INTERNATIONAL JOURNAL OF
RADIATION ONCOLOGY • BIOLOGY • PHYSICS
www.redjournal.org

PENTEC ORGAN SYSTEM REVIEW

Cardiac Disease in Childhood Cancer Survivors Treated With Radiation Therapy: A PENTEC Comprehensive Review

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Received Oct 16, 2022; Accepted for publication Mar 10, 2023

Purpose: Radiation therapy (RT) is an essential component in the treatment of many pediatric malignancies. Thoracic RT may expose the heart to radiation dose and thereby increase the risk of late cardiac disease. This comprehensive review from the Pediatric Normal Tissue Effects in the Clinic (PENTEC) initiative focused on late cardiac disease in survivors of childhood cancer treated with RT.

Methods and Materials: This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) methodology. We identified 1496 articles; 4 were included for dose-response modeling between mean cardiac radiation dose and risk of late coronary artery disease, heart failure (HF), valvular disease, and any cardiac disease.

Results: For each 10-Gy increase in corrected mean cardiac radiation dose in 1.8- to 2.0-Gy fractions, we estimated a hazard ratio of 2.01 (95% confidence interval [CI], 1.79-2.25) for coronary artery disease, of 1.87 (95% CI, 1.70-2.06) for HF, of 1.87 (95% CI, 1.78-1.96) for valvular disease, and of 1.88 (95% CI, 1.75-2.03) for any cardiac disease. From the same model, for each 100-mg/m^2 increase in cumulative anthracycline dose, the hazard ratio for the development of HF was 1.93 (95% CI, 1.58-2.36), equivalent to an increase in mean heart dose of approximately 10.5 Gy. Other nontreatment factors were inconsistently reported in the analyzed articles.

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James E. Bates, Tiziana Rancati, and Homa Keshavarz made equal contributions to this study.

M.C.A. acknowledges the support of the Engineering and Physical Research Council (grant number EP/T028017/1). E.Y. acknowledges the support of Memorial Sloan Kettering Cancer Center's Cancer Center Support Grant (NIH/NCI P30 CA008748). D.J.C. is supported by Cancer Research UK (C8225/A21133, PRCRPG-Nov21\100001) and the University of Oxford.

Disclosures: none.

Research data are not available at this time.

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.ijrobp.2023.03.045.

https://doi.org/10.1016/j.ijrobp.2023.03.045

Conclusions: Radiation dose to the heart increases the risk of late cardiac disease, but survivors of childhood cancer who receive a mean dose <10 Gy at standard fractionation are at low absolute risk (<∼2% approximately 30 years after exposure) of late cardiac disease in the absence of anthracycline exposure. Minimizing cardiac radiation dose is especially relevant in children receiving anthracyclines. When cardiac sparing is not possible, we recommend prioritizing target coverage. It is likely that individual cardiac substructure doses will be a better predictor of specific cardiac diseases than mean dose, and we urge the pediatric oncology community to further study these relationships.

Introduction

Radiation therapy (RT) is an essential component in the management of many pediatric malignancies. With thoracic RT, incidental exposure of the heart can predispose survivors to long-term cardiac complications. This comprehensive systematic review from the Pediatric Normal Tissue Effects in the Clinic (PENTEC) cardiovascular task forces presents a meta-analysis on the risk of select radiation-related late cardiac diseases in childhood cancer survivors, considers the effect of chemotherapy, and makes recommendations to inform therapeutic decision-making.

Clinical Significance

The optimal treatment of several pediatric malignancies includes RT that exposes cardiac structures to a potentially deleterious radiation dose. Mediastinal lymphomas in particular present clinical situations that garner attention to cardiotoxicities due to the frequent juxtaposition of tumor target volumes to the heart, and the common use of cardiotoxic anthracycline chemotherapy. Other cancers arising in the thorax such as sarcomas, thymomas, or neuroblastoma are also often treated with RT with significant heart exposure. Other treatment scenarios, such as whole lung RT (eg, for Wilms tumor or sarcomas), left-sided abdominal RT that includes the base of heart, total body irradiation for stem cell transplantation conditioning, and craniospinal RT for central nervous system malignancies may also result in clinically significant cardiac exposure depending on technique. In children and adolescents most of these clinical situations are associated with moderate-to-high 5-year survival rates with many expected life-years remaining. As such the consideration of late side effects is of critical importance. Technical advances in RT delivery such as intensity modulated RT (IMRT) and proton therapy can offer significant cardiac sparing, but some exposure is usually unavoidable.[1-3]

Cardiac disease is among the most common severe, life-threatening, or fatal late toxicities in long-term survivors of childhood cancer.[4] In the population of the Childhood Cancer Survivor Study (CCSS), among 5-year survivors treated from 1970 to 1999, the incidence of cardiac disease 30 years from diagnosis was 4.8% representing an absolute excess risk of 1.28 events per 1000 person-years.[5] The spectrum of cardiac toxicities is broad; survivors aged 30 to 50 years old are at a 5- to 6-fold risk of congestive heart failure, myocardial infarction, pericardial disease, and valvular abnormalities.[6] The absolute rates of cardiac disease in survivors of cancer increases with prolonged follow-up as the age-related background risk of cardiac disease increases. In addition to RT, commonly used chemotherapeutic agents in children, most notably anthracyclines, are an important contributor to late cardiac morbidity.[5] It remains unclear if the combination of RT and anthracyclines is additive or synergistic in causing toxicity; longer-term follow-up and larger study populations will be needed to elucidate this.

