Late effects of childhood cancer: Epidemiology and patient education
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Chapter 9

Summary, conclusion, general discussion and recommendations for clinical practice and future research
General discussion

The general aim of this thesis was two-fold: the first aim was to assess the prevalence and risk factors of two specific late effects of childhood cancer therapy, renal toxicity and short stature in adulthood. The second aim was to develop and evaluate a patient website for childhood cancer survivors, providing survivors with information about their past disease, treatment and especially about late effects. As part of an iterative and user-centred framework process, we first analysed the requirements, designed a website prototype, tested and evaluated the prototype with experts and end users, and performed a usability and content analysis with the website after it had been redesigned.

The studies addressing the first aim were performed in the context of the Emma Children’s Hospital/Academic Medical Center (EKZ/AMC) cohort of childhood cancer survivors, whereas the studies concerning the development and evaluation of the patient information website were carried out in the context of the Dutch Childhood Oncology Group (DCOG) Late Effects of Childhood Cancer (LATER) project. In this chapter we will briefly discuss the main findings of the studies presented in this thesis, their impact on (clinical) practice and we will provide recommendations for future research.

Main findings

Part 1: epidemiology of late effects of childhood cancer

The aim for Part 1 of this thesis was to assess the prevalence and risk factors for two types of late effects after childhood cancer: renal toxicity and short stature in adulthood. Concerning renal toxicity we performed a Cochrane systematic review and two cohort studies within the context of the EKZ/AMC cohort of childhood cancer survivors. Final height after treatment for childhood cancer was assessed within the EKZ/AMC cohort as well.

In Chapter 2 we presented a Cochrane systematic review of the literature to answer the following research question:
What is the existing evidence on the prevalence and risk factors for developing renal dysfunction and/or hypertension after treatment for childhood cancer with ifosfamide, cisplatin, carboplatin, radiotherapy involving the kidney region and/or a nephrectomy?

We were able to include 57 studies that met all inclusion criteria. Forty-eight studies (84%) suffered from methodological limitations. The prevalence of renal late adverse effects varied widely, from 0% to 84%. This large heterogeneity in reported prevalences may be caused by the diversity in studied patient populations, the prescribed treatment regimens, variations in the reported outcome measurements or outcome measurement definitions, and variations in the methodological quality of the studies. Glomerular filtration rate (GFR) was assessed in 32 of the 57 studies and an impaired glomerular function was found in 0%-50% of all assessed survivors. Of the included treatments of interest, only total body irradiation was reported as an independent risk factor for glomerular dysfunction in multivariable analyses. Other reported risk factors in multivariable analyses were concomitant treatment with aminoglycosides and vancomycin, amphotericin B, cyclosporine A, older age at treatment and longer follow-up duration. Proteinuria was present in 0% to 84% of all survivors (15/57 studies), but no study performed multivariable analysis to assess risk factors for proteinuria. Treatment with cisplatin and carboplatin were both associated with a significantly lower serum magnesium level in multivariable analyses and the reported prevalence of hypomagnesaemia varied between 0% and 29% in the six studies reporting on serum magnesium. Reported hypophosphataemia prevalences were low (range: 0%-8%; 5/57 studies), but the prevalence of impairment of the tubular phosphate reabsorption was much higher (range: 0%-63%; 11/57 studies). Higher cumulative ifosfamide dose, concomitant cisplatin treatment and nephrectomy were reported as risk factors for an impaired tubular phosphate reabsorption in multivariable analyses. Reported hypertension prevalence ranged from 0% to 18% (22/57 studies). As the large majority of the included studies had serious methodological limitations, the need for well-designed cohort studies is high. New research projects should particularly focus on complete data collection, well-defined outcome measurements and especially
on multivariate analysis methods. As the evidence gathered in this review was not conclusive, all CCS treated with cisplatin, carboplatin, ifosfamide, kidney or total body irradiation and/or nephrectomy should be included in prospective, longitudinal follow-up programs to gain insight in the prevalence and especially the risk factors for kidney disease.

