Radiation-associated adverse events after childhood cancer

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Chapter 3

The use of equivalent radiation dose in the evaluation of late effects after childhood cancer treatment

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Abstract

Purpose

Radiation-associated late effects after childhood cancer are usually analyzed without considering fractionation dose. According to radiobiological principles, fractionation dose is an important determinant of late effects. We aim to provide the rationale for using equivalent dose in 2-Gy fractions ($EQD2_{\alpha/\beta}$) as the measure of choice rather than total physical dose in epidemiologic research evaluating late effects.

Methods

Between 1966 and 1996, 597 (43.8%) children in our cohort of 1362 5-year childhood cancer survivors (CCS) received radiotherapy before the age of 18 years as part of their primary cancer treatment. We collected detailed information from individual patient charts and converted physical doses into the $EQD2_{\alpha/\beta}$, which includes total dose, fractionation dose, and the tissue-specific α/β ratio. We illustrate the use of $EQD2_{\alpha/\beta}$ in examples studies and describe different multivariable regression models using $EQD2_{\alpha/\beta}$ and physical dose.

Results

We succeeded in retrieving detailed radiotherapy information for 510 (85.4%) CCS. Multivariable analyses rendered different risk estimates for total body irradiation in models using $EQD2_{\alpha/\beta}$ vs. models using physical dose. For other radiotherapy regimens risk estimates were similar, a pattern consistent with radiobiological principles.

Conclusions

Using $EQD2_{\alpha/\beta}$ is the method of choice for late effects studies; it is radiobiologically correct, incorporating total dose, fractionation dose, and the tissue-specific α/β ratio. Hence, it enables comparisons across fractionation regimens and allows for summing doses delivered by various contemporary and future radiation modalities.

Implications for cancer survivors

Risk estimates of radiation-associated side effects expressed in $EQD2_{\alpha/\beta}$ provide more precise, clinically relevant information for cancer survivor screening guidelines.

Introduction

As a consequence of improved treatment modalities, long-term childhood cancer survival has increased impressively. Nevertheless, radiotherapy and other treatment modalities are associated with adverse effects that can potentially be life-threatening.[1,2] In this respect we must first acknowledge the careful and dedicated way in which pediatric radiation oncologists, physicists, biologists, and technologists work together to develop the optimal radiation treatment plan for each individual patient. Often this implies a delicate balancing act between required tumor doses and doses to several organs at risk, because radiation exposure to healthy tissues surrounding the tumor typically cannot be avoided entirely. The main determinants of radiation-induced late effects are total dose, fractionation dose, and irradiated volume.[3] Scientific research into late effects can help inform the process of decision making at the time of radiation treatment for future patients, by elucidating dose-effect relationships.

There are three main methods that are generally used to evaluate radiation-induced late effects in childhood cancer survivor cohorts. First, when information on physical dose is lacking, dichotomous (i.e., radiotherapy yes vs. no) or categorical (i.e., body site of treatment) indicators are used.[1,2] Second, when dose information is available, continuous or categorical dose variables (i.e., physical dose) are used.[4] Lastly, if sufficient details on treatment are available, retrospective dose reconstruction is used to estimate absorbed dose at the tissue of interest,[5,6] but such measurements are time consuming and rather expensive. Therefore, the first two methods are used mostly, but are not always adequate. Dichotomous or categorical variables based on body site of treatment without information on dose do not allow for in-depth evaluation of dose-effect relationships. Moreover, by using physical prescribed dose only, the fractionation dose is not taken into account correctly, whereas radiobiological studies have shown that higher fractionation doses will, at equal total dose, increase the risk of incidence and severity of late side-effects.[3,7,8] Furthermore, epidemiologic studies on late effects after radiation therapy in childhood cancer survivors often include wide ranges of time periods, during which radiotherapy delivery methods as well as treatment schedules have changed considerably.[9-11] Consequently, fractionation doses vary between patients and even within patients during the course of their fractionated radiotherapy. Moreover, there are also the large differences in dose delivery between conventional external beam radiotherapy and other forms of high-dose, localized radiotherapy such as brachytherapy and stereotactic radiotherapy. Of note, with the developments in modern radiotherapy, this heterogeneity with respect to dose distribution, volume, and fractionation schedules is increasing rapidly.