Endpoints and Toxicity Scoring

The reported grading of severity of cardiac toxicity varied both in terms of the reporting source (physician- vs patient-reported) and the scoring systems used across the studies considered. More complete details regarding this are stated in the section Review of Dose-Volume Response Data and Risk Factors. We did not have access to individual patient-level data, nor was a universal grading system used. Going forward, in future studies, it is our recommendation to use the Common Terminology Criteria for Adverse Events (CTCAE). This has become the standard reporting system for both acute and late effects of therapy, though does not differentiate acute versus late toxicity. The most recent fifth version typically defines grade 3 toxicities as "symptomatic" and requiring "intervention." However, there is some variation regarding grade 2 toxicities; for example, grade 2 heart failure is defined as symptomatic, whereas grade 2 myocardial infarction is defined as the asymptomatic minimal elevation of cardiac enzymes.[7]

Sufficient data were available for analysis of 4 endpoints: heart failure (HF), coronary artery disease (CAD), valvular disease (VD), and any (ie, all diagnoses of) cardiac disease combined.

Anatomy and Developmental Dynamics

Radiation induces damage to cardiac substructures through a variety of mechanisms. Endothelial injury results in a proinflammatory state that can activate myofibrobasts that produce collagenous extracellular matrix components. This leads to tissue stiffness that impairs structure elasticity and ultimately causes fibrosis of the coronary arteries, accelerating atherosclerosis.[8] Similar processes can result in fibrosis in valvular structures, accelerating valvular disease, and

fibrosis in the myocardium accelerating the development of nonischemic cardiomyopathy.

Furthermore, the temporal dynamics of cellular turnover within the heart throughout the lifespan may offer further clues as to the effects of cardiotoxic therapies at varying ages. Cardiomyocyte renewal varies with age, being at its highest in early childhood and gradually declining throughout the lifespan.[9] This age-related variation in cardiomyocyte turnover is consistent with the observed differential effect of cardiotoxic agents at varying stages of development. For example, it is well established that anthracycline chemotherapy affects the risk of heart failure in younger children to a greater extent than older children.[5,10] The relationship between developmental status and risk of radiation-induced heart failure is less clear, in part due to longstanding efforts to minimize thoracic RT in very young children. Conversely, endothelial and mesenchymal turnover is continuous throughout the lifespan.[9] It is unclear how these variations in cardiac cellular turnover may affect the relationship between age at exposure and the development of specific cardiac diseases.

Defining Volumes: Pediatric Imaging Issues

Although the data evaluated in this review treat the whole heart as a uniform organ, preliminary data support the relevance of radiation doses to specific cardiac substructures and thus the specific cardiac complications relating to those substructures. Although investigations confirming this remain sparse, there are emerging data in adult patients who mean left ventricular radiation dose is correlated with risk of heart disease, coronary artery dose is associated with risk of ischemic events, and valvular dose is associated with risk of valvular heart disease.[11-14] Prospectively collected data in children are vital to ascertain the relationships between radiation dose to cardiac substructures and risk of specific heart diseases. As such, for patients enrolled on prospective therapeutic or registry trials, we recommend contouring at least a limited set of cardiac substructures in children receiving modest doses (>5-10 Gy) to any portion of their heart. This set includes the left ventricle, left main coronary artery, and left anterior descending coronary artery. Contouring other chambers, coronary arteries, and cardiac valves in anatomic proximity to target volumes is also of potential use. Two contouring atlases for adult patients have been published; both are reasonably applicable to pediatric patients.[15,16] In routine clinical practice, the whole heart should be contoured as defined in the aforementioned atlases and mean heart dose calculated to facilitate both risk estimation and patient/family counseling as well as RT plan optimization. At present, aside from generic "as low as reasonably achievable" (ALARA) principles, there is not sufficient evidence for routine clinical decision-making based upon cardiac substructure dosimetry in pediatric patients. The use of intravenous iodinated contrast substantially increases the ease of cardiac contouring; however, we would not recommend routine contrast administration for the sole purpose of cardiac substructure delineation.[17] Similarly, the use of magnetic resonance imaging at time of simulation may also be useful but cannot yet be recommended routinely until evidence demonstrates a translation to improved outcomes.[18] The heart also moves throughout both the respiratory and cardiac cycles. With evolving technologies that help enable the gating of radiation delivery to specific portions of the respiratory or cardiac cycles, the location of the heart and its various substructures during the respiratory or cardiac cycles may become more pertinent. These technologies may also help mitigate the effect of these motions; however, we recognize that they are not in widespread clinical use currently.[17,19]

Review of Dose-Volume Response Data and Risk Factors

Methodology

This systematic review was undertaken in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[20,21] The search criteria were developed to locate all studies published from January 1, 1995, to October 2, 2017, that evaluated radiation dose/volume effects on the risk of cardiac disease among survivors of childhood cancer who received RT. In addition, we included 2 recently published updates to one of the initially identified studies that provided a more complete and accurate representation of the true heart radiation dose received.[5,22] Figure E1 provides further details of the search strategy. Table E1 presents an overview of our inclusion and exclusion criteria. Ten investigators (D.C., D.H., E.Y., G.G., H.V., H.K., L.S.C., M.H.C., S.A., T.R.) independently reviewed titles, abstracts, and full texts as necessary. In case of disagreement regarding eligibility, a third author adjudicated. For eligible studies, study design, source of data, population characteristics, and outcomes were extracted using an electronic data extraction form; we resolved disagreement by consensus with 4 authors (E.Y., D.H., D.C., or H. K.). Eligibility check of the included studies, risk of bias assessment, and data extraction were performed independently and in duplicate. Three authors (D.C., J.B., H.K.) used a modified version of the Newcastle-Ottawa instrument to assess risk of bias in the included studies.[23]

