Published in final edited form as:

Radiother Oncol. 2018 August ; 128(2): 209–213. doi:10.1016/j.radonc.2018.05.013.

Retrospective estimation of heart and lung doses in pediatric patients treated with spinal irradiation

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Abstract

Background and Purpose—The purpose of this study was to investigate whether treatment information from medical records can be used to estimate radiation doses to heart and lungs retrospectively in pediatric patients receiving spinal irradiation with conventional posterior fields.

Material and Methods—An algorithm for retrospective dosimetry in children treated with spinal irradiation was developed in a cohort of 21 pediatric patients with available CT-scans and

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Conflict of interest statement

Dr. Vogelius has a master research agreement with Varian Medical Systems and Dr. Aznar reports grants to the department from both Varian Medical Systems and Siemens, all outside the submitted work.

treatment plans. We developed a multivariable linear regression model with explanatory variables identifiable in case note review for retrospective estimation of minimum, maximum, mean and $V_{10\%}$ – $V_{80\%}$ doses to the heart and lungs. Doses were estimated for both linear accelerator (Linac) and ^{60}Co radiation therapy modalities.

Results—Age and spinal field width were identified as statistically significant predictors of heart and lung doses in multivariable analyses ($p < 0.01$ in all models). Models showed excellent predictive performance with $R^2 = 0.70$ for mean heart dose and 0.79 for mean lung dose, for Linac plans. In leave-one-out cross-validation analysis the average difference between predicted and actual mean heart dose was 6.7% and 7.6% of the prescription dose for Linac and ^{60}Co plans, respectively, and 5.2% and 4.9% for mean lung dose. Due to the small sample size and large inter-patient variation in heart and lung dose, prospective studies validating these findings are highly warranted.

Conclusions—The models presented here provide retrospective estimates of heart and lung doses for historical cohorts of pediatric patients, thus facilitating studies of long-term adverse effects of radiation.

Keywords

Pediatric spinal irradiation; Retrospective dosimetry; Heart and lungs; Linear regression models; Dose estimation models

Introduction

Pediatric cancer survivors comprise a rapidly growing group of young adults [1]. However, a longer survival is associated with long-term morbidity and mortality [2]. The most common cause of death among pediatric cancer survivors is cardiovascular disease [3]. Congestive heart failure in the form of coronary artery disease is also a serious late effect due to mediastinal radiation [4], other late effects, that also might cause death are pulmonary fibrosis, acute pulmonary toxicity and restrictive lung disease [5–7].

Recent technological advances in radiation therapy optimization and delivery, often provide several competing treatment options and the resulting dose distributions throughout the patient's body can vary considerably [8]. These in turn may yield substantially different risks of late complications such as severely debilitating cardiac and pulmonary toxicity. Considerable clinical research efforts have aimed at developing empirical models for clinical decision support in pediatric patients [9], as well as young adults with Hodgkin lymphoma [10] and breast cancer patients [11–13], relating the dose and dose distribution delivered to an organ-at-risk (OAR) to the risk of long-term toxicity. This is a challenging research field in both pediatric and adult patient populations, and due to the considerable differences between children and adults, it is not straightforward to translate results from an adult population directly to pediatric cohorts. However, important long-term outcome data emerging from large cohort studies of childhood cancer survivors has the potential to greatly improve our ability to predict the risk of late toxicity in patients treated today [14–17]. Furthermore, a comprehensive systematic review of available dose-volume data related to

toxicity after pediatric radiation therapy is currently undertaken by the Pediatric Normal Tissue Effects in the Clinic (PENTEC) collaboration [18].

Because of the long latent period of many late effects, for some endpoints 10–20 years or more, many dose response modeling studies of late-effects analyze outcome data from cohorts treated decades ago. This poses the further challenge of reconstructing the dose distribution for cases treated in an era without 3D computed tomography (CT) based planning and detailed dosimetry, and with radiation modalities that are less commonly used now. In some clinical indications at least a crude relationship exists between organ doses and patient characteristics that are available from case note review. If unadjusted for, these associations may confound the results of retrospective analyses if organ doses are solely based on the prescribed dose. For example, it is possible that the dose delivered to the heart and lungs of a pediatric patient correlates with patient age due to the relative change in body composition and organ size as the child grows. This may cause a bias in a retrospective analysis as an observed correlation between age at exposure and risk of toxicity could be wrongfully attributed to age, when in fact the heart or lung dose is driving the association. This issue and the need for accurate retrospective dosimetry have been well recognized in the adult setting for example in Hodgkin lymphoma [19–23].

