agents.

Keywords Ependymoma · Adult · Pediatric · Therapy

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Introduction

Ependymomas are primary central nervous system (CNS) neoplasms that are rare in adults but more common in the pediatric population. Among primary CNS cancers, ependymomas are estimated to constitute 8% to 10% of pediatric tumors whereas they account for fewer than 4% of adult nervous system tumors, combining both brain and spinal cord tumors. These tumors are thought to arise from the ependymal cells lining the cerebral ventricles, spinal cord central canal, and cortical rests (see Figs. 1 and 2).

Ependymomas have been classified by the World Health Organization (WHO) neuropathology group into grades I, II, and III [1]. Grade I tumors include myxopapillary ependymomas and subependymomas. Grade II tumors are designated by the name *ependymoma*, whereas grade III tumors are called *anaplastic ependymoma*. However, although grading criteria have been established by consensus, the prognostic relevance of the grade II versus grade III distinction remains controversial, particularly for pediatric tumors (reviewed by Godfraind [2]). Recent laboratory analyses strongly suggest there is great molecular heterogeneity when comparing each of the histologic subtypes, as well as significant differences when comparing spinal cord tumors with brain tumors of the same histologic type [3]. Genetic heterogeneity also has been noted in comparing pediatric and adult tumors of the same location and histology, although the differences by tumor location appear to be more profound than changes related to patient age. Location of tumor also has the most important impact on prognosis, trumping both WHO grade and patient age.

The relative rarity of the tumor has resulted in a paucity of large homogeneous series of patients, as often many subtypes and grades, as well as patients of all ages, are combined in published reports. Although some progress has

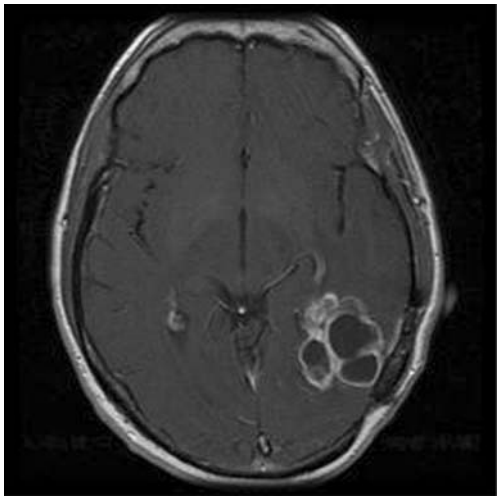

Fig. 1 Supratentorial anaplastic ependymoma in an adult patient. The image shows characteristic well-circumscribed enhancing abnormality

been made, largely by the efforts of multicenter pediatric groups, a consensus regarding the management of adults with ependymoma is lacking. Studies are ongoing that are designed to systematically characterize the molecular alterations in a large series of ependymomas, correlate these changes with prognosis, and use these molecular profiles to subcategorize ependymomas, hopefully uncover novel therapeutic targets, and ultimately develop individualized treatment strategies for patients with ependymoma.

Pathology and Classification

The WHO classification system for CNS neoplasms is nearly universally accepted as the standard. This system grades tumors on a scale from I to IV, with increasing degree of malignancy. The histologic grading system has been a critical element in developing treatments for patients with CNS cancers because these tumors rarely spread outside the CNS, making the standard cancer staging system, TNM, unusable, as *T* designates tumor size, *N* is for nodal metastases, and *M* reports metastases to additional organs.

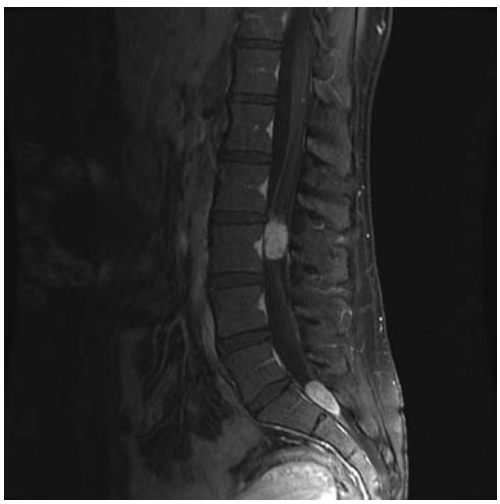

Fig. 2 Spinal cord ependymoma at the conus medullaris with evidence of a drop lesion at the distal end of the thecal sac

