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Feasibility of using CT volume as a predictor of specimen weight in a subgroup of patients with low risk Wilms tumors registered on COG Study AREN03B2: Implications for central venous catheter placement

Fernando A. Ferrer, M.D.^{1,*}, Katherine W. Herbst, M.S.², Conrad V. Fernandez, M.D.³, Geetika Khanna, M.D.⁴, Jeffrey S. Dome, M.D., Ph.D.⁵, Arlene Naranjo, Ph.D.⁶, Elizabeth A. Mullen, M.D.⁷, James I Geller, M.D.⁸, Eric J Gratias, M.D.⁹, Robert Shamberger, M.D.¹⁰, Michael Ritchey, M.D.¹¹, and Peter F. Ehrlich, M.D.¹²

¹Connecticut Children's Medical Center, 282 Washington Street, Hartford, CT 06106/University of Connecticut Medical School, 263 Farmington Avenue, Farmington, CT 06030. ²Connecticut Children's Medical Center, 282 Washington Street, Hartford, CT 06106.

kherbst@connecticutchildrens.org ³IWK Health Center, PO Box 9700 RPO CSC, Halifax, NS

B3K6R8. Conrad.Fernandez@iwbk.nshealth.ca ⁴Washington University School of Medicine, 660

S. Euclid Avenue St. Louis, MO 63110. khannag@mir.wustl.edu ⁵Children's National Medical

Center, 111 Michigan Avenue NW, Washington, DC 32607. JDome@childrensnational.org

⁶Children's Oncology Group Statistics & Data Center, 6011 NW 1st Place, University of Florida,

Gainesville, FL. anaranjo@cog.ufl.edu ⁷Children's Hospital of Boston, 300 Longwood Avenue,

Boston, MA 02115/Dana-Farber Cancer Institute, 450 Brookline Avenue, Boston, MA 02215.

Elizabeth_Mullen@dfci.harvard.edu ⁸Cincinnati Children's Hospital Medical Center, 3333 Burnt

Avenue, Cincinnati, OH. 45229/University of Cincinnati College of Medicine, 51 Goodman Drive,

Cincinnati, OH 45267. james.geller@cchmc.org ⁹Children's Hospital at Erlanger, 975 Third

Street, Chattanooga, TN 37403/University of Tennessee College of Medicine, 910 Madison,

Chattanooga, TN 38163. egratiasmd@comcast.net ¹⁰Children's Hospital of Boston, 300

Longwood Avenue, Boston, MA 02115/Harvard Medical School, 25 Shattuck Street, Boston, MA

02115. robert.shamberger@childrens.harvard.edu ¹¹Mayo Clinic College of Medicine, 550 E. Van

Buren, Phoenix, AZ 85004. michael.ritchey@gmail.com ¹²University of Michigan Medical School,

1301 Catherine, Ann Arbor, MI 48109. pehrlich@med.umich.edu

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* Corresponding author. Connecticut Children's Medical Center, 282 Washington Street, Hartford, CT 06106/University of Connecticut Medical School, 263 Farmington Avenue, Farmington, CT 06030, USA. fferrer@connecticutchildrens.org (F. A. Ferrer)..

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Conflict of interest

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Abstract

Objective—Patients with stage I Wilms tumor, age ≤ 2 years, tumor ≤ 550 g may not require therapy beyond nephrectomy. This study's aims were to determine: (1) if a linear relationship exists between tumor weight and computed tomography (CT) estimated volume; (2) describe the accuracy of a slope-intercept equation in estimating weight; and (3) determine the potential impact of weight estimation on port placement decisions.

Materials and methods—Tumor weight and port placement information were abstracted from 105 patients, age ≤ 2 years, with tumors ≤ 550 g, enrolled in COG AREN03B2. One radiologist estimated tumor size from CT scan. Prolate ellipse volume (PEV) was calculated, linear regression performed, slope-intercept equation calculated, equation estimated weight determined, and potential impact of the on port placement evaluated.

Results—A strong relationship exists between PEV and weight ($R^2=0.87$). The slope-intercept equation for weight was: $\text{weight}=1.04(\text{PEV})+58.75$. Overall median relative error for the equation was 0.9%, and -3% in tumors weighing 350-750 g. Fifty-five ports were placed, 29 in patients with tumor weight ≤ 550 g, and six not placed in patients with tumor weight >550 g.

Conclusions—The relationship between PEV and weight produced a reliable weight prediction equation. Preoperative consideration of specimen weight may diminish the number of ports placed in this population.

