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Primary Renal Ewing Sarcoma in Children and Young Adults

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Abstract

The Ewing sarcoma family of tumors (ESFT) are high-grade small round blue cell malignancies traditionally presenting in children and adolescents. The most common site of primary disease is bone, though extraskeletal primary sites are well-recognized.[1] We present six cases of primary ESFT of the kidney and one case of the adrenal gland. Patients were 11–18 years of age at diagnosis. Metastases at diagnosis were present in most cases (n=6). All patients underwent surgery, and most received radiation (n=5). Five patients relapsed after initial remission.

Comprehensive review of the primary renal ESFT literature was used to analyze various factors, including age, gender, disease metrics, metastases at diagnoses, and overall survival in a total of 362 cases. Notably, while the general ESFT population has reported rates of metastasis at diagnosis of 20–25%,[2] this rate in the renal ESFT population was 53% with a rate of 59% in adolescent and young-adult (AYA) patients (11–24 years). Nodal disease at diagnosis was present in 24% of renal ESFT cases compared with 3.2% in patients with primary skeletal ESFT.[3] While this malignant process may share histologic and molecular features with its bone and soft tissue counterparts, primary renal ESFT presentations appear to be more aggressive and have worse outcomes.

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Keywords

Ewing sarcoma; primary renal Ewing sarcoma; pediatric malignancy; small round blue cell tumors

Introduction

The Ewing sarcoma family of tumors (ESFT) is the second most common osseous malignancy in the pediatric population, and within this population, it is most often seen within the adolescent and young-adult age groups. Extraskeletal presentation, while well-recognized, is much less frequent. Primary presentation in the kidney is exceedingly rare, and confusion with other more common primary small round cell tumors of childhood, such as Wilms tumor or rhabdoid tumor of the kidney, is not infrequent, which results in misdiagnosis or delays in diagnosis. Despite the rarity in presentation, there are many case reports and several case series that echo the aggressive clinical features, high propensity for metastasis, and overall poor outcome.[1,4–10] In this paper, we present seven pediatric and young adult patients with primary renal ESFT and one patient with primary adrenal disease.

In addition, a meta-analysis was completed to elucidate the factors that contribute to the more aggressive disease process that has been reported in the literature. Patient characteristics included age at diagnosis, gender, disease laterality and extent at diagnosis, survival, and follow-up period after diagnosis. Disease extent included presence or absence of lymph node involvement, distant metastases, and renal vein or inferior vena cava (IVC) thrombosis. Disease characteristics were analyzed within the following subgroups: pediatric (<18 years), adolescent and young-adult patients (AYA, defined as ages 11–24 years), and adults (≥18 years).

Methods:

Patient selection

This series was an IRB-approved retrospective chart review of renal ESFT cases from four centers. At all institutions, patients were included if they had pathology-proven renal ESFT which consisted of positive EWSR1 rearrangement in 6 cases. An additional case of adrenal-primary ESFT (also with EWSR1 rearrangement) was included in the case series.

Literature review and analysis

For the meta-analysis, a PubMed search was carried out using the search terms “(renal[All Fields] OR kidney[All Fields]) AND (Ewing[All Fields] OR “neuroectodermal tumors, primitive, peripheral”[MeSH Terms] OR (“neuroectodermal”[All Fields] AND “tumors”[All Fields] AND “primitive”[All Fields] AND “peripheral”[All Fields]) OR “peripheral primitive neuroectodermal tumors”[All Fields] OR “pnet”[All Fields] OR “neuroectodermal tumors, primitive”[MeSH Terms]).” Publications from 1994–2018 were included and comprised 1,073 articles. Only publications that had full text available in English or translated into English were included. Excluded were publications that described non-primary renal neoplasms or non-ESFT lesions. Only newly described cases were included in the analysis. In total, 161 publications described 355 patients, and with the inclusion of the 6

patients newly reported in the current discussion, there were 362 patients analyzed. Chi-Square analysis using GraphPad Prism were used to determine correlation between different factors.

Results

The clinical characteristics and outcomes of the cases are listed in Table 1. Additional discussion regarding the complexity and complications in treatment of the patients follows.

