Published in final edited form as:

Pediatr Blood Cancer. 2015 June ; 62(6): 976–981. doi:10.1002/pbc.25400.

The Role of Chest Computed Tomography (CT) as a Surveillance Tool in Children with High-risk Neuroblastoma

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Abstract

Purpose—Standardization of imaging obtained in children with neuroblastoma is not well established. This study examines chest CT in pediatric patients with high-risk neuroblastoma.

Methods—Medical records and imaging from 88 patients with high-risk neuroblastoma, diagnosed at St. Jude Children's Research Hospital between January, 2002 and December, 2009, were reviewed. Surveillance imaging was conducted through 2013. Ten patients with thoracic disease at diagnosis were excluded. Event free survival (EFS) and overall survival (OS) were estimated. Size specific dose estimates for CT scans of the chest, abdomen, and pelvis were used to estimate absolute organ doses to 23 organs. Organ dosimetry was used to calculate cohort effective dose.

Results—The 5 year OS and EFS were $51.9\% \pm 6.5\%$ and $42.6\% \pm 6.5\%$, respectively. Forty-six (58.9%) patients progressed/recurred and 41 (52.6%) died of disease. Eleven patients (14%) developed thoracic disease progression/recurrence identified by chest CT (1 paraspinal mass, 1 pulmonary nodules, and 9 nodal). MIBG (metaiodobenzylguanidine) scans identified thoracic disease in 6 patients. Five of the 11 had normal chest MIBG scans; 3 were symptomatic and 2 were asymptomatic with normal chest MIBG scans but avid bone disease. The estimated radiation

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Conflict of Interest: The authors declare no potential conflicts of interest or financial disclosures

dose savings from surveillance without CT chest imaging was 42%, 34% when accounting for modern CT acquisition (2011-13).

Conclusions—Neuroblastoma progression/recurrence in the chest is rare and often presents with symptoms or is identified using standard non-CT imaging modalities. For patients with non-thoracic high-risk neuroblastoma at diagnosis, omission of surveillance chest CT imaging can save 35-42% of the radiation burden without compromising disease detection.

Keywords

neuroblastoma; chest CT; computed tomography; ALARA; radiation exposure

Introduction

Neuroblastoma is an aggressive childhood malignancy in which half of all patients are diagnosed with metastatic disease, most often to the bone, bone marrow and/or lymph nodes.[1, 2] Treatment for patients with high-risk disease comprises a multimodal approach that carries significant risks of treatment-related morbidities and subsequent malignancies. [3-7] Recent modifications to treatment strategies for high-risk disease have improved the survival rate to approximately 50% [8, 9] and as a consequence, the proportion of survivors at risk for treatment-related late effects will rise. Therefore, efforts should be made to limit exposure to ionizing radiation from repeated imaging in this population without compromising disease detection.

The extent and frequency of surveillance imaging for children with high-risk neuroblastoma is variable. A consensus report from the International Neuroblastoma Risk Group Project recently published guidelines for imaging and staging of neuroblastic tumors.[10] These guidelines describe the recommended imaging modalities that should be employed at the time of diagnosis in children with neuroblastoma. However, the use of cross-sectional imaging of the chest is left to the discretion of the provider.[10] Further, there are no concrete guidelines for surveillance imaging and imaging guidelines between treatment protocols are variable.

In patients with a non-thoracic primary neuroblastoma, metastases to the lung parenchyma, pleura and thoracic lymph nodes are infrequent. Pulmonary and pleural metastases at diagnosis are seen in only 3-4% of patients with high-risk disease [2, 11] and less is known about nodal disease in the chest. As such, the use of chest computed tomography (CT) is not routinely recommended. However, there is a paucity of information regarding the utility of surveillance chest CT in the identification of progression/recurrence in patients with neuroblastoma. This deficit of information likely contributes to the variability of imaging obtained in this patient population.

