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Clinical heterogeneity of Xp11 translocation renal cell carcinoma: impact of fusion subtype, age, and stage

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Xp11 translocation renal cell carcinomas harbor chromosome translocations involving the Xp11 breakpoint, resulting in gene fusions involving the *TFE3* gene. The most common subtypes are the *ASPSCR1-TFE3* renal cell carcinomas resulting from t(X;17)(p11;q25) translocation, and the *PRCC-TFE3* renal cell carcinomas, resulting from t(X;1)(p11;q21) translocation. A formal clinical comparison of these two subtypes of Xp11 translocation renal cell carcinomas has not been performed. We report one new genetically confirmed Xp11 translocation renal cell carcinoma of each type. We also reviewed the literature for all published cases of *ASPSCR1-TFE3* and *PRCC-TFE3* renal cell carcinomas and contacted all corresponding authors to obtain or update the published follow-up information. Study of two new, unpublished cases, and review of the literature revealed that 8/8 patients who presented with distant metastasis had *ASPSCR1-TFE3* renal cell carcinomas, and all but one of these patients either died of disease or had progressive disease. Regional lymph nodes were involved by metastasis in 24 of the 32 *ASPSCR1-TFE3* cases in which nodes were resected, compared with 5 of 14 *PRCC-TFE3* cases ($P = 0.02$).; however, 11 of 13 evaluable patients with *ASPSCR1-TFE3* renal cell carcinomas who presented with N1M0 disease remained disease free. Two *PRCC-TFE3* renal cell carcinomas recurred late (at 20 and 30 years, respectively). In multivariate analysis, only older age or advanced stage at presentation (not fusion subtype) predicted death. In conclusion, *ASPSCR1-TFE3* renal cell carcinomas are more likely to present at advanced stage (particularly node-positive disease) than are *PRCC-TFE3* renal cell carcinomas. Although systemic metastases portend a grim prognosis, regional lymph node involvement does not, at least in short-term follow-up. The tendency for *PRCC-TFE3* renal cell carcinomas to recur late warrants long-term follow-up.
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Xp11 translocation renal cell carcinomas are characterized by chromosome translocations involving the Xp11 breakpoint, resulting in gene fusions involving the *TFE3* transcription factor gene, which maps to this locus.[1,2] The most common subtypes of Xp11 translocation renal cell carcinomas are the *ASPSCR1-TFE3 (*also known as *ASPL-TFE3)* renal cell carcinomas resulting from a t(X;17)(p11;q25) translocation,[3] and the *PRCC-TFE3* renal cell carcinomas, resulting from a t(X;1)(p11;q21) translocation.[4] As most cytogenetically or molecularly confirmed cases have been described in case reports or small series, a formal clinical comparison of these two subtypes of Xp11 translocation RCC has not been performed.

We report two new genetically confirmed Xp11 translocation renal cell carcinomas, one with an *ASPSCR1-TFE3* gene fusion and the other with a *PRCC-TFE3* gene fusion. We review the literature for all published cases of *ASPSCR1-TFE3* renal cell carcinomas (41 cases, 20 publications) and *PRCC-TFE3* renal cell carcinomas (37 cases, 19 publications) and contacted all corresponding authors to

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obtain or update published follow-up information. We compiled and statistically analyzed the information received by age, gender, stage, treatment, and follow-up.

Materials and methods

The two new, unpublished cases are from the files of the authors. We reviewed the literature for other cases of genetically confirmed *PRCC-TFE3* renal cell carcinomas and *ASPSCR1-TFE3* renal cell carcinomas. Cases were considered to be genetically confirmed if they demonstrated on cytogenetics the characteristic chromosome translocations of the *PRCC-TFE3* renal cell carcinoma [t(X:1)(p11.2;q21)] or *ASPSCR1-TFE3* renal cell carcinoma [t(X;17)(p11.2;q25)], or demonstrated the characteristic *PRCC-TFE3* or *ASPSCR1-TFE3* fusion products on reverse transcriptase PCR (RT-PCR). Published cases were found in the literature by Pub Med search using search terms 'TFE3' and 'Xp11'. Forty-one *ASPSCR1-TFE3* renal cell carcinomas were identified in 20 publications and 37 *PRCC-TFE3* renal cell carcinomas were identified in 19 publications. Details of these cases, along with the two new cases reported herein, are presented in Tables 1 and 2. We attempted to contact all corresponding authors of the publications to update follow-up information, and add details of therapy which were not included in the original reports of these cases. As shown in Tables 1 and 2, updated follow-up information was obtained for 4 of 36 published *PRCC-TFE3* cases, and 16 of 40 previously published *ASPSCR1-TFE3* cases. Updated or new follow-up information not presented in the original publication is shown by italics in Tables 1 and 2. Stage was determined using the current 2010 American Joint Committee on Cancer staging system.[5]Comparisons between the *PRCC-TFE3* RCC and *ASPSCR1-TFE3* renal cell carcinomas were analyzed using the two-tailed Fisher exact test. Multivariate analysis of survival was performed by Cox regression, using age (as a continuous variable), stage, fusion type, and gender. Statistics were performed using STATA3 (College Station, TX, USA).