Cases

Case 1—The patient is a 16-year-old male who presented with abdominal pain and imaging demonstrating a right renal mass. He underwent right partial nephrectomy as noted in Table 1 and was diagnosed with Stage 1 Wilms tumor (original outside pathology report not available for this analysis), for which he received standard Wilms tumor therapy with vincristine and actinomycin. Liver relapse was detected twelve months after completion of initial treatment, which was sixteen months following diagnosis. He underwent liver biopsy, and small round blue cell tumor (SRBCT) appearance on histology prompted additional testing, which included positive FLI-1 immunohistochemistry, suggesting that the primary lesion was actually a ESFT. New pathologic studies of the kidney primary from original presentation were done at our institution and demonstrated a SRBCT with EWSR1 rearrangement on fluorescence in situ hybridization (FISH) and negative staining for WT-1 in tumor cell nuclei. Due to identification of two lesions in different hepatic lobes, the patient received neoadjuvant chemotherapy with vincristine, doxorubicin, cyclophosphamide alternating with ifosfamide, etoposide (VDC/IE) for a total of 21 weeks as well as radiation. He developed lung and bone (femur) metastatic disease 22 months after first relapse. A third line of therapy was started with irinotecan and temozolomide and patient developed widespread bone and soft tissue metastases. Tumor directed therapy was discontinued and patient subsequently died from disease nearly six years after initial diagnosis.

Case 2—The patient is an 11-year-old male who presented with several weeks of left flank and testicle pain with several days of fever, and ultrasound revealed a large left-sided perinephric mass. Imaging demonstrated significant osseous pelvic metastatic disease. Following left nephrectomy, pathology revealed an EWSR1 rearrangement, and he received VDC/IE. After induction and two cycles of consolidation, he received conditioning with busulfan, melphalan, and thiotepa with autologous stem cell rescue followed by a year of maintenance chemotherapy with daily everolimus. Nearly 5 years after completion of stem cell rescue (4 years after completion of everolimus), he presented with abdominal pain initially thought to be appendicitis. Attempted laparoscopic appendectomy revealed enlarged regional lymph nodes that were biopsied and positive for disease recurrence with the previously noted EWSR1 rearrangement identified, while PET/CT showed no additional foci of disease. Notably, chest CT demonstrated multiple <2mm bilateral pulmonary nodules that were of indeterminate nature and remained under surveillance. He started VIT and received six cycles of this therapy, after which he was switched to two cycles of VTC alternating with VIT, due to severe irinotecan-induced diarrhea. He is currently AWD 5 months after relapse and 5.5 years following diagnosis.

Case 3—The patient is an 18-year-old female who presented with right flank pain and hematuria with initial imaging demonstrating a 7.5 cm tumor in the right kidney with vena cava extension. Radical nephrectomy with removal of the adjoining vena cava tumor thrombus was performed with negative surgical margins following the additional vena cava excision. Positron emission tomography–computed tomography (PET-CT) revealed multiple non-FDG avid bilateral pulmonary nodules up to 1 cm in size, which were deemed likely metastatic disease. FISH of the surgical specimen demonstrated EWSR1 rearrangement and she received VDC/IE as well as radiation. No nodal disease. She remains alive with no evidence of disease (ANED) 4.7 years after diagnosis with a 3 mm pulmonary peripheral nodule that has been stable for over 1.5 years.

Case 4—The patient is a 17-year-old female who presented with disease limited to the kidney. EWSR1 rearrangement confirmed on pathology. This patient's initial resection was notable for positive surgical margins at the renal sinus and vein with no lymph node involvement. Patient then received VDC/IE until cycle 8 as well as radiation to the tumor bed. After cycle 8, chemotherapy was discontinued given toxicity. Five years after therapy, she has had an inguinal lymph node removed, which was determined to be reactive. In addition, liver MRI demonstrated a small sub-centimeter enhancing lesion with inconclusive Eovist scan. PET scan showed no increased metabolic activity, and the lesion was considered likely a hemangioma. She is currently ANED 5.8 years following diagnosis. She requires nephrology care for elevated creatinine.

Case 5—This patient is a 16-year-old female who presented with a left renal mass with extension to the left renal vein and inferior vena cava with metastases to the right lung. At time of presentation, the patient was pregnant at 37 weeks of gestation. She underwent caesarean section with biopsy of the renal lesion. After recovery and disease confirmation with EWSR1 rearrangement, she received six cycles of pre-operative VDC/IE, followed by surgery, which involved left nephrectomy with negative margins and lymph node specimens which were negative for disease. She completed additional VDC/IE cycles and radiation as shown in Table 1. She is currently ANED at 21 months (1.8 years) following diagnosis.

