**2017**

**Retinoblastoma, Germ Cell Tumors, and Hepatoblastoma**

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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?
   1. Intra-arterial chemotherapy
   2. External beam radiation therapy
   3. Systemic chemotherapy
   4. Enucleation
   5. Thermotherapy and cryotherapy  
        
      Answer: D (Enucleation)  
      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:
      1. Tumor touching the lens
      2. Tumor anterior to the vitreous involving the ciliary body or the anterior segment
      3. Diffuse infiltrating retinoblastoma
      4. Neovascular glaucoma
      5. Opaque media from hemorrhage
      6. Tumor necrosis with aseptic orbital cellulitis
      7. Phthisis bulbi

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

1. A 4-month-old infant has been diagnosed with bilateral retinoblastoma. An examination under anesthesia reveals bilateral Group C disease, and a plan to start with chemotherapy and intensive focal treatments is discussed with the family. Which of the following agents is more important in the systemic treatment of intraocular retinoblastoma?
   1. Cyclophosphamide
   2. Topotecan
   3. Carboplatin
   4. Cisplatin
   5. Doxorubicin  
        
      Answer: C (Carboplatin)  
      Platinum agents are the most effective class of drugs for treating retinoblastoma. Cisplatin is commonly used in the treatment of extraocular disease, but given its higher incidence of long-term effects, its use is not recommended for intraocular disease. Carboplatin as single agent or in combination with vincristine has been shown to be very effective in early stage intraocular disease. The standard regimen for advanced intraocular disease is carboplatin in combination with vincristine and etoposide.
2. A 7-month-old infant female presented with left leukocoria. An examination under anesthesia diagnosed her with group C retinoblastoma, with a normal right eye. After discussing all options with the family, treatment with intra-arterial chemotherapy is planned. What is the most effective and well-tested agent for intra-arterial chemotherapy of retinoblastoma?
   1. Carboplatin
   2. Melphalan
   3. Etoposide
   4. Busulfan
   5. Topotecan  
        
      Answer: B (Melphalan)  
      Melphalan as single agent or in combination with carboplatin or topotecan has been the standard intra-arterial chemotherapy for retinoblastoma. For treatment-naïve eyes, three to six infusions of melphalan through cannulation of the ophthalmic artery have consistently shown ocular salvage rates in excess of 80%. The ocular salvage rate is lower in patients receiving intra-arterial chemotherapy with melphalan for recurrent disease after other modalities. Carboplatin and topotecan have also been used, mostly in combination with melphalan in advanced or recurrent cases. Busulfan and etoposide have not been used in this scenario.
3. A 6-month-old male 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?
   1. *SMARCB1* mutation
   2. *11p15.5* Uniparental Disomy
   3. *APC* mutation
   4. *Xp11* translocation
   5. *CTNNB1* mutation  
        
      Answer: A (*SMARCB1* mutation)  
      Though *CTNNB1* is the most commonly mutated gene in hepatoblastoma, the young age of this patient, aggressive presentation, and low levels of AFP are very 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.
4. A 6-month-old infant with history of low-birth weight presents for evaluation of a right upper-quadrant mass. Laboratory evaluation shows alpha-protein 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?
   1. Low-birth weight
   2. Absence of lung metastases
   3. Elevated alpha-protein serum levels
   4. Pure fetal histology
   5. PRETEXT-II  
        