Now that more studies focus on late effects, and new studies are being set up to study late effects of modern radiation treatment modalities, risk estimations can no longer rely simply on physical dose.[12,13] Therefore, we propose a simple and biologically correct alternative to take care of these issues, by using the equivalent dose, $EQD2_{\alpha/\beta}$. In brief, the $EQD2_{\alpha/\beta}$ is defined as the total dose delivered by a reference treatment plan with a 2 Gray (Gy) fractionation dose, a common fractionation dose in radiation therapy, leading to the same biological effect as a treatment plan that was conducted with fractionation dose d and total absorbed dose D. The tissue-specific α/β ratio, also expressed in Gy, is determined by the intrinsic radiation sensitivity of the respective tissue; it describes how the biological effect of radiation changes due to changing fractionation dose.[3,14]

In clinical radiotherapy, the $EQD2_{\alpha/\beta}$ is commonly used, not only to compare various fractionation schedules in relation to toxicity,[15-17] but also to calculate the therapeutic window in case of re-irradiation of an area or organ that already was treated in the past.[18,19] To our knowledge, so far fractionation doses were only sporadically taken into account in epidemiologic studies. [20,21]

The added value of using the $EQD2_{\alpha/\beta}$ in epidemiological studies on late effects after childhood cancer treatment has not been described earlier. Here we present a series of studies in which we compare values of the physical prescribed dose with $EQD2_{\alpha/\beta}$ values, as well as the risk estimates obtained from different multivariable regression models using the $EQD2_{\alpha/\beta}$ and the physical prescribed dose.

Methods

Patients and data collection

The Emma Children's Hospital/Academic Medical Center (EKZ/AMC) childhood cancer survivor cohort is an ongoing single-centre cohort study, described in detail elsewhere.[22] For the studies on $EQD2_{\alpha/\beta}$,[23-25] the following inclusion criteria applied: 1) primary cancer diagnosis before age 18 years; 2) primarily treated in the Emma Children's Hospital / Academic Medical Center (EKZ/AMC); 3) diagnosed between January 1, 1966, and January 1, 1996; 4) survival of at least 5 years after primary cancer diagnosis. Survivors were identified using the hospital-based Childhood Cancer Registry which was established in 1966. The registry contains detailed treatment information regarding primary malignancy, recurrences, and subsequent tumors.

In 1996, the late effects outpatient clinic (Polikliniek Late Effecten Kindertumoren; PLEK) was started, and since then childhood cancer patients who survived at least 5 years after diagnosis are invited for medical assessment and clinical care of late adverse effects. Late effects were graded for severity according to the CTCAEv3.0.[2,23-25]

To investigate late effects in relation to radiation therapy, detailed information on radiation treatment fields and schedules including fractionation dose and total physical prescribed dose, were obtained from individual patients charts and simulation films. The physical prescribed dose is defined as the dose that was planned and administered to the patient according to the patients charts.

Calculation of the equivalent dose in 2-Gy fractions ($EQD2_{\alpha/\beta}$)

The formula to convert the physical dose into the equivalent dose in 2-Gy fractions ($EQD2_{\alpha/\beta}$) is based on the linear-quadratic model (LQ model) for cell survival, and accounts for the differences between late responding tissues as tumors, and normal tissue reactions. The LQ model is a theoretical construct, but extensive evaluation with clinical in vivo and in vitro data has confirmed its usefulness.[26,27] LQ survival curves are continuously bending with no straight portion either at low or high radiation doses. The shape of the curve is determined by the α/β ratio. The linear parameter α determines the effectiveness at low doses while the parameter β has an increasing contribution at higher radiation doses. The α/β ratio is the dose in Gy at which the linear contribution to cell damage or cell death equals the quadratic contribution. The α/β ratio is not constant, as it depends on the specific tissue of interest.[3] In general, the α/β ratio is high for tumor tissue ($\alpha/\beta \approx 10$ Gy), and low for late responding normal tissues ($\alpha/\beta \approx 1\text{-}4$ Gy). The formula below converts physical dose into the $EQD2_{\alpha/\beta}$:

$$EQD2_{\alpha/\beta} = D \bullet \frac{d + \alpha/\beta}{2 + \alpha/\beta}$$

in which the $EQD2_{\alpha/\beta}$ represents a theoretical dose given in reference fractions of 2 Gy that is biologically equivalent to a total physical dose D given in fractionation doses of d Gy according to the treatment schedule being studied. For the equivalent dose calculations in our cohort studies we used an α/β ratio of 2 Gy for late responding brain tissue ($EQD2_{2Gy}$)[25] and an α/β ratio of 3 Gy for other late responding healthy tissues ($EQD2_{3Gy}$).[23,24] We calculated the maximum dose to the smallest field, i.e. the total dose including boost dose delivered for a first malignancy.

Statistics

For the purpose of this paper, we present analyses using the $EQD2_{\alpha/\beta}$ as reported in previous[23-25] and in unpublished work, and we repeated the analyses using the total physical prescribed dose. Both $EQD2_{\alpha/\beta}$ and physical dose are continuous variables. Using multivariable logistic regression and Cox regression analyses, risks are expressed as odds ratios (ORs) and hazard ratios (HRs) respectively. All analyses were adjusted for gender, age at diagnosis, follow-up time, and the treatment-related risk factors surgery and chemotherapy. We used SPSS, version 21.0.1 (Statistical Package for the Social Sciences) for Windows, and the statistical program R, version 2.13.1 (http://www.R-project.org).

Results

Patients and data collection

Between 1966 and 1996, 2596 children <18 years were diagnosed and treated for a primary malignancy in the EKZ/AMC, of whom 1362 (52.5%) survived at least 5 years after their primary cancer diagnosis.[2] In total, 597 of 1362 (43.8%) survivors received radiotherapy as part of their primary cancer treatment. We calculated the $EQD2_{\alpha/\beta}$ for various treatment localizations, and we have currently complete and detailed information on radiation fields and fractionation doses for Wilms' tumor survivors (abdomen and/or thorax), survivors treated with

Table 1. Characteristics of the 597 EKZ/AMC 5-year childhood cancer survivors treated with radiation therapy for a primary malignancy or recurrence between 1966 and 1996[a]

Characteristic	N (%)	Complete RT dose and field information N (%)
Total RT cohort	597 (100)	510 (85.4)
Sex		
Male	317 (53.1)	272 (85.8)
Female	280 (46.9)	238 (85.0)
Primary cancer diagnosis		
Leukemia	151 (25.3)	147 (97.4)
Lymphoma	107 (18.0)	100 (93.5)
Kidney/Wilms' tumor	87 (14.6)	84 (96.6)
Brain/CNS tumor	88 (14.8)	83 (94.3)
Bone tumor	57 (9.6)	22 (38.6)[e]
Soft tissue sarcoma	58 (9.7)	39 (67.2)[e]
Neuroblastoma	21 (3.5)	11 (52.4)[e]
Other[b]	28 (4.7)	24 (85.7)
Age at diagnosis (years)		
Median (range)	6.47 (0-17.57)	
0-4	239 (40.0)	211 (88.3)
5-9	185 (31.0)	166 (89.7)
10-14	142 (23.8)	109 (76.8)
15-17	31 (5.2)	24 (77.4)
Surgery		
Yes	311 (52.1)	255 (82.0)
No	286 (47.9))	255 (89.2)
Chemotherapy		
Yes	508 (85.1)	440 (86.6)
No	89 (14.9)	70 (78.7)
Radiotherapy localization[c]		
Head and neck	339 (56.8)	328 (96.8)
Brain	259 (43.4)	250 (96.5)
Neck	39 (6.5)	37 (94.9)
Orbit	34 (5.7)	32 (94.1)
Other	28 (4.7)	27 (96.4)
Thorax/mediastinum	79 (13.2)	76 (97.5)
(Mini) Mantle field[d]	22 (3.6)	20 (91.0)
Abdomen	142 (23.8)	114 (80.3)
Spine	91 (15.2)	90 (99.0)
Extremities	51 (8.5)	12 (23.5)[e]
TBI	29 (4.9)	29 (100.0)
Brachytherapy	16 (2.7)	15 (93.8)

EKZ/AMC Emma Children's Hospital/Academic Medical Center, *N* number, *CNS* central nervous system, *TBI* total body irradiation

[a] Treatment for secondary malignant neoplasms was not included.

