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Original article

Heart volume reduction during radiotherapy involving the thoracic region in children: An unexplained phenomenon

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ABSTRACT

Background and purpose: Radiotherapy involving the thoracic region is associated with cardiotoxicity in long-term childhood cancer survivors. We quantified heart volume changes during radiotherapy in children (<18 years) and investigated correlations with patient and treatment related characteristics.
Material and methods: Between 2010 and 2016, 34 children received radiotherapy involving the thoracic region. We delineated heart contours and measured heart volumes on 114 CBCTs. Relative volume changes were quantified with respect to the volume on the first CBCT (i.e., 100%). Cardiac radiation dose parameters expressed as 2 Gy/fraction equivalent doses were calculated from DVHs. Chemotherapy was categorized as treatment with anthracyclines, alkylating agents, vinca-alkaloids, and other.
Results: The overall median heart volume reduction from the first to the last CBCT was 5.5% (interquartile range1.6–9.7%; $p < 0.001$). Heart volumes decreased significantly between the baseline measurement and the first week (Bonferroni's adjusted $p = 0.002$); volume changes were not significant during the following weeks. Univariate analysis showed a significant correlation between heart volume reduction and alkylating agents; however, no multivariate analyses could be done to further confirm this.
Conclusions: We found a significant heart volume reduction in children during radiotherapy. Elucidation of underlying mechanisms, clinical relevance, and possible long-term consequences of early heart volume reduction require a prospective follow-up study.

Childhood cancer survival has impressively improved over the last decades, with 5-year survival rates now approaching 80% [1,2]. Simultaneously, increased survival is accompanied by tumor- and treatment-related adverse events. Approximately 75% of long-term survivors experience at least one adverse event during their lifetime [3,4]. Cardiotoxicity is among the most serious adverse events after treatment with anthracyclines and/or radiotherapy involving the heart region [5–12].

Image-guided radiotherapy (IGRT) is applied to strive for accurate dose delivery to the target volume and to minimize dose to surrounding healthy tissues [13,14]. The application of IGRT also enables to identify changes in tumor and normal tissue volumes over time during treatment when using cone beam computed tomography (CBCT) imaging. In adult patients, treated with IGRT for esophageal cancer, a heart volume reduction was observed already early during the radiation course [15–17]. Retrospective analysis of cardiac volume change in 26 adults revealed a statistically significant median cardiac volume reduction of 8% during chemoradiation [15]. In a prospective study conducted in a similar cohort, it was found that the heart volume decrease was not accompanied by overt cardiac dysfunction, but by lower blood pressure, increased heart rate and decreased vena cava dimensions [17]. It suggested an intravascular volume depletion occurring during the course of treatment. In the present study, we aimed to quantify heart volume change during radiotherapy involving the thoracic region in children (<18 years) using retrospectively collected CBCTs, and to assess possible correlations with patient and treatment related characteristics.

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Material and methods

Study cohort

Patients younger than 18 years at time of treatment were eligible if they underwent radiotherapy involving the thoracic region, and if a pre-treatment planning CT scan and at least 2 CBCTs were available. CBCT imaging for pediatric IGRT purposes was clinically introduced at our department in 2010. Based on weekly measurements, the minimum interval between the first and the last CBCT had to be 7 days. Only first IGRT courses involving the thoracic region were included if pre-treatment planning CTs and CBCTs were available on which the heart was completely visible. One patient who had a pneumothorax was excluded. This resulted in a study cohort of 34 children treated between January 1st, 2010 and July 1st, 2016 (Fig. 1).

Patients and imaging procedure

Radiotherapy was delivered for various types of primary cancer, a recurrence, or metastatic disease. Primary cancer types included tumors of the central nervous system (CNS; $n = 16$), bone tumors ($n = 8$), lymphomas ($n = 3$), rhabdomyosarcomas ($n = 3$), neuroblastomas ($n = 2$), soft tissue sarcoma ($n = 1$) and pleuropulmonary blastoma ($n = 1$). Treatment fields included craniospinal axis ($n = 15$), (part of the) spine only ($n = 2$), and lung or mediastinum ($n = 17$).

For each patient, pre-treatment CT scans (LightSpeed RT16; General Electric Company, Waukesha, WI, USA) for planning purposes were acquired according to tumor-based radiotherapy protocols. The total number of 295 available CBCT scans were routinely acquired within the scope of radiation treatment for patient position verification before radiation delivery (Synergy, Elekta Oncology Systems, Crawly, UK); low-dose protocols were used since 2013 [18]. All CBCTs were acquired during free breathing, with acquisition times varying from 35 to 60 s, and 200° to 360° rotations, respectively. Depending on cancer diagnoses, radiation sites and fractionation schedules, daily online and offline position verification varied per patient. According to the ALARA principle, the preference in pediatric IGRT is using an offline position verification protocol; at our department a customized extended no-action level (eNAL) protocol is used whenever possible [19]. The eNAL protocol involves CBCT imaging and online correction at the first three radiation treatment sessions. After these sessions an a priori set-up correction is applied based on the average deviation of fractions 1–3, and checked at the 4th fraction. From the 5th fraction onward, the eNAL protocol is followed, i.e., weekly CBCT imaging. Only when eNAL results exceed tolerance limits, daily online position verification is performed. In our study cohort, the eNAL protocol was applied in 22 children, whereas in 12 patients daily online position verification was required. Application of online or offline protocols determined the frequency of CBCT acquisition and the number CBCTs per patient, but did not affect any of the heart volume measurements.

