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Radiation-associated adverse events after childhood cancer

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Chapter 1

Introduction and outline of the thesis

Introduction

Childhood cancer is a relatively rare disease. In 2010, 594 children younger than 18 years were diagnosed with cancer in the Netherlands, which comprises 0.6% of all new cancer cases in that year (Figure 1).¹ Still, it is the second most frequent cause of death in children in the Western world.²

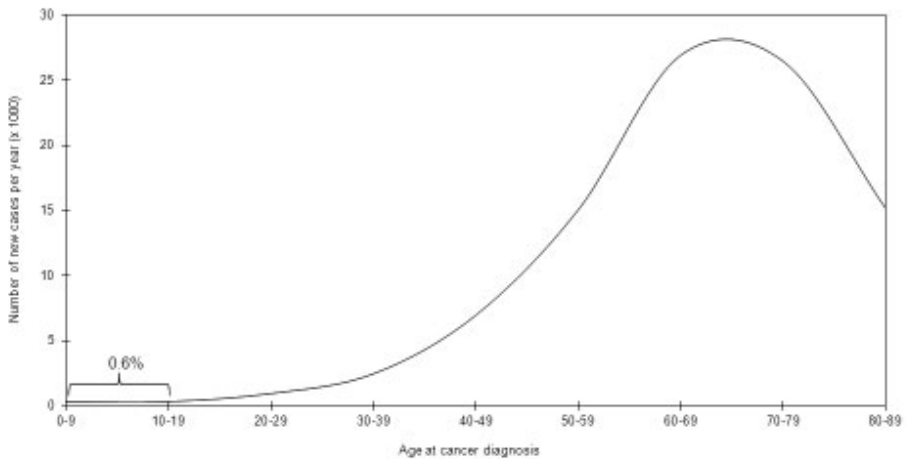


Figure 1. Age-specific cancer incidence in the Netherlands in 2010
Adapted from IKNL <http://www.cijfersoverkanker.nl/selecties>

Childhood cancer differs from adult cancer in presentation, biology and therapy. Most common non-solid cancers are leukemia and lymphoma, whereas the most frequently diagnosed solid tumors are brain tumors, sarcoma, Wilms' tumor, neuroblastoma and retinoblastoma, the last three are typical childhood cancers. Being different from adult cancer, treatment and survival are also non-comparable. Thanks to continuously improving diagnostic and treatment techniques, 5-year survival rates have increased from 65% thirty-five years ago up to 80% and higher in the last decades² (Figure 2), and the population of long-term survivors is expected to keep on growing.^{3,4}

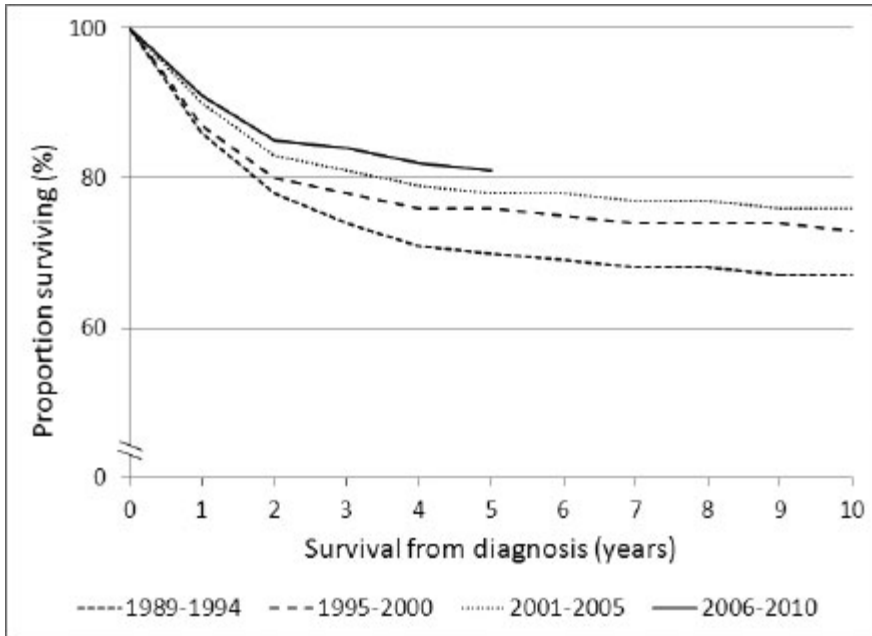


Figure 2. Survival rates for Dutch childhood cancer survivors diagnosed before the age of 18 years
Adapted from IKNL <http://www.cijfersoverkanker.nl/selecties>

