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Imaging Analysis of Hepatoblastoma Resectability Across Neoadjuvant Chemotherapy

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Abstract

Purpose—Hepatoblastomas often require neoadjuvant chemotherapy to facilitate partial hepatectomy, which necessitates freedom of tumor borders from the confluence of hepatic veins (COHV), portal vein bifurcation (PVB), and retrohepatic inferior vena cava (IVC). This study aimed to clarify the effect of incremental neoadjuvant cycles on the AHEP0731 protocol criteria of hepatoblastoma resectability.

Methods—Hepatoblastoma responses to neoadjuvant chemotherapy were analyzed among patients (n=23) treated at two children's hospitals between 1996 and 2010. Using digital imaging data, ellipsoid and point-based models were created to measure tumor volume regression and respective distances from tumor borders nearest to the COHV, PVB, and IVC.

Results—Hepatoblastoma volumes regressed with incremental neoadjuvant chemotherapy cycles ($p < 0.001$). Although tumor borders regressed away from the COHV ($p = 0.008$), on average only 1.1mm was gained. No change from tumor borders to the PVB was detected ($p = 0.102$). Distances from tumor borders to the IVC remained stable at one hospital ($p = 0.612$), but increased only 0.15mm every 10 days of therapy at the other ($p = 0.002$). Neoadjuvant chemotherapy induced slightly more tumors to meet the threshold vascular margin of 1cm (baseline to completion): COHV, 11 (47.8%) to 17 (73.9%; $p = 0.058$); PVB, 11 (47.8%) to 15 (65.2%; $p = 0.157$); IVC, 4 (17.4%) to 10 (43.5%; $p = 0.034$). No differences were detected in demographic or disease-specific

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characteristics between patients who did or did not achieve this 1cm margin after conclusion of chemotherapy.

Conclusion—Hepatoblastoma volumes regress significantly with increasing neoadjuvant chemotherapy cycles. However, tumors often remain anchored to the major hepatic vasculature, showing marginal improvement in resectability criteria.

Keywords

hepatoblastoma; AHEP0731; neoadjuvant chemotherapy; tumor volume; tumor regression

Introduction

The embryonal tumor, hepatoblastoma, is the most common pediatric liver cancer, yet only 100–150 cases are diagnosed annually in North America. [1, 2] Most children with hepatoblastoma present before 5 years of age, often harboring initially unresectable tumors requiring neoadjuvant chemotherapy to facilitate partial hepatectomy. [3, 4] Current cisplatin-based treatment protocols have contributed to an overall survival rate between 75–80%, but complete surgical resection remains the cornerstone of therapy with curative intent for hepatoblastoma. [5, 6]

Two strategies direct the timing of surgical resection versus orthotopic liver transplantation for the treatment of hepatoblastoma. First, the North American Children's Oncology Group (COG) schema is based on tumor histology and stage, and, second, the International Childhood Liver Tumor Strategy Group (SIOPEL) applies radiographic criteria to define the pretreatment extent of tumor burden (PRETEXT) based on the number of involved liver sections. [2, 7, 8] The current COG protocol (AHEP0731) utilizes both systems to optimize cure rates for high-risk disease and to minimize treatment toxicities for low-risk hepatoblastoma. Regardless of the decision strategy used, conventional surgical resection of hepatoblastoma requires freedom of tumor borders from the confluence of hepatic veins (COHV), portal vein bifurcation (PVB), and retrohepatic inferior vena cava (IVC). The AHEP0731 protocol advises surgical resection when radiographic margins from each of these key vascular structures reach 1cm.