[b] Includes 2 gonadal germ cell tumors, 11 retinoblastoma, 1 malignant histiocytosis, 14 miscellaneous.

[c] Localizations are not mutually exclusive because some patients have had radiotherapy to 2 or more fields, either as part of one course of treatment, or because of re-treatment of a recurrent primary tumor.

[d] Mantle field included mediastinum, supraclavicular/neck, bilateral axillary and part of the occiput; minimantle included upper mediastinum, supraclavicular/neck and part of the occiput.

[e] Our studies so far did not focus on survivors in these diagnosis or radiotherapy localization categories.

cranial radiation therapy (including total body irradiation; TBI), and survivors who received radiation to the heart region (including thorax, spine, left and/or whole abdomen and TBI); in total 510 of 597 (85.4%) irradiated survivors in our cohort. Table 1 shows the characteristics of the survivors who have been treated with radiation therapy.

Table 2 gives an overview of the results of the physical prescribed doses and corresponding $\text{EQD2}_{\alpha/\beta}$ values as calculated in four EKZ/AMC cohort studies,[23-25] and shows that the physical prescribed doses and the calculated $\text{EQD2}_{\alpha/\beta}$ values are not equal. Yet, the risk estimates resulting from the multivariable analyses are similar in the models with the physical prescribed dose or the $\text{EQD2}_{\alpha/\beta}$, except for the TBI treatment group (Figure 1). This reflects the biological effect of high fractionation dose resulting in a higher risk of late effects. Also note that the confidence interval for the OR expressed $\text{EQD2}_{\alpha/\beta}$ is smaller than when expressed in physical prescribed dose.

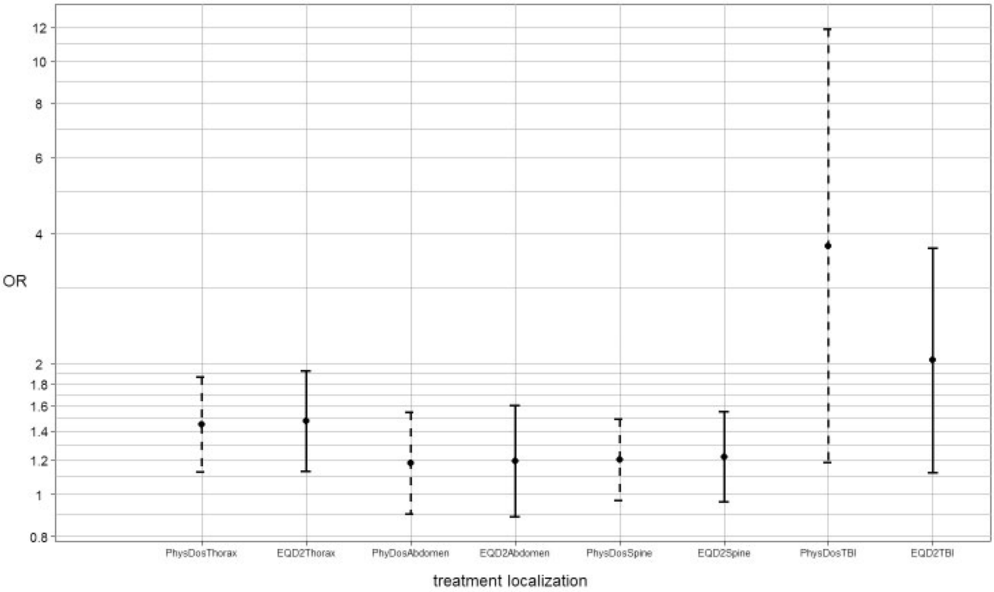

Figure 1. Odds ratios (ORs) for valvular abnormalities by physical prescribed dose and $\text{EQD2}_{3\text{Gy}}$ for 4 treatment localizations. ORs result from multivariable logistic regression analysis, corrected for gender, age at diagnosis, follow-up time, and the treatment-related risk factors surgery and chemotherapy. ORs express the risk per 10 Gy . $\text{EQD2}_{3\text{Gy}}$ equivalent dose in 2-Gy fractions using an α/β ratio of 3 Gy

To illustrate the different biological effect of treatment schedules that use higher fractionation doses, we converted the physical doses of several TBI schedules into the $\text{EQD2}_{\alpha/\beta}$ using an α/β of 3 Gy (Table 3). In spite of the equal total physical prescribed dose of 8 Gy, the biological effect of 8 Gy delivered in 1 fraction is not similar to that of 8 Gy delivered in 4 fractions of 2 Gy.