Historically, the use of radiation therapy has contributed to improved survival, in particular for childhood cancers such as acute lymphoblastic leukemia (ALL), Hodgkin's Lymphoma (HL), rhabdomyosarcoma, Wilms' tumor, and Ewing sarcoma.⁵ The successful survival rates, however, have been accompanied by an increasing incidence of late complications; 75% of the survivors are confronted with one or more late adverse effects,^{6,7} that are associated with treatment modalities including surgery, chemotherapy and radiotherapy. These treatment modalities are closely attuned, and it depends on the tumor type which combinations have to be applied. Simultaneously, the evolvement of chemotherapy has shown that many of the common childhood cancers are chemosensitive, and research and treatment according to international trials and protocols have currently resulted in a diminished role for radiotherapy as part of childhood cancer treatment. In 1973 to 1976, radiation therapy for ALL, non-Hodgkin's Lymphoma (NHL), and retinoblastoma amounted to 57%, 57%, and 30%, respectively, but declined to 11%, 15%, and 2% respectively, in 2005 to 2008.⁸ However, radiotherapy still is one of the most common treatment modalities of childhood cancers such as brain tumors, soft tissue sarcomas, bone tumors, and high-risk neuroblastomas and Wilms' tumors.

Teams of radiation oncologists, physicists, biologists and technologists work intensively together to develop the optimal radiation treatment plan for each individual patient. This implies a delicate balancing act between applying sufficiently high radiation doses to kill tumor tissue and prevent subclinical tumor growth, and keeping doses as low as reasonable

achievable for 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.

Risk factors for late adverse effects

Risk factors associated with late adverse effects can be distinguished in patient-related and treatment-related factors. Patient-related factors include sex, age at time of treatment and primary tumor type. Multiple studies have shown that female survivors are more likely to have any adverse effect, irrespective of severity, than male survivors.^{6,7,9} Older age at primary cancer diagnosis was significantly associated with reporting any health condition, or severe, life-threatening or disabling health conditions, or multiple conditions.⁷ On the other hand, the impact of primary cancer treatment at younger age has become visible in long-term outcomes such as final height, bone and soft tissue sequelae, neurocognitive deficits, and second cancers.¹⁰⁻¹³ The risk of late effects is also determined by the primary cancer type and the required treatment. Geenen *et al* showed that survivors who had been diagnosed and treated for a Wilms' tumor or leukemia had the lowest percentages of high and severe adverse events burden (12% each) as compared with brain/CNS (central nervous system) and bone tumor (37% and 64%, respectively).⁶ Similar results were shown by Oeffinger *et al*: Wilms' tumor survivors and leukemia survivors both had a significantly 4-fold increased risk of severe or life-threatening or disabling events, whereas survivors of CNS and bone tumors had a 13 and 39 times higher risk, as compared to siblings.⁷

Treatment without chemotherapy or radiation therapy was shown to be associated with the lowest risk of any adverse health condition,⁷ which however, does not imply that surgery alone does not increase the risk of late effects. Surgery showed to be associated with a significant 1.7-fold increased risk of a high or severe burden of events,⁶ and nephrectomy and splenectomy increased the risk of developing any event.⁷ Surgery as part of childhood cancer treatment is associated with important late effects, for example, due to amputation and brain surgery.⁶

Over the last decades, chemotherapy has achieved an extensive role in childhood cancer treatment and contributes to high cure rates. Even though follow-up times after treatment with chemotherapy are relatively shorter as compared to follow-up times after treatment with radiotherapy, chemotherapy-related late adverse effects have been described in numerous studies. Examples of chemotherapy-related late effects include cardiotoxicity, neurotoxicity and hearing loss. Treatment with anthracyclines is associated with cardiotoxic late effects, manifesting as asymptomatic cardiac dysfunction, and clinical heart failure.^{14,15} Vincristine and cisplatin exposure may increase the risk of neuropathic symptoms and long-term motor and sensory impairment.^{16,17} Platinum-based drugs such as carboplatin and cisplatin can cause ototoxicity, affecting the functions of the auditory and/or vestibular systems.^{18,19}

Childhood cancer survivors who had received radiotherapy as part of their treatment showed to have a significant 1.5-fold increased risk of a late adverse effect of at least moderate severity, compared with survivors treated with surgery only,⁶ and being treated with any irradiation resulted in a significantly 4.5-fold increased risk of having at least two adverse effects.⁷ The wide spectrum of radiation-associated late effects includes, among others, cardiovascular events,^{20,21} pulmonary events,²² tissue hypoplasia and orthopedic events,^{12,23} the induction of second malignancies,^{13,24} neurocognitive and psychosocial outcomes,^{25,26} hearing loss,²⁷ endocrine and metabolic disorders,²⁸ and fertility problems.^{29,30}

Radiotherapy assessment

Radiation-associated late adverse events in childhood cancer survivor cohorts are generally evaluated in three ways. The first one is to use dichotomous (i.e., radiotherapy yes vs. no) or categorical (i.e., body site of treatment) indicators, when no information on radiation dose is available.^{6,7} Second, when dose information is available, continuous or categorical dose variables (i.e., physical or prescribed dose) are used.³¹ Third, if sufficient treatment details are available, retrospective dose reconstruction can be used to estimate absorbed dose at the tissue of interest.^{32,33} However, this method is time consuming and rather expensive. Hence, the first two methods are mainly used but are not always adequate, in that they do not allow for evaluation of dose-effect relationships. Furthermore, by using physical prescribed dose only, the fractionation dose is not taken into account, whereas radiobiological studies have shown that fractionation dose also is an important determinant of late effects.^{34,35} Additionally, by using physical dose only, radiation treatment schedules that use different fractionation doses cannot be compared in a uniform way. Finally, large differences in dose delivery exist between conventional external beam radiotherapy and other forms of high-dose, localized radiotherapy such as brachytherapy and stereotactic radiotherapy. Consequently, doses delivered by different forms of radiation treatment cannot be compared or summed without the necessary adjustments that take into account the different biological effects.