In this study we test whether age, as well as several other characteristics that can be retrieved from treatment records, can be used to estimate doses to the heart and lungs in a group of pediatric patients treated with spinal irradiation. Furthermore, we investigate if different radiation beam qualities (i.e. ^{60}Co (^{60}Co) machines vs. linear accelerators (Linacs)) would yield a systematic difference in organ dose that may further confound retrospective studies.

Materials and Methods

Data collection

All patients, < 20 years of age at the time of treatment and who received spinal irradiation between 2005 and 2012 at our institution were retrospectively reviewed. We identified a cohort of 21 eligible patients that were included in the analysis (see table 1 for patient characteristics), all treated for medulloblastoma with Linac-based cranio-spinal radiation therapy using a 6 MV beam. Treatment plan information and CT scans were available for all patients in the treatment planning system (TPS, Eclipse™ v. 13.7 (Varian Medical Systems, Palo Alto, CA, USA). The heart and lungs were segmented (ARIA® contouring suite v. 13.6, Varian Medical Systems, Palo Alto, CA, USA) on the treatment planning CT scans. The heart was manually segmented and the lungs were automatically segmented with manual adjustment when needed.

Treatment plans were exported to CERR [24] and subsequently analyzed in MATLAB release 2014b (The MathWorks, Inc., Natick, MA, USA) and the minimum, maximum, mean and $V_{10\%}$ - $V_{80\%}$ doses to the heart and lungs were extracted from the spinal irradiation plan for each patient. Further patient characteristics that were extracted were the length and width of the spinal field (at the patient's skin level from the incident beam direction), age at exposure, sex, and patient positioning (prone or supine).

Comparison to ^{60}Co

To test the possible difference in minimum, maximum, mean and $V_{10\%} - V_{80\%}$ heart and lung doses from ^{60}Co and 6 MV Linac beams, we implemented a ^{60}Co machine in our TPS with beam data from a Siemens Gammatron-3. ^{60}Co treatment plans required the dose to be calculated using a pencil beam algorithm (i.e. a type A algorithm, PBC version 10.0.28), while the Linac plans were calculated using a Monte Carlo-like algorithm (i.e. a type C algorithm, Acuros XB[®], version 13.7). The field set-up was identical in the Linac and the ^{60}Co plans. All Linac and ^{60}Co plans were normalized to a reference point at the dorsal edge of the Th8-Th11 (depending on patient size) vertebral body receiving 90% of the prescribed dose. To assess the effect of differences between the Acuros XB[®] algorithm and PBC algorithm used for ^{60}Co calculations, all Linac plans were also calculated with the PBC algorithm.

Statistical analysis

Shapiro-Wilk tests and visual histogram inspection were used to test for a normal distribution of a variable. Bivariate associations between all patient characteristics (age, sex, position, field length and width) and heart or lung doses were quantified by Pearson's or Spearman's rank correlation coefficients for continuous variables and t-tests or Wilcoxon rank-sum tests for categorical variables, depending on the assessment of normality and linearity. Similarly, differences between heart and lung doses between Linac and ^{60}Co plans were assessed using paired t-tests or Wilcoxon sign-rank tests depending on the normality test.

Multivariable linear regression models were fitted for the various heart and lung dose metrics using all covariates with $p < 0.2$ from the tests of bivariate association as candidate predictor variables. Stepwise elimination was performed manually using a $p < 0.05$ cutoff for inclusion in the final models. The resulting multivariable linear regression models provide the following relationship for dose estimation:

$$D_{Est} = X_1\beta_1 + X_2\beta_2 + \dots + X_n\beta_n + k \quad (1)$$

where D_{Est} is the estimated dose metric, x_i is the value of the i :th predictor, β_i the corresponding regression coefficient and k a constant. Despite the large number of statistical tests performed, correction for multiple comparisons was not applied since it is expected that highly correlated dose metrics would depend on the same predictor variables, so it is unlikely that spurious associations would be found for a certain dose metric and not the others. However, a leave-one-out (LOO) cross-validation was performed to assess the predictive performance of the final models. This was done by fitting the regression coefficients of the final models to subsets of the data, subsequently leaving out each of the 21 patients. The heart and lung dose metrics for each excluded patient were then estimated using the models and compared to that patient's dose data from the TPS. The root-mean-square deviation (RMSD) of this difference was then calculated as an average estimate of how well the predicted doses compared to the actual values in the LOO setting. To determine

if the Linac-based models would be able to estimate doses from ^{60}Co and vice versa, the predicted doses from one radiation modality were compared to the TPS doses from the other.

