

EANS/UEMS European examination in neurosurgery

Variants of questions with answers (compilation - Vyacheslav S. Botev, Department of Neurosurgery, M.Gorky Donetsk National Medical University).

Brain Tumors

Questions

I. Tumor Markers

1. Which stain is the most specific marker of gliomas (especially astrocytomas and ependymomas)?
2. Which tumor type may be identified with α -fetoprotein (AFP)?
3. Which stain highlights neuroendocrine cells and may be useful for identification of pituitary adenomas?
4. Which tumor types may be suggested with positive cytokeratin staining?
5. Which tumor types may be suggested with positive epithelial membrane antigen (EMA) staining?
6. Which stains identify melanoma or melanocytes?
7. S-100 staining may also assist with identification of what other tumor types?

II. Primary Tumors

Low-Grade Gliomas

Basic Concepts

1. What kinds of glial cells may become gliomas?
2. Name the four categories of low-grade gliomas.
3. How does the “miscellaneous” category differ from the other low-grade gliomas?

Low-Grade Astrocytoma

1. What chromosomal abnormalities are most strongly associated with low-grade astrocytomas?
2. Which WHO grade I astrocytoma occurs most commonly in patients with neurofibromatosis type 1 (NF1)?
3. How would you generally describe this tumor?
4. True or false: Bilateral optic nerve involvement is a common presentation of this tumor.
5. How do pilocytic astrocytomas appear radiologically?

6. Can you use CT to visualize this lesion?
7. With what age group is this tumor associated?
8. Where would this type of lesion most commonly appear in this age group?
9. What are the common presenting signs and symptoms?
10. Are seizures common?
11. What would you expect to find histologically?
12. Is the presence of Rosenthal fibers necessary and sufficient for diagnosis?
13. Are these lesions GFAP-positive?
14. What is meant by “pennies on a plate?”
15. True or false: *p53* mutation and aberrant platelet-derived growth factor (PDGF) signaling play an important role in the development of pilocytic astrocytoma (PA).
16. Are the genetics of NF1-associated and sporadic pilocytic astrocytomas the same?
17. What is the prognosis with this lesion?
18. What type of change in the nature of these lesions is seen over time, if any?
19. When, rarely, a pilocytic astrocytoma undergoes malignant transformation, is it considered a glioblastoma?
20. How does the variant pilomyxoid astrocytoma differ from pilocytic astrocytoma?
21. What are the specific histological differences?
22. At what age does this tumor typically present?
23. What is the prognostic difference?
24. Why is pilomyxoid astrocytoma (formerly known as “infantile pilocytic astrocytoma”) considered a variant of pilocytic astrocytoma?
25. What WHO grade I tumor is the most common neoplasm associated with tuberous sclerosis?
26. Can SEGA occur without tuberous sclerosis?
27. Can this tumor occur congenitally?
28. How does it present clinically?
29. How does SEGA arise?
30. Is SEGA GFAP-positive?
31. What “meningocerebral” grade II astrocytoma arises supratentorially in <90% of cases?
32. In which lobe is this neoplasm most commonly found?
33. In what age group are the majority of PXA cases found?
34. How do these patients tend to present?
35. To what does the term pleomorphic refer?
36. What are some of the various cytological features that may be observed?
37. What about “xanthoastrocytoma?”
38. What other finding is characteristic of PXA?

39. This feature is particularly helpful for differentiating it from what other neoplasm?
40. PXA is immunoreactive for which three antibodies?
41. Is there any association with hereditary tumor syndromes?
42. Is *p53* a major player in PXA?
43. What is the prognosis with this tumor?
44. What factors are most indicative of a favorable outcome?
45. What WHO grade II astrocytoma is characterized by a high degree of cellular differentiation and slow growth but commonly progresses to anaplastic astrocytoma and/or GBM?
46. What is another term commonly used for diffuse astrocytoma?
47. Diffuse astrocytoma is responsible for what percentage of astrocytic brain tumors?
48. What is the peak age of incidence?
49. Where in the brain is it most commonly found?
50. What are common presenting signs and symptoms?
51. How does the tumor appear on CT scans?
52. On MRI?
53. Does it enhance with gadolinium?
54. Are mitoses present microscopically in fibrillary astrocytoma?
55. Is fibrillary astrocytoma GFAP positive?
56. What is the growth fraction by K_i -67/MIB-1 labeling index?
57. What is necessary for a diagnosis of gemistocytic astrocytoma?
58. How do gemistocytes appear?
59. Are they GFAP positive?
60. What tumor markers do they express?
61. Though the K_i -67/MIB-1 growth fraction is also $<4\%$, what is the difference in prognosis with gemistocytic versus fibrillary astrocytoma?
62. What is the genetic susceptibility associated with diffuse astrocytoma?
63. What other genetic change is observed in diffuse astrocytoma?
64. Is there a consistent way to judge time to progression of higher grade tumor?
65. What are clinical predictors of better prognosis?

Oligodendroglioma

1. How do most patients with oligodendroglioma present (clinically)?
2. True or false: Patients with oligodendrogliomas have an increased risk of hemorrhage.
3. What is its localization?
4. How does it appear on CT and MRI?
5. What would a heterogeneous appearance on imaging suggest?

6. Aside from a “fried egg” appearance, what features would you expect to see on microscopy?
7. What other microscopic findings would you expect with an anaplastic oligodendroglioma?
8. What is the prognosis for a patient with oligodendroglioma?

Oligoastrocytoma

1. What is an oligoastrocytoma?
2. What is its WHO grade?
3. In what age range and sex would you expect to find this tumor?
4. Is there a virus associated with this lesion?
5. What is the typical survival time with this tumor?

High-Grade Gliomas

Basic Concepts

1. Which tumors are considered to be high-grade gliomas?
2. Which tumor variable is most directly related to prognosis?
3. What scale (based on recursive partitioning statistical analysis [RPA]) is widely used to predict survival in patients with high-grade glioma?
4. Why is surgical resection not indicated when a patient already has significant neurological deficit?
5. What is the role of radiotherapy in the treatment of high-grade gliomas?
6. How is it administered?
7. What is the role of chemotherapy as an adjuvant in the treatment of high-grade gliomas?
8. What is temozolomide?

Anaplastic Astrocytoma

1. Can anaplastic astrocytoma arise de novo?
2. What is its WHO grade?
3. What is its mean age of presentation?
4. What tumor does its behavior closely mimic?
5. How does it differ from a diffuse astrocytoma microscopically?
6. What K_i -67/MIB-1 growth fraction would you expect with this lesion?
7. What are the major genetic changes associated with AA?
8. What is the prognosis with this lesion?

Glioblastoma (GBM)

1. Where does glioblastoma most commonly occur?
2. What other sites are common in children?
3. What are essential histopathological findings in GBM?
4. What are “secondary structures?”
5. What is the typical proliferative index associated with GBM?
6. What are the three mechanisms of GBM vascularization?
7. What is the major driving force of GBM angiogenesis?
8. What is the mechanism of vascular dysfunction in GBM?
9. What is the hallmark feature of necrosis in GBM?
10. What are the major genetic changes associated with GBM?
11. Alteration of *p53* is associated more with primary or secondary GBM?
12. Are there any other genetic changes that present more commonly in secondary than in primary GBM?
13. Are *EGFR* changes present in young patients with GBM?
14. What other genetic changes are more commonly associated with primary than secondary GBM?
15. What is the genetic profile of pediatric high-grade astrocytoma?
16. What variant of glioblastoma is associated with de novo presentation in patients with mean age 42?
17. What are the special features of this variant?
18. Which variant has a genetic and population profile that is very similar to primary GBM, yet is characterized by a “marbled” pattern of glial and mesenchymal differentiation?
19. What is this variant’s defining characteristic?
20. What characterizes gliofibroma?
21. Are there any familial syndromes associated with GBM?
22. What are some of the characteristics of GBM that make it so difficult to treat?
23. What causes a “butterfly glioma?”
24. True or false: GBM often invades the subarachnoid space and metastasizes via CSF.
25. How do the cysts of GBM differ from cysts seen in low-grade astrocytoma?
26. Do primary or secondary GBM arise more commonly in younger patients?
27. How is this significant for prognosis?
28. Are primary or secondary GBMs more common?
29. Aside from differences in prognosis, why is it important to differentiate between primary and secondary lesions?

Meningiomas

1. What kind of intracranial neoplasm is most common when autopsy data are considered together with tumors of clinical significance?
2. What is a meningioma?
3. What is its WHO grade?
4. Where in the CNS does it most commonly localize?
5. How does its incidence relate to age?
6. Does it preferentially affect one sex?
7. Can meningioma occur in children?
8. Is trauma a cause of meningioma?
9. What about radiation?
10. Is it common for patients to have multiple meningiomas?
11. Why is it difficult to understand the “natural history” of meningiomas?
12. So what is a useful way to estimate the “natural history” of these lesions?
13. What is the imaging modality of choice to examine meningiomas?
14. What is an advantage of CT versus MRI?
15. What are the three most common histological subtypes of meningioma?
16. How would you characterize a meningothelial meningioma?
17. What pattern is characteristic of a fibrous meningioma?
18. What pattern is characteristic of a transitional meningioma?
19. What is a psammomatous meningioma, and where would you expect to find it?
20. Describe an angiomatous meningioma.
21. What is a secretory meningioma?
22. What is the most common genetic abnormality in meningiomas?
23. Which three meningioma subtypes are considered WHO grade II lesions?
24. Describe clear cell meningioma.
25. What is chordoid meningioma?
26. What characterizes atypical meningioma?
27. Name the three WHO grade III meningioma subtypes.
28. How would you describe a papillary meningioma?
29. How would you describe a rhabdoid meningioma?
30. What characterizes an anaplastic (malignant) meningioma?
31. Is invasion of surrounding tissue sufficient to make the diagnosis of anaplastic meningioma?
32. Where do allelic losses frequently occur in atypical and anaplastic meningiomas?
33. Are there any familial syndromes that may predispose a patient to meningioma?
34. For which antigens are meningiomas generally immunoreactive?

35. What is the significance of progesterone-receptor presence?
36. What management options exist for meningiomas?
37. For which patients is observation considered the most appropriate option?
38. Is any preoperative medical treatment indicated for those who wish to pursue surgery?
39. What is the most important prognostic factor with respect to likelihood of recurrence?
40. What general principles should be considered when optimizing surgical resection of a meningioma?
41. What steps can be taken to ensure early tumor devascularization?
42. Why is internal decompression followed by extracapsular dissection so important?
43. True or false: Meningiomas frequently have feeders that come directly from the main intracranial arterial (ICA) trunks.
44. What is appropriate postoperative management and follow-up of patients with benign meningiomas?
45. How about in a patient with atypical meningioma?
46. What is the role of radiotherapy in malignant meningiomas?
47. So what is the optimal timing for radiotherapy?

Pineal Region and Intraventricular Tumors

Basic Concepts

1. How do patients with tumors in these locations most commonly present?
2. What is the implication for management?
3. What is Parinaud syndrome?
4. What is the role of angiography in the management of these tumors?
5. For pineal region lesions (or tumors of germ cell origin), what other tests should be included in the initial workup?
6. What treatment options are available?
7. What are the most important surgical approaches to keep in mind when operating on these eloquent regions?
8. Discuss the complications and challenges of these approaches.
9. How can colloid cysts result in sudden death?
10. What are the different surgical approaches to colloid cysts near the foramen of Monro?

