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Childhood cancer survivors: Evidence and care

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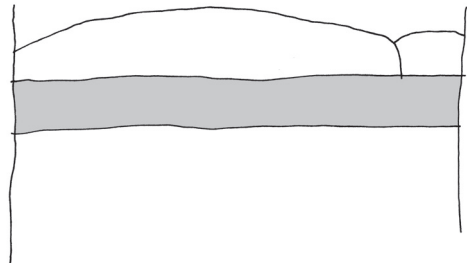
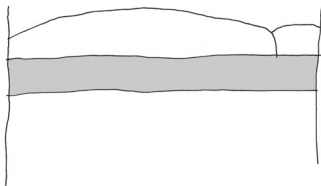
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Chapter 9

Summary and general discussion



The **general objective** of this thesis was to increase evidence of (1) late adverse effects of childhood cancer treatment and (2) optimal care for childhood cancer survivors, with the ultimate goal to improve quality of care and quality of life of survivors. In the current chapter, we will summarize and discuss the main findings of the seven previous chapters in which we studied these broad themes. In the introduction of this thesis, we discussed the suitable study designs in childhood cancer survivorship research and the discussion places the studies of this thesis within that perspective. We will discuss strengths and limitations of the studies and formulate a general conclusion. The general discussion concludes with recommendations for future studies within the field of childhood cancer survivor research and recommendations for clinical practice in childhood cancer survivor care.

Part I. Late adverse effects of childhood cancer treatment

In **Part I** of this thesis, we aimed to increase evidence of late adverse effects of childhood cancer treatment using two study designs: a cohort study and a systematic review. Within the first three studies in this part of the thesis, our topics of interest were study design and general clinical consequences of childhood cancer treatment. The final study in this part of the thesis focusses on childhood cancer patients and survivors at risk for cardiac late effects of treatment.

In order to give readers the opportunity to assess the quality of evidence it is essential to provide a complete overview of the methodology and baseline characteristics of a primary study. In **Chapter 2**, we introduced in detail the cohort that was the basis for subsequent studies described in chapters 3 and 4. Our aim was as follows:

1. *To describe the study design, methodology, clinical characteristics, data availability and outcomes of the EKZI/AMC cohort study of childhood cancer survivors.*

In addition, we thoroughly assessed the strengths and limitations of our study of which readers should be aware. The underlying population of childhood cancer patients consisted of all 3183 children primarily treated for a primary cancer in the EKZI/AMC between 1966 and 2003. Of these 3183 children, 1822 (57.2%) survived at least five years since primary cancer diagnosis and were thus included in our retrospective cohort study. Primary cancer treatment characteristics were complete for 97.7% of survivors. Since 1996, structured clinical follow-up has been offered at a specialized outpatient clinic for late effects of childhood cancer. At the end date of the current study (January 2009), 79.7% of survivors had attended this clinic at least once, 6.9% of survivors received any other form of medical

follow-up at the EKZ/AMC related to their previous cancer and treatment, 4.7% of survivors died before the start of our study and 0.9% of survivors died before they received medical follow-up in the EKZ/AMC. For 7.8% of eligible survivors no medical follow-up was available due to various reasons. Duration of clinical follow-up ranged from 5 to 42 years after primary cancer diagnosis.

There were no substantial differences in the most important prognostic factors (gender, age at diagnosis and treatment) between the cohort that 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 conducted, of which 30 studies included solely ≥ 5 year childhood cancer survivors of the EKZ/AMC. These studies contributed to the current evidence of late effects of childhood cancer treatment.

An important limitation we faced in our clinical cohort study is the fact that no reference population to compare outcomes with is available. In addition, a general limitation of cohort studies with clinical follow-up is that people will get lost-to-follow-up, leading to risk of attrition bias. Finally, it is very time-consuming to assemble longitudinally all clinical outcomes of interest from patients. We therefore aimed to overcome some of the limitations of our cohort study by performing a medical record linkage study between the clinical cohort and the national Hospital Discharge Register (LMR), which registers almost all hospitalizations in the Netherlands. However, while some countries can use a unique person identifier to link individuals directly with hospitalization registers, in the Netherlands linkage of individuals to the LMR is only possible based on a non-unique combination of variables, including postal code of an individual. Therefore, it was previously not feasible to study hospitalizations over long periods in the Netherlands due to loss of persons after change of address. By primary linkage to the Municipal Personal Records Database (GBA), a national registry with individual postal code history available, the incompleteness of longitudinal hospitalization data due to changes in address could be overcome. In this thesis, we therefore first evaluated our medical record linkage study design in which we linked the EKZ/AMC cohort of childhood cancer survivors with national administrative register in order to study clinical consequences of late adverse effects of childhood cancer treatment (by way of hospitalizations) in comparison to the general population. The aim of **Chapter 3** was:

