The Natural History of Wilms Tumor—A Case Comparison of Two Different Tumors

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Due to the rarity of Wilms tumor (WT) and the relative urgency with which pediatric renal tumors are treated, there is little reported data on the natural history and growth of WTs. Historical reports of estimated doubling times of WTs were based on time to disease recurrence after initial diagnosis and treatment, and were published before the current advancements in molecular biomarker testing. We compare 2 cases of WT with sequential imaging, and postulate how the growth parameters of these tumors may be associated with differing chromosomal traits.   UROLOGY 130: 151−154, 2019. © 2019 Elsevier Inc.

Considering they are generally treated or resected quite promptly, very little is known about the natural history of Wilms tumor (WT) left *in situ*. Reported doubling times (DT) and growth rates (GR) are based largely on historical data extrapolated from tumor recurrences. Recent genetic studies have identified chromosomal abnormalities, that if present in WT, negatively impact recurrence and survival, but have an unknown effect on tumor growth. We present 2 cases, 1 with and 1 without loss of heterozygosity (LOH) at chromosome 1p and 16q, and postulate how this tumor characteristic may affect DT and GR.

CASE-PRESENTATION

A 4-year-old male was referred to our tertiary care center with a right retroperitoneal bleed diagnosed on computed tomography (CT) after flank trauma. His initial scan was suspicious for a 2.40 cm ×2.34 cm × 2.47 cm underlying renal mass (Fig. 1A-C). After extensive counseling, the family elected conservative management with short interval follow-up imaging. Renal ultrasound 4 weeks later identified a more obvious renal mass with vascular flow. A repeat CT was obtained, which confirmed the presence of a now 2.91cm × 2.77 cm × 2.43 cm solid right renal mass (Fig. 1D-F). After discussion with the pediatric oncology team, the decision was made to proceed with an open,

right partial nephrectomy and lymph node dissection (LND). Final pathology revealed stage II favorable histology (FH) WT. Zero of 3 nodes (0/3) were positive, and the tumor was positive for LOH at chromosome 1p and 16q. He initiated Children's Oncology Group (COG) AREN0532 protocol, and because of his +LOH, he received regimen DD4A (25 weeks of vincristine (VCR), dactinomycin (DACT), and doxorubicin). Twelve months after the initial diagnosis, he remains disease free.

The second case involves a 17-year-old male who was diagnosed at an outside hospital with a 5.28 cm × 5.53 cm × 6.51 cm "renal hematoma" (Fig. 2A-C) a year prior to intervention. He was lost to follow-up after his initial presentation but represented with a palpable left flank mass and was then referred to our tertiary care center. Updated chest and abdominal CT were obtained, which revealed growth of a solid renal mass to 14.30 cm × 13.65 cm × 14.00 cm in the left kidney without associated lymphadenopathy or metastasis (Fig. 2D-F). He underwent left radical nephrectomy and LND with pathology significant for stage II favorable histology Wilms tumor (FHWT). Zero of 53 nodes (0/53) were positive, and LOH testing at chromosome 1p and 16q was negative. He was started on COG AREN0532 protocol with regimen EE4A (19 weeks of VCR and DACT). After 10 months of follow-up, he remains free of disease.