      Answer: d (Pure fetal histology)  
      The absence of lung disease and PRETEXT-II stage are good prognostic indicators. However, the evidence of pure fetal histology is the strongest prognostic factor in this case, because this patient could be cured with surgery only, without adjuvant chemotherapy.
5. A 14-year-old post-menarchal 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 most likely arising from the left ovary. As you document family history, what malignancy would you consider finding in other family members?
   1. Adrenocortical carcinoma
   2. Retinoblastoma
   3. Pleuropulmonary blastoma
   4. Yolk sac tumor
   5. Malignant peripheral nerve sheath tumorAnswer: C (Pleuropulmonary blastoma)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 sec-cord tumors, uterine cervix embryonal rhabdomyosarcoma, Wilms’ tumor, cervical primitive neuroectodermal tumor, ciliary body medulloepithelioma, medulloblastoma, and seminoma, among others.
6. 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 negative chest CT. Laboratory evaluation shows serum AFP levels of 230,000 ng/ml and B-HCG of 3 ng/ml. A right orchiectomy is performed, and in subsequent weeks the alpha-protein 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?
   1. Adjuvant therapy with four cycles of cisplatin, etoposide, and bleomycin
   2. Retroperitoneal lymph node dissection
   3. Observation
   4. Retroperitoneal lymph node dissection followed by four cycles of cisplatin, etoposide, and bleomycin
   5. Two cycles of single-agent cisplatin  
        
      Answer: C (Observation)  
      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, it is not recommended as initial treatment of pediatric testicular germ cell tumors.

8. 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 her 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. Massive choroidal involvement

D. Subretinal seeding

E. Prelaminar optic nerve involvement

**Answer:** C

**Explanation:** High-risk pathology is defined by massive choroidal involvement (>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 also is indicated. Prelaminar optic nerve involvement 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.

9. You are being asked to see a 1-week-old infant born to a mother with a history of bilateral retinoblastoma. The ophthalmologist has already performed an examination under anesthesia, and both retinas appear normal. Genetic counseling is also in progress, and germline mutational analysis of the RB1 gene has been requested. While awaiting the results of the genetic testing, what is the most important next step?

A. MRI of the brain and orbits

B. Repeat a funduscopic examination in 4 weeks

C. Repeat a funduscopic examination in 6 months

D. Head and neck angiogram in anticipation of intra-arterial chemotherapy

E. Bilateral electroretinogram

**Answer:** B

**Explanation:** This infant has an approximately 50% chance of carrying a germline mutation of the *RB1* gene and thus developing retinoblastoma. Most *RB1* mutant carriers develop retinoblastoma in the first 2–3 months of life and thus need to be examined very frequently, typically every 3 to 4 weeks, with dilated funduscopic examinations. In this case, while waiting for the results of genetic testing, the recommendation would be to continue monthly examinations even with a normal exam at birth. Delaying the funduscopic examination for 6 months is not appropriate in the absence of information regarding *RB1* germline status. MRI of the brain and orbits should be performed in all patients with a new diagnosis of retinoblastoma, but it is not necessary at this point; trilateral retinoblastoma usually develops 2–3 years after the diagnosis of bilateral retinoblastoma. Electroretinograms are of no diagnostic utility in retinoblastoma.

10. A 2-month-old infant son of a survivor of bilateral retinoblastoma has been referred to you after genetic testing has confirmed that he carries the same germline *RB1* mutation of his father. An examination under anesthesia performed at birth and at 1 month of age shows no evidence of retinoblastoma. You discuss the risk of developing retinoblastoma with the infant’s parents, and you indicate to them that the risk is

A. Less than 50%

B. Approximately 25%

C. More than 90%

D. Approximately 75%

E. Less than 10%

**Answer:** C

**Explanation:** Germline *RB1* mutation results in a very high penetrance for the development of retinoblastoma, with more than 90% of carriers developing retinoblastoma. All infants with a known genetic mutation should be examined with dilated funduscopic examinations at least monthly during the first year of life.

11. 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

**Answer:** C

**Explanation:** This is a typical presentation of patients with bilateral retinoblastoma. Upfront enucleation typically is only recommended 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, make 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 in this patient, require chemoreduction first, followed by focal treatments. This patient has a good chance of ocular salvage, particularly the group B eye, and thus bilateral enucleation typically is not recommended.

12. A 4-year-old girl who 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 (ATRT)

C. Optic pathway glioma

D. Pineoblastoma

E. Choroid plexus carcinoma

**Answer:** D

**Explanation:** Survivors of bilateral retinoblastoma have an increased risk of pineoblastoma, which occurs in up to 10% of the cases. It also is called trilateral retinoblastoma, and it usually occurs 2–3 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, ATRT, optic pathway gliomas, and choroid plexus carcinomas is not significantly increased in children with bilateral retinoblastoma.