2. *To determine the feasibility and validity of studying hospitalizations over time in a study cohort using a two-step medical record linkage approach linking a cohort of childhood cancer survivors with (1) GBA and (2) LMR.*

First, we linked our EKZ/AMC childhood cancer survivor cohort with the GBA using deterministic linkage. Within GBA, we also sampled a reference population of 28255 individuals from the general Dutch population, matched on year of birth, gender and calendar year. Second, we extracted hospitalizations from the LMR with a date of discharge during unique follow-up (based on date of birth, gender and postal code in GBA). We assessed the quality of the linkage process by exploring the potential threats to validity of the linkage process and determined the validity of hospitalization registration by defining the agreement of being hospitalized according to LMR and to available cohort data.

We found that of the 1564 childhood cancer survivors who were eligible for linkage, 1477 (94%) could be retrieved from GBA. Of the 1477 childhood cancer survivors and 28255 reference persons identified in the GBA 94% contributed to unique follow-up time based on date of birth, gender and postal code in GBA and thus had potential hospitalization data available. The unique follow-up time and consequently the total time information of potential hospitalizations was available constituted 87% (childhood cancer survivors) and 83% (reference population) respectively of the potential follow-up time. Characteristics of childhood cancer survivors and reference persons contributing to unique follow-up time were comparable. The agreement of hospital admissions during unique follow-up time according to our study registry and LMR was 94%. We concluded that in absence of unique identifiers in the Dutch hospitalization register, it is feasible and valid to study hospitalizations longitudinally using a two-step medical record linkage approach. Important pitfalls to take into account are left-truncation and loss of individuals and unique follow-up time due to the record linkage procedure.

Our study in chapter 3 showed that there is great potential for clinical cohort studies of, for example, (childhood) cancer survivors in the Netherlands to assess long-term clinical events using medical record linkage with Dutch administrative registries. Using this study design, we wanted to increase evidence about the burden of late adverse effects of childhood cancer treatment over time, by way of hospitalization rates and hospitalization characteristics. The aim of the study described in **Chapter 4** was therefore:

3. *To define the burden of unfavorable health conditions in childhood cancer survivors, as measured by trends in hospitalization rates.*

For this study, we used the methodology and available hospitalization data as described in chapter 2 and 3. We determined relative hospitalization rates, hospitalization rates over time, and hospitalization characteristics of 1382 childhood cancer survivors and 26583 reference persons from the general population. We found that the clinical consequences of cancer treatment during childhood are substantial. Childhood cancer survivors had an average 2.2-fold increased hospitalization rate compared to the general Dutch population and increased

hospitalization rates up to at least 30 years after primary cancer diagnosis. Starting with high hospitalization rates 5 year after primary cancer diagnosis, we found an initial decline towards the reference population between the 10th and 15th follow-up year. However, between 20th and 30th follow-up year a steep increase was seen in the hospitalization rate of childhood cancer survivors compared to the general population. In addition, compared to the general population childhood cancer survivors have very high hospitalization rates for neoplasms and endocrine/nutritional/metabolic disorders, but the risk of several other hospitalization diagnoses is also increased. We showed that on average childhood cancer survivors were hospitalized longer, at younger age and more frequent in university hospitals, suggestive for more complex and/or serious health problems and a higher burden on health care resources. Survivors treated with radiotherapy, especially radiotherapy to head and/or neck, are at highest risk of hospitalization. We concluded that there is a high and long-term burden of unfavorable health conditions after childhood cancer compared to the general population and that this burden is likely related to the previous childhood cancer.

