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Defining Hepatoblastoma Responsiveness to Induction Therapy as Measured by Tumor Volume and Serum α -fetoprotein Kinetics

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Abstract

Purpose—Hepatoblastoma is commonly unresectable at presentation, necessitating induction chemotherapy before definitive resection. To refine the paradigm for timing of resection, we questioned whether a plateau in hepatoblastoma responsiveness to neoadjuvant therapy could be detected by calculating tumor volume (TV) and serum α -fetoprotein (sAFP) kinetics.

Methods—To calculate TV and sAFP as measures of treatment responsiveness over time, infants having initially unresectable epithelial-type hepatoblastomas were identified at a single institution (1996–2008). Effects of therapy type, therapy duration, and lobe of liver involvement on TV, sAFP, margin status, and toxicity were analyzed.

Results—Of 24 infants treated for epithelial-type hepatoblastoma during this interval, 5 were resected primarily, and 15 had complete digital films for kinetics analysis. Both TV and sAFP decreased dramatically over time ($p < 0.0001$). No statistically significant difference in mean TV or sAFP was detected after chemotherapy cycle 2. Left lobe tumors had greater presenting levels of and significantly slower decay in sAFP compared to right lobe tumors ($p = 0.005$), although no statistically significant differences in TV existed between liver lobes. Resection margins did not change with therapy duration.

Conclusions—Measuring TV and sAFP kinetics accurately reflects hepatoblastoma responsiveness to induction therapy. Treatment toxicities may be reduced by earlier resection and tailoring of chemotherapeutic regimens.

Keywords

hepatoblastoma; serum alpha-fetoprotein; tumor volume; tumor decay

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Hepatoblastoma is the most common primary tumor and malignancy arising in the infant liver (1-3). Overall incidence is rare, however, as approximately 150 new cases are reported annually in the United States (1). Although the principal predictor of hepatoblastoma survival is complete surgical resection, the majority of children present with initially unresectable Stage III tumors (North American Staging System) (2,4-6). Nevertheless, the introduction of cisplatin-based therapies has achieved remarkably effective cytoreduction and greater delayed resectability (4,7,8).

The primary recommended algorithm emanating from the Intergroup Liver Study, INT-0098, was that children harboring initially unresectable hepatoblastomas (Stage III or IV) should receive four cycles of induction chemotherapy with cisplatin, 5-fluorouracil, and vincristine (CFV), each cycle separated by a minimum of three weeks (4). Post-induction resection should then be considered after the fourth cycle. However, if complete resection could not be accomplished at this treatment interval, then children should receive an additional four cycles of induction therapy, followed by a second attempt at resection.

Concern has been raised regarding the extent of treatment toxicity associated with the CFV regimen and algorithm recommended by the Intergroup Liver Study (now adopted by the Children's Oncology Group, COG). Various regimens have been analyzed prospectively against the CFV protocol and have included cisplatin and continuous infusion of doxorubicin, as well as alternating cisplatin with carboplatin in order to intensify the former (8,9). Neither of these two alternative regimens proved superior to CFV treatment efficacy, and both resulted in greater toxicity.

Adhering to the recommendations of the Intergroup Liver Study and COG, our experience has been that primary hepatoblastoma size does not appear to change appreciably after the second or third cycle of CFV. Indeed, Medary et al. reported that in three cases of hepatoblastoma, a rapid initial reduction in primary tumor volume could be observed and that a plateau in any further tumor decay appeared after cycle two (treatment according to Children's Cancer Group, CCG-8881) (10). These authors suggested that post-induction complete resection of hepatoblastoma could be accomplished after chemotherapy cycle two or three. Of note, these authors further analyzed tumor cell density before initiation of cytoreductive therapy and posited that any additional therapy in the absence of tumor volume reduction may select chemo-resistant clones of hepatoblastoma, which may prove a risk factor for future disease-relapse or progression.

Serum alpha-fetoprotein (sAFP) is a sensitive marker of active and viable hepatoblastoma and also of its development in infants having the cancer predisposition syndrome, Beckwith-Wiedemann (11,12). Furthermore, hepatoblastoma infants responding poorly to induction therapy, as estimated by persistently elevated sAFP levels, manifest a significantly worse outcome (11). However, actual sAFP decay curves have not been described for children receiving induction therapy for hepatoblastoma nor have sAFP kinetics been characterized as a measure for ongoing tumor responsiveness.