Ependymoma

1. What is the intraventricular tumor that is typically sharply demarcated and does not enhance with contrast?
2. Where is it most commonly found?
3. What is the typical patient population affected?
4. True or false: These lesions are often found incidentally at autopsy.
5. Are calcification and/or hemorrhage consistent with this diagnosis?
6. What is the genetic alteration associated with subependymoma?
7. What is the WHO grade of the typical ependymoma?
8. If you were told that a patient has an infratentorial ependymoma, how old would you expect the patient to be?
9. Are adults also affected by ependymomas?
10. What is the most common location for ependymoma?
11. True or false: Ependymomas may present extraneurally.
12. What is the typical clinical presentation of ependymoma?
13. What would you expect to see on an MRI of this lesion?
14. How do the nuclei of ependymomas appear?
15. What is another hallmark feature of ependymomas?
16. What are the three histological variants of intracranial ependymoma?
17. Describe cellular ependymoma.
18. What would you expect to see in a papillary ependymoma?
19. What is the significance of GFAP positivity?
20. What other tumor might be considered in your differential, and how would you differentiate it?
21. How would you describe a clear-cell ependymoma?
22. What other lesions would you need to consider on a differential with clear-cell ependymoma?
23. What features can help in making the distinction?
24. Is “clear-cell ependymoma of the foramen of Monro” still considered a clear-cell ependymoma?
25. Are there any familial syndromes associated with ependymoma?
26. Do we know of any cytogenetic changes in these lesions?
27. Are anaplastic ependymomas more commonly found in the spine or intracranially?
28. What is the WHO grade for anaplastic ependymoma?
29. How do these differ clinically from grade II ependymomas?
30. What histopathological characteristics distinguish this lesion?
31. What are some of the negative prognostic indicators associated with anaplastic ependymoma?

Choroid Plexus Tumors

1. What are the three grades of choroid plexus tumors?
2. Do choroid plexus tumors of the lateral ventricle typically present in a certain age group?
3. What about fourth ventricle tumors?
4. What is the typical presenting symptom?
5. How does CPP appear on MRI?
6. What about CPC?
7. How does CPP appear macroscopically?
8. How does CPP appear microscopically?
9. For which antigens is CPP positive by immunohistochemistry?
10. How is atypical CPP defined?
11. What other features may be present in atypical CPP?
12. What would you expect to see in CPC?
13. How does the immunohistochemical profile of CPC differ from CPP?
14. What would EMA and/or CEA positivity suggest in a lesion that appears to be CPC?
15. Which familial syndromes are associated with choroid plexus tumors?
16. What are some of the indicators of poor prognosis?

III. Embryonal Tumors

Basic Concepts

1. True or false: CNS tumors are the most common malignancy of childhood.
2. What risk factors are associated with the development of these lesions?
3. What accounts for the observed increasing incidence of all pediatric brain tumors?
4. What is the WHO grade of all embryonal tumors?
5. What are these tumors composed of?
6. True or false: These lesions tend to disseminate through the subarachnoid space.
7. Despite recent discoveries of differences in the molecular biology of these tumors, why are they all still treated similarly?
8. What is Collins's rule?

Medulloblastoma

1. Name the embryonal tumor of the cerebellum for which preterm children are at increased risk.
2. Has any other etiology been definitively established?
3. For over 75 years, the histogenesis of medulloblastoma has been controversial. What are the two major hypotheses entertained today?
4. What are the strengths of the external granular layer hypothesis?
5. What are the strengths and weaknesses of the PNET concept?
6. What “dual origin” hypothesis may be most likely?
7. What is the typical age at presentation?
8. Where does it most commonly occur?
9. What are the usual presenting signs and symptoms?
10. What is a possible mechanism by which vomiting might temporarily relieve the headache associated with posterior fossa tumors?
11. How does medulloblastoma typically appear on CT and MRI?
12. In adults with lesion of the peripheral cerebellar hemisphere, how might it appear?
13. What does a “grape-like” pattern seen on MRI indicate?
14. What proportion of patients demonstrate CSF-borne metastasis at initial presentation?
15. What are the major histopathological features of medulloblastoma?
16. What are the unique microscopic features of the large cell variant of medulloblastoma?
17. What is the prognostic significance of this variant?
18. What is the role of apoptosis in medulloblastoma?
19. To which antigens may medulloblastoma be immunoreactive?
20. With what genetic syndromes has medulloblastoma been associated?
21. What is the most common cytogenetic abnormality in this tumor?
22. What genetic changes are associated with poor prognosis?
23. Is there any marker of good outcome?
24. Which signaling pathways may play a role in the development of medulloblastoma?
25. Discuss the role of PTCH in the Hedgehog pathway.
26. What is the significance of APC in the Wnt pathway?
27. How does the Notch pathway contribute to medulloblastoma?
28. What clinical criteria are consistent with a poor prognosis?
29. What is the role of surgery in treating medulloblastoma?
30. Does every patient with medulloblastoma require an EVD prior to surgery, regardless of the amount of hydrocephalus visualized?
31. What is the role of lumbar puncture?

32. When is the best time to perform LP?
33. What is the typical role of adjuvant chemotherapy in the treatment of medulloblastoma?
34. What is the optimal dosage of radiotherapy for treatment?

IV. Brain Metastases

1. What is the most common intracranial tumor?
2. Roughly what percentage of cancer patients demonstrate CNS metastasis at autopsy?
3. What are the three most common tumors that metastasize to the CNS?
4. Which lesion is positive for S-100, HMB-45, and microphthalmia transcription factor?
5. Which other tumor types would you also strongly consider in a patient with CNS metastases?
6. Which of these tumors would you expect to produce multiple CNS lesions?
7. Which primaries typically cause single CNS metastasis?
8. In approximately 80% of cases, the primary tumor is discovered before the metastasis. Name the primary tumor that is most likely to be discovered as CNS metastasis before it is found in its primary location.
9. What is the most common location for brain metastasis?
10. What is the overall pattern that metastases follow?
11. Would you expect to find metastasis in a watershed region?
12. Which tumors tend to spread via venous routes?
13. What is leptomeningeal carcinomatosis?
14. Which neoplasms most commonly cause this phenomenon in adults?
15. Which neoplasms are most commonly responsible for brain metastases in children?
16. What is the preferred method of neuroimaging for visualizing CNS metastases?
17. How does the appearance of metastases typically differ from primary brain tumor?
18. What is the complication of metastatic brain cancer that most commonly requires treatment?
19. What is the preferred treatment?
20. Is this a long-term solution?
21. Should asymptomatic patients be given steroids?
22. What about long-term anticonvulsants?
23. In which patients is biopsy indicated?
24. What is the median survival in untreated CNS metastasis?
25. What are the three mainstays of treatment for cerebral metastasis?

26. Who qualifies for radiation therapy?
27. What improvement in outcome may be expected with radiation therapy?
28. What is the standard dose?
29. What are the downsides of radiation?
30. When is radiosurgery indicated?
31. In a metastasis that could be treated by open surgery or radiosurgery, which is the better option?
32. What is the primary goal of open surgical resection in the management of brain metastasis?
33. What are its other benefits?
34. Why are solitary brain metastases more commonly removed than multiple metastases?
35. What are the general contraindications to open surgical resection?
36. What is an absolute exception to those guidelines?
37. Are chemotherapeutic agents that are effective against primary solid tumors also useful against brain metastases?
38. Why not?
39. Tumors arising from which primary origin are most likely to respond to chemotherapeutic agents?
40. What “last-ditch” agent is currently showing some promise in ongoing research?

V. CNS Lymphoma

1. What virus is most responsible for the increase in incidence of primary CNS lymphoma?
2. What is the other major cause of the increase in incidence of primary CNS lymphoma?
3. What other virus is associated with an increased risk of CNS lymphoma?
4. Which congenital immunodeficiencies are associated with an increased risk?
5. What other class of disease predisposes patients to developing CNS lymphoma?
6. How can CNS lymphomas be differentiated pathologically as primary or secondary?
7. The majority of primary CNS lymphomas are derived from what cell lineage?
8. Which immunohistochemical markers may be helpful in identifying these lesions?
9. If the lesion showed scattered large cells that were CD15+ and CD30+ in a mixed inflammatory background, what diagnosis would you give?
10. What gross findings would you expect to see in a primary CNS lymphoma?
11. What microscopic findings would you expect?

12. Is perivascular or leptomeningeal involvement significant for prognosis?
13. What is the typical 5-year survival rate of these lesions?
14. True or false: Primary CNS lymphoma is highly radiosensitive.
15. What is the recommended dose?
16. Is surgical resection a useful treatment?
17. What about chemotherapy?
18. What are the pros and cons of corticosteroids?
19. Why is methotrexate more efficacious than cyclophosphamide?
20. What is a danger of using methotrexate?
21. What is one method for avoiding this complication?
22. How can chemotherapy efficacy be optimized?
23. What trend for treatment is currently being studied?

Brain Tumors

Answers

I. Tumor Markers

1. Glial fibrillary acidic protein (GFAP).
2. Embryonal carcinoma, yolk sac tumor.
3. Chromogranin, synaptophysin.
4. Carcinoma, craniopharyngioma, chordoma, epithelial cysts.
5. Carcinoma, meningioma, epithelial cysts, ependymoma (along luminal surfaces and dot-like staining of cytoplasmic vacuoles).
6. HMB-45 (human melanoma black-45), S-100 (100% soluble in ammonium sulfate at neutral pH), Melan-A/ Mart-1 (melanocytic antigen recognized by cytotoxic T lymphocytes from melanoma patients), MITF (microphthalmia transcription factor, a nuclear stain).
7. Glioma, primitive neuroectodermal tumor (PNET), schwannoma, neurofibroma, chondroma, chordoma.

II. Primary Tumors

Low-Grade Gliomas

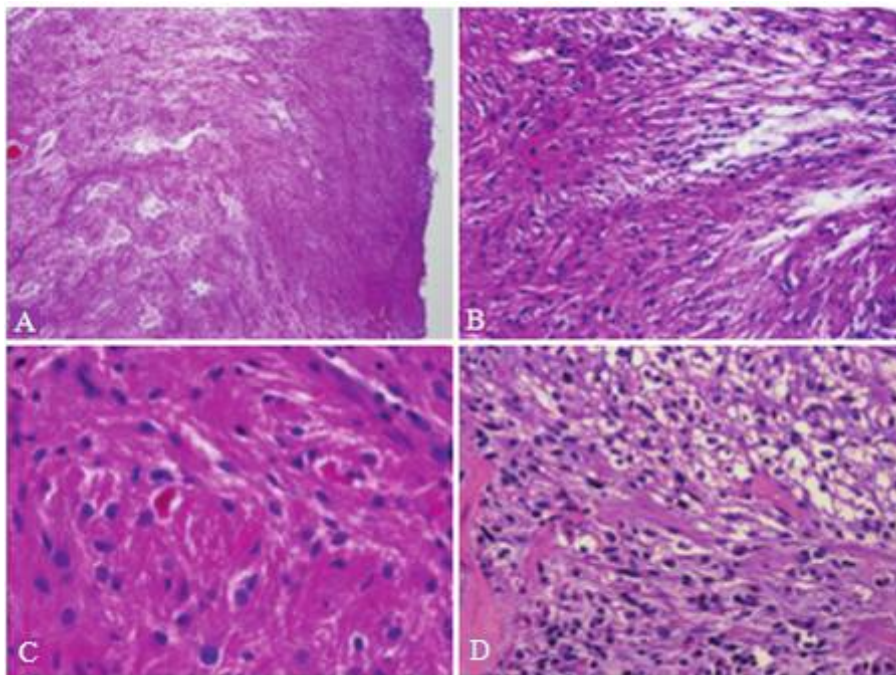
Basic Concepts

1. Astrocytes > oligodendrocytes > ependymal cells.
2.
 - Astrocytoma (grades I and II)
 - Oligodendroglioma
 - Mixed oligoastrocytoma
 - Miscellaneous (pleomorphic xanthoastrocytoma, ganglioglioma, and other glioneuronal tumors).
3. These tumors all tend to have distinct radiological appearance and they may be completely resected (though serial follow-up is still indicated as they may recur).