In Chapter 3 we describe the results of a cross-sectional cohort study of all five-year survivors who visited the EKZ/AMC outpatient clinic. The research question we addressed was:

*What are the prevalence and risk factors for the development of renal dysfunction or elevated blood pressure in the EKZ/AMC cohort of 5-year childhood cancer survivors at their first visit to the outpatient clinic?*

We assessed the estimated GFR, albuminuria, hypomagnesaemia, hypophosphataemia and blood pressure (BP) in 1442 survivors at least 5 years after diagnosis and used multivariable logistic regression to estimate the effects of chemotherapy, nephrectomy and radiotherapy on the five included outcome measures. A diminished GFR (<90 ml/min/1.73m²) was present in 4.5% of the cohort. A higher cumulative ifosfamide dose, use of high-dose cyclophosphamide and having had a nephrectomy had the strongest association with a diminished glomerular function. Cumulative doses of cisplatin and carboplatin and time since cancer diagnosis were independent risk factors as well. No survivors required renal replacement therapy. Hypomagnesaemia was present in 36 of 534 assessed survivors (6.7%). Cumulative cisplatin dose and having had a nephrectomy were independent treatment related risk factors. For hypophosphataemia (prevalence: 3.0%) no treatment related risk-factors were found. The prevalence of albuminuria was higher: 14.5%. Cumulative ifosfamide dose and use of carboplatin were independent risk factors for the development of albuminuria. Elevated BP was found in 14.5% of all survivors, with a lower prevalence in the group of survivors treated with potentially nephrotoxic therapies than in the group treated without [12.3% vs. 18.7%; P=0.002]. Overall almost 30% of all survivors suffered from one or more kidney-related late adverse effects. This is clinically relevant as a diminished GFR, proteinuria and
hypertension are all independently associated with a higher risk of mortality in the general population.\textsuperscript{1,2} Children treated with ifosfamide, cisplatin, carboplatin, high-dose cyclophosphamide, radiotherapy including the kidney region and/or a nephrectomy should be monitored for renal function impairments. Blood pressure should be monitored in all CCS, irrespective of the received treatment.

In Chapter 4 we continued our investigations regarding late renal adverse effects with a longitudinal cohort study investigating glomerular function patterns over time in the EKZ/AMC cohort of CCS. The research question we wanted to answer was:

\textit{What are the time trends and associated risk factors for glomerular function in long-term survivors of childhood cancer in the EKZ/AMC cohort?}

As we found in Chapters 2 and 3, follow-up duration is one of the risk factors for glomerular dysfunction in CCS. From literature it is known that the decline in GFR over time is a normal and expected consequence of aging.\textsuperscript{3–5} Our study was the first to compare the glomerular function over time in survivors treated with and without potentially nephrotoxic cancer treatment (defined as cisplatin, carboplatin, ifosfamide, high-dose [HD] methotrexate, HD cyclophosphamide, radiotherapy to the kidney region and nephrectomy). We fitted multivariable linear random effects models for GFR as a continuous outcome variable, and multivariable logistic regression models for GFR as a dichotomous outcome variable. CCS treated with potentially nephrotoxic treatment had worse glomerular function than CCS treated without potentially nephrotoxic treatment, from the first moment of follow-up at 5 years up till 35 years after diagnosis. Especially ifosfamide, HD-cisplatin and nephrectomy were associated with a lower GFR and with glomerular dysfunction [GFR $<90$ ml/min/1.73m\textsuperscript{2}] in CCS, which persisted during the entire follow-up period. However, the deterioration rate of glomerular function was not higher in CCS treated with versus without nephrotoxic therapy, indicating that the initial difference between both groups at the start of follow-up must have originated from irreversible acute toxicity or from damage developed between end of treatment and the first follow-up measurement performed at least 5 years after diagnosis. As the deterioration
rates of glomerular function did not differ between these groups of survivors, a single glomerular function assessment at the first follow-up moment 5 years after diagnosis is perhaps be a better predictor for the pattern of glomerular function over time than the initial treatment regimen. Future studies should investigate the predictive value of such a measurement and should focus on the longitudinal assessment of other outcomes related to glomerular function, including proteinuria and hypertension. Until more evidence is available on the aetiology and predictors of glomerular function impairment after nephrotoxic therapy, survivors treated with potentially nephrotoxic treatment should receive regular screening of glomerular function.