Over the past decade, numerous groups have described the radiation exposure risks associated with CT and the increased risk to children due to a higher inherent sensitivity to the negative effects of ionizing radiation.[12-16] In an effort to better understand the utility of surveillance chest CT and eliminate unnecessary scans, thereby decreasing radiation exposure without compromising clinical care, we examined the role of routine chest CT

surveillance in pediatric patients with high-risk neuroblastoma treated at our center. Further, we examined the rate of thoracic relapse and long-term survival. Finally, we estimated the associated patient exposure to ionizing radiation from CT and investigated the potential radiation dose savings when excluding chest imaging for follow-up care.

Patients and Methods

Patient Inclusion/Exclusion for the study

With institutional review board approval, we retrospectively identified 88 patients diagnosed with high-risk neuroblastoma who were treated at St. Jude Children's Research Hospital between January, 2002 and December, 2009. High-risk disease was defined by the Children's Oncology Group risk-based stratification based on the analysis of prognostic factors including age at diagnosis, international neuroblastoma staging system (INSS) stage, DNA index, tumor histopathology and MYCN amplification status.[17] Surveillance imaging for disease recurrence was conducted through December, 2013. Ten patients had thoracic disease (pulmonary nodules and/or nodal disease in the chest) present at diagnosis and were excluded from this analysis. For the remaining 78 patients, we analyzed outcome and recorded patient demographics, stage of disease at diagnosis, treatment regimen, disease progression/recurrence, location of progression/recurrence, and the number of CT scans each patient underwent. Tumors were staged according to the INSS staging system. All data were managed in compliance with the Health Insurance Portability and Accountability Act of 2006.

Computed Tomography Technique

Patients were scanned on one of three CT scanner models from 2002 through 2013: GE Lightspeed Ultra 8 detector (2002-2007), GE VCTXT 64 detector (2008-2011) (General Electric Medical Systems, Milwaukee, WI), and VCTXTe 64 detector with ASiR™ reconstruction (2011-2013). Prior to 2008, patients received nonionic intravenous contrast with 300mg/ml concentration of iodine. From 2008 to 2013, patients received nonionic intravenous contrast with 270 mg/ml concentration of iodine (iodixanol was used after March, 2009). All CT examinations were performed following the administration of oral and intravenous contrast (up to 2.0 ml/kg).

Patient dosimetry

For patient dosimetry, we analyzed 67 patients (of the 78) who underwent 1,978 CT examinations, including 671 chest, 681 abdomen, and 626 pelvis scans. All CT scans were performed as routine on-therapy and post-therapy surveillance imaging. Eleven patients were excluded from dose estimations since patient dosimetry data [(i.e., volume computed tomography dose index (CTDI_{vol}))] were not archived.

Individual patient organ dose values were estimated based on patient size specific dose estimate (SSDE) calculations.[18-20] A total of 23 organ/tissue doses were calculated: thyroid, lungs, breast, esophagus, thymus, heart wall, bone marrow, bone surface, skin, liver, kidneys, gall bladder, pancreas, adrenal gland, spleen, stomach, colon, bladder, intestines, prostate, testes, ovaries, and uterus. A patient-specific SSDE was calculated separately for

each individual or combined chest, abdomen, and pelvis CT examination for patients within the population cohort. SSDE was calculated based on the formulation described in AAPM Report 204.[21, 22] SSDE was calculated by measuring the patient's body dimensions and calculating their effective body diameter,

$$effective\ diameter = \sqrt{AP * LAT} \quad (Eq. 1)$$

where anteroposterior (*AP*) and lateral (*LAT*) measurements were made using electronic calipers from reconstructed transaxial CT images (Figures 1A-C). Patient effective diameter was measured at the center of the scan volume for each anatomical region. Chest study volumes included the region extending between the lung apices to the mid liver. Abdominal study volumes included the diaphragm to the iliac crest, and pelvic study volumes spanned the iliac crest to perineum (inferior aspect of symphysis pubis). The patient's effective diameter was used to scale the CT scanner dose index (i.e., $CTDI_{vol}$) using a conversion factor (*f*-s coefficient) based on the diameter of the CTDI phantom (Figure 2):

$$SSDE_{patient} = CTDI_{vol}^{16or32} * f_{size}^{16or32} \quad (Eq. 2)$$

$CTDI_{vol}$ values used for the SSDE calculation were obtained from the CT dose report archived with every patient CT examination (Fig. 1D). Separate $CTDI_{vol}$ values were archived for chest and abdominopelvic scanned regions. To calculate a SSDE for the pelvic region, the $CTDI_{vol}$ value corresponding to the abdominopelvic region was used in conjunction with the pelvic effective diameter.