Table 2. Physical prescribed radiation doses, corresponding $EQD2_{\alpha/\beta}$s and risk estimates as calculated in four EKZ/AMC cohort studies

1. Cumulative radiation dose and risk of Grade 1-5 AE vs no AEs in Wilms' tumor survivors [23]						
Treatment localizations	Physical dose (Gy) median (range)	$EQD2_{3Gy}$ (Gy) median (range)	*N* available	*N* missing	OR per Gy physical dose (95% CI)	OR per Gy $EQD2_{3Gy}$ (95% CI)
Flank/abdominal RT	30.00 (13.0-41.1)	27.69 (11.60-38.95)	78	3	1.075 (1.038-1.112)	1.083 (1.043-1.125)
Chest RT	25.00 (18.0-45.0)	27.00 (16.20-43.70)	13	1	1.006 (0.953-1.062)	1.006 (0.952-1.064)
2. Cumulative radiation dose and risk of symptomatic cardiac events [24]						
Treatment localizations	Physical dose (Gy) median (range)	$EQD2_{3Gy}$ (Gy) median (range)	*N* available	*N* missing	HR per 10 Gy physical dose (95% CI)	HR per 10 Gy $EQD2_{3Gy}$ (95% CI)
RT involving the heart region	25.00 (5.00-93.04)	24.80 (3.73-88.46)	256	10	1.747 (1.434-2.129)	1.755 (1.422-2.165)
3. Cumulative radiation dose and risk of alopecia after cranial radiation therapy [25]						
CRT stratified by 1st cancer type	Physical dose (Gy) median (range)	$EQD2_{2Gy}$ (Gy) median (range)	*N* available	*N* missing	OR per Gy physical dose (95% CI)	OR per Gy $EQD2_{3Gy}$ (95% CI)
Brain tumor	54.75 (36.00-104.0)	49.68 (34.20-94.61)	83	5	1.063 (1.018-1.109)	1.058 (1.017-1.102)
Other cancers	25.00 (6.27-57.75)	24.75 (9.59-54.14)	190	7	1.145 (1.112-1.178)	1.147 (1.114-1.181)
4. Cumulative radiation dose and risk of valvular abnormalities grade mild or higher [unpublished work]						
Treatment localizations	Physical dose (Gy) median (range)	$EQD2_{3Gy}$ (Gy) median (range)	*N* available	*N* missing	OR per 10 Gy physical dose (95% CI)	OR per 10 Gy $EQD2_{3Gy}$ (95% CI)
Thoracic RT	24.75 (10.80-55.80)	23.82 (9.47-53.57)	58	4	1.451 (1.128-1.867)	1.477 (1.133-1.926)
Abdominal RT	30.00 (4.50-42.00)	27.00 (3.73-39.63)	43	1	1.181 (0.900-1.548)	1.194 (0.888-1.606)
Spinal RT	34.50 (17.50-52.20)	30.44 (15.00-50.11)	57	0	1.203 (0.970-1.491)	1.221 (0.961-1.551)
TBI	7.50 (7.00-12.00)	15.75 (14.00-21.60)	18	0	3.752 (1.184-11.89)	2.040 (1.124-3.701)

EKZ/AMC Emma Children's Hospital/Academic Medical Center, *AE* adverse event, $EQD2_{2Gy}$ *and* $EQD2_{3Gy}$ equivalent dose in 2-Gy fractions using an α/ß ratio of 2 and 3 Gy respectively, *Gy* Gray, *N* number, *RT* radiotherapy, *CRT* cranial radiation therapy, *TBI* total body irradiation

