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Radiation-associated adverse events after childhood cancer

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Chapter 9

Summary and general discussion

Summary and general discussion

Childhood cancer treatment techniques that have continuously improved over time have resulted in remarkably high survival rates of 80% and higher in the last decades,¹ and the population of long-term survivors is expected to keep on growing.^{2,3} At the same time, 75% of the survivors are confronted with one or more tumor- and treatment-related adverse effects later in life.^{4,5} Multidisciplinary treatment modalities as surgery, chemotherapy and radiotherapy are closely attuned, and it depends on the tumor type which treatment combination is needed.

Historically, surgery and radiation therapy have been used mainly in childhood cancer treatment. In the meantime, the evolvement of chemotherapy has shown that many of the common childhood cancers respond well to chemotherapy, and treatments according to international trials and protocols have led to a diminished role of radiotherapy. Still, radiotherapy is an important cornerstone of childhood cancer treatment. Teams of radiation oncologists, technicians, physicists, and radiobiologists work intensively together to develop the optimal radiation treatment plan for each individual patient. This implies a delicate deliberation of applying sufficiently high radiation dose to kill tumor tissue, and keeping doses as low as reasonable achievable (the ALARA principle) to spare surrounding healthy tissues. However, radiation exposure to healthy tissues surrounding the tumor typically cannot be avoided entirely, which increases the risk of late radiation-associated adverse effects.

The general objective of this thesis is to evaluate radiation-associated adverse events after childhood cancer. In a cohort of long-term childhood cancer survivors, we have evaluated the prevalence and severity of adverse events and we have assessed treatment-related risk factors for the occurrence and severity of adverse events, focusing on radiotherapy treatment. In this final chapter, we will summarize the results, and discuss study strengths and limitations, including the methodology of using the equivalent dose in 2-Gy fractions (EQD₂) to assess dose-effect relationships for adverse events. A secondary objective, as declared in **Chapter 1** of this thesis, is to present the concept of equivalent dose to the community of late effects research, and to convince our peers to collect data on fractionation doses, to adopt these standards in current and future studies, and to take these concepts into account when translating evidence from late effect studies into clinical practice.

In **Chapter 2** we have presented a detailed description of the design and characteristics of the longitudinal childhood cancer survivors cohort study that was initiated in 1996 in the EKZ/AMC. The objective of this study was to describe the methodology, clinical characteristics, and data availability of our ongoing cohort study of childhood cancer survivors. In addition, we provided an overview of results of the studies performed within the cohort. Finally, we described its unique features and assessed the strengths and limitations that readers of our studies should be aware of.

The cohort described in this study was frozen at January 1, 2009 and comprised 3183 eligible childhood cancer patients who were diagnosed and treated in the EKZ/AMC between January 1, 1966 and January 1, 2003. The 1822 (57.2%) children who survived five years or longer after their primary cancer diagnosis were included in the retrospective cohort study. Baseline primary cancer treatment characteristics were complete for 1781 (97.7%) survivors.

Since 1996, long-term survivors are invited to the outpatient clinic for late effects after childhood cancer, for the assessment of and care for tumor and treatment-related adverse events. Up to January 2009, 1452 (79.7%) of the 1822 eligible survivors visited the outpatient clinic at least once, 120 (6.9%) were followed up by other specialists at the EKZ/AMC, 86 (4.7%) died before the start of the study, and 16 (0.9%) died before they received medical follow-up in the EKZ/AMC. For 143 (7.8%) survivors no medical follow-up was available due to various reasons. At most recent follow-up, the median attained age was 24.8 years, with 1467 (80.6%) survivors younger than 35 years. The median follow-up duration from diagnosis is 17.7 years (range, 5.0-42.5).

There were no significant differences in the most important prognostic factors (gender, age at diagnosis and treatment) between the survivors who visited the late-effects outpatient clinic and the complete cohort. Survivors without medical follow-up at the late-effects outpatient clinic generally had shorter follow-up time and a lower attained age at the end of follow-up. A larger proportion of these survivors also had suffered a recurrence, and had died at the end of follow-up.

Since the start of the EKZ/AMC childhood cancer survivor cohort in 1996, 54 studies have been carried out within our cohort, of which 30 (56.6%) studies included solely patients meeting all EKZ/AMC childhood cancer survivor cohort eligibility criteria. These studies have increased our knowledge of late tumor- and treatment-related adverse events.

