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Supplemental computational phantoms to estimate out-of-field absorbed dose in photon radiotherapy

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Abstract

The purpose of this study was to develop a straightforward method of supplementing patient anatomy and estimating out-of-field absorbed dose for a cohort of pediatric radiotherapy patients with limited recorded anatomy. A cohort of nine children, aged 2–14 years, who received 3D conformal radiotherapy for low-grade localized brain tumors (LBTs), were randomly selected for this study. The extent of these patients' computed tomography simulation image sets were cranial only. To approximate their missing anatomy, we supplemented the LBT patients' image sets with computed tomography images of patients in a previous study with larger extents of matched sex, height, and mass and for whom contours of organs at risk for radiogenic cancer had already been delineated. Rigid fusion was performed between the LBT patients' data and that of the supplemental computational phantoms using commercial software and in-house codes. In-field dose was calculated with a clinically commissioned treatment planning system, and out-of-field dose was estimated with a previously developed analytical model that was re-fit with parameters based on new measurements for intracranial radiotherapy. Mean doses greater than 1 Gy were found in the red bone marrow, remainder, thyroid, and skin of the patients in this study. Mean organ doses between 150 mGy and 1 Gy were observed in the breast tissue of the girls and lungs of all patients. Distant organs, i.e. prostate, bladder, uterus, and colon, received mean organ doses less than 150 mGy. The mean organ doses of the younger, smaller LBT patients (0–4 years old) were a factor of 2.4 greater than those of the older, larger patients (8–12 years old). Our findings demonstrated the feasibility of a straightforward method of applying supplemental computational phantoms and dose-calculation models to estimate absorbed dose for a set of children of various ages who received radiotherapy and for whom anatomies were largely missing in their original computed tomography simulations.

Keywords

analytical model; out-of-field dose; photon radiotherapy; stray radiation; pediatric intracranial tumors; computational phantoms

1. Introduction

Patients who receive radiotherapy are at risk for radiogenic subsequent malignant neoplasms (SMNs) and other late effects that can result in morbidity or mortality. Children who receive radiotherapy are at increased risk for SMNs compared to adults who receive radiotherapy because, in general, they have longer remaining lifetimes, are more sensitive to side effects from radiation, and have organs that are in closer proximity to the treatment fields (Hall 2006). The late effect of greatest concern for childhood cancer survivors is a SMN (Armstrong *et al* 2009, Kamran *et al* 2016). We have transitioned into a paradigm in pediatric radiotherapy in which the goal is not only to cure the primary cancer, but also to mitigate the probability or severity of late effects such as SMNs, to the point at which the latter impacts routine clinical decisions and technological advancements.

Providing quantitative answers to caregivers regarding the risk of SMNs is essential and of growing importance. To predict the risk of a SMN in the radiotherapy setting or associated effects recorded in epidemiological data of radiation dose, absorbed dose must be estimated throughout patients' bodies. Two challenges hinder the estimation of absorbed doses in organs and tissues at risk of SMNs from radiotherapy. First, in most radiotherapy cases, only the anatomy near the target region is represented in their computed tomography (CT) simulation image sets, and anatomy farther away from the target region is not imaged. Second, although clinical treatment planning systems (TPSs) accurately calculate the dose within the treatment fields (Hasenbalg *et al* 2007), they have been shown to inaccurately estimate the absorbed dose outside of the field edge, i.e. beyond the 50% isodose surface (Howell *et al* 2010, Huang *et al* 2013). Therefore, additional methods are needed for estimating out-of-field dose in organs and tissues.

Several methods have been developed to overcome these challenges. To address the missing patient anatomy, previous research studies have replaced entire patients' anatomies with surrogate generic phantoms (Stovall *et al* 2006, Fontenot *et al* 2008, Taddei *et al* 2008, Newhauser *et al* 2009). Out-of-field dose estimations have been made using specialized Monte Carlo simulation codes (Kry *et al* 2006, 2007b, Lehmann *et al* 2006, Rijkee *et al* 2006, Bednarz and Xu 2009, Court 2009, Joosten *et al* 2011, Chofer *et al* 2012), analytical models (Francois *et al* 1988, Benadjaoud *et al* 2012, Taddei *et al* 2013, Bezin *et al* 2015, Jagetic and Newhauser 2015), and measurements (Stovall *et al* 1989, 1995, 2004, 2006). For large cohorts, in-phantom measurements and detailed Monte Carlo simulations can both be time consuming. In an effort to balance speed, accuracy, and available resources, Taddei *et al* (2013) created an anthropomorphic measurement-based analytical model to accurately estimate the out-of-field dose for children receiving craniospinal irradiation (CSI). They later applied this model in subsequent studies that compared risks of SMNs in proton CSI versus photon CSI (Taddei *et al* 2015, Taddei *et al* 2018). This approach was innovative in

that a computationally inexpensive and fast method to calculate out-of-field dose could be applied to many patients if missing anatomy were made available. However, in these studies, whole or nearly whole patient anatomies were available in the CT image sets. Yet to be established was a simple method for supplementing missing patient anatomy and applying a dosimetric model such that the out-of-field organ and tissue doses could be estimated.

The purpose of this study was to develop a straightforward method of supplementing patient anatomy and estimating out-of-field absorbed dose for a cohort of radiotherapy patients with limited recorded anatomy. For nine children who received localized external-beam radiotherapy for intracranial lesions, we applied this method to estimate the absorbed dose in their organs and tissues at risk for SMNs. We supplemented the patients' existing anatomies captured in their planning CT image sets with those of patients having similar age, height, and mass but more complete CT image sets. In-field organ doses were taken directly from the TPS. Out-of-field absorbed doses were estimated using a previously developed analytical model for absorbed dose versus distance from the composite field edge. Parameters for the model were re-fit based on new in-anthropomorphic-phantom measurements.