We identified 1496 unique references at title and abstract screening and excluded 1212 studies based on review of title and abstract and an additional 142 after review of the full text (Fig. 1). Six studies were identified that met our inclusion criteria; in total these studies represent 30,041 survivors of childhood cancer under the age of 21 at initial diagnosis and cover a broad spectrum of clinical conditions. Approximately 80% of those survivors came from analysis of the CCSS. All patients in the included studies received a diagnosis in 1999 or earlier and thus were treated with 2-

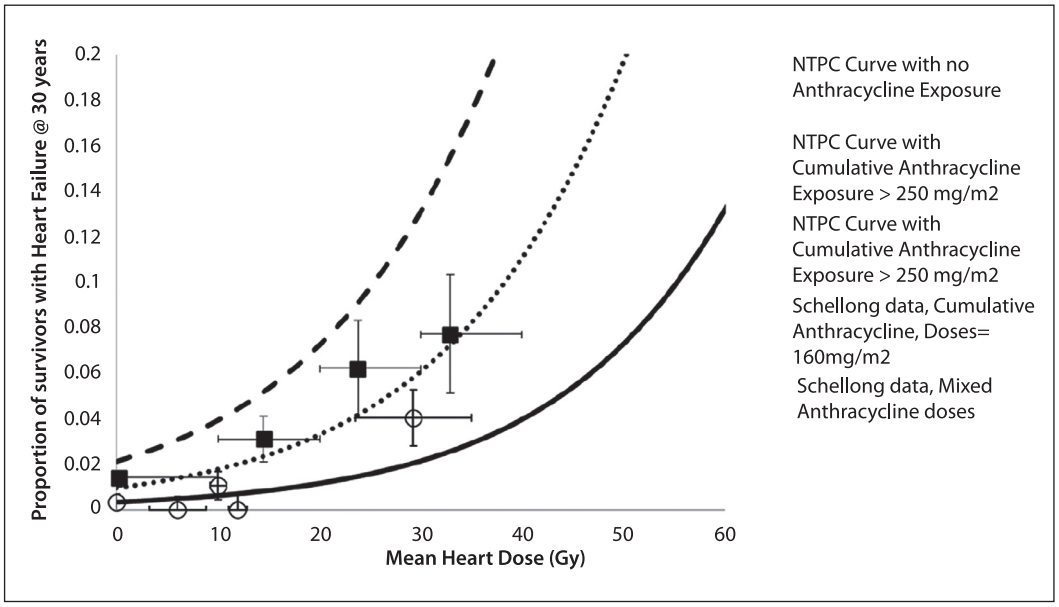

Fig. 1. Dose-response curves for long-term risk of heart failure in survivors of childhood cancer based on data from the Childhood Cancer Survivor Study (Shrestha et al[22]), Dutch childhood cancer survivors (van der Pal[24]), Hodgkin disease survivors (Schellong et al[25]), and Wilms tumor survivors (Green et al[26]). These curves represent NTCP models using hazard ratios derived from the data; however, the baseline incidence at 30 years (H_0) was not fit to the data but determined from a Childhood Cancer Survivor Study sibling population; the mathematical modeling is described more fully in the text of the article. Given the important contribution anthracycline exposure has in influencing risk of heart failure, this figure shows this effect as a dichotomized risk factor (above or below 250 mg/m^2 of cumulative dose) based on Childhood Cancer Survivor Study analysis (Bates et al[5]). Data points are not included for Dutch data because the article included only modeling data. *Abbreviation*: NTCP = normal tissue complication probability.

dimensional or 3-dimensional approaches that are substantially different from modern RT techniques.[5,24-28] Table 1 summarizes these studies. We considered that all doses were given with standard daily fractionation of approximately 1.8 to 2.0 Gy/fraction.

Review of dose-volume data

Four articles addressed at least 1 of the 4 outcomes investigated (CAD, HF, VD, any cardiac disease). Two of the articles addressed all 4 outcomes in broad cohorts of childhood cancer survivors across the range of pediatric malignancies. Van der Pal et al analyzed CTCAE version 3.0 grade 3 or higher cardiac toxicities in 1392 Dutch 5-year survivors of childhood cancer treated from 1966 to 1996 fit to a no-threshold model and noted a hazard ratio (HR) ≈1.8 for any cardiac disease for each 10-Gy increase in prescription dose.[24] Bates et al report the experience of the CCSS including 24,214 North American 5-year survivors of childhood cancer treated from 1970 to 1999.[5] This report was updated from a prior study from a previous decade by Mulrooney et al.[6] Their study showed that mean heart RT doses >10 Gy (based on dose reconstruction on age-specific phantoms) increased the risk of any cardiac disease, heart failure, and coronary artery disease in a dose-dependent manner.[5] They additionally showed that an increasing volume of the heart receiving ≥20 Gy (V20) and >50% of the volume of the heart receiving >5 Gy (V5) were both positively correlated with increasing cardiac risk. An update from Shrestha et al confirmed these relationships with a significantly enhanced cardiac model,[22] which increased the accuracy of cardiac dosimetry.[29] In these articles, CTCAE version 4.03 grade 3 or higher toxicities were considered.