Table 3. Comparison of various possible TBI treatment schedules

TBI schedule	Physical prescribed dose (Gy)	$EQD2_{3Gy}$ (Gy)
1 x 8.00 Gy	8.00	17.60
1 x 7.50 Gy	7.50	15.75
2 x 6.00 Gy	12.00	21.60
2 x 5.00 Gy	10.00	16.00
2 x 4.50 Gy	9.00	13.50
4 x 2.00 Gy	8.00	8.00
6 x 1.67 Gy	10.02	9.36

TBI total body irradiation, *$EQD2_{3Gy}$* equivalent dose in 2-Gy fractions using an α/ß ratio of 3 Gy for late responding healthy tissues, *Gy* Gray

Discussion

We have shown that total physical prescribed doses are not equal to cumulative $EQD2_{\alpha/\beta}$ values, and that risk estimates for radiation-related late effects for treatments using non-standard fractionation schedules (such as TBI) are different in models using the $EQD2_{\alpha/\beta}$ compared to those using the physical prescribed dose. This is typically the consequence of the higher fractionation doses used in TBI treatment. For radiation treatments other than TBI risk estimates are largely similar. Risk estimates are also expected to be different in case of brachytherapy, a treatment modality with a non-standard fractionation schedule; however, the presented studies do not include survivors treated with brachytherapy.

Radiobiologically, the $EQD2_{\alpha/\beta}$ is preferred over the physical prescribed dose because it includes fractionation dose, an important determinant of late effects,[3] and because it enables concurrent evaluation of different fractionation schedules and very different radiotherapy techniques. The latter will become increasingly important in the future for re-irradiation and for patients treated with non-standard treatment modalities.

The clinical relevance of converting physical dose into the $EQD2_{3Gy}$ can be illustrated with the example of guidelines for cardiomyopathy surveillance in childhood cancer survivors. Current screening guidelines recommend cardiomyopathy surveillance in survivors treated with chest radiation doses ranging from 15 to more than 35 Gy. This is based on hazard ratios (HRs) for cardiovascular disease ranging from 2 to 6 for survivors exposed to cardiac (physical) radiation doses of 15 Gy or more compared to non-irradiated survivors.[28] Consequently, survivors who would have been treated with one single high dose fraction of 7.5 Gy, or two times 5 Gy (i.e., physical prescribed total dose 7.5 and 10 Gy, respectively), would not be screened according to the current guidelines. However, Table 2 shows clearly that measures of relative risk are above 2 for TBI survivors too. Given that the biologically equivalent doses amount to 15.8 and 16.0 Gy respectively, screening is justified according to the guideline when $EQD2_{3Gy}$ values are used.[24] This is yet another indication that $EQD2_{\alpha/\beta}$ is to be preferred over physical dose.

A few studies were published using a similar measure, the biologically effective dose (BED).[20,21] Both, $EQD2_{\alpha/\beta}$ and BED, are based on the principle of linear-quadratic bio-effect modeling, which uses mathematic models to relate the radiation dose at the tissue of interest to the incidence of a specific radiation-induced effect.[3,14] However, BED calculations result in numerically much higher dose values than the maximum physical prescribed dose to be delivered to patients without serious harm or death. Therefore, these unrealistically high numbers cannot be interpreted very easily, whereas $EQD2_{\alpha/\beta}$ values approach radiation doses as prescribed in everyday clinical practice,[3] which simplifies the interpretation of dose values and risk estimations for clinicians.