Case 6-Primary adrenal ESFT case—The patient is a 13-year-old female with one month of back and abdominal pain that progressed to lower extremity neuralgias, neurogenic bladder, and ataxia. MRI revealed a large heterogeneous mass involving the left adrenal gland and kidney with significant spinal involvement. Additional sites of metastatic disease were identified in bone, bone marrow, lungs and liver by PET scan. Bone metastases included multiple vertebrae, bilateral iliac bones, bilateral femurs, and bilateral humeri. Pathology was consistent with ESFT and EWSR1/FLI1 fusion was detected. The patient received six cycles of preoperative VDC/IE with interval response followed by left radical nephrectomy and partial ureterectomy with negative surgical margins. Post operatively, she received 8 cycles of consolidation therapy with VDC/IE. Despite therapy, her disease progressed and care was redirected. She died 12 months following initial diagnosis.

Case 7—The patient is a 15-year-old female who presented with left abdominal and back pain with ataxia. Imaging studies revealed a large left renal mass, complete occlusion of the

IVC, and bilateral pulmonary metastasis. She underwent left nephrectomy with partial ureterectomy and IVC thrombectomy, complicated by tumor spill intraoperatively. FISH analysis of cells from the resected specimen revealed EWSR1 gene rearrangement. Bone marrow involvement was also confirmed by FISH. Post operatively, she received one cycle of VDC/IE. She developed significant Fanconi syndrome post ifosfamide administration and subsequent cycles were replaced with cyclophosphamide. Partial response to induction was noted, with some residual tumor in one lung nodule. Consolidation therapy with VDC/CE and pulmonary radiation followed. She experienced relapse with metastasis to the liver and lungs 6 months after completion of therapy. Treatment included two cycles of chemotherapy and one cycle of salvage therapy with persistent progression of disease. Care was redirected and the patient died 2.5 years following initial presentation.

Meta-analysis

Patient characteristics, including gender, age at diagnosis, disease extent, primary tumor metrics, and mortality, are summarized in Table 2 and raw data is available in Supplemental Digital Content Tables S1, http://links.lww.com/JPHO/A367&S2, http://links.lww.com/JPHO/A368. The different age groups analyzed included: <18 years, adolescent and young-adult patients (AYA, defined as ages 11–24 years), and ≥18 years (Fig. 1).

The newly reported 6 patients with primary renal ESFT had a metastatic rate of 67% at diagnosis, and the meta-analysis determined a rate of metastasis at diagnosis of 53.2% in all reported patients with renal ESFT in which information regarding metastasis at diagnosis was available (n=317, Fig. 2).

Meta-analysis demonstrated lymph node involvement at diagnosis in 24.0% of the primary renal ESFT population. While patients <18 years had rates of nodal involvement at diagnosis of 13.9%, compared with 28.4% in adults, this difference did not reach statistical significance (P = 0.07). Notably, all age groups showed a male predilection for nodal involvement, with significant gender differences seen in the AYA and adult groups (P=0.007 and P=0.002, respectively, Fig. 2).

Prior studies have established tumor volume of ≥200 ml or length ≥8 cm as a poor prognostic indicator.[11] At diagnosis, 78% of patients had tumor length ≥8 cm (n=222) and 75% had volume ≥200 ml (n=79). The relationship between distant metastases and tumor size ≥8 cm at diagnosis was significant (P=0.0011, n=210) as was the relationship between distant metastases and volume ≥200 ml at diagnosis (P=0.033, n=75). No significant relationship between tumor metrics with nodal involvement or tumor thrombus present at diagnosis was seen. Tumor volume ≥200 ml at diagnosis was significantly associated with increased risk of death at 1 and 3 years following diagnosis (P=0.047 and P=0.002, respectively).

In addition, gender differences within this renal ESFT population were assessed. Notably, renal ESFT patients demonstrated a statistically significant relationship between gender and age at presentation with females making up a majority of the cases in patients <18 years old (59.7%), while males made up a majority of cases in patients ≥18 years old at diagnosis (59.4%) (P=0.0069). There were no significant differences between genders with respect to

lesion size or volume at presentation, presence of renal vein or IVC thrombosis (Fig. 2), or overall survival.