In Chapter 5 we evaluated the height of all adult survivors of childhood cancer in the EKZ/AMC cohort, to answer the following research question:

*What is the risk of short stature in adulthood after treatment for childhood cancer and what are the determinants of final height?*

We were able to include 573 adult survivors of childhood cancer for whom height measurements were available at diagnosis and at follow-up in adulthood. Heights were converted to standard deviations scores (SDS) based on national age- and sex-matched reference data. At a median age of 20.3 years (range: 18.0-44.7), survivors had a significant reduced final height SDS in comparison to their height at diagnosis (mean loss of height SDS: -0.29; \( P < 0.001 \)), as well as in comparison to the general population (\( P < 0.001 \)). Short stature (defined as a height SDS \( \leq -2 \) SDS) was present in 51 of 573 survivors (8.9%). All multivariable regression analyses showed that height SDS at diagnosis is a strong determinant for final height SDS. Additionally, multivariable linear regression models on final height SDS showed that total body irradiation (TBI), cranial irradiation and spinal radiation were significant risk factors for a lower final height SDS when entered as dichotomous variables in the model. When these dichotomous variables were replaced with continuous variables representing the radiotherapy doses expressed in equivalent doses in 2 Gray fractions (\( \text{EQD}_2 \)), abdominal irradiation dose became an additional significant risk factor. Treatment with anthracyclines was also associated with a lower final height SDS, as was younger age at diagnosis.
In multivariable logistic regression analyses of determinants associated with short stature and/or receiving growth hormone (GH) we identified total body irradiation, cranial irradiation and spinal irradiation as important risk factors, as were their cumulative doses in EQD₂. Children treated with total body irradiation, cranial irradiation or spinal irradiation should be monitored periodically for growth velocity, body weight, the development of GH deficiency and the onset of puberty, so that a paediatric endocrinologist can instigate timely interventions when necessary.

**Part 2: methods for the development and evaluation of a patient information website for childhood cancer survivors**

In Part 2 of this thesis we set out to develop and evaluate a patient information website aimed at childhood cancer survivors and their family. We first assessed their survivorship-related information needs. In the next step we developed a concise framework for the development and evaluation of patient information website and implemented the framework in a case study on the DCOG LATER website. As a final step we evaluated the perceived usability and satisfaction with website content in a survey amongst childhood cancer survivors.

In **Chapter 6** we presented the results of a survey study amongst childhood cancer survivors and their parents to answer the research question:

*What are the information needs of long-term childhood cancer survivors and their family and are there identifiable determinants for differences in information needs and health-related use of the Internet?*

We asked 160 childhood cancer survivors or their parents to complete a survey about their baseline characteristics, their [health-related] Internet use and their requirements for a website about late effects. We asked respondents to rate potential requirements, defined as 22 items involving different kinds of information, on a 5-point Likert-scale (1: very unimportant to 5: very important). One hundred and forty five respondents completed the questionnaire (90.6%), of whom 72 were parents of younger survivors (aged < 12 years), 49 were adult
survivors [aged ≥18 years] and 24 were adolescent survivors [aged ≥12 and <18 years]. Of the 69 respondents that visited a late effects outpatient clinic, 20 patients [29%] had questions left after the consultation. Approximately 50% of the respondents used the Internet for personal health education. However, only very few respondents stated to search the Internet for information on late effects of childhood cancer. Of the 15 respondents that did only 4 were able to find the information they were searching for. Respondents that did search for late effects more often indicated they had questions left after a consultation \( P < 0.01 \).

Respondents rated the majority of the 22 possible information items as important. Three items received a median score of very important: information on recognizing late effects, personalized information on late effects treatment and information on self-care regarding late effects. Parents of survivors gave higher scores for information items than survivors themselves. On the question “Would you visit a late effects website when it is available?“ only 6 respondents answered negatively.