Two previous reports examining tumor kill and the kinetics of hepatoblastoma regression across neoadjuvant therapy suggested rapid responsiveness generally within the first two cycles of chemotherapy.[9, 10] Neither study, however, provided an analysis of how the relationship between tumor borders and the major hepatic vasculature changes with each additional cycle of chemotherapy. The current study aimed to clarify the effect of incremental chemotherapy cycles on the achievement of 1cm radiographic margins from hepatic vascular structures by 1) determining the extent of tumor border regression from the COHV, PVB, and IVC and 2) ascertaining the proportion of tumors that reach the COG benchmark 1cm radiographic margin from these three vascular landmarks. To quantify the relationship of tumor borders to key hepatic vascular structures with incremental chemotherapy cycles, we developed a novel computer program that employed ellipsoid-based estimation of tumor volume and tracked changes between the tumor ellipsoid and key vascular structures over time.

1.0 Methods

1.1 Study Design and Inclusion Criteria

To characterize the effects of neoadjuvant chemotherapy on hepatoblastoma resection criteria as defined by the current COG protocol, AHEP0731, we queried the medical records of all patients treated for COG stage III or IV hepatoblastoma at the Monroe Carell Jr.

Children's Hospital at Vanderbilt (VCH) and the St. Jude Children's Research Hospital (SJCRH) between 1996 and 2010. All aspects of this study were conducted with prior approval from the respective institutional review boards. Patients were included who had *epithelial-type* hepatoblastoma and abdominal CT scans or MRIs that were DICOM-formatted or amenable to DICOM conversion. Included patients also had abdominal imaging performed at the time of hepatoblastoma diagnosis and at various intervals throughout neoadjuvant chemotherapy. Patients having histologic subtypes of small cell undifferentiated and mixed mesenchymal hepatoblastomas were excluded because of the variability in chemotherapy regimens often administered.

1.2 Image analysis

Intra-patient image alignment was performed for each subject's 3D digitized scan in order to compare tumor changes longitudinally. Images were aligned using a registration algorithm that optimized a mutual information image metric [11]. These aligned images were used for manual selection of study-related data points set in a Cartesian volumetric space (x,y,z).

Points were collected to represent entire tumor borders and the *centers* of the inferior vena cava (IVC), the portal vein bifurcation (PVB), and the confluence of hepatic veins (COHV). The superior and inferior tumor endpoints were identified along the axial plane, as well as a series of points outlining the tumor boundaries at one quarter, one half, and three-quarters the length of the diameter between these two selected endpoints. For each two-dimensional (2D) slice, data values were interpreted between the manual selected points using a cubic spline interpolation [12]. In addition a final tumor boundary was approximated with an ellipsoid fitted to the manually selected data points using least squares fitting. For the IVC, points were selected at the center of the vessel along multiple scan image slices permitting interpolation of the vessel axially through the tumor, and allowing distance measurements between the tumor surface and IVC throughout the length of the scan. Single points were chosen at the centers of the PVB and COHV for additional distance measurements. Data points were collected for each time-point available from baseline (pre-treatment) to the final pre-surgical scan.

Principal axes, radii, and centers of ellipsoids were calculated using the principal axis theorem [13]. Tumor volume was calculated using the equation $(4/3)abc$, where a , b and c are the radii along the calculated principal axes. Distances were calculated between the ellipsoid center and the centers of the COHV, PVB, and IVC using the distance formula:

$$d_{c,p} = \sqrt{(x_c - x_p)^2 + (y_c - y_p)^2 + (z_c - z_p)^2},$$

where (x_c, y_c, z_c) is the ellipsoid center, and (x_p, y_p, z_p) is the relevant hepatic point.

1.3 Statistical Analysis

Continuous variables (e.g., age at diagnosis, alpha fetoprotein) were summarized using the median, 25th, and 75th percentiles. Categorical variables (e.g. gender, histology) were summarized using frequency counts and percentages. The 4 primary outcome measurements [tumor volume (TV), distance from tumor surface to the retrohepatic inferior vena cava (DSTIVC), distance from tumor surface to the portal vein bifurcation (DSTPVB), or distance from the tumor surface to the confluence of the hepatic veins (DSTCOHV)] were not normally distributed. Therefore, the natural log transformation was applied to each comparison to better meet the parametric assumptions of the statistical modeling. The associations between the main exposure (days on chemotherapy since baseline) and the above mentioned volume and distance endpoints (TV, DSTIVC, DSTPVB, DSTCOHV)

were investigated by multivariable linear mixed models, adjusting for potential confounding by age at diagnosis, tumor stage, baseline tumor volume, PRETEXT status, institution, and baseline DSTIVC, baseline DSTPVB, or baseline DSTCOHV for the corresponding endpoint model. All data analyses were performed using R 2.13.1. (R Development Core Team, Vienna, Austria). A significance level of 0.05 was used for statistical inference unless otherwise noted. We made no attempt to control the experiment wise type I error rate.