2. Methods and materials

2.1. Patient cohort and treatment planning

A cohort of nine pediatric patients treated for intracranial lesions in our clinic were selected under protocol of the American University of Beirut Medical Center's (AUBMC's) Institutional Review Board. These localized brain tumor (LBT) patients were chosen using the systematic random sampling method (Lunsford and Lunsford 1995) of the first five females and four males, sampling backwards chronologically, who met the following criteria:

1. Diagnosed with a low-grade LBT such that they had a moderate to good probability of long-term survival
2. Treatments performed according to the standard of care at AUBMC, which follows the guidelines of the National Comprehensive Cancer Network
3. Treatment plans constructed between 1 January 2009 to 30 September 2011
4. Availability of radiotherapy planning CT image sets in AUBMC's archives
5. Ages distributed between 2 to 14 years old

The intent of radiotherapy for these LBT patients was to eradicate the primary tumor or eliminate residual cancer cells following surgical resection of the tumor. The diagnoses, gross tumor volumes (GTVs), and radiotherapy prescriptions of the selected patients are listed in table 1. All brain tumors were low grade (grades 1 or 2) with the exception of three patients with anaplastic ependymoma, which were high-grade tumors (grade 3). We included them because the number of patients with purely low-grade tumors was insufficient and also because patients with anaplastic ependymoma, despite having high-grade tumors, have an acceptable long-term survival (Merchant *et al* 1997). Each patient received 6 megavoltage (MV) external beam radiotherapy at AUBMC.

The CT simulation image set and radiotherapy treatment plan for each patient was collected retrospectively from archives and imported into AUBMC's clinical TPS. For CT imaging, each patient had been placed in the head-first supine position, and the extent of the image acquisition was from the top of the head to a level that varied between patients from the neck to the shoulders. 6 MV 3D conformal radiation therapy (3DCRT) treatment plans were created using a commercial TPS (Panther version 5.01, Prowess Inc., Concord, California) that had been commissioned for clinical service at AUBMC. Absorbed dose was calculated using the collapsed cone convolution superposition algorithm (Ahnesjö 1989) with heterogeneity correction. Unlike routine clinical practice for these tumors, for this research study, boost fields were not considered. To maintain consistency between patients, the treatment plan for each patient was normalized to a prescription of 54 Gy in the planning target volume (PTV), where the PTV was covered by the 95% isodose surface.

2.2. Supplemental computational phantoms

To estimate dose in missing anatomy, supplemental computational phantoms were fused to the CT image sets of the LBT patients. Each supplemental phantom consisted of a CT image set and structure set of a pediatric patient from a previous CSI study (Taddei *et al* 2018). Supplemental phantoms spanned all ages and both sexes of young children. A supplemental phantom of matching sex, height, and mass was assigned to each LBT patient (table 1). The CT image sets of the computational phantoms extended from the top of the head to variable locations between the mid-thighs and the feet. A secondary advantage of fusing matched CT image sets and structure sets from the CSI study was that organs and tissues at risk for SMNs had been contoured. The two CT image sets were geometrically aligned through rigid fusion (Kessler 2006) using commercial software (version 6.3.2, MIM Maestro™, MIM Software, Inc., Cleveland, Ohio).

A final structure set for each patient was derived from both the primary (LBT) and secondary (CSI) structure sets in the following manner. Portions of structures that were in the primary CT image set were contoured using the TPS. Contours for anatomy partially or fully outside the primary CT image set were extracted from the secondary CT image set but cut off at the inferior edge of the primary CT image set. The result was a composite phantom comprising upper anatomy (contours from the patient) and lower anatomy (contours from the computational phantom). The final structure set consisted of the entire body of the composite phantom ('body'), brain minus GTV, thyroid, red bone marrow, remainder, skin, breast tissue, lungs, liver, stomach, uterus, ovaries, prostate, testicles, bladder, and colon, which included the rectum. Contours for the body, skin, red bone marrow, and remainder comprised upper portions from the patient and lower portions from the computational phantom. The upper portions were taken directly from the contours of the primary CT image set, and the lower portions were generated using a Boolean subtraction of the specified contour (i.e. body, skin, red bone marrow, or remainder) of the secondary CT image set and the body contour of the primary CT image set.

2.3. Estimation of absorbed dose

The absorbed dose in each voxel, D_v , was estimated in- and out-of-field for each patient's anatomy. The in-field D_v values (i.e. from therapeutic radiation) were calculated using

AUBMC's clinically commissioned TPS, so that the in-field D_v was calculated to an uncertainty of the acceptable limit for clinical operations, i.e. within 5% of the prescribed dose (ICRU 1978).

The out-of-field D_v values were calculated by a previously developed measurement-based analytical model (Taddei *et al* 2013). The model calculated D_v as a function of distance from the field edge. In order to apply the model to this cohort of LBT patients, we re-fit the parameters based on original measurements for intracranial fields. The measurements are described in section 2.4 and the model fitting is detailed in section 2.6.

2.4. In-anthropomorphic phantom measurements

A male anthropomorphic phantom (ATOM® Adult Male 701, Computerized Imaging Reference Systems (CIRS), Inc., Norfolk Virginia) loaded with 248 thermoluminescent dosimeters (TLDs) was treated as if it was a pediatric patient with an intracranial lesion. This phantom was designed to resemble a small adult male and consisted of tissue-equivalent epoxy resins, which simulated the electron densities of bone, spinal cord, spinal disks, soft tissue, inflated lung, and brain (CIRS 2010). First, the anthropomorphic phantom underwent CT simulation where the acquisition was identical to the LBT cohort except the scan length extended from the top of the head to the thighs. Second, the treatment fields of the 12-year-old boy with anaplastic ependymoma (table 2) were applied to the base of the skull of the phantom. This patient's fields were chosen for the fitting of the model because his height (144 cm) was the closest match to that of the anthropomorphic phantom (173 cm). Additionally, in the phantom's treatment plan, a field-weighting calculation point was placed at the center of the PTV in the location of a TLD plug. This was done to verify that the therapeutic dose was delivered in the prescription point for each measurement run, which is described later in this section. Shown in figure 1 are axial, coronal, and sagittal images from the CT simulation of the anthropomorphic phantom along with the dose distribution generated from the applied treatment fields.

