

Physical, social and school functioning in pediatric patients during early clinical remission of cancer

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ABSTRACT

Background: Due to increasingly rigorous multimodal therapies the overall survival rates of all childhood cancers have improved drastically. However, these multimodal therapies have significant short- and long-term impact on health and wellbeing in childhood cancer survivors. Therefore, there is a growing demand for outcome measures which reflect a patients overall wellbeing and subjective evaluation of health status and quality of life. Assessing physical, social and school functioning in the clinical remission phase is highly relevant as this is often the moment in which children return to their daily activities.

Aim: To assess the level of physical, social and school functioning in pediatric patients during early clinical remission of cancer compared to norm values.

Methods: For this cross-sectional study, pediatric patients (5-18 years old) during early clinical remission of cancer were recruited from the outpatient clinic of the Princes Maxima Center. Physical, social and school functioning were assessed using the Pediatric Quality of Life Inventory Generic Core Scales questionnaire. Children (8-18 years old) or parents (of children 5-7 years old) were asked to fill in the online questionnaire. Scores on physical, social and school functioning were compared with norm values.

Results: A total of 64 patients were included in this study. Pediatric patients during early clinical remission of cancer between 5-7 years old reported significant lower physical ($p < 0.001$), social ($p = 0.017$) and school functioning ($p = 0.004$) compared to healthy age-matched controls. No significant differences were found on physical and school functioning among the older pediatric patients (8-18 years old) during early clinical remission of cancer compared to healthy controls.

Conclusion: The younger pediatric patients (5-7 years old) during early clinical remission of cancer might experience lower physical, social and school functioning compared to healthy controls. They may experience short and/or long term side effects of the treatment.

Implication of key findings: Individual interventions regarding physical and social functioning might be beneficial among the younger children during early clinical remission of cancer. In which physiotherapists and/or social workers can play a significant role.

Key words: *child, neoplasms, remission induction, quality of life*

INTRODUCTION

Cancer is the second leading cause of death in children from five to 14 years old.¹ The incidence of childhood cancer is 160.000 per year worldwide.² Childhood cancer types differ from adult cancer types.² The most common types of pediatric cancers are leukaemia (34%), brain or central nervous system tumors (23%), and lymphomas (11%).² Furthermore, certain types of childhood cancer arise from embryonic cells, such as neuroblastoma, Wilms tumor or nephroblastoma, medulloblastomas, rhabdomyosarcomas and retinoblastoma.³ Treatment modules vary among the different types of cancer, although the most frequent applied treatment options are chemotherapy, surgery, radiation therapy, and stem cell or bone marrow transplantation.⁴ Due to increasingly rigorous multimodal therapies the overall five-year survival rates of all childhood cancers have improved drastically from below 60% to $\geq 80\%$ over the past twenty years.⁴

However, these multimodal therapies have significant short- and long-term impact on health and wellbeing in childhood cancer survivors.⁴ Consequently, a growing number of studies on morbidity and mortality rates in pediatric patients with cancer have been published over the years.⁴⁻⁶ For example, studies indicate that survivors of childhood cancer have an increased risk of early mortality, second malignancies, musculoskeletal abnormalities, and other physical impairments or diseases.⁵ However, there is a lack of knowledge regarding validated outcome measures which reflect the patients overall wellbeing and subjective evaluation of their health status and quality of life (QoL)⁷, such as reduced physical performance, emotional wellbeing, school participation, chronic fatigue and pain.^{5,8} Type of cancer, type of treatment and disease duration (in)directly affect health status and the level of QoL as a result of the impact and side effects caused by the treatment.^{6,7} Furthermore, patient characteristics such as age at assessment and gender seems to have an association with reported QoL.⁷

Various studies reported decreased QoL, social participation, physical functioning or performance, reduced motor performance and functional capacity in pediatric patients with cancer.^{7,9-14} However, the majority of these studies included children during treatment^{7,10,12-14} or more than five years after treatment^{7,9,11,12,14}. Still very little is known regarding these outcome measures during the clinical remission phase (0-5 years after treatment). During this phase children should return to their daily life activities and participate in society again, such as school attendance, sports and social life. Assessment of the level of physical, social and school functioning is vital during this period as this is a fragile period in which additional interventions might be needed to support or improve these outcomes, if these levels are affected. As these outcome measurements during this phase are very scarce, research is needed to attain more knowledge regarding the degree of reduction.