Immunohistochemical labeling for TFE3 was performed for both of the new cases using 4-μm sections deparaffinized in xylene for 30 min and rehydrated using graded ethanol concentrations. Antigen retrieval was performed using steaming. Immunohistochemical labeling was performed using the avidin–biotin peroxidase complex technique and 3′,3′-diaminobenzidine as the chromogen. We used the P16 polyclonal antibody (Santa Cruz Biotechnology, Santa Cruz, CA, USA; steam in EDTA buffer, 1:600), which binds to the C-terminal portion of TFE3 protein downstream of known fusion breakpoints as previously described.[6] RT-PCR for the *ASPSCR1-TFE3* fusion product was performed as previously described.[3]

One patient's clinical course deserves special attention. This is a patient who was previously reported to have developed both an *ASPSCR1-TFE3* renal cell carcinoma (*ASPSCR1-TFE3* Case 6) and a contralateral *PRCC-TFE3* renal cell carcinoma (*PRCC-TFE3* Case 13) in the setting of long-term cyclophosphamide therapy for systemic lupus erythematosis, which led to the realization that Xp11 translocation renal cell carcinomas may be associated with prior exposure to chemotherapy.[7] This patient subsequently developed an abdominal recurrence of renal cell carcinoma. As slides from the recurrence are not available and the subtype of this recurrence was not determined, it is impossible for us to determine if this is a recurrence of his *ASPSCR1-TFE3* renal cell carcinoma or *PRCC-TFE3* renal cell carcinoma. Therefore, outcome data on this patient is excluded from the current analysis.

Results

PRCC-TFE3 Renal Cell Carcinoma Case Report

This patient was a 14-year-old boy who suffered trauma while playing soccer and developed uncontrollable abdominal hemorrhage. Intra-operatively, he was found to have a left renal neoplasm, which had ruptured into the peritoneal cavity. The child underwent left nephrectomy, which revealed a 7 cm hemorrhagic mass with a calcified capsule. Microscopically, the neoplasm demonstrated both nested and papillary architectures, and was composed of cells with moderate amounts of clear to faintly eosinophilic cytoplasm (Figure 1). Scattered psammoma bodies were present. Intrarenal vascular invasion was present, but perirenal lymph nodes were not identified for microscopic examination. The neoplasm demonstrated diffuse nuclear immunoreactivity for TFE3. Cytogenetic analysis revealed a t(X;1) (p11.2;q21) translocation, which characteristically results in a *PRCC-TFE3* gene fusion.

Five months after surgery, the patient began ironotecan adjuvant therapy, but did not tolerate it and could not complete the treatment course. Two years later, the patient developed metastasis to the left neck (likely representing lymph node metastasis). The patient developed multiple abdominal recurrences over the next 2 years, which were treated by multiple debulking procedures, and received two cycles of ironotecan and vincristine during this time. He received three cycles of sunitinib, which stabilized his condition for approximately 6 months at which time he developed a metastasis to the psoas muscle, which was then debulked. He received carboplatin and paxlitaxel, but developed further metastatic disease. He received gemcitabine, doxorubicin, and oxaliplatin, but progressed on these and died 2 months later, 5.5 years after nephrectomy, at the age of 20 years. His last imaging study revealed masses in the left renal

Table 1 Genetically confirmed *PRCC-TFE3* renal cell carcinomas

Case	*Reference*	*Age (years)/ gender*	*Stage TNM/AJCC*	*Diameter (cm)*	*Follow-up*
1	Unpublished	14/M	pT3aNX, III (rupture)	7	DOD 6 years; stabilized on sunitinib; failed ironotecan, carboplatin, paclitaxel
2	Argani,[4] Case 1; Tonk [8]	15/M[a]	pT2NO, I	7	NED 9 years
3	Argani,[4] Case 2	29/F	pT2NO, II	14	NA
4	Argani,[4] Case 3, Dal Cin[9]	54/F			Ileal metastasis after 30 years
5	Argani,[4] Case 4	27/F	pT1aNX, I	3	NA
6	Argani,[4] Case 5; Perot,[10] Case 2	9/F	pT3aNO, III	5	NA
7	Argani,[4] Case 6; Yenamandra[11]	10/M	pT2NX, II	13	Peritoneal recurrence at 30 months; Kleinfelters syndrome
8	Argani,[4] Case 7	9/M	pT3aNX, III	7.5	Liver metastasis at 2 years
9	Argani,[4] Case 8, Desangles[12]	23/F	pT3aNX, III	7	NA
10	Argani,[4] Case 9; Perot,[14] Case 1	11/M	pT1bNX, I	4.5	NED 2 years
11	Argani,[4] Case 10; Zattara-Cannoni[13]	64/F	pT3aNX, III		NA
12	Argani,[4] Case 11; Perot, Case 2[14]	13/F	pT2NI, III	9	Retroperitoneal/mediastinal metastases at 2 years
13	Argani,[7] Case 2	22/M	pT4N1MX, IV	5	s/p *ASPSCR1-TFE3* RCC*; developed unclassified RCC recurrence*[a]
14	Onder[15]	9/M	pT1aNX, I	3.1	s/p contralateral classic CMN; *NED 5 years, ESRD*
15	Sidhar,[16] Case 1	30/M			NA
16	Sidhar,[16] Case 2	21/F			NA
17	Sidhar,[16] Case 3	45/F			NA
18	Camparo,[17] Case 2	10/F	pT1bNI, III	5	NED 30 months
19	Camparo,[17] Case 4	16/F	pT1bNOMO, I	5.5	NED 32 months
20	Altinok,[18] Case 7	14/F	pT1bNOMX, I	4.5	*NED 10 years, NAT*
21	Altinok,[18] Case 8	13/F	pT1aNOMX, I	1.3	*NED 10 years, NAT*
22	Sangkhathat,[19]	2/M	pT1aNOMO, I	2.0	NED 1 year; MELAS syndrome (inherited mitochondrial DNA defect)
23	Meloni[20]	20/M			NA
24	Meloni,[21] Case 1	68/M	pT3bNXMX, III		NA
25	Meloni,[21] Case 2	55/M	pT3bNX,III		NA
26	Meloni,[21] Case 3	NA/M			NA
27	Meloni,[21] Case 4	24/M	pT3aNX, III		NA
28	Shipley,[22] Case 1	30/M			NA
29	Shipley,[22] Case 2	21/F			NA
30	De Jong[23]	2/M			NA
31	Kardas[24]	14/F	pT1NX, I	1.5 cm	NA
32	Dijkhuizen[25]	69/F			NA
33	Perot,[10] Case 1	9/F			20 Year intrarenal recurrence
34	Komai,[26] Case 2	40/M	pT2N1M0, III	10	Developed retroperitoneal lymph node metastases 5 years*; DOD 10 years (liver metastasis). Resistant to Interferon, sunitinib*
35	Hung,[27] Case 1	20/F	pT4cN0M0 (stage IV, peritoneal spread)	17	NA
36	Macher-Goeppinger,[28] Case 3	28/F	pTxN1, III	NA	Lung metastasis, DOD 20 months
37	Pan,[29] Case 9	20/F	pT3aN0M0, III	10	DOD 54 months