The purpose of this study was to analyze the responsiveness of epithelial-type hepatoblastoma to induction chemotherapy using tumor volume (TV) and sAFP as primary kinetic measures. Characterizing tumor decay more precisely might identify an earlier time point in the induction phase of therapy when complete resection could be accomplished and thereby permit tailoring of total cumulative therapy. Additionally, because hepatoblastoma shows a predilection to arise more commonly in the right lobe of the liver, we questioned whether any biologic difference in responsiveness to induction therapy could be detected between right and left hepatic lobes by measuring TV and sAFP. Finally, we aimed to characterize the long-term toxicity profile of hepatoblastoma survivors.

Methods

The Institutional Review Board of the Vanderbilt University School of Medicine approved all aspects of this study (IRB# 080671).

1.1 Study Design

To characterize the response kinetics of epithelial-type hepatoblastoma to induction chemotherapy, we retrospectively reviewed the charts of all children treated for any hepatoblastoma at our institution between January 1996 and October 2008. This time interval was chosen specifically to capture the introduction of digital computed tomography (CT) scanning at the Vanderbilt Children's Hospital.

According to the North American Staging system for hepatoblastoma, children having primary resection of Stage I and II tumors were excluded from TV and sAFP kinetic analysis, whereas those children determined to be unresectable at presentation, and who required biopsy and induction therapy (Stage III and IV), were included. Only children having epithelial-type hepatoblastoma, containing mixed fetal and embryonal elements on the initial biopsy, were included. Infants having small cell undifferentiated hepatoblastoma were excluded because these tumors appear to have different biology and absent or minimal sAFP production (13). All children treated for any stage epithelial-type hepatoblastoma were included in the toxicity to therapy analysis.

1.2 Hepatoblastoma Treatment at Vanderbilt Children's Hospital

The treatment algorithm for epithelial-type hepatoblastoma at our institution has been constant over the study period. Vanderbilt originally was a CCG-affiliated institution, and was enrolled in the Intergroup Liver Study INT-0098 (CCG-8881) (4,8). Briefly, children treated at Vanderbilt for Stage III epithelial-type hepatoblastoma were recommended to receive four cycles of CFV as induction therapy, and then definitive resection, followed by two additional cycles of CFV. The Vanderbilt Children's Hospital also participated in the COG study 9645, and has continued to treat children having hepatoblastoma similarly with CFV (8). Only one patient received carboplatin in place of cisplatin as part of 3-drug induction therapy during this study interval. Of note, three infants were biopsied and initiated on 4-drug (CFV plus doxorubicin) induction therapy: two of these patients ultimately received total hepatectomy and orthotopic liver transplant (OLT), while the third had right hepatectomy.

1.3 Tumor Volume and sAFP Measurements

To define hepatoblastoma responsiveness to induction therapy, tumor volumes (TV) and sAFP levels were measured as kinetic variables.

All children diagnosed with an epithelial-type hepatoblastoma had a sAFP level determined and digital CT imaging performed on presentation. After biopsy confirmed an epithelial-type hepatoblastoma, induction therapy was then instituted, and was considered cycle I. In accordance with INT-0098 and COG-9645, a minimum period of 3 weeks was allowed to elapse between cycles of chemotherapy. On admission for each subsequent cycle of induction therapy, sAFP level and digital CT imaging were obtained before administration of this next cycle and so were considered to reflect the previous cycle.

All pre-resection, digital CT studies for each patient diagnosed with an epithelial-type hepatoblastoma were reviewed on the picture archiving and communication system (PACS; IMPAX, AGFA Health Care; Ridgefield Park, NJ). To generate volumetric data, tumors were measured on each successive preoperative scan in the greatest transverse, craniocaudal, and anteroposterior planes. Coronal and sagittal reformatting were performed to assist in the

measurements. Tumor volumes were then calculated using the equation for a prolate ellipsoid according to the formula, $\frac{4}{3} \times \pi \times a/2 \times b/2 \times c/2$. If a patient had more than one tumor, each tumor volume was calculated separately from the preoperative scan and then summed.

