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Correlation between CT-estimated tumor volume, pathologic tumor volume, and final pathologic specimen weight in children with Wilms' tumor

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Abstract *Objective:* To evaluate the relationship of Wilms' tumor (WT) volume to weight, and evaluate computed tomography (CT) scan-derived final pathologic specimen weight estimation models.
Methods: We retrospectively reviewed WT patients from 2003 to 2011 who had a pre-operative CT scan, final pathologic specimen weight, and tumor dimensions. A partial nephrectomy tumor cohort ($n = 12$) was used derive WT density. A radical nephrectomy cohort ($n = 45$) was used to develop a simplified estimation equation of final pathologic specimen weight, and analysis of all known estimation models was performed.
Results: Fifty-two patients were identified. WT volume and weight were not equivalent ($p = 0.0410$). WT density was 1.3091 g/cm^3. WT volume and final pathologic specimen weight were not significant ($p = 0.0007$). Our model ($p = 0.9983$) and CT estimated ellipsoidal volume ($p = 0.0741$) were able to estimate final pathologic specimen weight in all tumors. However, CT-estimated ellipsoidal volume failed to estimate final pathologic specimen weight in specimens $<$ 250 g ($p = 0.0066$).
Conclusion: Pathologic WT volume is not equivalent to final pathologic specimen weight. Final pathologic specimen weight can be estimated from a pre-operative CT scan, which suggests that it may be used to improve pre-operative surgical planning and to reduce treatment morbidity.

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Introduction

In 1963, Garcia et al. [1] published a Wilms' tumor (WT) staging system that included *tumor volume* to assess for its prognostic value, like nearly all other solid tumors. In tumors with volume $> 550\ cm^3$, they reported a dismal overall survival of 0% [1]. Ten years later, Cassady et al. [2] published a sentinel article on WT outcomes. They used the staging system of Garcia et al. [1], but substituted *pathologic specimen weight* for tumor volume as a variable for stage I disease. At a specimen weight $<$ 550 g, they demonstrated improved survival compared with larger tumors and compared with prior studies, including Garcia et al. [2]. These studies first raised the potential value of WT size as a prognostic indicator in this subset of WT patients. Today, final pathologic specimen weight has been proposed to guide adjuvant therapy in very low-risk WT patients (stage I, favorable histology, age $\leq$ 2 years, tumor $<$ 550 g) [3–6].

Tumor weight and tumor volume have been used interchangeably in many studies looking at prognostics of WT size [1,2,4–7]. However, there has been no published research on the actual relationship between WT pathologic volume, WT pathologic weight, and final pathologic specimen weight. Additionally, several studies have shown that computed tomography (CT)-derived tumor volume may accurately predict final pathologic specimen weight. The aim of this study was to evaluate the relationship of pathologic WT volume and pathologic WT weight to the final pathologic specimen weight, and to evaluate the accuracy of CT-derived tumor volume to predict final pathologic specimen weight. We hypothesize that pathologic WT volume and weight are not equivalent to the final pathologic specimen weight and that tumor volume derived from preoperative CT scan provides an accurate estimate of final pathologic weight.

Materials and methods

After institutional review board approval was obtained (COMIRB# 11-0238), we conducted a retrospective review of patients with a primary diagnosis of WT (International Classification of Diseases 9th edition code 189.0) treated from 2003 to 2011 at the Children's Hospital Colorado (Aurora, CO, USA). Patients were excluded if they did not have pathologic confirmation of WT, pre-operative CT scan images, final pathologic specimen weight, or final pathologic tumor dimensions. Patients were then divided into radical nephrectomy and partial nephrectomy cohorts. Seventeen patients were excluded (Fig. 1). In the radical nephrectomy cohort, six patients were excluded owing to surgically unresectable disease and associated concerns regarding potential inclusion of other organs that were removed at the time of nephrectomy in the pathologic specimen weight.