Abbreviations: AJCC, American Joint Committee on Cancer; CMN, congenital mesoblastic nephroma; DOD, died of disease; F, female; M, male; NA, not available; NAT, no adjuvant therapy, surgery only; NED, no evidence of disease; TNM, tumor, node, metastasis.
Italics = updated from original publication.
[a]History of chemotherapy exposure.

fossa, left paracolic gutter, left psoas muscle, left presacrum, and left pleura.

ASPSCR1-TFE3 Renal Cell Carcinoma Case Report

A 16-year-old white girl presented with a left upper quadrant mass. Computerized tomography revealed a calcified renal mass, with several enlarged perirenal lymph nodes, lytic destruction of the L1 vertebra, and two small lung nodules. A left radical nephrectomy was performed with removal of the left renal hilar lymph nodes as well as a left periaortic lymph node dissection. The upper pole mass measured 15 cm in greatest dimension, and on sectioning had a tan-white, friable appearance with cysts and hemorrhagic areas. Microscopically, the mass had a prominent papillary architecture and areas with solid nest formation

Table 2 Genetically confirmed *ASPSCR1-TFE3* renal cell carcinomas

Case	*Reference*	*Age (years)/ gender*	*Stage TNM/AJCC*	*Diameter (cm)*	*Follow-up*
1	Unpublished	16/F	pT3N1M1 (lung, bone, retroperitoneum), IV	8	AWD-progressive metastatic disease (lung, bone) at 1 year
2	Argani,[3] Case 1; Tomlinson[30]	8/F	pT1aN0MX, I	3.3	*NED 14 years, NAT*
3	Argani,[3] Case 2	2/M	pT4NIMX, IV	10.1	AWD 10 year
4	Argani,[3] Case 3; Renshaw,[31] Case 4	7/F	pT3aNIMX, III	3.5	*NED 19 years, NAT*
5	Argani,[3] Case 4	17/F	pT1aNIMX, III	2.7	NED 2.5 years[a]
6	Argani,[3] Case 5	17/M	pT3aNXMO, III	8	Developed *PRCC-TFE3* RCC *and later unclassified recurrence of RCC*[a]
7	Argani,[3] Case 6	17/F	pT4NIMI (bone), IV	14	DOD 2 years
8	Argani,[3] Case 7; Renshaw,[31] Case 7	15/M	pT4NXMO, IV	2.3	*Developed lung metastases at 1 year, underwent multiple surgeries, AWD 13 years*
9	Argani,[3] Case 8	4/M	pT3aNIMO, III	4	*NED 10 years*
10	Zambrano[32]	9/F	pT3NOMO, III	4.0	*NED 10 years, NAT*
11	Argani,[33] Case 1	68/F	pT1bNXMX, I	5.0	*NED 8 years*
12	Huang[34]	16/M	pT1bNIM0, III	5.0	Died of ESRD at 28 months, NAT, NED at death[b]
13	Heimann,[35] Case 1	5/F	pT1aNIMO, III	1.0	NA
14	Heimann,[35] Case 2	5/F	pT1aNIMO, III	1.0	NA
15	Geller,[36] Case 10	17/F	pTXNXMI (lung, liver), IV	NA	DOD 14 months
16	Chen[37]	6/M	pT1aNOMO, I	2.4	NED 18 months, NAT
17	Ramphal,[38] Case 3	6/F	pT4N1, IV		*NED 11 years, XRT for residual retroperitoneal disease*
18	Ramphal,[37] Case 10	8/F	NX, I		*NED 8 years, NAT*[a]
19	Ramphal,[38] Case 12	7/M	pTXNIMI (supraclavicular lymph node, bone), IV		DOD 9 months failed IL-2, vinblastine, celecoxib
20	Camparo,[17] Case 10	28/M	pT3aN1MI, IV	9	Terminal, 26 months
21	Camparo,[17] Case 19	11/F	pT1NOMO, I	4	NED 17 months
22	Camparo,[17] Case 24	21/F	pT1N1, III	5	NED 20 months
23	Hernandez-Marti[39]	8/M	pT1aNI, III	3.5	NA
24	Carcao[40]	6/F	pTXNIMX, III		NED 3 years, NAT
25	Barroca[41]	1/F	pT1N1MX, III	6.6	*NED 4.5 years, NAT*
26	Kuroda[42]	73/F	pT1NX, I	2	NED 2 months
27	Komai,[26] Case 3	41/M	pT1bN0M0, I	6	Developed liver metastases, no response to interferon, IL-2, DOD 26 months
28	Komai,[26] Case 4	24/F	pT1bN0M1 (lung), IV	6	*AWD, progessive 45 months, (Lung and adrenal metastases) treated with IFN-a and sunitinib*
29	Rakheja,[43] Case 3	11/M	pT1aN1MX, III	2.5	*NED 9 years, NAT*
30	Rakheja,[43] Case 4	10/F	NX		NA
31	Zhong,[44] Case 1	38/F	pT4NXMX, IV (omentum)	14	*Liver and soft tissue metastasis, AWD 21 months*
32	Zhong,[44] Case 2	65/F	pT3N1MX, III	9.5	*NED 19 months*
33	Klatte[45]	5/M	pT3N1M1 (Liver), IV	12	NED 4.5 years after interferon 2 alpha and vaccine tumor lysate-pulsed dendritic cells
34	Klatte[45]	42/F	pT2N0M0, II	8	NED 8 years
35	Sukov,[46] Case 3	50/F	pT1aNX, I	4	DOD 8.9 years
36	Macher-Goeppinger,[28] Case 6	4/M	pTXN1MX, III	NA	NED 129 months
37	Gaillot-Durand[47]	21/F	pT1bN1, III	5	NED 7 years
38	Mir,[48] Case 4	75/M	pT1bN0M0, I	5	*DOD 40 months*
39	Mir,[48] Case 5	68/M	pT3bN1M0, III	8	*DOD 31 months*
40	Hou[49]	18/M	pT3N1M1 (lung, pleura, bone, skin), IV		DOD 15 months, responded to sorafenib
41	Pan,[29] Case 3	24/F	pT3N1M0, III	8.5	Retroperitoneal metastasis 14 months, DOD 26 months; failed sunitinib, sorafenib, temsirolimus