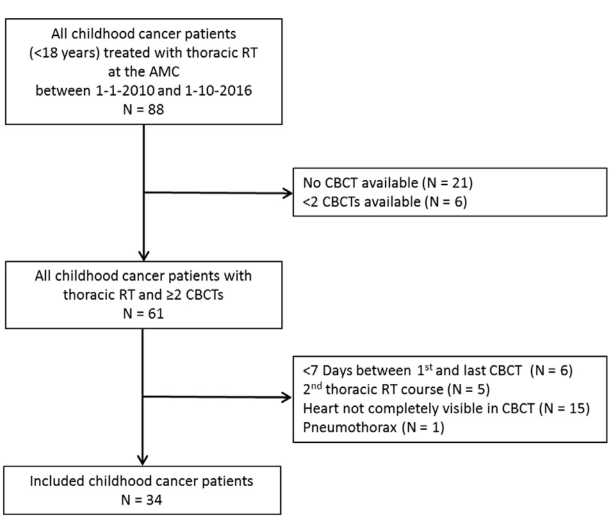

Fig. 1. Flowchart of included childhood cancer patients. *Abbreviations:* AMC, Academic Medical Center; RT, radiotherapy; CBCT, cone beam CT scan.

Patient and treatment characteristics

To investigate possible correlations between patient and/or treatment characteristics with heart volume change, we calculated age at the first radiation fraction and we collected data on gender, height and weight, concurrent chemotherapy, radiation fields and delivered cardiac radiation doses. Concurrent chemotherapy was categorized as treatment with anthracyclines, alkylating agents, vinca-alkaloids, and other. Furthermore, administered doses of specific agents were investigated. To calculate the cardiac radiation doses, fraction doses were multiplied by the number of received fractions prior to the acquisition of the CBCT used for heart volume measurement. Doses were converted into equivalent doses of 2 Gy per fraction (EQD2; $\alpha/\beta = 3$ Gy) [20–22]. We used CT-based dose–volume histograms (DVHs) to calculate the cardiac EQD2 parameters: $D_{90\%}$, $D_{70\%}$, $D_{50\%}$, $D_{30\%}$ and $D_{10\%}$, (i.e., $D_{x\%} = y$ Gy denotes that x% of the heart volume received at least a dose of y Gy), and the mean (D_{Mean}), and maximum (D_{1cc}, $D_{0.1cc}$) cardiac radiation doses.

Heart volume measurements

Images were imported in and processed with Velocity software to delineate heart contours (VelocityAI, Velocity Medical Solutions; Varian, Palo Alto, CA, USA). Heart contours were delineated on the pre-treatment planning CT scans by a single observer (I.v.D.) using the heart atlas developed by Feng et al. [23]; all delineations were validated by an experienced pediatric radiation oncologist (B.V.B.). For each patient, the CT and the first CBCT were registered, after which the heart delineations were adjusted to the heart contour as visible to the first CBCT. On all subsequent CBCTs, the heart contour was delineated based on co-registration with the first CBCT, and the heart volumes measured on the first CBCT were used as reference volumes (Vol_{Ref}). Heart volume differences were calculated by subtracting Vol_{Ref} from volumes measured on the subsequent CBCTs (Vol_{Next}). Relative heart volume differences ($Vol_{RelDiff}$) were then calculated: $Vol_{RelDiff} = 100\% \times (Vol_{Next} - Vol_{Ref})/Vol_{Ref}$; negative results indicate heart volume reduction. Fig. 2 shows an example of an overlay of heart delineations on the first and last CBCT.

CBCTs acquired within three days after each preceding CBCT were not included. Thus, based on weekly heart volume measurements, 114 out of 295 CBCTs acquired over a maximum of six weeks were used to delineate the heart contours (Table 1). Due to the image quality of CBCT scans, substructures of the heart are not distinctly visible. Since the bifurcation of the trachea is distinguishable on CBCTs, the cranial border of the heart was defined at the level of the trachea bifurcation. The pericardium was used as a substitute for myocardium border [15]. The image quality of CBCTs is generally lower than that of the treatment planning CT scan. To avoid any bias, heart volumes on the treatment planning CT scans were not included in the analysis.

To investigate the possible observer bias induced by knowledge on the image acquisition dates (i.e., the expectancy of heart volume diminishing as a function of time), the acquisition dates of 24 CBCTs in seven patients were blinded prior to delineation, and

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