In addition to the mentioned observational studies we performed ourselves, we also summarized studies performed by others to define risks of late adverse effects of childhood cancer treatment. **Chapter 5** describes a systematic review that synthesizes the benefits and risks within children of a specific chemotherapy developed to decrease adverse cardiac events during and after cancer treatment. Our aim was:

4. *To summarize all available evidence on the benefits and risks of liposomal anthracyclines in children with cancer.*

For this study, we searched several literature databases, reference lists of relevant articles and ongoing trial databases for relevant studies. Two reviewers independently performed study selection, data extraction and quality assessment of included studies. We could not identify any relevant randomized controlled trials (RCTs) or controlled clinical trials (CCTs). We included fifteen observational studies that described the use of liposomal anthracyclines in children with cancer, but the quality of the studies was low. This precluded any conclusions about beneficial effects of liposomal anthracyclines. In addition, most patients included in these studies had been treated extensively in the past, making it difficult to estimate the exact risks of liposomal anthracyclines in children. However, some patients developed cardiotoxicity, serious allergic reactions, mucositis, infections, hematotoxicities and/or hepatotoxicity after treatment that at that moment only included a liposomal anthracycline. We therefore concluded that there is no evidence available from RCTs or CCTs about the benefits and risks of liposomal anthracyclines in children with cancer, but that the limited literature suggests that children treated with liposomal anthracyclines are at risk for developing cardiotoxicity and other serious toxicities. Consequently, this systematic review

also showed the ability to identify research gaps and that in the absence of appropriate intervention research some conclusions can be drawn about adverse effects of a treatment.

Part II. Optimal care for childhood cancer survivors

In **Part II** of this thesis, we aimed to increase evidence of optimal care for childhood cancer survivors using three study designs: a cohort study, a systematic review and a clinical practice guideline. In these three studies we focused on late effects of the heart, the organ that is commonly affected by late effects of cancer treatment, especially after anthracycline-based chemotherapy and radiotherapy to the heart region.

In **Chapter 6** we performed a prospective cohort study to assess the additional predictive value of a diagnostic tool (exercise echocardiography) to detect anthracycline-induced cardiotoxicity in childhood cancer survivors, in addition to the already recommended screening with resting echocardiography. Specifically, our aim was:

5. *To determine the added value of monitoring childhood cancer survivors with exercise echocardiography compared to monitoring with resting echocardiography alone to predict anthracycline-induced cardiotoxicity.*

Secondary aims we formulated for this study were to evaluate change in resting cardiac function over 10 years and to determine risk factors for late cardiotoxicity. The study was a prospective cohort study of 110 originally asymptomatic anthracycline-treated childhood cancer survivors from the Royal Children's Hospital in Melbourne, Australia. All survivors had undergone cardiac tests including exercise echocardiography between 1995 and 1997. Of the original cohort of 110 survivors, 92 underwent cardiac follow-up a median of 10.5 years later. These survivors underwent a resting echocardiogram at both evaluations. At first evaluation, a repeat echocardiogram was performed following peak exercise. Resting echocardiographic parameters were converted to standardized (z) scores.

We found that our measure of resting cardiac function (resting fractional shortening z score, RFSz) decreased from -0.18 to -0.93. We also confirmed evidence from other studies that higher cumulative anthracycline dose was a risk factor for abnormal RFSz at late follow-up ($P=0.0002$). However, adding exercise fractional shortening (XFS) to a model containing RFSz did not improve prediction of abnormal RFSz at late follow-up. We concluded that although several studies have shown an impaired cardiac function after exercise in anthracycline-treated children, monitoring with exercise echocardiography has no added value to monitoring with resting echocardiography alone in predicting late anthracycline-induced cardiotoxicity in childhood cancer survivors.

In **Chapter 7** we synthesized the evidence about medical treatment options for patients with anthracycline-induced cardiotoxicity. Specifically, our aim was:

6. *To compare the effect of medical interventions on anthracycline-induced cardiotoxicity in childhood cancer patients or survivors with the effect of placebo, other medical interventions or no treatment.*

For this Cochrane systematic review, we searched for evidence in several databases for articles about potentially relevant studies. We also searched in reference lists of relevant articles, conference proceedings and ongoing trial databases. Studies met the criteria if they were an RCT or CCT comparing the effectiveness of medical interventions to treat anthracycline-induced cardiotoxicity with either placebo, other medical interventions or no treatment. We identified two RCTs. One trial (135 patients) compared enalapril with placebo in childhood cancer survivors with asymptomatic anthracycline induced cardiac dysfunction. The other trial (68 patients) compared a two-week treatment of phosphocreatine with a control treatment (vitamin C, ATP, vitamin E, oral coenzyme Q10) in leukemia patients with anthracycline-induced cardiotoxicity.