Results

Age and the size of the spinal irradiation field (length and width) showed strong association with mean heart and lung doses (table 2), with similar trends for the other analyzed dose metrics (see supplementary material). The association with age supports the general assumption that age is a good surrogate for heart and lung volume, which is confirmed in our data where age showed a strong correlation with both heart volume (Spearman's $r_s = 0.85$ with 95% CI: 0.64–0.95, $p < 0.001$) and lung volume $r_s = 0.79$ with 95% CI: 0.51–0.94, $p < 0.001$).

In multivariable analysis only age and spinal field width were found to be significant predictors of heart and lung dose as shown in table 3 for mean doses ($p < 0.01$) and supplementary material (tables S1 and S2) for other dose metrics. Since the length of the heart and lungs in the superior-inferior direction was fully encompassed by the spinal fields for all patients we found that field length was not a significant predictor of heart and lung doses. The models based on age and spinal field width showed excellent predictive performance with 69.7% of the variance in mean heart dose, and 78.9% of the mean lung dose, explained by the model for the Linac plans. Patient position, sex and field length were not significant predictors of heart and lung dose in multivariable analysis.

Figure 1 shows the association between age and mean heart and lung dose for the Linac plans and figure 2 shows the corresponding association for spinal field width, along with box-and-whiskers plots of the population mean heart and lung doses. We further explored the association between organ volume and mean heart and lung dose to demonstrate whether age indeed acts as a surrogate marker for this association. In fact, heart volume seems to be a good predictor for mean heart dose ($R^2 = 50.5\%$ in univariable linear regression), as compared to $R^2 = 31.5\%$ using age as the only predictor variable. Conversely, lung volume does not appear to be a particularly good univariable predictor for mean lung dose ($R^2 = 5.6\%$) and rather it appears that the combination of age and spinal field width ($R^2 = 78.9\%$) provides a surrogate measure for the proportion of the lungs receiving incident irradiation (arbitrarily defined as the proportion receiving $>10\%$ of prescription dose, $R^2 = 98.8\%$).

The leave-one-out analysis shows that the models based on age and spinal field width provide fairly accurate estimates of the heart and lung doses when compared with the actual dose for the excluded patients. The average relative accuracy (given by the RMSD_{LOO}) of the estimates of the mean heart dose was 6.7% and 7.6% of the prescribed dose for Linac and ^{60}Co plans respectively. The respective RMSD_{LOO} for the mean lung dose was 5.2% and 4.9%. Table 4 shows the relative accuracy for Linac and ^{60}Co models for the heart and lung dose metrics through calculating the RMSD. Furthermore, table 4 shows that using the Linac-based models to estimate ^{60}Co doses and vice versa provides less accurate estimates compared to the LOO analysis within the same modality, suggesting that separate dose estimation models are needed for patients treated with Linac and ^{60}Co irradiation. To ensure that this was not simply attributable to the use of different calculation algorithms, we

compared the results when using the PBC algorithm to calculate Linac doses and concluded that this had minimal effect on the various dose metrics (see supplementary figure S1).

Discussion

The models including age and spinal field width derived in this study provide an effective means of retrospectively estimating heart and lung doses in pediatric patients treated with spinal irradiation, when 3D dose data from a TPS are not available. Based on figures 1 and 2 it is clear that there is considerable variation in the heart and lung doses between patients and estimating organ doses based on prescription dose alone could lead to biased results.

There are various databases with long-term follow-up of large cohorts of pediatric cancer patients treated up to several decades ago [14–17]. Along with these laudable efforts of collecting data on long-term toxicity, we believe that the models derived in this study can considerably aid the process of linking doses to the heart and lungs with the documented long-term effects. Furthermore, it should be possible to expand this analysis to encompass other OAR in a similar manner and to further refine OAR dose estimation for example by following the suggestions in the AAPM TG-158 report on out of field dosimetry [25]. Similarly, due to the relatively large inter-patient variation in heart and lung dose, prospective studies validating these results are warranted.