Mortality from disease was also analyzed at different time points, and within 1 year of diagnosis, 21.5% of patients had died of disease (DOD) (information available for 191 cases), and this mortality rose to 59.7% at 3 years following diagnosis (n=124). Metastases and lymph node involvement at diagnosis were correlated with lowered survival (P<0.0001 and P=0.0052, respectively, Fig. 3).

Discussion

Ewing sarcoma is an aggressive osseous and soft tissue malignancy with the predominant patient population in the AYA age group (Fig. 1). Only osteosarcoma is more prevalent as a primary bone malignancy in the pediatric population. While Ewing sarcoma and primitive neuroectodermal tumors were previously categorized as distinct entities, more recent advances in molecular and cytogenetic changes have led to an understanding of a spectrum of neoplastic diseases termed the ESFT. The incidence of this malignancy has been reported as 3.5% of cancers in children 10–14 years of age and 2.3% of cancers in children 15–19 years of age.[10]

Primary renal neoplasms in children and young adults have a broad differential diagnosis including Wilms Tumor (WT), renal cell carcinoma, and clear cell sarcoma, among many others. The differential narrows when considering SRBCTs of renal origin to blastemal predominant Wilms tumor, extraskeletal ESFT, and CIC-DUX4 fusion-positive sarcoma.[12] The type of primary renal malignancy may be refined by the presenting age; congenital mesoblastic nephroma presents in infancy, Wilms tumor, clear cell sarcoma, and rhabdoid tumor present in children, and extraskeletal ESFT and CIC-sarcoma present in adolescents and young adults. In the infant group, the cellular variant of congenital mesoblastic nephroma can be confirmed by cytogenetic analysis showing the chromosomal translocation t(12;15)(p13;q25) which results in ETV6-NTRK3 gene fusion.[13] In SRBCTs of children, adolescents, and young adults, morphology, and cytogenetic and immunohistochemical studies aid in the diagnosis (Table 2). WT1 by immunohistochemistry is positive in both Wilms tumor and CIC-sarcoma; however, histologic features such as early tubule formation can distinguish the former. ESFT and CIC-sarcoma often stain for CD99 and FLI-1 by immunohistochemistry. Immunostaining for NKX2.2, a homeodomain transcription factor, is predictive of tumors that harbor an EWS-FLI1 translocation, while CIC-DUX4 fusion identifies CIS-sarcomas.[14] CCSKs demonstrate strong cyclin D1 positivity by immunohistochemistry, and molecular studies demonstrate BCOR internal tandem duplications while a minority have YWHAE-NUTM2 fusion. Rhabdoid tumor tumors demonstrate loss of nuclear staining for INI1. There are rare reports of other primary renal SRBCTs, including desmoplastic small round cell tumor and primary renal lymphoma.[15–18] While primary renal ESFTs are rare, this etiology must be considered in the differential for a primary renal tumor, to prevent incorrect diagnoses with misdirected treatment.

The presence of metastasis at diagnosis has been noted to carry the greatest prognostic significance with regard to survival for patients diagnosed with ESFT. Protocol AEWS0031

from the Children's Oncology Group treated patients with localized Ewing sarcoma with VDC/IE and local control; five-year event-free survival rates were 67% and 74% depending on the cohort dosing frequency.[19] In contrast, the Euro-EWING 99 trial analyzed dose-intensive chemotherapy outcomes in primary disseminated multifocal ESFT (excluding isolated pulmonary metastases) and reported event-free survival (EFS) and overall survival (OS) at 3 years for 281 patients as 27±3% and 34±4%, respectively.[20] While the rates of metastases at diagnosis for all-comers with ESFT have been 22–36%,[2,3] the renal primary ESFT population demonstrated a rate of metastases at diagnosis of 53.2%. Population studies have reported pulmonary metastases as the most common site of disease spread with outcomes analyses suggesting a slightly less dire prognostic consequence (overall survival 29–52%) compared with patients with other sites of metastasis, such as bone marrow, with overall survival <30%.[11,20]