The classification of ependymoma includes types designated as grade I (myxopapillary or subependymoma), grade II (ependymoma with possible designations as cellular, papillary, clear cell, or tanycytic), and grade III (designated anaplastic ependymoma) by WHO criteria [1]. Importantly, grade I tumors are biologically distinct from grade II and III tumors because these tumors tend not to be infiltrative into surrounding normal brain or spinal cord parenchyma, making cure possible with complete surgical excision, and the malignant transformation into a higher-grade tumor is extremely rare. Conversely, grade II ependymomas have a much lower rate of cure, even with extensive resection, and have the potential to transform to grade III neoplasms. Grade III tumors are almost never cured with surgical resection because infiltration into surrounding normal parenchyma, although less prominent than that of malignant astrocytomas, is a frequent cause of tumor recurrence. Controversy remains regarding the prognostic implications of a grade II compared with a grade III tumor, in both the pediatric [2, 4] and adult [5] populations. Several studies suggest the distinction may predict event-free survival but not overall survival. Ki-67 immunolabeling has been suggested as a reproducible marker of prognostic importance, with a low Ki-67 index associated with a favorable outcome [6].

Diagnosing ependymoma may be difficult because there are several primary CNS tumors that are similar in appearance. As a consequence, some series using central review of putative ependymomas discovered that nearly 30% actually were misdiagnosed [7•]. Among the CNS neoplasms that are similar in appearance are oligodendroglioma, central neurocytoma, pilocytic astrocytoma, astroblastoma, papillary glioneuronal tumor, and monomorphous angiocentric glioma [2].

Prognostic Factors

The prognostic factors for adult patients with ependymoma may differ from those for pediatric patients with this disease. However, most reports focus exclusively on or represent an analysis of all age groups. Analysis of patient outcomes from the Surveillance, Epidemiology and End Results (SEER) database encompassed all patients with a diagnosis of ependymoma recorded between 1973 and 2005, yielding a total of 2,408 cases [8•]. Prognostic factors from multivariate analysis, including higher grade, younger

age, male gender, intracranial tumor location, and failure to undergo extensive surgical resection, were associated with a worse clinical outcome. However, this registry does not mandate central pathology review, and there is concern that some of the reported cases were not truly ependymoma.

There are only a few studies of clinical prognostic factors exclusively in adults with ependymomas. The report by Reni et al. [9•] describes the outcomes in 70 patients older than 17 years with intracranial tumors. In this study, older age and supratentorial location were significant on univariate analysis of survival factors and only age was significant on multivariate analysis. A recent study by Guyotat et al. [7•] examined prognostic factors in 106 adult patients with infratentorial ependymomas. This study showed that a good preoperative Karnofsky performance score (>80), no extension of tumor into the lateral recess of the fourth ventricle, and a low histologic grade were associated with a significant improvement in survival.

The group at M. D. Anderson Cancer Center compiled their institutional collection of adults with ependymoma and analyzed this group for predictors of outcome [10•]. Their study included 123 patients older than 17 years, 80 with spinal cord tumors and 40 with intracranial tumors, including 16 with supratentorial tumors and 24 with infratentorial tumors. Three patients had both spinal cord and intracranial tumors. Ninety percent of the patients had grade II tumors at diagnosis based on WHO criteria; however, 15 of these patients were found to have a grade III ependymoma at the time of tumor recurrence. Multivariate analysis determined that tumor grade III and intracranial location were significantly associated with worse progression-free and overall survival. Other clinical variables, such as extent of tumor resection and use of postoperative adjuvant radiation, also have been reported as potential prognostic factors [11].

Molecular prognostic factors also have been reported for ependymoma. Chromosomal gain of 1q correlated with shortened progression-free survival and overall survival [12]. Similarly, amplification of the epidermal growth factor receptor (EGFR) and increased expression of this protein have been found to be an independent indicator of poor prognosis [12]. Human telomerase reverse transcriptase overexpression also is associated with worse outcome, a finding confirmed in several studies [12, 13].