Patient organ dose data ($D_{T,R}$) were converted to an estimate of risk by calculating patient population averaged effective dose. The patient organ dose data were multiplied by an organ and tissue weighing factor (W_T) specified by ICRP 103 [23] and by a radiation weighting factor (W_R) :

$$E (mSv) = \sum W_T \cdot W_R \cdot D_{T,R}; \quad (Eq. 3)$$

where W_R for x-rays is equal to unity.[24] In accordance to the recommendations of ICRP 103, all patient-specific organ doses were averaged prior to being multiplied by the sex- and age-averaged W_T , thus rendering the calculation of effective dose gender and age neutral.

Statistical Methods

Overall survival (OS) was defined as the time interval between the date of diagnosis and the date of death from any cause or the date of last follow-up. Event-free survival (EFS) was defined as the time interval between the date of diagnosis and the date of first event or the date of last follow-up. Events included recurrent or progressive disease, second cancer, or death from any cause. Overall survival and EFS distributions were estimated using the method of Kaplan and Meier. Outcome estimates are reported with ± 1 standard error. Statistical analyses were performed using the SAS statistical software package (version 9.3; SAS Institute, Inc., Cary, NC).

Results

Patient and Tumor Characteristics

The median age at diagnosis was 2.7 years (range, 4 months to 12.7 years). The majority of patients were male (64.1%) and 58 (74%) were white. Seventy patients (89.7%) had stage 4 disease and 8 (10.3%) had stage 3 disease. The median patient age at last follow-up was 7.2 years (range, 2.6 years to 14.2 years).

Treatment

All patients treated during this time were eligible to receive intense induction chemotherapy, consolidation therapy including an autologous stem cell transplant and radiation therapy and minimal residual disease therapy with retinoic acid. The majority of the patients received similar induction regimens which included cyclophosphamide, doxorubicin, vincristine, etoposide, cisplatin and topotecan. Nearly all patients underwent an autologous stem cell transplant with carboplatin, etoposide and melphalan as the conditioning regimen. Fourteen patients (18%) received anti-GD2 antibody therapy during their treatment.

Patient Outcome

The 5 year OS and EFS for the 78 patients were $51.9\% \pm 6.5\%$ and $42.6\% \pm 6.5\%$, respectively. The median follow-up of the population was 6.8 years (0.9-11.2 years) and 86% of the survivors were seen or contacted within the last year. Forty-six (58.9%) patients progressed or recurred at a median of 15.6 months (range 1-90.5 months). Forty-one patients (52.6%) have died of disease.

Eleven patients (14%) developed thoracic disease progression/recurrence identified by routine chest CT (Table 1). Of these patients, 1 developed pulmonary nodules, 1 had a new paraspinal mass and 9 patients had new thoracic nodal disease. All 11 patients had MIBG-(metaiodobenzylguanidine) avid disease at the time of diagnosis. However, at the time of disease progression or recurrence, MIBG scans identified thoracic disease in only 6 (55%) patients. Of the remaining five patients with a normal MIBG of the chest, 3 presented with clinical symptoms suggestive of thoracic disease (including cough, shortness of breath and chest pain) and 2 were asymptomatic with normal chest MIBG scans but MIBG avid bone disease. Ten of the patients with thoracic disease have died of disease and 1 is alive with disease. The patient who is currently living had symptomatic disease in the chest and a positive MIBG scan in the chest and bones at the time of recurrence.