Lymph node staging plays a key role in the work up and risk stratification of patients with ESFT. Analyzing data from the Surveillance, Epidemiology and End Results Program (SEER) database, Applebaum et al. reported that patients with primary extraskeletal tumors had higher rates of regional nodal involvement, compared to patients with primary skeletal disease (12.4% versus 3.2%, respectively).[3] Zöllner et al., looking exclusively at patients with primary renal ESFT, reported a rate of lymph node involvement of 33.3% from the German database of GPOH Ewing sarcoma trials, compared with a literature analysis showing lymph node involvement in 42.9% of patients (n=156).[21] The present meta-analysis determined a rate of lymph node involvement in 24.0% of the primary renal ESFT population (n=217). When controlled for age, metastatic status, tumor site, and soft tissue origin, regional lymph node disease has been reported to be an independent predictor of inferior overall survival.[3] The current review also demonstrated worse survival for patients with lymph node disease at diagnosis (Fig. 3). Taken together, these findings suggest that work-up of a primary renal SRBCT suspicious for possible ESFT should include careful examination of lymph node status as positive involvement is more likely in this extraskeletal presentation of ESFT and is suggestive of a worse prognosis.

Renal function in survivors of primary renal ESFT must be considered, as current standard of care includes neoadjuvant chemotherapy followed by surgical resection with the goal of negative margins, which entails nephrectomy in patients with primary renal disease. Following nephrectomy, the remaining kidney must undergo rapid physiologic changes to increase the glomerular filtration rate to ensure fluid and electrolyte balance. Importantly, standard ESFT therapy includes ifosfamide with known nephrotoxic effects partly through direct metabolite toxicity to tubular cells. In addition, ifosfamide can induce Fanconi syndrome, defined as a proximal tubule transport defect that can involve mild dysfunction or partial reabsorption defects in sodium, potassium, glucose, amino acids, bicarbonate and phosphorus that can persist long-term.[22] In addition, these patients may require abdominal radiation, which increases the risk of radiation nephritis.

Primary renal ESFT presents major diagnostic and management hurdles for providers, as these patients most often present with advanced staging with extrarenal extension and metastases.[4–9] The optimal management of ESFT continues to be debated. However, current standard of practice invokes a combination of chemotherapy, surgical resection, and/or

radiotherapy. Typically, patients will undergo preoperative chemotherapy for approximately 8–12 weeks, by local control with surgical resection with the goal of negative margins, followed post-operative chemotherapy with the possible addition of radiation therapy, especially to metastatic fields. Chemotherapy protocols continue to be researched and refined, but standard induction therapy in the United States involves vincristine, doxorubicin, and cyclophosphamide alternating with ifosfamide and etoposide (VDC/IE), and following local control, patients receive VDC/IE consolidation cycles. In Europe, the Euro-EWING 99 and EWING-2008 studies employed induction with vincristine, ifosfamide, doxorubicin, and etoposide (VIDE) cycles and consolidation courses of vincristine, actinomycin, and ifosfamide (VAI) or high-dose busulfan and melphalan (BuMel) prior to autologous stem cell transplant. The introduction of chemotherapy into treatment regimens for ESFT originating in the bone have improved survival rates from 10% to the current survival rate of 70–80%.[2,11,23] However, the outcome for primary renal ESFT is inferior compared with other primary sites. Survival for primary renal ESFT is estimated around 55% for patients with localized disease, while those with metastatic disease at diagnosis have markedly lower survival rates despite aggressive treatment.[2] A longstanding controversy regarding ESFT chemotherapy is whether or not a consolidation phase of high-dose chemotherapy with autologous stem cell rescue improves outcomes. The European trials, with BuMel preceding autologous stem cell rescue or standard chemotherapy consolidation with radiation, reported no significant difference in event-free survival and overall survival between groups, though the BuMel group had experienced treatment-related acute toxicities than the standard chemotherapy group.[23,24]