Therefore, the primary objective of this study is to assess the level of physical, social and school functioning in pediatric patients during early clinical remission of cancer

compared to norm values. Additionally, several clinical and theoretical relevant patient characteristics, such as type of cancer, type of treatment, disease duration, age and gender will be analysed as possible associating factors for the level of physical, social and school functioning.

METHODS

Study population and domain

The Princes Maxima Center in Utrecht is a center specialized in pediatric oncology. All patients during early clinical remission of cancer were invited to complete online questionnaires as part of their usual care. Patients were included in this cross-sectional study from June 2004 until May 2017. The following inclusion criteria were applied: (1) age between five to 18 years old, (2) in early clinical remission of cancer treatment (within the first year after treatment stops), and (3) visiting the outpatient clinic of the Princes Maxima Center for clinical remission follow-up appointments. The following exclusion criteria were applied: (1) did not have an e-mail address or, (2) did not have sufficient Dutch language skills.

Data collection

The KLIK (Dutch acronym for Quality of Life in Clinical Practice) method is introduced in 2012 as a new part of standard care. This online system (www.hetklikt.nu) enables monitoring and discussion of electronic patient reported outcome measurements (PROMs) regarding QoL.^{15,16} Parents of eligible patients were approached by the KLIK coordinators (2 research psychologists) within 1 to 3 weeks after diagnosis. Verbal and written information regarding this study were given during either inpatient hospitalization or outpatient clinic visit, or by phone. Patients and/or parents gave consent on the website (www.hetklikt.nu) (appendix I) whether they agree to their data being used for scientific purposes. Medical information regarding type of cancer, type of treatment and disease duration were collected from medical records. Disease duration and treatment regimens were established based on type of cancer and severity according to the specified protocol compiled by the Dutch Childhood Oncology Group, which can be found on the website (www.skion.nl). Furthermore, patient characteristics such as age, gender, length and weight were extracted from the medical records. All data were extracted from medical records under supervision of the principle investigator of this study (S. L. Nijhof) and an independent researcher (A. van Eijndhoven). This study was approved by the Medical Ethical Committee at the University Medical Center Utrecht (UMCU) (protocol number: 16-707/C).

Outcome measurements

Physical, social and school functioning were measured using the Dutch version of the Pediatric Quality of Life Inventory Generic Core Scales (PedsQL-GCS) (appendix II).¹⁷ The PedsQL-GCS contains four subscales: physical, emotional, social and school functioning. The internal consistency of the Dutch version of the PedsQL-GCS varies from 0.82-0.85 on total scores, 0.61-0.69 on physical functioning, 0.67-0.76 on social functioning and 0.53-0.62 on school functioning.¹⁷ Research has shown that the Dutch version of the PedsQL-GCS is able to differentiate between children with and without chronic health diseases.¹⁷ The PedsQL-GCS included child self-reports (8-18 years old) and parent proxy reports (5-7 years old). Norm

values of healthy children were used to determine whether the outcomes of the PedsQL-GCS among the pediatric patients during early clinical remission of cancer differed from normal health related QoL levels. Norm values regarding the PedsQL-GCS were used from the study of van Engelen et al.¹⁷ These norm values were assessed among 496 Dutch children between 5 – 18 years old. Van Engelen et al also used child self-reports (8-18 years old) and parent proxy reports (5-7 years old) of the PedsQL-GCS.¹⁷

Data analysis

Statistical Packages for Social Sciences (SPSS version 22, Inc, Chicago, Illinois, USA) was used for all analyses. Differences in clinical and patient characteristics between participants and the reference group were examined with t-tests for continuous variables and χ^2 tests for categorical variables. Participants were not able to complete the questionnaire unless they answered all the items. Therefore, corrections for missing data were not applicable. The assumption of equality of variances was tested using a histogram, Q-Q plot and the Kolmogorov-Smirnov test.¹⁸ The Mann Withney U test was used to compare the scores on the subscales physical, school and social functioning on the PedsQL-GCS with norm values assessed by Engelen et al¹⁷, since the data was not normally distributed. Univariate regression analysis was performed to identify possible associations between clinical or patient characteristics and physical, social and school functioning among pediatric patients during early clinical remission of cancer. Possible associating factors were entered to the stepwise multivariate regression model if the p-value was below 0.15.¹⁹ All tests were two-sided and considered significant if $p < 0.05$.^{18,20} Based on sample size calculation the number of participants required for the study was 64 (appendix III).²¹