Low-Grade Astrocytoma

1. Loss of sex chromosome or p53 (17p).
2. Pilocytic astrocytoma.
3. Slow growing, well-circumscribed, variably enhancing grade I lesion.
4. True.

5. Well-circumscribed, with a variably enhancing solid component (94% enhance), either with microcysts or predominantly cystic with a mural nodule; the majority are periventricular.
6. Yes; pilocytic astrocytoma will enhance on both CT and MRI.
7. Children and young adults (first two decades of life).
8. Cerebellum (67%).
9. Focal neurological deficits or nonlocalizing signs such as macrocephaly, headache, endocrinopathy, increased ICP.
10. No, because the cerebral cortex is seldom involved.
11. A biphasic (loose and compact) tissue pattern, with astrocytes that have elongated nuclei and thin bipolar processes. Rosenthal fibers, eosinophilic granular bodies, hyaline droplets, microcysts, and areas with regressive changes (degenerating nuclei, hyalinized blood vessels) may be seen. Mitotic figures are rare.

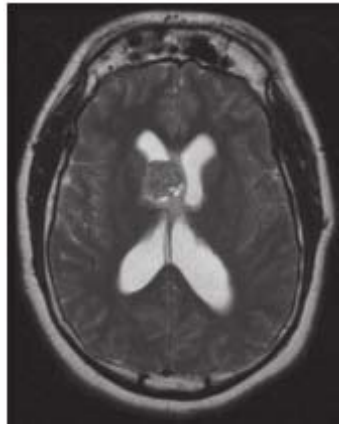


Pilocytic astrocytoma shows a biphasic pattern at low magnification (A), with areas showing cystic change. Piloid astrocytes show elongated nuclei and bipolar processes (B). Rosenthal fibers seen in compact areas (C). Areas may also show oligodendroglia-like morphology (D).

12. No and no. Though they may be helpful in diagnosis, they are not required, and they may be found both in other neoplastic processes (ganglioglioma) and in chronic reactive gliosis.

13. Yes
14. This phrase describes the circumferential location of nuclei in large/giant degenerating cells.
15. False; unlike diffuse astrocytomas, pilocytic lesions lack p53 involvement and instead exhibit increased immune response genes and aberrant neurogenesis. Recently, *BRAF* mutations have been strongly associated with PA.
16. No. NF1-associated lesions show loss of normal NF1 expression and constitutive RAS (RAt Sarcoma protein) activation resulting in downstream mTOR (mammalian Target Of Rapamycin) hyperactivity. Sporadic lesions do not show loss of NF1 expression; they may even show NF1 hyperexpression.
17. More than 95% of patients have a 25-year survival rate if the enhancing portion of the tumor is totally resected.
18. Regressive/degenerative rather than anaplastic change.
19. No, even with malignant transformation, the prognosis is not necessarily poor, so the term *anaplastic pilocytic astrocytoma* is preferred.
20.
 - Grade II tumor
 - Histological differences
 - Age at presentation (younger in pilomyxoid)
 - No association with NF1
21.
 - Prominent myxoid/ mucoid matrix
 - Monomorphous cells that are angiocentric (may resemble pseudorosettes)
 - Absence of Rosenthal fibers and eosinophilic granular bodies
 - Mitotic figures may be present.
22. Mean age 18 months, but it can occur in older children.
23. More likely than pilocytic astrocytoma to recur locally and/or have cerebrospinal spread.

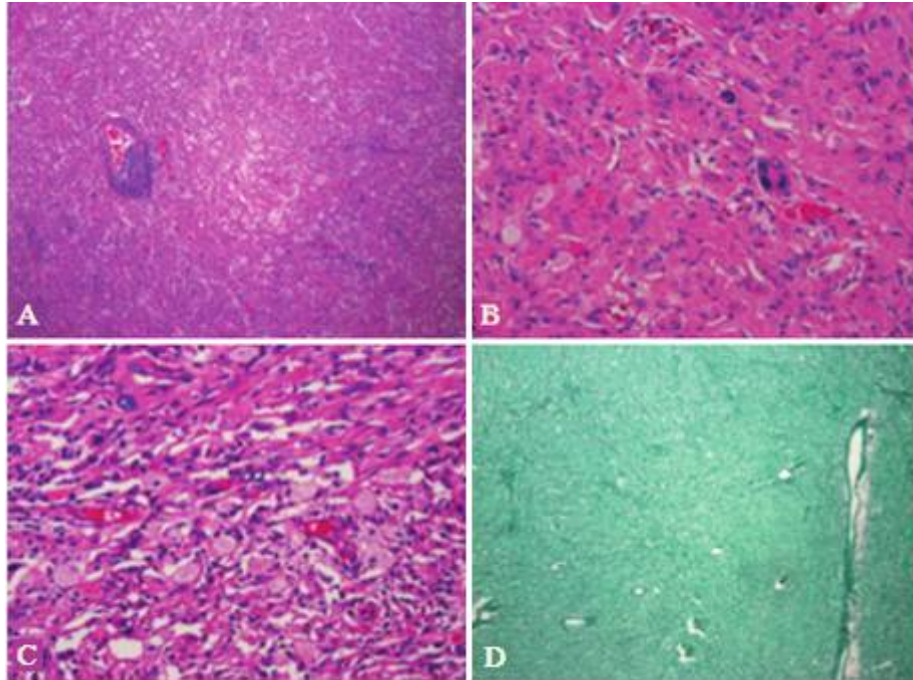
24. Because the tumor may occasionally phenotypically convert to a typical pilocytic astrocytoma.
25. Subependymal giant cell astrocytoma (SEGA); incidence of 6 to 14% in patients with tuberous sclerosis.



MRI T2-weighted axial image demonstrating SEGA at the level of the foramen of Monro.

26. This is debatable. SEGA is one of the major diagnostic criteria for tuberous sclerosis.
27. Yes, though it most commonly occurs during the first two decades of life.
28. Either with worsening epilepsy or signs of increased ICP (due to obstructive hydrocephalus).
29. From the subependymal hamartomas of tuberous sclerosis along the surface of the lateral ventricles.
30. Yes.
31. Pleomorphic xanthoastrocytoma (PXA) (called “meningocerebral” due to its arising in the superficial cerebral cortex and often involving meninges).
32. Temporal lobe.
33. <18 years of age; can also occur in adults between 62 and 82 years of age.
34. A long history of seizures.
35. The cells in this tumor have highly variable cytological features.
36. Mono- or multinucleated giant astrocytes with abundant eosinophilic cytoplasm, admixed with spindle cells and xanthomatous cells. Eosinophilic granular bodies and perivascular lymphocyte aggregates are also frequent.

37. Large cells with abundant intracytoplasmic vacuoles due to lipid accumulation.



Pleomorphic xanthoastrocytoma is a solid neoplasm, showing areas of xanthomatous cells as well as perivascular lymphoid aggregates (A). Large cells with multiple nuclei are seen (B), as are smaller spindle-shaped cells (C). Silver stain highlights the abundant pericellular deposition of reticulin fibers (D).

38.

- Pericellular deposition of reticulin fibers (visualized with silver stain)
- Perivascular lymphocyte aggregates.

39. Glioblastoma (GBM)

40. S-100, GFAP, and synaptophysin.

41. PXA is weakly associated with NF1.

42. No. There has been little association with *p53*; the most common chromosomal alteration is -9 (50% of cases).

43. 80% survival at 5 years and 71% at 10 years.

44.

- Complete surgical resection
- Low mitotic index.

45. Diffuse astrocytoma.

46. Fibrillary astrocytoma, as it is the most common histological subtype. Other subtypes recognized by the WHO include gemistocytic and protoplasmic.

47. 10 to 15%

48. 30 to 40 years of age.

49. Supratentorially, in the frontal and temporal lobes.

50.

- Seizures (50%)
- Subtle changes in speech, sensation, vision, or motor function
- Personality changes (if located in frontal lobe).

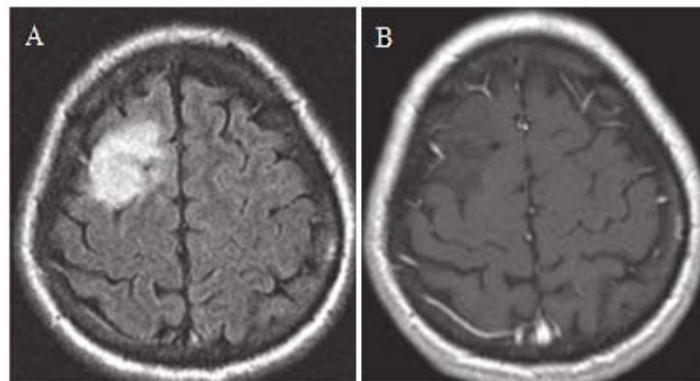
51. Typically as an ill-defined, homogeneous mass of low density without enhancement.

52.

T1: hypointense.

T2: hyperintense.

53. No



Low-grade astrocytoma. (A) FLAIR T2 demonstrates a hyperintense frontal lesion. (B) No enhancement is seen in a T1-weighted postgadolinium image, characteristic of a low-grade, rather than anaplastic, lesion.

54. No, nor is necrosis or microvascular proliferation present. Increased cellularity and nuclear atypia (enlarged, cigar-shaped, or irregular hyperchromatic nuclei) are diagnostic.

55. Yes, and often S-100 positive as well.

56. Typically <4%.

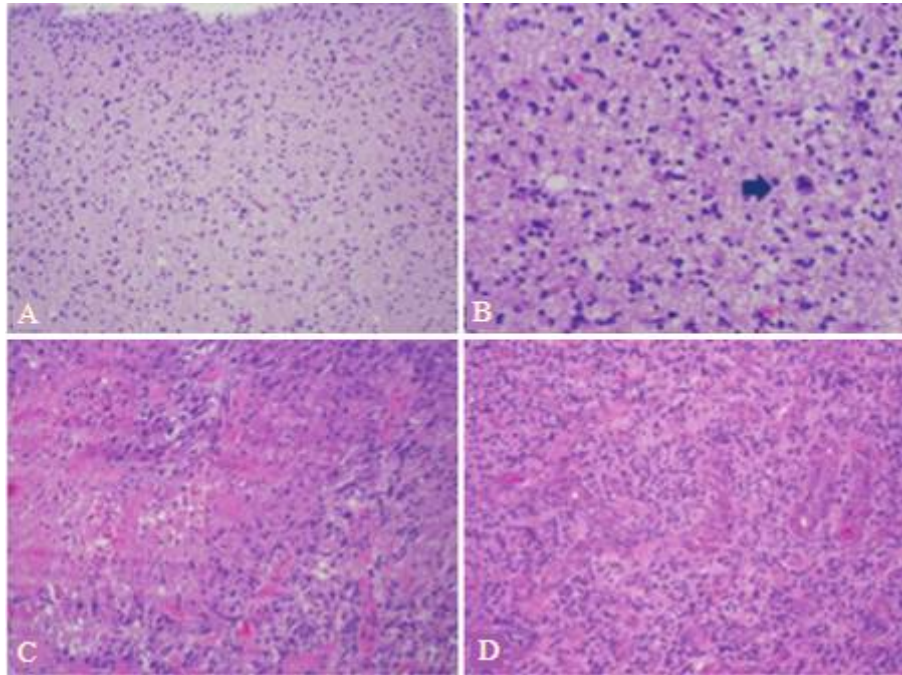
57. >20% of all tumor cells are gemistocytes (usually approximately 35%)

58. Plump, glassy, eosinophilic cell bodies with stout processes; eccentric nuclei, usually with distinct nucleoli.

59. Yes

60. p53 and bcl-2

61. The gemistocytic variety is more prone to progress to anaplastic astrocytoma.
62. *TP53* germline mutations and Li-Fraumeni syndrome.
63. Increased mRNA expression of platelet-derived growth factor receptor- α .
64. No; early detection of p53 changes has not been shown to correlate. However, *IDH1* and *IDH2* mutations may predict a less rapid progression.

