Intracranial Ependymoma

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Learning Objectives

- Explain classification of ependymomas.
- Describe clinical presentation and work-up of ependymomas.
- Outline prognostic factors.
- Describe current management guidelines.
- Outline role of radiation therapy in management of ependymomas.

Introduction/Epidemiology

Ependymomas are uncommon tumors arising from the ependymal cells lining the ventricles, central canal, filum terminale, or choroid plexus [1]. The origin of these cancers, possibly neuroectodermal, remains controversial; recently a possible glial origin has been speculated [1–3]. Ependymal tumors constitute approximately 1.8% of primary brain and central nervous system tumors diagnosed in the United States between 2009 and 2013 with 1420 estimated new cases in 2017 as per the Central Brain Tumor Registry of the United States (CBTRUS) Statistical Report [4]. Historically, they were first described by Percival Bailey in 1924 as an independent histopathological entity [5]. They are usually childhood tumors and relatively less common in adults with a bimodal peak distribution at ages 5 and 35 years [6]. Ependymal tumors in adults are most common in the spinal canal, comprising the majority of patients in most reports [3, 7, 8]. Among intracranial ependymomas, 50–60% are supratentorial [7]. The clinical presentation depends on the tumor location and size/mass effect [1, 9] as detailed in the Table 28.1.

Table 28.1 Clinical presentation of ependymoma

Location	Clinical symptoms	Pathophysiology
Supratentorial	Confusion, lethargy, seizures, focal neurological deficits	Mass effect
Intraventricular	Headaches, nausea, vomiting, papilledema, ataxia, vertigo, CN deficits	Increase in intracranial pressure
Infratentorial	Visual disturbances, ataxia, dizziness, neck pain/stiffness, CN palsies, hemiparesis (rare)	Compression of posterior fossa structures (posterior fossa syndrome)

Diagnosis and Prognosis

The work-up for patients with adult intracranial ependymoma should include a detailed history, physical examination, contrast-enhanced magnetic resonance imaging (or computerized tomography if MRI is contraindicated) of the brain and entire neuraxis, biopsy (if applicable), and cerebrospinal fluid (CSF) cytology (at least 2 weeks after surgery). Heterogeneous enhancement (more pronounced with higher grade) is usually appreciated on MRI and could be considered diagnostic if there is characteristic involvement through the foramen of Luschka [1, 9, 10]. CSF evaluation is critical with incidence of spinal seeding ranging from 1.6% for supratentorial tumors and 2–4.5% for low-grade lesions to 9.7% for infratentorial lesions and 8.4–20% for high-grade tumors [1, 11, 12].

As per the recently updated 2016 World Health Organization (WHO) pathologic classification, adult ependymal tumors can be classified as grade I (subependymoma

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Table 28.2 World Health Organization (WHO) pathologic classification of ependymoma

Classification	Tumor cell	Mitotic activity	Key histological features
WHO grade I [myxopapillary]	Cuboidal	Absent/very low	Mucoid matrix with GFAP expression and lack of cytokeratin expression
WHO grade I [subependymoma]	Isomorphic	Absent/very low	Dense fibrillary matrix with frequent microcysts
WHO grade II [ependymoma (papillary, clear cell, tanycytic subtypes)]	Monomorphic	Rare/absent	Perivascular pseudorosettes and ependymal rosettes
WHO grade III [anaplastic]	Cellular/nuclear pleomorphism	High	Perivascular rosettes, pseudopalisading necrosis, endothelial proliferation

or myxopapillary), grade II [ependymoma (with papillary, clear cell, tanycytic subtypes)], or grade III (anaplastic) as summarized in the Table 28.2 [1, 13]. However, as acknowledged in the updated 2016 classification, current WHO criteria is difficult to apply and of questionable clinical utility [13]. Hence, a more prognostic and reproducible classification/grading scheme is warranted.