Accurate models linking organ dose to late toxicity can aid in the clinical decision making when competing radiation techniques are considered and could help identify patients in need of closer post-treatment surveillance for late adverse events.

Previous studies of adult malignancies have investigated the possibility of applying individual retrospective estimates based on a type of standard phantom or standard patient [12, 20–22]. One such example is retrospectively estimating cardiac doses from breast cancer radiation therapy based on a standardized female patient [12]. Other studies used virtual simulation and CT scans to reconstruct treatment fields [19, 23]. There have also been studies that instead chose to utilize dose measured to a water phantom, along with tumor location details from clinical records, to estimate the doses at the site of secondary tumor development [21]. Hybrid computational phantoms created from CT scans have been shown to be feasible for retrospective heart dosimetry following breast irradiation [26]. By also adding the use of Monte Carlo based dose calculations to pediatric hybrid phantoms, organ doses could be reconstructed to add further accuracy in future secondary cancer risk studies [27].

Given the relatively homogenous setup of spinal irradiation between different patients, the simple models based on age and field width developed here may be sufficient to explain most of the dosimetric variation, and this information can be extracted from previous treatment records. Although the leave-one-out analysis provides an internal validation of the models' accuracy, potential institutional variation in treatment setup and prescription depth was not considered. Since all data came from a single institution the generalizability to patient cohorts and treatment techniques employed in other institutions may be limited. It

should also be mentioned that these models are derived from a relatively small patient sample and are only applicable to treatments with conventional posterior spinal fields.

In conclusion, this study provides a simple recipe for retrospectively estimating heart and lung doses from pediatric spinal irradiation, giving researchers a useful tool to aid them in analyzing heart and lung dose effect relationships in retrospective studies of late effects in long-term pediatric cancer survivors.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

Drs Björk-Eriksson and Munck af Rosenschöld acknowledge financial support from the Swedish Childhood Cancer Foundation and the Danish Child Cancer Foundation. Dr. Brodin acknowledges support from the NIH/National Center for Advancing Translational Science (NCATS) Einstein-Montefiore CTSA Grant Number KL2TR001071 and UL1TR001073. Dr. Bentzen acknowledges support from the Kirsten and Freddy Johansen Foundation. Thanks to Medical Physicists Søren Lassen and Bob Smulders (Rigshospitalet, Copenhagen, Denmark) for aiding in the extraction of treatment data.

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Figure 1.

Mean heart dose (circles) and, mean lung dose (triangles) vs. patient's age with the multivariable linear regression models. The boxplots represent the distribution of mean heart and lung doses among the 21 patients given as mean, 25th – 75th percentile and range. Please note that the range of the boxplots overlap.

Figure 2.

Mean heart dose (circles) and, mean lung dose (triangles) vs. spinal field width with the multivariable linear regression models. The boxplots represent the distribution of mean heart and lung doses among the 21 patients given as mean, 25th – 75th percentile and range. Please note that the range of the boxplots overlap.

Table 1:

Characteristics of the 21 pediatric patients included in the study.

	Median	Range
Age (y)	9	2 - 20
Sex	n	%
Male	11	52
Female	10	48
Position		
Supine	15	71
Prone	6	29
	Mean	SD
Field length (cm)	31.1	3.7
Field width (cm)	6.2	1.2

Table 2:

Results of the analysis of bivariate associations between mean heart and lung dose and the various patient characteristics for Linac and ^{60}Co plans. As sex and position are categorical variables, correlation coefficients can't be given.