Two additional studies report cardiac disease risks in specific cancer populations. Schellong et al reported dose-dependent cardiac risks after therapy in 1132 pediatric survivors of Hodgkin lymphoma treated on the DAL-HD studies from 1978 to 1995. The incidence of cardiac disease 25 years after mediastinal RT was 3%, 5%, 6%, 10%, and 21% in patients prescribed to receive 0, 20, 25, 30, and 36 Gy, respectively. This study used American College of Cardiology/American Heart Association guidelines for classifying the severity of valvular disease (and did not consider minimal disease) but does not report how other cardiac diseases were graded.[25] Green et al reported the outcomes of 2710 pediatric survivors of Wilms tumor treated in the National Wilms' Tumor Studies (NWTS-1 to -4) through 1998. They reported relative risks of heart failure of 1.6 and 1.8 per 10 Gy of prescribed dose of lung RT and 10 Gy of left abdominal RT, respectively. They defined heart failure as requiring treatment with digoxin or diuretics.[26] Although

Table 1 Summary of included studies

First author, year (country)	Recruited (study type)	Population (survivors)	Setting	Primary childhood cancer	Outcome(s)
Van der Pal, 2012 (Netherlands)	1966-1996 (cohort)	5-y childhood cancer survivors (1362)	Children's hospital/ academic medical center	Any cancer	Any cardiac disease Heart failure
Bates, 2019/ Shrestha, 2021 (North America)	1970-1999 (cohort)	5-y childhood cancer survivors (24,214)	North American survivors of childhood cancer in Childhood Cancer Survivors Study	Any cancer	Any cardiac disease Heart failure Coronary artery disease Valvular disease
Schellong, 2010 (German −Austrian)	1978-1995 (cohort)	Hodgkin lymphoma survivors (1132)	German−Austrian pediatric Hodgkin lymphoma trials (DAL-HD)	Hodgkin lymphoma	Any cardiac disease Heart failure Coronary artery disease Valvular disease
Green, 2001 (United States)	1969-1995 (cohort)	Wilms tumor survivors (2710)	National Wilms' Tumor Studies (NWTS-1, -2, -3, and -4)	Wilms tumor	Heart failure
Armstrong, 2013 (United States)	Treated through 2000 (cohort)	10-y childhood cancer survivors (498)	Treated at St. Jude Children's Research Hospital (SJLIFE)	Any cancer	Echocardiographic valvular disease (not included in valvular disease analysis)
Christiansen, 2014 (Norway)	1970-2000 (matched control)	Norwegian survivors of pediatric lymphoma (220)	Cancer Registry of Norway	Lymphoma	Echocardiographic valvular disease (not included in valvular disease analysis)

it is possible that there is some overlap in study population between the NWTS studies and the CCSS, the NWTS studies were open at more institutions than those that participate in the CCSS and not all participants in the NWTS studies enrolled in the CCSS; as such, we continued to keep this study in our models. Both studies included patients who had received anthracycline-based chemotherapy that also contributes to cardiac disease risk. Of note, regarding anthracycline dose, the CCSS analysis reports doxorubicin-equivalent dose and all survivors in the DAL-HD studies and the NWTS studies received doxorubicin alone. However, the survivors in the van der Pal et al study are only reported as "anthracycline dose," and it is possible that other anthracyclines were used which may contribute some uncertainty to any analyses including anthracycline dose.

We identified 2 analyses of echocardiographic, rather than clinical, endpoints pertaining to valvular dysfunction. Armstrong et al reported results from 498 survivors at St. Jude Children's Research Hospital across the spectrum of primary cancer diagnosis and found that, among survivors receiving ≥20 Gy of thoracic-directed RT, there was a nearly 3.5-fold increase in risk of abnormal tricuspid regurgitant jet velocity.[27] Christiansen et al performed a similar echocardiography-driven study in 220 Norwegian survivors of pediatric lymphoma and found that 55% of survivors had left-sided valvular dysfunction after mediastinal RT.[28] We do not show modeling for these echocardiographic data because the clinical significance of screening-detected echocardiographic abnormalities is unclear relative to the remainder of reports that considered only symptomatic cardiac disease.

Dosimetric analysis

A full review of the approaches used to estimate the dose received by the heart in each article incorporated into our modeling was performed (M.A.). Although the articles using the CCSS data used reconstruction methods to estimate the dose received by the heart,[5,30] the majority of articles used the prescription dose as a surrogate for heart dose. Based on published planning studies describing the difference between prescription dose and mean heart dose (primarily in populations of patients with hematologic malignancies), we determined that the incorporated studies using prescription dose as a surrogate of heart dose overestimated mean cardiac doses by anywhere from 30% to 60%.[31,32] This is consistent with a prior report that prescription dose overestimated mean heart dose in adult patients with Hodgkin

lymphoma treated with involved field RT by as much as 40%.[1,33] It is important to note that the general overestimation of cardiac dose implies that the resulting risk may be underestimated in published studies. To include as much of the published data as possible, we "corrected" the published prescribed chest dose estimates before incorporating them in our model. A detailed description of the averaged corrections and their rationale is provided in Table E2.

Mathematical models

The probability of the development of each specific endpoint 30 years after the receipt of radiation therapy was described as a function of mean heart dose. We a priori described this using a sigmoid-shaped dose-response curve as used in the QUANTEC analysis of cardiac toxicty[34]:

$$\mathrm{NTCP}(\mathrm{D},\ @30\mathrm{years}) = 1 - \exp[-\mathrm{H}_0(30\mathrm{years}) * \exp(\beta * \mathrm{D})]$$

The β values were obtained from the HR generated in each meta-analysis such that $\beta = \ln(\mathrm{HR})$. For analysis of heart failure and any cardiac disease (the 2 outcomes in which we had sufficient data to evaluate the effect of anthracyclines), we considered 2 scenarios based on the manuscripts incorporated into this analysis, which both allow for mutual adjustment of the chest RT and anthracycline effects, respectively, in multivariable models. The first scenario addresses anthracyclines as a dichotomized dose variable, conforming to modeling used in the CCSS analysis (with a cut point of ± 250 mg/m^2 cumulative anthracycline dose).[5] The following 2 equations were made for these scenarios:

$$\mathrm{NTCP}\left(\mathrm{D},\ @30\mathrm{years},\ \mathrm{d}_{\mathrm{ANT}} < 250\mathrm{mg/m}^2/\mathrm{d}_{\mathrm{ANT}} > 250\mathrm{mg/m}^2/\right) = 1 - \exp\left[-\mathrm{H}_0(30\mathrm{years}) * \exp\left(\beta * \mathrm{D} + \beta_{\mathrm{ANT},<250}\right)\right]$$

$$\mathrm{NTCP}\left(\mathrm{D},\ @30\mathrm{years},\ \mathrm{d}_{\mathrm{ANT}} < 250\mathrm{mg/m}^2/\mathrm{d}_{\mathrm{ANT}} > 250\mathrm{mg/m}^2/\right) = 1 - \exp\left[-\mathrm{H}_0(30\mathrm{years}) * \exp\left(\beta * \mathrm{D} + \beta_{\mathrm{ANT},>250}\right)\right]$$