Abbreviations: AJCC, American Joint Committee on Cancer; AWD, alive with disease; DOD, died of disease; F, female; IFN-α, interferon-α; M, male; NA, not available; NAT, no adjuvant therapy, surgery only; NED, no evidence of disease; XRT, radiation therapy; TNM, tumor, node, metastasis.
Italics = updated from original publication.
[a]History of chemotherapy exposure.
[b]Prior chemotherapy exposure.

(Figure 2). The neoplastic cells had abundant eosinophilic cytoplasm and nuclei with prominent central nucleoli. Multiple psammoma bodies were identified, which correlated with the calcifications seen in imaging. Multifocal vascular invasion was seen. A left hilar lymph node and multiple lymph nodes in the left periaortic lymph node dissection were involved by metastatic renal cell carcinoma.

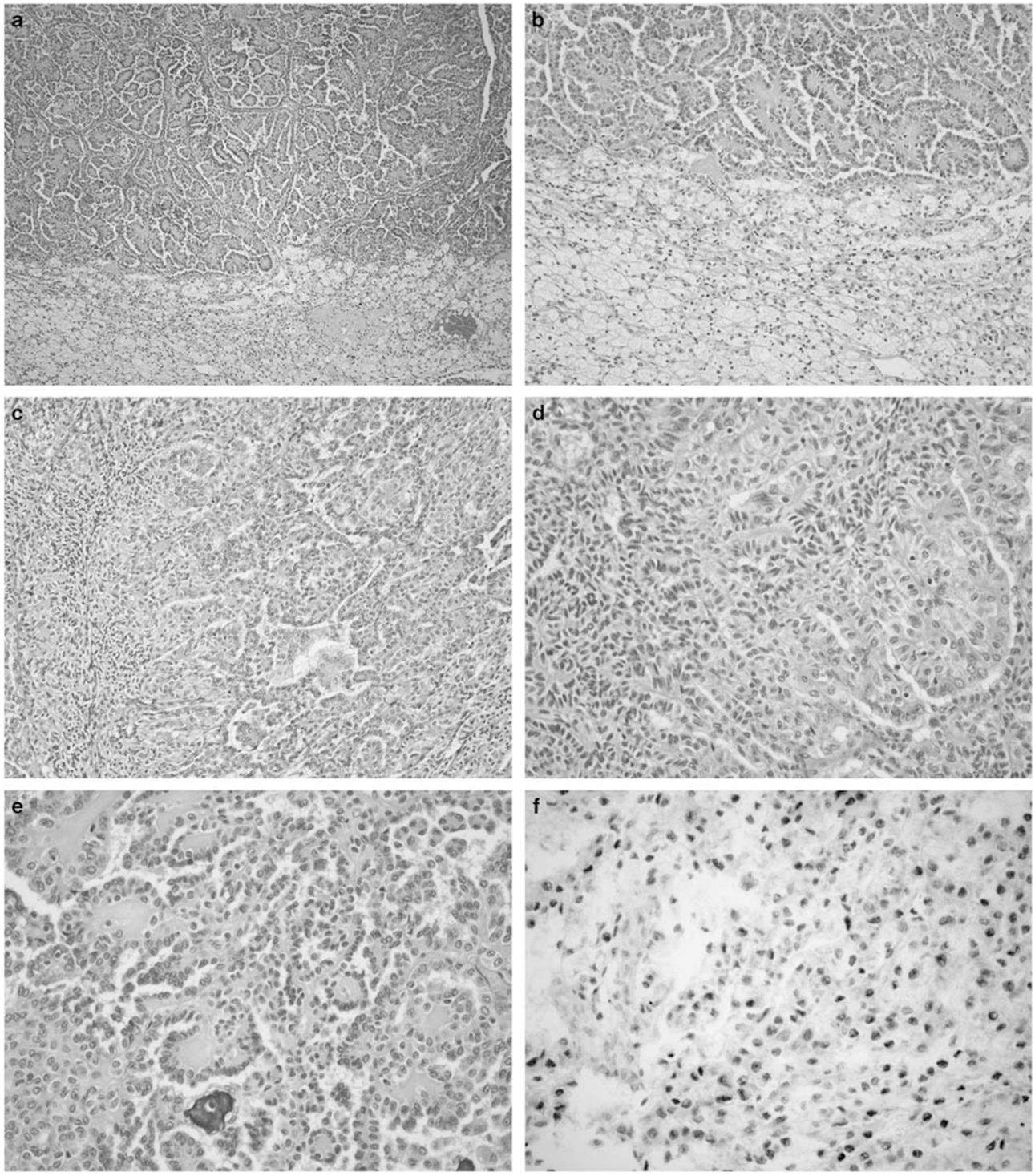

