**Retinoblastoma**

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1. A 3-year-old boy has been referred for evaluation of right leukocoria. An examination under anesthesia is consistent with group E disease. His left eye has a normal retina.

What would be the most appropriate treatment for this child?

A. Intra-arterial chemotherapy

B. External beam radiation therapy

C. Systemic chemotherapy and focal treatments

D. Enucleation

E. Thermotherapy and cryotherapy

**Explanation**

According to the International Classification of Retinoblastoma, a group E eye is defined by the presence of advanced intraocular disease, with the presence of one or more of the following poor prognosis features:

 i. Tumor touching the lens

 ii. Tumor anterior to the vitreous involving the ciliary body or the anterior segment

 iii. Diffuse infiltrating retinoblastoma

 iv. Neovascular glaucoma

 v. Opaque media from hemorrhage

 vi. Tumor necrosis with aseptic orbital cellulitis

 vii. Phthisis bulbi

In the presence of these factors, ocular salvage treatments are not indicated, and enucleation is the recommended treatment.

2. A 2-year-old boy with unilateral retinoblastoma has undergone enucleation of the right eye. Pathology of the enucleated eye shows a retinoblastoma occupying 90% of the vitreous cavity with massive choroidal involvement and disease past the lamina cribrosa but without extending to the cut end of the optic nerve. MRI of the brain, bone scan, bone marrow aspirates and biopsies, and cerebrospinal fluid are negative for disease.

What would be your treatment recommendation?

A. Cisplatin-based chemotherapy followed by consolidation with high-dose chemotherapy and autologous hematopoietic stem cell rescue

B. Observation

C. Adjuvant chemotherapy with six cycles of vincristine, carboplatin, and etoposide (VCE)

D. Orbital radiation therapy

E. Adjuvant chemotherapy with six cycles of VCE and orbital radiation therapy

**Explanation**

This patient has high-risk pathology and elevated risk of recurrence, and therefore adjuvant chemotherapy is indicated. However, radiation therapy is not indicated because of the absence of trans-scleral disease or involvement of the cut end of the optic nerve. Intensive chemotherapy and autologous hematopoietic stem cell rescue is indicated only in the setting of metastatic disease.

3. A 3-year-old girl presented with left eye leukocoria. Examination under anesthesia revealed advanced intraocular retinoblastoma (group E) of the left eye and no evidence of disease in the right eye. An enucleation of the left eye was performed.

Which of the following histological features in the enucleated eye would indicate the need for adjuvant chemotherapy?

A. Massive vitreous seeding

B. Complete retinal detachment

C. Focal choroidal involvement

D. Subretinal seeding

E. Optic nerve involvement past the lamina cribrosa

**Explanation**

High-risk pathology is defined by massive choroidal involvement (more than 3 mm in thickness), scleral invasion, or involvement of the optic nerve past the lamina cribrosa. Patients presenting with any of these features in the enucleated eye should receive adjuvant chemotherapy. For patients with trans-scleral involvement or extension of the disease to the cut end of the optic nerve, radiation therapy is also indicated. Focal involvement of the choroid is common but is not associated with an increased risk of dissemination. Vitreous and subretinal seeding are important for response to treatment and ocular survival but are not associated with increased risk of extraocular spread. A complete retinal detachment is not uncommon in advanced intraocular retinoblastoma but has no prognostic relevance.

4. You are asked to see a 4-week-old infant born to a mother with history of bilateral retinoblastoma. Genetic testing done at birth shows the presence of a germline *RB1* mutation. However, examination under anesthesia shows normal retinas with no evidence of retinoblastoma.

As you discuss all of these results with the parents, what would be your recommendation for the next step?

A. Funduscopic examination under anesthesia in 4 weeks

B. Repeat genetic testing

C. MRI of brain and orbits

D. Chemotherapy with single-agent carboplatin

E. Dilated eye examination in 6 months

**Explanation**

This infant has hereditary retinoblastoma; the presence of a germline mutation of the *RB1* gene carries a high risk of developing bilateral retinoblastoma. Tumors typically develop throughout the first 2 years of life but are not always present at birth. Therefore, regardless of disease status at birth, these infants need to be examined very frequently, typically every 3 to 4 weeks, with dilated funduscopic examinations under anesthesia. Delaying the funduscopic examination for 6 months is not appropriate. MRI of brain and orbits should be performed in all patients with new diagnosis of retinoblastoma but is not necessary at this point; trilateral retinoblastoma usually develops 2 to 3 years after the diagnosis of bilateral retinoblastoma. There is no proven role for chemotherapy to prevent the development of disease.

