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Methods for Image-guided and Intensity-modulated Radiation Therapy in High-Risk Abdominal Neuroblastoma

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Abstract

Purpose—Our purpose was to determine methods for image-guided intensity-modulated radiation therapy (IMRT) in pediatric abdominal high-risk neuroblastoma and to quantify the degree of normal tissue dose-reduction by using volumes compliant with International Commission on Radiation Units and Measurements (ICRU) Report 62.

Methods and Materials—Eight consecutive children with high-risk abdominal neuroblastoma (median age, 2.5 y; range, 20 months to 5 y) were treated with IMRT using volumes accounting for physiologic motion (IMRT_phys) and daily pretreatment cone beam CT localization. Comparative IMRT planning using conventional volumes (IMRT_std) provided quantification for dose reduction to normal tissues.

Results—The IMRT_phys plan reduced the mean planning target volume (PTV) from 668.8 ± 200.6 cc to 393.0 ± 132.5 cc ($p < 0.001$) and reduced mean body V50 from 1774.4 ± 383.9 cc to 1385.7 ± 365.7 cc ($p < 0.001$). The IMRT_phys plan reduced the percent mean dose to the ipsilateral kidney from $70.1\% \pm 4.3\%$ to $66.0\% \pm 5.2\%$ ($p = 0.002$); that to the contralateral kidney was reduced from $56.3\% \pm 7.0\%$ to $40.7\% \pm 9.5\%$ ($p < 0.001$), and that to the liver was reduced from $57.8\% \pm 16.0\%$ to $22.1\% \pm 6.8\%$ ($p = 0.001$).

Conclusions—For IMRT planning, ICRU 62-compliant volume definition with image guidance in the pediatric abdomen enables volumetric reduction of the PTV and reduces normal tissue dose. These methods provide a framework for more conformal treatment planning in the pediatric abdomen.

Keywords

IMRT; IGRT; ICRU 62; neuroblastoma

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Introduction

Few studies have described intensity-modulated radiation therapy (IMRT) in the pediatric abdomen. Of those studies that do describe it, none had implemented an International Commission on Radiation Units and Measurements Report 62 (ICRU 62)–compliant method for dose delivery [1, 2]. This paucity of data is further complicated by a primarily distant failure pattern in approximately two-thirds of high-risk children, thus lowering the priority for local control studies and making radiotherapy (RT) studies difficult to conduct.

Within the last decade, significant advances in image-guided radiation therapy (IGRT) have improved the ability to increase the dose gradient between normal and target tissue, helping to spare normal tissue while enhancing local control. Daily imaging-based target localization and four-dimensional computed tomography (4DCT)-based treatment planning have been steadily integrated into daily clinical practice.

In this study, we describe the implementation of IGRT-based IMRT in the pediatric abdomen; this process accounts for physiologic motion and setup error and is based on established prospective work at our institution [3, 4]. Additionally, ICRU 62–compliant IMRT volumes were compared to conventional target volumes and used to quantify the reduction in the dose delivered to various normal tissues. The value of 4DCT in estimating a near-class solution for target/organ motion is demonstrated in this setting.

Methods and Materials

Chart review

We retrospectively reviewed the records of 8 consecutive pediatric patients (5 girls) with a diagnosis of high-risk abdominal neuroblastoma (NB) who were treated with IMRT during a 14-month period (July 2009 through September 2010). Pathologic confirmation included cytogenetic analysis of *MYCN* amplification and histologic grading by the Shimada classification system. No child had evidence of macroscopic residual disease, thus each child received a cumulative dose of 23.4 Gy to address microscopic disease. A combined modality, single autologous transplant treatment paradigm was used in each case and included chemotherapy, surgical resection, radiotherapy, and immunotherapy. This study was approved by the institutional review board.

Simulation with CT, 4DCT, and MRI

General anesthesia was induced with propofol in all cases. Non–contrast-enhanced computed tomography (CT) and magnetic resonance imaging (MRI) constituted the fundamental dataset used for IMRT planning in these patients. Approximately 1 week before the planned initiation of treatment, patients underwent CT simulation, 4DCT, and MRI to maximize visualization of physiologic organ motion, potential macroscopic residual tumor, involved soft tissues, and draining lymphatics. A Somatom CT scanner (Siemens, Erlangen, Germany) using low-dose–emitting, dual-source/24-detector spiral CT technology acquired 3-mm axial images from the mid-thorax through the ischial tuberosities.