Figure 1 New *PRCC-TFE3* renal cell carcinoma with t(X;1)(p11;q21). (**a–d**) H&E sections of compact, nested clear cell areas with abrupt transitions to papillary areas. (**e**) Psammomatous calcification. (**f**) Strong nuclear labeling for TFE3 protein.

Immunohistochemical studies revealed diffuse nuclear immunoreactivity for TFE3 protein and minimal labeling for S 100 protein. Rare cells were labeled for epithelial membrane antigen, cytokeratin AE1/AE3, and cytokeratin 7. At the submitting institution, reactions for glial fibrillary acidic protein, chromogranin, desmin, and actin were all negative.

Ultrastructural examination revealed moderately preserved cells with swollen mitochondria and membrane-bound lysosomal structures. There was no crystalline-like material present. RT-PCR with

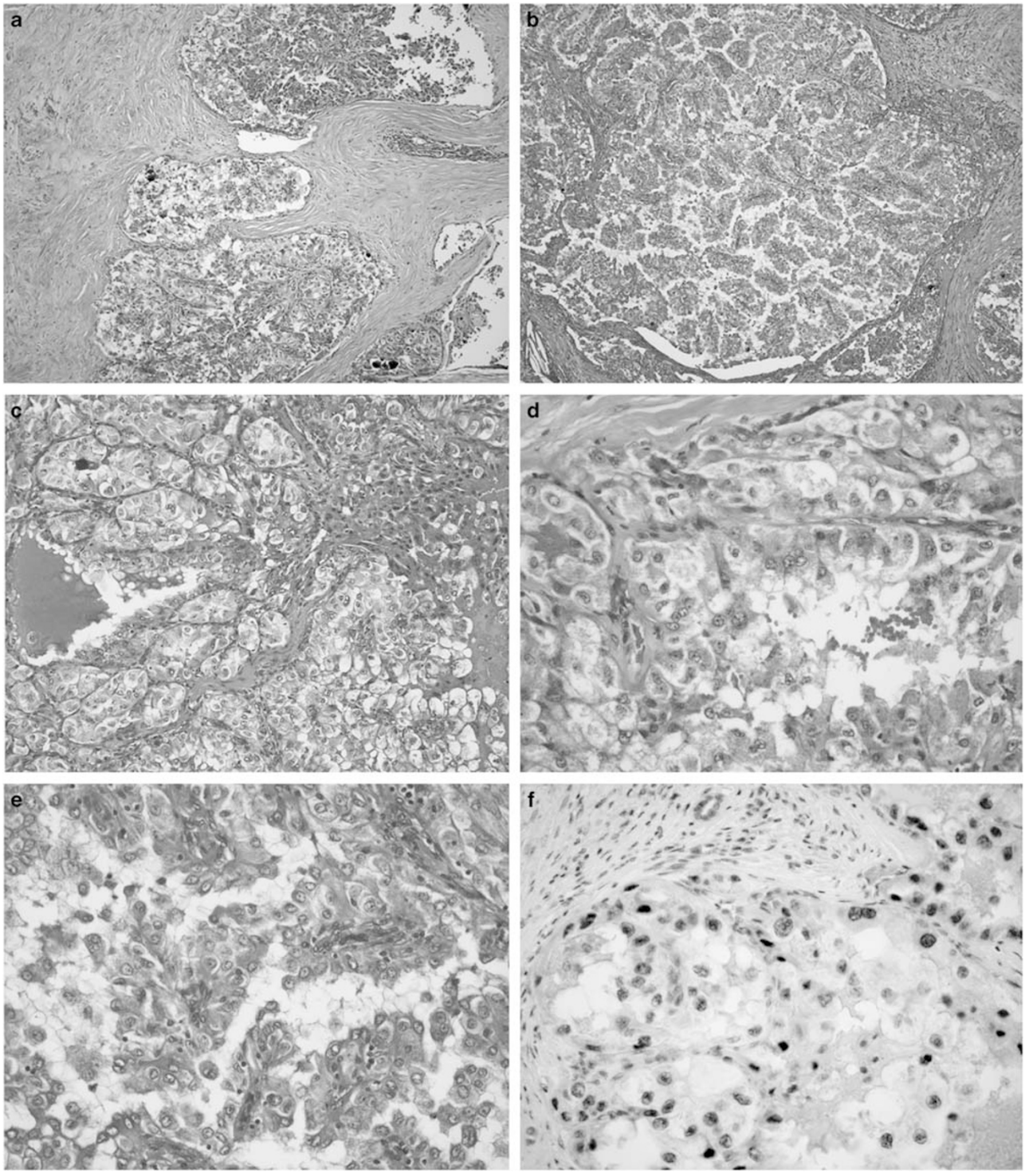

Figure 2 New *ASPSCR1-TFE3* renal cell carcinomas with t(X;17)(p11;q25). (**a–e**) H& E-stained sections of nested pseudopapillary growth pattern featuring dyscohesive cells with voluminous cytoplasm. (**f**) Strong, nuclear labeling for TFE3 protein.