To determine the precise hepatic lobe of origin for each tumor, involved liver segments were identified and recorded according to the Couinaud system, and consensus regarding the segment number was agreed upon between the pediatric surgeon (HNL) and the pediatric radiologist (MH). The involved liver segments were identified and recorded on the first and last preoperative scans, incorporating surgical and / or pathological findings.

sAFP levels were determined through the Vanderbilt chemistry laboratory, and were recorded as ng/ml (normal range, 0-9.9 ng/ml).

1.4 Evaluation of Long-term Treatment Toxicity

Survivorship from epithelial-type hepatoblastoma therapy is expected, although it is not without adverse effects. To determine the late toxic effects of chemotherapy for epithelial-type hepatoblastoma, we reviewed data compiled in our Survivorship Clinic. At the completion of therapy, children are seen every one to three months for the first year. After surviving two years off therapy, children are referred to our Survivorship Clinic, and are evaluated annually by our team with physical examination, laboratory monitoring of sAFP, blood counts and routine chemistries, an annual audiology examination, and a screening for speech and learning difficulties. Our survivorship assessment and care are determined by toxicities for which children may be at risk depending upon their chemotherapy regimen and doses. Children treated with CFV are at high risk for ototoxicity based on cumulative cisplatin dose, and as a result of high frequency hearing loss, may also develop speech difficulties. If the family reports that the child is having speech or learning difficulties, then formal speech therapy consultation is obtained, along with a referral to a neuropsychiatrist for neurocognitive testing.

Cisplatin also can cause renal dysfunction that may not become apparent until 10 years after therapy; so, we continue to monitor renal function annually. Recently, the COG Long-term Effects Group has required neurocognitive evaluations of children receiving ototoxic therapy.

1.5 Statistical Analysis

Primary measurements included patient demographics, treatment regimens, resection dates, and tumor margins at resection, and summary statistics were performed.

Since we cannot assume normality among the several measures in this study, continuous variables were summarized using the median, 25th and 75th percentiles. Categorical variables were summarized in contingency tables. The Wilcoxon rank sum test and non-parametric (Spearman) correlation statistics were used to assess between-group differences and linear correlations for continuous variables (e.g. duration of therapy, margin status). The chi-square goodness-of-fit test was used to assess whether the distribution of the number of resections was uniform across cycles of chemotherapy.

Neither TV nor sAFP was normally distributed. Therefore, we applied the natural log transformation to meet the assumption of our parametric analyses of these two endpoints. We used reduced monotonic regression to evaluate the synchronicity of TV and sAFP change after each cycle of induction chemotherapy (14). Further, the effects of baseline covariates including gender, type of chemotherapy, and primary lesion site (e.g., right versus left lobe) on log(AFP) and log(TV) were analyzed over days on therapy using mixed models analysis of variance (ANOVA) for repeated measures. The AR(1) correlation structure was chosen over an unstructured covariance and compound symmetric covariance based on the Bayesian information criterion. The incidence of toxicities was reported with exact 95% confidence

intervals. All analyses were conducted using SAS (SAS Institute, Cary, NC) and graphics were created using R (15).

Results

2.1 Study Population

For the study period, we treated 24 infants having an epithelial-type hepatoblastoma. Demographics of this patient group are shown in Table 1. Five infants had primary resection (Stage I) and four (Stage III) had non-digital hard copy CT images; the remaining fifteen infants, who had initially unresectable Stage III or IV tumors and complete digital CT imaging, were included for response-to-induction therapy analysis. All patients were initiated on therapy according to INT-0098 or COG-9645 recommendations. Intervals between chemotherapy cycles are shown in Table 1. However, the distribution of resections varied with therapy cycle and was not absolutely consistent with recommendations of INT-0098 (Figure 1).

2.2 Tumor Volume and sAFP Decay

Both TV and sAFP measures were highly skewed (tails to the right). Consequently, subsequent summaries and modeling of the data were made on the natural log-transformed scale of raw values to better meet the normality assumptions of our analyses. Both TV and sAFP decreased dramatically over time (Figure 2 A, B; mixed models ANOVA $p < 0.0001$). No statistically significant difference in mean TV or sAFP was detected after chemotherapy cycle 2. TV increased in one individual to a high of 443 mm³ following cycle 1 and resulted in a higher median TV than at baseline. However, median TV declined every cycle thereafter to a median of 47 mm³ following cycle 5. For sAFP, the highest median raw values occurred at presentation (60,500 ng/ml) and decreased thereafter to a median value of 23 ng/ml after cycle 5.