CT simulations were performed with patients lying supine in neutral position with their arms over their head and with adequate upper torso wing-board and vac-lock support out of the plane of treatment ports to prevent brachial plexopathy. Figure 1 shows how blocks behind the knees were used to flatten the lower spine against the treatment table without other immobilization devices to support the abdomen on the table; only a draw cloth was used between the child and the CT table's surface. The legs were raised sufficiently to create a near-90° angle between the femur and CT table. This step ensured reproducible flattening of the natural lordotic posture of the lumbar spine. Two axial planes were marked for each

patient: one set of markers was used to align the torso at or near the level of the xiphoid process; another was marked at the top of the pelvic girdle, along the anterior superior iliac spine, to provide optimal setup reproducibility. General anesthesia was used to enhance re-positioning accuracy, as measured by daily cone-beam CT. Subsequently, a 4DCT was acquired with each child in the treatment position. A sensor belt (AZ-773V, Anzai Medical, Tokyo, Japan) attached to a respiratory-gating monitor system (Anzai Medical) was placed around the abdomen and close to the dome of the diaphragm, without placing the sensor over costal cartilage. Multiple respiratory traces were obtained and reconstructed through 8 respiratory phases. These 8 phases were exported to the Siemens multi-modality workstation for evaluation by InSpace software [4].

Immediately after the 4DCT, the patient was moved to an adjacent open 0.23T MRI suite with laser bridges for positioning (Philips Panorama, Eindhoven, Netherlands). After repositioning the patient to the isocenter, MR images with post-contrast T1 and balanced fast-field echo sequences were obtained to aid in defining soft tissues when obscured by post-operative change, and macroscopic residual disease, when present.

These imaging data sets were fused to the simulation CT. The serial acquisition of simulation CT, 4DCT, and MRI required approximately 65 minutes for each child. This timeframe includes each imaging series and re-positioning from CT to MRI. Postinduction, preoperative imaging and postsurgical, pretransplant diagnostic-quality imaging was used to delineate the preoperative extent of disease and extent of chemorefractory metastasis, respectively. Additionally, meta-iodobenzylguanidine scintigraphy and/or [^{18}F]fluorodeoxyglucose positron-emission tomography imaging were used to determine tumor volume, although fusion was generally less effective because of temporal changes in morphology between available scans. Organs at risk were defined on the simulation CT dataset.

During therapy, each child received general anesthesia before being immobilized in the simulation position. The target localization was refined by using a low-dose pretreatment cone-beam computed tomography [3]. This daily pre-treatment technique helped us to visualize the spine, kidneys, liver, and any hemostatic clips that might function as fiducials.

IMRT Planning

Two IMRT treatment plans were created for each patient. The first plan (IMRT_phys) included an ICRU 62-compliant planning target volume (PTV) that incorporated an internal target volume (ITV) with physiologic motion data and was used for treatment. The second plan (IMRT_std) used conventional volumetric construction without adopting the ITV concept, as stipulated in the latest national cooperative group protocol for high-risk NB.

For each set of IMRT plans, identical contours for gross tumor volume and an anatomically constrained clinical target volume (CTV) were constructed based on ICRU 50 and ICRU 62 definitions [5, 6]. For the actual treatment plan (IMRT_phys), we used an ITV surrounding the CTV and accounting for physiologic organ motion of 1 mm radially and inferiorly and 4 mm superiorly. Although no class solution works for all cases, a near-class solution was found suitable for each of these 8 cases on the basis of individual review of 4DCT data and estimation of renal motion in these uniformly young children [4]. In each patient, the adjacent renal organs served as surrogates to estimate the tumor bed/target motion due to the retroperitoneal/adrenal primary location of each tumor bed. Cine reconstructions and grid measurements allowed direct measurement of tumor bed and renal motion through any plane of interest. Although these ITV values might reflect differences in patient-specific application, they proved reasonable for all cases studied here when measured at the extremes of motion in cine reconstructions. Because of surgical changes commonly seen at the

juncture of the resected adrenal gland and superior pole of the kidney, questionable measurements were treated with conservatively large volumes to accommodate the ITV concept. The PTV margin for this dataset was 2 mm about the ITV. This margin choice was based on previously published work examining cone-beam CT data of sedated abdominal NB patients in supine position; that study assessed pretreatment and posttreatment daily cone-beam CT to detect lateral, longitudinal, and vertical setup margin changes in 10 children with abdominal high-risk NB by using setup margins of 1.5, 2.1, and 1.7 mm, respectively [3].