Prognostic Factors

All of the published data on prognostic factors are derived from retrospective analyses extending over several decades. The prognostic factors reported in the literature include extent of resection, tumor grade, age at time of diagnosis, Karnofsky performance status (KPS), tumor location, and adjuvant radiation therapy [14]. Low-grade histology ($p = 0.052$) was found to be a significant prognostic factor for progression-free survival (PFS) in a study of 31 patients with age at diagnosis ranging from 1 to 56 years (median 9 years) [15]. Grade III (anaplastic) histology ($p < 0.01$), supratentorial location ($p < 0.01$), and subtotal resection (STR) ($p < 0.01$) were found to be significant adverse prognostic factors on multivariate Cox proportional hazard model analysis of the Collaborative Ependymoma Research Network (CERN Foundation) data from 19 institutions that included 282 adult ependymoma patients (46% spine, 35% infratentorial, 19% supratentorial) [16]. Rooney et al. retrospectively analyzed 42 adult patients (>18 years; median age, 36.8 years; 26/42 patients with grade II and 14/42 with grade III histology) with supratentorial ependymoma diagnosed between 1969 and 2008 from the Mayo Clinic tumor registry; they found that extent of resection ($p = 0.009$), lack of recurrence ($p = 0.02$), and age ≤ 40 years ($p = 0.05$) were significantly favorable factors for improved overall survival (OS) [17]. Metellus et al. analyzed 114 adult patients (mean age 48 years, range 18–82 years) with intracranial WHO grade II ependymomas from 32 French neurosurgical centers diagnosed between 1990 and 2004. With multivariate analyses, they demonstrated that improved OS rates were associated with higher preoperative KPS score ($p = 0.027$), greater extent of surgery ($p = 0.008$), and infratentorial vs. supratentorial tumor location ($p = 0.012$) [18]. Supratentorial tumors are usually of higher grade, and it is more difficult to achieve gross total resection (GTR) [8]. Among patients who underwent STR, adjuvant radiation therapy was correlated with a significant improvement in both overall ($p = 0.005$) and PFS ($p = 0.002$) [18]. Gender and age group (<55 and ≥55) were not significant [18]. Extent of resection and tumor grade were found to be significant prognostic factors for PFS and OS in a study of 109 adult supratentorial hemispheric ependymomas patients (clinical information for 101 patients was collected from literature review, and the remaining eight patients were retrospectively accrued from the University of Michigan) [14].

Management

The management of intracranial ependymoma in adults remains controversial due to the rarity of the disease and lack of prospective clinical trials. As per the National Comprehensive Cancer Network (NCCN) guidelines, the standard of care remains maximum safe resection as the first-line treatment [8]. Not only is extent of resection important prognostic factor; it also provides tissue for pathologic diagnosis, opportunity for GTR/debulking, and possible alleviation of cerebral spinal fluid (CSF) obstruction [1]. If maximum resection is not feasible, then stereotactic/open biopsy is recommended with consideration of second-look surgery to complete the resection. Postoperative contrast-enhanced MRI of the brain and spine should be obtained along with CSF cytology. Adjuvant radiation therapy is recommended for WHO grade II tumors after incomplete resection and for all WHO grade III tumors. Supratentorial WHO grade I/II ependymoma after GTR could be observed; alternatively, adjuvant fractionated external beam radiation therapy could also be considered. These recommendations are consistent with a population-based analysis by Ghia et al. of 92 patients [median age 17.5 years (range 1–83 years); 75% Caucasian; 58% female] with non-anaplastic supratentorial ependymoma; there was not a significant difference in 5- and 10-year cause-specific survival (CSS) and estimated overall survival between patients who underwent GTR alone vs.

GTR followed by adjuvant radiotherapy (50% of patients; radiotherapy mean/median dose unknown) [5]. Rogers et al. evaluated 37 adult patients (age ≥ 18 years; median age 44; 23 male) with nondisseminated intracranial ependymomas (33/37 infratentorial; 32/37 low grade) treated between 1975 and 2001 with GTR alone (20/37), GTR + radiotherapy (8/37), STR + radiotherapy (8/37), or STR alone (1/37); adjuvant radiotherapy (mean posterior fossa dose 54 Gy in 30 fractions) was associated with an improvement in 10-year local control from 51% (GTR alone) to 100% (GTR + radiotherapy) for infratentorial ($p = 0.07$) and 56% (GTR alone) to 88% (GTR + radiotherapy) for all intracranial ependymoma patients ($p = 0.15$) [19]. However, for patients with posterior fossa ependymomas, adjuvant postoperative radiation therapy does significantly improve local control and is recommended for patients with GTR and STR [20]. In an analysis of 45 patients with posterior fossa ependymomas, adjuvant radiation therapy was delivered to 13 patients after GTR and 12 patients after STR. The 10-year actuarial local control rates for patients with GTR + radiotherapy, GTR alone, and STR + radiotherapy were 100%, 50%, and 36%, respectively, with significant differences between GTR + radiotherapy and GTR alone cohorts ($p = 0.018$) and GTR + radiotherapy and STR + radiotherapy cohorts ($p = 0.003$) [20]. Management for patients with evidence of metastatic disease within the CSF and/or brain and spinal canal includes craniospinal axis irradiation (CSI), but is not covered in this chapter [8]. Currently, there is no well-defined role of chemotherapy in adjuvant setting either [8].