DISCUSSION

There are few publications assessing the natural history or GR of WT. Previously reported estimated WT DTs are based on historic data extrapolated from time to disease recurrence and range from 11-40 days.[1,2] These DTs have been used to create screening recommendations for patients who are at risk for developing WT, who are currently monitored with renal ultrasound every 3-4 months.[3]
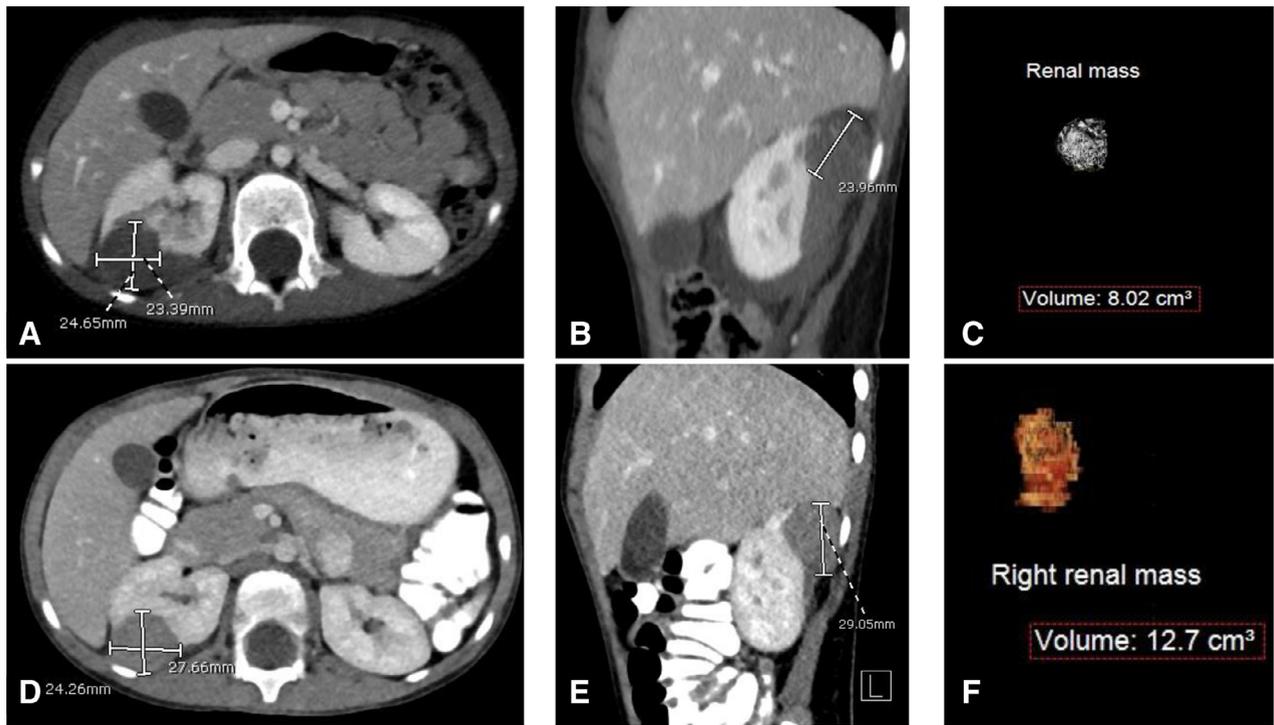
Figure 1. Contrast enhanced computed tomography (CT) of the tumor identified in case 1. Representative images from the initial CT in the axial (**A**), sagittal (**B**), and 3D volume rendering reconstruction (**C**) views show a primarily hypodense and slightly heterogeneous lesion in the upper pole of the right kidney with surrounding hemorrhage in the perinephric region. Follow-up imaging of the same patient in the axial (**D**), sagittal (**E**), and 3D volume rendering reconstruction (**F**) views demonstrates interval increase in size of the lesion with resolution of the perinephric hematoma.
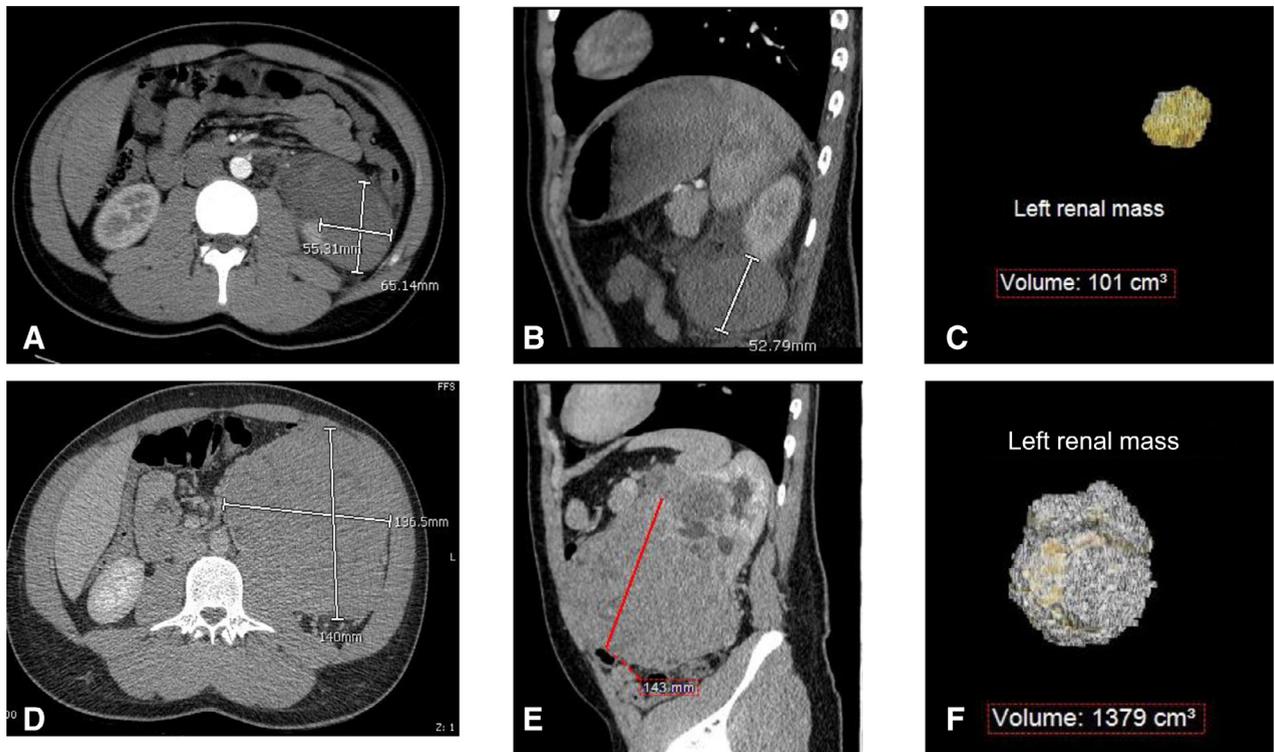
Figure 2. Contrast enhanced computed tomography (CT) of the tumor identified in case 2. Representative images from the initial CT in the axial (**A**), sagittal (**B**), and 3D volume rendering reconstruction (**C**) views of the tumor. Images demonstrate a solid, hypodense lesion in the left lower renal pole with overlying measurements. Follow-up CT imaging of the same patient in the axial (**D**), sagittal (**E**), and 3D volume rendering reconstruction (**F**) views demonstrate marked interval enlargement of the tumor.