However, with respect to the evaluation of adverse events in relation to radiotherapy, we have noticed some gaps. Although maximum radiation dose was available for 98% of the radiation fields delivered for the primary cancer, for 95% of the fields for recurrences, and for 90% of the fields for second cancers,⁶ specific and detailed information on radiation treatment schedules was, and still is incomplete. Consequently, in most of the studies conducted in the EKZ/AMC cohort, radiation-associated late effects have been evaluated using dichotomous (i.e., radiotherapy yes vs. no) or categorical (i.e., body site of treatment) variables only. Or, when dose information was available, continuous or categorical dose variables based on the maximum dose delivered, have been used, without considering radiation treatment schedules. To overcome this issue, we have introduced the use of the equivalent dose in 2-Gy fractions (EQD₂) to evaluate radiation-associated adverse events after childhood cancer in

Chapter 3.

All studies within this thesis include the first EKZ/AMC childhood cancer survivors cohort comprising 1362 long-term survivors diagnosed and treated between 1966 and 1996. Of

these 5-year survivors 597 (43.8%) have received radiotherapy before the age of 18 years as part of their primary cancer treatment. We have collected detailed information from individual patient charts and converted physical doses into the EQD₂, which includes total dose, fractionation dose, and the tissue-specific α/β ratio.

We have illustrated the use of EQD₂ in four examples studies performing different multi-variable regression models using EQD₂ and physical dose. The analyses resulted in different risk estimates for total body irradiation in models using EQD₂ vs. models using physical dose. For other radiation schedules, with fractionation doses approaching 2 Gy, risk estimates were similar. This is consistent with radiobiological principles; higher fractionation doses increase the risk of late effects.

In **Chapter 4** we have focused on one diagnosis, assessing the prevalence of and risk factors for late adverse events in long-term Wilms' tumor survivors. This subcohort of the EKZ/AMC childhood cancer survivor cohort consisted of 185 survivors, diagnosed and treated between 1966 and 1996. Of these survivors, 85 were treated with radiotherapy to the flank and/or abdomen, and 14 received chest irradiation as part of their treatment. Calculation of the EQD₂ resulted in the EQD_{2,flank/abdomen} for 77 (90.6%) of 85 survivors and the EQD_{2,chest} for 13 (92.9%) of 14 survivors.

We have evaluated the prevalence and severity of a wide range of adverse events (AEs), that were graded according to the Common Terminology Criteria for Adverse Events version 3.0 (CTCAEv3.0). The CTCAE is a descriptive terminology which can be used for reporting both acute and chronic AEs, and presents Grades 1 through 5. Grades 1 and 2 are mild and moderate AEs respectively, Grade 3 is a severe AE, Grade 4 is a life-threatening or disabling AE, and Grade 5 is an AE-related death. Furthermore, we have assessed treatment-related risk factors, with special attention to radiotherapy.

Medical follow-up was complete for 98% of survivors. After a median follow-up of 18.9 years, and at a median attained age of 22.9 years, 123 survivors had 462 AEs, of which 392 were mild (Grade 1) and moderate (Grade 2) events. Radiotherapy to flank/abdomen significantly increased the risk of any AE, and of specific events such as orthopedic events and second tumors. Chest irradiation significantly increased the risk of pulmonary events. Both flank/abdominal and chest irradiation were associated with a higher risk of cardiovascular events and tissue hypoplasia.

With this study we have demonstrated that the prevalence of AEs in long-term WT survivors is high, especially after radiotherapy and treatment with anthracyclines. But radiotherapy and anthracyclines have been used only in higher risk patients to improve their cure rates. Considering that the majority of AEs were mild or moderate, continuation of this treatment is justified. Our study emphasizes that follow-up programs for these survivors are essential.

In our next study, described in **Chapter 5**, we have focused on one type of exposure: cranial radiation therapy (CRT). The prevalence and severity of clinical adverse events (AEs), and

treatment-related risk factors have been evaluated in childhood cancer survivors treated with CRT, with the aim of assessing dose-effect relationships.

This study included the complete cohort of 5-year childhood cancer survivors treated between 1966 and 1996, thus comprising a wide variety of diagnoses. Of the 1362 survivors, 285 were treated with CRT delivered as brain irradiation (BI), and/or as part of craniospinal irradiation (CSI), and/or as total body irradiation (TBI). Individual CRT doses were converted into the equivalent dose in 2-Gy fractions (EQD₂). A complete inventory of CTCAEv.3.0 AEs was available from our hospital-based late-effect follow-up program. We used multivariable logistic and Cox regression analyses to examine the EQD₂ in relation to the prevalence and severity of AEs, correcting for sex, age at diagnosis, follow-up time, and the treatment-related risk factors surgery and chemotherapy.