ASPSCR1 and *TFE3* primers was positive for the type 1 *ASPSCR1-TFE3* fusion product. A computed tomography scan performed 1 year later showed progression in the retroperitoneal lymph nodes as well as in the hilum of the left lung. At this point, the patient was lost to follow-up.

Literature Review of *PRCC-TFE3* Renal Cell Carcinomas and *ASPSCR1-TFE3* Renal Cell Carcinomas

PRCC-TFE3 cases. The new *PRCC-TFE3* renal cell carcinoma case and results of the literature review

are presented in Table 1.[4,8–29] Follow-up for these cases ranged from 1 to 30 years (mean 4.5 years, median 7.1 years). The mean age of these patients was 24 years and the median 20 years (range 2–69 years). The gender distribution of these cases was nearly equal (17 males and 20 females). Among these 37 cases, stage was reported in 26: 9 were stage 1; 2 were stage 2; 13 were stage 3; and 2 were stage 4. Among patients with stage 1 disease, all nine on whom there was follow-up showed no evidence of disease. The one stage 2 patient with follow-up recurred at 2.5 years following resection. Among the seven stage 3 patients on whom there is follow-up, four died of disease. Two developed metastases (retroperitoneum and liver) 2 years after resection, and one patient showed no evidence of disease after 30 months. Two patients presented with stage 4 disease due to locally advanced primary tumors (T4 disease) but follow-up was not available on those patients.

Lymph node status was evaluable in only 14 of the 37 patients; in the remaining cases, lymph nodes were not examined microscopically. Among the patients for whom lymph nodes were examined, nine had uninvolved nodes (N0 disease), whereas five had involved nodes (N1 disease). Four patients in the node-positive group had stage 3 disease (ie, no evidence of distant metastasis or T4 disease). Among these patients, two died of disease at 10 years and 20 months, respectively, whereas one developed retroperitoneal metastases at 2 years. One patient showed no evidence of disease at 36 months follow-up. No patient with *PRCC-TFE3* presented with distant metastases (M1 disease).

ASPSCR1-TFE3 cases. The new *ASPSCR1-TFE3* renal cell carcinoma case and cases from the literature review are presented in Tables 2 and 3.[17,26,28–49] Follow-up for these cases ranged from 0.17 to 19 years (median 2.75 years, mean 5.35 years), which on average is less than that for the *PRCC-TFE3* renal cell carcinomas. The mean age of these patients was 21 years and the median age was 13 years (range 1–75 years). There was a female predominance (25 F: 16M). Stage was evaluable in 40 of the 41 *ASPSCR1-TFE3* renal cell carcinomas in the literature. Among these cases, 9 presented at stage 1, 1 at stage 2, 18 at stage 3, and 12 at stage 4. Among patients with stage 1

Table 3 Comparison of *ASPSCR1-TFE3* and *PRCC-TFE3* renal cell carcinomas

	ASPSCR1-TFE3 *RCC (n = 41)*	*Outcome*	PRCC-TFE3 *RCC (n = 37)*	*Outcome*
Age (years)				
Mean	22	NA	24	NA
Median	13	NA	20	NA
Gender				
Male	16 (49%)	6/14 NED; 2/14 AWD;1/14 AWPD; 5/14 DOD	17 (46%)	4/8 NED; 2/8 AWPD; 2/8 DOD
Female	25 (61%)	15/22 NED; 3/22 AWPD; 4/22 DOD	20 (54%)	4/9 NED; 3/9 AWD; 2/9 DOD
Overall stage				
I	9 (22.5%)	6/9 NED (mean 5.5 year follow-up); 3/9 DOD (8.9, 3.3, 2.2 year)	9 (34.6%)	9/9 NED (mean 6 year follow-up)
II	1 (2.5%)	1/1 NED 8 years	2 (7.7%)	1/1 Peritoneal recurrence at 2.5 years
III	18 (45%)	12/14 NED (mean 7 year follow-up); 2/14 DOD	13 (50%)	4/7 DOD; 2/7 AWD (progressive) at 2 years; 1/7 NED 2.5 years
IV	12 (30%)	4/12 DOD; 4/12 AWPD; 2/12 AWD; 2/12 NED (11, 4.5 years)	2 (7.7%)	NA
Unknown	1		11	
Nodal status				
N0	8 (25%)	5/8 NED; 1/8 AWPD; 2/8 DOD	9 (64.3%)	5/6 NED;1/6 DOD
N1	24 (75%)**	13/21 NED; 1/21 AWD; 2/21 AWPD; 5/21 DOD	5 (35.7%)**	1/4 NED; 1/4 AWPD; 2/4 DOD
NX	9	2/7 NED; 1/7 AWD; 2/7 AWPD; 2/7 DOD	23	2/5 NED; 2/5 AWPD; 1/5 DOD
N1 stage III	16	11/13 NED (mean 7 year follow up); 2/13 DOD	4	2/4 DOD; 1/4 AWPD; 1/4 NED 3 years
M1 at presentation	8*	4/8 DOD; 3/8 AWPD; 1/8 NED 4.5 years	0*	NA
Recurrence after 5 years	0	NA	2 (6%)	One intrarenal recurrence at 20 years, one bone metastasis at 30 years

Abbreviations: AWD, alive with disease; AWPD, alive with progressive disease; DOD, dead of disease; NA, not applicable; NED, no evidence of disease.
*$P = 0.02$.
**$P = 0.02$.