5. A 9-month-old infant has been diagnosed with bilateral retinoblastoma. Examination under anesthesia shows group B disease in the right eye and group D disease in the left eye. What would be the most appropriate initial management of this patient?

A. Enucleation of the group D eye and focal therapy of the group B eye

B. Bilateral radiation therapy

C. Systemic or intra-arterial chemotherapy and focal treatments with laser and cryotherapy

D. Bilateral enucleation

E. Bilateral laser and cryotherapy only

**Explanation**

This is a typical presentation of patients with bilateral retinoblastoma. Upfront enucleation is typically recommended only for group E eyes, and focal treatments only, with no chemotherapy, is only recommended for group A eyes. In all other scenarios, the standard of care is to use chemotherapy to reduce the intraocular tumor burden and then proceed with aggressive focal consolidation. Chemotherapy can be given systemically or by direct delivery into the ophthalmic artery. Although radiation therapy as sole mode of therapy is a reasonable option, the risk of second malignancies and orbital growth delay, particularly significant at this age, makes radiation a less desirable treatment in the upfront setting. Radiation is now more commonly used as salvage treatment in patients with disease progression after more conservative treatments. Laser therapy (thermotherapy or photocoagulation) and cryotherapy are extremely important in the management of intraocular retinoblastoma; however, group B and D eyes, as is seen in this patient, need chemoreduction first, followed by focal treatments. This patient has a good chance of ocular salvage, particularly the group B eye, and thus bilateral enucleation is not typically recommended.

6. A 4-year-old girl you have been treating for bilateral retinoblastoma presents to the clinic with a 1-week history of headaches, vomiting, and progressive lethargy. What intracranial malignancy do you suspect as you evaluate the patient?

A. Medulloblastoma

B. Atypical theratoid rhabdoid tumor

C. Optic pathway glioma

D. Pineoblastoma

E. Choroid plexus carcinoma

**Explanation**

Survivors of bilateral retinoblastoma have an elevated risk of pineoblastoma, which occurs in up to 10% of cases. It is also called trilateral retinoblastoma, and it usually occurs 2 to 3 years after the diagnosis of retinoblastoma; most tumors are in the pineal gland, but a small proportion of cases present with a supratentorial neuroectodermal tumor. The incidence of medulloblastoma, atypical teratoid rhabdoid tumor, optic pathway gliomas, and choroid plexus carcinomas is not significantly elevated in children with bilateral retinoblastoma.

7. You are counseling the parents of a 7-year-old girl who was treated for bilateral retinoblastoma at 18 months of age and who was successfully treated with chemotherapy and focal treatments, without needing radiation therapy. The parents are interested in knowing more about the risk of second cancers.

What malignancy is your patient at highest risk of developing?

A. Leiomyosarcoma

B. Breast cancer

C. Pineoblastoma

D. Melanoma

E. Osteosarcoma

**Explanation**

All the tumors listed may occur in survivors of bilateral retinoblastoma. Osteosarcomas account for approximately 30% of second cancers in survivors of bilateral retinoblastoma and are the most common second malignancies both inside and outside the irradiation fields. Approximately 50% of osteosarcomas occur within the irradiation fields, and 25% to 30% of tumors occur in the extremities. Leiomyosarcoma is one of the most common soft tissue sarcomas in this population, and it typically occurs in the uterus; therefore, female survivors of bilateral retinoblastoma, as with the case under discussion, should be counseled about this possibility. Pineoblastoma, also called trilateral retinoblastoma, occurs in a small proportion of patients with bilateral retinoblastoma, typically before 5 years of age. Melanoma is also a common malignancy among survivors of bilateral retinoblastoma, and those with family history appear to have a higher incidence.