RESULTS

Patient characteristics

The PedsQL-GCS questionnaire was completed by 64 pediatric patients during early clinical remission of cancer. The response rate of the questionnaire was 100%. Patients in early clinical remission of cancer differed from the healthy pediatric controls in age ($p < 0.001$). The healthy controls were mostly between the age of 8-12 years old (44.2%), whereas patients were mostly between the age of 5-7 years old (40.6%). Therefore, comparison with norm values has been done between children belonging to the same age group. Gender was equally distributed in both groups. Patient and healthy control characteristics are shown in Table 1.

Physical, social and school functioning compared to norm values

Children from the age of 5–7 years old during early clinical remission of cancer had a significant lower score on the subscale physical functioning (median=71.9, IQR=53.1–87.5, $p < 0.001$) compared to healthy age-matched controls (median=90.6, IQR=82.0–93.8). Furthermore, significant differences were found in social and school functioning between patients from 5-7 years old (median=80.0, IQR=60.0–90.0, $p=0.017$; median=75, IQR=65.0–90.0, $p=0.004$ respectively) and healthy age-matched controls (median=90.0, IQR=75.0–100.0; median=85.0, IQR=76.3–95.0 respectively). No significant differences were found between children during early clinical remission of cancer in the age category 8-12 years old and the age category 13-18 years old compared to healthy controls on the subscales physical ($p=0.118$; $p=0.900$ respectively), social ($p=0.497$; $p=0.127$ respectively) and school functioning ($p=0.682$; $p=0.777$ respectively). Median scores and interquartile ranges (IQR) are presented in Table 2.

Factors associated with physical, social and school functioning

Age at the moment of assessment and disease duration in months were considered as possible associating factors for the level of physical and social functioning among children during early clinical remission of cancer and were therefore entered to the stepwise multivariate regression model. Furthermore, gender was added to the stepwise multivariate regression model for the level of social functioning. Univariate regression analysis showed no possible associating clinical and patient characteristics in pediatric patients for the level of school functioning. Therefore, no model for univariate or multivariate regression to assess associations with the level school functioning among pediatric patients during early clinical remission of cancer could be computed.

Disease duration in months is significant negatively associated with physical functioning (regression coefficient = -0.629, $p=0.039$) and social functioning (regression coefficient = -0.601, $p=0.024$) in all pediatric patients during early clinical remission of cancer. Furthermore, age at the moment of assessment is significant positively associated with social

functioning (regression coefficient =1.058, p=0.028) among pediatric patients during early clinical remission of cancer. The explained variation on the level of physical functioning by disease duration in months is 0.067. Disease duration in months and age at assessment explained 0.201 of the variation on the level of social functioning. The calculated regression coefficients with 95% confidence intervals are shown in Table 3.

Table 1. Descriptive statistics and clinical characteristics of pediatric patients during early clinical remission of cancer compared to healthy pediatric controls.

	<i>Pediatric patients during early clinical remission of cancer (n = 64)</i>	<i>Healthy pediatric controls (n = 496)</i>	
	N (%)	N (%)	p-Value
Sex (male)	32 (50.0%)	227 (45.8%)	0.382
Age in years – M (SD)	9.4 (4.1)	11.4 (4.4)	<0.001
Age			<0.001
- 5 - 7 years old	26 (40.6%)	92 (18.5%)	
- 8 – 12 years old	23 (35.9%)	219 (44.2%)	
- 13 – 18 years old	15 (23.4%)	185 (37.3%)	
Length in cm – M (SD)	139.4 (24.2)	NA	
Weight in kg – M (SD)	39.3 (23.6)	NA	
Body Mass Index in kg/m ² – M (SD)	18.6 (4.5)	NA	
Type of cancer		NA	
- Neuroblastoma	10 (15.6 %)		
- ALL	17 (26.6%)		
- Wilms tumor	11 (17.2%)		
- Hodgkin lymphoma	6 (9.4%)		
- Others	20 (30.3%)		
Type of treatment		NA	
- Chemotherapy	29 (45.3%)		
- Surgery	4 (6.3%)		
- Chemotherapy + surgery	9 (14.1%)		
- Chemotherapy + radiation therapy + surgery	9 (14.1%)		
- Chemotherapy + stem cell transplantation	3 (4.7%)		
- Others	10 (15.6%)		
Disease duration		NA	
- 0 – 6 months	15 (23.4%)		
- 6 – 12 months	12 (18.8%)		
- 12 – 24 months	16 (25.0%)		
- > 24 months	21 (32.8%)		