13. You are counseling the parents of a 12-year-old girl who was treated for bilateral retinoblastoma at 18 months of age and received bilateral radiation therapy. You inform the parents of the risk of a second malignancy in the radiation field but also inform them of the risk of tumors outside the radiation field. What is the most common second cancer outside the radiation field?

A. Leiomyosarcoma

B. Breast cancer

C. Pineoblastoma

D. Melanoma

E. Osteosarcoma

**Answer:** E

**Explanation:** All of 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%–30% of tumors occur in the extremities. Leiomyosarcoma is one of the most common soft tissue sarcomas in this population, typically occurring in the uterus; therefore, female survivors of bilateral retinoblastoma, such as 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 also is a common malignancy among survivors of bilateral retinoblastoma, and those with family history appear to have a higher incidence.

14. 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 AFP 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 AFP serum concentration is declining appropriately after surgery. As you discuss the diagnosis and 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 following rhabdoid tumor guidelines

E. Radiation to the tumor bed

**Answer:** A

**Explanation:** Pure fetal histology hepatoblastoma is associated with an excellent prognosis. This histological variant accounts for approximately 5%–10% of the cases. Patients with stage I disease (as is the case with 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 following 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.

15. A 6-month-old infant presents with a distended abdomen, and imaging studies show a large unresectable hepatic mass and lung metastases. The 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

**Answer:** C

**Explanation:** More than 95% of primary liver tumors in patients younger than 5 years of age are hepatoblastomas. Small cell undifferentiated hepatoblastoma accounts for approximately 5% of hepatoblastomas and 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 hSNF5 gene and thus is considered a member of the rhabdoid family of tumors. Pure fetal histology hepatoblastoma also presents 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 fibrollamelar 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.

16. You have been asked to see a 13-month-old boy who presented with a large hepatic mass and AFP 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

**Answer:** D

**Explanation:** Familial adenomatous polyposis syndromes such as familial adenomatous polyposis and Gardner syndrome are associated with an increased 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.

17. A 23-month-old girl with a stage IV hepatoblastoma with involvement of all four liver sectors (PRETEXT 4) has been receiving cisplatin-based chemotherapy. She has had a good clinical response, and evaluation after two cycles of chemotherapy shows complete resolution of the lung lesions and appropriate decline of AFP serum concentrations. However, the primary liver mass continues to involve all the liver sectors. What would be the next step in the management of this patient?

A. Continue with the same chemotherapy regimen and refer the patient for liver transplant.

B. Switch chemotherapy to a second-line regimen, and re-evaluate after two more cycles.

C. Continue the same chemotherapy with the addition of transarterial chemoembolization (TACE) and re-evaluate.

D. Stop treatment with curative intent and start palliative measures.

E. Consolidate with high-dose chemotherapy and autologous hematopoietic stem cell transplant (HSCT) and re-evaluate surgical options.

**Answer:** A

**Explanation:** Surgery is the mainstay of curative therapy in hepatoblastoma. Patients for whom a conservative surgical approach is not feasible should be promptly referred for liver transplantation, which is required in approximately 10% of the cases. The presence of metastatic disease at diagnosis is not a contraindication, provided the patient responds well. Given the good response to standard cisplatin-based chemotherapy, switching treatment to a salvage regimen is not indicated. TACE is an option for some cases, although typically it is used for patients with hepatocellular carcinoma, and has shown efficacy. High-dose chemotherapy with autologous HSCT has not been used to improve resectability in patients with hepatoblastoma.

18. A 14-year-old previously healthy male 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. 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. Hepatocellular carcinoma, conventional type

C. Pure fetal histology hepatoblastoma

D. Epithelial hepatoblastoma

E. Hepatocellular carcinoma, fibrolamellar type

**Answer:** E

**Explanation:** More than 90% of primary liver tumors in adolescents are hepatocellular carcinomas (HCC). The fibrolamellar variant accounts for approximately 25% of HCC, and it typically is associated with a younger age (median 12 years) and absence of pre-existing 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.