**Hepatoblastoma**

1. An 8-month-old infant presents with a distended abdomen, and a CT of the abdomen shows a mass in the right lobe of the liver. The alpha-fetoprotein is 350,000 ng/mL. You review the case with the surgeon, who believes that the tumor is resectable, and you decide to proceed with upfront resection. Pathology shows completely resected pure fetal histology hepatoblastoma. A CT of the chest is negative, and the alpha-fetoprotein serum concentration is declining appropriately after surgery.

As you discuss the diagnosis and ongoing treatment with this infant’s parents, what would be your recommendation?

A. Observation

B. Six cycles of cisplatin-based therapy

C. Two cycles of cisplatin-based therapy

D. Intensive multiagent chemotherapy according to rhabdoid tumor guidelines

E. Radiation to the tumor bed

**Explanation**

Pure fetal histology hepatoblastoma is associated with an excellent prognosis. This histological variant accounts for approximately 5% to 10% of cases. Patients with stage I disease (as is the case for this infant) can be observed without adjuvant chemotherapy. Administration of two cycles of adjuvant chemotherapy is the recommended treatment for all other cases of stage I non–small cell undifferentiated hepatoblastoma. Intensive treatment according to rhabdoid tumor guidelines is a consideration for patients with advanced small cell undifferentiated hepatoblastoma. Radiation therapy is not commonly used in the upfront management of hepatoblastoma.

2. A 6-month-old infant presents with a distended abdomen, and imaging studies show a large unresectable hepatic mass and lung metastases. The alpha-fetoprotein (AFP) serum concentration is 80 ng/mL.

Which of the following is the most likely diagnosis?

A. Pure fetal histology hepatoblastoma

B. Conventional hepatocellular carcinoma

C. Small cell undifferentiated hepatoblastoma

D. Embryonal sarcoma of the liver

E. Fibrolamellar hepatocellular carcinoma

**Explanation**

More than 95% of primary liver tumors in patients younger than 5 years are hepatoblastomas. Small cell undifferentiated hepatoblastoma accounts for approximately 5% of hepatoblastomas, and it is associated with a worse prognosis. Clinically, a more aggressive clinical behavior and typically normal or only slightly elevated AFP characterize this variant. Molecularly, it is associated with aberrations in the *SMARCB1* gene and thus is considered a member of the rhabdoid family of tumors. Pure fetal histology hepatoblastoma presents also during the first months of life; however, it has a much more favorable clinical behavior, presenting as localized disease and with high AFP. Hepatocellular carcinoma is a tumor of older patients; the fibrolamellar variant may present in younger patients (typically in the second decade of life), and AFP may not be elevated. Embryonal sarcoma of the liver typically occurs in older children, and metastases are rare.

3. You have been asked to see a 13-month-old boy who presented with a large hepatic mass and alpha-fetoprotein serum concentration of 257,000 ng/mL. As you review the past medical and family history with the parents, which of the following familial conditions would be relevant in this case?

A. Familial hemochromatosis

B. Hereditary tyrosinemia

C. Alpha-1 antitrypsin deficiency

D. Gardner syndrome

E. Li-Fraumeni syndrome

**Explanation**

Familial adenomatous polyposis syndromes such as familial adenomatous polyposis and Gardner syndrome are associated with an elevated risk of hepatoblastoma. These syndromes are characterized by germline *APC* mutations, and the relative risk of developing hepatoblastoma is close to 800. Familial hemochromatosis, hereditary tyrosinemia, and alpha-1 antitrypsin deficiency are associated with hepatocellular carcinoma. Hepatocellular carcinoma also has been associated with Li-Fraumeni syndrome.

4. A 15-year-old previously healthy boy presents with a 3-month history of right upper abdominal quadrant pain and progressive abdominal distension. Imaging studies show a large mass originating from the liver parenchyma with lung metastases. The alpha-fetoprotein (AFP) serum concentration is 15 ng/mL.

Which of the following diagnoses would you place at the top of your differential?