The measurements were performed in two separate runs, each delivered in a single setting. This was done to ensure that the dose readouts were within the range of high accuracy for the TLDs. Lithium fluoride TLD-100 powder capsules (Quantaflux Radiological Services, San Jose, California) were used and have been shown to be appropriate for measuring out-of-field absorbed dose in 6 MV photon radiotherapy with an uncertainty of less than 12% (Kry *et al* 2007a, Scarboro *et al* 2011, Taddei *et al* 2013). In the first run, the monitor unit (MU) values calculated by the TPS were normalized to deliver 32.4 Gy in the calculation point, and TLDs were placed throughout and on the surface of the phantom. In the second run, in each location in which the dose fell below the useable dose range of the TLDs (i.e. below 25 cGy) a new TLD was placed and the MUs were scaled to deliver 648 Gy at the calculation point (i.e. increased by a factor of 20). A photograph of the experimental setup is displayed in figure 2. The TLDs were processed by certified technicians at MD Anderson's Imaging and Radiation Oncology Core and dose values were returned to us. Two or more background TLDs accompanied each set of irradiated TLDs from annealing to reading, except that they were kept outside the treatment room while the others were irradiated. These TLDs were used to measure and subtract the background radiation. The absorbed

dose in each TLD, $D_{\text{TLD},i}$ in cGy at each location, i , was normalized to the prescription point dose of the associated run, D_{R_x} , in Gy, resulting in a TLD measurement at each location in terms of absorbed dose per therapeutic dose, $D_{\text{TLD},i}/D_{R_x}$ in cGy Gy⁻¹. These measured data were the basis for the new fitting parameters for the double-Gaussian model.

2.5. Distance from the field edge for TLD measurements

$D_{\text{TLD},i}/D_{R_x}$ was plotted as a function of distance from the composite field edge; r . r was determined using previously established methods which are summarized in this section (Taddei *et al* 2013). First, the Cartesian coordinate of each TLD was located in the digital imaging and communications in medicine (DICOM) standard patient coordinate system (IEC 2000). The location of each TLD was determined in the TPS within ± 0.5 cm. Second, the 50% isodose surface, i.e. the field edge, was automatically converted into a structure using the TPS. Third, the 50% isodose structure was exported as a DICOM-RT Structure Set file, comprising coordinates of vertices of the 50% isodose surface as a polygon. Fourth, using in-house computational codes on the DICOM file, the coordinates of the vertices describing the polygon were extracted, and the coordinate of the closest vertex was located for each TLD. Finally, the distance between the Cartesian coordinates of the TLD and closest vertex was calculated using the Euclidean norm to within 0.5 cm. The overall uncertainty of r was determined by adding in quadrature the uncertainty of locating the TLD and the closest vertex, which resulted in an overall uncertainty of ± 0.7 cm for each value of r .

2.6. Analytical model fitting

Following previously established methods for CSI at 6 MV (Taddei *et al* 2013), we used the new measured data to re-fit the parameters for 6 MV composite intracranial fields to the following equation:

$$D_v/D_{R_x} = \frac{\alpha_1}{\sqrt{2\pi}\sigma_1} e^{-\frac{(r-\mu_1)^2}{2\sigma_1^2}} + \frac{\alpha_2}{\sqrt{2\pi}\sigma_2} e^{-\frac{(r-\mu_2)^2}{2\sigma_2^2}}, \quad (1)$$

where μ_1 and μ_2 were the means of each Gaussian, σ_1 and σ_2 were the corresponding standard deviations of each Gaussian, and α_1 and α_2 were constants that scaled the corresponding magnitudes of each Gaussian. Least-squares fitting was performed using commercial software (Excel and the Solver add-in, Microsoft, Redmond, Washington) where these six parameters were allowed to vary in order to minimize the root mean square deviation (*RMSD*) (cGy Gy⁻¹), between the dose calculated by the model, $D_{\text{model},i}$, and $D_{\text{TLD},i}$ for $n = 194$ TLD locations. The equation for the *RMSD* is as follows:

$$RMSD = \sqrt{\frac{\sum_{i=1}^n (D_{\text{model},i} - D_{\text{TLD},i})^2}{n}}. \quad (2)$$

All TLD locations outside of the composite field edge were included in the model with the following exceptions. First, TLDs near the field edge, $r < 0.3$ cm, where there is a large dose gradient, were excluded because the uncertainty in determining the TLDs' locations leads to higher uncertainties in dose. Second, due to the couch rotation in the treatment plan, some TLDs that were located outside the composite 50% isodose surface received absorbed dose from the primary beam. This would not have occurred in an actual patient's treatment plan, but it was an artifact from copying the patient's plan to the phantom. Therefore, we excluded these TLD data from the re-fitting procedure.

2.7. Correcting out-of-field dose in the dose matrices

For all voxels at distances where the out-of-field dose model more accurately estimated $D_{\text{TLD},i}$ compared to the TPS's calculations, D_v calculated by the TPS was replaced with D_v calculated by the model, as had been done previously by Taddei *et al* (2015). In this section, the methods are briefly described. First, the 50% isodose structure and the dose matrix were exported from the TPS as DICOM-RT Structure Set and DICOM-RT Dose files. Second, the dose value and Cartesian coordinates contained within each voxel of the dose matrix were read using in-house codes and commercial software (version R2014a, MATLAB, The MathWorks, Inc., Natick, Massachusetts) along with the coordinates of the vertices describing the polygon of the 50% isodose structure. Third, using parallel processing, the minimization of the Euclidean norm was used to determine the distance from the field edge and replace the TPS's calculated dose with the model's calculated dose for all distances where the model was resolved to be applicable. In the far out-of-field dose region, the TPS was inaccurate (Taddei *et al* 2013) and the model underestimated $D_{\text{TLD},i}$; therefore, an average value from all TLDs in that range was applied.

2.8. Mean absorbed dose in organs, tissues, and target volumes

Mean absorbed dose, D_T , was determined for each organ and tissue, T , at risk for SMNs, the body, and each PTV. D_T was calculated directly for organs that were either completely in the primary or secondary CT image sets. For organs that were partially contained in both CT image sets (i.e. body, skin, red bone marrow, and remainder), D_T was determined using the volume-weighted average of the absorbed dose in the respective upper and lower contours. For organs that extended very far away from the treatment fields, at which portions were also not included in the supplemental anatomy—body, red bone marrow, remainder, and skin—the average absorbed doses were multiplied by the ratio of the mass of the CSI patient contained within the secondary CT image set and the LBT patient's actual mass at the time of CT simulation. This approximation assumes that the dose in these inferior regions is negligible compared to the superior anatomy.

