1. A 2-year-old girl has a diagnosis of overall stage IV favorable histology Wilms’ tumor with pulmonary metastases and local stage III disease due to finding positive lymph nodes. After she completes 6 weeks of vincristine/dactinomycin/doxorubicin (DD4A) chemotherapy, restaging shows complete resolution of some but not all lung nodules. Tumor genetic testing reveals combined loss of heterozygosity for 1p and 16q.

Which of the following would be the most appropriate treatment plan?

A. Continue chemotherapy with vincristine, doxorubicin, and dactinomycin to complete 25 weeks of therapy. Administer radiation to lungs and flank.

B. Continue chemotherapy with vincristine, doxorubicin and dactinomycin to complete 25 weeks of therapy. Radiation to flank only. No lung radiation.

C. Continue chemotherapy with vincristine, doxorubicin and dactinomycin, add cyclophosphamide and etoposide to complete 33 weeks of therapy. Radiation to flank only. No lung radiation

D. Continue chemotherapy with vincristine, doxorubicin and dactinomycin, add cyclophosphamide and etoposide to complete 33 weeks of therapy. Radiation to lungs and flank.

E. Continue chemotherapy with vincristine, doxorubicin and dactinomycin to complete 25 weeks. Whole abdomen radiation and lung radiation.

Choices A, and B are incorrect as treatment with 5 drugs is superior to 3 drugs with lung radiation in patients with stage IV FHWT with either slow incomplete response, or pulmonary metastases, and/or in patients with combined loss of heterozygosity (LOH; 1p and 16q). Option C is incorrect because lung radiation therapy (RT) is indicated both for patients with LOH of 1p and 16q and for patients with slow incomplete response of pulmonary lesions.

Option D is correct because the use of vincristine/dactinomycin/doxorubicin (DD4A) with the addition of cyclophosphamide and etoposide (Regimen M), along with lung radiation, was shown to improved event-free survival (EFS) and overall survival (OS) from treatment with DD4A and radiation therapy for patients with stage IV FHWT with slow incomplete response of pulmonary nodules, as well as for the group of patients with combined LOH of 1p and 16q. As this patient has both risk factors, Regimen M chemotherapy and appropriate radiotherapy fields would be the recommended therapy.

Option E is incorrect as whole abdomen radiation is not indicated for stage III local disease due to positive lymph nodes and as noted above, the addition of cyclophosphamide and etoposide improves clinical outcomes in patients with stage III and IV disease with combined LOH of 1p and 16q.

Dix DB, Seibel NL, Chi YY, et al. Treatment of stage IV favorable histology Wilms tumor with lung metastases: a report from the Children's Oncology Group AREN0533 study. *J Clin Oncol.* 2018;36(16):1564-1570. doi: 10.1200/JCO.2017.77.1931.

2. A 3-month-old female presents to the emergency room with vomiting and abdominal distension. She has a left-side abdominal mass, and an abdominal ultrasound confirms an 8-cm mass arising from the left kidney. Liver lesions are also noted. Nephrectomy is performed and reveals a histologic diagnosis of malignant rhabdoid tumor of the kidney (MRTK). Which of the following is *not* a true statement about the management of this patient?

A. Most patients with rhabdoid tumor of the kidney present in infancy.

B. Most patients with rhabdoid tumor of the kidney present with metastatic (stage III or IV) disease.

C. She has an excellent prognosis with surgery, chemotherapy, and radiation.

D. Germline testing for SMARCB1/INI1 mutation on chromosome 22 is recommended, with brain MRI every 3 months until she is 5 years old, if testing is germline positive for SMARCB1/INI1.

E. EZH2 methyltransferase inhibitors are under investigation as potential therapeutic agents for rhaboid tumors because of their mechanism of action.

Options A and B are both true statements, so they are incorrect.

Option C is the correct answer because this is *not* a true statement. Prognosis is poor for patients with renal rhabdoid tumor despite intensive chemotherapy, surgery, and radiation; it is especially poor for young infants with metastatic disease.