Radiation Dose, Target Volume Delineation, Tumor Control, and Survival

Based upon the prescribed doses that were utilized in published studies, generally 54–60 Gy in 1.8–2 Gy fractions is prescribed to the tumor bed with 1–2 cm circumferential margins. One can choose to generate a volume expanded (1–2 cm) clinical target volume (CTV), appropriately modified to exclude regions unlikely to harbor disease, and then add an additional PTV margin to account for setup uncertainty (which would be treatment machine and institution dependent) [8, 21]. The predominant site of recurrence for both low-grade and high-grade ependymomas is local recurrence [1]. A predominance of local (vs. spinal) recurrence is consistent with data from Paulino et al. who analyzed 28 patients [18 male; median age 12 years (range, 2–81 years)] with posterior fossa ependymoma treated between 1984 and 1998 with median follow-up of 127 months [22]. In this small series, 3 of 11 patients who received craniospinal or whole brain radiotherapy developed recurrences, of which one was a local recurrence and another posterior fossa outside of tumor bed + spine recurrence. Among nine patients who had tumor bed radiotherapy alone and six who did not receive radiotherapy, there were three relapses, all within the tumor bed. In another study, 31 patients with age at diagnosis ranging from 1 to 56 years (median 9 years), 19 of whom had anaplastic tumors were analyzed, and all 16 relapses were at the primary intracranial sites with no spinal failures [15]. Additionally, this study also analyzed prescribed dose; patients treated to a dose greater than or equal to 50 Gy experienced improved long-term PFS ($p = 0.04$), although this was not significant on multivariate analysis [15]. The only treatment variable found to be significant for PFS was volume of cranial irradiation favoring local fields ($p = 0.002$) [15].

A recent population-based National Cancer Database (NCDB) study identified 2507 adult patients with intracranial WHO grades I–III ependymoma treated between 1998 and 2012 and failed to demonstrate significant overall survival with adjuvant radiation therapy [23]. Forty-five percent of patients underwent radiotherapy with a median dose of 54 Gy (<54 Gy = 20.5%, 54–59.3 Gy = 50.3%, ≥ 59.4 Gy = 29.2%). With median follow-up of 49 months, the unadjusted 5-year overall survival was 73% (95% CI of 70–76%) in irradiated patients versus 75.8% (95% CI of 73.2–78.4%) who underwent observation [23]. Subset analysis of tumor grade, extent of resection (GTR vs. STR), size, and location (supratentorial vs. infratentorial) also did not show significant overall survival improvement with radiotherapy [23]. Presently, this data is only published in an abstract form, and a careful review of manuscript is needed.

Though treatment with radiotherapy was not associated with improved outcomes in the NCDB and other studies, this may reflect a bias in that patients who received radiotherapy were perhaps more likely to have had adverse risk factors. Given the retrospective nature of these studies, specific recommendations about which situations warrant radiotherapy cannot be readily ascertained, though higher-grade disease, STR, and tumor location warrant more serious consideration of adjuvant radiation therapy. The 10-year overall survival ranges approximately from 50% to 72.5% as summarized in the Table 28.3.

Table 28.3 Published survival outcomes of adult ependymoma patients

Study	OS (10 year)	Comment
Schwartz et al. [24]	72.5%	Adults with supratentorial ependymoma
Stuben et al. [25]	58%	Heterogeneous study population (age > 16 years)
Reni et al. [26]	50%	Multi-institutional experience with adult intracranial ependymomas (age > 17 years; 70 patients)

Acute- and Late-Term Sequelae of Radiation Toxicity

Acute side effects from radiation therapy depend on the tumor location and generally include fatigue, headache, nausea, vomiting, radiation dermatitis, and alopecia. Long-term side effects include memory loss, apathy, concentration difficulties, personality changes, and delayed leukoencephalopathy with cognitive dysfunction, sometimes even in patients with Karnofsky performance status ≥90% [1]. Long-term cognitive impairment has also been correlated with volume of supratentorial brain in the radiation field and fraction size ≥2 Gy [1, 5]. Occasionally, cranial nerve dysfunction and endocrine dysfunction (even for tumors away from hypothalamus-pituitary axis) are also reported [1]. There is also a risk of radionecrosis dependent on radiation dose and volume, usually at median of 1–2 years post-radiotherapy and with an estimated risk of 5% with biologically effective dose (BED) of 120 Gy and 10% with BED of 150 Gy, for conventional fractionated radiation therapy (<2.5 Gy fraction size) [27].