To assess whether TV and sAFP decay were synchronous, we assumed that the true relationship between chemotherapy cycle and both log(TV) and log(AFP) would be monotonic (Figure 2 C). For both measures, we modeled the average of all values attributable to a cycle across cycle number using reduced monotonic regression. This analysis partitioned the means across cycles into two level sets for both log(TV) (p -value = 0.002) and log(AFP) (p -value = 0.002). Mean log(TV) and log(AFP) for presentation and cycle 1 form the first set, and means on or after cycle 2 form the second set. Both TV and sAFP declined after cycle 2, although these changes were not statistically significant. While these data suggest synchronicity between TV and sAFP variations after each chemotherapy cycle, more observations are needed to confirm this result and to conclude a relative plateau before and after cycle 2.

2.3 Tumor Volume and sAFP Decay According to Hepatic Lobe of Origin

To determine any effect of hepatic lobe of origin on TV or sAFP decay, we analyzed these two variables between right ($n=11$) or left lobe tumors ($n=4$) using mixed models ANOVA. These data support a linear relationship between sAFP and days of therapy for both right and left lobe tumors (quadratic p -value < 0.05). A statistically significant days-by-lobe interaction was observed for sAFP decay ($p=0.005$). Interestingly, for right compared to left hepatic lobe of origin, sAFP levels were lower at presentation and decreased faster (Figure 3 A; slope = -0.062 versus slope = -0.028, respectively). We detected statistically significant curvature for decay of log(TV) ($p=0.01$). Although visual distinction in TV decay between right and left lobe tumors could be made, decay values over time were highly variable and therefore these differences did not reach statistical significance. (Figure 3 B; $p=0.449$).

2.4 Effects of Therapy Duration on Margin Status

Median (25th-75th percentile) margin status among 10 patients with right and 3 patients with left lobe tumors measured 0.25 (0.06 - 0.38) cm and 0.2 (0.15 - 0.25) cm, respectively (Wilcoxon signed rank test $p=0.932$). Neither therapy duration or cycle or type affected resection margin status (Figure 4 A, B). The remaining two infants had total hepatectomy and orthotopic liver transplantation, so were not included in margin analyses.

2.5 Treatment Toxicity

The principal toxicities of hepatoblastoma treatment analyzed in this study included ototoxicity, chronic renal insufficiency and neurocognitive deficits. The incidence of each toxic treatment effect is shown in Table 2. Exact 95% confidence intervals that exclude zero suggest toxicity is significantly higher than zero ($p<0.05$).

Discussion

We have shown that epithelial-type hepatoblastoma responsiveness to induction chemotherapy can be monitored accurately by measuring tumor volume and sAFP decay after each cycle. Our data suggest that hepatoblastoma decay does not change significantly after the second cycle of induction therapy using cisplatin, 5-fluorouracil, and vincristine. Nevertheless, current treatment protocols for initially unresectable hepatoblastoma, stemming from the INT-0098 and COG-9645 studies, continue to advocate four cycles of induction therapy, post-induction resection, and two additional cycles if the patient is deemed disease-free.

Medary et al. reported the kinetics of primary embryonal tumor regression in 24 children having rhabdomyosarcoma ($n=16$), neuroblastoma ($n=5$), or hepatoblastoma ($n=3$) (10). These authors measured tumor volume decay over time and initial cell counts, but did not include sAFP kinetics as a measure of hepatoblastoma response to induction therapy. Consistent with our study, these three hepatoblastomas were noted to show minimal decay after cycle two of induction therapy. These authors concluded that after two cycles of induction therapy, any additional exposure to these agents might increase the risk of establishing clonal resistance. As a result, these authors proposed earlier resection after cycle two or three. In our study, by measuring tumor volumes and a biomarker of tumor viability, sAFP, each as estimates of hepatoblastoma decay, we have identified a specific time point in the course of treatment, also cycle two, after which earlier resection might be feasible.