Extent of tumor invasion, as assessed by evaluation of tumor histologic preparations, combined with expression of selected matrix metalloproteinases (MMPs) also has been shown to correlate with outcome [14]. Patients with evidence of tumor microinvasion and elevated levels of MMP2 and MMP14 were more likely to have tumor recurrence after resection, suggesting that these laboratory findings may help identify patients most likely to benefit from adjuvant (postsurgical) treatment.

Incidence and Epidemiology

Ependymomas represent 3% to 6% of all CNS tumors. In children, the incidence of ependymomas is higher than in adults. Ependymomas are the third most common form of pediatric tumors of the CNS, accounting for 8% to 10% of all pediatric CNS tumors. There appear to be significant differences in the relative frequency of tumor location based on patient age. McGuire et al. [15] performed a comprehensive analysis of incidence patterns of ependymoma using data from the SEER database. They confirmed that ependymoma is more frequent in males and that pediatric tumors are mostly intracranial, whereas adult tumors are more frequently in the spinal cord. Further analysis confirmed that younger children are more likely to have tumors in the posterior fossa than supratentorial tumors, which occur more commonly in older children and adults.

Currently, both the SEER program and the Central Brain Tumor Registry of the United States (CBTRUS) monitor the incidence of ependymomas [16]. However, both groups combine all grades of ependymomas for reporting purposes. According to the CBTRUS report on the incidence rates between 1998 and 2002, 1,126 ependymomas and anaplastic ependymomas were diagnosed, for an adjusted rate per 100,000 person-years of 0.26. This rate is slightly higher in males (0.29) than females (0.22) and in whites (0.27) versus blacks (0.12).

Molecular Profiles

Despite recent efforts, ependymomas are not as well characterized as other primary brain tumors, such as the malignant gliomas or medulloblastomas. However, the studies that have been performed do provide some potential insight into the pathogenesis of the disease, which may help define the origin of the ependymoma stem cell, generate prognostic markers, and, most importantly, yield therapeutic targets, particularly those focused on signal transduction modulators. Several studies suggest that the tumor biology and outcome are more closely related to tumor location (spinal cord vs intracranial, and supratentorial vs infratentorial for the brain ependymomas) than to age or grade.

Chromosomal Abnormalities

Ependymomas, particularly intramedullary spinal cord tumors, have a very high incidence of loss of heterozygosity (LOH) on chromosome arm 22q, often with accompanying NF2 mutations. An 11q LOH, also common, is associated with mutations in the MEN1 gene (located at 11q13) and,

interestingly, is found most often in tumors that do not demonstrate the 22q LOH. Interestingly, in a few cases, the MEN1 gene was intact when the tumor was low grade (WHO grade II), but the mutation was found at tumor recurrence, with malignant transformation to a grade III neoplasm, suggesting the MEN1 gene mutation is associated with malignant transformation. Genomic losses also have been reported on 2q, 4q, 5q, 6q, 7q, 15q, 16q, 17p, and 19p, although these are much less common [17–19]; chromosome 10q LOH is rare. Chromosomal gains, as determined by comparative genomic hybridization, have been detected in a large percentage of ependymomas, but with a high degree of variability. These gains have been found on both arms of chromosome 17, 9q, 12p, 13q, 20q, and 22q. A recent analysis suggests that in adult ependymomas, there are distinct patterns of chromosomal changes based on tumor location, with distinct changes associated with spinal, infratentorial, and supratentorial locations [18]. However, most of the chromosomal abnormalities have not been clearly associated with genetic changes that contribute to tumorigenesis or biology.

Molecular Pathway Abnormalities

Ependymomas appear to have several characteristic pathway abnormalities. ErbB2 and ErbB4 receptor overexpression was found in more than 75% of pediatric ependymomas and correlated with tumor proliferative index and prognosis [20], with similar findings in adult supratentorial ependymoma. Other studies reported additional molecular changes, including increased expression of integrin $\alpha_v\beta_3$ in a high percentage of intracranial ependymomas, as well as expression of annexin A1 and cyclooxygenase 2 [21–23]. A single nucleotide polymorphism in the platelet-derived growth factor (PDGF) receptor-α gene promoter region in ependymomas has been reported, suggesting that the PDGF pathway may have a functional role in tumor biology [24].