2.0 Results

2.1 Description of Study Cohort

Of 29 eligible epithelial-type hepatoblastoma patients, 6 were excluded due to absence of DICOM-formatted images; 23 met inclusion criteria for imaging analysis (Vanderbilt, n=11; SJCRH, n=12). Demographic and clinical comparisons between patients from each institution revealed no significant differences in gender, premature birth, comorbid Beckwith-Wiedeman syndrome, stage of disease, time to resection or transplant, mortality, chemotherapy regimen, chemotherapy toxicity, tumor histology, or patient follow-up (Table 1).

2.2 Tumor Volume Analysis

In univariate analysis, hepatoblastoma volumes regressed with incremental neoadjuvant chemotherapy cycles ($p<0.001$). Adjusting for age at diagnosis, tumor stage, baseline tumor volume, PRETEXT status, and institution, tumor volume decreased significantly ($p<0.001$) the longer a patient was on chemotherapy (Figure 1A; Table 2). Tumor volume decreased on average by 14.16% for each additional ten days of chemotherapy. Tumor volume response increased with increasing baseline tumor volume ($p=0.035$; table 2; Figure 1B) and decreased with less time since the baseline CT scan ($p<0.001$).

2.3 Analysis of Distance from Nearest Tumor Surface to the Confluence of the Hepatic Veins (DSTCOHV)

In univariate analysis, although tumor borders regressed away from the COHV ($p=0.008$), on average only 1.1mm was gained (Figure 2A–B). In the multivariate model adjusting for age at diagnosis, tumor stage, baseline tumor volume, baseline DSTCOHV, PRETEXT status, and institution, no effect was demonstrated on DSTCOHV over time ($p=0.458$), nor were any tested variables associated with an increase in DSTCOHV (table 3). For the COHV, 11 of 23 (47.8%) patients had a vascular margin >1 cm at baseline and 17 (73.9%) patients had a margin >1 cm at conclusion of neoadjuvant chemotherapy ($p=0.058$).

2.4 Analysis of Distance from Nearest Tumor Surface to the Portal Vein Bifurcation (DSTPVB)

In univariate analysis, no change from tumor borders to the PVB was detected ($p=0.102$; Figure 2C–D). In the multivariate model adjusting for age at diagnosis, tumor stage, baseline tumor volume, baseline DSTPVB, PRETEXT status, and institution, DSTPVB increased significantly as patients stayed longer on chemotherapy ($p=0.038$; Table 3). The DSTPVB increased by 5.0% for each additional ten days of chemotherapy. DSTPVB was greater over time for older children ($p=0.026$; Table 3). For every 6 months older in age at diagnosis, the estimated distance from the nearest tumor surface to the PVB increased 10.17%. For the PVB, 11 of 23 (47.8%) patients had a margin >1 cm at baseline, and 15 (65.2%) had a margin >1 cm at conclusion of neoadjuvant chemotherapy ($p=0.157$).

2.5 Analysis of Distance from the Nearest Tumor Surface to the Retrohepatic Inferior Vena Cava (DSTIVC)

In univariate analysis, we observed an institutional effect on response of DSTIVC over time; distances from tumor borders to the IVC remained stable at VCH ($p=0.612$) but increased 0.15mm every 10 days of therapy at SJCRH ($p=0.002$; Figure 2E–F). In the multivariate model adjusting for age at diagnosis, tumor stage, baseline tumor volume, baseline DSTIVC, PRETEXT status, and institution, DSTIVC did not change appreciably over time ($p=0.826$). However, changes in DSTIVC were associated with older age at diagnosis ($p=0.006$) and smaller baseline tumor volume ($p=0.032$; Table 3). For the IVC, 4 of 23 (17.4%) patients had a margin >1 cm at baseline and 10 (43.5%) had a margin >1 cm at conclusion of neoadjuvant chemotherapy ($p=0.034$).