Table 1. Wilms tumor growth parameters and loss of heterozygosity status

	Volume Change (mL) = (V − V₀)	Doubling Time (d) = (T − T₀) × log2/log(V/V₀)	Specific Growth Rate = ln (V/V₀)/(T − T₀)	LOH Status
Case 1	+4.68	48.25	0.014	Positive
Case 2	+1278	99.44	0.007	Negative

LOH, loss of heterozygosity; T, date of most recent tumor imaging; T_0, date of initial tumor imaging; V, most recent computed tomography 3D reconstruction volume; V_0, initial computed tomography 3D reconstruction volume.

Multiple studies have published on the DTs and GRs of renal tumors.[4,5,7-12] Most of these studies calculate tumor volume based on CT measurements, which have been shown to correlate with pathologic renal specimen volumes.[4] The 2 most common modalities to determine tumor volume used throughout these publications are either 3D CT reconstruction software or an ellipsoid volume equation based on planar tumor measurements:

$$\text{Ellipsoid volume} = l \times w \times h \times (\pi/6)$$

Rkein et al demonstrated that CT 3D reconstruction techniques for determining tumor volumes were more reliable with less intra- and interobserver variability, especially for irregularly shaped tumors.[5] Therefore, for our cases, tumor volumes were calculated using a TeraRecon 3D workstation (TeraRecon Inc., iNtuition Ed. Ver.4.4.13.P2).

DT is typically calculated using the Schwartz equation for volumetric doubling time (VDT)[6]:

$$\text{VDT} = (T - T_0) \times \log2/\log(V/V_0)$$

Mehrara et al published on tumor specific GR (SGR) in malignancies such as pancreatic carcinoma, lung cancer, and hepatocellular carcinoma as being a more accurate assessment of tumor growth than DT alone[7]:

$$\text{SGR} = \ln(V/V_0)/(T - T_0)$$

Using these standardized equations and reconstruction software, we calculated tumor volume, VDT, and SGR for each case mentioned above (Table 1). VDT for the +LOH tumor in case 1 was noted to be 2× shorter than the -LOH tumor from case 2 (48.25 vs 99.44 days). Likewise, this corresponded to a 2× higher SGR (0.7% vs 1.4%). For comparison, typical DT for adult renal cell carcinoma (RCC) is reported between 150 and 1200 days.[8,9] The wide ranges of reported VDT and GR in RCC have been shown to be related to disease stage, Fuhrman grade, and biomolecular differences in the tumors.[9-11] In addition to these tumor characteristics, Secil et al reported that overall tumor volume may be predictive of survival in patients with RCC.[12]

The 2 tumors in our case were similar regarding histology and stage at presentation (stage II FHWT), but had notably different cytogenetic findings at chromosomes 1 and 16. Although the discrepancy in length of follow-up and the small number of cases make it difficult to draw definitive conclusions, the growth parameters of these 2 tumors, 1 with LOH at 1p and 16q and 1 without, appear to be quite different.

LOH on chromosome 1p and 16q is a known risk factor for decreased overall survival and increased relapse rates in patients with FHWT. For patients with stage I and II FHWT, LOH at both regions resulted in a relative risk of recurrence of 2.9 and death of 4.3 compared to patients without LOH at either locus.[13] In line with these findings, COG recommends that patients with +LOH have intensified therapy with the addition of doxorubicin to the standard VCR and DACT chemotherapy. There is also elongation of treatment from 19 to 25 weeks.[14] Because LOH positive tumors are known to be more aggressive, it is possible that this characteristic may also translate to a more rapidly growing tumor.