2.9. Effective dose and risk of a SMN fatality

Effective dose, E , is a radiation protection quantity having tissue weighting factors, w_T , that relate to the proportional risk of stochastic effects, e.g. a radiation-induced cancer fatality, as recommended by the International Commission on Radiological Protection (ICRP) (ICRP 2007). For each patient, the effective dose was calculated as

$$E = \sum_T w_T H_T = \sum_T w_T w_R D_T, \quad (3)$$

where D_T was the mean absorbed dose from the given radiation type R in each tissue T , and w_R was the radiation weighting factor (ICRP 2007). w_R accounts for the relative biological effectiveness of the given type of radiation and its energy, whereas w_T accounts for the given tissue's relative sensitivity to radiation. Because D_T was mainly from photon radiation incident on the patients' bodies, we applied the recommended w_R for photons of 1 (ICRP 2007). Values of w_T recommended by the ICRP for red bone marrow, lungs, breast tissue, colon (which includes the rectum), stomach, remainder, gonads (ovaries or testicles), thyroid, bladder, liver, esophagus, bone surface, skin, salivary glands, and brain are listed in table 3 (ICRP 2007) and were applied directly to the organs and tissues in this study with the following exceptions. The first exception was that the normal brain tissue was defined as the brain minus the GTV in order to exclude cancerous tissue. The second exception was that the bone surface, salivary glands, and esophagus were included in the remainder volume and their w_T values were added to the w_T of the remainder. The reason for this exception was that these organs were joined together with the remainder in the previous study, which did not calculate E , so their contours were not available as supplemental phantoms in the current study.

To put these radiation protection quantities into perspective and motivate the need for further investigation, we provided a rough estimate for the corresponding attributable excess lifetime risk of SMN fatality for a population receiving the same E . Specifically, we followed the recommendations of the National Council on Radiation Protection and Measurements (NCRP) of 12.8% per Sv for girls and 8.1% per Sv for boys receiving these E (NCRP 1997).

3. Results

3.1. Analytical model fitting

The fitted analytical model is shown in figure 3 along with $D_{TLD,i}/D_{Rx}$. Fitting parameters for the model are listed in table 4. The model was determined to be an improved estimation of $D_{TLD,i}/D_{Rx}$ compared to the TPS for distances of $3 \text{ cm} < r < 50 \text{ cm}$, in which the *RMSD* was 0.86 cGy Gy^{-1} , i.e. 7.6% of the dose at the field edge. At $r > 50 \text{ cm}$, we applied an average $D_{TLD,i}/D_{Rx}$ of $0.0221 \text{ cGy Gy}^{-1}$ rather than the model-determined value, which underestimated $D_{TLD,i}$ by 76%, on average. At $r < 3 \text{ cm}$, the TPS value was applied (data not shown) because the model did not improve the estimate of $D_{TLD,i}/D_{Rx}$ near the field edge (Taddei *et al* 2013). Figure 3 depicts the applied analytical model for distances of $3 \text{ cm} < r < 50 \text{ cm}$ and the constant term of $0.0221 \text{ cGy Gy}^{-1}$ for distances of $r > 50 \text{ cm}$, which together produced a *RMSD* of 0.75 cGy Gy^{-1} , i.e. 6.6% of the dose at the field edge. The distribution of D_v throughout the 8-year-old boy's anatomy and the computational phantom anatomy is shown in figure 4. An example of an organ at risk in the moderate-dose region is the thyroid, which is also shown in the figure. This image illustrates that, in using the patient's original CT image set, it was not possible to determine D_T in the thyroid, but after supplementing the

anatomy below the inferior cutoff of the primary CT image set with that of the computational phantom, the thyroid dose could be estimated.

3.2. Mean absorbed dose in organs and tissues

Values of D_T are presented in table 5 along with the average D_T values across all nine patients. Mean doses greater than 1 Gy were found in the brain minus GTV, red bone marrow, remainder, thyroid, and skin of the patients in this study. Mean organ doses between 150 mGy and 1 Gy were observed in the breast tissue of the girls and lungs of all patients. Distant organs, i.e. prostate, bladder, uterus, and colon, received mean organ doses less than 150 mGy.

On average, the mean organ doses of the girls in this study were a factor of 1.21 greater than the boys. Furthermore, the mean organ doses of the younger, smaller LBT patients (0–4 years old) were a factor of 2.4 greater, on average, than the older, larger patients (8–12 years old) in the cohort. For example, the average dose in the body was 3.43 and 1.50 Gy for patients 0–4 and 8–12 years old, respectively.

3.3. Effective dose

Values of E are listed in table 6. E varied from 0.65 to 1.60 Sv across all nine LBT patients. The average E for the girls was 1.31 Sv, and the average E for the boys was 1.21 Sv. In general, the average E was higher for the younger children aged 0–4 years (1.44 Sv) than for the older children aged 8–12 years (0.93 Sv).

4. Discussion

In this study, we applied supplemental anatomy, organ at risk contours, and a measurement-based model for out-of-field dose to a set of pediatric patients with LBT treatment plans to determine doses in organs and tissues at risk for SMNs. For these pediatric patients, we found the mean organ doses to be non-negligible in the red bone marrow, remainder, thyroid, skin, breast tissue, lungs, and healthy brain tissue. Among these organs and tissues at risk for SMNs, the mean organ doses were highest in the red bone marrow, remainder, thyroid, skin, and healthy brain tissue. Additionally, we observed the younger, smaller patients in our study to have an increased D_T compared to the older, larger patients, which is a consequence of the smaller patients' organs and tissues being inherently closer to the field of treatment. We also observed that the girls in this study experienced a higher D_T compared to the boys. This increase in D_T for the girls could be because the girls were younger and smaller on average compared to the boys. The average age of the girls was 5 years old and their average height was 106.4 cm, whereas the average age of the boys was 6.5 years old and their average height was 114.8 cm.

We found, for these young children receiving localized brain radiotherapy for intracranial lesions, that the average E values were 1.35 and 1.21 Sv for the girls and boys, respectively. As a rough approximation for populations of girls and boys, these effective doses would correspond to theoretical excess lifetime risks of radiation-induced fatal cancer of 16.8% and 9.8%, respectively. That is, among survivors, 168 out of every 1000 girls and 98 out of every 1000 boys who undergo 3DCRT for LBTs as described in this study would be at risk of

predicted fatalities from radiation-induced SMNs. Although these risks are not small, the benefits of treatment far outweigh these risks.