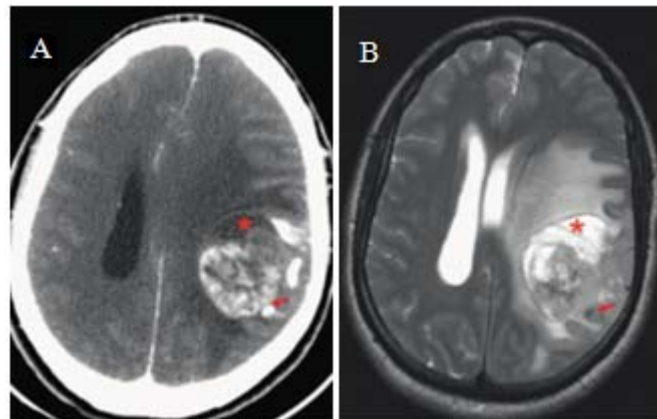


At low magnification, diffuse astrocytomas infiltrate the brain parenchyma, giving it a hypercellular appearance (A). The tumor cells have irregular, elongated or slipper shaped, hyperchromatic nuclei. The presence of mitoses (B, arrow) corresponds to a diagnosis of anaplastic astrocytoma, WHO grade III. The presence of necrosis (often pseudopalisading) (C) and microvascular proliferation (D) is diagnostic of glioblastoma, WHO grade IV.

65. Younger age, smaller tumor, seizure as only presenting syndrome (rather than focal neurological deficit).

Oligodendroglioma

1. Two-thirds of patients present with seizures.
2. True; their risk is approximately 20%.
3. Cortex and white matter of the frontal lobe >temporal lobe > parietal lobe > occipital lobe.
4. CT: hypo- or isodense, well circumscribed, with or without calcification
MRI: T1: hypointense, T2: hyperintense.
5. Intratumoral hemorrhage/cystic degeneration.



Oligodendroglioma. CT with contrast (A) and T2-weighted MRI (B) show a well-demarcated corticosubcortical lesion in the left parietal lobe with a cystic degeneration component (*asterisk*) and calcification (*arrow*). Such extensive edema is typically associated with anaplastic (grade III) oligodendrogliomas.

6.
 - Increased cellularity
 - Uniform, round to oval nuclei in low-grade oligodendrogliomas
 - Tumoral cells may be larger, with eccentric cytoplasm (mini-gemistocytes)
 - Occasional mitoses
 - Microcalcifications

7.
 - Increased nuclear pleomorphism
 - Prominent microvascular proliferation
 - Areas of necrosis, including pseudopalisading necrosis

8.
 - 5-year survival: 71%
 - 10-year survival: 54%

Median survival: 16.3 years.

Most studies suggest a more favorable prognosis with oligodendroglioma than with diffuse astrocytoma.

Oligoastrocytoma

1. A diffusely infiltrating glioma that is a mix of cells resembling both oligodendroglioma and diffuse astrocytoma.
2. II
3. 35- to 45-year-old man (though there is only a slight male predominance)
4. Yes; JC virus sequences have been detected in human oligoastrocytomas, but a definitive link between the two has yet to be found.
5. 6.3 years.
5-year survival: 58%,
10-year survival: 32%.
Better prognosis associated with loss of 1p/19q (as with pure oligodendroglioma).

High-Grade Glioma

Basic Concepts

1.
 - Anaplastic astrocytoma (AA)
 - Anaplastic oligodendroglioma (AO)
 - Anaplastic oligoastrocytoma (AOA)
 - Anaplastic ependymoma
 - Glioblastoma (GBM)
2. Histopathological grade, but age at presentation and KPS score are also significant.
3. The Radiation Therapy Oncology Group's scale, which grades patients from I to VI.
4. Preoperative deficit is the best indicator of postoperative outcome, so patients who are already significantly affected are less likely to have good postoperative course.
5. It remains the most effective adjuvant available.

6. 180 cGy fractions to a total dose of approximately 60 Gy to treat the bulk tumor plus the margin of increased T2 signal.

7.

- Response rates are on the order of 30 to 40%.

Overall, survival has been shown to increase by a few months.

- PCV therapy (procarbazine, chloroethylcyclohexyl-nitrosourea [CCNU], and vincristine) is useful for AO and AOA, especially lesions with deletion of 1p or 19q.

- Temozolomide is an oral chemotherapeutic agent that has been shown to increase survival when used as an adjuvant in high-grade glioma treatment.

- Interferon therapy is currently under trial and has shown promising phase 1 results when combined with temozolomide in the adjuvant treatment of high-grade glioma.

8.

- Temozolomide is an oral alkylating agent that acts as an MGMT (O⁶-methylguanine-DNA methyl-transferase) inhibitor.

- It is FDA approved in initial relapse of anaplastic astrocytoma that had been treated with nitrosourea or de novo GBM.

- It is now the standard of care to use this agent as adjuvant in recurrent high-grade gliomas.

- Off label use includes newly diagnosed AA, progressive low-grade astrocytomas, and oligoastrocytomas.

Anaplastic Astrocytoma

1. Yes, it may progress from a diffuse astrocytoma or arise de novo.

2. III

3. Typically mid-40s

4. Diffuse astrocytoma, in terms of localization, clinical signs and symptoms (though it may follow a more rapid course of progression), and histology

5. Increased cellularity, distinct nuclear atypia (variation in nuclear size and shape and increasing nucleolar prominence), and mitotic activity.

6. 5 to 10%

7.

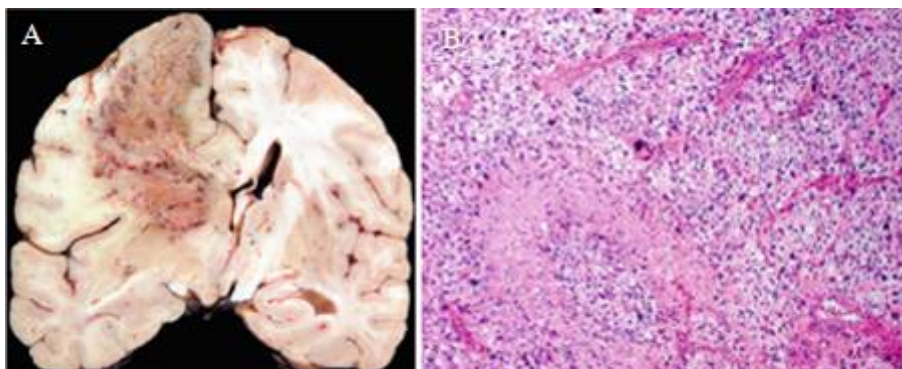
- High frequency of *p53* mutation/loss of 17p

- Unlike diffuse astrocytoma, loss of 19q

8. Likely progression to GBM (over an average of 2 years).

Glioblastoma (GBM)

1. Cerebral hemispheres: temporal > parietal > frontal > occipital.
2.
 - Basal ganglia and thalamus
 - Brainstem (“malignant brainstem glioma”)
3.
 - Anaplastic glial cells
 - Microvascular proliferation
 - Necrosis
4. Morphological findings due to interaction between glioma cells and host brain structures (e.g., subependymal region), around neurons and blood vessels, aka “satellitosis,” or in the subpial zone of the cortex. They exemplify the infiltrative nature of gliomas.
5. 15 to 20% by Ki-67/MIB-1 labeling.
6.
 - Vessel co-option
 - Classic angiogenesis
 - Vasculogenesis (homing of blood marrow cells that encourage growth)
7. Hypoxia, via intracellular stabilization of the hypoxia regulating gene hypoxia-inducible factor 1 α (HIF-1 α), which activates >100 genes that control angiogenesis.
8. Vascular endothelial growth factor (VEGF) is produced by hypoxic perinecrotic palisading cells to increase angiogenesis, vascular permeability (edema), and homing of bone marrow–derived cells.
9. Pseudopalisading pattern, which is equally common in primary and secondary lesions. These cells have high rates of apoptosis, low rates of proliferation, and strong expression of HIF-1 α and VEGF.



(A) Large glioblastoma with mass effect. (B) Histological section (H&E stain) of glioblastoma with pseudopalisading necrosis (*lower left*) and microvascular proliferation (*upper right*).

10.

- Loss of heterozygosity (LOH) of chromosomes 10q (63–70% of first-degree and second-degree GBM) and 17p
- *EGFR* (epidermal growth factor receptor) amplification/overexpression.

11. Secondary GBM (>65%). It is almost always present in precursor lesions as well. Only about a quarter of primary lesions have associated p53 mutations.

12.

- IDH mutations
- LOH 19q (54% vs. 6%)
- LOH 22q (82% vs. 41%)

13. No, there have been no reported cases of anyone <35 years of age with *EGFR* changes in GBM. The amplification is more associated with primary disease (36% vs. 8% in secondary).

14.

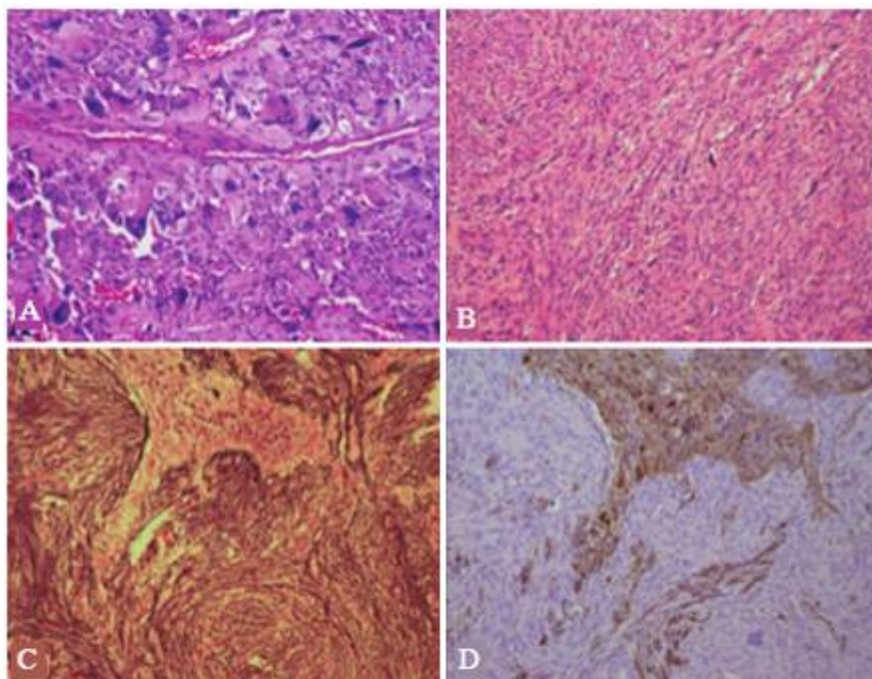
- Mutation of *PTEN*, a tumor suppressor gene (25% vs. 4%)
- Deletion of *p16^{INK4a}*, a negative inhibitor of mitosis progression from G1 to S phase (31% vs. 19%).