3.0 Discussion

This study showed that hepatoblastoma tumor volumes regress continually with incremental neoadjuvant cycles of chemotherapy. However, improvements in resectability criteria, specifically the radiographic margins of tumor surface to major hepatic vasculature, do not show consistent improvement in univariate or adjusted models, particularly when the AHEP0371 criteria of a 1 cm margin from the COHV, PVB, and IVC are utilized.

With respect to the COHV, there is *statistically* significant tumor regression, but it is not clear that a 1.1mm mean change in distance between the tumor edge and the COHV would be *clinically* significant and would likely not improve resectability. Given that there was no demonstrated multivariate effect, it is possible that the increase in the proportion of patients with a COHV margin > 1 cm at the end of chemotherapy was due to a population effect. From the standpoint of the PVB, multivariate analysis did reveal a treatment effect with additional chemotherapy, particularly in older children. In our sample size, we did not detect a significant increase in the proportion of patients with a PVB margin > 1 cm, but it is possible that a larger study would have demonstrated significance. We were able to demonstrate a significant increase in the proportion of patients with an IVC margin > 1 cm. The most likely explanation for the difference in results across institutions was a difference in patient populations.

The continued volumetric regression of hepatoblastoma throughout neoadjuvant chemotherapy expands on our previous study of Vanderbilt hepatoblastoma patients, which showed significant tumor volume reduction through the second cycle of induction chemotherapy, after which each additional cycle achieved a continued, but statistically insignificant, regression in volume.[9] In the current study, monotonic regression analysis identified the largest decrease in tumor volume between cycles 1 and 2 of chemotherapy, confirming that the benefits of volume regression occur early in the course of treatment (data not shown). As a result, the current standard of care, requiring four to six cycles of chemotherapy prior to surgical resection, may achieve diminishing returns in both tumor regression and regression away from major vascular structures much earlier than would be expected. While reduction in tumor volume is often critical to achieve adequate remnant liver volume for resection of large hepatoblastomas, the effect of neoadjuvant chemotherapy on volume alone does not account for tumor behavior at the vascular margins.

In an effort to reduce treatment-associated toxicity, the main goal of the current COG study, AHEP0731, is to achieve surgical resection of all tumors after the fourth cycle of chemotherapy, even if this requires complete hepatectomy and orthotopic liver transplant (OLT). The protocol recommends surgical resection after either the 2nd or 4th cycle for intermediate-risk Stage III or IV patients, and after the 4th cycle for high-risk patients, when vascular margins reach 1 cm. The early benefits of chemotherapy (greatest volume decline

by the 2nd cycle of chemotherapy) and the inconsistent improvement in hepatoblastoma resectability criteria over increasing cycles of neoadjuvant chemotherapy found in the present study support the collective goals of AHEP0731 to minimize treatment toxicity and to achieve earlier resection of hepatoblastoma, either in the form of partial or total hepatectomy with OLT. It is important to note the trend in *individualization* of therapy in the AHEP0731 protocol compared to earlier treatment protocols, which corresponds to the fact that individual tumors may have different degrees of responsiveness to chemotherapy based on aspects of tumor biology that we do not yet understand. Individualized therapy allows for each patient to maximize the benefits of chemotherapy in terms of tumor regression while minimizing the risk of ineffectual chemotherapy.