We compared the results of our study to those of a Monte Carlo study by Athar *et al* (2010), who estimated the out-of-field mean organ doses in five children with intracranial tumors. These children received 6 MV intensity modulated radiation therapy (IMRT), where their radiation fields were designed to be circular to match proton treatment fields. For the mean organ doses of the 12-year-old female examined in our study, near-field and intermediate out-of-field organs such as the thyroid and lungs were an order of magnitude higher than the mean organ doses of the 8-year-old female studied by Athar *et al* (2010). Conversely, for the distant out-of-field organs such as the uterus, the mean organ doses were an order of magnitude higher for the 8-year-old female in the Athar *et al* (2010) study. This latter result could be expected because the far out-of-field dose in IMRT should be higher than 3DCRT due to the increased MUs, and therefore increased head leakage, which dominates the dose profile at far distances. Yet, for the near and intermediate out-of-field distances where scatter from within the patient and from the collimator of the machine dominate the dose profile, we would expect the mean organ doses to be more similar. Deviation could be due to differences in the location of the primary cancer and, subsequently, the field edge. This could also be attributed to the differences in dosimetry methods. Athar *et al* (2010) used computational phantoms and Monte Carlo to calculate dose. Additionally, because the Monte Carlo did not account for the head leakage or the increased scatter radiation emanating from the multileaf collimators due to the greater number of MUs in IMRT compared to 3DCRT, the authors applied a factor of 3.5 to the scatter portion of the beam. We view our measurement-based analytical model as an improvement on these dosimetry methods, because the measurement-based model has increased accuracy in determining out-of-field dose while requiring vastly less computational resources compared to detailed Monte Carlo simulations.

The out-of-field dose calculations in this study were computed in approximately 8 h for each patient on a single CPU. Consequently, a workstation with 64 cores would require approximately 10 min to calculate each patient. Therefore, these methods could be applied in a routine clinical setting for pediatric patients whose dose in organs at risk for SMNs are not typically calculated.

We also found the mean organ doses for these pediatric LBT treatments to be less than those of a previous CSI study. In table 5, the average absorbed dose across all nine LBT patients is compared to a previous study examining the absorbed dose in pediatric regional CSI, where doses were normalized to the prescription of 23.4 Gy (Taddei *et al* 2018). Surprisingly, the mean red bone marrow doses were comparable between the two treatment sites where the average red bone marrow dose was 5.77 and 5.84 Gy for the LBT and CSI patients, respectively. Otherwise, the CSI patients received generally higher mean organ doses compared to the LBT patients. In particular, the average thyroid dose across all CSI patients was 17.09 Gy compared to 1.07 Gy for the LBT patients. As anticipated, the LBT patients had minimal dose to the colon (0.08 Gy) compared to the CSI patients who received a significant dose (5.82 Gy). Although the CSI patients had higher mean organ doses, the LBT patients still received non-negligible doses that have implications for the risk of SMN development.

Our fitted parameters for the analytical model apply only to similar clinical treatment sites and environments. For dissimilar radiotherapy treatment plans or environments, the fitting parameters should be recalculated. Nevertheless, the methods developed in this study can be applied to any treatment site. This is made evident in comparing our analytical model for 3DCRT of intracranial tumors to that of CSI. The bottom panel of figure 3 compares the out-of-field dose (cGy Gy^{-1}) determined by the respective analytical models for the CSI (Taddei *et al* 2013) and LBT treatments. For the near-field region, $r < 4$ cm, the calculated dose was much higher for the LBT analytical model. However, for the intermediate out-of-field region, $4 \text{ cm} < r < 20$ cm, the analytical model for the LBT treatment estimated lower dose compared to the analytical model of the CSI treatment. For distances beyond 20 cm, head leakage becomes the main contributor of the out-of-field dose, and thus, the normalized out-of-field dose (cGy Gy^{-1}) calculated by the respective analytical models for the CSI and LBT treatments converge.

The measurement-based analytical model can also be compared to the out-of-field measured data in Task Group (TG) 36 of the American Association of Physicists in Medicine (Stovall *et al* 1995). The data that most closely matches our clinical setup is the 6 MV, jaw delimited $5 \times 5 \text{ cm}^2$ field size, which was either measured with diodes or TLDs in a water or polystyrene phantom. In general, there was good agreement between the dose calculated by our out-of-field analytical model and the TG 36 measured data, where the model's dose was greater than the measured data by 10% at 10 cm, 25% at 20 cm, and 60% at 30 cm. However, the model's dose was less than the TG 36 measured data by 45% at 50 cm and greater by 5% at 70 cm. Overall, this is excellent agreement considering the large variability in measured out-of-field dose (Xu *et al* 2008). Discrepancies could be due to the differences in the measurement environment of the TG 36 dataset, such as the linear accelerator's shielding design, the lack of tertiary multileaf collimators, and the water-equivalent medium used for measurement.

The methods used in this study were prototypical in nature and can be further developed for automation and clinical or research implementation. First, we anticipate being able to better match patients in the future by accruing more computational phantoms, i.e. anonymized patients with full CT simulation image sets and structure sets. This is possible because the feasibility of automatically anonymizing patients' DICOM-RT files while maintaining data integrity has been demonstrated by Newhauser *et al* (2014). Additionally, it is possible to use automatized workflows in MIM, and other commercial software, to perform all Boolean operations immediately following the rigid fusion. This rapidly creates all new contours that are needed for supplementing missing anatomy with the computational phantom. Therefore, it would be feasible to apply these methods to a large number of patients. The potential for automation of our methods establishes the prospect of including stray radiation and determining dose in organs at risk for late effects throughout low-dose regions of the body routinely, either in clinical or research studies. We perceive that combining these methods with long-term patient follow-ups will improve risk prediction models and our understanding of dose–response relationships for children receiving radiotherapy.

This study had the following limitations. First, a systematic error could arise from an increased or decreased percent red bone marrow content in the cranium of the LBT patients

compared to patients of similar age or those predicted by Cristy's mathematical model (Cristy 1981). Higher percent red bone marrow content in the cranium would result in an increased mean red bone marrow dose and an inflated predicted risk of leukemia. This is problematic for researchers who aim to use this cohort, or cohorts like it, to establish dose-response relationships, conjecture absolute risk estimates, or compare treatment modalities. To limit this potential systematic bias, the same physician contoured the red bone marrow in the CSI patients and the LBT patients using identical methods. Specifically, for each patient, he segmented the bones by identifying a range of Hounsfield Units between 150 and 3000 and then automatically created the red bone marrow volume as a 3D symmetric 0.2 cm inner margin of the bones, excluding the teeth, with minor manual post-processing performed (e.g. small cavities filled and small volumes removed). We also compared roughly the percent red bone marrow content in the cranium of the CSI patients to the percentages in Cristy's mathematical model. We observed only a slightly larger percent red bone marrow content in the cranium and mandible region for these patients. Second, we recognize that estimating risk based on effective dose is controversial and may not be applicable for medical applications (ICRP 2007, Brenner 2008) where the risk of developing SMNs has many factors including age at exposure, attained age, and sex. Furthermore, the NCRP risk coefficients used in this study (NCRP 1997) correspond to an age group of 0–19 years old, whereas the oldest patient in this cohort was 12 years old. As younger children are at a higher risk of radiation-induced cancers (Hall 2006), we would anticipate that these risk predictions are an underestimation of the true risk. Therefore, further investigation is warranted to more precisely quantify the risk of developing treatment-related SMNs and motivates the need for new treatment techniques to reduce the radiation dose to these children.