Survivors often have knowledge deficits regarding their primary diagnosis and treatment and are unaware of the risk of late adverse effects, hampering their ability to seek appropriate care and to participate in designated follow-up programs. The results of this survey confirm this, as only a small proportion of survivors stated to use the Internet as an information source regarding late effects. However, the high rating for almost all information items by the study participants and the fact that most respondents would visit a late effects website when available indicate the need for a patient information website for childhood cancer survivors. Such a website should address the information needs of both parents of survivors and adolescent/young adult survivors of childhood cancer and focus on personalized information on late effects, follow-up strategies and preventive healthcare.

The application of user-centred and iterative design, development and evaluation is an essential component of modern day website development. In Chapter 7 we proposed a concise and practical framework for the development of patient
information websites and implemented the framework in the development of the DCOG LATER website, to answer the following the research question:

*How can a limited subset of the Website Developmental Model for the Healthcare Consumer (WDMHC) Framework be implemented to deliver a high-quality website with few usability problems, aimed at a specific patient population?*

The WDMHC framework is a framework for the iterative development and evaluation of websites for healthcare consumers in the broadest sense, consisting of more than fifteen steps in four phases that incorporate well-documented user-centred design principles. However, for projects with a limited scope and with limited resources the WDHMC framework is too extensive and costly. In this study we hypothesized that implementation of a subset of the WDHMC principles is sufficient for the development and evaluation of a patient information website aimed at a specific medical patient population, in this case study childhood cancer survivors, whilst maintaining high usability, high quality content and minimizing the burden on a project's resources. For our subset of the WDMHC we decided a priori that we had to include at least one method for the requirements phase, the website development phase and for the evaluation phase. We then selected those methods that we reckoned to give the best results with the lowest associated costs. We made one exception to this premise: we included the think aloud method, known for its high costs, as we wanted to include at least one end user evaluation method to test whether end-users could read, understand the website and would trust the website content. Our multifaceted approach consisted of six steps in three phases: 1) information needs analysis (described in chapter 6), mock-up creation and focus group; 2) website prototype development; 3) heuristic evaluation and think aloud analysis.

Based on the results of Chapter 6 we created mock-ups of the website, including a search structure where survivors could search information in a linked network of diagnoses, their associated treatments and the potential late effects caused by these treatments. During a focus group with survivors, parents of survivors, a paediatric oncologist and two human factors and usability experts these mock-ups were received very positively and based on the discussions a prioritization of
requirements could be made. A first prototype of the website was developed by an external web design company. This prototype was evaluated with a heuristic evaluation performed by three double experts (knowledgeable both in the field of human factors engineering and in the domain of interest, in this case childhood cancer survivorship). Twenty nine unique usability problems were discovered using Nielsen’s set of heuristics, of which thirteen were found by more than one evaluator or were perceived as a major usability problem (severity rating $> 2$). In the think aloud evaluation eight potential end users of the website completed three scenarios that covered all website functionality. The testers encountered 67 usability issue occurrences which could be classified in to eleven unique usability problem types. As both usability evaluations were carried out simultaneously we could compare the results of both methodologies. All the major usability issues discovered in the heuristic evaluation were likewise revealed by the think aloud user test sessions and vice versa. The four additional issues revealed by heuristic evaluation concerned cosmetic design flaws, whereas the two additional problems revealed by think aloud were related to website content. However, the costs for the think aloud analysis were much higher than the costs of the heuristic evaluation. Heuristic evaluation may therefore be sufficient to discover all usability problems on a patient information website, especially when double experts are used as evaluators.

Overall, the implementation of the user-centred framework in the case study on the DCOG LATER website resulted in the delivery of a prototype website that closely matched the expectancy of the end-users and resulted in relatively few usability problems during end-user testing. All usability problems were translated into redesign recommendations which were communicated as feedback to the website developers. The redesigned website was launched in 2009 and reached over 12,000 unique visitors and over 35,000 page views in 2012.

In Chapter 8 we present the results of the final evaluation of the DCOG LATER website, in which we addressed the following research question:

*What are the perceived usability and satisfaction with content of a national patient information website aimed at childhood cancer survivors and what are
possible determinants related to website usability and content satisfaction?