Both studies had methodological limitations. The RCT on enalapril showed no (statistically) significant differences in overall survival, mortality due to heart failure, development of clinical heart failure and quality of life between treatment and control group. A post-hoc analysis showed a decrease (i.e. improvement) in one measure of cardiac function (left ventricular end systolic wall stress (LVESWS): -8.62% change) compared with placebo (+1.66% change) in the first year of treatment ($p=0.036$), but not afterwards. Patients treated with enalapril had a higher risk of dizziness or hypotension (relative risk 7.17, 95% confidence interval 1.71 to 30.17) and fatigue (Fisher's exact test, $p=0.013$). The RCT on phosphocreatine found no differences in overall survival, mortality due to heart failure, echocardiographic cardiac function and adverse events between treatment and control group. Based on one RCT, we concluded that although there is some evidence that enalapril temporarily improves one parameter of cardiac function (LVESWS), it is unclear whether it improves clinical outcomes in survivors of childhood cancer with anthracyclines-induced cardiac dysfunction. Enalapril was associated with a higher risk of dizziness or hypotension and fatigue. Limited data with a high risk of bias showed no significant difference between phosphocreatine and control treatment on echocardiographic function and clinical outcomes. We did not identify any RCTs or CCTs studying other medical interventions for symptomatic or asymptomatic cardiotoxicity in childhood cancer patients or survivors.

Based on the currently available evidence, we recommended clinicians to weigh the possible benefits with the known side effects of enalapril in childhood cancer survivors with asymptomatic anthracycline-induced cardiotoxicity. This study also clearly showed that high-quality studies are lacking and should be a priority for future research agenda's within childhood cancer survivor-research.

The final step from evidence to care is to summarize evidence on a specific health problem and formulate recommendations for clinical practice. In **Chapter 8** we reported on such a multidisciplinary clinical practice guideline for the follow-up care of childhood cancer survivors at risk for cardiac disease. The overall aim of the study was:

7. *To ensure optimal and uniform follow-up care for all childhood cancer survivors in The Netherlands with respect to late cardiac health problems in childhood cancer survivors.*

For this clinical practice guideline we focused on asymptomatic cardiac dysfunction in childhood cancer survivors. Within our multidisciplinary working group, we specified clinical questions that should be answered to get to recommendations for childhood cancer survivors with or at risk for asymptomatic cardiac dysfunction. We carried out short or extensive evidence summaries and determined methodological quality of studies and levels of evidence in order to answer our clinical questions. When evidence was lacking for childhood cancer survivors, we carefully extrapolated evidence from other populations. Our final recommendations were based on evidence and consensus.

We found that there was high-level evidence for the increased risk of cardiac dysfunction in childhood cancer survivors and its main risk factors, but that evidence was lacking regarding the prognosis, diagnosis and treatment of cardiac dysfunction in childhood cancer survivors. We recommended echocardiographic screening for asymptomatic cardiac dysfunction in childhood cancer survivors treated with anthracyclines and/or cardiac radiotherapy and counseling about potential advantages and disadvantages of our screening recommendations.

Overall conclusions

Within the broad themes of late adverse effects of cancer treatment in childhood cancer survivors and optimal care for childhood cancer survivors, this thesis includes some important findings. There are a few we would like to highlight:

1. The EKZ/AMC cohort of childhood cancer survivors is a longitudinal cohort study with a low risk of selection and information bias and with complete patient, cancer and treatment information in order to adjust for confounders
2. In absence of unique identifiers in the Dutch hospitalization register, it is feasible and valid to study hospitalizations within a study cohort longitudinally using a two-step medical record linkage approach
3. Childhood cancer survivors are hospitalized more often than the general population up to at least 30 years after primary cancer diagnosis. It is likely that these hospitalizations