5. Conclusions

We developed a straightforward method of applying supplemental computational phantoms and dose calculation models to estimate absorbed dose for a set of children of various ages who received radiotherapy and for whom anatomies were largely missing in their original CT simulations. This study represented, to our knowledge, the first proven solution to whole-body dosimetry in the radiotherapeutic setting using simple methods, even when anatomy was largely missing. These methods could be applied to any treatment site. Similar methods of applying supplemental anatomy and contours from generic computational phantoms and models of out-of-field dose may be used to determine organ doses in clinical and research radiotherapy studies when the actual patient anatomies are not available.

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References

- Ahnesjö A 1989 Collapsed cone convolution of radiant energy for photon dose calculation in heterogeneous media *Med. Phys* 16 577–92 [PubMed: 2770632]

- Armstrong GT, Liu Q, Yasui Y, Neglia JP, Leisenring W, Robison LL and Mertens AC 2009 Late mortality among 5-year survivors of childhood cancer: a summary from the childhood cancer survivor study *J. Clin. Oncol* 27 2328–38 [PubMed: 19332714]
- Athar BS, Bednarz B, Seco J, Hancox C and Paganetti H 2010 Comparison of out-of-field photon doses in 6 MV IMRT and neutron doses in proton therapy for adult and pediatric patients *Phys. Med. Biol* 55 2879–91 [PubMed: 20427856]
- Bednarz B and Xu XG 2009 Monte Carlo modeling of a 6 and 18 MV Varian Clinac medical accelerator for in-field and out-of-field dose calculations: development and validation *Phys. Med. Biol* 54 N43–57 [PubMed: 19141879]
- Benadjaoud MA, Bezin J, Veres A, Lefkopoulos D, Chavaudra J, Bridier A, de Vathaire F and Diallo I 2012 A multi-plane source model for out-of-field head scatter dose calculations in external beam photon therapy *Phys. Med. Biol* 57 7725–39 [PubMed: 23123826]
- Bezin JV, Veres A, Lefkopoulos D, Chavaudra J, Deutsch E, de Vathaire F and Diallo I 2015 Field size dependent mapping of medical linear accelerator radiation leakage *Phys. Med. Biol* 60 2103–6 [PubMed: 25675153]
- Brenner DJ 2008 Effective dose: a flawed concept that could and should be replaced *Br. J. Radiol* 81 521–3 [PubMed: 18443016]
- Chofor N, Harder D, Willborn KC and Poppe B 2012 Internal scatter, the unavoidable major component of the peripheral dose in photon-beam radiotherapy *Phys. Med. Biol* 57 1733–43 [PubMed: 22398213]
- CIRS 2010 ATOM® Dosimetry Phantoms: Models 700–705 (Norfolk, VA: Computerized Imaging Reference Systems, Inc)
- Court LE, Ching D, Schofield D, Czerminska M and Allen AM 2009 Evaluation of the dose calculation accuracy in intensity-modulated radiation therapy for mesothelioma, focusing on low doses to the contralateral lung *J. Appl. Clin. Med. Phys* 10 34–42
- Cristy M 1981 Active bone marrow distribution as a function of age in humans *Phys. Med. Biol* 26 389–400 [PubMed: 7243876]
- Fontenot J, Taddei P, Zheng Y, Mirkovic D, Jordan T and Newhauser W 2008 Equivalent dose and effective dose from stray radiation during passively scattered proton radiotherapy for prostate cancer *Phys. Med. Biol* 53 1677–88 [PubMed: 18367796]
- Francois P, Beurtheret C and Dutreix A 1988 Calculation of the dose delivered to organs outside the radiation beams *Med. Phys* 15 879–83 [PubMed: 3237145]
- Hall EJ 2006 Intensity-modulated radiation therapy, protons, and the risk of second cancers *Int. J. Radiat. Oncol. Biol. Phys* 65 1–7 [PubMed: 16618572]
- Hasenbalg F, Neuenschwander H, Mini R and Born EJ 2007 Collapsed cone and analytical anisotropic algorithm dose calculations compared to VMC++ Monte Carlo simulations in clinical cases *J. Phys.: Conf. Ser* 74 021007
- Howell RM, Scarboro SB, Kry SF and Yaldo DZ 2010 Accuracy of out-of-field dose calculations by a commercial treatment planning system *Phys. Med. Biol* 55 6999–7008 [PubMed: 21076191]
- Huang JY, Followill DS, Wang XA and Kry SF 2013 Accuracy and sources of error of out-of field dose calculations by a commercial treatment planning system for intensity-modulated radiation therapy treatments *J. Appl. Clin. Med. Phys* 14 186–97
- ICRP 2007 Publication 103: Recommendations of the International Commission on Radiological Protection (Oxford: Pergamon)
- ICRU 1978 Dose Specification for Reporting External Beam Therapy with Photons and Electrons (Report 29) (Washington, DC: International Commission on Radiation Units and Measurements)
- IEC 2000 International Standard, Amendment 1: Radiotherapy equipment—Coordinates, Movements and Scale (Geneva: International Electrotechnical Commission)
- Jagetic LJ and Newhauser WD 2015 A simple and fast physics-based analytical method to calculate therapeutic and stray doses from external beam, megavoltage x-ray therapy *Phys. Med. Biol* 60 4753–75 [PubMed: 26040833]
- Joosten A, Bochud F, Baechler S, Levi F, Mirimanoff R-O and Moeckli R 2011 Variability of a peripheral dose among various linac geometries for second cancer risk assessment *Phys. Med. Biol* 56 5131–51 [PubMed: 21775792]