The other scenario considered addresses cumulative anthracycline dose as a continuous variable, based on data from the articles published by van der Pal et al and Green et al.[24,26] This resulted in the following formula being considered:

$$\mathrm{NTCP}(\mathrm{D},\ @30\mathrm{years},\ \mathrm{d}_{\mathrm{ANT}}) = 1 - \exp\left[-\mathrm{H}_0(30\mathrm{years}) * \exp\left(\beta * \mathrm{D} + \mathrm{d}_{\mathrm{ANT}} * \beta_{\mathrm{ANT,\,cont}}\right)\right]$$

where $\mathrm{d}_{\mathrm{ANT}}$ is the dose of anthracyclines.

HRs in these models were fit to the data; however, the baseline incidence of each endpoint at 30 years posttreatment (H_0) was obtained from the incidence in the CCSS sibling cohort. For CAD, the H_0 was 0.53%, for HF 0.33%, for VD 0.14%, and for any cardiac disease 1.08%. Given the nature of normal tissue complication probability (NTCP) modeling, the absolute risk generated at any dose level is highly dependent on the baseline risk considered.

Figures 1 to 4 show NTCP models with anthracycline administration considered as a dichotomous variable (eg, the first scenario), and Figs. E2 and E3 show NTCP models with anthracycline dose considered as a continuous variable. To show the effect of changes in the baseline incidence of respective cardiac diseases (H_0) on these NTCP models, we have included Fig. E4 showing the risk of coronary artery disease if the baseline incidence in the CCSS survivor population who did not receive radiation was used instead of the sibling population.

RT was associated with each endpoint (HF, CAD, VD, and any cardiac disease) in a dose-dependent manner (Table 2, Figs. 1-4). As we used nonthreshold risk models, we did not have the capacity to clearly identify a dose below which there was no increased risk, even if one existed. For each 10 Gy increase in corrected mean cardiac RT dose, and adjusted for cumulative anthracycline dose (dichotomized), we estimated a HR of 1.87 (95% CI, 1.70-2.06) for HF, of 2.01 (95% CI, 1.79-2.25) for CAD, of 1.87 (95% CI, 1.78-1.96) for VD, and of 1.88 (95% CI, 1.75-2.03) for any cardiac disease. To give an example of projected absolute incidence of late cardiac toxicity, we used absolute incidences of these conditions reported in the CCSS sibling population and the aforementioned NTCP models. Using these data, the projected absolute risk of developing any cardiac disease after a mean cardiac RT dose of conventionally fractionated RT of 20 Gy at 30 years posttreatment is 2.0% (95% CI, 1.9%-2.2%) in the absence of anthracyclines. The point estimate of any cardiac disease at 30 years posttreatment with cumulative anthracycline exposure <250 mg/m^2 after 10 Gy is 3.4% (95% CI, 3.2%-3.7%); with >250 mg/m^2, 4.8% (95% CI, 4.4%-5.1%). These are estimates incorporating the average age at diagnosis of a pediatric cancer cohort. It is important to consider that, in the general population, cardiac disease is associated with increasing attained age; thus, these estimates may underestimate absolute risk for adolescents and young adults undergoing treatment.

Chemotherapy

Exposure to anthracyclines is an established risk factor for HF, with increasing dose and younger age at exposure associated with higher risk. NTCP modeling of data evaluated in this study indicated that for each 100 mg/m^2 increase in cumulative anthracycline dose, the HR for the development of HF was 1.93 (95% CI, 1.58-2.36). Based on our analysis, this is equivalent to a mean heart dose increase of 10.5 Gy. Although we did not have sufficient data to analyze the relationship between age at diagnosis and magnitude of anthracycline-induced cardiac risk, prior studies (eg, of children treated for leukemia) have established that the youngest children are at greatest risk of heart failure.[10] Contemporary analyses in children have typically found additive, but not supra-additive, effects of anthracycline and RT exposure on