Gene Array-Based Profiles

Gene expression has been studied using microarray technology in a variety of ependymomas [25–27]. Korshunov et al. [26] analyzed 39 newly diagnosed ependymomas and uncovered patterns that could distinguish grade II from grade III supratentorial ependymomas and spinal from cranial tumors; however, they could not find a similar pattern for infratentorial tumors. Gene expression profiles were found with typical spinal cord ependymomas that differed from myxopapillary tumors. Suarez-Merino et al. [27] examined 19 pediatric ependymomas and found 112 genes that were abnormally expressed compared with normal brain. These genes included those involved in the cell cycle, cell adhesion, and proliferation, notably the oncogene WNT5A and the p53 homologue p63. The NF2-associated gene *SCHIP1* was underexpressed, a potential alternative to NF2 loss, as described earlier. Lukashova-v Zangen et al. [25] examined 47 ependymomas and were able to identify a gene profile, with 27 genes associated with a good prognosis (defined as survival >10 years). No uniform set of prognostic, "location," or age-specific genes was identified, likely because of the diversity of the specimens investigated, including differences in patient age, tumor location, histology, and tumor grade.

Epigenetic Studies

Epigenetic mechanisms have been proposed as an alternative explanation for gene inactivation in ependymoma. Hypermethylation of the promoter region may help account for the relative infrequency of mutations of established tumor suppressor genes [3]. The methylation status of the gene promoter region of several known tumor suppressor and related genes has been examined in ependymomas [28–30]. The tumor suppressor gene *RASSF1A* was methylated in a high percentage of ependymomas in two separate studies [28, 29]. Interestingly, the *MGMT* gene rarely was methylated in ependymomas. Additionally, some apoptosis-associated TRAIL pathway genes also were hypermethylated [29]. The putative tumor suppressor gene *HIC1* was hypermethylated exclusively in intracranial ependymomas but not in spinal cord tumors, providing further evidence of differences in the pathogenesis of these tumors [30].

Ependymoma Stem Cells

Based on work from the Gilbertson laboratory, radial glia have been proposed as the stem cells for ependymomas [31••]. Molecular profile comparisons demonstrate that ependymoma stem cells from cranial and spinal cord tumors recapitulate the molecular profiles of the location-specific radial glial cells found during development. Studies of the radial glial cells may provide insights into the pathogenesis of ependymomas and potential therapeutic targets. For example, loss of the adherens gene α-epithelial catenin and dysregulation of the NOTCH cell signaling pathway have been found to alter the behavior of radial glial cells, emulating ependymoma activity.

Implications for Prognosis and Treatment

The pathologic diagnosis of ependymoma encompasses a variety of neoplasms that have a similar histologic

appearance but vary widely in their genetic alterations, affecting tumor biology and, ultimately, prognosis and treatment. Laboratory investigations suggest several potential therapeutic targets, including ErbB2 (Her2) and, in some cases, ErbB1 (EGFR) [20]. A polymorphism of the PDGRα gene promoter that causes dysregulation of this pathway was reported, suggesting that blocking this receptor may be a potential treatment strategy [24]. Similarly, overexpression of the $\alpha_v\beta_3$ integrin was found in a high percentage of ependymomas, and there now are specific agents targeting this integrin [21]. The finding that most ependymomas overexpress *MGMT* may provide insight into the overall poor response of ependymoma to conventional cytotoxic chemotherapy, as this enzyme is a major mechanism of resistance to alkylating agents [32]. Therefore, strategies to modulate *MGMT* activity may have benefit in ependymomas. Finally, development of ependymoma models using a cancer stem cell system should facilitate testing of new treatment regimens before implementation in clinical trials.

Treatment

Intracranial Tumors

Surgical resection is the most important therapeutic intervention. This procedure establishes the diagnosis; in some cases, re-establishes normal cerebrospinal fluid flow, reversing hydrocephalus; and with an extensive tumor resection, may directly affect survival. Most series report that extensive resection is associated with improvement in both progression-free and overall survival [6, 33–37]. Some series report that complete resection, using MRI for verification, may be achieved in 50% to 75% of patients. Increasingly, there has been support for reoperation if the initial procedure was incomplete and a complete resection is possible with the additional procedure [6, 36]. Some tumors are not amenable to complete resection, including intrinsic brainstem tumors and tumors adhering to vascular structures, cranial nerves, or the ventricular surface, for which resection is inadvisable.