More recent COG studies have evaluated the effect of another WT chromosomal abnormality, gain of 1q. Gratias et al showed that patients with FHWT and 1q gain versus those without demonstrated inferior 8-year overall and event free survival, 88% versus 96% and 77% versus 90%, respectively.[15] In comparison to LOH at 1p and 16q, gain of 1q in FHWT is much more common (28% vs 11%)[14,15], which makes it an attractive prognostic indicator for future risk-stratified therapy protocols. It is unknown if gain of 1q impacts tumor GR.

CONCLUSION

Previously reported WT DT and GR are based on historical data in a time prior to the currently available molecular biomarkers. Based on our experience, DT and GR for FHWT can vary widely, which could possibly be due to known or unknown genetic variations within the tumor. As more is learned about the differing biology of WT, in particular regarding chromosomes 1 and 16, this knowledge may be used to better risk-stratify WT patients.

References

1. Shackney SE, McCormack GW, Cuchural GJ. Growth rate patterns of solid tumors and their relation to responsiveness to therapy: an analytical review. *Ann Intern Med.* 1978;89:107–121.
2. Collins V, Loeffler R, Tivey H. Observations on growth rates of human tumors. *Am J Roentgenol Radium Ther Nuclear Med.* 1956;76:988–1000.
3. Scott RH, Walker L, Olsen ØE, et al. Surveillance for Wilms tumour in at-risk children: pragmatic recommendations for best practice. *Arc Dis Childhood.* 2006;91:995–999. https://doi.org/10.1136/adc.2006.101295.
4. Choi SM, Choi DK, Kim TH, et al. A comparison of radiologic tumor volume and pathologic tumor volume in renal cell carcinoma (RCC). *PLoS One* 2015;10. https://doi.org/10.1371/journal.pone.0122019.

5. Rkein AM, Harrigal C, Friedman AC, Persky D, Krupinski E. Comparison of the accuracy of CT volume calculated by circumscription to prolate ellipsoid volume (bidimensional measurement multiplied by coronal long axis). *Acad Radiol*. 2009;16:181–186. https://doi.org/10.1016/j.acra.2008.08.013.

6. Schwartz M. A biomathematical approach to clinical tumor growth. *Cancer*. 1961;14:1272–1294. https://doi.org/10.1002/1097-0142(196111/12)14:6<1272::AID-CNCR2820140618>3.0.CO;2-H.

7. Mehrara E, Forssell-Aronsson E, Ahlman H, Bernhardt P. Specific growth rate versus doubling time for quantitative characterization of tumor growth rate. *Cancer Res*. 2007;67:3970–3975. https://doi.org/10.1158/0008-5472.CAN-06-3822.

8. Lee JY, Kim CK, Choi D, Park BK. Volume doubling time and growth rate of renal cell carcinoma determined by helical CT: a single-institution experience. *Eur Radiol*. 2008;18:731–737. https://doi.org/10.1007/s00330-007-0820-x.

9. Lee SW, Sung HH, Jeon HG, et al. Size and volumetric growth kinetics of renal masses in patients with renal cell carcinoma. *Urology*. 2016;90:119–125. https://doi.org/10.1016/j.urology.2015.10.051.

10. Zhang L, Yin W, Yao L, et al. Growth pattern of clear cell renal cell carcinoma in patients with delayed surgical intervention: fast growth rate correlates with high grade and may result in poor prognosis. *BioMed Res Int*. 2015;2015:1–8. https://doi.org/10.1155/2015/598134.

11. Zhang L, Yao L, Li X, Jewett MAS, He Z, Zhou L. Natural history of renal cell carcinoma: an immunohistochemical analysis of growth rate in patients with delayed treatment. *J Formos Med Assoc*. 2016;115:463–469. https://doi.org/10.1016/j.jfma.2015.05.003.

12. Secil M, Cullu N, Aslan G, et al. The effect of tumor volume on survival in renal cell carcinoma patients. *Diagn Interv Radiol* 2012;. https://doi.org/10.4261/1305-3825.DIR.5346-11.1.

13. Grundy PE, Breslow NE, Li S, et al. Loss of heterozygosity for chromosomes 1p and 16q is an adverse prognostic factor in favorable-histology Wilms tumor: a report from the National Wilms Tumor Study Group. *J Clin Oncol*. 2005;23:7312–7321. https://doi.org/10.1200/JCO.2005.01.2799.

14. AREN0532: treatment for very low and standard risk favorable histology Wilms tumor [www document], n.d. URL Available at: https://childrensoncologygroup.org/index.php/aren0532 (Accessed December 9, 2018).

15. Gratias EJ, Dome JS, Jennings LJ, et al. Association of chromosome 1q gain with inferior survival in favorable-histology Wilms tumor: a report from the Children's Oncology Group. *J Clin Oncol*. 2016;34:3189–3194. https://doi.org/10.1200/JCO.2015.66.1140.