The decrease in tumor volume without accompanied improvement in radiologic vascular resection criteria indicates that a significant proportion of tumors shrink toward the major hepatic vasculature rather than regress centripetally (e.g. toward the center of the tumor; Figure 3 and Figure 4). It is important to note that the principle of “regression to the mean” explains the fact that these effects are often hidden, demonstrating a significant overall effect even when a number of tumors do not respond as expected. This observation of regression toward key vascular structures is potentially explained by biologic anchoring along a tumor’s blood supply. Despite the conventionally held notion that epithelial-type hepatoblastomas are uniquely responsive to chemotherapy relative to many other liver tumors, the tumor regression toward the major hepatic vasculature demonstrated in our vector and volume analyses should caution surgeons that increasing chemotherapy cycles may shrink the tumor overall, but may not yield improvement in vascular resection criteria. Therefore, our findings support the aim of AHEP0731 to reduce treatment toxicity by defining the operative strategy for a given hepatoblastoma patient after the 2nd or 4th cycle of chemotherapy (i.e. if the tumor has not become resectable by the end of the 4th cycle of chemotherapy, transplant is likely the best option to achieve cure in the absence of both surgical resectability and response to chemotherapy).

Due to its retrospective nature, the current study was limited by variability and lack of standardization in abdominal imaging protocols. For example, baseline scans from the SJCRH patient population, which was accrued from broadly diverse referral institutions, had been performed at a variety of hospitals and had variable imaging protocols, including use of either CT or MRI and differing contrast administration and slice thickness. Importantly, these limitations underscore the need for referring institutions to adhere to standardized imaging protocols established in COG studies such as AHEP0731. Appropriately, imaging protocols evolved over the time period of this study (14 years), which illustrates the need for larger, prospective, multi-center studies performed over a more narrow time period. Also, future imaging protocols used to monitor the responsiveness of hepatoblastoma to neoadjuvant therapies could apply diffusion-weighted MRI and other emerging technologies to predict onset of tumor necrosis, differentiation, or continued viability, all of which could help direct the timing of resection or need for additional therapies.[14] Although our current and previous studies demonstrate the early benefits of neoadjuvant chemotherapy to reduce tumor volumes profoundly, both are subject to potential selection bias, because unresponsive tumors appeared more likely to receive additional cycles of chemotherapy, whereas responsive tumors were more promptly resected.

It is important to note that although the margins of tumor surface to major hepatic vasculature demonstrated inconsistent improvement in resectability criteria in this study, a proportion of tumors did indeed become resectable with neoadjuvant chemotherapy, even after the fourth cycle. Therefore, for this subpopulation of patients, the risks of ongoing chemotherapy and accompanied toxicity must be weighed against the risks of liver transplant. The AHEP0731 protocol currently aims to determine whether the 4th cycle of

chemotherapy is an appropriate time point to make this risk-benefit analysis, which represents fewer cycles of chemotherapy when compared to previous treatment protocols.

In summary, although additional cycles of neoadjuvant chemotherapy may appear enticing to administer given the documented effect on tumor volume regression, our data indicate that a significant proportion of hepatoblastomas show little clinically relevant to no improvement in their major vascular margins, despite incremental cycles of neoadjuvant chemotherapy. These data call for an *earlier* and *individualized* assessment of resectability criteria, to move towards earlier resection, whether that can be achieved by partial hepatectomy or OLT, in an effort to reduce excessive treatment toxicity.

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Figure 1.

(A) Hepatoblastoma tumor volumes regressed with time and with incremental neoadjuvant chemotherapy cycles ($p < 0.001$). For every 10 more days a patient was on chemotherapy, on average, the tumor volume decreased by 14.16%. (B) Both baseline tumor volume ($p = 0.035$) and days of chemotherapy ($p < 0.001$) were found to have a statistically significant impact on tumor volume over the course of neoadjuvant treatment.

Figure 2.