To answer this research question we recruited childhood cancer survivors and their parents through the EKZ/AMC late effects follow-up program and via online media to complete an online survey regarding their baseline characteristics, medical decision style and the usability and content of the website. To measure perceived usability we used the System Usability Scale [range: 0-100],\textsuperscript{13} for the content rating we constructed a 6-item scale [range: 1-5; Cronbach's $\alpha$: 0.83]. Respondents could also give free-text comments, which were analysed qualitatively. Ninety eight respondents completed the questionnaire, their median age was 41 years [range: 17-58 years]. The mean SUS-score for perceived usability was 72.5 [95%-CI: 69.2-74.9] and the mean content rating was 3.7 [95%-CI: 3.5-3.8]. It was not possible to associate any patient characteristics with the SUS score or the content rating using multivariable analyses, which indicates that there were no subgroups identifiable that rated the website significantly higher or lower than the rest of the study population. However, the qualitative analysis of the free-text comments provided additional insights in potential usability issues and flaws in the website's content. Several respondents, predominantly with a higher education, requested more in-depth and more scientifically based information on late effects of childhood cancer treatment. Additionally, several survivors stated that they preferred a higher level of detail in the targeting of information, like exact dose-toxicity relationships and the risks of late effects after a combination of different treatments. As this evidence is often not available, the website should explicitly state what evidence is available, for example by adding a “What do we already know” and “What is not known yet” paragraph to all late effects information pages, in a way similar to evidence summaries in guidelines and systematic reviews.

Strengths and limitations of our studies

Part 1: epidemiology of late effects of childhood cancer

Strengths of the Cochrane systematic review presented in Chapter 2 include the extensive search strategy that was deployed to find all relevant available
evidence and the independent selection of eligible studies, data extraction from and quality assessment of the included studies by two reviewers. The selection of relevant clinical outcomes reported the most often and the most consistently may have introduced reporting bias, as the reporting of a certain outcome in a study may be directly related to the nature and direction of its results. Furthermore selection bias of studies may have occurred as we only included studies written in English, German, French, Italian and Spanish.

One of the most important strengths of the EKZ/AMC cohort, studied in Chapters 3 to 5, is the long and near-complete follow-up of childhood cancer survivors. All survivors are identified and included through the local Childhood Cancer Registry (CCR), which was established in 1966. The CCR tracks all patients diagnosed with and treated for a paediatric malignancy in the EKZ/AMC. As patients are already included at the time of initial diagnosis, selection bias by survivorship, outpatient clinic visits or the diagnosis of late adverse effects are effectively ruled out. Another strength is that comprehensive and detailed treatment information is available from the registry for all survivors in the cohort, independent of their follow-up status. This makes it possible to assess potential attrition bias by comparing demographic and treatment characteristics between survivors who did and did not visit the outpatient clinic. The fact that all outcomes registered in our cohort are based on clinical follow-up poses an additional strength in comparison to other survivor cohorts that obtain outcomes from questionnaires and/or population registries.14–16

Another strength of studies presented in Chapter 3 to 5 is the use of multivariable regression analyses. As shown in the systematic review in Chapter 2, the majority of studies on late adverse effects after childhood cancer do not adjust their analyses for potential confounders. This poses serious limitations to the interpretation of risk factor analyses, as univariable analysis may both over- and underestimate the real effect of a risk factor. Due to the large size of our cohort and the availability of detailed information on the types and doses of chemo- and radiotherapy that survivors received, we were able to make accurate, multivariable models for the assessment of determinants for renal function and
final height.

An additional strength of Chapter 5 was the use of the equivalent dose in 2-Gray fractions \([\text{EQD}_2]\). The association between radiotherapy and late effects is often analysed using dichotomous variables (yes/no), dose categories or total dose. However, the development of late effects is also dependent on the fractionation dose.\(^{17}\) The \(\text{EQD}_2\) accounts for both the total- and the fractionation dose, adjusting for the biological effect of differences in dosage. This allows for a more precise assessment of the relation between radiotherapy exposure and late effects and makes it easier to compare patients treated with different protocols over time.

