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Original Articles

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 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.

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].

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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}Cobalt (^{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).

Table 1
Characteristics of the 21 pediatric patients included in the study.

	Median	Range
Age (y)	9	2–20
	n	%
Sex		
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

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

The 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's 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's 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:

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

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.

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