15.

Typically de novo development:

- High frequency of *p53* mutations (approximately 40%) in older children
- Low frequency of *p53* mutations in children <3 (12%)
- Absence of *IDH* mutations
- Low frequency of *EGFR* amplification (6%), *p16^{INK4a}* deletion (19%)

16. Giant cell glioblastoma.



GBM variants. (A) Giant cell glioblastoma can be distinguished from PXA by the presence of frequent mitoses, microvascular proliferation and tumor necrosis. (B) Gliosarcoma is composed of malignant spindle cells admixed with conventional GBM. (C) Silver stain highlights pericellular reticulin deposition in the spindle cell areas, and is negative in the area of conventional GBM. (D) Immunostain for GFAP, in contrast, is positive in the areas of conventional GBM and is negative in the spindle cells.

17.

- Bizarre, multinucleated giant cells
- Often abundant reticulin network
- Frequent *p53* mutations and *PTEN* mutations

18. Gliosarcoma

19. GFAP-negative, clearly malignant mesenchymal component, with abundant pericellular reticulin deposition. The malignant astrocytic component is GFAP-positive.

20. Gliofibroma is a variant that mostly affects children (mean age = 14 years) in the cerebrum or spinal cord comprising a glial component and a non-sarcomatous fibroblastic component. This lesion often lacks necrosis and vascular microproliferation. It often follows an indolent course and thus has a much more favorable outcome than GBM.

21.

- Turcot syndrome
- Li-Fraumeni syndrome
- NF1
- Multiple enchondromatosis

22.

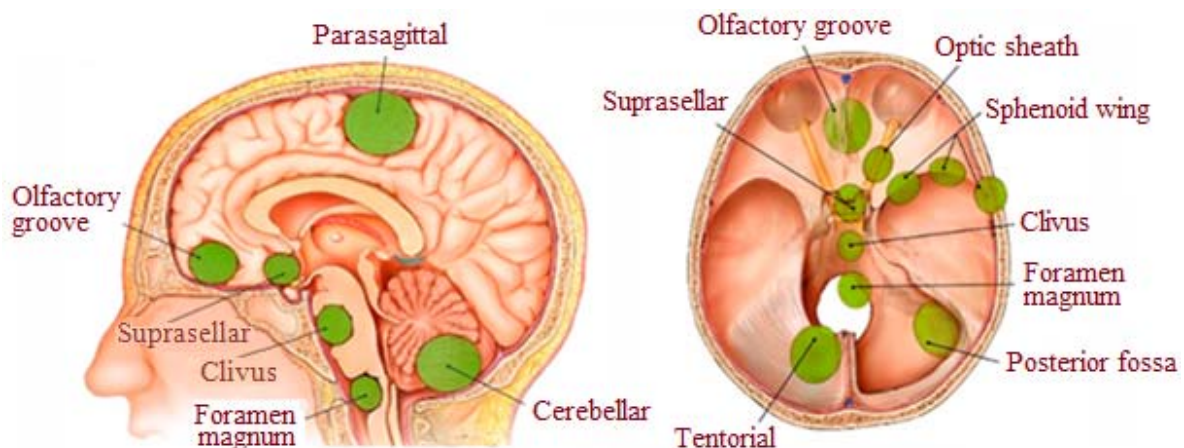
- Poor delivery of chemotherapeutic agents due to the blood–brain barrier
- Genomic instability resulting in heterozygous cell population that is difficult to treat with a single agent
- Invasiveness of the tumor (ability to cross midline and intact blood–brain barrier)
- Neural-stem-cell–like cells that may harbor resistance mechanisms
- Retention of DNA repair machinery that makes chemotherapy and radiotherapy less effective

23. Rapid invasion of the lesion through the corpus callosum into the contralateral hemisphere.
 24. False, though peritoneal metastasis via VP shunt has been seen, invasion of the dura, bone, vessel lumen, and venous sinus are all exceptional.
 25. They are areas of liquefactive tumor necrosis as opposed to retention cysts.
 26. Mean age for secondary (having progressed from a lower grade astrocytoma) GBM is 45, approximately 10 years younger than for primary GBM.
 27. Younger patients have a better life expectancy; it is not fully understood if age alone or the secondary nature of these tumors confers a survival advantage (7.8 months vs. 4.5 months).
28. Primary (approximately 90%)
 29. With the exception of loss of heterozygosity of 10q, the lesions have different genetic profiles and they differ in response to therapy.

Meningiomas

1. Meningioma. Incidental meningiomas are found at autopsy in 3% of those over 60 (in 2.3% of autopsy patients overall).
2. A neoplasm arising from arachnoid cap cells (specialized cells of arachnoid granulations) within the leptomeninges.
3. About 94% are WHO grade I, but there are atypical (approximately 5%) meningiomas corresponding to WHO grade II and anaplastic meningiomas (approximately 1%) that correspond to WHO grade III.

4.



- Cerebral convexities (especially parasagittal, in association with the falx and venous sinus) (44%)
- Sphenoid ridges (11.9%)
- Olfactory grooves (9.8%)
- Optic nerve sheath
- Para/suprasellar regions
- Petrous ridges
- Posterior fossa
- Thoracic spine

5. Increases with age; most common in middle-aged and elderly, peaking in the sixth and seventh decades.

6. Yes, women are more affected than men, particularly spinal meningiomas. However, atypical meningiomas are more prevalent in men.

7. Yes, though rarely. Pediatric meningiomas are more likely to be intraventricular and aggressive than are adult lesions. Meningiomas associated with hereditary tumor syndromes (e.g., neurofibromatosis) also occur in younger patients.

8. Probably not. Though anecdotal evidence suggests a higher incidence of meningiomas in trauma patients, a systemized review found that this phenomenon is probably due to a higher rate of detection of asymptomatic “incidentalomas.”

9. Yes. Both low- and high-dose radiation have been linked to meningiomas (latency to tumor ranges from 19 to 35 years, inversely related to the dose of radiation). Radiation-induced meningiomas more commonly occur among younger patients, are multifocal, and are higher grade.

10. No; less than 10% of meningioma patients exhibit multiple lesions. The incidence of multiple lesions is higher in patients with familial syndromes (NF-2) and secondary to high-dose irradiation.

11. Because historically only those that were symptomatic were detected, whereas in the past 20 years, imaging studies have increased the finding of asymptomatic “incidentalomas”.

12. Measuring the doubling time of residual tumor volume (Td) after resection, with or without bromodeoxyuridine (BUdR) or K_I-67 labeling. Magnetic

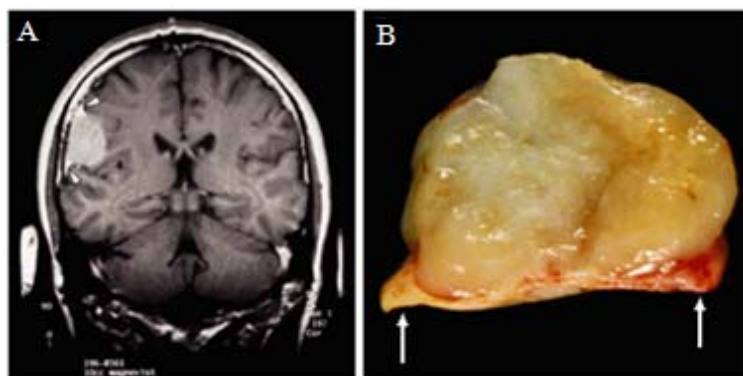
resonance spectroscopy (MRS) is also being investigated as a potential noninvasive means of assessment.

13. MRI, with and without gadolinium, to determine the full extent of lesion and associated edema.

T1: most lesions are isointense (or slightly hyperintense)

With contrast: dramatic enhancement, especially of the “dural tail”

T2: hyperintense or isointense.



A. The meningioma uniformly enhances and has distinct dural tails (white arrows). Notice how the brain shows almost no mass effect and only minimal edema around the tumor. B. An intact tumor has a similar dural tail (white arrows). The nodular growth of this meningioma is typical and reminiscent of a uterine fibroid.

14. CT is better for demonstrating calcification within the lesion as well as hyperostosis in the adjacent part of the skull.

15.

- Meningothelial
- Fibrous
- Transitional

16. Lobules of tumor cells may be demarcated by thin collagenous septa (large lobules should not be confused with the “sheeting” of atypical meningioma). Whorls and psammoma bodies may be present, but tend to be poorly formed. Groups of uniform epithelioid cells appear syncytial, with indistinct cell borders. Nuclei have delicate chromatin and occasional central clearing or intranuclear cytoplasmic pseudoinclusions.

17. Spindle-shaped cells in a collagen-rich matrix with infrequent whorls, psammoma bodies. Focal groups with meningothelial-type nuclei are present.

18. Tight whorls, psammoma bodies, and a coexistence of meningothelial and fibrous patterns.
19. A meningioma with more psammoma bodies than tumor cells. These may become confluent, forming irregular calcified masses or bone. They are commonly found in the thoracic spinal region of middle-aged women.
20. These lesions feature more blood vessels than tumor cells. Most of the vessels are small with markedly hyalinized walls. Degenerative nuclear atypia is seen commonly. Though not an aggressive lesion, adjacent cerebral edema may be marked.
21. Pseudopsammoma bodies (lobules containing PAS-positive, eosinophilic secretion within intracellular lumina. These cells are immunoreactive for CEA (carcinoembryonic antigen).
22. Deletion of band q12 on chromosome 22, which occurs in approximately half of the cases.
23.
 - Clear cell meningioma
 - Chordoid meningioma
 - Atypical meningioma
24. Composed of clear, polygonal cells with glycogenrich cytoplasm and prominent collagen. This variant is PAS-positive and has diastase-sensitive cytoplasmic clearing because of its glycogen accumulation.
It is found in the cerebellopontine angle and cauda equina region, frequently in children and young adults. It frequently recurs, and may have CSF seeding.
25. A tumor resembling chordoma, with cords of eosinophilic, vacuolated cells in an abundant mucoid matrix background. These groups are frequently interspersed with more typical meningioma. It is typically a large, supratentorial tumor that recurs frequently after subtotal resection.
26. Increased mitotic activity (4+ mitoses/10 high-power fields) and/or brain invasion, and/ or three or more of the following features: increased cellularity, high nuclear/cytoplasmic ratio, prominent nucleoli, patternless/sheet-like growth pattern, and foci of necrosis.

27.

- Papillary meningioma
- Rhabdoid meningioma
- Anaplastic (malignant) meningioma.

28. A rare variant with a perivascular pseudopapillary pattern and a 50% mortality rate; 75% of these lesions have local brain invasion: 20% metastasize (mostly to the lungs), and 55% recur. This variant is frequent in younger patients, including children.

29. Also a rare variant composed of sheets of rhabdoid cells (plump cells with eccentric nuclei that contain intermediate filaments within the cytoplasm) with a high proliferative index.

30. Obvious malignant cytology resembling carcinoma, melanoma, or high-grade sarcoma or a markedly elevated mitotic index (20+ mitoses/10 high-power fields). Median survival with this subtype is less than 2 years.

31. No

32. Chromosomes 1p, 10, and 14q.

33. NF2 > rare tumor syndromes (Gorlin, Werner, Cowden) > familial history of benign brain tumors, melanoma, or breast cancer.

34. Vimentin, epithelial membrane antigen, progesterone receptor.

35. These lesions tend to be lower grade and smaller (and thus have a better prognosis) than those that lack progesterone receptors.

36.

- Observation
- Surgery
- Radiation alone
- Adjuvant radiation following surgery

37.