ASPSCR1-TFE3 renal cell carcinoma, six showed no evidence of disease in follow-up, whereas three patients died by disease at 26 months, 40 months, and 8.9 years. The solitary patient with stage 2 disease showed no evidence of disease at 8 years. Among the 18 patients with stage 3 *ASPSCR1-TFE3* renal cell carcinomas, 14 had follow-up. Twelve of these patients showed no evidence of disease including three patients who received no adjuvant therapy and had prolonged follow-up (9 years, 10 years, and 19 years, respectively). Two patients died of disease at 31 months and 23 months, respectively. Among the 12 patients with stage 4 *ASPSCR1-TFE3* renal cell carcinoma, 4 died of disease, 4 are alive with progressive disease, 2 are alive with disease, and 2 showed no evidence of disease at 4.5 and 11 years follow-up.

Among the 41 cases of *ASPSCR1-TFE3* renal cell carcinoma, 32 had nodes examined microscopically. Of these, 24 had involved lymph nodes (N1 disease), whereas 8 had uninvolved lymph nodes (N0 disease). Among 16 *ASPSCR1-TFE3* renal cell carcinoma patients with N1 stage 3 disease (ie, no evidence of distant metastasis or T4 disease which would make them stage 4), 11 showed no evidence of disease, including the 3 patients noted above who had no adjuvant therapy and prolonged follow-up. Two patients died of disease at 31 months and 23 months, respectively, whereas follow-up was not available on three of these cases.

Eight patients with *ASPSCR1-TFE3* renal cell carcinoma presented with distant metastases (M1 disease). Four of these patients died of disease, whereas three are alive with progressive disease. One patient who presented with a liver metastasis shows no evidence of disease with 4.5 years of follow-up. This patient had received interferon-2 alpha and vaccine tumor lysate-pulsed dendritic cells.

Comparison of *ASPSCR1-TFE3* and *PRCC-TFE3* Renal Cell Carcinomas

The data reported above are summarized in Table 3 for comparison. The ages of patients with *ASPSCR1-TFE3* renal cell carcinoma and *PRCC-TFE3* renal cell carcinoma were not statistically different. Although the numbers are small, *ASPSCR1-TFE3* renal cell carcinomas were statistically more likely to present with involved nodes (24 of 32 evaluable cases) than were *PRCC-TFE3* renal cell carcinomas (5 of 14 evaluable cases ($P=0.02$). All eight patients from the literature who presented with distant metastases (M1 disease) had *ASPSCR1-TFE3* renal cell carcinomas. Stated differently, 8 of 40 patients with *ASPSCR1-TFE3* renal cell carcinoma on whom stage was recorded presented with distant metastasis, whereas none of the 26 such patients with *PRCC-TFE3* renal cell carcinoma did ($P=0.02$). However, the patients with N1 stage 3 disease (ie, involved nodes but no evidence of T4 disease or distant metastases) tended to have different outcomes. Although the difference was not statistically significant, three of the four patients with N1 stage 3 *PRCC-TFE3* renal cell carcinomas either died of disease or progressed, whereas only 2 of 13 evaluable *ASPSCR1-TFE3* renal cell carcinomas presenting with N1 stage 3 disease progressed ($P=0.06$).

On multivariate analysis, only older age (hazard ratio 1.04, $P=0.003$) and advanced stage at presentation (stage 4 *versus* stage 1, 2, and 3; hazard ratio 5.1, $P=0.018$) independently predicted death. Fusion subtype ($P=0.287$) and gender ($P=0.848$) were not independent significant predictors of death. A Kaplan–Meier plot of survival *versus* stage is presented in Supplementary Figure 1.

Discussion

We report new cases of *PRCC-TFE3* and *ASPSCR1-TFE3* renal cell carcinoma, and review the existing literature on these neoplasms (mostly small series and case reports). We attempted to contact the authors of all reports in the literature to provide the most current update of knowledge on these neoplasms. One striking finding of our study is that there was a tendency for *ASPSCR1-TFE3* renal cell carcinomas to present at more advanced stage than the *PRCC-TFE3* renal cell carcinomas. This tendency for advanced stage was reflected in a greater likelihood of having involved regional lymph nodes (N1 disease), as well as a greater likelihood of presenting with distant metastases (M1 disease). In our original reports of these distinctive neoplasms, we noted a trend toward a difference in the tendency to present at advanced stage,[3,4] but review of the literature provides additional cases, which make this difference statistically significant. Furthermore, we note that urologists performing nephrectomies often perform a lymph node dissection only if the lymph nodes seem enlarged by radiography or intraoperative examination. Along these lines, the greater frequency of lymph node sampling among the *ASPSCR1-TFE3* renal cell carcinomas (32 of 41 cases) compared with the *PRCC-TFE3* renal cell carcinomas (14 of 37 cases) supports the concept that the former spreads to lymph nodes more frequently.

It is tempting to speculate that the difference in clinical presentation between the *ASPSCR1-TFE3* and *PRCC-TFE*3 renal cell carcinomas reflects functional differences between the two fusion proteins, which are postulated to act as transcription factors, which drive the underlying biology of these neoplasms. Along these lines, we previously noted that the *ASPSCR1-TFE3* renal cell carcinomas tend to have higher nuclear grade and more voluminous cytoplasm than the *PRCC-TFE3* renal cell carcinomas.[3,4] A further more objective difference between these neoplasms is their differential immunohistochemical expression of the cysteine protease cathepsin K.[50,51] We have previously shown that a

majority (12 of 14, or 86%) of *PRCC-TFE3* renal cell carcinomas diffusely express cathepsin K, whereas all eight *ASPSCR1-TFE3* renal cell carcinomas tested have been negative for this immunohistochemical marker. As cathepsin K expression is typically driven by the transcription factor MITF, which is in the same family as TFE3 and TFEB, and has overlapping activity, our hypothesis has been that the PRCC–TFE3 fusion protein is better able to activate cathepsin K expression compared with the ASPSCR1–TFE3 fusion protein. It seems plausible that biological distinctions such as this and others between these two neoplasms may drive the differing clinical behavior documented in this report. We caution, however, that the overall numbers of cases in this literature review are still small, and the level of statistical significance of the difference is not robust. Furthermore, we recognize that the cases reviewed here were resected, processed, and treated at different institutions using different protocols, so that differences in surgical approach, pathologic examination, and treatment could potentially have influenced the data. Furthermore, we noted considerable clinical heterogeneity in the cases, with some patients with advanced disease dying rapidly, whereas others followed a more indolent course. Therefore, we believe that further experience and prospective data are required before our observations can be confirmed.