19. You are seeing for the first time a 3-week-old infant who was born with a large sacrococcygeal mass that was completely resected at 10 days of age and showed an immature teratoma on pathology. On the day of the visit, the AFP serum concentration is 11,000 ng/mL. What would be your recommendation for future management?

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

B. Adjuvant chemotherapy with four cycles of carboplatin, etoposide, and bleomycin

C. Observation

D. Retroperitoneal lymph node dissection

E. Radiation therapy to tumor bed

**Answer:** C

**Explanation:** This infant has stage I immature teratoma. Although there is no information on the preoperative AFP serum concentration, an AFP serum concentration of 11,000 ng/mL is within normal range at 3 weeks of age. The most appropriate management for this patient is observation with serial determinations of AFP levels to document normalization. Chemotherapy would not be indicated at this point. If AFP fails to normalize, you should suspect a malignant residual component; repeat imaging studies and review of the original specimen for evidence of yolk sac histology would be the most appropriate next steps in that scenario.

20. A 4-year-old boy presented with a right testicular mass and AFP serum concentration of 180,000 ng/mL. Imaging studies showed no evidence of disease in the pelvis, abdomen, or chest. An orchiectomy was performed, and pathology showed a yolk sac tumor. You are seeing the patient 2 weeks after surgery, and repeat laboratories show an AFP serum concentration of 43,000 ng/mL. As you discuss the plan with the family, what would be your recommended management?

A. Retroperitoneal lymph node dissection and adjuvant chemotherapy as dictated by pathology findings

B. Treatment with four cycles of cisplatin, etoposide, and bleomycin

C. Treatment with two cycles of single-agent cisplatin

D. Treatment with four cycles of carboplatin, etoposide, and bleomycin

E. Observation with close monitoring of AFP levels

**Answer:** E

**Explanation:** This patient has stage I testicular yolk sac tumor, as shown by the absence of nodal or distant metastases and appropriate decline of AFP serum concentration. The recommended approach for children with stage I testicular germ cell tumors (GCT) is observation with close monitoring of AFP to document normalization. If levels fail to normalize, the patient should be considered to have stage II disease and should be treated accordingly. Standard of care in pediatrics for stage II GCT is to use a cisplatin- or carboplatin-based regimen, either with etoposide and bleomycin (PEB or JEB) or with etoposide and ifosfamide (VIP). Retroperitoneal lymph node dissection is considered an option in adults with testicular nongerminomatous cell cancer, but surveillance is preferred.

21. 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. As you prepare the patient for surgery, what is the most likely diagnosis?

A. Dysgerminoma

B. Ovarian carcinoma

C. Choriocarcinoma

D. Sertoli-Leydig tumor

E. Yolk sac tumor

**Answer:** D

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

22. 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. AFP serum concentration is 320,000 ng/mL. A biopsy of the primary mass is performed, and pathology is pending. What would be the most likely histology?

A. Embryonal carcinoma

B. Germinoma

C. Yolk sac tumor

D. Immature teratoma

E. Choriocarcinoma

**Answer:** C

**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 a yolk sac tumor. The high AFP serum concentration is consistent with this diagnosis. Choriocarcinoma typically is associated with elevated beta-HCG, and germinomas, embryonal carcinomas, and immature teratomas typically are associated with normal (or only mildly elevated) serum AFP.

23. A 15-year-old male presents with chest pain and respiratory distress. A chest CT reveals a large anterior mediastinal mass, AFP serum concentration is 12,000 ng/mL, and beta-HCG is 75 ng/mL. Which of the following clinical syndromes could be associated with this presentation?

A. Klinefelter syndrome

B. *DICER1* syndrome

C. Isochromosome 12 p

D. Cowden syndrome

E. Gardner syndrome

**Answer:** A

**Explanation:** This patient has a mediastinal mixed malignant germ cell tumor, most likely with yolk sac and choriocarcinoma components. Patients with gonadal dysgenesia, such as Klinefelter syndrome, are at increased 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. *DICER1* 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.