In patients who met the inclusion and exclusion criteria, age, gender, mortality, surgical date, CT scan date, and pathologic specimen details (stage, histology, final pathologic specimen weight, final pathologic specimen dimensions, and final pathologic tumor dimensions) were collected as data points from the medical record. In the total nephrectomy cohort, the pathologic specimen weight included normal renal parenchyma and associated perinephric tissue removed at the time of nephrectomy in every instance.

In calculating WT volume based on CT scan and pathologic measurements, we assumed that the natural shape of WT most closely resembled that of an ellipsoid. This formula also allows for accurate estimation of smaller WT, which are typically more spherical in shape. The geometric formula for the volume of an ellipsoid that we utilized is:

$$\text{Vol of Ellipsoid } (cm^3) = (4/3)\pi(D/2)(L/2)\ (W/2)$$

A database was originated and analyzed with Excel 2010 (Microsoft, Seattle, WA, USA). *P*-values $<$ 0.05 were considered statistically significant.

Analysis of pathologic WT volume and WT weight

The partial nephrectomy cohort was used for this analysis. We assumed that partial nephrectomy specimens allow for an accurate estimation of both WT volume and WT weight owing to the lack of substantial additional tissue in the specimen. WT volume was defined as the volume of the tumor only and was derived from tumor dimensions listed in the pathology report. WT weight was defined as the weight of the tumor only and was obtained from the final pathologic specimen weight listed in the pathology report. The relationship between mass and volume of a substance depends on the density of the substance (Density = Mass/Volume). Using simple linear regression, we derived an estimate of WT density. Statistical significance was tested via a comparison of means using a two-tailed, paired Student's *t* test.

Final specimen weight estimated from CT scan

The radical nephrectomy cohort was used to derive tumor volume estimation from the pre-operative CT scans. These were individually reviewed and measurements recorded using the standard measuring tool provided in the picture archiving and communication software (PACS) at our institution. Tumor depth (D) and width (W), in centimeters, were obtained on axial CT images where the tumor appeared to be the largest in size relative to other slices. Tumor length (L) (cranial–caudal dimension) was similarly obtained on sagittal CT images (Fig. 2). In those scans that did not include sagittal reconstruction, the CT scan slice width was used to estimate the length (L) from the axial images, starting at the most cranial and ending at the most caudal extent of the tumor. Review of our measurements was confirmed by a board-certified pediatric radiologist (KLH) who was blinded to the pathologic measurements.

As previously described, CT-estimated tumor volume was derived from the geometric formula of an ellipsoid. To most accurately estimate final pathologic weight, a linear regression model was used to account for both the additional mass that accompanies the WT specimen and the density of the entire specimen. Mathematical substitution and a reduction of constants were performed to derive a simpler version of the model used to estimate final pathologic weight.