- are related to previous childhood cancer and treatment, especially radiotherapy to the head and/or neck
4. Childhood cancer survivors are at highest risk of hospitalization for neoplasms and endocrine disorders
 5. Although liposomal anthracyclines were designed to prevent anthracycline-related cardiotoxicity, limited evidence suggests that children treated with these agents are still at risk of cardiotoxicity
 6. We found no evidence to recommend exercise echocardiography for regular cardiac follow-up in childhood cancer survivors
 7. Although ACE-inhibitors improve clinical outcomes in adults with cardiac dysfunction, there is as yet no evidence of similar effects of ACE-inhibitors in childhood cancer survivors with anthracycline-induced cardiotoxicity
 8. There is high quality evidence that childhood cancer survivors are at increased risk of cardiac dysfunction, but evidence is lacking regarding the prognosis, diagnosis and treatment of cardiac dysfunction in childhood cancer survivors
 9. Follow-up care for childhood cancer survivors should always include counseling about potential advantages and disadvantages of the recommended screening

Overall strengths and limitations of this thesis

Strengths

An important strength of this thesis is that within all studies the risks of bias were critically appraised, adjusted for when needed and possible, and always acknowledged.

Within the limits of childhood cancer survivorship research, as mentioned in the introduction, we tried to design and perform cohort studies with a low risk of bias. Selection bias occurs when the selection of patients is related to the risk of the outcome studied. As has been shown in chapter 2, the EKZ/AMC cohort studied within this thesis had a low risk of this type of bias, as the patients were selected at the time of their primary cancer when no late adverse effect had yet occurred. In addition, the loss of information through the medical record linkage process (chapter 2 and 3) did not seem related to the risk of hospitalization. Information bias occurs when there is a problem in the quality of the information about an exposure or outcome variable. An important strength of our cohort studies was therefore the very complete patient, cancer and treatment information available. This is in contrast to most other large childhood cancer survivor cohorts.¹⁻⁴ The completeness of outcome data in our cohort studies was high, ranging from 84 to 88%, and outcomes were assessed independent of or blinded to the cancer treatment exposure of the survivors. Finally, confounding variables (i.e. variables that correlate with both the exposure and the outcome) can lead to bias. Due to the complete baseline

characteristics available, we were able to adjust for several important confounders in our cohort studies.

Additional strengths of our cohort studies were the longitudinal design, rather than cross-sectional, with long-term follow-up since primary cancer diagnosis and including survivors treated in recent years. We also studied relatively large number of childhood cancer survivors. The study on exercise echocardiography was one of the first diagnostic studies that performed long-term follow-up to define the predictive value of an abnormal test during follow-up in childhood cancer survivors. Finally, in contrast to many other cohort studies of childhood cancer survivors, we were able to study a reference population (chapter 3 and 4) or retrieve appropriate reference values to compare our outcomes with (chapter 6).

A specific strength of the medical record linkage design used in chapter 3 and 4 is that we had data available of the timing of the clinical event of interest of members of the cohort. We were therefore able to perform time-to-event statistical analyses, in contrast to previous studies within our cohort.^{5, 6} This was an important strength, since time-to-event analyses are more informative than prevalent studies for most outcomes.

Our systematic reviews and guideline were complete, transparent and used appropriate tools to appraise the available literature. A very important strength of our guideline was that all disciplines caring for childhood cancer survivors as well as patient organizations were involved in the guideline process and the final recommendations, making it more likely that involved health care professionals will adhere to it.

A strength of all studies in this thesis is that we aimed to study clinically relevant outcomes when possible and limit the assessment of subclinical outcomes. The consequences and natural course of subclinical abnormalities, such as abnormal test results, are often unknown and may not always be relevant to the individual patient and health care professional. However, as discussed in the introduction of this thesis, childhood cancer survivorship research faces the issue of relatively low patient numbers. It was therefore not always possible to adhere to this aim, such as in chapter 6. Nevertheless, we feel that within the possibilities of childhood cancer survivorship research, this is a strength of this thesis.

Limitations

A limitation of the cohort study in chapter 6 is that survivors were selected after the exposure to cancer treatment. The study was thus at risk for selection bias, but this risk was reduced by selecting asymptomatic survivors consecutively at the outpatient clinic.