In the next section, we critically appraise the use of $EQD2_{\alpha/\beta}$. First, the $EQD2_{\alpha/\beta}$ in our studies represents the prescribed dose to a certain radiation field, which is not the same as the actually absorbed dose. This absorbed dose is the actual 3-dimensional dose distribution within the patient due to the radiation treatment. The absorbed dose just outside the target region is usually lower than the prescribed dose, typically about 50% at the treatment field borders, and decreases to about 0.1% far away from the target region. Without a 3-dimensional dose distribution computed on a CT scan, or measured doses on anatomically correct phantoms, it is hard to acquire a good estimate of the absorbed dose. Both for Wilms' tumor survivors and for survivors treated with cranial radiation we converted the physical prescribed dose into the $EQD2_{\alpha/\beta}$ for treatment fields including boost fields[23,25] as a surrogate for the absorbed dose. In these studies, the $EQD2_{\alpha/\beta}$ thus represents the maximum dose on the smallest field. This approach would enable us to devise risk models for organs outside the treatment field, receiving much lower doses. Such models might be relevant for other fields of epidemiology, such as radiation accidents or exposure to radiation for diagnostic purposes. Furthermore, we evaluated wide ranges of late effects, including effects occurring outside the radiation field, without the possibility to estimate the absorbed dose received by organs at risk. In other words, the $EQD2_{\alpha/\beta}$ determined by maximum physical prescribed dose to the smallest field as we used, likely overestimated the $EQD2_{\alpha/\beta}$ of the absorbed dose at sites of interest at the borders of the field (not included in the boost) and certainly those outside the radiation field. Therefore, risk estimates for out-of-field tissues are likely underestimated. Note that this also applies when using physical dose, and that this is not relevant for TBI as it includes the full-body, except for blocked organs. In the cardiac studies, we checked simulation films to assure whether the organs at risk (i.e., the heart or the heart valves) were located within the primary treatment fields and/or boost fields.[24] Still, the $EQD2_{\alpha/\beta}$ represents the prescribed dose, which was not necessarily the exact cardiac dose. The next logical step will thus be to combine $EQD2_{\alpha/\beta}$ calculations with dose reconstruction methods using phantom measurements and computer planning techniques.[5,6] Second, it was not feasible to include irradiated volume in our analyses, because appropriate information was not available for the majority of the survivors in our cohort. We intend to include volume by using dose volume histograms (DVHs) in future studies. Third, we calculated the $EQD2_{\alpha/\beta}$ for TBI delivered in one single high dose fraction of 7.5 to 8 Gy, or two fractions of 6 Gy. As yet, there is not a substantial amount of empirical evidence justifying the use of the simple LQ-model at such high fractionation doses.[3] One of the studies on this topic showed that the LQ-model was the best method to convert physical lung dose into $EQD2_{3Gy}$ values for predicting radiation pneumonitis in patients treated with high fractionated lung radiation.[29] The LQ-model was also applied to calculate the BED to evaluate dose-effect relationships for cataract induction after single-dose TBI.[21] In that study, the dose rate was also taken into account. Furthermore, when summing doses from treatments for recurrences, we have ignored the time between the initial treatment and the re-irradiation, which varied from months to years. Lastly, it is important to realize that the α/β ratio depends on the tissue under consideration. Although initially derived from cell survival curves and animal studies, α/β ratios for human tissues are increasingly being estimated and/or validated in clinical studies.[15] This is time consuming, and requires very large numbers of patients included, who were treated with a variety of fractionation schedules to allow for sufficient variation on radiation doses in order to observe variation in the risk of side effects.[30] Thus, considerable uncertainty remains for some tissues. So far, there were very few occasions that allowed for empiric studies on α/β ratios for very long-term effects (i.e. >10 years post treatment), because the follow-up for standard clinical trials typically is not sufficiently long. Moreover, to our knowledge, there are few studies focusing on a possible heterogeneity in the α/β by age; since we know from epidemiologic studies that age at treatment can be a strong effect modifier of the dose-effect relationship,[31-33] it is quite plausible to expect that α/β ratios for children differ from those for adults. Given the importance of the α/β ratios in radiotherapy planning, it is imperative to address these questions. Large childhood cancer survivors' cohorts with detailed information on radiation treatments and long-term, high-quality follow-up have a unique potential to fulfill this need, when focusing on late effects in specific tissues.

In conclusion, using the $EQD2_{\alpha/\beta}$ is radiobiologically correct, since it includes besides total physical dose, the fractionation dose and the tissue specific α/β ratio. We have shown the added value of using the $EQD2_{\alpha/\beta}$ in epidemiological studies on late effects after childhood cancer treatment. $EQD2_{\alpha/\beta}$ values enable us to compare various radiation schedules, and different treatment modalities in a uniform way. Therefore, we propose to incorporate these measures in new analyses of radiation-related effects.

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