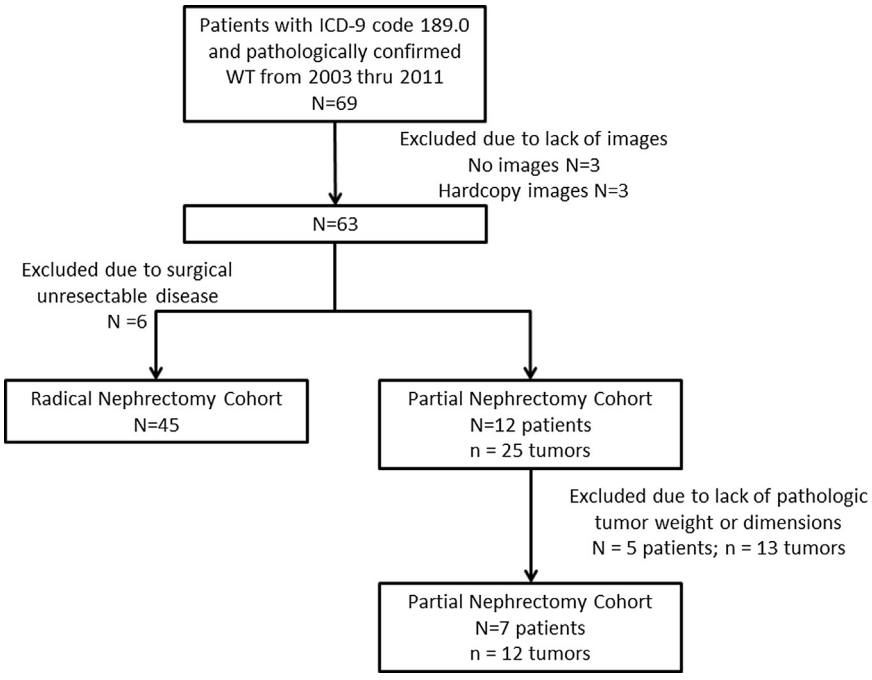

Figure 1 Flowchart demonstrating results of Electronic Medical Record search and resulting exclusions. *Note*. ICD-9 = International Classification of Diseases 9th edition; WT = Wilms' tumor.

Analysis of all known final pathologic specimen weight estimation methods

To identify all known final pathologic specimen weight estimation methods, we performed a bibliographic search on the PubMed online database from 1980 to 2012, and Google Scholar using the keywords "Wilms' tumor" and "computerized tomography volume". Twenty-two articles and one abstract were identified. All were reviewed by the primary and senior authors (TJP and VMV). Based on three articles and one abstract, we identified two regression models, as well as CT-estimated ellipsoid tumor volume, as the estimation methods previously used to estimate final pathologic weight [2,8—10].

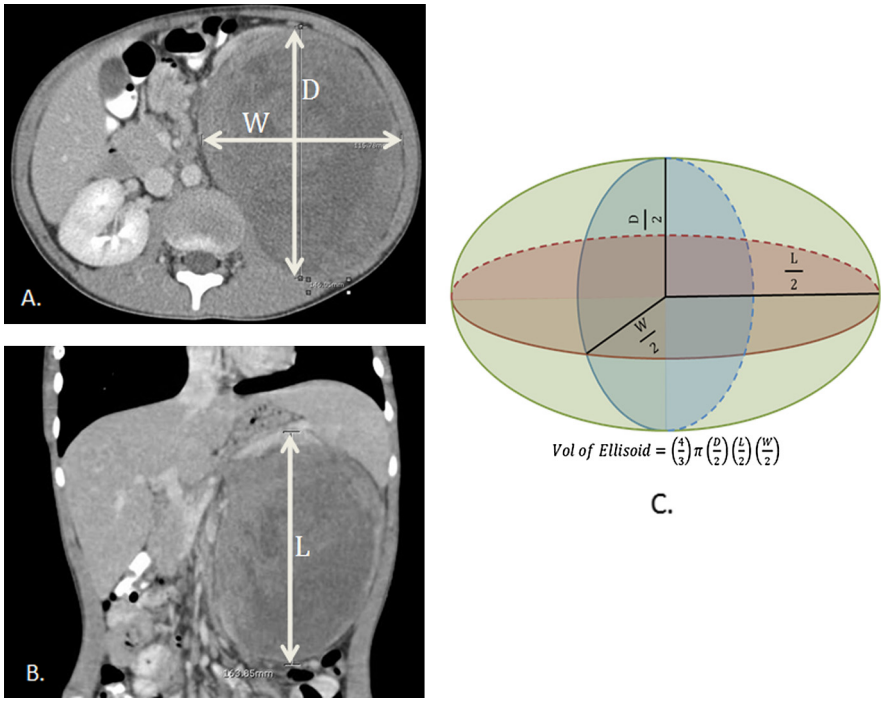

Figure 2 A. Example estimating depth (*D*) and width (*W*) in axial view of computed tomography (CT) scan. B. Example estimating length (*L*) in sagittal view of CT scan. C. Formula used to estimate tumor volume.