No ITV was added to the standard IMRT plan using conventional volumes (ie, IMRT_std). The PTV for IMRT_std plans incorporated a geometric expansion of 10 mm around the CTV to incorporate a reasonable setup error as required by the current Children's Oncology Group high-risk protocol. Data supporting this expansion were further derived from a single institutional investigation of localization that used weekly portal imaging instead of using cone-beam CT and an additional estimation of internal motion [3]. Estimated setup error with portal imaging was 7 mm for PTV expansion and was combined with an additional 3 mm estimation of internal motion.

Because imaging did not show that disease extended into the vertebral bones, the volumetric expansion was tailored to exclude these bones from the CTV/ITV, allowing geometric expansion of only the PTV into bone; the PTV was not expanded to cover the entire vertebral body at affected levels. However, with the potential for primary site spread along the dorsal sympathetic ganglia, the risk for disease existing either within the neural foramina or thecal sac did exist. Therefore, target volumes included the narrow strip of soft tissue between the ipsilateral kidney and vertebral body.

Plan Comparison: IMRT_phys vs. IMRT_std

All dose calculations in this comparison were performed by using the analytical anisotropic algorithm in Eclipse v8.9. The dose to 95% of the PTV was set to the prescription dose of 23.4 Gy, and the normal tissue contours for optimization included ipsilateral and contralateral kidneys, liver, spleen, spinal cord, and whole-body dose. The ipsilateral kidney's mean dose was constrained to 12 Gy, and the contralateral kidney's mean dose was constrained to between 6 Gy and 8 Gy. The number and angle of the beams for a particular patient were not changed between the 2 plan optimizations, which also used the same initial constraints. However, if a particular normal tissue goal was met, then that constraint was tightened until PTV coverage was affected. Key parameters that were analyzed included the mean dose to the ipsilateral and contralateral kidneys, the mean liver dose, the volume of the body that received 50% of the prescription dose (body V50), and the volume of the PTV.

Vertebral bodies were not considered to be at risk, but plan evaluation showed that dose deposition in these areas was within 80% of the prescribed dose. Attempts to ensure dose uniformity within each vertebral body in the region-of-interest would have resulted in considerably more normal tissue volume receiving the full dose. By intentionally excluding the full vertebral body from the targeted PTV, treatment volumes were substantially reduced and the antero-lateral rim of vertebral bone received the full dose. Two patients had large, bilateral tumors, requiring calculation of both kidneys as ipsilateral organs and bilateral incorporation of the dorsal sympathetic ganglia tissues, which led to greater dosing of associated vertebral bones.

Results

Patient Characteristics

The median age of these 8 children was 2.5 years (range: 20 months to 5 years), and median follow-up was 1.3 years (range: 0.6 to 1.8 years). All patients presented with metastatic stage 4 disease; 6 of these were evenly divided between left and right adrenal primary sites, and 2 presented with large bilateral retroperitoneal tumors. Additionally, 3 had high levels of *MYCN* gene amplification. Although no child had loco-regional progression, 1 child had distant metastases to the brain that required resection and whole-brain irradiation.

Dose Distribution and Organ Sparing

Figure 2 shows the target volumes and relative dose distribution associated with the IMRT_std and IMRT_phys plans in a representative patient. The target isodose conformity is superior when accounting for minimal pediatric physiologic motion and spares more visceral and bony anatomy. The ipsilateral renal sparing significantly reduced the percent mean dose, and contralateral renal sparing was more pronounced. As would be predicted, the percent dose differences were even more marked with increasing distance from the isocenter, notably in the liver.

The mean PTV was 393.0 ± 132.5 cc for the IMRT_phys plans and 668.8 ± 200.6 cc for the IMRT_std plans (*t*-test, $p < 0.001$). The mean body V50 was 1385.7 ± 365.7 cc for the IMRT_phys plans and 1774.4 ± 383.9 cc for the IMRT_std plans ($p < 0.001$). This comparative approach quantifies substantial normal-tissue sparing as seen in Figure 3.

Percent Mean Dose in Critical Structures

The percent mean dose delivered to the liver was $22.1\% \pm 6.8\%$ (5.2 ± 1.6 Gy) using the IMRT_phys plans and $57.8\% \pm 16.0\%$ using the IMRT_std plans ($p = 0.001$). In the ipsilateral and contralateral kidneys, the percent mean dose was $66.0\% \pm 5.2\%$ using the IMRT_phys plans and $70.1\% \pm 4.3\%$ using the IMRT_std plans ($p = 0.002$) and $40.7\% \pm 9.5\%$ for the IMRT_phys plans and $56.3\% \pm 7.0\%$ for the IMRT_std plans ($p < 0.001$), respectively. The dosimetric details for each patient are listed in Table 1.