*N = number, M = mean, SD = standard deviation, cm = centimeter, kg = kilogram, m = meter, NA = not applicable

Table 2. Physical, social and school functioning in pediatric patients during early clinical remission of cancer compared to healthy pediatric controls.

	Pediatric patients in clinical remission of cancer		Healthy pediatric controls		p-Value
	N	median [IQR]	N	median [IQR]	
Physical functioning					
- 5-7 year	26	71.9 [53.1 – 87.5]	92	90.6 [82.0-93.8]	<0.001**
- 8-12 year	23	81.3 [62.5 – 96.9]	219	87.5 [78.1 – 90.6]	0.232
- 13-18 year	15	89.1 [61.7 – 100.0]	185	87.5 [78.1 – 93.8]	0.900
Social functioning					
- 5-7 year	26	80.0 [60.0 – 90.0]	92	90.0 [75.0 – 100.0]	0.017*
- 8-12 year	23	90.0 [70.0 - 100.0]	219	90.0 [80.0 – 95.0]	0.710
- 13-18 year	15	100.0 [85.0 - 100.0]	185	95.0 [82.5 – 100.0]	0.127
School functioning					
- 5-7 year	26	75.0 [65.0 – 90.0]	92	85.0 [76.3 – 95.0]	0.004*
- 8-12 year	23	85.0 [70.0 – 90.0]	219	80.0 [70.0 – 85.0]	0.601
- 13-18 year	15	67.5 [55.0 – 100.0]	185	75.0 [65.0 – 85.0]	0.766

N = number of individuals, IQR = interquartile range, **=p<0.001, *=p<0.05

Table 3. Standardized and unstandardized betas for multiple linear regression evaluating the association between patient characteristics and disease duration with physical, social and school functioning among pediatric patients during early clinical remission of cancer.

	Physical functioning		Social functioning		School functioning
	Standardized Beta	Regression coefficient (95% CI)	Standardized Beta	Regression coefficient (95% CI)	
Age at the moment of assessment in years	0.122	NA	0.272*	1.058* (0.118; 1.999)	Not entered
Gender <i>Boys (ref. girls)</i>	Not entered	Not entered	-0.148	NA	Not entered
Disease duration in months	-0.258*	-0.629* (-1.226; -0.032)	-0.280*	-0.458* (-0.853; -0.063)	Not entered

CI = confidence interval, * = $P < 0.05$, NA = not available, Not entered = not entered in the stepwise multivariate regression model, ref. = reference

DISCUSSION

This cross-sectional study assessed the level of physical, social and school functioning among pediatric patients during early clinical remission of cancer compared to norm values. Pediatric patients during early clinical remission of cancer within the age range 5-7 years reported significant lower physical, social and school functioning compared to healthy age-matched controls. Furthermore, disease duration seems to be negatively associated with the level of physical and social functioning among all pediatric patients during early clinical remission of cancer in this study.