We analyzed the other estimation methods by comparing their results to our linear regression model, CT estimated ellipsoid volume, and the final pathologic specimen weight, which was categorized in 250-g increments. The two previously published regression models assessed were the Al-Shanafey et al. model [8] [Estimated Specimen Weight = 1.15 (CT Estimated Volume of an Ellipsoid) + 96.5.] and the Children's Oncology Group (COG) model [10] [Estimated Specimen Weight = 0.54 (CT Estimated Volume of a Cube) + 58.75]. Statistical significance was tested via a comparison of means using a two-tailed, paired Student's *t* test.

Results

Forty-five patients met inclusion and exclusion criteria in the radical nephrectomy cohort. Seven patients with 12 tumors met the inclusion and exclusion criteria for the partial nephrectomy cohort (Fig. 1). Overall patient characteristics are shown in Table 1.

Analysis of pathologic WT volume and WT weight

Based on analysis of pathologic measurements in our partial nephrectomy cohort, we estimated the density of WT to be approximately 1.3091 g/cm^3. There was a statistically significant difference between WT weight and volume ($p = 0.0410$). Although this result is limited by the small sample size, this finding suggests that WT weight and WT volume are not equivalent, and that this difference is owing to tumor density.

Final specimen weight estimated from CT scan

Fig. 3 demonstrates our linear regression estimation model of all radical nephrectomy patients derived from final pathologic specimen weight and CT-estimated tumor volume. This produced a coefficient of determination (R^2) equal to 0.966, indicating a near perfect linear relationship between the CT-estimated tumor volume and the actual pathologic specimen weight. The simplified equation to estimate final pathologic specimen weight is:

$$\text{Estimated Pathologic Weight} = 0.5(\text{DLW}) + 44$$

Table 1 Patient characteristics.

	Total nephrectomy patients ($n = 45$)	Partial nephrectomy patients ($n = 7$)
Gender		
M	23	3
F	22	4
Mean age (range)	3.0 yrs (0.1—10)	2.3 yrs (0.5—6.1)
Mean time between nephrectomy and CT scan (range)	1.7 days (0—5)	17.9 days(0—74)
No. tumors	45	12
Final pathologic stage		
I	13 (29%)	0
II	16 (36%)	0
III	11 (24%)	0
IV	5 (11%)	1 (14%)*
V	0	6 (86%)

*Patient with WAGR (Wilms' tumor, aniridia, genitourinary anomalies, and mental retardation) syndrome who underwent a percutaneous biopsy. M = male; F = female; CT = computed tomography.

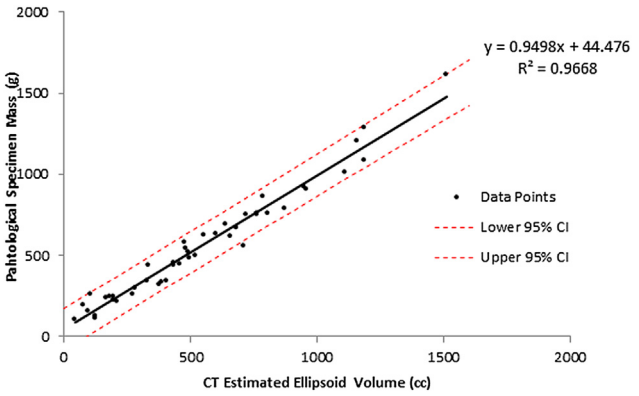

Figure 3 Computed tomography (CT) ellipsoidal volume-derived estimation of final pathologic specimen weight. *Note*. CI = confidence interval.

Analysis of all known final pathologic specimen weight estimation methods

Table 2 lists the comparison of all known final pathologic specimen weight estimation methods in our radical nephrectomy cohort. The two previously published regression models resulted in statistically significant differences from the estimated final pathologic weights when compared with the actual mean pathologic weights ($p < 0.0001$). Overall, CT-estimated ellipsoid volume provided the closest estimate of final pathologic specimen weight. The radical nephrectomy cohort had a mean CT-estimated tumor volume of 538 cm^3, which was not significantly different from the actual mean pathologic weight of 555 g ($p = 0.0741$).