CT studies and patient dosimetry

In total, 67 patients underwent 1,978 CT examinations, including 671 chest, 681 abdomen, and 626 pelvis scans. The relative risk calculated for CT examinations from 2006-13 was 3.2 ± 2.1 mSv, 3.0 ± 2.5 mSv, and 1.5 ± 0.8 mSv for the chest, abdomen, and pelvis, respectively (Figure 3A). Without chest imaging, relative risk reduction was reduced by 42% (3.5/7.7) (Figure 3B). When considering more modern imaging techniques (i.e., from 2011-13) which included dose reduction from use of iterative reconstruction techniques[25, 26], the relative risk calculated from 167 CT examinations obtained from 2011-2013 was 1.5 ± 0.3 mSv (n = 50), 1.9 ± 0.3 mSv (n = 57), and 1.0 ± 0.2 mSv (n = 60) (Figure 3C).

Excluding chest imaging, the relative risk reduction from 2011-13 was 34% (2.9/4.4) (Figure 3D).

Discussion

Patients with high-risk neuroblastoma are heavily treated, have significant treatment-related morbidities and are at an increased risk of developing subsequent malignancies.[3-7, 27, 28] Over the past decade as survival rates for this disease have improved, so too has the movement to limit radiation exposure from routine imaging in pediatric patient populations. Specifically, the ALARA (as low as reasonably achievable radiation) principles instituted at numerous institutions across the country have contributed to drastic reduction in exposure to ionizing radiation from CT imaging by adjusting CT techniques and tailoring exposures to the size of the patient.[29, 30] While the implemented changes in imaging protocols have been effective at reducing radiation exposure, clinicians must diligently evaluate the risks and benefits of surveillance imaging.

There has been considerable debate surrounding the utility of surveillance imaging in patients with pediatric cancer.[30-33] For high-risk neuroblastoma, surveillance imaging practices vary among institutions and the use of routine chest CT as an initial staging and surveillance tool is debatable. Although the risk of metastatic thoracic neuroblastoma at diagnosis is low, the risk of disease in the chest increases at the time of first progression/relapse. In a review of 648 patients treated on the CCG3881 study, DuBois et al. reported that approximately 20% of patients who relapse develop disease in the lungs/pleura and lymph nodes at the time of first progression.[2] This cause for concern may have promoted clinicians to use computed tomography of the chest when screening for disease.

Fourteen percent (n=11) of our patients with non-thoracic primary neuroblastoma developed disease progression/recurrence in the chest. The 11 patients had clinically suspicious disease identified by chest CT at the time of progression or recurrence. Although all patients had positive metaiodobenzylguanidine (MIBG) scintigraphy avid disease at diagnosis, only six had MIBG avid disease in the thorax at the time of progression or recurrence. The remaining five were either clinically symptomatic (n=3) and/or had MIBG avid disease (n=2) in an anatomically non-thoracic location consistent with relapse.

In a population of heavily treated patients with high-risk neuroblastoma, abnormal findings on chest CT may represent an infectious process, radiation pneumonitis and or neuroblastoma. However, in our study the lack of MIBG avidity in the chest was not an indicator of absent disease as three of the five patients with symptomatic disease had biopsy-proven thoracic neuroblastoma and the remaining two asymptomatic patients had obvious disease progression in the chest with enlarging lymph nodes, elevated urine catecholamines and a negative infectious work-up for bacteria, viruses and fungi. Omission of surveillance chest CT would not have compromised detection of tumor progression or recurrence in the 78 patients included in this study.

Historically, patients with high-risk neuroblastoma who develop disease progression or recurrence have a poor long-term prognosis with a survival rate <10%.[34-36] In our 11

patients with progressive or recurrent thoracic disease, 10 died from disease and one is alive with disease. Although surveillance screening may have led to earlier detection of disease in the chest, it would likely not impact overall survival. Further, in our study we observed that all patients with disease in their chest would have been identified as having disease progression or recurrence without the surveillance chest CT. Thus, in this patient population we recommend only using chest CT if the patient has symptoms concerning for disease or as needed for re-staging at the time of recurrence.