Although the pediatric patients in this study were in early clinical remission, they may already experience short and/or long term effects of the cancer and its treatment. For example we know that chemotherapy treatment for childhood acute lymphoblastic leukemia (ALL) can result in neurotoxicity of both the central and peripheral nervous system.²² According to Harila – Saari et al. children with ALL have adverse effects of chemotherapy treatment in the entire motor neuron pathways.²³ This side effect of chemotherapy treatment, known as the vincristine neuropathy,²⁴ might explain the lower level of physical functioning among the younger pediatric patients during early clinical remission of cancer after chemotherapy treatment. The lower reported physical functioning among pediatric patients within the age range 5-7 years is in line with the studies of Rueegg et al. and Ness et al., which reported lower physical performance and physical activity in childhood cancer survivors.^{9,25} Ness et al. assessed self-reported physical performance limitations among 11481 childhood cancer survivors compared to healthy siblings.²⁵ However, these self-reported physical limitations were detected by using series of six questions instead of using an existing validated questionnaire such as the PedsQL-GCS, which was applied in this study. Besides

subjective self-reported physical limitations, also physical fitness levels assessed with objective performance tests seem to be lower among children with cancer or with a history of cancer.^{11,26-28} Warner et al. reported significant reduced oxygen uptake ($VO_{2\text{ peak/kg}}$) among ALL survivors (n=35) compared to controls.²⁸ This lower exercise capacity is assessed in survivors who received treatment for ALL more than five years ago in contrary to the pediatric patients in this study who are in early clinical remission (<1 year after treatment) of different types of cancer.

In addition, this study found significant differences in social and school functioning among pediatric patients during early clinical remission of cancer between the age of 5-7 years compared to healthy controls. Psychosocial factors such as distress and mental wellbeing are reported among childhood cancer survivors.¹⁰ According to Zeltzer et al²⁹ most adolescent and young adult survivors of childhood cancer are psychologically healthy, however a subgroup experience significant psychological distress or mental health problems. Although the studies of Zebrack et al¹⁰ and Zeltzer et al²⁹ are among childhood cancer survivors, their results are similar to those from this study among the younger pediatric patients during early clinical remission. The phase of early clinical remission is the moment when treatment stops and children have to return to their normal daily activities such as school attendance. Furthermore, they have to get used to living with the uncertainty about the recurrence of the disease and possible long-term side effects. Therefore, also during this fragile phase of clinical remission children might experience lower levels of social and school functioning.

Remarkable is that significant differences were found in the age category where parents completed the questionnaire (5-7 years old) and no significant differences were found in the age categories where children completed the questionnaire themselves (8-18 years old). According to Johnsten et al. parents of patients with cancer tend to rate their children's QoL poorer than children report themselves.³⁰ It is possible that although parents may over report QoL problems, self-reports of children with cancer may underestimate QoL problems.³⁰ Due to extensive treatment and the life-threatening illness they experience during treatment for cancer, the children may change their standard of QoL and thereby underestimate QoL problems after treatment. This phenomenon is known as 'response shift' and might explain why no significant differences were found among the older pediatric patients during early clinical remission of cancer compared to healthy controls.^{31,32}

Longer treatment duration seems to be related to poorer health related QoL.^{7,33} This corresponds to the results of this study where disease duration is negatively associated with physical and social functioning. A possible explanation is that pediatric patients with a poor prognosis probably have been treated more intensively and thereby have been treated for a longer period. This might result in more physical and psychosocial limitations. Additionally, several studies reported a significant association between the type of cancer and health related QoL.³⁴⁻³⁹ However, no significant association was found in this study between the type

of cancer and physical, social and school functioning. This might be due to the distribution of types of cancer among the participants in this study. Most of the children in this study underwent treatment for ALL (n=17), neuroblastoma (n=10) or Wilms tumor (n=11). Median scores on physical functioning did differ among these three groups (ALL=53.13; neuroblastoma=62.50; Wilms tumor=84.37), however no test was performed to analyze this due to the small number of patients per group.

Several factors must be considered when interpreting the results of this study. First of all, physical functioning was only measured using a questionnaire and not combined with objective physical performance tests. Therefore it is not possible in this study to compare subjective physical limitations with objective physical performances. Moreover, this study was performed in a specialized oncology center in the Netherlands, so results should be generalized to other settings with caution. Furthermore, all types of childhood cancer were included in this study. Due to a small number of participants with certain types of cancer, difficulties were found to differentiate between the different types of cancer. All types of cancer were therefore analyzed together, even though earlier research reported significant association between QoL and type of cancer. However, a strong aspect of this study is the moment of assessment. This is one of the first studies, which investigates the patient's subjective wellbeing and health status during the fragile phase of clinical remission in pediatric patients with cancer (0-5 years after treatment). Previous studies regarding health related QoL outcomes were among pediatric patients during cancer treatment or among childhood cancer survivors (more than 5 year after treatment).