So far, in epidemiologic studies on late effects after treatment for childhood cancer, fractionation doses were only sporadically taken into account.^{36,37} Modern radiotherapy is developing rapidly, which leads to an increasing heterogeneity with respect to dose distribution, volume and fractionation schedules. Consequently, in (future) studies physical prescribed dose is not only inadequate to compare late effects in a mixed group of childhood cancer survivors, but also not sufficient to evaluate the total radiation exposure in survivors who underwent different forms of radiation treatment. In the studies presented in this thesis, we have used the equivalent dose in 2-Gy fractions to assess dose-effect relationships, which is a biologically correct alternative to take care of the above-mentioned issues.

Equivalent dose in 2-Gy fractions (EQD₂)

To quantify the biological effect of dose-fractionation schedules on tumor control and on

adverse effects in healthy tissues, mathematical models or isoeffect models were introduced and developed.³⁴ The concept of biological effective dose (BED), originating from the linear-quadratic (LQ) model was developed in 1982, by Barendsen.^{38,39} The BED enables to compare different radiation schedules, to explain different results after clinical use, and to predict effects before application. A disadvantage of calculated BED values is that they are much higher than normally clinical prescribed radiation doses. Instead of the BED, the mathematically comparable equivalent dose in 2-Gy fractions (EQD₂) can be used. EQD₂ values are easier to relate to daily clinical practice.³⁴ The EQD₂ represents the dose given in fractions of 2 Gy that is biologically equivalent to a total dose D given in a fraction dose of d Gy. The EQD₂ is calculated with the formula: $D * (d + \alpha/\beta) / (2 + \alpha/\beta)$. The α/β ratio is not constant and its value depends on the specific tissue of interest. In general, the α/β ratio is high for acute responding tissues like tumor cells (≈ 10 Gy), and low for late responding normal tissues (1 to 4 Gy). In clinical radiotherapy, the EQD₂ is commonly used, not only to compare various fractionation schedules in relation to toxicity,⁴⁰⁻⁴² but also to calculate the therapeutic window in case of reirradiation of a region or organ that was previously treated.^{43,44}

Objectives and outline of this thesis

The general objective of this thesis is to investigate radiation-associated adverse events after childhood cancer. We have analyzed the prevalence and severity of adverse events in a cohort of long-term childhood cancer survivors, defined as having lived at least 5 years from the date of diagnosis, and we have assessed treatment-related risk factors for the occurrence and severity of adverse events with a focus on radiotherapy treatment. Assessment of dose-effect relationships using the EQD₂ has enabled us to more precisely examine the effect of radiation dose on specific categories of adverse events. We aim to introduce this concept 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.

After the general introduction (**Chapter 1**), this thesis continues in **Chapter 2** with a detailed description of the design and characteristics of the longitudinal childhood cancer survivor cohort study that was initiated in 1996 in the Emma Children's Hospital/Academic Medical Center (EKZ/AMC). In **Chapter 3**, the use of the equivalent dose in 2-Gy fractions (EQD₂) to evaluate radiation-associated adverse events after childhood cancer is introduced. In **Chapter 4**, we focus on one childhood cancer diagnosis, assessing the prevalence of and risk factors for late adverse events in long-term Wilms' tumor survivors. **Chapter 5** shows dose-effect relationships for adverse events after cranial radiation therapy in the EKZ/AMC childhood cancer survivor cohort. We have stratified the results for survivors who received cranial irradiation for a primary brain tumor, and for survivors who had cranial irradiation for other types of cancer, such as leukemia. In **Chapter 6**, radiation-associated cerebrovas-

cular events, including hemorrhagic and ischemic stroke, are investigated in our childhood cancer survivor cohort. In **Chapter 7** one outcome is analyzed, i.e., echocardiographically detected valvular abnormalities in childhood cancer survivors who had been treated with radiotherapy involving the heart region and/or with anthracyclines. **Chapter 8** includes the protocol for the Cochrane systematic review on breast cancer in female survivors of childhood, adolescent or young adult cancer after radiotherapy involving the chest for their primary malignancy. Finally, the general discussion in **Chapter 9** is preceded by a review of the main results and conclusions of the studies in this thesis, and provides recommendations for future research on radiation-associated late adverse events. This thesis concludes with summaries in English and Dutch.

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