Follow-Up

NCCN guidelines recommend follow-up with serial MRIs every 3–4 months for the first year, then 4–6 months for the second year, and then every 6–12 months for at least 12 years [8].

Case Presentation: Highlight Radiation Therapy Management with Neuroimaging and Thought Process

A 23-year-old man presented with a 3-month history of daily headaches and four episodes of associated expressive aphasia. His past medical history was significant for childhood acute lymphoblastic leukemia (ALL) status post chemotherapy (vincristine, mercaptopurine, and methotrexate) and whole brain radiation therapy (WBRT) to 18 Gy with twice-daily radiotherapy in March 1990 at age 2½ on a prospective protocol in which he was randomized to receive WBRT. MRI of the brain during work-up of his headache showed a mass centered in the left thalamus measuring 3.7 × 3.6 cm with compression of the third ventricle and extension into the left lateral ventricle. MRI of the cervical-thoracic-lumbar spine did not demonstrate any evidence of metastatic disease. He underwent GTR, and final pathology results demonstrated WHO grade III ependymoma with Ki67 15%. Postoperative MRI did not reveal any residual tumor, and the CSF was negative. We recommended adjuvant radiation therapy to the tumor bed, and he received total dose of 58 Gy in 29 once-daily fractions to clinical target volume (CTV) and 52.2 Gy in 29 once-daily fractions to planning target volume (PTV) using intensity-modulated radiation therapy (IMRT) as illustrated in Figs. 28.1, 28.2, 28.3, and 28.4. He tolerated treatment very well with-

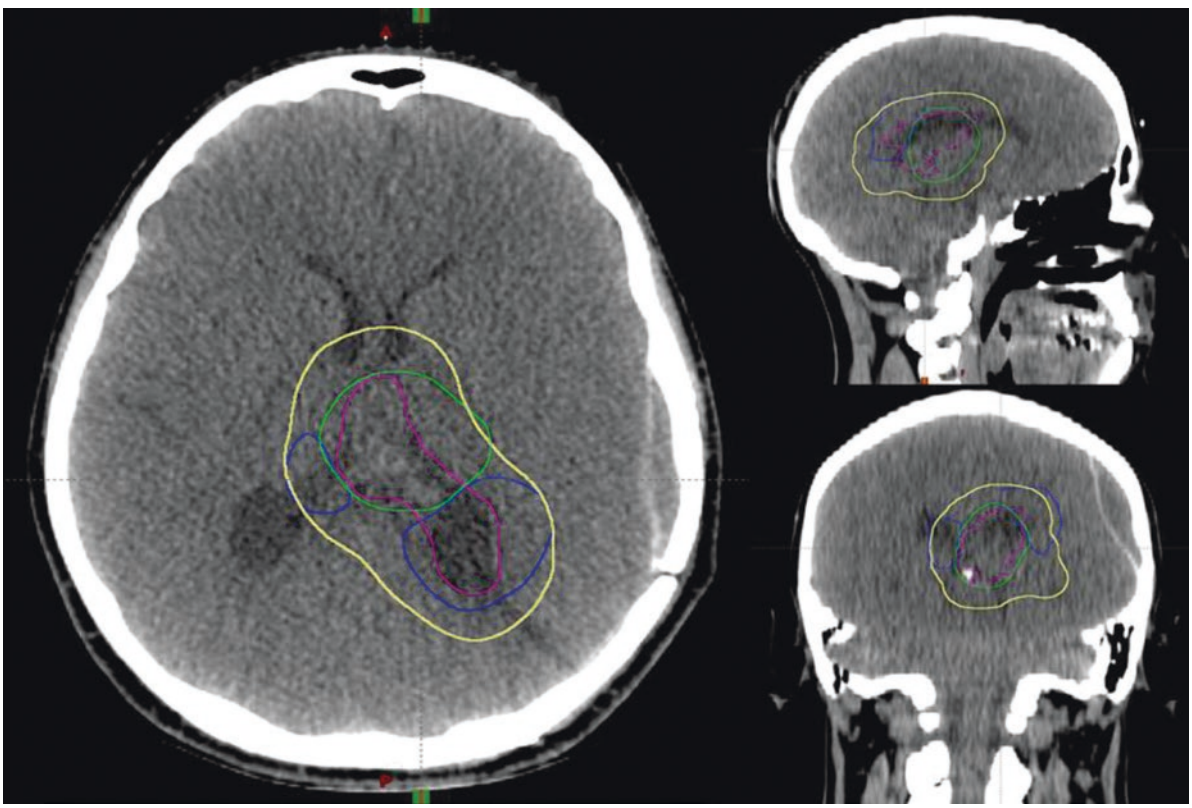

Fig. 28.1 Planning CT treatment volumes: pre-op tumor (green), pre-op cyst (blue), CTV (pink), and PTV (yellow)