Variable	Mean heart dose		Mean lungs dose	
	Corr. Coef.	P-value	Corr. Coef.	P-value
Age	-0.56 (r_p)	0.008	-0.43 (r_p)	0.05
Sex		0.13		0.17
Position		0.11		0.36
Field length	0.38 (r_s)	0.09	0.47 (r_s)	0.03
Field width	0.55 (r_p)	0.01	0.72 (r_p)	< 0.001

Variable	Mean heart dose		Mean lungs dose	
	Corr. Coef.	P-value	Corr. Coef.	P-value
Age	-0.50 (r_p)	0.02	-0.36 (r_p)	0.11
Sex		0.10		0.14
Position		0.11		0.43
Field length	0.34 (r_s)	0.13	0.47 (r_s)	0.03
Field width	0.49 (r_p)	0.02	0.75 (r_p)	< 0.001

Abbreviations: r_p = Pearson's product-moment correlation coefficients; r_s = Spearman's rank correlation coefficients

Table 3:

Final multivariable regression models for mean heart and lung dose for Linac and ^{60}Co plans, respectively. Model performance is given by R^2 and RMSD_{LOO} .

Predictor variable Linac	Regression coefficient (β)	95% CI	p-value
Mean heart dose ($R^2 = 0.70$, $\text{RMSD}_{\text{LOO}} = 6.7\%$)			
Age (y)	-1.37	(-1.95 , -0.78)	< 0.001
Field width (cm)	5.68	(3.17,8.18)	< 0.001
Constant	31.4		
Mean lungs dose ($R^2 = 0.79$, $\text{RMSD}_{\text{LOO}} = 5.2\%$)			
Age (y)	-1.05	(-1.51 , -0.59)	< 0.001
Field width (cm)	6.69	(4.73 , 8.64)	< 0.001
Constant	-7.90		
Predictor variable ^{60}Co	Regression coefficient (β)	95% CI	p-value
Mean heart dose ($R^2 = 0.58$, $\text{RMSD}_{\text{LOO}} = 7.6\%$)			
Age (y)	-1.17	(-1.82 , -0.51)	0.001
Field width (cm)	5.85	(2.54,9.17)	0.002
Constant	34.4		
Mean lungs dose ($R^2 = 0.78$, $\text{RMSD}_{\text{LOO}} = 4.9\%$)			
Age (y)	-0.88	(-1.31 , -0.45)	< 0.001
Field width (cm)	7.64	(5.45 , 9.84)	< 0.001
Constant	-6.37		

Abbreviations: RMSD_{LOO} = The root-mean-square deviation for the leave-one-out cross validation

Table 4:

The RMSD_{LOO} comparisons show the performance of using Linac derived models to estimate Linac doses and ^{60}Co derived models to estimate ^{60}Co doses for all dose metrics. The $^{60}\text{Co}_{\text{Unac}}$ comparisons show the performance of using the Linac dose models to estimate ^{60}Co doses, and vice versa.

Variable	RMSD_{LOO}		$\text{RMSD} (\%)$	
	Linac	^{60}Co	$^{60}\text{Co}_{\text{Linac}}$	Linac ^{60}Co
Mean heart dose	6.7	7.6	7.5	7.3
Min. heart dose	1.3	4.0	4.0	2.4
Max. heart dose	6.2	10.5	9.7	7.6
V _{10%} heart dose	8.3	8.3	12.8	13.3
V _{20%} heart dose	8.7	8.9	11.2	11.8
V _{30%} heart dose	9.1	9.4	9.9	10.3
V _{40%} heart dose	9.2	10.0	9.7	9.8
V _{50%} heart dose	9.5	12.1	12.1	11.1
V _{60%} heart dose	10.9	13.5	17.6	16.7
V _{70%} heart dose	11.6	11.2	16.1	16.7
V _{80%} heart dose	8.3	7.0	8.0	9.1
Mean lungs dose	5.2	4.9	5.8	5.2
Min. lungs dose	0.3	0.4	0.7	0.7
Max. lungs dose	7.6	12.6	11.6	8.5
V _{10%} lungs dose	7.0	6.5	9.8	8.6
V _{20%} lungs dose	6.6	6.4	9.6	8.5
V _{30%} lungs dose	6.3	6.4	8.2	7.1
V _{40%} lungs dose	6.6	7.7	7.3	6.3
V _{50%} lungs dose	6.1	6.5	7.2	6.2
V _{60%} lungs dose	6.1	6.6	7.8	7.1
V _{70%} lungs dose	6.3	5.6	7.5	7.6
V _{80%} lungs dose	5.5	4.1	6.3	6.8

Abbreviations: RMSD = The root-mean-square deviation for the final model; RMSD_{LOO} = The root-mean-square deviation for the leave-one-out cross validation