Discussion

In our study, the pattern of intra-abdominal organ dosimetry differed markedly between IMRT_phys and IMRT_std planning. In the IMRT_phys plan, a small rim of mesial renal calyx and neurovascular bundle received the full therapeutic dose; yet, the more lateral, cortical nephrons were largely spared from a significant dose. The dose to the remaining viscera and spine continue to be an ongoing concern for planning. Because of the heterogeneity of visceral/spinal volume among patients, the extent of body V50 dose absorbed by each patient was determined and used as a surrogate to assess differences in integral body dosimetry. The mean body V50 associated with treatment on the IMRT_phys plan was approximately 400 cc less than that with the IMRT_std plans. For comparison, 400 cc is a volume slightly larger than a 12 ounce can of soda, which is relatively large for this cohort, having an average age of 2.5 years.

Vertebral body dosing may cause late-term structural growth abnormalities and myelosuppressive toxicity in very young children. However, these bones were excluded from the CTV because of the expected benefit of reduced myelosuppression in children who are still expected to obtain the majority of survival outcome benefit from cytotoxic systemic therapy. Similar concerns, have partially contributed to the development of double autologous transplant regimens with reduced-dose irradiation [7, 8]. Continued follow-up

and toxicity assessment will be necessary to make substantive decisions about the necessity of extending homogeneous treatment to the vertebral bodies.

Our method of immobilization and localization confers reasonable confidence in the reduction of geometric expansion for a pediatric abdominal PTV to 2 mm, although physical limitations of setup calibration may make reduction below 3 mm difficult to maintain in clinical practice [3]. The higher reproducibility requirements for IMRT are accomplished with simple adjustments to the simulation procedure. By elevating the femur/thigh with a behind-the-knee block to maintain perpendicularity with the simulation table, the natural lordosis of the lumbar spine is reduced. To ensure maximal reproducibility, tabletop sponges are not used for setup. Additionally, external fiducials are used in dual planes representing the lower and superior margins of the abdominal field, which correspond with the anterior superior iliac spine and xiphoid process, respectively. Simulation personnel are accustomed to ensuring spinal positioning within a single plane when possible, and the added care in the setup of a simulation ensures improved reproducibility for treatment.

To optimize setup reproducibility, respiratory gated delivery with use of 4DCT was considered. However, our retrospective analysis of 20 pediatric patients with intra-abdominal tumors showed negligible (≤ 2 mm) organ motion for all circumferential vectors in the subset of patients younger than 9-years-old [4]. Tissues close to the diaphragm moved considerably more than did tissues associated with the lower half of the kidney. Renal motion, in particular, was age-dependent and height-dependent. Furthermore, within the age group associated with NB, respiratory gating conferred marginal benefit to normal tissues at the cost of prolonged general anesthesia and therapy time.

Analysis of the IMRT_phys plan data suggests that enhancing target volume coverage with the full intended dose will change dose deposition, with possible reduction in visceral organ toxicity and the potential for improved local control. A retrospective review showing the benefit of improved dose uniformity was recently completed. After a median follow-up time of 2 years, no local failures have occurred in 20 children with high-risk abdominal NB treated at our institution as per the prevailing high-risk disease paradigm and using IMRT_phys volumes. Of these 20 patients, 8 had macroscopic postoperative residual disease, 6 of whom received 30.6 Gy to the primary site (2 received 36 Gy). The remaining 12 of these children received anti-Gd2 antibody. Excellent local control was obtained in all cases by using improved dose conformity as the salient difference, which includes smaller volumes that are based on measured physiologic motion.

The conventional method of dose delivery with standard 2D or 3D conformal radiation therapy incorporates broad fields constrained to the lowest common denominator in terms of regional normal tissue tolerance. Once renal organ tolerance is met at 14.4 Gy, the off-kidney boost is often limited to the narrow space between the kidneys, which, at best, includes a portion of the tumor bed, draining lymphatics, and dorsal sympathetic ganglia. In many cases, off-kidney boost target volumes that are designed to spare the kidneys result in significant underdosing of the intended target volume at some point between the kidney tolerance dose and microscopic residual disease dose levels—commonly a minimum of 4–5 fractions or 7.2–9.0 Gy differential. With less conformal therapy, this necessary abrogation of protocol dose uniformity may be a notable component of loco-regional failure and, eventually, mortality.