Keywords

Wilms tumor; Computed tomography; Central venous catheter; Nephrectomy; Nephroblastoma

Introduction

The Children's Oncology Group (COG) AREN0532 study for children with very low risk and standard risk favorable histology Wilms tumors (WT) aims to determine if nephrectomy only for children ≤ 2 years, with stage I, favorable histology WT ≤ 550 g, and documented negative lymph nodes is associated with an acceptable event-free survival and overall survival approaching 100%. AREN0532 aims to replicate the findings of NWTS-5 in which nephrectomy alone was used for this group of patients. In that study, accrual of patients was halted when 2-year event-free survival dropped below the anticipated 90%. Eleven of 75 patients (15%) experienced relapse or the occurrence of metachronous disease in the other kidney [1]. Long-term follow-up revealed that, although the event-free survival was below expectations, the estimated 5-year overall survival was 98%, setting the stage to readdress the efficacy of a surgery-only arm in the AREN0532 study [2]. This approach allows for a significant number of patients to avoid central line placement, chemotherapy, and its associated adverse effects.

Volume, the quantity of three-dimensional space occupied by an object, and weight, the pull of gravity on an object, are not equal. While it is known that tumor size correlates with weight, the ability of the preoperative computed tomography (CT) scan derived volume to accurately estimate specimen weight has not been carefully evaluated within the context of a surgery only protocol [3-5]. For the purposes of initial risk classification on AREN03B2, the

pathology nephrectomy specimen weight is used to determine the treatment arm. This evaluation, however, typically does not occur in real time. Optimally, patients needing a central venous catheter (CVC) would have it placed under the same anesthetic. Conversely, CVC placement can be a morbid procedure, associated with vascular accidents, thrombosis, and infection, which could be avoided if surgeons were alerted preoperatively that a patient may be a candidate not to receive adjuvant chemotherapy.

The primary aim of this study was to evaluate a cohort of patients enrolled on the COG AREN03B2 Renal Tumor Biology and Classification Study to assess the ability of preoperative CT scan-based volume to estimate final specimen weight. We also attempted to address how this information may have impacted decision-making relative to CVC placement.

Materials and methods

Data for this study was obtained by reviewing patient records from the COG AREN03B2 Renal Tumors Classification, Biology, and Banking Study. AREN03B2, first initiated in February 2006, contains patient data from 192 sites and over 3700 enrollees. The majority of patients enrolled (75%) report a histologic diagnosis of Favorable Histology (FH) Nephroblastoma (WT). Among other data, the study collects the institutional pathology and operative report, a copy of CT imaging of the chest and abdomen, and representative pathological slides.

Patients were included in this study if they were: (1) enrolled in AREN03B2; (2) 2 years of age at time of study enrollment; and (3) had a pathological diagnosis of unilateral Stage I FH WT. Pilot data from 60 patients with the same inclusion criteria were used to estimate the sample size needed to maintain a 95% confidence interval of ± 0.04 from the sample slope. For a two-sided 95% confidence interval, assuming a sample slope of 0.50, a sample size of 105 patients was found to be adequate. Based on this estimate, the records of 105 of the most recently enrolled patients who met the inclusion criteria were reviewed. Age at study enrollment, gender, tumor weight, CVC placement at time of tumor resection, and CVC placement timing (before/after) relative to the nephrectomy were recorded.

Preoperative CT scans were reviewed by a COG Renal Tumor Committee radiologist (GK) to determine tumor size. The prolate ellipse volume formula (PEV), $(\text{length} \times \text{width} \times \text{height} \times \pi)/6$, was used to calculate volume as it has been reported to be the most effective geometric mathematical equation for estimating tumor mass based on visual assessment of CT scan [6].

Estimation of tumor weight by the patient's surgeon as >550 g was *a priori* defined as the decision to place a CVC during tumor removal surgery. We recognized that other factors may influence this decision, including lack of familiarity with current protocols, uncertainty of pathological stage, and preoperative family decision not to accept nephrectomy only as treatment if confirmed to be WT, and accepted these as possible confounders for the purpose of this analysis.