(A–B) Plot of distances from the tumor surface to the confluence of the hepatic veins (COHV) by (A) cycle and (B) days of neoadjuvant chemotherapy. Although tumor borders regressed away from the COHV ($p=0.008$), on average only 1.1mm was gained. (C–D) Plot of distances from the tumor surface to the portal vein bifurcation (PVB) by (C) cycle and (D) days of neoadjuvant chemotherapy. No change from tumor borders to the PVB was detected ($p=0.102$) over the treatment period. (E–F) Plot of distances from the tumor surface to the inferior vena cava (IVC) by (E) cycle and (F) days of neoadjuvant chemotherapy. We observed an institutional effect on response of DSTIVC over time; distances from tumor borders to the IVC remained stable at VCH (red; $p=0.612$) but increased 0.15mm every 10 days of therapy at SJCRH (blue; $p=0.002$).

Figure 3.

Vector analysis of volume regression during neoadjuvant chemotherapy demonstrates the phenomenon of vascular anchoring. Directional vectors (purple lines) are of greater magnitude on the periphery of the tumor, and show regression toward the IVC. Despite significant volume regression, the tumor remains intimately associated with the IVC at the conclusion of neoadjuvant chemotherapy.

Figure 4.

3D and anatomic representation of HBL tumor volume and vascular relationships before (blue ellipsoids) and after (red ellipsoids) neoadjuvant chemotherapy. In the patient 1 (left), the pretreatment tumor (blue ellipsoid) envelops the IVC (blue line) and COHV (blue asterisk). The post-therapy analysis shows a significant reduction in tumor volume (red ellipsoid), yet a continued intimate association with the portal vein bifurcation (red dot) and inferior vena cava (red line), demonstrating the phenomenon of vascular anchoring. Patient 2 (right) similarly demonstrates minimal regression (scale in mm) away from the COHV and PVB.

Table 1

Patient Characteristics

	N	St. Jude N= 12	Vanderbilt N=11	Combined N=23
Gender	23			
Female		25.0% (3)	36.4% (4)	30.4% (7)
Male		75.0% (9)	63.6% (7)	69.6% (16)
Ethnicity	23			
African American		33.3% (4)	0.0% (0)	17.4% (4)
Caucasian		66.7% (8)	72.7% (8)	69.6% (16)
Other		0.0% (0)	27.3% (3)	13.0% (3)
Beckwith-Wiedemann syndrome	23			
No		91.67% (11)	100.00% (11)	95.65% (22)
Yes		8.33% (1)	0.00% (0)	4.35% (1)
Stage (COG criteria)	23			
III		58.33% (7)	90.91% (10)	73.91% (17)
IV		41.67% (5)	9.09% (1)	26.09% (6)
Time of Resection	23			
Delayed		72.73% (8)	72.73% (8)	72.73% (16)
No Surgery		9.09% (1)	0.00% (0)	4.54% (1)
Transplant		18.18% (2)	27.27% (3)	22.73% (5)
Survival Status	23			
No		25% (3)	0% (0)	13% (3)
Yes		75% (9)	100% (11)	87% (20)
Chemotherapy CFV	23			
Yes		100% (12)	100% (11)	100% (23)
No		0% (0)	0% (0)	0% (0)
Chemotherapy Doxorubicin	23			
No		83.3% (10)	72.7% (8)	78.3% (18)
Yes		16.7% (2)	27.3% (3)	21.7% (5)
Chemotherapy Other	23			
No		83.3% (10)	72.7% (8)	78.3% (18)
Yes		16.7% (2)	27.3% (3)	21.7% (5)
Ototoxicity	23			
No		33.3% (4)	36.4% (4)	34.8% (8)
Yes		66.7% (8)	63.6% (7)	65.2% (15)
Neurocognitive Toxicity	23			
No		91.67% (11)	72.73% (8)	82.61% (19)
Yes		8.33% (1)	27.27% (3)	17.39% (4)
Nephrotoxicity	23			
No		100% (12)	100% (11)	100% (23)