An important limitation of the EKZ/AMC childhood cancer survivor cohort is that there is no readily available control population. Due to the clinical-based longitudinal follow-up it is not possible to assess controls in a similar fashion as survivors. In Chapters 3 and 4 we tried to solve this by comparing risks between treatment groups (those treated with and without potentially nephrotoxic treatment). In Chapter 5 we were able to use national reference data to compare the height in our cohort with the general population. Furthermore the sample sizes of patients in some of the treatment groups were relatively small, resulting in limited power to detect an effect of the treatment or its cumulative dose on renal toxicity or final height. Another limitation of the EKZ/AMC cohort is that it is hospital-based and not population-based, which may have influenced the external validity of the reported prevalences and risk estimates. Future nationwide studies performed by the SKION LATER initiative will eliminate these limitations.

The use of estimation formulas for the calculation of estimated glomerular filtration rate was a limitation in the study results of Chapters 3 and 4. It is well established that the Schwartz- and the CKD-EPI formulas are not as reliable as the golden standard clearance measurements, such as the \(^{51}\text{Cr}-\text{EDTA}\) or \(^{99}\text{Tc}-\text{DTPA}\) clearance. However, these golden standard measurements are cumbersome, invasive tests involving radioisotopes, rendering them unsuitable for application in a screening setting. In a systematic review comparing the performance of the CKD-EPI and the MDRD formulae, Earley et al. found that the CKD-EPI formula
was the estimation method of preference for public health and general clinical practice usage.¹⁸

**Part 2: methods for the development and evaluation of a patient information website for childhood cancer survivors**

The core strength of the studies described in Chapters 6 to 8 is the structured approach in which we applied user centred development principles by involving potential end users throughout the complete process of the development and evaluation of a website aimed at childhood cancer survivors. By firstly identifying the user needs, discussing those needs during a focus group, and by iteratively evaluating and redesigning the prototype website we were able to deliver a website that childhood cancer survivors and their parents were satisfied with. With the applied and validated methodology as described in the case study in Chapter 7 we provide developers with a small, clear and easily applicable framework for the development of healthcare websites aimed at specific medical populations, that can overcome the drawbacks of more general and extensive frameworks as the Website Developmental Model for the Healthcare Consumer framework.¹⁰,¹¹ Another strength of the website is that all content on the website was developed in a cooperative fashion by paediatric oncologists, late effects specialists and members of the Dutch Childhood Cancer Parenting Organization, ensuring that all information offered was correct as well as easily apprehensible for laymen.

A possible limitation of the studies in the second part of this thesis was the scope of the website under study. Use of the website was uncomplicated as the system mainly consisted of static information content with some dynamic behaviour implemented through JavaScript. Although user-centred, iterative development and usability evaluation testing is essential irrespective of the size and scope of the website, future studies should validate our deployed methodology during the development and evaluation of more advanced patient information websites, targeting larger and different patient populations, that offer a larger amount of content and require more complex navigation structures and hence more
complex user interactions. The methodology could also be validated in other online healthcare applications, including patient self-management tools and web-based personalized health records.

Furthermore, selection bias may have influenced the results of the studies in chapter 8, as the majority of study participants were either patients who previously participated in the survey in Chapter 6 or volunteers recruited via the internet. Although we recruited additional participants through the EKZ/AMC outpatient clinic, it is possible that the study group represented a subgroup of survivors with a higher than average interest in their previous disease and the related late effects and who may potentially be willing to give better ratings for the website.

**Recommendations for practice**

**Part 1: epidemiology of late effects of childhood cancer**

The studies presented in this thesis have implications for both future cancer patients and survivors. Chapters 2 to 5 show that long-term survivors of childhood cancer are at risk for the development of renal function impairment, elevated blood pressure and growth impairment. Both survivors and healthcare professionals should be aware of the risks of these treatment-induced late effects. Childhood cancer survivors should receive individualised screening and appropriate follow-up care in order to detect the development of these potential late effects as early as possible. Early detection can prevent deterioration of the affected organ systems by providing medical- or lifestyle interventions, ultimately maintaining or increasing quality of life of childhood cancer survivors.