A. Small cell undifferentiated hepatoblastoma

B. Embryonal sarcoma of the liver

C. Pure fetal histology hepatoblastoma

D. Epithelial hepatoblastoma

E. Hepatocellular carcinoma, fibrolamellar type

**Explanation**

More than 90% of primary liver tumors in adolescents are hepatocellular carcinoma (HCC). The fibrolamellar variant accounts for approximately 25% of HCCs, and it is typically associated with a younger age (median 12 years) and absence of preexisting cirrhosis. The serum concentrations of AFP are usually normal or only mildly elevated in fibrolamellar HCC, and patients present with a more protracted course. Small cell undifferentiated hepatoblastoma also presents with low AFP but at a much younger age, typically in the first year of life. Epithelial and pure fetal histology hepatoblastoma typically present in the first 3 years of life and are associated with high concentrations of AFP. Embryonal sarcoma of the liver usually presents in the first decade of life, and metastases are rare.

5. A 6-month-old boy presents with a large right upper-quadrant mass. Imaging studies reveal an unresectable primary liver mass with lung metastases. Alpha-fetoprotein (AFP) is 47 ng/mL. A percutaneous biopsy is performed, and tissue is sent for additional molecular studies.

What genomic alteration is likely to be found in this tumor?

A. *SMARCB1* mutation

B. *11p15.5* uniparental disomy

C. *APC* mutation

D. *Xp11* translocation

E. *CTNNB1* mutation

**Explanation**

Although *CTNNB1* is the most commonly mutated gene in hepatoblastoma, the young age of this patient, aggressive presentation, and low levels of AFP are highly suggestive of the small cell undifferentiated variant of hepatoblastoma, which is characterized by *SMARCB1* mutations. Beckwith-Wiedemann syndrome (germline 11p15 uniparental disomy) and familial adenomatous polyposis (germline APC mutations) are associated with standard embryonal histology hepatoblastoma and elevated AFP levels. Xp11 translocations are typical of renal cell carcinoma.

6. A 6-month-old infant with history of low birth weight presents for evaluation of a right upper quadrant mass. Laboratory evaluation shows alpha-fetoprotein serum levels of 358,000 ng/mL. Imaging studies show a PRETEXT-II liver mass and no lung metastases. A resection of the mass is performed, and pathology shows a completely resected pure fetal histology hepatoblastoma.

Which presenting feature is the strongest predictor of outcome?

A. Low birth weight

B. Absence of lung metastases

C. Elevated alpha-fetoprotein serum levels

D. Pure fetal histology

E. PRETEXT-II

**Explanation**

Absence of lung disease, pure fetal histology, and PRETEXT-II are all good prognostic indicators in this case. Of them, pure fetal histology is the strongest prognostic factor, and this patient could be cured with surgery only, without adjuvant chemotherapy.

7. You have been asked to see a 6-month-old infant with a new diagnosis of Beckwith-Wiedemann syndrome, and you prepare to counsel the family about cancer risk. What is the most common malignancy in these patients?

A. Adrenocortical carcinoma

B. Neuroblastoma

C. Wilms tumor

D. Rhabdomyosarcoma

E. Hepatoblastoma

**Explanation**

Children with Beckwith-Wiedemann syndrome have an elevated risk of cancer; malignancy risk is close to 10% in the first decade of life. Wilms tumor is the most common neoplasm, followed by hepatoblastoma, adrenocortical tumors, and other malignancies.

**Germ Cell Tumors**

1. A 14-year-old postmenarchal girl presents with abdominal pain and distension and secondary amenorrhea. Physical examination reveals a large pelvic mass, hirsutism, and facial hair. The parents also report that the girl’s voice is deeper. Imaging studies show a mass arising from the left ovary.

What is the most likely diagnosis?

A. Dysgerminoma

B. Ovarian carcinoma

C. Choriocarcinoma

D. Sertoli-Leydig tumor

E. Yolk sac tumor

**Explanation**

Stromal sex-cord tumors (Sertoli-Leydig and juvenile granulosa cell tumors) must be included in the differential diagnosis of ovarian solid masses, particularly for postpubertal female patients. Sertoli-Leydig tumors are typically associated with elevated levels of testosterone causing secondary amenorrhea and virilization. Inhibin levels also usually are elevated and are a good marker for diagnosis and follow-up.

2. A 28-month-old girl presents with abdominal and lower back pain and urinary retention. Imaging studies show a midline pelvic mass with retroperitoneal nodal enlargement and multiple lung and bone metastases. Alpha-fetoprotein (AFP) serum concentration is 320,000 ng/mL. A biopsy of the primary mass is performed, and pathology is pending.