Option D is a true statement. Patients with rhabdoid tumor should be offered germline testing for SMARCB1 (also known as INI1) on chromosome 22 because patients with germline mutations have an increased risk to develop rhabdoid tumors in the brain.1

Answer E is also a true statement, as EZH2 inhibition blocks the oncogenic proliferation in some tumors INI1 mutations, and is under investigation in therapeutic trials for MRTK.2

1. Sultan I, Qaddoumi I, Rodríguez-Galindo C, Nassan AA, Ghandour K, Al-Hussaini M. Age, stage, and radiotherapy, but not primary tumor site, affects the outcome of patients with malignant rhabdoid tumors. *Pediatr Blood Cancer.* 2010;54(1):35-40. doi: 10.1002/pbc.22285.

2. Foulkes WD, Kamihara J, Evans DGR, et al. Cancer surveillance in Gorlin syndrome and rhabdoid tumor predisposition syndrome. *Clin Cancer Res.* 2017;23(12):e62-e67. doi: 10.1158/1078-0432.CCR-17-0595.

3. A 3-year-old nonsyndromic, well-appearing male with no significant past medical history presents with an abdominal mass palpated by his mother when giving him a bath. CT imaging reveals a 9-cm right renal mass without involvement of the inferior vena cava (IVC) and no evidence of tumor thrombus by ultrasound. The left kidney appears normal, and there is no imaging evidence of tumor rupture or adherence to surrounding organs. There are diffuse, bilateral pulmonary metastases from which he is asymptomatic with a normal respiratory rate and no supplemental oxygen requirement. Following the National Wilms Tumor Study Group (NWTS)/Children’s Oncology Group (COG) approach to pediatric renal tumors, which of the following are appropriate next steps?

A. Core biopsy of the renal mass followed by three drug chemotherapy—vincristine, actinomycin, and doxorubicin

B. Nephrectomy with lymph node sampling followed by chemotherapy based on histology and stage

C. Fine-needle aspiration followed by three drug chemotherapy—vincristine, actinomycin, and doxorubicin

D. Neoadjuvant three drug chemotherapy—vincristine, actinomycin and doxorubicin—followed by nephrectomy at week 6

E. Neoadjuvant three drug chemotherapy—vincristine, actinomycin, and doxorubicin—followed by diagnostic biopsy at week 6 if primary tumor is showing good response to therapy

The correct answer is B. By age and presentation, this patient most likely has favorable-histology Wilms’ tumor (FHWT) with pulmonary metastases; however, this can only be confirmed by histologic diagnosis. With this presentation, other pediatric renal tumors remain in the differential, including diffuse anaplastic Wilms’ tumor, clear cell sarcoma of the kidney, or malignant rhabdoid tumor.

The National Wilms Tumor Study Group (NWTS)/Children’s Oncology Group (COG) recommends upfront nephrectomy over biopsy for all patients (except bilateral or bilaterally predisposed) when feasible. Although the patient has pulmonary metastases, and her disease is therefore designated as overall stage IV, the local stage (kidney) may still be stage I or II. There is no evidence of tumor thrombus (extending to above the level of the hepatic veins), and the tumor is below the size at which risk of intraoperative rupture is increased (12-14 cm). If the diagnosis of this patient is FHWT, with upfront nephrectomy, depending upon intraoperative findings and lymph node status, this patient may be spared flank radiation if stage I or II for nephrectomy.

Option A is incorrect. Although option A can be an appropriate approach in some presentations of renal tumors, following the NWTS/COG approach, upfront biopsy is not recommended when nephrectomy is possible. Option C is incorrect. Fine-needle aspirations are always discouraged for tissue diagnosis in renal tumors because they are inadequate for obtaining important tumor biology and often inadequate for histologic diagnosis. Option D is incorrect. This approach could be appropriate according to treatment guidelines of The International Society of Paediatric Oncology (SIOP), which would recommend initiation of chemotherapy with vincristine, actinomycin, and doxorubicin; however, these drugs would only be appropriate if the diagnosis is FHWT. This is not the recommended NWTS/COG approach. Option E is incorrect because this management approach is not recommended from either group.

4. A 9-month-old male with macroglossia and hemihypertrophy is referred to you for evaluation after genetics evaluation reveals germline hypermethylation of 11p15 imprinting center 1 (ICI). Which of the following are the appropriate surveillance recommendations for this patient?