Although the *ASPSCR1-TFE3* renal cell carcinomas were more likely to present at advanced stage than the *PRCC-TFE3* renal cell carcinomas, we note that those patients with node positive but non-metastatic (N1 stage 3 disease) tended to have a worse outcome when they had a *PRCC-TFE3* renal cell carcinoma than if they had an *ASPSCR1-TFE3* renal cell carcinoma, although the difference was not statistically significant. Moreover, *PRCC-TFE3* renal cell carcinomas have been documented in the literature to recur late (20 and 30 years after diagnosis). Hence, advanced local stage at presentation may not reflect the overall long-term outcome of these patients. As these neoplasms typically demonstrate low proliferation rates (typically less than 5%)[3,4] and are known to have the capacity to recur late, long-term (over 20 year) follow-up is needed to more accurately determine their biologic behavior. Furthermore, a low proliferative rate may explain the relatively indolent course of *ASPSCR1-TFE3* renal cell carcinoma in patients 3 and 8 who have each survived with disease for over 10 years.

It should be noted that there is a precedent for the association of different fusion subtypes within the same translocation-associated neoplasm with differing biological features and clinical outcomes. For example, among Ewing sarcomas, the type 1 *EWS–FLI1* fusion (fusing exon 7 of *EWS* with exon 6 of *FLI1*) is associated with lower transcriptional activity, lower proliferative rate, and a more favorable outcome than are other variant *EWS–FLI1* gene fusions,[52–54] although current treatment protocols have eliminated this prognostic advantage.[55] Among alveolar rhabdomyosarcomas, those tumors with the *PAX7–FOXO1* gene fusion have a more favorable outcome than those with the *PAX3–FOXO1* gene fusion.[56] Further differences include the fact that *PAX7–FOXO1* fusion gene is amplified in the majority of alveolar rhabdomyosarcomas, whereas the *PAX3–FOXO1* is not.[57] Finally, the *SYT1–SSX2* gene fusion in synovial sarcoma has been more strongly associated with monophasic spindle cell histology compared with the *SYT1–SSX1* gene fusion,[58] although whether fusion status is an independent predictor of outcome is debated.[59,60] Although these examples highlight the potential for fusion subtype to impact patient care, they emphasize the need for prospective data to validate these distinctions. Regardless, as Barr *et al* have pointed out,[61] fusion subtype has relevance in detection of minimal residual disease, in design of potential antisense-targeted therapy, and in distinction of second primaries from recurrences, regardless of any prognostic implications.

The reported cases have raised the possibility that older age is an unfavorable prognostic factor for Xp11 translocation renal cell carcinomas.[29,33,46] This was confirmed in our multivariate analysis, in that older age and advanced stage independently predicted death. The association of older age with worse outcome is supported by recent genetic data by Malouf *et al*,[62] who found more genetic alterations (particularly chromosome 17q gain) in adult Xp11 translocation renal cell carcinomas compared with pediatric cases. Although the *ASPSCR1-TFE3* renal cell carcinomas tended to present at advanced stage, advanced stage (specifically stage 4 disease) but not fusion type independently predicted death. This likely reflects the relatively indolent course of patients with stage 3 N1M0 *ASPSCR1-TFE3* renal cell carcinomas, which counterbalances the aggressive course of *ASPSCR1-TFE3* patients with stage 4 disease. We caution, however, that the number of cases in our series is small, and it is possible that node status impacts long-term outcome. We recognize that the limited power of our study because of the small number of cases does not allow one to definitely conclude that node status is not important.

Finally, review of the literature on these renal cell carcinomas as well as that of other genetically confirmed Xp11 translocation renal cell carcinomas provides some useful information for clinicians who must treat patients with this disease. We note that one of the patients in this series (*ASPSCR1-TFE3*-case 40) responded to sorafenib, and that the new *PRCC-TFE3* renal cell carcinoma case reported in this study stabilized under sunitinib therapy. Moreover, two other genetically confirmed Xp11 translocation renal cell carcinomas in the literature (fusion partner not determined) responded to sunitinib.[63,64] These data suggest the possible efficacy of utilizing tyrosine kinase inhibitors in treating these neoplasms. The Juvenile Renal Cell Carcinoma network

has reported a partial response and disease stabilization in patients receiving mammalian target of rapamycin inhibitor therapy, although it is not clear how many of these cases were confirmed to be Xp11 translocation renal cell carcinomas genetically.[65] However, we note that other patients in our review failed to respond to these same treatments. Moreover, the one patient who has survived with no evidence of disease despite hematogenous metastasis (M1 disease; *ASPSCR1-TFE3* Case 33) responded to immune therapy including tumor vaccine and interleukin 2 treatments, whereas these treatments have been ineffective in other patients (such as case 12 of reference 38 and case 2 of reference 26). These reports highlight that a single effective treatment remains out of reach at the current time for these neoplasms, and underscore the importance of further genetic analysis[66,67] to identify potential targets such as MET (known to be induced by *TFE3* gene fusions[66]) for effective, nontoxic therapies for these patients.

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Disclosure/conflict of interest

The authors declare no conflict of interest.

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