An important limitation of our two cohort studies is that they were both hospital-based. A (selection within a) hospital-based cohort study may result in other overall risk estimates when compared to a study within a complete population. In chapter 2 we showed that the EKZ/AMC generally treats childhood cancer patients with a slightly different distribution of diagnoses compared to the complete population, although it is difficult to deduce if our

cohort would be at higher or lower risk compared to the complete Dutch population of childhood cancer survivors. Hospital-based cohort studies can thus influence the generalizability of the results, but treatment specific risk estimates are unlikely to be influenced by this study design. Another limitation of our cohort studies is that even though we studied a relatively large number of childhood cancer survivors, numbers were still too low for detailed risk factor analyses. In the nearby future, both limitations will be solved for many research questions, when the EKZ/AMC cohort of childhood cancer survivors will be incorporated in the nation-wide Dutch Childhood Oncology Group - Late Effects after Childhood Cancer (DCOG-LATER) Study of childhood cancer survivors (<http://www.skionlaterstudie.nl/english/>).

A criticism on this thesis could be that the outcomes that we studied in part of the studies were not patient-based outcomes. Only within the systematic reviews and clinical practice guideline measures of quality of life were included when possible. This is in fact an important limitation of medical record linkage studies, in which quality of life measures are not possible to study. Based on available literature, we assumed that it is likely that hospitalizations increase the burden for patient, health care and society, but we have not studied this assumption.

A final limitation is that we have not evaluated the benefits and risks of our guideline yet. Ideally, implementation of a new health care strategy should be evaluated in an interventional study. Such an evaluation will certainly be a topic of future studies.

Recommendations for future studies

Several findings within this thesis have implications for future studies. We would like to focus on two topics that can contribute to improvement of evidence of late adverse effects of childhood cancer treatment and of follow-up care for survivors: medical record linkage studies and studies on improvement of follow-up care.

Medical record linkage studies

Within this thesis, we showed that medical record linkage provides excellent opportunities to study clinical health problems in relation to detailed cancer treatment in childhood cancer survivors. Record linkage studies also have the unique opportunity to compare outcomes in survivors to the general population. The first outcomes we defined were mortality, hospitalization rates and hospitalization characteristics, but there are many more clinical outcomes registered in Dutch administrative databases that are relevant for our cohort of childhood cancer survivors. Examples of available outcomes in the Netherlands are cause of death, (second) cancer and socio-demographic outcomes (including socio-economic status, income, educational achievement, unemployment, the need for disability benefits).

In addition, the extensive available information of hospitalizations yields possibilities for many more studies on specific clinical consequences based on hospitalizations. Trends over time, such as long-term treatment risks, effects of contemporary cancer treatments and aging of survivors can be studied in more detail using medical record linkage studies. Finally, we feel that medical record linkage can play an important role in the evaluation of follow-up care programs for survivors. Evaluation of health care use, costs, second cancer and mortality are all very relevant outcomes in the evaluation of the quality of care that can be obtained through medical record linkage.

Other cohort studies of cancer survivors should also consider medical record linkage as a study design to study late effects of cancer treatment and their trends over time. The large nationwide DCOG LATER cohort of childhood cancer survivors will be able to study these consequences in much more detail, due to its larger sample size. With currently improving survival rates in adults with cancer, the clinical consequences of cancer treatment in adult cancer survivors should also be studied. In the light of the current paucity of medical follow-up facilities for survivors of adult cancer, our medical record linkage design may be a very helpful tool to gain more insight in the clinical consequences of cancer treatment in this recently emerging population.⁷

Studies on improvement of care

In the first part of this thesis, we showed that childhood cancer survivors are at high risk of hospitalization, that some survivors are at higher risk than others are and that the characteristics of the hospitalization vary widely. Subsequent studies should define the characteristics of these hospitalizations and risk factors in more detail. This information can help to determine potential interventions to prevent hospitalizations and health problems.

In the second part of this thesis, we showed that there is not yet enough evidence about follow-up care for childhood cancer survivors at risk for cardiac disease to come to completely evidence-based recommendations for follow-up care. It is thus essential that future studies focus on the diagnostic and therapeutic follow-up care that should be given to childhood cancer survivors in order to improve their health conditions and quality of life. In these studies, the harms of follow-up care should be included as outcomes because not all medical interventions (diagnostic or therapeutic) are beneficial. In addition, it is of importance that available evidence and guidelines are continuously updated and evaluated, in order to provide the most up-to-date evidence-based care recommendation. Because the development of clinical practice guidelines is labor-intensive work (international) collaboration within the field of childhood cancer survivors is essential.⁸ Such collaborations can also lead to a common research agenda to define priorities in further research. Finally, as already mentioned, implementation of health care interventions should be evaluated. In addition to objective outcome measures obtained from (for example) medical record linkage studies, patient-based outcomes should also play a role in such studies.