A. Abdominal ultrasound every 3 months to screen for Wilms’ tumor and hepatoblastoma

B. Abdominal ultrasound every 3 months to screen for neuroblastoma with urine catecholamine screening

C. Annual whole body MRI to screen for sarcoma and ultrasound every 3 to 4 months to evaluate for adrenocortical carcinoma

D. Brain MRI every 6 months to evaluate for pineoblastoma

E. Brain MRI every 6 months to evaluate for central nervous system rhabdoid tumor

The correct answer is A. This patient has clinical characteristics and genetic confirmation of Beckwith-Wiedemann syndrome (BWS). This is an overgrowth syndrome in which patients present with macroglossia, abdominal wall defects, unilateral overgrowth (hemihypertrophy), and enlarged organs. These patients are at risk for embryonal tumors such as Wilms’ tumor and hepatoblastoma. Of genetic alterations associated with BWS, hypermethylation of 11p15 has the highest associated risk for developing Wilms’ tumor. It is recommended that this screening continue through age 7 years.1

Option B is incorrect. This approach would be appropriate for patents with neuroblastoma predisposition.2 Option C is incorrect because this approach would be appropriate for Li-Fraumeni screening.3 Option D is incorrect because this would be an appropriate screening approach for retinoblastoma (RB) with germline RB mutation.2 Option E is incorrect; this would be appropriate for screening for occurrence of rhabdoid tumor for children with germline SMARCB1 mutation.4

1. Brioude F, Kalish JM, Mussa A, et al. Expert consensus document: Clinical and molecular diagnosis, screening and management of Beckwith-Wiedemann syndrome: an international consensus statement. *Nat Rev Endocrinol.* 2018;14(4):229-249. doi: 10.1038/nrendo.2017.166.

2. Kamihara J, Bourdeaut F, Foulkes WD, et al. Retinoblastoma and neuroblastoma predisposition and surveillance. *Clin Cancer Res.* 2017;23(13):e98-e106. doi: 10.1158/1078-0432.CCR-17-0652.

*3. Kratz et al. Cancer Screening Recommendations for Individuals with Li-Fraumeni Syndrome. Clin Cancer Res 2017;23:e38-e45.*

*4.* Foulkes WD, Kamihara J, Evans DGR, et al. Cancer surveillance in Gorlin syndrome and rhabdoid tumor predisposition syndrome. *Clin Cancer Res.* 2017;23(12):e62-e67. doi: 10.1158/1078-0432.CCR-17-0595.

5. A 5-year-old child is found to have a renal mass, and a nephrectomy is performed. Which constellation of findings might you expect to see?

A. Triphasic histology showing epithelial, blastemal, and stromal components; germline gain of 1q; and tumor p53 mutation

B. A metastatic bone lesion in pelvic bone on initial imaging, *BCOR* internal tandem repeats, and histology showing cords and nests of pale-stained tumor cells with abundant extracellular matrix separated

C. Pathology described as cellular subtype, a finding of a 12:15 translocation in tumor cells, hypercalcemia, and germline INI loss

D. Previous history of malignancy, tumor with marked nuclear expression of TFE3, and germline Xp11 translocation

E. Highly cystic fluid filled mass, sibling with history of pleuropulmonary blastoma, and germline 11p15 hypermethylation

Option B is correct. These are fitting clinical, histologic, and molecular characteristics of stage IV clear cell sarcoma of the kidney (CCSK).

Option A is incorrect. Gain of 1q is a genetic alteration seen in favorable-histology Wilms’ tumor (FHWT), not germline. One would not expect a tumor p53 in triphasic FHWT. Option C is incorrect. Cellular subtype, 12:15 translocation in tumor cells, and hypercalcemia all fit with a diagnosis of cellular-type congenital mesoblastic nephroma (CMN). However, one would not expect germline INI loss, and CMN would be highly unusual in a 5 year old (occurs almost always in infants under 6 months of age). Option D is incorrect. Nuclear expression of TFE3 and previous history of malignancy would fit with translocation-associated renal cell carcinoma (TRCC), but the Xp11 translocation would be found in the tumor, not germline. Five years would also be young for this entity. Option E is incorrect. Findings of cystic mass and a sibling with pleuropulmonary blastoma (PPB) are concerning for germline *DICER* mutation and renal tumor diagnosis of cystic nephroma (CN). Germline hypermethylation of 11p15, however, would be indicative of Beckwith-Wiedemann syndrome, which is not related to CN or PPB.