In the subset of tumors < 250 g, the COG model allowed for accurate estimation of final pathologic weight, while CT-estimated volume underestimated the final pathologic weight. This suggests that CT-estimated volume may not be valid for very small tumors and is most likely a result of associated benign tissue included in the final pathologic specimen weight. It also suggests that a regression equation, which has the ability to account for this additional benign tissue, is necessary to accurately estimate the final pathologic specimen weight in very small tumors.

Discussion

Our study has three significant findings. First, we have shown that pathologic WT volume and WT weight are not equivalent. We have also shown that WT volume and final pathologic specimen weight are not equivalent. These differences are owing to the density of WT being greater than 1.0 g/cm^3 and the final pathologic specimen containing more tissue that the tumor itself. Assuming a specimen does not contain any additional tissue, using our estimated

WT density alone suggests that a 550-cm^3 pathologic tumor volume would have a final pathologic specimen weight of 715 g. Thus, the substitution of WT volume for final specimen weight may have attributed to the drastic difference in overall survival reported in early WT studies [1,2].

Second, our study shows that final pathologic specimen weight can be predicted from a pre-operative CT scan. Estimating tumor burden from a CT scan has had significant clinical applications in other oncologic diseases where it has been used to stratify patients in clinical trials, guide therapy, and assess chemotherapeutic responses to new drugs [11–13]. In the WT population, the ability of CT to predict WT pathologic weight was initially described in two patients in 1984 [14]. More recently, two regression models have reported final specimen weight predictability [8,10]. However, when we attempted to validate these models with our dataset, there were substantial, statistically significant differences in the estimation of final pathologic weight. There are likely several reasons for this. First, the majority of the Al-Shanafey et al. [8] CT estimates were generated from manual measurements on hard-copy films, which are less accurate than today's computerized enhancement and zoom capabilities employed to obtain digital measurements. With regard to the COG model [10], although a larger dataset was used, patients older than 2 years of age were excluded and the majority of the tumors studied were <550 g. This coupled with CT-estimated *cuboidal volume* instead of an *ellipsoidal volume* likely limits the generalizability of their model.

We found that estimated CT ellipsoid volume performed better than the previously published regression models. The estimated CT ellipsoid volume consistently overestimated the actual pathologic WT volume in tumors > 250 g. This suggests that CT measurements are larger than the tumor measurements obtained on the pathology workbench. One likely factor is the blood flow through the tumor causing it to appear larger on imaging than the exsanguinated gross specimen. This overestimation appears to adequately compensate for the additional weight of the benign tissue in the final specimen weight. However, in tumors < 250 g, CT estimation underestimates weight. This discrepancy is likely owing to insufficient compensation for associated benign tissue where the ratio of WT tumor to benign tissue is greater. As a result, a regression model that accounts for these differences, such as the one derived in our study, is necessary to more accurately estimate final pathologic weight, especially in smaller tumors.

The ability to accurately estimate final pathologic weight has a potential impact on future prospective trials aimed at morbidity reduction treatment strategies in two key areas. The first is in very low-risk, stage I WT patients who may be cured by nephrectomy alone [3–6]. While the COG still considers this treatment investigational, AREN0532 is underway to analyze this potential treatment option. Unfortunately, patient accrual into this trial is below expectations. One of the reasons cited for poor enrollment was "central line already placed". In fact, 7% (1/14) of parents and 20% (2/10) of physicians listed this as one or more of the reasons that child was not enrolled the trial [3].

In addition to being a risk factor precluding clinical trial enrollment, placement of an unnecessary central venous catheter is not without cost and complications [15,16]. A recent presentation by Ferrer et al. [10] retrospectively reviewed a large cohort of very low-risk WT patients from the AREN03B2 COG study. They estimated that 28% of patients had a mediport placed which could have been avoided, and 6% did not have a mediport placed that should have been. Thus, our study highlights the potential benefit of pathologic specimen weight estimation in minimizing the risk of central venous catheter placement.