- Those with <10 to 15 years of life expectancy
- Those with small lesions, minimal/no symptoms, and little to no edema
- Skull base or difficult to access meningiomas (especially those that are small and/or cause few symptoms)

For all of the above, ensure patients will comply with serial radiographic and neurological follow-up.

38. In certain cases, yes.

- Dexamethasone is started for patients with significant peritumoral edema.
- Anticonvulsants are started preoperatively only in patients who have had seizure events.

39. Extent of initial resection, as proposed and stratified by Simpson in 1957 and confirmed by more recent series.

Simpson's classification:

Simpson Grade	Completeness of resection	10-year recurrence
Grade I	Complete removal including resection of underlying bone and associated dura	9%
Grade II	Complete removal with coagulation of dural attachment	19%
Grade III	Complete removal without resection of dura or coagulation	29%
Grade IV	Subtotal resection	44%
Grade V	Simple decompression with or without biopsy	100%

40.

- Optimal patient positioning and surgical approach
- Early tumor devascularization
- Internal decompression or extracapsular dissection
- Early localization and preservation of adjacent neurovasculature
- Removal of involved bone and dura

41.

- Preoperative endovascular embolization
- Coagulation of dural feeding vessels before opening dura in superficial tumors
- Circumferential durotomy before beginning tumor removal
- Appropriate choice of approach for meningiomas in other locations

42. These techniques allow for the arachnoid to be separated gently from the tumor capsule, thus protecting the brain from surgical trauma.

43. False; thus, no vessels coming directly off the ICA, basilar artery, or vertebral artery should be coagulated.

44.

- MRI to confirm total resection

- Follow-up MRI every 1 to 3 years depending on Simpson grade I or II resection
- Annual follow-up MRI for subtotal resection
- Adjuvant radiotherapy/radiosurgery PRN if there is clinical or radiographic tumor.

45.

- Follow-up MRI every 6 months for the first 2 years
- As with benign lesions, adjuvant radiotherapy/radiosurgery PRN if there is clinical or radiographic progression of the tumor.

46. Many argue that a dose of 6000 cGy is appropriate immediately after operation, regardless of the extent of resection, due to high rates of recurrence.

47. It is still controversial. Side effects are being reduced through more directed, sophisticated delivery mechanisms (e.g., gamma knife, brachytherapy, intensity-modulated radiation therapy, and 3D-conformal radiotherapy), but many argue that these risks are still serious enough to reserve radiotherapy for tumors that recur. More studies are necessary before a definitive conclusion may be made, but the rule of thumb seems to be:

- Surgery for accessible, benign lesions
- Radiotherapy alone for surgically inaccessible lesions
- Low threshold for adjuvant radiotherapy in resected atypical lesions
- Adjuvant radiotherapy in malignant lesions.

Pineal Region and Intraventricular Tumors

Basic Concepts

1. They present with symptomatic hydrocephalus.
2. Urgent treatment is often needed, regardless of whether the lesion is benign or malignant.
3. Paralysis of upward gaze and convergence due to compression and invasion of the midbrain tectum.
4. Angiography allows for the visualization of the deep venous system in especially large or highly vascular lesions.
5.
 - MRI of the spinal axis (postcontrast sagittal view)
 - Lumbar puncture

- Serum measurement of α -fetoprotein (AFP), β -human gonadotropin (β -HCG), placental alkaline phosphatase (PLAP), and carcinoembryonic antigen (CEA).

6.

- Primarily surgical resection, which can be difficult given the location of these lesions
- Biopsy followed by radiation therapy.

7.

- Approaches in the sitting position are frequently employed to resect pineal region tumors such as:
 - Occipital transtentorial approach
 - Supracerebellar infratentorial approach.

8.

- Higher risk of air embolism (have precordial Doppler and central line available)
- Risk of deep venous injury: employ gentle retraction, do not sacrifice important deep veins
- Difficult to access tumor location: have long instruments (bipolar, dissectors), an arm rest, and a good operating microscope.

9. By intermittently obstructing the foramen of Monro.

10.

- Midline transcallosal
- Transcortical (with large ventricles)
- Endoscopic
- Ventriculoperitoneal (VP) shunt (may need bilateral shunts)
- Stereotactic needle biopsy and cyst evacuation.

Ependymoma

1. Subependymoma, which is clinically and biologically distinct from ependymoma, and less likely to grow.
2. 60 to 70% of cases are in the fourth ventricle and 30 to 40% are in the lateral ventricles. Less common sites include the third ventricle, septum pellucidum, and spinal cord.
3. Middle-aged.

4. True. Subependymoma is a very slow-growing intraventricular lesion that may remain clinically silent.
5. Yes, either or both may be present.
6. None has yet been identified.
7. II
8. Around 6 years old (mean age at diagnosis)
Range: 1 month to 81 years.
In adults, infratentorial and spinal ependymomas arise with almost equal frequency, whereas in children infratentorial ependymomas are more common.
9. Yes. Children and adults are similarly affected by supratentorial lesions, and spinal lesions predominately affect adults.
10. Fourth ventricle and spinal cord > lateral ventricle > third ventricle.
11. True (albeit rarely); extraneural ependymoma may be found in the ovaries, the broad ligaments, soft tissues, mediastinum, and sacrococcygeal area.
12. Location-dependent signs and symptoms, which may include hydrocephalus and increased ICP with an infratentorial lesion; ataxia, visual changes, and paresis in a posterior fossa lesions; supratentorial ependymomas may also present with focal neurological deficits and seizures; spinal ependymomas present with motor and sensory deficits.
13. Well-circumscribed lesion with varying degrees of contrast enhancement, frequently accompanied by mass-effects and hydrocephalus/syrinx formation
14. Uniform; round to oval; speckled chromatin gives them a “salt-and-pepper” appearance.
15. Rosettes: true ependymal rosettes and perivascular pseudorosettes.
16.
 - Cellular
 - Papillary
 - Clear cell
17. Conspicuous cellularity with infrequent mitoses. Pseudorosettes are occasionally present; true ependymal rosettes usually aren't seen. More

commonly extraventricular.

18. Typical papillary projections (fibrovascular cores lined by a single layer of cuboidal ependymoma cells, giving them a finger-like appearance). GFAP-positive.
19. Choroid plexus papillomas and metastatic carcinomas also form papillary projections, but they are not as GFAP-positive.
20. Medulloblastoma, which has more mitoses, larger nuclei, and Homer Wright pseudorosettes. It is also positive for synaptophysin.
21. A tumor mostly affecting young patients supratentorially. Cells have oligodendrocyte-like, clear perinuclear halos.

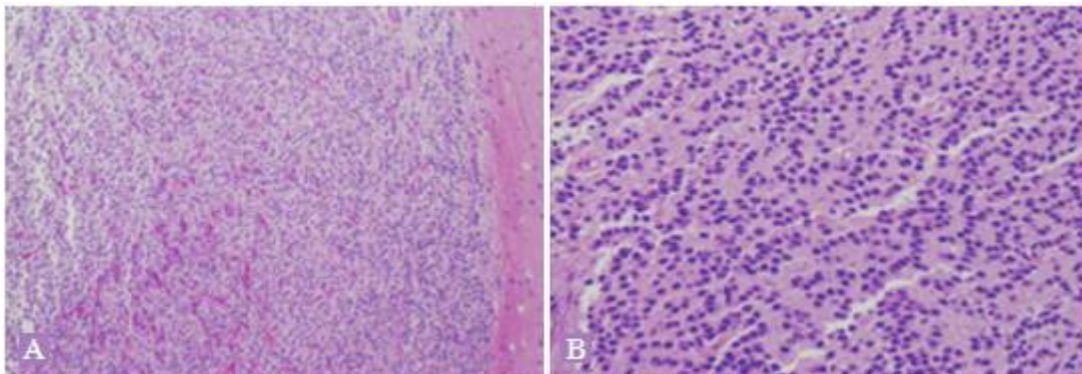
22.

- Oligodendroglioma
- Central neurocytoma
- Clear-cell meningioma
- Pilocytic astrocytoma
- DNT
- Clear-cell carcinoma
- Hemangioblastoma

23.

- Ependymal and perivascular rosettes
- Immunoreactivity for GFAP and EMA
- Ultrastructural studies.

24. No, it is now classified as a central neurocytoma.



(A) Neurocytoma is a solid tumor that is well demarcated from the adjacent brain parenchyma. The cells have round nuclei and may have perinuclear

“halos,” resembling oligodendrocytes. (B) Areas with fine, fibrillary neuropil are characteristic.

25. NF2 (and NF1 to a lesser extent).

26.

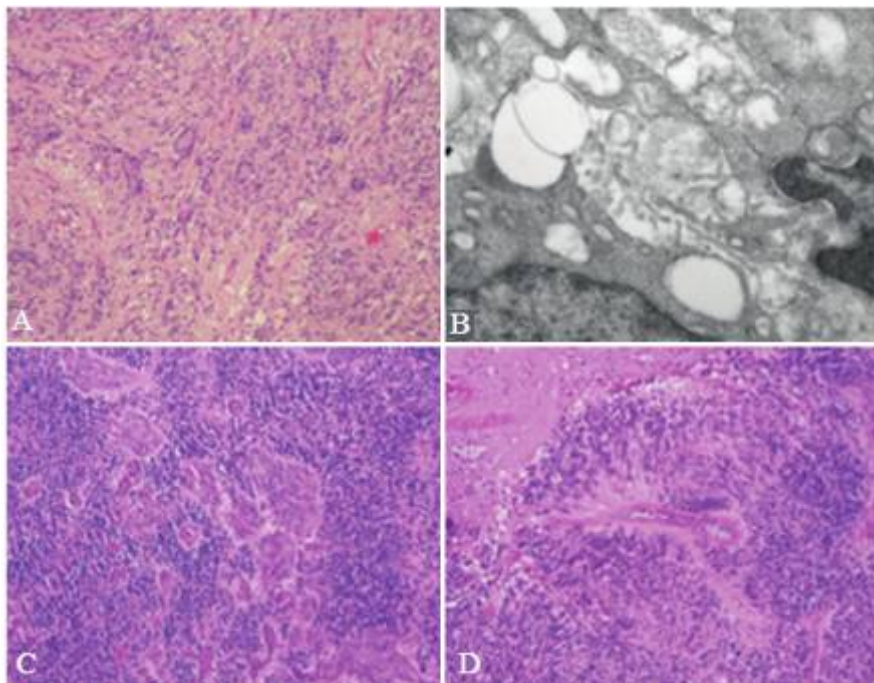
- Loss of, or translocations of, chromosome 22
- Loss of chromosome 9 (supratentorial)
- Gain of 1q in clear cell (versus loss of 1p/19q in oligodendroglioma).

27. Intracranially, most commonly as posterior fossa tumors in children

28. III

29.

- More rapid development
- Earlier presentation with increased ICP
- Contrast enhancement on MRI



(A) Ependymoma showing ependymal canals and perivascular pseudorosettes. (B) On electron microscopy, cilia and microvilli can be seen projecting into the lumina of microrosettes. Anaplastic ependymoma shows increased cellularity, frequent mitoses, microvascular proliferation (C), and may also show areas of necrosis (D).

30.

- Increased cell density
- Poorly differentiated cells
- Brisk mitotic activity
- Microvascular proliferation

- Pseudopalisading necrosis
- Perivascular pseudorosettes
- Less GFAP expression
- No ependymoblastic rosettes
- No embryonal components

31.

- Age <3 years
- Incomplete tumor resection
- CSF metastases.

Choroid Plexus Tumors

1.