There was a high prevalence of AEs in the CRT group; over 80% of survivors had more than 1 AE, and almost half had at least 5 AEs, both representing significant increases in number of AEs compared with survivors not treated with CRT. Additionally, the proportion of severe, life-threatening, or disabling AEs (Grade 3 and 4) was significantly higher in the CRT group. The most frequent AEs were alopecia, and cognitive, endocrine, metabolic, and neurologic events. Using the EQD₂, we have found significant dose-effect relationships for these and other AEs.

Chapter 6 describes the study in which we have assessed the prevalence and severity of radiation-associated symptomatic cerebrovascular accidents (CVAs) occurring 5 years or later after the primary cancer diagnosis. Furthermore, we have estimated treatment related risk factors, focusing on two radiation treatment locations; cranial radiation therapy (CRT) and supradiaphragmatic radiation therapy (SDRT), for which we have assessed dose-effect relationships using the EQD₂.

The study included the complete cohort of 1362 childhood cancer survivors treated for a primary malignancy between 1966 and 1996 in the EKZ/AMC. Two survivors who experienced a first symptomatic CVA within 5 years after diagnosis were excluded from the cohort and from all analyses. Of the remaining 1360 survivors, 438 (32.2%) had been treated with CRT and/or SDRT for their primary malignancy, recurrences and subsequent tumors. Detailed information on radiation schedules enabled us to calculate the EQD₂ for 411 (93.8%) of these survivors. CVAs were defined and graded for severity in a standardized manner using the CTCAEv.3.0.

After a median follow-up of 24.9 years (range 5.6 – 41.2 years), and at a median age of 31.2 years (range 15.1 – 46.5 years), 28 survivors experienced a first symptomatic CVA. Eighteen survivors had an ischemic event Grade 3 or 4, and 10 had hemorrhagic Grade 2 through 5 CVAs. Two survivors had a second and third CVA. The 35-year cumulative incidence in the CRT only group was 13.1% (95%CI, 3.5-21.8%), and in the SDRT only group 6.3% (95%CI, 0-12.3%). For the group treated with both CRT and SDRT, the 35 year cumulative incidence was 22.6% (95%CI, 6.2-36.0%). The incidence rate was 108.2 per 100,000 person-

years (95%CI, 74.6-156.7 per 100,000 person-years). Multivariable Cox regression showed that both CRT and SDRT were the only risk factors that significantly increased the risk of CVAs in a dose-dependent way ($HR_{CRT} 1.02 Gy^{-1}$; 95%CI, 1.01-1.03, and $HR_{SDRT} 1.04 Gy^{-1}$; 95%CI, 1.02-1.05, respectively).

In **Chapter 7** we have presented a study in which we focused on one outcome, i.e., valvular abnormalities detected by echocardiography. The study cohort consisted of all 626 eligible survivors diagnosed with childhood cancer in the EKZ/AMC between 1966 and 1996, who had been treated with cardiotoxic therapy defined as treatment with radiotherapy involving the heart region and/or anthracyclines. We have determined the presence of valvular abnormalities based on echocardiogram, and we have identified associated risk factors, by means of multivariable logistic regression models, including sex, age at primary cancer diagnosis, cumulative dose of a number of chemotherapeutic agents, radiation dose to the heart region, and congenital heart disease. Physical radiation doses were converted into the EQD₂.

We identified 225 non-physiological echocardiographic valvular abnormalities in 169 (31%) of 545 survivors of whom an evaluable echocardiography was available. The median follow-up time was 14.9 years (range 5.1-36.8), and the median attained age was 22.0 years (range 7.0-49.7). Most common abnormalities were tricuspid valve disorders (N=119; 21.8%) and mitral valve disorders (N=73; 13.4%). The risk of valvular abnormalities was significantly associated with increasing radiotherapy dose to the heart region, especially after thoracic and total body irradiation. Furthermore, the presence of congenital heart disease significantly increased the risk of valvular abnormalities. There was no evidence that anthracyclines or other chemotherapeutic agents increased the risk of valvular abnormalities.