6. A 4-year-old patient is found to have renal mass, and a nephrectomy is performed. A histologic diagnosis of triphasic favorable-histology Wilms’ tumor is made. Which of the following tumor genetic and germline mutations would you expect to see?

1. Germline chromosome 22q11.2 mutation, with tumor demonstrating loss of heterozygosity of 1p and 16q
2. No germline mutation, and tumor WT2 (11p15) mutation
3. Germline mutation of chromosome 3 and tumor 12:15 translocation
4. Germline 11p13 deletion and tumor p53 mutation
5. Finding of sickle trait hemoglobinopathy and tumor with *BCOR* internal tandem duplicates (ITDs)

Option B is correct. WT2 mutations are found in 30% of Wilms’ tumor (WT); in many, there is no associated germline WT2 mutation.

Option A is incorrect. Germline 22q11.2 is a mutation of *INI-1* (or *SMARCB1*) and is associated with increased risk of rhaboid tumor. There is no association with an occurrence of WT. Option C is incorrect. Mutation of chromosome 3 is associated with Von Hippel-Lindau syndrome, with risk for renal cell carcinoma (RCC); 12:15 tumor translocation is seen in cellular congenital mesoblastic nephroma (CMN). Option D is incorrect because 11p13 (WT1) germline mutations are seen in patients with WAGR syndrome, and p53 tumor mutations are seen in anaplastic WT. Children with WAGR are at risk for favorable-histology Wilms’ tumor (FHWT) but are extremely rarely found to have anaplastic WT. In this scenario, the patient has FHWT, and the finding of a p53 tumor mutation would not be expected. Option E is incorrect. Renal medullary carcinoma occurs exclusively in patients with sickle hemoglobinopathy; the tumors have *INI-1* loss, and patients are usually older than 10 years. Patients with sickle cell trait can also develop FHWT, but the tumor would not have *BCOR* internal tandem duplicates; these are seen in clear cell sarcoma of the kidney.

7. A 14-year-old male with sickle cell trait presents to the emergency department with abdominal pain and hematuria. Abdominal ultrasound reveals a right-side renal mass. CT confirms a 12-cm right-side renal mass with pulmonary metastases. Which of the following tumors is known to be associated with sickle cell trait?

1. Favorable histology Wilms’ tumor
2. Rhabdoid tumor of the kidney
3. Anaplastic Wilms’ tumor
4. Renal medullary carcinoma
5. Clear cell sarcoma of the kidney

Renal medullary carcinoma is a highly aggressive renal tumor almost exclusively seen in patients with sickle cell trait. It accounts for less than 0.5% of all renal carcinomas and carries a poor prognosis. It presents with abdominal pain, abdominal mass, flank pain, and hematuria. It is most commonly seen in adolescents and young adults and is more common in males than in females. Wilms’ tumor and sarcoma are also in the differential for a pediatric patient with a renal mass; however, given sickle cell trait, renal medullary carcinoma should be considered.

Beckermann KE, Sharma D, Chaturvedi S, et al. Renal medullary carcinoma: establishing standards in practice. *J Oncol Pract.* 2017;13(7):414-421. doi: 10.1200/JOP.2017.020909.

A 12-year-old girl presents with a large renal mass that is resected and diagnosed as Wilms’ tumor. She is also found to have pulmonary and hepatic metastases. Which of the following factors is most predictive of poor outcome?

A. Age older than 18 months

B. Diffuse anaplasia

C. Presence of pulmonary and liver metastases

D. Combined loss of heterozygosity (LOH) of 1p and 16q

E. *MYCN* amplification

Option B is the correct answer. Although combined loss of heterozygosity (LOH) of 16q and 1p and the presence of metastatic disease are prognostic for outcome for favorable-histology Wilms’ tumor (FWHT), the most predictive factor for outcome is the presence of diffuse anaplasia. Only 5% of all Wilms’ tumors have diffuse anaplasia; however, this group accounts for almost 60% of Wilms’ tumor–associated deaths. Recent results of the National Wilms Tumor Study 5 and COG AREN0321 have shown that patients with stage IV diffuse anaplastic Wilms’ tumor have an event-free survival (EFS) of less than 50%. Patients with stage IV disease and LOH of 1p/16q with FHWT had EFS greater than 85%.

Options A and E are factors that are prognostic for neuroblastoma.