- WHO grade I: choroid plexus papilloma (CPP)
- WHO grade II: atypical CPP
- WHO grade III: choroid plexus carcinoma (CPC)

2. Yes; 80% of these lesions present in patients <2 years old. The median age is 1.5 years for lateral and third ventricle CPPs.

3. No, they are evenly distributed across all age groups, with a median age of 22.5 years. Cerebellopontine angle CPPs present at a median age of 35.5 years.

4. Hydrocephalus and raised ICP due to increased CSF production and/or CSF pathway blockage.

5.

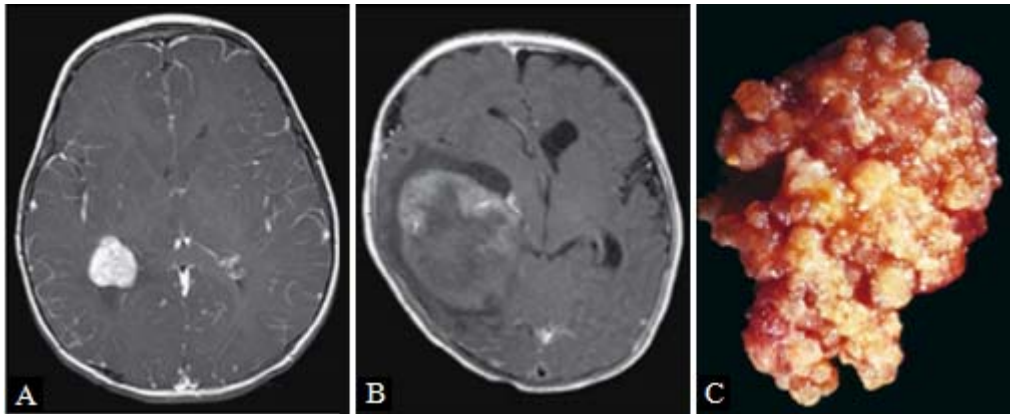
T1: isointense

T2: hyperintense

Irregularly enhancing, typically well-delineated tumor

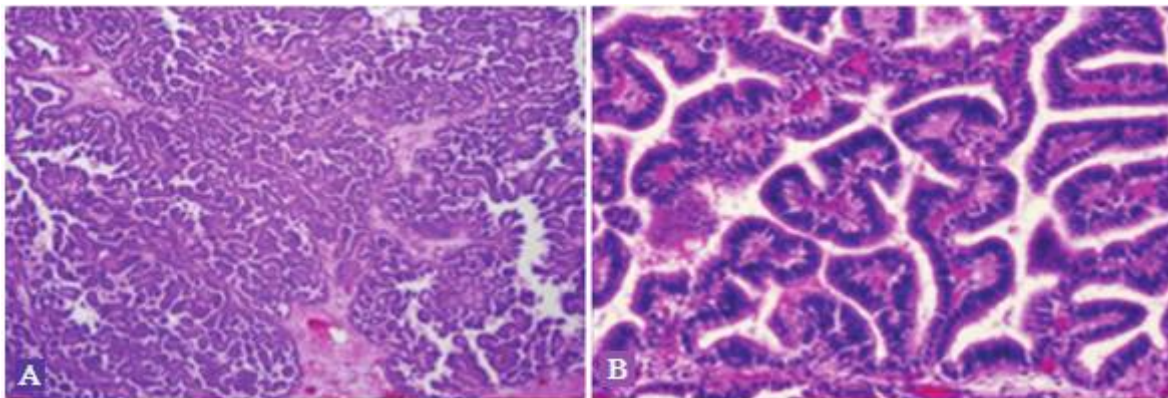
6. Large intraventricular lesion with heterogeneous signal, irregular enhancing margins, edema in adjacent brain, dissemination of tumor, and hydrocephalus.

7. Like a cauliflower!



(A) Contrast-enhanced T1-weighted magnetic resonance imaging (MRI) showing a solid well-demarcated intraventricular choroid plexus papilloma (CPP) with intense enhancement. (B) Contrast-enhanced T1-weighted MRI showing irregularly enhancing large ventricular choroid plexus carcinoma with areas of necrosis, irregular margination, and surrounding edema. (C) CPP with classic cauliflower-like gross appearance.

8. CPP looks much like normal choroid plexus, but cells tend to be elongated or stratified and more crowded. Mitotic activity is very low. Some degenerative features may be present.



(A) Choroid plexus papilloma, showing a papillary architecture on low magnification. (B) The cells lining the fibrovascular cores are more elongated and crowded than normal choroid plexus.

9. Always: vimentin, cytokeratin, podoplanin, INI1 Transthyretin (approximately 70%), S-100 (in 50–95%) and GFAP (25–55%)

10. CPP with increased mitotic activity (2+ mitoses/10 randomly selected high-power fields).

11.

- Increased cellularity
- Nuclear pleomorphism
- Areas of solid growth, with blurring of papillary pattern
- Necrosis

12.

At least four of the following:

- Frequent mitoses (>5 per 10 high-power fields [HPF])
- Increased cellular density
- Nuclear pleomorphism
- Blurring of the papillary patterns with sheets of tumor cells
- Necrosis
- Diffuse brain invasion

13.

- Cytokeratin also expressed
- S-100, transthyretin, and GFAP less commonly expressed
- Epithelial membrane antigen (EMA) typically not expressed

14. That the carcinoma may be of metastatic origin.

15.

- Li-Fraumeni syndrome
- *p53* mutations
- Aicardi syndrome (CPP)
- Rhabdoid predisposition syndrome (atypical teratoid/ rhabdoid tumors)

16.

- Mitoses (two or more per 10 HPF)
- Necrosis
- No immunoreactivity for transthyretin
- Decreased expression of S-100
- Brain invasion

III. Embryonal Tumors

Basic Concepts

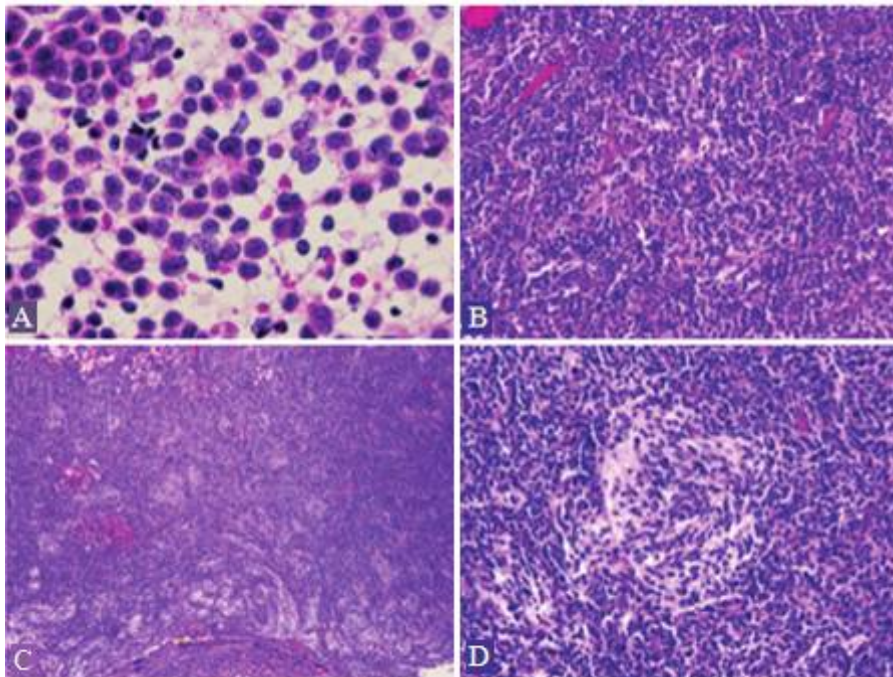
1. False; they are the most common solid tumor but the second-most common malignancy (leukemia being more common).

2. Most cases are sporadic, though familial syndromes (Li-Fraumeni, rhabdoid tumor predisposition syndrome) increase risk, as does previous radiotherapy.
3. Improved diagnostic technologies are thought to be responsible. (Environmental factors have been suggested, but epidemiological data fail to support the hypothesis.)
4. IV
5. Poorly differentiated neuroectodermal cells
6. True; they also tend to recur at the primary site.
7. They have common histological appearance and have traditionally been thought to arise from a common precursor.
8. The period in which an embryonal tumor is most likely to recur is the child's age at diagnosis plus 9 months (e.g., if a child were diagnosed at 24 months, tumor recurrence would most likely be within 33 months).

Medulloblastoma

1. Medulloblastoma
2. No. Studies have suggested polyomaviruses (JC virus, SV40) as potential causes, but these findings have not been reproducible, so their role remains unclear. Another study suggested that maternal folate supplementation may have a protective effect, but again, these findings were not reproducible.
3.
 - Medulloblastoma arises from the **external granular layer (EGL)** of the cerebellum.
 - PNET concept: medulloblastoma arises from the **subependymal matrix cells**.
4.
 - The Sonic Hedgehog morphogenetic gene controls the proliferation of precursor neurons in the EGL.
 - Murine medulloblastoma models have demonstrated the significance of Hedgehog activation.
 - Gene expression patterns in the cerebellar EGL and medulloblastoma are very similar.
5.
 - Subependymal matrix cells, including those in the fourth ventricle, give rise to neuronal and glial cells.
 - Evidence suggests that medulloblastomas (infratentorial PNETs) and supratentorial PNETs show different genetic alterations.

6. That classic medulloblastoma may arise from the ventricular zone and nodular tumors come from EGL cells.
7.
 - Peak: 7 years
 - 70% occur in those under 16 years.
 - Of adult-onset tumors, 80% arise in those of ages 21 to 40 years.
8. 75% arise in the vermis and project into the fourth ventricle. In adults, tumor is more likely to extend laterally.
9.
 - Gait disturbance
 - Truncal ataxia
 - Increased ICP (lethargy, headache, morning vomiting, papilledema, diplopia).
10. Hyperventilation-induced hypocarbia.
11. Dense, intensely contrast-enhancing solid mass.
12. As extra-axial lesions similar to meningioma or Schwannoma.
13. Medulloblastoma with extensive nodularity.
14. About a third.
15. Densely packed cells with round-to-carrot-shaped nuclei and high nuclear/cytoplasmic ratios and high mitotic activity. Homer Wright rosettes and spongioblastic arrangements with parallel arrangement of tumor cell nuclei may be present. Necrosis is not typical, but is often found in a pseudopalisading pattern when present.



(A) Medulloblastoma falls under the morphological category of “small, round, blue cell neoplasms.” Homer Wright rosettes may be seen even on cytological preparations. (B) Histological sections show a densely cellular neoplasm composed of poorly differentiated cells with high nuclear/cytoplasmic ratios, and hyperchromatic, irregular nuclei. (C) Multiple pale “islands” may be seen in

the nodular variant of medulloblastoma. (D) These nodules represent regions of neuronal maturation, with the internodular areas showing features of conventional medulloblastoma.

16. Monomorphic cells with large, round, vesicular nuclei with prominent nucleoli and a variable amount of eosinophilic cytoplasm. The cells lack cohesiveness and have an abundance of mitotic and apoptotic figures. Anaplastic regions may also be present.

17. This variant is associated with higher frequency of metastatic disease.

18.

- Major contributor to cell loss
- Apoptotic indices usually mirror mitotic indices (except in desmoplastic medulloblastomas, which have a low growth fraction)
- Many regulators of apoptosis (Bcl-2, Caspase-8, Survivin, REN [Hedgehog antagonist and tumor suppressor], etc.) are expressed in varying degrees in medulloblastoma.
- “Focal” apoptosis may be associated with better prognosis than tumors exhibiting “diffuse” and/or “extensive” apoptosis.