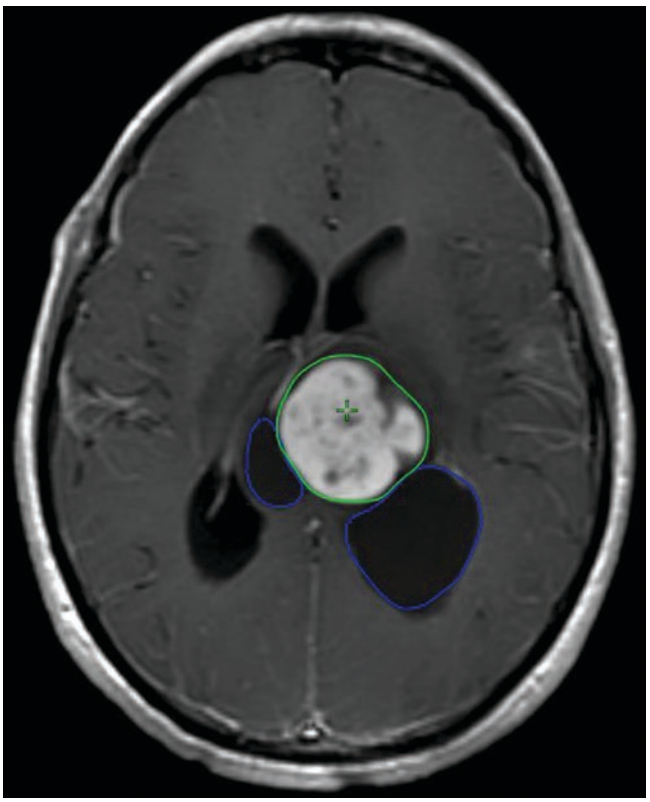

Fig. 28.2 Delineation of the treatment volumes on diagnostic pre-op MRI: pre-op tumor (green) and pre-op cyst (blue)

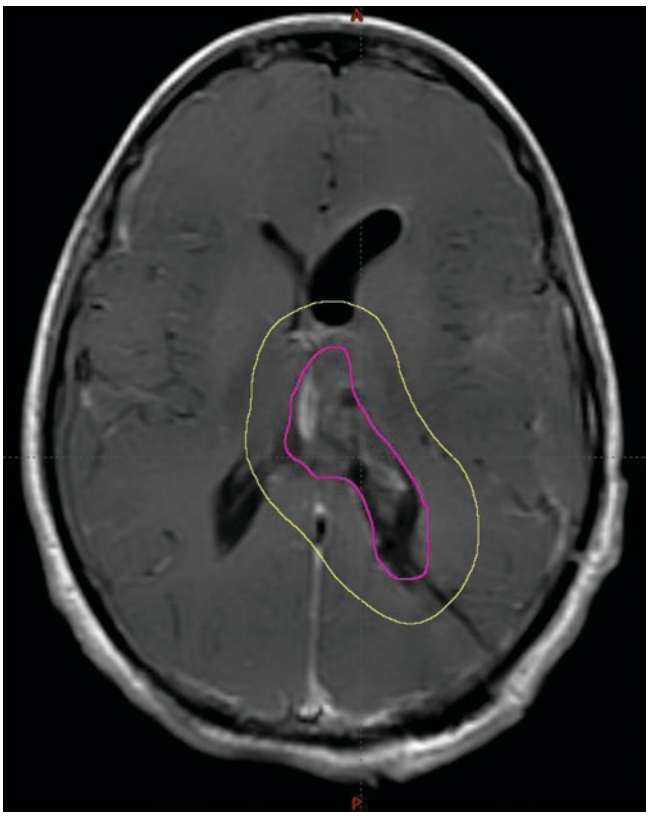

Fig. 28.3 Delineation of the treatment volumes on diagnostic post-op MRI: CTV (pink) and PTV (yellow)