The last part of the thesis, **Chapter 8**, consists of the protocol of the Cochrane Systematic Review on breast cancer in female survivors who had received radiotherapy involving the chest for their primary malignancy. The aim of this review is to summarize the existing evidence regarding the effects of radiotherapy involving the chest for childhood, adolescent and young adult cancer on breast cancer risk in female cancer survivors. Firstly, we will describe the overall breast cancer risk, as reported in all eligible studies. Secondly, we will summarize the breast cancer risk associated with (a) characteristics of treatment for a previous cancer, (b) survivor characteristics, and (c) modifying traditional predictors for breast cancer. The actual review is currently in progress.

Overall conclusions

Within this thesis we have introduced a simple and biologically correct method to evaluate radiation-associated adverse events after treatment for childhood cancer. In four cohort studies, total physical dose has been converted into the EQD₂. Thus far, to our knowledge,

equivalent dose values have only been sporadically used in epidemiologic studies on late effects after childhood cancer, whereas in clinical radiotherapy, the EQD₂ is commonly used to compare various fractionation schedules in relation to toxicity. We summarize the most important conclusions from this thesis:

- EKZ/AMC childhood cancer survivor cohort studies have contributed to an increased knowledge concerning treatment-related risks of adverse events. In the near future, the Dutch LATER cohort provides ongoing research opportunities to focus on gaps in the current evidence, including those with regard to radiation-associated adverse events.
- The EQD₂ is preferred over the physical prescribed dose because it enables concurrent evaluation of different fractionation schedules and very different radiotherapy techniques, which will become increasingly important in future cohort studies that include patients treated with non-standard innovative treatment modalities.
- Wilms' tumor survivors in our cohort show a high prevalence of adverse events, especially after radiotherapy and treatment with anthracyclines, that have been used only in higher risk patients to improve their cure rates. Considering that the majority of adverse events are mild or moderate, continuation of this treatment would be justified.
- Cranial radiation therapy leads to a high risk of severe, life-threatening, or disabling adverse events, showing different dose-effect relationships in survivors treated for other cancers than in survivors treated for brain tumor.
- Childhood cancer survivors are at high risk of cerebrovascular accidents (CVAs), especially after cranial and supradiaphragmatic radiation in a dose-dependent way. Longitudinal follow-up with special attention for preventive strategies to reduce the risk of CVAs is needed.
- Childhood cancer survivors treated with radiotherapy to the heart region and/or anthracyclines have an increased risk of valvular abnormalities, and need watchful follow-up. Additional research is necessary to investigate whether the asymptomatic valvular abnormalities will worsen over time.
- The rationale of conducting a review on radiation-associated breast cancer in female childhood cancer survivors is that information on risk groups and on the amount of absolute excess risk of breast cancer after treatment for childhood cancer is urgently needed to inform early detection programmes for breast cancer among childhood cancer survivors.

Interpreting these results, one should be aware that our conclusions are based on currently available data, thus representing the present state of the knowledge. With longer follow-up times, the picture may change in the future. It is important to consider effects of later introduced treatment modalities such as chemotherapy, and novel radiation treatment techniques. Therefore, longitudinal studies are necessary to allow for repeated analyses at certain time intervals. Moreover, further research should involve more organs at risk and other treatment modalities than have been investigated in this thesis.

Overall strengths and limitations of this thesis

Strengths

All cohort studies presented in this thesis have been conducted within the first EKZ/AMC childhood cancer survivor cohort, that consisted of 1362 out of 2596 childhood cancer patients who were diagnosed and treated in the EKZ/AMC between 1966 and 1996, and who survived their primary malignancy at least 5 years after diagnosis.⁴ One of the strengths of the EKZ/AMC cohort is that it includes all childhood cancer patients diagnosed for a wide range of primary cancers in a specific calendar period. Accordingly, the selected cohort is independent of specific outcomes, which prevented selection bias based on outpatient clinic visits or diagnosis of late adverse events.⁶

Since 1966, the EKZ/AMC childhood cancer patients have been registered in the hospital-based Childhood Cancer Registry. From this registry, comprehensive and detailed treatment information is available for each survivor, not only for primary cancer treatment and recurrences, but also for subsequent tumors. The majority of the data have been registered prospectively during the childhood cancer treatment,⁷ which allowed us to acquire high-quality data independent of the outcome of interest.

In our studies we have converted physical total dose into the EQD₂, a radiobiologically correct method to assess dose-effects relationships in cohorts that include wide ranges of childhood cancer diagnoses and accordingly various radiation treatment schedules. Furthermore, EQD₂ values include fractionation dose, an important determinant of late effects.⁸ Calculation of EQD₂ values is only possible when detailed and specific information on radiotherapy, including fractionation schedules and total dose are available. We have completed these calculations for 510 (85.4%) of the 597 children who received radiotherapy. The EQD₂ allows us to evaluate various radiation schedules and different treatment modalities in a uniform way. As we have noted in chapter 2, and illustrated in chapter 9 of this thesis, this will become relevant in future studies, when modern radiation treatment modalities for subsequent tumors such as brachytherapy, stereotactic radiosurgery will be included in the evaluation of adverse events.