Based on the results of Chapters 2 to 5 we can make the following recommendations for screening:

- Childhood cancer survivors treated with cisplatin, carboplatin, high-dose cyclophosphamide abdominal radiotherapy or a nephrectomy should be regularly screened for an impaired glomerular or tubular function.
• All childhood cancer survivors should receive regular screening for hypertension.
• Childhood cancer survivors treated with cranial, spinal or total body irradiation should be monitored regularly for growth velocity, body weight and the development of growth hormone deficiency.

Studies like the ones presented in the first part of this thesis provide new evidence regarding late effects continuously. To assure that the cumulative evidence will be applied in clinical practice, clinical practice guidelines need to be developed and updated on a regular basis as well. Fortunately several initiatives have already started to translate the available evidence into guidelines for surveillance of late effects in childhood cancer survivors. In the Netherlands the national evidence-based guidelines for follow-up after treatment for childhood cancer were published in 2010, providing risk-based follow-up recommendations based on the treatment exposures. A more recent and global approach is the initiative of the International Guideline Harmonisation Group for Late Effects of Childhood Cancer, an international collaboration for the harmonisation of the different late effects surveillance guidelines available in the different participating countries. The harmonization process starts with a comparison of recommendations from all available (national) guidelines. For all concordant and discordant recommendations supporting evidence is collected from the guidelines or from the scientific literature, after which uniform recommendations are formulated. Gaps in knowledge are added to a research agenda. In order to keep the guidelines up to date, the group plans to update the guidelines bi-annually. An online platform could facilitate this (international) process, for example by providing a database for the systematic collection and appraisal of new evidence and collaboration tools like wiki’s for the continuous updating of the guidelines to which the new evidence leads.

Part 2: methods for the development and evaluation of a patient information website for childhood cancer survivors

The DCOG LATER patient information website is one of the first websites in the world focusing on targeted, online patient education based on survivors’ previous
diagnosis and treatment. Additionally the website gives general information on late effects and late effects care in the Netherlands. Although the availability of such a website provides a continuous opportunity for childhood cancer survivors and healthcare professionals to find information regarding survivorship issues and late effects, it is by no means a definitive solution to counter knowledge deficits and lack of awareness about late effects among survivors. During survivor’s visit to the LATER outpatient clinics the attending physician should provide individualised counselling and educate survivors on the risks of late effects and the importance of a healthy lifestyle.

The upcoming DCOG LATER Q2008 study, which will start in 2013, will provide a perfect opportunity for counselling and educating childhood cancer survivors. In this study all approximately 7000 Dutch childhood cancer survivors will be invited to visit a LATER outpatient clinic to assess long-term morbidity. Trained data managers from the seven Dutch paediatric oncology centres collect detailed information from patient records on survivors’ medical history, tumour diagnoses and the received treatments. All data is registered in a web-based central registry compliant with the Dutch privacy regulations; all information that can be linked to an individual patient is removed and replaced with a unique but anonymous patient identifier. Only the centre that coordinates the care for a survivor can link this patient identifier to the patient’s personal details. This web-based registry also offers advanced functionality to conduct questionnaires amongst study participants. Physicians can provide survivors with a personalized login and password with which they can securely access the registry system to complete the questionnaires they are invited for.

The infrastructure that is now readily available for the LATER registry would be perfectly fit to integrate with the patient information website as described in Part 2 of this thesis. As survivors currently have to remember what types of treatment they received in order to be able to get targeted information about the late effects they are at risk of, the wealth of information available in the online registry can serve to provide targeted or even tailored patient education regarding late effects. The questionnaire functionality also provides a flexible
yet powerful platform to address new patient related late effects research questions. In the near future the registry will be extended to allow the data entry of a pre-defined set of all relevant clinical outcomes related to childhood cancer survivorship. When functionality for survivors would be added to communicate all the information in the registry back to the survivors, in combination with additional (education) resources, the LATER registry web application can form the basis of an electronic, personalized health record (PHR) that can be accessed by both the patient and the physician. Such an online system could then be extended to be used as a communication channel between survivors and health care providers, for example to share the results from laboratory tests or other screening modalities or to keep a patient diary that can be perused by the physician. It could also serve as community-like platform where survivors can communicate with each other. Interventions for late effects-related issues (e.g. psychosocial- or health behaviour interventions) could be offered on the same site as well. For health care professionals the platform could be used for communication and collaboration as well, for example for the development and updating of guidelines [see the previous section], the discussion of treatment protocols, the recruiting of patients of trials and for the dissemination of new insights regarding paediatric oncology and childhood cancer survivorship.