The dosimetry methods described in this work have several limitations. First, no attempt was made to differentiate between initial diagnostic and ongoing surveillance CT examinations for the patients used to estimate patient dosimetry. Although this may have overestimated the exposure slightly, the bulk of the imaging performed was surveillance. Additionally, patient exposure data were calculated from examinations that were performed on 3 different scanners used from 2006-2013. Finally, institutional emphasis on ALARA and reduction of radiation exposure from CT has led to changes in CT acquisition techniques to administer a CT dose as low as possible without compromising low contrast lesion detectability. In recognition of the radiation dose reductions made in the ALARA era, we calculated and report the radiation dose savings from imaging obtained pre-ALARA and post-ALARA implementation.

In conclusion, for patients with neuroblastoma who lack thoracic disease at diagnosis, our retrospective review does not support the routine use of surveillance chest CT in children with high-risk neuroblastoma unless clinically indicated. Omitting chest CT from surveillance, off-therapy follow-up, of patients with high-risk neuroblastoma saves an average 34-42% of the effective dose of radiation without compromising progression or recurrence detection. In light of the increased risks of subsequent malignancies and the findings of this study, we recommend omitting surveillance chest CT in asymptomatic patients without thoracic disease at diagnosis altogether.

Acknowledgments

This study was supported in part by Cancer Center Support Grant CA21765 from the US National Institutes of Health (NIH), and by the American Lebanese Syrian Associated Charities (ALSAC). These supporting entities were not involved in the design, conduct or reporting of this study.

This study is supported in part by the Cancer Center Support CORE Grant P30 CA 21765 from the National Cancer Institute and by the American Lebanese Syrian Associated Charities.

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Figure 1. Patient-specific SSDE calculation. SSDE is calculated based on the lateral and anteroposterior dimension of a patients (A) chest, (B) abdomen, and (C) pelvis region. The patient's size is used to look up a conversion factor that (D) scales the scanner CTDI_{vol} value based on the CTDI phantom diameter (i.e., head 16 or body 32).

Figure 2. Patient effective diameter conversion factors from AAPM Report 204 [ref #20]. Two separate conversion factor curves were developed for patient specific size measurements based on 16 cm and 32 cm CTDI phantom diameters.

Figure 3. Patient population average effective dose calculation. Effective dose was calculated as a relative risk metric for neuroblastoma patients undergoing surveillance CT between 2006-13 (A) with and (B) without chest scans. Similarly, effective dose was calculated for neuroblastoma patients undergoing surveillance CT using more modern CT scan techniques between 2011-13 (C) with and (D) without chest CT demonstrating institutional CT dose optimization.

Table 1
Characteristics of the 11 patients at the time of disease progression or recurrence in the chest

Patient	Sex	Age at Diagnosis	MYCN Amplified	Elevated HVA/VMA	Biopsy at Progression	Time to Progression	Suspicion of Disease at Progression			Status
							CT of Chest	MIBG	Symptoms	
1	Female	2yr 7mo	No	Yes	Yes	22mo	+	+ch	-	DOD
2	Male	2yr 7mo	Yes	No	Yes	11mo	+	+ch	-	DOD
3	Female	1yr	Yes	No	Yes	24mo	+	+ch	-	DOD
4	Male	4yr 6mo	No	No	Yes	19mo	+	-ch	+	DOD
5	Male	2yr 9mo	Yes	Yes	Yes	9mo	+	-ch	+	DOD
6	Female	9yr 11mo	Yes	No	Yes	16mo	+	-ch/+bone	-	DOD
7	Female	3yr 2mo	No	No	Yes	17mo	+	+ch	-	DOD
8	Male	6yr 5mo	No	No	No	4mo	+	-ch	+	DOD
9	Female	1yr 5mo	Yes	Yes	Yes	18mo	+	-ch/+bone	-	DOD
10	Male	7yr 6mo	No	No	Yes	4mo	+	+ch	+	DOD
11	Male	7yr 2mo	No	Yes	Yes	23mo	+	+ch	+	AWD

Abbreviations: mo, months; ch, chest; DOD, dead of disease; AWD, alive with disease.