Staging of the CNS is recommended because ependymoma can disseminate via the cerebrospinal fluid. Although estimates of dissemination vary widely in the literature, overall it has been reported in approximately 15% of patients and is more common in those with posterior fossa tumors or anaplastic ependymomas. The occurrence of this complication at the time of presentation is less than 5% [38]. Following the established paradigm for medulloblastomas, analysis of cerebrospinal fluid soon after tumor resection may be misleading; therefore, it is advisable to wait a minimum of 2 weeks after surgery. The frequency of surveillance of the spine for evidence of dissemination in patients with ependymoma remains uncertain; however, although the incidence is relatively low, early diagnosis may affect treatment options and prevent irreversible neurologic injury.

Radiotherapy commonly is used after patients recover from the surgical procedure. There is consensus that radiation treatment is indicated for patients with anaplastic (grade III) ependymoma, but there have not been extensive clinical trials demonstrating a clear dose–response relationship [39, 40]. In the past, craniospinal or whole-brain radiation was used, but recent studies demonstrate that in the absence of evidence of dissemination, regional radiation with total doses up to 60 Gy is of equal benefit, with less toxicity [41•].

The role of radiation treatment for grade II ependymoma is more controversial [6, 9•]. Reports in the literature demonstrate benefit, particularly in patients with visible residual disease after the initial surgical procedure, with better local control if the dose exceeds 50 Gy [6, 42–44]. However, some authors advocate that if the surgical resection is complete, radiation may be deferred, provided there is a plan for careful monitoring. Therefore, in the absence of randomized studies, after complete resection of a grade II ependymoma, either early implementation of radiation or careful observation with MRI is an acceptable option.

The role of chemotherapy is less well established. Few prospective clinical trials have been performed evaluating chemotherapy regimens in adults with recurrent ependymoma. Most series are retrospective collections, often a compilation of a divergent series of patients or treatment regimens used [45, 46]. Some series suggest that the response rate with platinum-based regimens is higher than that of regimens without a platinum agent. The pediatric literature supports the use of cisplatin over carboplatin; however, this has not been addressed in the adult patient population. There are anecdotal reports from investigators using a variety of chemotherapy regimens including irinotecan, ifosfamide, idarubicin, and tamoxifen in combination with isotretinoin [47].

Temozolomide has been tested in small series of patients. Aside from a single report of a prolonged response, there have been conflicting reports regarding the level of activity of temozolomide when administered using conventional dosing schedules [48, 49]. The report by Chamberlain and Johnston [48] showed minimal activity, whereas the ongoing study at the University of Torino has shown promising early results [50]. However, recent reports suggest that a large percentage of ependymomas express high levels of MGMT, an enzyme that confers resistance to alkylating agents such as temozolomide [32]. This suggests that alternative schedules, such as more prolonged, dose-

dense schedules, may have improved efficacy because these have been shown to deplete MGMT in peripheral blood lymphocytes.

The use of agents that target signal transduction pathways has not been investigated extensively. A recent article in the pediatric oncology literature suggests that developing individualized treatment regimens based on tumor-specific molecular profiles represents the best chance for progress [51]. However, this strategy has yet to be implemented in treatment regimens. Bevacizumab has been used in a small number of patients; in a retrospective series of eight patients, most of whom were heavily pretreated, objective responses were noted in six [52]. However, some of these responses were not durable, and the median progression-free survival was only 6.4 months. The Collaborative Ependymoma Research Network (CERN) currently is accruing patients to a clinical trial combining a dose-dense schedule of temozolomide with lapatinib, a dual inhibitor of EGFR and Her2 (ErbB2), both potential targets based on laboratory studies.