In conclusion, in our case series and meta-analysis, we posit that primary renal Ewing sarcoma is a distinct presentation site of ESFTs with an aggressive clinical behavior and overall poor outcome. Notably, limitations of literature review must be considered, including reporting bias and incomplete analysis. Improvements and availability of next generation sequencing and molecular profiling may help to elucidate the biological aggressiveness of this ESFT.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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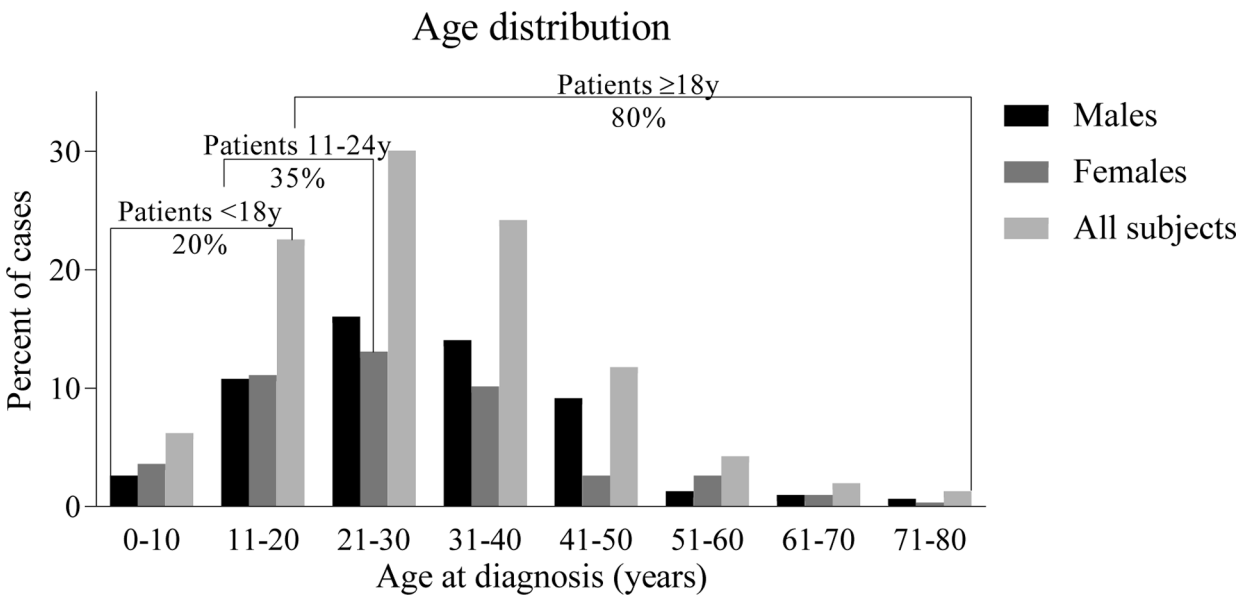

FIGURE 1.
Age distribution of primary renal ESFT patients in the literature.

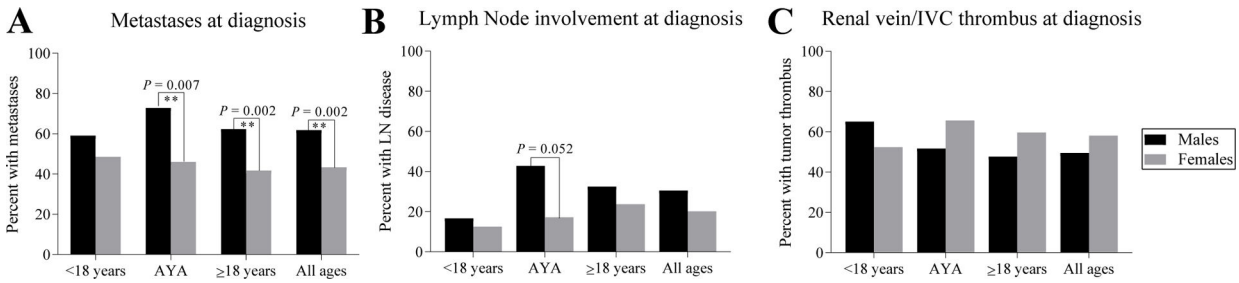

FIGURE 2. Disease extent at diagnosis.

Reported cases in the literature were analyzed by age grouping with respect to presence of (A) metastases, (B) lymph node involvement, or (C) renal vein or inferior vena cava (IVC) thrombosis at the time of diagnosis.