	N	St. Jude N= 12	Vanderbilt N=11	Combined N=23
Yes		0% (0)	0.00% (0)	0% (0)
Histology	23			
Mixed epithelial		91.67% (11)	100% (11)	95.65% (22)
Pure Fetal		8.33% (1)	0.00% (0)	4.35% (1)
Gestational Age (weeks)	23	30.0, 38.5, 40.0	37.8, 38.0, 38.0	35.2, 38.0, 39.5
Age at Diagnosis (months)	23	11.8, 25.0, 39.8	6.0, 9.0, 15.0	9.0, 14.0, 27.0
Days before chemotherapy				
Cycle 1	23	14.8, 21.0, 22.5	23.0, 24.0, 28.0	20.5, 22.0, 26.0
Cycle 2	22	18.5, 21.5, 25.8	23.2, 24.0, 25.8	21.0, 24.0, 25.8
Cycle 3	22	24.5, 27.0, 31.2	21.0, 24.5, 26.5	22.2, 25.5, 27.8
Cycle 4	20	29.5, 32.5, 44.5	31.5, 36.5, 48.0	30.0, 32.5, 45.2
Cycle 5	15	21.0, 30.0, 44.2	27.0, 30.0, 34.5	22.5, 30.0, 39.0
Total follow-up time (months)	19	63.0, 105.5, 124.2	27.5, 38.0, 83.0	30.0, 56.0,

A, B, C represent the lower quartile *a*, the median *b*, and the upper quartile *c* for continuous variables.

N is the number of non-missing values.

Numbers after percents are frequencies

Table 2

Effects on log(Tumor Volume)

	Estimate	Std. Error	p-value
Age at diagnosis (months)	−0.0091	0.0104	0.398
Stage (IV vs. III)	0.4899	0.4736	0.317
Log(baseline TV) (log(cm ³))	0.8110	0.3489	0.035
PreTEXT (II vs. I)	−0.2420	0.4186	0.572
PreTEXT (III–IV vs. I)	0.3496	0.4118	0.409
Institution (Vandy vs. St. Jude)	−0.2068	0.3726	0.587
Days since baseline	−0.0153	0.0018	0.000

Table 3

Effects of clinical variables on distances from tumor surfaces to key vascular structures

Effects on log(DSTCOHV)			
	Estimate	Std. Error	p-value
Age at diagnosis (months)	0.0177	0.0091	0.073
Stage (IV vs. III)	-0.0628	0.4174	0.883
Log(baseline TV) (log(cm ³))	-0.5771	0.3298	0.102
Log (baseline DSTCOHV) (log(mm))	0.1382	0.1972	0.495
PreTEXT (II vs. I)	0.0285	0.3841	0.942
PreTEXT (III-IV vs. I)	-0.2568	0.3800	0.510
Institution (Vandy vs. St. Jude)	-0.0609	0.3546	0.866
Days since baseline	0.0014	0.0018	0.458
Effects on log(DSTPVB)			
	Estimate	Std. Error	p-value
Age at diagnosis (months)	0.0161	0.0064	0.026
Stage (IV vs. III)	0.0003	0.2963	0.999
Log(baseline TV) (log(cm ³))	-0.2556	0.2203	0.267
Log(baseline DSTPVB) (log(mm))	0.3338	0.1780	0.083
PreTEXT (II vs. I)	-0.0928	0.2698	0.736
PreTEXT (III-IV vs. I)	0.2606	0.2798	0.369
Institution (Vandy vs. St. Jude)	-0.5036	0.2412	0.057
Days since baseline	0.0049	0.0022	0.038
Effects on log(DSTIVC)			
	Estimate	Std. Error	p-value
Age at diagnosis (months)	0.0646	0.0199	0.006
Stage (IV vs. III)	-0.2724	0.9367	0.775
Log(baseline TV) (log(cm ³))	-1.6794	0.7033	0.032
Log(baseline DSTIVC) (log(mm))	0.3083	0.2598	0.255
PreTEXT (II vs. I)	0.0373	0.8312	0.965
PreTEXT (III-IV vs. I)	0.0608	0.8109	0.941
Institution (Vandy vs. St. Jude)	-1.3852	0.7689	0.093
Days since baseline	-0.0010	0.0043	0.826