Although our institution participated in both INT-0098 and COG-9645 trials, chemotherapeutic regimens did not differ significantly among the 15 infants analyzed for response kinetics. Three patients did receive doxorubicin in addition to CFV, but no specific benefit regarding greater tumor volume reduction or earlier normalization of sAFP was observed; on the other hand, no increase in doxorubicin-associated toxicity, such as cardiotoxicity or mucositis, was encountered. One infant received carboplatin as a cisplatin alternative along with 5-fluorouracil and vincristine without obvious benefit or risk. However, despite the consistency in chemotherapeutic regimens over the study period, we did observe considerable variability in time to operation. Interestingly, margin status did not lengthen with increasing induction therapy duration or therapy cycle. Of the 13 infants who had partial hepatectomy for definitive surgical resection, ten had negative microscopic margins less than 1 cm, and two were noted to have positive microscopic margins. Importantly, no patient in our series experienced a local relapse. It has been shown recently that a narrow resection margin less than 1cm for hepatoblastoma does not adversely affect outcome when compared with margins greater than 1 cm (16). Also evident from our study group, earlier timing of resection (after cycle 2 or 3 of induction therapy) did not adversely affect margin status. To date, only one of the entire 24 patients treated for an epithelial-type hepatoblastoma during this study period is deceased,

tragically from an all terrain vehicle accident seven years after completing therapy. However, the incidence of toxicity in our series to achieve this ideal overall survival is not trivial. Ototoxicity appeared with greatest frequency, likely related to cisplatin, and neurocognitive deficits were also prevalent in our patients. Nephrotoxic effects were observed but were relatively minor overall.

Our data also suggest a different and unique biologic response between hepatoblastomas of right or left lobe origin. When compared to right lobe tumors, response kinetics of left lobe tumors appeared slower as measured by sAFP decay and tumor volume, although more observations are required to support the latter statistically. As a result, children harboring right lobe tumors may reach an earlier effective tumor kill than those with left lobe tumors. It is unclear currently why a difference in tumor decay would exist between hepatic lobes of origin. No patient demographic or tumor histologic variable we tested was associated with the statistically significant difference in sAFP decay being faster in right lobe tumors. From this observation, we can only conclude that right lobe tumors may be slightly more chemosensitive and perhaps require less overall treatment than left lobe tumors.

Because we have not experienced a tumor-related death in this 12-year study period, but have documented significant toxic treatment effects, we have questioned whether room exists to reduce exposure to the recommended 6-cycle cumulative dose of chemotherapy. Notably, three patients presented with Stage IV disease, each of whom had complete resolution of pulmonary metastases with chemotherapy only, and only one other infant developed metachronous pulmonary metastases. This latter patient had two thoracic procedures performed for multiple metastectomies separated by four years. This patient currently is disease-free ten years off therapy. Evidence exists that pulmonary metastectomy, in the setting of controlled hepatic disease, may indeed improve survival (3,17).

We had two of 24 patients in this study period who required total hepatectomy and orthotopic liver transplantation (OLT) to provide surgical control of hepatoblastoma. Both of these patients received significantly more cycles of induction CFV (>8) while awaiting a compatible donor. Both babies are currently free of disease 36 and nine months following OLT. By following tumor volume and sAFP decay, one may determine earlier whether definitive tumor resection may be accomplished with partial hepatectomy. If the plateau in tumor decay has been met, and radiographically the tumor is deemed to remain unresectable, then earlier referral for transplant evaluation is reasonable, with the ultimate goals to identify a more suitable donor sooner and to reduce the total amount of exposure to toxic therapies. Because patients who receive CFV may develop secondary malignancies, and because immunosuppressive therapies necessary to control graft rejection after OLT lower the threshold for lymphoproliferative disorders, then sound rationale exists to limit chemotherapy exposure to patients who are deemed persistently unresectable when the decay plateau has been reached. However, despite encouraging results accumulating for OLT in the surgical algorithm for hepatoblastoma, our data regarding margin status continue to support aggressive partial hepatectomy, given limited organ resources and the need for life-long immunosuppression (18,19).

Our study has some limitations, so the results must be interpreted cautiously. First, hepatoblastomas are rare, and for any single institution to gather sufficient observations within a concise treatment era is challenging. However, we have cared for a relatively large number of epithelial-type hepatoblastoma patients in a time frame defined by a consistent treatment algorithm, which minimizes variability in analyzing therapy effects. Specifically, we have managed a series of patients having epithelial-type hepatoblastoma with a standard approach since participation in INT-0098 over our 12-year study. Second, we further restricted our study numbers to an interval and patient population that had digital CT imaging only. Our results certainly might have varied had we included the other four patients with outside hard copy

films only. Nevertheless, to provide the most accurate CT tumor volume measurements, we believed it was necessary to exclude those four patients to eliminate any differences arising from use of two techniques to calculate tumor volumes. Third, the retrospective study design may introduce potential flaws of medical record keeping and a non-standardized method of tracking and assessing patient outcomes, particularly as to how toxicities are evaluated and documented. Nevertheless, we believe our Survivorship Clinic is an excellent means with which to monitor patient outcomes, and this Clinic adheres strictly to the recommendations of the COG.