Since the establishment of the Outpatient Clinic for Late Effects of Childhood Cancer in 1996, survivors have been invited this clinic for the medical assessment of adverse events.^{4,6} A strength of our cohort is that the outcomes that we studied are not self-reported by questionnaires or interviews, but are mainly based on medical follow-up, as in contrast with other childhood cancer survivor cohorts.⁹⁻¹² Furthermore, in a number of studies,^{13,14} the outcomes have been defined and graded for severity in a standardized manner, using the CTCAEv.3.0,¹⁵ which appeared to be a reliable scoring instrument for assessing the severity of adverse events.⁴

Limitations

The EKZ/AMC cohort is hospital-based and not population-based or nationwide. Compared to the complete Dutch population of childhood cancer patients, the EKZ/AMC treats a rela-

tively high proportion of children with solid tumors, and a relatively low number of children with leukemia, lymphoma or central nervous system tumors. It is possible that, historically, patients with more complicated childhood cancer diagnoses have been treated in the EKZ/AMC and, as a consequence, treatment was more intensive in our cohort than in a nationwide study. This may influence the absolute risk, but the consequences for the relative risk or the relevance of risk factors will be minimal.

Another limitation of the EKZ/AMC childhood cancer survivor study is the lack of a readily available control population, contrary to some other cohorts.^{10-12,16} An acceptable solution is comparing risks between treatment groups within the cohort, but it might be complicated to reveal risk factors that are dominated by other, preponderant risk factors. In that case, population-based reference values, such as incidence or prevalence rates could be used, as we did in chapters 6 and 7.

Due to the professional practice of performing the follow-up, it is not possible to blind the physician in the outpatient clinic to prognostic factors. However, the risk of detection bias is reduced by using standardized protocols. Furthermore, due to the clinical nature of our follow-up, survivors do not always attend from the same follow-up year onwards, for example, because of cancer recurrence treatment. This is one of the reasons we always adjust our analyses for the follow-up duration of that individual patient.

Furthermore, we cannot rule out the presence of attrition bias due to the fact that survivors with late effects could be either less or more likely to visit the outpatient clinic than survivors without medical problems, leading to an under- or overestimation of the risk.^{17,18} This is a similar issue that studies using questionnaires face.^{9,11,12,16} Moreover, the sample sizes of patients in some of the treatment groups are relatively small. Consequently, it is not always feasible to examine late adverse effects in relation to more detailed chemotherapy and radiotherapy groups.

A critical appraisal of using the EQD₂ as we have done, underlines some issues. The EQD₂ in our studies represents the prescribed dose to a certain radiation field, which is not the same as the actual absorbed dose. In the studies on adverse events in Wilms' tumor survivors, and in survivors treated with cranial radiation therapy, the EQD₂ values result from treatment fields including boost fields as a surrogate for the absorbed dose,^{13,14} thus representing the maximum dose on the smallest field. Additionally, it has not been feasible to include irradiated volume in our analyses, because appropriate information was not available for the majority of the survivors in our cohort. We evaluated wide ranges of late effects, including effects occurring outside the radiation field, without having the possibility to estimate the absorbed dose received by organs at risk.

Clinical practice

The goal of radiation treatment teams is for each individual patient to create the optimal treatment plan, delivering sufficient high doses to kill tumor cells while limiting doses to

surrounding healthy tissues. In general, doses should be kept as low as reasonably achievable (the ALARA principle), and treatment volumes as small as acceptable. Evolving radiation technologies have contributed to reach this goal. The transition from orthovolt to megavolt radiation therapy has shown a decrease in secondary tumor development^{19,20} thanks to less radiation scattering.