The studies in this thesis focused on childhood cancer survivors at risk of late effects of cancer treatment. However, this implies that there is also a subgroup of the childhood cancer survivor population that hardly encounters late effects of treatment during their course of life.⁹ In our view this is a key topic of childhood cancer survivor research that has received only little scientific attention thus far.¹⁰ Future studies should also focus on this subgroup, further define their characteristics and, importantly, determine if these survivors may not need the currently recommended (and rather demanding) medical follow-up, with associated risks of false-positive findings.

Recommendations for clinical practice

Throughout this thesis, we showed the considerable risk of late adverse effects childhood cancer survivors are confronted with, even many years after their primary diagnosis. These findings therefore support the aim of DCOG-LATER and several other cooperative groups that childhood cancer survivors should have access to follow-up care after primary cancer survival.¹¹⁻¹⁴ We also showed that for specific health conditions in childhood cancer survivors such as cardiac disease, important evidence about optimal follow-up care is lacking. Based on the findings in this thesis we would like to focus on two topics and their associated recommendations for clinical practice: implementation of available evidence and availability of information for survivors and health care professionals.

Implementation of available evidence into clinical practice

Absence of evidence is not evidence of absence.¹⁵ In other words, with the relatively low number of childhood cancer survivors it is inevitable that currently considerable evidence on optimal follow-up care is lacking. However, this does not mean that follow-up care should not be available for survivors of childhood cancer. The clinical practice guideline in chapter 9 of this thesis is an example of the translation of available evidence into clinical practice. It also showed that in the absence of evidence, recommendations about follow-up care can still be made. However, the development of an evidence- or consensus-based guideline for follow-up care is not enough for equal access to high-quality care for every individual childhood cancer survivor. To ensure this, implementation of the guideline into daily practice is essential.¹⁶

Potential tools for guideline implementation and guideline adherence include the involvement of all stake holders in the development of the guideline, dissemination of the guideline to health care professionals involved in the care for childhood cancer survivors and provision of a supportive tool for daily practice (such as a website or a summary booklet with all recommendations). Within our DCOG LATER guideline, these tools were used

to ensure implementation and adherence. Next steps will be the evaluation of guideline adherence, for example by analyzing indicators of guideline adherence.

Availability of information for survivors and health care professionals

Availability of information about late adverse effects of cancer treatment and about follow-up care for the survivor is essential because of three reasons. First, only with clear information about all the potential benefits and risks, the survivor can make an informed decision about his/her preferences about follow-up care.¹⁷ Provision of information should include the evidence as well as the uncertainties about the individual risk of late effects of childhood cancer treatment. It should inform about possibilities for medical follow-up at the LATER outpatient clinics, about the possibility to contact these clinics in case of questions or health problems and about the potential benefits and risks of additional screening.

Second, as we showed that clinical health problems occur far beyond childhood, it is critical that individuals are aware about their individual health problems and risks. The importance of proper transition of care, including knowledge about one's own health problems, has been shown in many chronic pediatric conditions with which patients now reach adulthood.¹⁸ The knowledge about disease and risk is essential in becoming an independent individual who can take care of his/her own medical needs.

And third, with a growing population of childhood cancer survivors and a broad spectrum of health problems and hospitalization diagnoses, it is increasingly likely that general practitioners and other (adult) health care professionals are confronted with a childhood cancer survivor with specific health problems. These health care professionals should thus at least be aware of this vulnerable patient population as well as the consultation possibilities of the LATER outpatient clinics.

Within the Netherlands, steps in information provision have been made. A website has been built at www.later.skion.nl with information about potential risks of treatment-specific late effects, about recommendations for follow-up and about the LATER outpatient clinics.¹⁹ Next steps should thus be consistent counseling of individual survivors at the LATER clinics, development of models for transition into adult health care and provision of information to other health care professionals.

Our recommendations hopefully add to continuous increases in evidence about late adverse effects of childhood cancer and about optimal follow-up care for the young and vulnerable patient group of childhood cancer survivors.

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