In summary, we have shown that hepatoblastoma responsiveness to induction therapy can be effectively monitored by measuring tumor volumes and sAFP levels after each cycle. Because we observed no statistically significant tumor decay after cycle two of induction therapy, and because surgical margins did not increase with therapy duration, we propose that the paradigm for timing of resection may be shifted to earlier in the course of treatment, potentially after cycle two of induction therapy. Furthermore, tailoring of total exposure to chemotherapy may help reduce toxic effects, which were neither uncommon nor trivial in our series. Given the remarkable chemosensitivity of epithelial-type hepatoblastomas, we believe a national trial is warranted to investigate whether reduction in total therapy exposure to limit toxic effects may be achieved without compromising event-free and overall survival. For example, randomization might be for all epithelial-type hepatoblastoma stage III patients to receive either two or four induction cycles of CFV, followed by definitive resection. If microscopic margins were negative in either group, then only two additional CFV cycles would be administered. If microscopic margins were positive, then these patients would be randomized again to receive either two or four postoperative cycles of CFV. Such a study might help clarify whether therapy reduction could limit toxic effects without compromising event-free or overall survival.

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Figure 1.
Graph shows number of patients having hepatoblastoma resection after each cycle of induction therapy.

Figure 2.

Hepatoblastoma decay after each induction therapy cycle, as estimated by sAFP (A) and TV (B) kinetics. (C) Reduced monotonic regression curves show similar decay patterns between sAFP (red) and TV (blue) measurements.

Figure 3.

Hepatoblastoma decay according to lobe of origin (left lobe, blue; right lobe, red). (A) Left lobe tumors present with higher sAFP levels and show slower decay. (B) TV changes according to lobe of origin. P-values represent mixed models ANOVA tests of lobe by time interactions.

Figure 4. Resection margins do not lengthen with increasing duration (A) or cycles (B) of induction therapy (ρ = Spearman correlation).

Table 1
Study group demographics

Gender		n (%)
	Male	16 (67%)
	Female	8 (33%)
Ethnicity		n (%)
	Caucasian	19 (80%)
	Latino	2 (8%)
	African American	1 (4%)
	Asian American	1 (4%)
	Mixed	1 (4%)
Gestational Age (weeks)	n (%)	Median (25th-75th)
Term	17 (71%)	38.0 (38.0 - 38.0)
Preterm	7 (29%)	33.0 (26.5 - 34.0)
Age @ Diagnosis (months)		12.0 (8.5-20.0)
Beckwith-Wiedemann		n = 3 (12.5%)
Stage		n (%)
	I	5 (21%)
	II	0
	III	16 (67%)
	IV	3 (12%)
Tumor characteristics		
Kinetic analysis (n = 15)	Solitary	12 (80%)
	Multinodular	3 (20%)
Total group (n = 24)	Right lobe	18 (75%)
	Left lobe	6 (25%)
Interval between	Cycle number	Median (25th-75th)
chemotherapy cycles (days)	1	24.0 (23.0 - 27.5)
	2	24.0 (21.0 -25.5)
	3	24.5 (21.0 -26.8)
	4	32.0 (26.0 -49.0)
	5	33.0 (24.8 -43.5)
Timing of resection		n (%)
	Primary	5 (21%)
	Delayed	17 (71%)
	Transplant	2 (8%)
Follow up (months)		Median (25th-75th)
	Off therapy	34.5 (8.8-84.3)
	Total	37.0 (15.5-88.5)
Survival		

	Event-free	96%
	Overall *	100%

n = number; (25th-75th) = range between 25th and 75th percentile

* One child is deceased from trauma 7 years after completion of therapy.

Table 2
Incidence of long-term treatment toxicity

Toxicity	Incidence	
	Estimate	Exact 95% Confidence Interval
Hearing loss	0.74	(0.49, 0.91)
Renal dysfunction	0.16	(0.03, 0.40)
Neurocognitive deficits	0.42	(0.20, 0.67)