Spinal Cord Ependymomas

Spinal cord ependymomas occur predominantly in adults. These tumors fall into one of two distinct histologic subtypes. Myxopapillary ependymomas are classified as WHO grade I and usually arise in the cauda equina with occasional extension into the conus medullaris. There are reported cases of dissemination via cerebrospinal fluid throughout the neuraxis, although this is uncommon. The second type of spinal cord ependymoma is the classic ependymoma, similar in histologic findings to intracranial ependymoma. These tumors typically are classified as grade II by WHO criteria, although a small subset are anaplastic, and they occur most commonly in the cervical spinal cord and less frequently in the thoracic region.

Spinal cord ependymomas are thought to have a relatively low risk of dissemination; however, recent studies suggest that dissemination is a potential life-limiting outcome if myxopapillary ependymomas are removed piecemeal, because the opening of the tumor capsule allows for tumor cell spillage into the surrounding cerebrospinal fluid [53, 54]. In both myxopapillary and classic ependymoma, extracranial spread is very rare.

Extent of surgical resection remains one of the key determinants of prognosis for spinal cord tumors [55, 56]. An en block resection of an intrinsic spinal cord ependymoma, either myxopapillary or classic, may result in cure [54]. Conversely, as described earlier, compromise of the tumor capsule may lead to tumor dissemination for myxopapillary tumors. Similarly, incomplete resection of classic spinal ependymomas has a high recurrence rate in the absence of additional treatment. Most investigators support the use of postoperative local radiation treatment for incompletely resected tumors and for the rare anaplastic ependymomas [57]. Some studies suggest that total radiation doses greater than 50 Gy may be superior to lower doses when given to the region of the tumor [58]. Although higher doses are associated with an increased risk of radiation-induced myelopathy, it is estimated that 55 Gy has a less than 2% risk of significant spinal cord injury [59]. More extensive radiation treatment, such as complete spine or craniospinal radiation, is reserved for patients with evidence of dissemination.

Management of patients with recurrent disease may include re-resection, often followed by reirradiation with either conventional external beam treatment or use of a more focused radiation technique, such as the CyberKnife system (Accuray, Sunnyvale, CA) [60]. This approach may provide good local control, although the risk of myelopathy from the radiation increases with repeated treatment.

Chemotherapy does not have a proven role in the treatment of patients with spinal cord ependymoma. A variety of agents have been tried, including chronic oral etoposide, with modest success [61]. An intriguing article reported on a minor response using imatinib in a spinal ependymoma that expressed the PDGF receptors [62].

Future Directions

Challenges remain in the management of patients with ependymoma. The relative rarity of the disease in adults limits the ability to conduct large-scale clinical trials, and even single-institution pilot investigations are limited by accrual issues. Despite a marked similarity of tumor appearance by routine histologic evaluation, laboratory investigations increasingly are recognizing significant molecular heterogeneity among these tumors. Advances, therefore, will require a collaborative endeavor including a strong clinical research effort combined with tumor-based correlative studies. The correlative studies will help identify unique clinical and molecular profiles that will enable recognition of optimal treatment regimens for ependymoma subtypes. Although ependymoma is an uncommon disease, this approach should warrant great interest, attention, and support, as preliminary data suggest that ependymomas may be less genetically complex than high-grade gliomas and that the successful integration of molecular characterization with clinical trials would provide compelling evidence that this integrated approach is a useful paradigm. The CERN (www.cern-foundation.org) has been established to follow this research plan with ongoing clinical trials and concordant tumor molecular investigations.

Conclusions

Ependymomas in adults, which are still uncommon, are more heterogenous than was previously appreciated. Treatment approaches and regimens frequently have been adopted from experience with the more common pediatric ependymomas. However, certain principles of therapy have been established across both the pediatric and adult patient populations. Most studies strongly support the benefit of maximum surgical resection and, in the case of spinal cord myxopapillary ependymoma, removal of tumor without breaching the tumor capsule, which may prevent dissemination. Many studies support postoperative "adjuvant" radiation in cases of low-grade tumor with residual disease and in patients with the higher-grade, anaplastic ependymomas. Treatment of recurrent disease is less well defined, although reoperation and reirradiation commonly are used for pediatric patients and are feasible in many adults. Although the role of chemotherapy is evolving and the optimal chemotherapeutic regimen is uncertain at present, it is hoped that ongoing clinical trials with correlative molecular studies will help individualize treatment in the future.

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