The second potential area of impact is in estimating tumor size pre-operatively to determine the potential benefit of chemotherapy in those tumors that are at high risk for intraoperative rupture. A randomized control trial by the United

Table 2 Comparison of all known final pathologic weight estimation methods.

	Actual pathologic weight (g)	Our model (g)	COG model [10] [a] (g)	Al-Shanafey et al. model [8],[b] (g)	Pathologic WT vol. (cm^3)	CT estimated ellipsoid vol. (cm^3)
	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD	Mean ± SD
		p	*p*	*p*	*p*	*p*
All tumors	555 ± 339	555 ± 333	614 ± 361	715 ± 403	467 ± 304	538 ± 350
(n = 45)		***0.9983***	0.0000	0.0000	0.0007	***0.0741***
>750 g	978 ± 260	975 ± 222	1069 ± 241	1223 ± 269	852 ± 205	979 ± 234
n = 13		***0.8755***	0.0005	0.0000	***0.1139***	***0.9467***
500–750 g	595 ± 64	595 ± 83	656 ± 90	763 ± 100	491 ± 117	579 ± 87
n = 10		***0.9703***	0.0318	0.0001	0.0166	***0.5027***
250–500 g	361 ± 82	372 ± 105	415 ± 114	493 ± 127	275 ± 80	345 ± 110
n = 13		***0.5029***	0.0107	0.0000	0.0038	***0.3647***
<250 g	181 ± 54	171 ± 53	196 ± 57	250 ± 64	161 ± 116	133 ± 56
n = 9		***0.4446***	***0.3040***	0.0015	***0.4953***	0.0066

Bold values represent statistically insignificant results that do not differ from the actual pathological weight.
$p < 0.05$ considered to be statistically significant from the actual pathologic weight. COG = Children's Oncology Group; WT = Wilms' tumor; CT = computed tomography.

[a] Based upon presented model of specimen weight = 0.54 (CT estimated volume of a cube) + 58.75.

[b] Based upon published model of specimen weight = 1.15 (CT estimated volume of an ellipsoid) + 96.5.

Kingdom Children's Cancer Study Group demonstrated a reduction of tumor spillage from 15% to 0% in those who received pre-operative chemotherapy [17]. The large Société Internationale D'oncologie Pédiatrique studies demonstrated a reduction of tumor spillage from 27% to 5% when treated with pre-operative chemotherapy [18]. While it is generally accepted that a pre-operative CT is unable to accurately predict final pathologic stage or pre-operative WT rupture, a recent series by Barber et al. [9,19—21] showed that a pre-operative CT estimated volume $> 1000\ cm^3$ was the sole risk factor for intra-operative tumor spillage. While treating large tumors with pre-operative chemotherapy to reduce spillage remains controversial, our study suggests that final specimen weight can be accurately estimated by a pre-operative CT scan, regardless of tumor size, which could have potential clinical impact if the findings by Barber et al. [9] are confirmed in larger-scale, prospective trials.

There are several limitations to our study. First, this is a single-site retrospective review with a relatively small number of patients. As a result, the generalizability of our findings may be limited and require external validation. Second, our model assumes that the radiological measurements would be obtained uniformly by all practitioners; however, given the widespread use of the PACS system, our methodology should be reproducible in the majority of clinical settings. Despite these limitations, our study suggests that final pathologic tumor weight can be estimated from CT scan-derived ellipsoid volume measurements and that this estimated weight can be used to improve pre-operative treatment decisions and risk stratification. Further studies are needed to validate our findings and to establish the clinical significance of this approach.

Conclusions

In children with WT, WT volume and WT weight are not equivalent to final pathologic specimen weight. However, pre-operative CT scan-derived tumor volume can provide an accurate estimate of final pathologic specimen weight. These data suggest that the pre-operative CT scan may be used in the pre-operative risk stratification of WT patients. If externally validated, this may reduce preventable morbidity associated with treating WT, including unnecessary placement of central venous catheters.

Conflict of interest

None.

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