Up to the 1990s, megavolt treatment plans were created according to the two dimensional radiation therapy approach (2D-RT), in which a conventional x-ray simulator was used to generate planar radiographs. Bony structures and radio-opaque fluids were used to delineate field borders. Modern imaging technologies such as computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) have led to better diagnostic procedures, and to the implementation of three and four dimensional conformal radiation therapy (3D- and 4D-CRT). From that moment on, virtual computer simulation for defining tumor and organs at risk (OARs), and the set-up of treatment beams, is common practice. In general, as compared to 2D-RT, a greater number of radiation beams is used, leading to improved tumor coverage and better sparing of OARs. Intensity modulated radiation therapy (IMRT), and image guided radiation therapy (IGRT), more advanced forms of 3D- and 4D-CRT, can achieve dose distributions that narrowly adapt the prescribed dose to the target volume while avoiding specific sensitive OARs.²¹⁻²³ The drawback of IMRT is the potential to increase the risk of radiation-induced second cancers, because larger volumes of healthy tissue are exposed to lower radiation doses.²⁴ Dose volume histograms (DVHs) are produced to evaluate the target dose and dose to OARs.

Currently, there is a growing interest in using proton radiation therapy in the management of childhood cancer. As a result of the unique physical properties of the depth dose curve, dose reduction to normal tissues is better achieved compared with conventional radiation techniques.²⁵ Children who are treated with a curative intent should have prior access to proton therapy. Also, this advent treatment modality, as well as the long-term outcomes should be monitored intensively. Attentive follow-up and counseling of treated patients according to structured guidelines will lead to early diagnosis of several late effects, in order to be treated timely. Finally, the current knowledge enables us better than before to balance pros and cons in the process of shared decision making, leading towards tailored treatment strategies.

Future perspectives

Thanks to long follow-up times, retrospective cohorts harbor valuable information on treatment-related adverse effects. Combining these outcomes with modern radiation treatment planning techniques offers opportunities for future research.

First, thus far it has not been feasible to include irradiated volume in our analyses, because appropriate information was not available for the majority of the survivors in our cohort, being treated in the 2D-RT era. The translation of retrospective 2D-RT data into 3D- and

4D-CRT calculations will enable us to evaluate DVHs, and estimate absorbed doses to OARs.

Second, where we have used the EQD₂ representing the prescribed dose, other research groups have performed dose reconstruction methods using phantom measurements and computer planning techniques.^{26,27} The next logical step will be to combine these methods.

Third, EQD₂ calculations include the tissue-dependent α/β ratio, initially derived from cell survival curves and animal studies, and increasingly being estimated and/or validated in clinical studies,²⁸ but mostly for adults. Since age at treatment can be a strong effect modifier of the dose-effect relationship,²⁹⁻³¹ 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 survivor 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.

Recommendations for future research

Several points of interest for future research can be identified:

- Prospective data collection

Currently, patients are treated with 3D- and 4D-CRT techniques, with modern technologies and facilities to store data. It is recommended to selectively store data based on outcomes and the knowledge that we gained from retrospective cohort studies including survivors treated in the 2D-RT era. From these studies we now know which OARs are important to evaluate, and thus should be delineated. From that point of view we also know which DVHs should be calculated. Furthermore, guidelines for data collection should be developed, while interim evaluations can help us to adjust and improve the data collection when necessary.

- Dosimetric studies

Epidemiologic studies that investigate radiation-associated adverse events in childhood cancer survivors normally use the cumulative physical prescribed radiation dose. In our studies, we used the EQD₂ to compare different dose schedules and treatment modalities in a uniform way. However, the EQD₂ is also a surrogate for the prescribed dose. Dosimetric studies are justified for the verification of the actual absorbed dose, both in target volume as in OARs.

- Normal tissue complication probability (NTCP) modelling

Theoretical NTCP-models are used to calculate and describe relationships between dose distributions in OARs and the development of radiation-associated adverse effects. Based on the outcomes that are known from retrospective late effects studies, NTCP modelling for radiation therapy should also include clinical features to predict which patients and tumors are expected to benefit from specific treatment modalities, and to deliver individual tailored treatments. To evaluate treatment-related tissue complications it is essential to define unambiguous endpoints.

- Image guided radiation therapy (IGRT)

Last but not least, more attention should be paid to position verification and movements of

tumor and OARs during radiation treatment. IGRT is frequently used in adult cancer treatment, but still in a developmental stage for children.

In the Netherlands, proton radiation therapy will soon become available, a promising radiation treatment modality in the management of childhood cancer, expecting to prevent or reduce radiation-associated adverse effects in certain patient groups. All abovementioned points of interest do not only apply to conformal beam radiation therapy, they especially form major challenges in the field of proton radiation therapy. These challenges call for close national and international collaborations between pediatric oncologists, radiation treatment teams, and epidemiologists with the ultimate goal of developing treatment strategies that will benefit future patients in terms of increasing survival rates and diminishing radiation-associated adverse events.

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