- Kamran SC, Berrington de Gonzalez A, Ng A, Haas-Kogan D and Viswanathan AN 2016 Therapeutic radiation and the potential risk of second malignancies *Cancer* 122 1809–21 [PubMed: 26950597]
- Kessler ML 2006 Image registration and data fusion in radiation therapy *Br. J. Radiol* 79 S99–108 [PubMed: 16980689]
- Kry SF, Price M, Followill D, Mourtada F and Salehpour M 2007a The use of LiF (TLD-100) as an out-of-field dosimeter *J. Appl. Clin. Med. Phys* 8 169–75
- Kry SF, Titt U, Followill D, Pönisch F, Vassiliev ON, White RA, Stovall M and Salehpour M 2007b A Monte Carlo model for out-of-field dose calculation from high-energy photon therapy *Med. Phys* 34 3489–99 [PubMed: 17926952]
- Kry SF, Titt U, Pönisch F, Followill D, Vassiliev ON, White RA, Mohan R and Salehpour M 2006 A Monte Carlo model for calculating out-of-field dose from a varian 6 MV beam *Med. Phys* 33 4405–13 [PubMed: 17153419]
- Lehmann J, Stern RL, Daly TP, Rocke DM, Schwietert CW, Jones GE, Arnold ML, Siantar CLH and Goldberg Z 2006 Dosimetry for quantitative analysis of the effects of low-dose ionizing radiation in radiation therapy patients *Radiat. Res* 165 240–7 [PubMed: 16435922]
- Lunsford T and Lunsford B 1995 The research sample, part I: sampling *J. Prosthet. Orthot* 7 105–12
- Merchant TE, Haida T, Wang M-H, Finlay J and Leibel S 1997 Anaplastic ependymoma: treatment of pediatric patients with or without craniospinal radiation therapy *J. Neurosurg* 86 943–9 [PubMed: 9171172]
- NCRP 1997 National Council on Radiation Protection and Measurements Report No. 126: Uncertainties in Fatal Cancer Risk Estimates Used in Radiation (Bethesda, MD: NCRP)
- Newhauser WD et al. 2009 The risk of developing a second cancer after receiving craniospinal proton irradiation *Phys. Med. Biol* 54 2277–91 [PubMed: 19305036]
- Newhauser W, Jones T, Swerdloff S, Newhauser W, Cilia M, Carver R, Halloran A and Zhang R 2014 Anonymization of DICOM electronic medical records for radiation therapy *Comput. Biol. Med* 53 134–40 [PubMed: 25147130]
- Rijkee AG, Zoetelief J, Raaijmakers CPJ, Marck SCVD and Zee WVD 2006 Assessment of induction of secondary tumours due to various radiotherapy modalities *Radiat. Prot. Dosim* 118 219–26
- Scarboro SB, Followill DS, Howell RM and Kry SF 2011 Variations in photon energy spectra of a 6 MV beam and their impact on TLD response *Med. Phys* 38 2619–28 [PubMed: 21776799]
- Stovall M, Blackwell CR, Cundiff J, Novack DH, Palta JR, Wagner LK, Webster EW and Shalek RJ 1995 Fetal dose from radiotherapy with photon beams: report of AAPM Radiation Therapy Committee Task Group No. 36 *Med. Phys* 22 63–82 [PubMed: 7715571]
- Stovall M, Donaldson SS, Weathers RE, Robison LL, Mertens AC, Winther JF, Olsen JH and Boice JD Jr 2004 Genetic effects of radiotherapy for childhood cancer: gonadal dose reconstruction *Int. J. Radiat. Oncol. Biol. Phys* 60 542–52 [PubMed: 15380591]
- Stovall M, Smith SA and Rosenstein M 1989 Tissue doses from radiotherapy of cancer of the uterine cervix *Med. Phys* 16 726–33 [PubMed: 2509867]
- Stovall M, Weathers R, Kasper C, Smith SA, Travis L, Ron E and Kleinerman R 2006 Dose reconstruction for therapeutic and diagnostic radiation exposures: use in epidemiological studies *Radiat. Res* 166 141–57 [PubMed: 16808603]
- Taddei PJ et al. 2018 Low- and middle-income countries can reduce risks of subsequent neoplasms by referring pediatric craniospinal cases to centralized proton treatment centers *Biomed. Phys. Eng. Exp* (in press) (10.1088/2057-1976/aaalce)
- Taddei PJ, Fontenot JD, Zheng Y, Mirkovic D, Lee AK, Titt U and Newhauser WD 2008 Reducing stray radiation dose to patients receiving passively scattered proton radiotherapy for prostate cancer *Phys. Med. Biol* 53 2131–47 [PubMed: 18369278]
- Taddei PJ, Jalbout W, Howell RM, Khater N, Geara F, Homann K and Newhauser WD 2013 Analytical model for out-of-field dose in photon craniospinal irradiation *Phys. Med. Biol* 58 7463–79 [PubMed: 24099782]
- Taddei PJ, Khater N, Zhang R, Geara FB, Mahajan A, Jalbout W, Pérez-Andújar A, Youssef B and Newhauser WD 2015 Inter-institutional comparison of personalized risk assessments for second malignant neoplasms for a 13-year-old girl receiving proton versus photon craniospinal irradiation *Cancers* 7 407–26 [PubMed: 25763928]

Xu XG, Bednarz B and Paganetti H 2008 A review of dosimetry studies on external-beam radiation treatment with respect to second cancer induction *Phys. Med. Biol* 53 R193–241 [PubMed: 18540047]

Figure 1. Dose distribution from applying the treatment fields of the 12-year-old boy to the anthropomorphic phantom, showing in axial (left), sagittal (middle), and coronal (right) planes superimposed on the CT images of the phantom. The colored lines depict the 95% isodose (red line), 50% isodose (light blue line), 5% isodose (purple line), PTV (dark blue line), and gross tumor volume (green line) on the color wash.

Figure 2.
Anthropomorphic phantom in the treatment position for the measurement.

Figure 3. (Upper panel) Double-Gaussian model fit (red line) and measured TLD data (blue circles) from the LBT treatment fields. The inset zooms in on the out-of-field dose region of less than 0.5 cGy Gy^{-1} . (Lower panel) Analytical models of out-of-field dose versus distance to the field edge for the LBT fields of the current study (solid line) and the CSI fields of a previous study (Taddei *et al* 2013) (dashed line).

Figure 4.