What is the most likely histology?

A. Embryonal carcinoma

B. Germinoma

C. Yolk sac tumor

D. Immature teratoma

E. Choriocarcinoma

**Explanation**

This is a typical presentation of a stage IV sacrococcygeal germ cell tumor originating from an untreated sacrococcygeal teratoma. The most common histology in this scenario is yolk sac tumor. The high AFP serum concentration is consistent with this diagnosis. Choriocarcinoma is typically associated with elevated beta-HCG, and germinomas, embryonal carcinomas, and immature teratomas are typically associated with normal (or only mildly elevated) serum AFP.

3. A 15-year-old boy presents with chest pain and respiratory distress. A chest CT reveals a large anterior mediastinal mass. Alpha-fetoprotein (AFP) serum concentration is 12,000 ng/mL, and beta-HCG is 75 ng/mL.

What clinical syndrome could be associated with this presentation?

A. Klinefelter syndrome

B. DICER-1 syndrome

C. Isochromosome 12p

D. Cowden syndrome

E. Gardner syndrome

**Explanation**

This patient has a mediastinal mixed malignant germ cell tumor, probably with yolk sac and choriocarcinoma components. Patients with gonadal dysgenesia such as Klinefelter syndrome are at elevated risk of malignant germ cell tumors. Isochromosome 12p is a common genetic abnormality found in malignant germ cell tumors in adolescents and young adults, but this is a somatic event, not a germline defect. DICER-1 syndrome is associated with pleuropulmonary blastoma, cystic nephroma, and Sertoli-Leydig tumors, among others. Patients with Cowden syndrome typically develop hamartomas of the mucosal membranes and are at risk of developing breast, thyroid, and endometrial cancer. Patients with Gardner syndrome are at risk of colon carcinoma and hepatoblastoma.

4. A 14-year-old postmenarchal girl presents with large abdominal mass and a 4-month history of secondary amenorrhea. Physical examination reveals a large pelvic mass, hirsutism, and facial hair. Imaging studies show a mass probably arising from the left ovary.

As you document family history, what malignancy would you expect to find in other family members?

A. Adrenocortical carcinoma

B. Retinoblastoma

C. Pleuropulmonary blastoma

D. Yolk sac tumor

E. Malignant peripheral nerve sheath tumor

**Explanation**

This patient has a virilizing ovarian mass, consistent with a testosterone-producing stromal sex-cord tumor such as Sertoli-Leydig cell tumor, which is associated with germline DICER-1 mutations in 50% of the cases. The DICER-1 syndrome is characterized by a very broad phenotype. The most common malignancy is pleuropulmonary blastoma. Other malignancies described in the syndrome include cystic nephroma, stromal sex-cord tumors, uterine cervix embryonal rhabdomyosarcoma, Wilms tumor, cervical primitive neuroectodermal tumor, ciliary body medulloepithelioma, medulloblastoma, and seminoma.

5. A 2-year-old boy presents with a right scrotal mass. Ultrasound of the scrotum shows a right testicular mass; additional imaging studies show no evidence of retroperitoneal lymph node enlargement, and chest CT is negative. Laboratory evaluation shows serum alpha-fetoprotein (AFP) levels of 230,000 ng/mL and beta-HCG of 3 ng/mL. A right orchiectomy is performed, and in subsequent weeks the AFP levels normalize. Pathology indicates a yolk sac tumor. You are meeting with the family to discuss the next steps in care.

What would be the most appropriate next step in treatment?

A. Adjuvant therapy with four cycles of cisplatin, etoposide, and bleomycin

B. Retroperitoneal lymph node dissection

C. Observation

D. Retroperitoneal lymph node dissection followed by four cycles of cisplatin, etoposide, and bleomycin

E. Two cycles of single-agent cisplatin

**Explanation**

With normalization of the AFP, this patient has stage I testicular malignant germ cell tumor, which has an excellent prognosis with surgery and observation. Adjuvant chemotherapy is not recommended in this scenario. Retroperitoneal lymph node dissection, a procedure that is commonly prescribed in the management of seminoma in adults, is not recommended as initial treatment of pediatric testicular germ cell tumors.