However, the initial focus should be on the provision of survivors with tailored information regarding the risks of late effects, as this can increase adherence to lifestyle recommendations, which ultimately increases the quality and duration of survivorship. In addition, well-informed survivors may be more eager to visit the long-term follow-up outpatient clinics and may be more compliant with prescribed medication and lifestyle advices.

**Recommendations for future research**

**Part 1: epidemiology of late effects of childhood cancer**

Although the studies in this thesis answered several questions regarding the prevalence and risk factors of renal function, elevated blood pressure and growth impairment, several recommendations can be formulated based on the
results of the presented studies and the remaining gaps in knowledge. Studies investigating late adverse effects after treatment for childhood cancer should: 1) incorporate multivariable analyses when assessing potential risk factors to correct for possible confounders; 2) include pre-treatment data on the outcome of interest as a confounder for the correct interpretation of tumour- and treatment related risk factors and 3) assess the development of late effects over time to be able to provide evidence-based timeframes for the frequency of follow-up screening.

Future studies investigating renal function should focus on the predictive value of the first glomerular function assessment five years after diagnosis, as this assessment may be a sufficient predictor for glomerular function over time, enabling a reduction in screening frequency for survivors at low risk for glomerular dysfunction. More research is needed regarding the development of comorbidities over time, including proteinuria and hypertension, and on their influence on glomerular function. Additional risk factors should be evaluated for the development of hypertension, including cranial irradiation and genetic variations that are already identified as risk factors for cardiotoxicity. The impact of varying radiotherapy doses (in EQD\textsubscript{2}) should be evaluated for the development of renal function impairments and hypertension. Regarding growth, prospective studies are needed to establish the effect of growth hormone treatment on growth velocity in childhood cancer survivors with growth hormone deficiency. Additionally, adding delta arm length (D-SDS arm) and/or sitting height ratio to total body height may be interesting in the future to validate catch-up growth after cranial versus spinal radiation therapy.

**Part 2: methods for the development and evaluation of a patient information website for childhood cancer survivors**

Based on the results of the studies in the second part of this thesis, several recommendations for future research can be proposed. The framework for the development and evaluation of patient information websites as described in Chapter 7 should be implemented and evaluated in projects with a larger scope.
Although the framework was created specifically for the development of patient information websites aimed at pre-defined and specific patient populations such as childhood cancer survivors, the relatively small size and complexity of the website and the limited amount of interaction it required may have contributed positively to the results of implementation of the framework in achieving a website that was appreciated by childhood cancer survivors.

Future research should also determine the effect of the content of educational materials written for childhood cancer survivors. Although it is generally accepted that raised awareness about late effects can positively influence survivor’s ability to search appropriate care, engage in dedicated follow-up programs and increase the adherence to a healthy lifestyle, there have been no studies that assessed the influence of [online] educational materials on changes in patient behaviour or clinical outcomes either quantitatively or qualitatively. There is also very little evidence on the psychological impact of offered information. As late effects can have a profound impact on the quality of life, the discovery that one has an increased risk for these late effects through online education materials may cause anxiety and stress. Psychological distress seems correlated with coping variables like suppression of negative thoughts and low optimism. A web-based, personalized electronic health record for childhood cancer survivors could also serve as a platform for research on these kind of psychosocial outcomes. A randomized trial where survivors are educated using varying educational materials, to assess the impact of different ways of informing patients on psychosocial outcomes like anxiety and stress, would be one of the possibilities of such a platform.

References


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