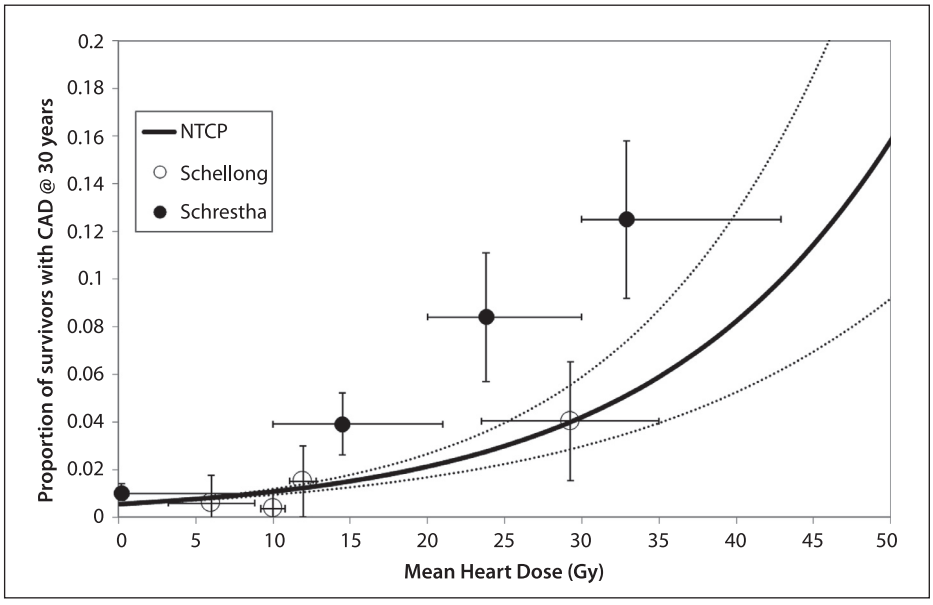

Fig. 2. Dose-response curves for long-term risk of coronary artery disease in survivors of childhood cancer based on data from the Childhood Cancer Survivor Study (CCSS; Shrestha et al[22]) and Hodgkin disease survivors (Schellong et al[25]). These curves represent NTCP models using hazard ratios derived from the data; however, the baseline incidence at 30 (H_0) years was not fit to the data but determined from a CCSS sibling population; the mathematical modeling is described more fully in the text of the article. Figure E3 shows the same model if baseline incidence in the CCSS unirradiated survivor population were used instead. *Dotted lines represent 95% confidence interval. *Abbreviations*: CAD = coronary artery disease; NTCP = normal tissue complication probability.

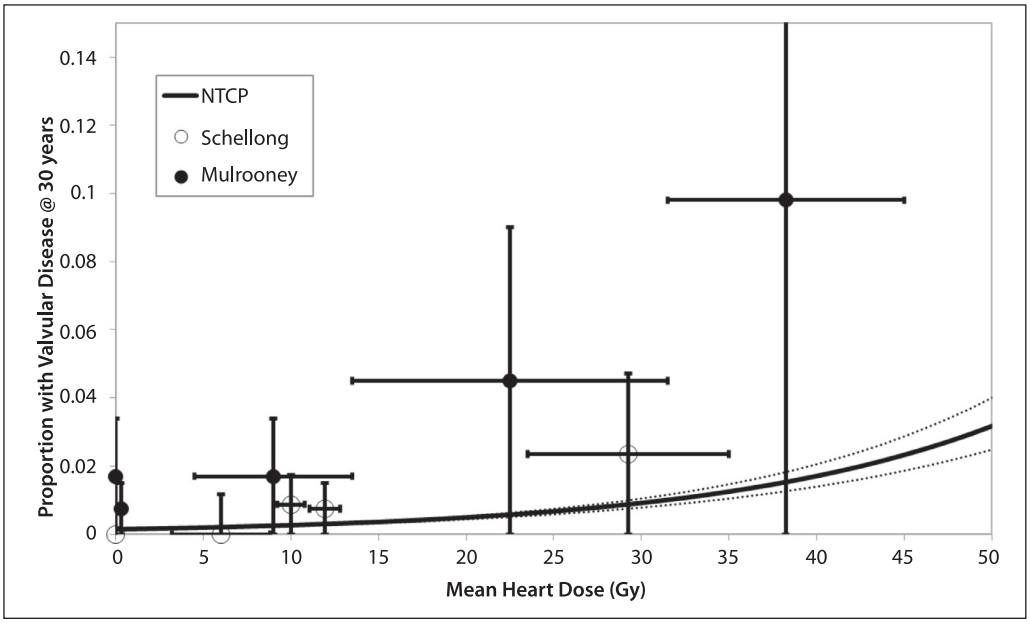

Fig. 3. Dose-response curves for long-term risk of valvular disease in survivors of childhood cancer based on data from the Childhood Cancer Survivor Study (Mulrooney et al[6]) and Hodgkin disease survivors (Schellong et al[25]). These curves represent NTCP models using hazard ratios derived from the data; however, the baseline incidence at 30 years (H_0) was not fit to the data but was determined from a Childhood Cancer Survivor Study sibling population; the mathematical modeling is described more fully in the text of the article. *Dotted lines represent 95% confidence interval. *Abbreviation*: NTCP = normal tissue complication probability.