Sagittal views of the dose distribution from the primary fields of the 8-year-old boy on the original CT image set (upper) and dose distribution from in-field (TPS) and out-of-field (model) components on the fused secondary CT image set (lower). Although these two image sets overlay, they have been presented separately for improved viewing. The composite phantom was a combination of subsets of these two image sets. The displayed isodose lines are 100% (yellow), 95% (red), 50% (black), 10% (purple), 1% (green), 0.5% (blue), and 0.1% (bright green). The location of the thyroid in the secondary image set is contoured in red (lower).

Table 1.

Cancer diagnosis, size of GTV, and prescribed dose for all patients. Patient index denotes each patient's sex and age in years. For example, the 2-year-old male was indexed as 2yom. Heights and masses of each patient and matched computational phantom are listed.

Patient Index	Height (cm)	Mass (kg)	Diagnosis	GTV (cm ³)	Prescribed Dose (Gy)	Phantom Height (cm)	Phantom Mass (kg)
2yom	88	10	Anaplastic ependymoma	62.61	41.4	101	12.8
2.5yof	87	12	Ependymoma	40.53	50.4	85	11.9
3yof	103	21.5	Ependymoma	100.61	54	115	26.9
3.5yof	104	16	Anaplastic ependymoma	83.50	45	115	26.9
4yof	103	18	Glioma	93.64	54	115	26.9
4yom	94	12	Pilocytic astrocytoma	28.29	54	101	12.8
8yom	133	28.4	Glioma	33.12	54	130	29.6
12yof	135	39	Suprasellar germinoma	62.72	30.6	147	42.6
12yom	144	40	Anaplastic ependymoma	36.09	50.4	130	29.6

Table 2.

Description of the 12-year-old boy's treatment plan (7 fields, 6 MV photon, 3DCRT).

Field	1	2	3	4	5	6	7
Monitor units	960	631	631	421	127	913	772
Gantry angle (°)	320	73	118	73	73	305	273
Couch angle (°)	90	0	305	0	0	0	0
Collimator angle (°)	90	0	350	0	0	145	0
X1 jaw (cm)	3.9	-1	-2.9	-1	-0.9	4.3	11.3
X2 jaw (cm)	4	10.7	13	10.7	10.8	5.8	-1.2
Y1 jaw (cm)	5.5	10.5	6	10.5	10	-2.5	10.5
Y2 jaw (cm)	4	-1	2.5	-1	-1	12	-1
Effective square (cm)	7	8.9	7.6	7.8	6.9	7.4	7.9
Source-to-surface distance (cm)	93.1	93.4	91.9	93.4	93.4	92.9	92.7
Water equivalent depth of calculation point (cm)	16.34	10.21	10.82	10.21	10.21	10.34	8.07

Table 3.

Tissue weighting factors, w_T , as defined by the ICRP in Publication 103 (ICRP 2007).

Organs and tissues	w_T
Bone marrow	0.12
Lung	0.12
Breast	0.12
Colon	0.12
Stomach	0.12
Remainder	0.12
Gonads	0.08
Thyroid	0.04
Bladder	0.04
Liver	0.04
Esophagus	0.04
Bone surface	0.01
Skin	0.01
Salivary glands	0.01
Brain	0.01

Table 4.

Fitted parameters for the analytical model.

Parameter	Value
α_1 (cm cGy Gy ⁻¹)	771.6
μ_1 (cm)	-3.8
σ_1 (cm)	3
σ_2 (cm cGy Gy ⁻¹)	46.3
μ_2 (cm)	-10
σ_2 (cm)	22

Table 5.

Mean absorbed doses (Gy) in organs and tissues at risk for SMNs for patients with LBTs. These values were averaged across all localized brain tumor patients (Avg. LBT) and compared with those of a previous study of children who received craniospinal irradiation (Avg. CSI) (Taddei *et al* 2018). The doses were normalized to prescriptions of 54 and 23.4 Gy for the LBT and CSI treatments, respectively.

Organs and Tissues	2yom	2.5yof	3yof	3.5yof	4yof	4yom	8yom	12yof	12yom	Avg. LBT	Avg. CSI
Body	4.16	3.23	3.89	2.78	3.1	3.43	1.51	1.48	1.39	2.77	5.15
Bladder	0.06	0.07	0.02	0.03	0.02	0.06	0.01	0.01	0.02	0.03	2.12
Red bone marrow	5.57	7.56	5.72	5.52	8.22	7.18	6.38	4.2	1.59	5.77	5.84
Breast tissue	—	0.27	0.20	0.24	0.23	—	—	0.17	—	0.22	2.03
Liver	0.18	0.19	0.13	0.17	0.15	0.19	0.11	0.11	0.13	0.15	4.87
Lungs	0.29	0.28	0.19	0.24	0.21	0.3	0.2	0.21	0.23	0.24	3.76
Ovaries	—	0.07	0.02	0.03	0.06	—	—	0.01	—	0.04	1.72
Prostate	0.04	—	—	—	—	0.04	0.01	—	0.01	0.03	0.93
Remainder	2.04	1.49	1.09	1.09	0.8	2.06	0.45	0.67	0.9	1.18	5.76
Skin	1.21	1.37	1.86	0.86	1.11	1.14	0.52	0.64	0.5	1.02	2.67
Stomach	0.21	0.22	0.12	0.16	0.14	0.21	0.1	0.09	0.12	0.15	4.42
Thyroid	2.3	0.87	0.25	1.26	0.42	1.94	0.35	0.73	1.55	1.07	17.09
Uterus	—	0.07	0.02	0.03	0.02	—	—	0.01	—	0.03	1.5
Testicles	0.04	—	—	—	—	0.04	0.01	—	0.01	0.03	0.78
Colon	0.13	0.14	0.07	0.09	0.08	0.13	0.04	0.04	0.05	0.08	5.82
Brain minus GTV	23.49	17.43	27.72	20.06	30.86	18.42	21.66	27.48	17.79	22.77	—

Table 6.

The effective dose in Sieverts (Sv) was calculated according to the recommended method of the International Commission on Radiological Protection (ICRP 2007) for each patient and averaged across all nine patients.

Patient	Effective Dose (Sv)
2yom	1.46
2.5yof	1.52
3yof	1.27
3.5yof	1.22
4yof	1.56
4yom	1.60
8yom	1.13
12yof	1.00
12yom	0.65
Average	1.27