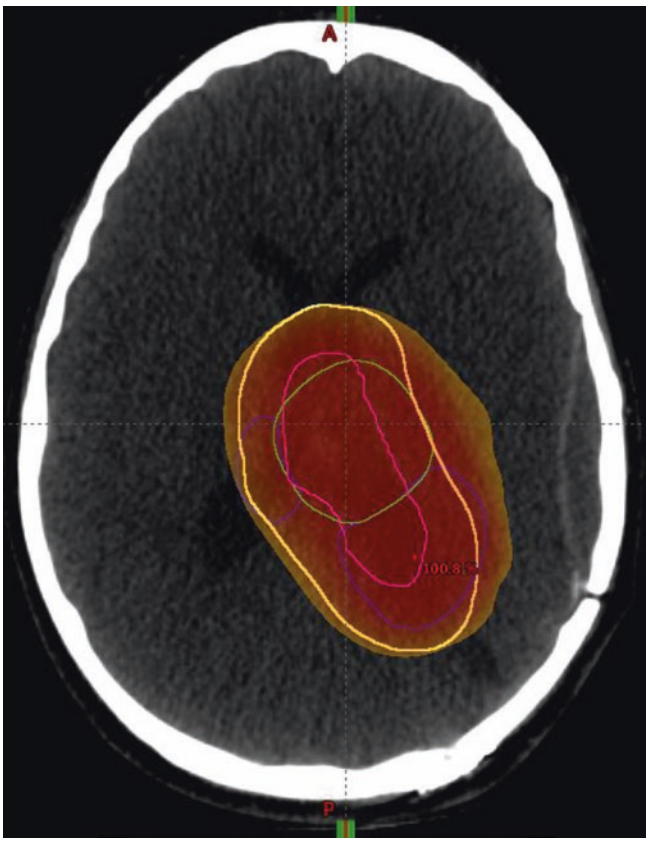

Fig. 28.4 IMRT plan with treatment volumes [pre-op tumor (green), pre-op cyst (blue), CTV (pink), and PTV (yellow)] and dose color wash

out any significant side effects. He continues to do very well with no evidence of disease recurrence, now >6 years since completion of radiation therapy. His only long-term toxicity seems to be concentration difficulties being managed with methylphenidate.

Summary

- Ependymomas are uncommon tumors arising from the ependymal cells lining the ventricles, central canal, filum terminale, or choroid plexus.
- Clinical presentation depends on the tumor location.
- As per WHO 2016 pathologic classification, ependymal tumors can be classified as grade I (subependymoma or myxopapillary), grade II [ependymoma (with papillary, clear cell, tanycytic subtypes)], or grade III (anaplastic).
- Prognostic factors include extent of resection, tumor grade, age at time of diagnosis, Karnofsky performance status (KPS), tumor location, and adjuvant radiation therapy, with arguably extent of resection being the most significant factor.
- Predominant pattern of recurrence is local.
- Management of adult intracranial ependymoma remains controversial, and multi-institutional prospective trials are needed.

Self-Assessment Questions

1. Which of the histologic subtypes of ependymoma is associated with the worst prognosis?
   A. Myxopapillary
   B. Subependymoma
   C. Classical
   D. Anaplastic

2. Compared to pediatric ependymoma, adult ependymoma predominantly occurs in?
   A. Frontal lobe
   B. Spinal cord
   C. Cerebellum
   D. Brain stem

3. What seems to be the most important prognostic factor in adult intracranial ependymoma?
   A. Radiation therapy dose
   B. Supratentorial location
   C. Extent of resection
   D. Age at diagnosis

4. Which of the following statements about adult intracranial ependymoma is true?
   A. Adjuvant radiation therapy dose is around 50.4 Gy.
   B. Predominant pattern of recurrence is local.
   C. Gross total resection is more common for supratentorial location.
   D. Adjuvant chemotherapy is always recommended for anaplastic histology.

5. Observation would be an acceptable management option for which of the following?
   A. Supratentorial WHO grade I ependymoma after GTR
   B. Infratentorial WHO grade II ependymoma after GTR
   C. Supratentorial WHO grade III ependymoma after GTR
   D. Infratentorial WHO grade III ependymoma after GTR

Answers

1. D
   (Please refer to "Prognostic Factors" section for explanation)
2. B
   (Please refer to "Introduction/Epidemiology" section for explanation)
3. C
   (Please refer to "Prognostic Factors" section for explanation)
4. B
   (Please refer to "Radiation Dose, Target Volume Delineation, Tumor Control, and Survival" section for explanation)
5. A
   (Please refer to "Management" section for explanation)

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