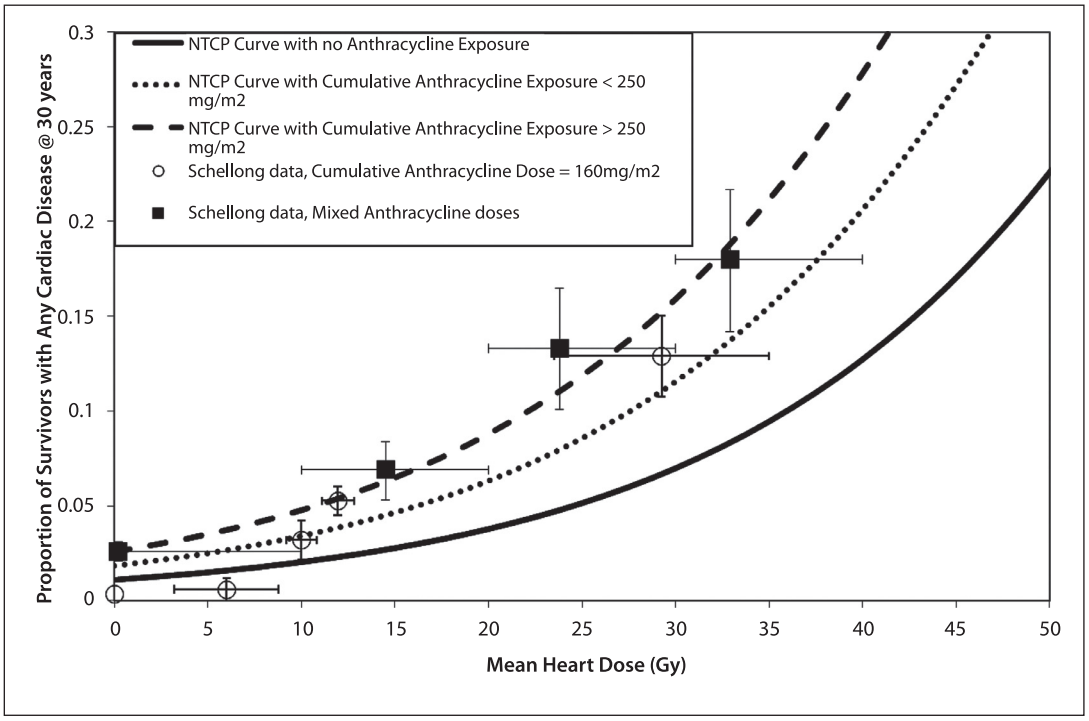

Fig. 4. Dose-response curves for long-term risk of any cardiac disease in survivors of childhood cancer based on data from the Childhood Cancer Survivor Study (CCSS; Shrestha et al[22]), Dutch childhood cancer survivors (van der Pal et al[24]), and Hodgkin disease survivors (Schellong et al[25]). These curves represent NTCP models using hazard ratios derived from the data; however, the baseline incidence at 30 years (H_0) was not fit to the data but determined from a CCSS sibling population; the mathematical modeling is described more fully in the text of the article. Given the important contribution anthracycline exposure has in influencing risk of heart disease, this figure shows this effect as a dichotomized risk factor (above or below 250 mg/m^2 of cumulative dose) based on CCSS analysis (Bates et al[5]). *Abbreviation*: NTCP = normal tissue complication probability.

the risk of heart failure.[35] This relationship underscores the need to pay particular attention to minimizing the cardiac RT dose in children receiving anthracycline-containing chemotherapy regimens. We did not have sufficient pediatric data to analyze the relationship between anthracycline dose and CAD or VD, though prior CCSS analysis found no such associations for CAD.[5]

Other risk factors

Non−treatment-related risk factors for late cardiac disease were inconsistently analyzed across the included studies. Sex was evaluated in 2 studies (the CCSS and DAL-HD studies), and females had an increased risk of heart failure (HR, 1.5; 95% CI, 1.2-2.0). In both analyses, female sex numerically increased risk of valvular disease; however, this association was only statistically significant in the CCSS analysis (HR, 1.6; 95% CI, 1.2-2.1).[6] The CCSS also reported that males had a greater risk of coronary artery disease (HR, 1.3; 95% CI, 1.0-1.7).

Age at treatment may also have a role in cardiac risk. Earlier analysis of the CCSS showed that younger age at diagnosis was associated with an increased relative risk of heart failure (HR for every 5 years below 15 years: 1.9) and valvular disease (HR for every 5 years below 15 years: 1.9), but no relationship was seen for coronary artery disease.[6]

Table 2 Meta-hazard ratios calculated for various cardiac endpoints

Outcome	HR/10 Gy	95% CI	Absolute risk 30 y post-RT after mean heart dose of 20 Gy	95% CI
Heart failure	1.87	1.70−2.06	1.1%	0.9%−1.4%
Coronary artery disease	2.01	1.79−2.25	2.1%	1.7%−2.7%
Valvular disease	1.87	1.78−1.96	0.5%	0.4%−0.5%
Any cardiac disease	1.88	1.75−2.03	3.8%	3.2%−4.4%

Abbreviations: CI = confidence interval; HR = hazard ratio.

However, in the updated analysis used in this article's analyses, there was no relationship between age at diagnosis and risk of cardiac disease, which was a variable included in the piecewise exponential models reported.[5] Similarly, the DAL-HD studies found no significant association between age at diagnosis and heart failure in multivariate analyses, it should be noted though, that these studies include few children treated for cancer in the first decade of life.[25] Congenital heart disease was associated with increased risk of heart failure in the medical-records based Dutch analysis among childhood cancer survivors (HR, 9.9; 95% CI, 2.2-44).[24] This was not studied in other included investigations. With advancing attained age, modifiable risk factors and corelated conditions that may develop including hypertension, dyslipidemia, diabetes, and obesity, all can increase the risk of various cardiac diseases, as shown in a cohort of adult patients with Hodgkin lymphoma and likely applicable to all survivors.[12] Moreover, many other treatments for childhood cancer affect ≥1 components of metabolic syndrome; it is quite likely that any analysis of RT and cardiac outcomes represents an oversimplified version of a very complex multicausal etiologic model that has not been entirely elucidated to date.[36] It is important to ensure that survivorship plans include education on general healthy habits through adolescence and young adulthood.[37]