Statistics were performed using SPSS 17.0 (IBM Corporation, Armonk, NY, USA). Linear regression was performed to identify the degree of association between CT-derived volume and actual weight. Pearson's R^2 was calculated to determine goodness of fit. A slope-intercept equation (prediction equation) was calculated based on the linear regression line, with weight as the criterion variable and PEV as the predictor variable. Percent relative error $[(\text{estimated weight} - \text{true weight})/\text{true weight}] \times 100$ was used to report accuracy of the prediction equation. Positive predictive value (PPV), sensitivity, and specificity were calculated for both the prediction equation's estimated tumor weight and the surgeon's estimate of tumor weight using actual tumor weight as the gold standard.

This research, which used de-identified data, was not considered human subjects research in accordance with the Common Rule (45CFR §46.102[f]) and the policy of the Connecticut Children's Medical Center Institutional Review Board. However, the AREN03B2 study, which served as the mechanism to collect the data, was reviewed and approved by the pediatric central IRB (PCIRB) and the institutional IRBs, if applicable.

Results

Data from 105 of the most recently enrolled patients meeting the inclusion criteria were analyzed. Gender was almost evenly divided with 53 male and 52 female patients. Median on-study age was 14 months. Median tumor weight was 409 g. Median PEV was 342 cc. Median PEV for tumors ≤ 550 g was 260 cc (Table 1).

Linear regression demonstrated a strong relationship between PEV and tumor weight ($R^2 = 0.87$, $p < 0.001$) (Fig. 1). The prediction equation for PEV was $\text{weight} = 1.04(\text{PEV}) + 58.75$ (95% confidence limits: 0.96-1.12 for PEV; 21.02-96.47 for intercept). Median relative error was 0.9% for the cohort as a whole. When divided into weight categories, median relative error was -7.1% for tumors over 750 g, -3.1% for tumors between 350 g and 750 g, and 8.0% for tumors under 350 g.

A total of 55 central venous access devices were placed at the time of nephrectomy, with 82% placed before the tumor was excised. Assuming it was desired to place a CVC in tumors >550 g and not desired to place a CVC in tumors ≤ 550 g, the correct decision was made 67% of the time by the patient's surgeon. Most of the opportunity seen represented unnecessary CVC placement (Type I error), as 29 CVCs were placed in patients with tumors weighing ≤ 550 g. Six patients with tumors >550 g did not undergo CVC placement (Table 2). The prediction equation resulted in the correct decision made 90% of the time within the teaching cohort, with five patients undergoing unnecessary CVC placement, and five patients with tumors >550 g not undergoing CVC placement (Table 3).

Discussion

Our findings demonstrate that tumor volume calculated from preoperative CT scan can, with a good degree of accuracy, ascertain patients who may be candidates for surgery only treatment, thus identifying patients unlikely to need CVC procedures. Our findings support our earlier published findings of a linear relationship between CT derived WT volume and WT weight within 1131 of the first 2000 patients enrolled in COG AREN03B2 who

underwent a primary unilateral nephrectomy for favorable histology and which included a wider range of WT sizes and patient ages [7]. These updated findings are derived from a cohort of patients ≥ 2 years of age and a pathological diagnosis of Stage I, FH WT.

The prediction equation had a median relative error of $<1\%$ overestimation of weight within the teaching cohort. The equation tended to overestimate smaller tumors, with a median relative error of 8% in tumors <350 g, and underestimate larger tumors, with a median relative error of 7% underestimation in tumors >750 g. Importantly, the prediction equation was most accurate in tumors weighing 350-750 g, with a median relative error of 3% underestimation. This is significant as the greatest uncertainty in physician tumor weight estimation most likely falls within this critical weight range.

CVC placement at the time of tumor resection is considered optimal, allowing for both procedures to be accomplished under a single anesthetic. This is an important consideration as there is a growing body of literature based on animal studies showing that prolonged and repeated anesthesia can adversely affect neurologic, cognitive, and social development of neonates and young children [8].

The combination of both procedures may also expedite initiation of chemotherapy after the patient has sufficiently recovered from surgery, likely the primary indication for CVC in these patients. Other potential indications include utility for blood drawing, hemodynamic monitoring, administration of vasoactive medicines, and total parenteral nutrition.

Despite their many uses, CVC placement is not without associated risk, mandating that their placement be performed judiciously. Potential complications include arterial puncture, which occurs in roughly 6-8% of placements. This may lead to hematoma, hemothorax, pseudoaneurysm, embolic events, or arteriovenous fistula. Other well-known complications include pneumothorax in 2% of patients, CVC malpositioning in up to 10% of patients, thrombosis with variable recorded rates from 12% to 28%, and blood stream infections [9]. CVC placement may also influence the decision to administer chemotherapy simply due to its presence [10].