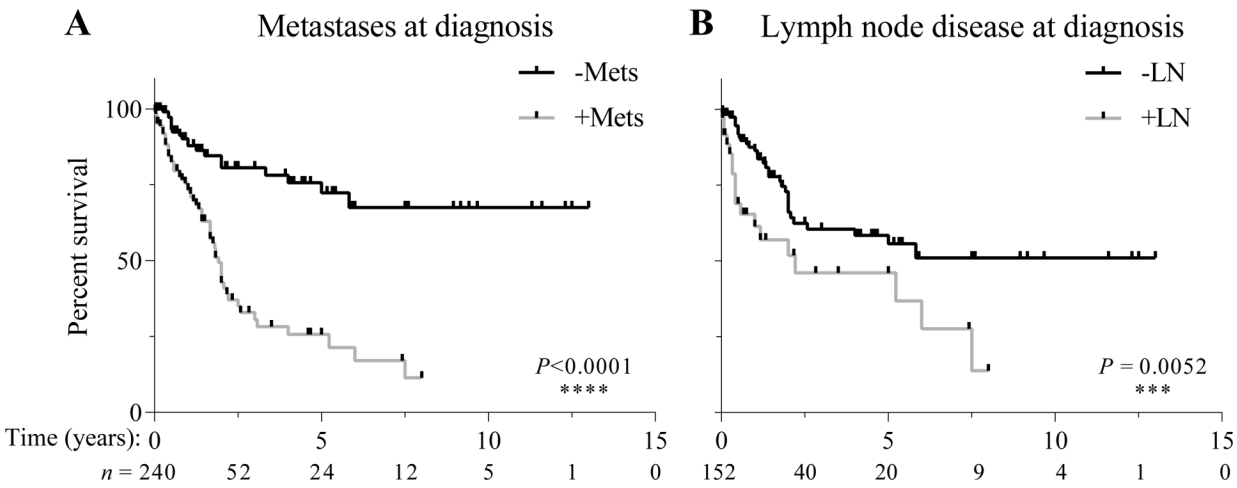

FIGURE 3. Survival plots.

Survival of reported cases were analyzed with respect to (A) metastases at diagnosis and (B) lymph node involvement at the time of diagnosis.

TABLE 1

Characteristics of Seven Cases

Case	Age (yr), Sex	Issues at diagnosis	Side/Size (cm)	Location of metastases at diagnosis	Surgical intervention	Surgical margins	Lymph node status at diagnosis	Treatment received	Radiation dose	Recurrence status	Time from remission to relapse	Outcome	Molecular data
1	16,M	Initial diagnosis of Wilms	Right	N/A (relapsed with liver lesions)	Partial nephrectomy	-	-	VA; VDC/IE; IT; VTC/ Bevacizumab; PARP inhibitor trial; GemDox; ICE	Liver 48 Gy, Ilium 20Gy, Femur 20 Gy, Liver 40 Gy (after relapse)	Relapsed	13 months (18 months from diagnosis)	DWD, 5.8y following diagnosis	EWSR1 rearrangement
2	11,M		Left/ 28×17×7.3	Multiple osseous metastases in pelvis	Nephrectomy	+	-	VDC/IE; auto SCT; everolimus	N/A	Relapsed	4.5 years (5 years from diagnosis)	AWD, 5mo following relapse	EWSR1 rearrangement
3	18,F	Hematuria	Right/ 6.8×6.2×6.0	Lung, IVC thrombus	Radical nephrectomy, IVC tumor removal	-	-	VDC/IE	50.4 Gy	N/A	N/A	ANED, 4.7y following diagnosis	EWSR1 rearrangement
4	17,F			N/A	Tumor resection	+	-	VDC/IE	45 Gy	N/A	N/A	ANED, 5.4y following diagnosis	EWSR1 rearrangement
5	16,F	37 weeks Pregnant	Left/ 25×18×19	Renal vein, IVC thrombus, Lung	Gross total resection	-	-	VDC/IE	45 Gy	N/A	N/A	ANED, 1.8y following diagnosis	EWSR1 rearrangement
6 *	13,F	Spinal cord compression	Left/ 6.8×14×13	Bone, bone marrow, lung, liver, soft tissue	Nephrectomy, following neoadjuvant chemotherapy	-	Para-aortic PET positive	VDC/IE	N/A	Progression	N/A	DWD, 12 months following diagnosis	EWSR1 rearrangement
7	15,F	Elevated urate and creatinine	Left/21	Lungs, IVC thrombus, bone marrow	Radical nephrectomy, partial ureterectomy, IVC thrombectomy	Tumor spill	-	VDC/IE switched to VDC/CE for ifosfamide nephrotoxicity	Tumor bed 54 Gy, Lungs 15 Gy	Relapsed	6 months	DWD, 2.5y following diagnosis	EWSR1 rearrangement

* Primary Adrenal ESFT case

Abbreviations:

VA= Vincristine and Actinomycin; **VDC/IE**= Vincristine, Doxorubicin, Cyclophosphamide/Ifosfamide, Etoposide; **IT**= irinotecan and temozolomide; **VTC**= vincristine, topotecan, and cyclophosphamide; **PARP**= poly (ADP-ribose) polymerase-1; **GemDox**= Gemcitabine and docetaxel; **ICE**= Ifosfamide, carboplatin, and etoposide; **VIT**= vincristine, irinotecan, and temozolomide; **SCT**= Stem cell transplant; **VDC/CE**= Vincristine, Doxorubicin, Cyclophosphamide/Cyclophosphamide, Etoposide;

ANED= alive, no evidence of disease; **AWD**= alive, with disease; **DWD**= dead, with disease; **DNED**= dead, no evidence of disease;

M= male; **F**= female; **ESWR1**= Ewing sarcoma breakpoint region 1; **IVC**= inferior vena cava; **Gy**= gray; **PET**= Positron emission tomography

TABLE 2

Meta-analysis Summary Results with Current Cases

		All Cases		Pediatric (<18 years)		AYA (11–24 years)		Adults (≥18 years)	
		Value	**Information available (*n* cases)**	**Value**	**Information available (*n* cases)**	**Value**	**Information available (*n* cases)**	**Value**	**Information available (*n* cases)**
Gender	Male	55.4%	307	40.3%	62	49.1%	106	59.4%	244
	Female	44.6%		59.7%		50.9%		40.6%	
Age	Mean	29.4 years	313	12.7 years	63	18.6 years	109	33.6 years	250
	Median	28 years		14 years		19 years		31 years	
	Range	3–78 years		3–17 years		11–24 years		18–78 years	
Metastases at diagnosis	Present	53.2%	317	52.5%	59	59.2%	98	54.0%	224
Lymph node involvement at diagnosis	Present	24.0%	217	13.9%	36	28.6%	56	28.4%	141
Renal vein/IVC thrombus	Present	52.2%	232	55.9%	34	58.6%	58	52.2%	138
Laterality	Left	48.1%	270	34.8%	46	46.3%	80	51.6%	190
	Right	51.9%		65.2%		53.8%		48.4%	
Largest Dimension	Mean	12.3 cm	222	12.4 cm	38	13.0 cm	76	12.3 cm	183
	Median	12 cm		10.5 cm		11.5 cm		12 cm	
	Range	2.4–34.5 cm		4–27.5 cm		3.1–34.5 cm		2.4–34.5 cm	
Volume	Mean	849 ml	79	963 ml	22	1185 ml	31	808 ml	56
	Median	607 ml		563 ml		1005 ml		571 ml	
	Range	7.2–4477 ml		47–4477 ml		47–4477 ml		7–3870 ml	
Mortality at 1 year post diagnosis		21.5%	191	16.7%	42	19.7%	66	23.0%	148
Mortality at 3 years post diagnosis		59.7%	124	46.2%	26	56.1%	41	63.9%	97

Publications included N=162, published 1994–2018; **Patients** N=361

TABLE 3

Proposed Diagnostic Pathology Work-up for Primary Renal Malignancies*

Small Round Blue Cell Tumor Histology		
Diagnosis	**Age**	**Ancillary studies**
Wilms tumor	2–3 years peak (90% < 10 years)	**IHC**: WT1 +, PAX-8 +, PAX-2 +
Rhabdoid tumor	0–2 years	**IHC**: Loss of INI1
Extraskeletal Ewing sarcoma	10–19 years peak	**IHC**: NKX2.2 +, FLI-1 +, CD99 + Cytogenetics
***CIC*-fusion sarcoma**	6–62 years	**IHC**: NKX2.2 -, FLI-1 +, CD99 + Cytogenetics
Non-Small Round Blue Cell Tumor Histology		
Diagnosis	**Age**	**Ancillary studies**
Congenital mesoblastic nephroma, cellular variant	0–1 year	**IHC**: SMA + Cytogenetics
Clear cell sarcoma (CCSK)	2–3 years peak (2 months to 14 years)	**IHC**: WT1 – (usually), cyclin D1 + Molecular studies

*Excluding renal cell carcinoma and urothelial carcinoma

Abbreviations:

IHC= Immunohistochemistry, **SMA**= smooth muscle actin, **INI1**= Integrase interactor 1, **WT1**= Wilms tumor protein, **PAX**= Paired box, **NKX2.2**= NK2 Homeobox 2, **FLI-1**= Friend leukemia integration 1 transcription factor, **CIC**= capicua transcriptional repressor