19. Synaptophysin, class III β -tubulin, neuron-specific enolase, microtubule-associated protein 2, neuronal adhesion molecules, INI1

20.

- Li-Fraumeni syndrome
- Gorlin syndrome/nevoid basal cell carcinoma syndrome (NBCCS)
- Turcot syndrome
- Coffin-Siris syndrome
- Rubinstein-Taybi syndrome
- Wilms' tumor
- Other complex malformations (e.g., omphalocele, intestinal malrotation, bladder exstrophy)

21. Isochromosome 17q (30 to 40% of tumors)

22.

- Loss of 17p
- Amplification of c-myc
- Overexpression of ErbB2

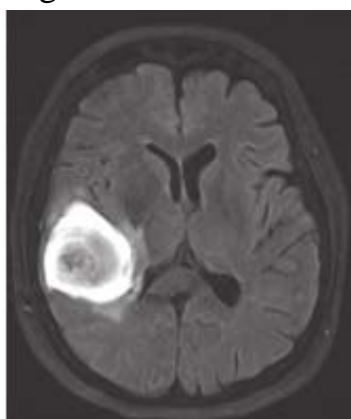
23. Nuclear accumulation of β -catenin, a Wnt gene activation marker.

24. Hedgehog, Wnt, and Notch all play a critical role in the development of the cerebellum among other organs (both cerebral and not).
25. PTCH is an inhibitor of the Hedgehog pathway (inactivating mutations of PTCH have been found in almost 10% of cases; the gene is also altered in NBCCS).
26. APC (of familial adenomatous polyposis fame, known as Turcot syndrome when medulloblastoma is also present) is a negative regulator of the Wnt pathway; missense mutations often occur in sporadic medulloblastoma.
27. Notch2 promotes proliferation of external granular cell layer progenitor cells; elevated levels of signaling have been found in medulloblastoma. γ -secretase inhibitors block Notch signaling and slow the growth of medulloblastoma.
28.
 - Age <3 years
 - Incomplete surgical resection (>1.5 cm remaining)
 - Metastatic disease at presentation.
29. Resection is the mainstay of treatment because it provides immediate relief of symptoms (including hydrocephalus and brainstem compression) and tissue for histological analysis.
30. No. However, up to a third of patients require chronic CSF diversion postoperatively; thus, EVD may be desirable up front, especially if hydrocephalus is present before surgery.
31. Allows for tumor staging (leptomeningeal spread).
32. At time of surgery, after induction of anesthesia but before cranial incision. Remember that avoiding the removal of more CSF than the strictly required for cytology analysis.
33. Studies in the 1970s demonstrated that adjuvant chemotherapy (vincristine + lomustine) in addition to radiation did not improve outcome overall, but showed an advantage in children with brainstem involvement and large tumors or large tumors and subarachnoid metastases.
34. A study in the mid-1980s showed that 3600 Gy improved event-free survival to 67% over 52% with 2300 Gy, yet the higher dose of radiation shows a

greater intellectual morbidity, especially in children younger than 8. Studies are ongoing to improve regimens.

IV. Brain Metastases

1. Metastasis
2. 15 to 30%
3. Lung, breast, melanoma (each of these three is responsible for 10 to 48% of metastases in different series).
4. Malignant melanoma.
5. Renal cell and gastrointestinal carcinoma
6. About half of patients with CNS metastasis have multiple lesions, most commonly with melanoma and lung cancer.
7. Breast, abdominal, and pelvic cancers
8. Lung
9. In the parenchyma at the gray-white junction (supratentorial and frontal or parietal).
10. Hematogenous flow: areas of greater blood flow are more prone to metastases.
11. Yes, this is an exception to the previous rule. Tumor cells may easily lodge in the end vessels of such regions due to the marked change in vessel caliber.
12. Pelvic and retroperitoneal tumors may spread via Batson's plexus (an anastomotic pelvic-vertebral venous plexus).
13. Diffuse spread of metastatic carcinoma to the leptomeninges, seen in approximately 20% of cancer patients.
14. Breast, lung, and melanoma. Testicular cancer may also, albeit rarely
15. Hematological tumors and PNETs.
16. MRI with gadolinium
17. Metastases tend to be discrete, spherical masses that push on the surrounding tissue rather than infiltrating it.



Axial FLAIR sequence demonstrating a hemorrhagic right temporal lobe lesion, which proved to be metastatic melanoma.

18. Cerebral edema.
19. Dexamethasone due to lack of mineralocorticoid effect.
20. No; steroids are only efficacious in the short term. Changes are typically evident within a day and peak within a week.
21. No; they are only indicated for symptomatic patients.
22. No; antiepileptic drugs are indicated only for short-term use postoperatively in high-risk patients (e.g., those with mesial temporal lesions or tumor in the motor strip).
23. Patients with a solitary lesion for whom nonsurgical treatment is planned. Those with multiple lesions do not typically require biopsy (unless no primary lesion is localized on whole body imaging).
24. Approximately 1 month.
25.
 - Radiation (whole brain, local fractionated, or radiosurgery)
 - Surgery (open resection)
 - Chemotherapy
26. Almost all patients with brain metastases, but those who respond best are under 65 with a high Karnofsky performance score and a well-controlled primary tumor.
27. Median survival increases from 1–2 months (untreated or treated with steroids alone) to 3–6 months with whole brain radiation and steroids.
28. 30 Gray (Gy) in 10 fractions over 2 weeks.
29. Acute: fatigue, nausea/vomiting, headache
Long-term: Dementia, ataxia, and incontinence.
30. For tumors of less than 10 cm³ volume, particularly in surgically inaccessible areas.
31. Most studies of risk and outcome for open surgery versus radiosurgery for a single metastasis have shown equivocal results, though whole brain radiation (or postoperative radiosurgery) is recommended after resection.
32. Rapid relief of mass effect.

33.

- Provides tissue for histological analysis and identify a possible site of origin.
- Increases the chances of survival in conjunction with adjuvant therapies.

34. More data are available on the efficacy of surgery in patients with a single metastasis. Some advocate the aggressive resection of multiple metastases, but studies are not yet available to support or refute this strategy.

35.

- Inaccessible location
- Multiple metastases
- Extensive systemic disease

36. If there is a metastasis located in a life-threatening location, such as the posterior fossa (with mass effect on the brainstem or hydrocephalus), then resection may be indicated regardless of the number of other lesions or the extent of disease.

37. No.

38. It's not fully understood. The blood–brain barrier may partially contribute, but lipid-soluble agents and those administered intrathecally also show reduced efficacy, so this remains an ongoing area of research.

39. Breast cancer, small cell lung cancer, and choriocarcinoma.

40. Temozolomide (with or without whole brain radiation).

V. CNS Lymphoma

1. HIV

2. Immunosuppression due to organ transplantation

3. EBV

4.

- Severe combined immunodeficiency syndrome
- X-linked lymphoproliferative syndrome
- Chediak-Higashi syndrome
- Ataxia-telangiectasia
- IgA deficiency

5. Autoimmune disorders

6. Primary lymphomas are typically parenchymal.
Secondary lesions are typically leptomeningeal.

7. B-lymphocytes

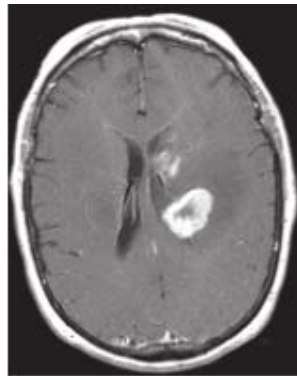
8.

- Leukocyte common antigen (CD45RB)
- B-cell markers (CD20, CD79a)
- T-cell marker (CD3)

9. Hodgkin's disease (classic Reed-Sternberg cells).

Hodgkin's is rare in the CNS. When it does present, it has the same features as non-CNS disease.

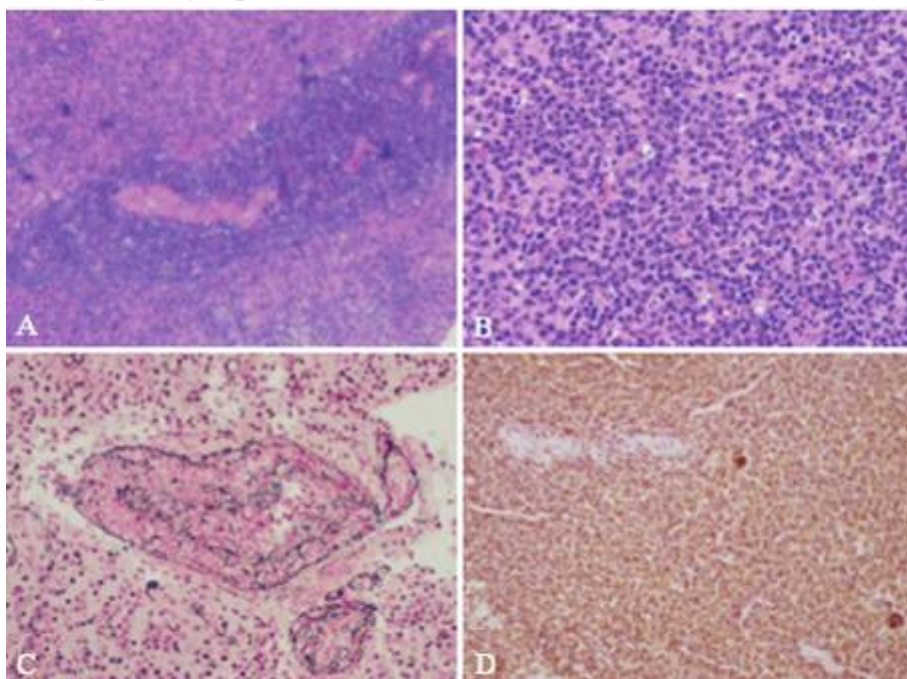
10. Single or multiple firm, friable, hemorrhagic, focally necrotic lesions in the cerebral hemispheres, often near a ventricle.



Axial, T1-weighted MRI of primary CNS lymphoma. Note edema and periventricular location.

11.

- Perivascular dense aggregates of a single population of atypical lymphoid cells
- Concentric perivascular reticulin deposition
- Infiltrative atypical lymphoid cells



Primary CNS lymphomas (PCNSL) show a (A) marked angiocentric pattern of (B) malignant lymphoid cells. (C) Silver stain demonstrates reticulin deposition in the walls of involved blood vessels. (D) Over 95% of PCNSL are of the large B-cell type, and show diffuse membranous staining for CD20 on immunohistochemistry.

12. Yes; this involvement typically indicates poor prognosis.
13. 25 to 45% in otherwise healthy patients; outcome is even worse for those who are immunocompromised.
14. True: radiotherapy shows good short-term effect but has proven ineffective for long-term therapy.
15. 40 to 50 Gy to the primary tumor.
16. No; craniotomy does not confer a survival benefit. Surgery is only useful for biopsy purposes, to provide tissue for definitive diagnosis.
17. Outcome for patients who receive both chemotherapy and radiation is better than for those who receive radiation alone. Drugs used are those also effective in systemic disease.
18. Pros: lyse tumor cells and induce remission.
Cons: brief effect, systemic side effects, difficulty in diagnosing biopsied lesions due to extensive tumor cell lysis.
19. Greater ability to cross the blood–brain barrier
20. Associated with a higher incidence of cognitive impairment, especially when given after radiation.
21. Giving chemotherapy prior to radiation.
22. By administering chemotherapeutic agents intrathecally or after blood–brain barrier disruption.
23. Chemotherapy alone with radiation reserved in case of failure.