Recommended Dose-Volume Limits

Although it is evident that at high RT doses (>20-Gy mean heart dose) the risk of cardiac disease among childhood and adolescent cancer survivors is meaningful, the effect of RT at low and moderate doses remains less clear. Anthracyclines, which are commonly used in the treatment of pediatric malignancies, significantly increase this risk. We could not determine a threshold radiation dose to the heart below which there is no significant increase in cardiac risk, partially because our models were not designed to assess this question; however, the largest analysis within our model (from the CCSS) reported that at mean heart doses <10 Gy, there was no statistically significant increase in risk. This was in a multivariate model including anthracycline dose. It is challenging to define what is an "acceptable" risk of late cardiac disease in childhood cancer survivors, especially given the numerous decades of prolonged survivorship they may have in which to develop clinically significant cardiac disease. Of note, the cited studies include survivors and person-years in the attained age window up to 40 years and sometimes 50 years. A mean RT dose to the heart of <10 Gy places long-term survivors of childhood cancer at an acceptable absolute risk (~2%) of late cardiac disease in the first 3 decades of survivorship; however, this absolute risk may increase as survivors age into their 50s and 60s when the underlying incidence of cardiac disease markedly increases in the general population. These dose levels are especially relevant in children receiving anthracycline-based chemotherapy as part of their clinical management; even more stringent dosimetric constraints may be considered (such as <5 Gy mean heart dose when clinically possible) to minimize the risk of late cardiac disease, especially in children with prolonged expected survival. We emphasize that this 5 Gy value is arbitrary, and there is likely no radiation dose to the heart without some biologic effect on the heart (especially in children with long life expectancies and exposures to other cardiotoxic agents) and thus the principles of ALARA should be applied. At the same time, we also recognize that underdosage of target tissue needs to be avoided and that dose to other intrathoracic structures can also cause clinically significant toxicities, so incidental cardiac irradiation often is unavoidable.

We recommend using modern RT techniques that are reasonably available including deep inspiratory breath hold (if age appropriate), IMRT/volumetric modulated arc therapy, and proton therapy. However, it remains critical to balance the risk of tumor control and late complications from RT, and in cases where cardiac sparing is not possible with advanced technologies, we would typically recommend prioritizing target coverage.

Furthermore, it is likely that dose to individual cardiac substructures will be the best predictor of specific cardiac diseases and urge the radiation oncology (and entire pediatric oncology) community to further study the relationships between specific cardiac substructure RT doses and risk of specific late cardiac disease, especially given the increasing conformality of modern RT plans. In this regard, mean dose, while a very convenient and useful measure, likely does not fully describe the risks of subsequent injury; different dose distributions can result in similar mean doses, but may carry substantially different risk profiles.

Toxicity Scoring and Reporting Recommendations

As previously discussed, the data reported regarding late cardiac complications in survivors of childhood cancer are heterogeneous. We recommend using the CTCAE version 5.0 criteria for scoring toxicity. We further recommend that future reports align their data reporting to allow for more streamlined pooling of data. We recommend that the following information should be reported: age of patient at time of treatment, sex, race, cancer diagnosis, prescribed RT dose and fractionation, RT modality (eg, photons, protons), mean heart dose, V20, V5, at least mean RT doses for individual cardiac substructures considered, chemotherapy agents used and dosages (especially for anthracycline chemotherapy), and a description of the toxicity scoring system used. Investigators should make use of available guidelines to facilitate the conduct of high-quality observational studies.[38,39]

Future Investigations

The next generation of studies investigating cardiac risk in long-term survivors of childhood cancer should address as

many as possible of the 4 primary questions left unanswered by the current literature.

1. How will the relative risks reported herein evolve with increasing follow-up? Will the relative risks reported persist into the sixth and seventh decade of life, resulting in a very large absolute burden of cardiac disease in long term survivors as cardiac disease becomes more prevalent in the general population and as tissues senesce, or does RT instead lead to an early expression of underlying cardiac risk? This will be critical to address as the number of aging childhood cancer survivors dramatically increases in the coming decades.
2. Will the reported dose-response relationships for whole heart dose metrics, such as mean heart dose, persist in patients treated with contemporary RT techniques/modalities such as IMRT or proton therapy? The bulk of children contributing to our current knowledge of RT-related risk were treated with 2-dimensional and basic 3-dimensional techniques that resulted in relatively homogeneous doses to large portions of the heart. Does that confer a similar risk profile as more modern techniques that may deliver a high dose of RT to a small portion of the heart or low doses to large portions of the heart? Similarly, with modern photon techniques (IMRT), a reduction in dose to one organ (eg, the heart) may be associated with an increase in dose to another (eg, the lungs); how do these interactions affect cardiac risk? It will be crucial to ascertain the veracity of these relationships to both to identify RT plans with a global minimum cardiac risk and to guide screening protocols for children treated in the modern era.
3. What is the optimal dosimetric strategy to reduce long-term cardiac disease risk? Modern treatment techniques allow for significantly improved conformality and avoidance of organs at risk. Are specific substructures of the heart particularly sensitive to RT or more critical to cardiac health and thus preferentially be avoided? It is logical that dose to the coronary arteries, ventricles, or valves may be more effective than dose to the atria, but we do not currently have evidence to suggest that this is true in children. There is a growing evidence base that cardiac substructure dose is relevant in an adult population, but it remains an unanswered question. Furthermore, can modern gating techniques allow us to deliver RT at times in the cardiorespiratory cycles that are most advantageous anatomically (and potentially biologically). Knowing which structures of the heart are most sensitive to RT will drastically improve our treatment planning approaches.
4. How do treatment-related risk factors (RT dose and anthracycline dose) interact with non—treatment-related risk factors such as variation in anthracycline metabolism or genetic predisposition to cardiac disease? There is evidence suggests that multiple rare genetic variants may predispose survivors to chemotherapy-induced cardiac disease.[40] Data from the CCSS suggests treatment exposures may affect epigenetic age acceleration.[41] Furthermore, how does the treatment-related risk interact with the risk driven by the later development of chronic conditions such as diabetes, hypertension, or metabolic syndrome—influenced by background risk factors as well as various elements of childhood cancer treatment—that also increase cardiac risk? Knowing which children are at greatest risk at time of treatment based on other factors will help personalize treatment recommendations; knowing which survivors are at greatest risk in the long term based on their health status will help improve screening regimens. Furthermore, these factors may help guide the development of strategies used to mitigate the development of RT-associated cardiac disease.

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