Our results suggest that, in some cases, preoperative CT scan-based weight estimates may alert the surgeon to patients that might qualify for surgery only protocols, thus avoiding unnecessary CVC placement. Successful application of this concept would require deferring placement of CVC until the tumor and kidney are removed and weighed. Those patients with weights >550 g could then go on to have line placement after nephrectomy. In this study, over half of the CVCs were placed in children with tumors ≤ 550 g, with the majority of CVCs placed before the tumor was resected. Six children did not have devices placed that ultimately required access for chemotherapy. Therefore, it is clear that some degree of preoperative discussion with the oncology team would be required to apply this strategy.

This study was limited by our inability to abstract all factors influencing the physician's decision to place a central venous access device. Although a tumor may be small, the accuracy of determining lymph node status, and thus stage, based on CT scan is limited [11,12] and parental decision-making with the oncology team may opt for chemotherapy.

Therefore, it is likely that the opportunity to limit CVC placement is less than our data would suggest. We would argue, however, that at least some placements could be avoided.

Additionally, accuracy of estimating volume from geometric mathematical equations based on visual assessment of CT scan is known to contain error because of several factors including inter-observer variability of measurements, variation in patient respiration and motion, quality of image, ability to accurately identify tumor boundary, and irregularity of biological shapes [13-15]. As accuracy of deriving a prediction equation and the prediction equation's results are highly dependent on the accurate estimation of volume, inherent error is unavoidable, and can have a dramatic effect on weight estimation. Taking all of this into account, we state again that the estimated weight should not be the final word. Actual specimen weight should be the final arbiter and the preoperative weight estimate used only to alert surgeons to patients that might be enrolled in surgery only protocols.

Finally, caution should be used when applying the prediction equation as the equation should only be applied to patients ≥ 2 years of age with a diagnosis of unilateral WT suspected to be less than 550 g.

Conclusions

A strong relationship exists between CT derived WT volume and actual WT weight, allowing for a viable slope-intercept equation with an overall median relative error within the teaching cohort of approximately 1% overestimation of actual weight, and approximately 3% underestimation in tumors weighing 350-750 g. PPV of the prediction equation was 84% compared with a PPV of 47% among our surrogate measure, and specificity rose from 60% to 93% when predicting weight with the equation. The use of preoperative estimate of specimen weight may provide an opportunity to limit placement of CVCs, presuming that safety of nephrectomy only is confirmed on the current AREN0532 study, and that tumor weight is retained as a classifier in future studies (biologic criteria are playing an ever increasing role). Attention to preoperative CT volume and the potential to avoid CVC placement will require further provider education, early CT identification of patients who may fall into surgery only categories, and deferring upfront line placement until real-time specimen weight is confirmed.

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Figure 1. Linear relationship between prolate ellipse tumor volume and tumor weight with 95% confidence interval.

Table 1

Patient and tumor characteristics

Number of patients	105
Male	50 (53)
On-study age (months)	14 (<1–24)
Actual specimen weight (g)	409 (37–1366)
Prolate ellipse volume (cc)	342 (2–1179)
Prolate ellipse volume for specimens ≤ 550 g (cc)	260 (2–913)
Prolate ellipse volume for specimens > 550 g (cc)	664 (380–1179)
Prediction equation weight (g)	414 (61–1285)
Percent relative error	
Total cohort	0.9 (–31.0–105.1)
WT weight >750 g	–7.1 (–27.8–11.9)
WT weight 350–750 g	–3.1 (–27.1–85.1)
WT weight <350 g	8.0 (–31.0–105.1)
Central venous access device placement during tumor removal surgery	
Before tumor removed	82 (45)
After tumor removed	18 (10)

Data in table are given as % (n) or median (range).

Table 2

Accuracy of physician driven tumor weight estimate

		Actual tumor weight		
		+ (>550 g)	- (≤ 550 g)	
Surgeon's decision regarding CVC placement	CVC placed	26	29 Type I Error	PPV 0.47
	CVC not placed	6 Type II Error	44	NPV 0.88
		Sensitivity 0.81	Specificity 0.60	

Table 3

Accuracy of prediction equation estimated weight

		Actual tumor weight		
		+ (>550 g)	– (≤ 550 g)	
Prediction equation estimated tumor weight	+ (>550 g)	27	5 Type I Error	PPV 0.84
	– (≤ 550 g)	5 Type II Error	68	NPV 0.93
		Sensitivity 0.84	Specificity 0.93	