The short follow-up in the current study limits the ability to determine whether these dose reductions translate into reduced incidence and severity of late toxicities, including secondary malignancies. Furthermore, this study appears to define the edge of machine and physical tolerances for delivery of highly conformal dose delivery by estimating organ edge

motion, with limited resolution of axial 4DCT, and table, couch, and collimation tolerances for treatment. Finally, no data from the pediatric population shows reproducibility of inter-fraction motion with serial studies. However, the culmination of this refinement in target volume design has implications for abdominal pediatric radiotherapy and proton therapy in particular.

Within the past decade, the number of U.S. centers capable of delivering proton therapy to pediatric patients has more than doubled. This number is likely to double yet again in the next 10 years. Paramount to this is an improved ability to define target volumes that account for physiologic motion and both inter- and intra-fraction target motion. The complexities of volume definition in ICRU 78 are considerably greater than those found in the ICRU 62 guidelines. However, this method lays the groundwork for the next generation of highly conformal therapy, capable of adjusting for real-time, measurable changes in target position and the positions of critical avoidance structures.

This work describes a process to design ICRU 62-compliant volumes for pediatric abdominal IMRT delivery that takes into account physiologic motion of the abdomen while providing objective data quantifying dose reduction to the vertebral body, liver, and kidneys. Radiation dose limits are fundamentally tied to these organs and make planning a regimen of high-dose pediatric abdominal irradiation difficult. This method offers a means to achieve high-dose uniformity in concordance with guidelines stipulating dose escalation for macroscopic residual disease in NB, the most prevalent extracranial malignancy in pediatrics. A prospective trial is ongoing to estimate toxicity reduction and the effect on local control.

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Figure 1. Positioning of a 2-year-old child with high-risk abdominal neuroblastoma in AP view (upper panels) and lateral view (lower panels) with and without load-sensor belt while administering general anesthesia for four-dimensional computed tomography simulation.

Figure 2.

Axial and coronal isodose colorwash emphasizing differential coverage of (a,c) planning target volume in the standard IMRT plan (PTV_std, blue contour) and (b,d) planning target volume accounting for physiologic motion (PTV_phys, black contour).

Figure 3.

Three-dimensional depiction of planning target volumes (PTVs) and select organs at risk treated with (a) intensity-modulated radiation therapy using volumes accounting for physiologic motion (IMRT_phys) or (b) intensity-modulated radiation therapy using conventional volumes (IMRT_std). (c) Three-dimensional depiction of overlaid PTVs in a child with high-risk abdominal neuroblastoma simulated while under general anesthesia.

Table 1
Target and critical structure volume, dose and PTV D95/V95 based on conventional IMRT volumes and ICRU 62-compliant volumes

Pt	Mean contralateral kidney [% of prescribed dose]		Mean ipsilateral kidney [% of prescribed dose]		Mean liver [% of prescribed dose]		Body V50 [cc]		PTV [cc]		PTV			
	Std	Phys	Std	Phys	Std	Phys	Std	Phys	Std	Phys	Std	Phys	Std	Phys
1	54.3	34.7	67.4	67.8	54.1	26	1539	1143	622	326	2350	2349	96.6	96.4
2	66.7	48.1	76.3	70.8	54.3	17	1550	1145	558	338	2346	2341	97.5	98.6
3	49.5	31.6	61.7	53.9	24.7	30	2270	1946	975	572	2337	2350	97.7	98.0
4	48.4	30.5	73.4	67.8	76.4	24	1505	1128	602	358	2336	2332	97.1	97.4
5*	-	-	72.5 67.4	68.9 62.5	71.5	21	2472	1923	991	624	2227	2066	95.0	95.0
6*	-	-	69.8 68.8	71.1 62.1	64.1	13	1448	1046	471	262	2325	2350	96.5	98.2
7	61.4	51.7	69.4	66.9	65.4	31	1754	1510	614	378	2330	2327	96.3	97.0
8	57.4	47.7	74.7	68.2	52.0	15	1658	1244	517	286	2330	2341	96.4	98.5
Mean	56.3	40.7	70.1	66.0	57.8	22.1	1774.4	1385.7	668.8	393.0	2322	2307	96.6	97.4
SD	7.0	9.5	4.3	5.2	16.0	6.8	383.9	365.7	200.6	132.5	39.5	97.7	0.8	1.2
t-test	$p < 0.000412$		$p < 0.001978$		$p < 0.001049$		$p < 0.000004$		$p < 0.000014$		$p < 0.000014$			

* Patients 5 & 6 had bilateral tumors; both kidneys were planned as ipsilateral avoidance structures.