To determine the course of health related QoL outcomes such as physical, social and school functioning among pediatric patients during clinical remission of cancer, a longitudinal study design is recommended. By using a longitudinal study design, the moment of deterioration or improvement of health related QoL outcomes can be determined more precisely. Furthermore, it is advised to assess both children and parents instead of either one of them. When assessing both children and parents the possible presence of the earlier mentioned 'response shift' could be established, which could partially clarify the results of this study.

CONCLUSION

Younger pediatric patients during early clinical remission of cancer between the ages of 5-7 years might experience lower physical, social and school functioning compared to healthy children. Individual interventions regarding physical or social functioning might be considerable among these younger cancer survivors. Particularly among patients with a poor prognosis and thereby increased disease duration and treatment, since physical and social functioning seems to be negatively associated with disease duration and can be influenced by severe adverse effects of longer/ intensive treatment regimes. Physiotherapists and/or

social workers might play a significant role in these interventions. Physical, social and school functioning did not differ between pediatric patients during early clinical remission of cancer from the age of 8-18 years old and healthy controls. To fully understand longitudinal studies during clinical remission should be performed to assess trajectories and predictors in this population.

REFERENCES

1. Murphy SL, Xu J, Kochanek KD. Deaths: final data for 2010. *Natl Vital Stat Rep* [Internet]. 2013 May 8 [cited 2016 May 16];61(4):1–117. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/24979972>
2. Kaatsch P. Epidemiology of childhood cancer. *Cancer Treat Rev* [Internet]. 2010;36(4):277–85. Available from: <http://dx.doi.org/10.1016/j.ctrv.2010.02.003>
3. American Cancer Society. Cancer in Children & Adolescents. *Spec Sect Cancer Child Adolesc* [Internet]. 2014;1(ICCC):25–42. Available from: <http://www.cancer.org/research/cancerfactsstatistics/cancerfactsfigures2014/>
4. Noll RB. The Integration of Psychology in Pediatric Oncology Research and Practice. 2015;70(2):146–58.
5. Ness KK, Gurney JG. Adverse Late Effects of Childhood Cancer and Its Treatment on Health and Performance. 2007;
6. Geenen MM, Cardous-ubbink MC, Kremer LCM, Heinen RC, Jaspers MWM, Koning CCE, et al. CLINICIAN ' S CORNER Medical Assessment of Adverse Health Outcomes in Long-term Survivors of Childhood Cancer. 2016;297(24):2705–15.
7. Klassen AF, Anthony SJ, Khan A, Sung L, Klaassen R. Identifying determinants of quality of life of children with cancer and childhood cancer survivors: a systematic review. 2011;1275–87.
8. Werker CL, Nijhof SL, Putte EM Van De. *Clinical Practice: Chronic fatigue syndrome*. 2013;1293–8.
9. Rueegg CS, Gianinazzi ME, Michel G, von der Weid NX, Bergstraesser E, Kuehni CE. Do childhood cancer survivors with physical performance limitations reach healthy activity levels? *Pediatr Blood Cancer* [Internet]. 2013;60(10):1714–20. Available from: <http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L369569994>
10. Zebrack BJ. Psychological , Social , and Behavioral Issues for Young Adults With Cancer *. 2011;2289–94.
11. Brussel MVAN, Takken TIM, Net JVANDER, Engelbert RHH, Bierings M, Schoenmakers MAGC, et al. Physical function and fitness in long-term survivors of childhood leukaemia. 2006;9(July):267–74.
12. Braam KI, van der Torre P, Takken T, Veening MA, van Dulmen-den Broeder E, Kaspers GJL. Physical exercise training interventions for children and young adults during and after treatment for childhood cancer. *Cochrane database Syst Rev*. 2013;4:CD008796.
13. Deisenroth A, Söntgerath R, Schuster AJ, Von C, Huber G, Eckert K, et al. Muscle strength and quality of life in patients with childhood cancer at early phase of primary treatment. 2016;18(December).

14. Winter C, Müller C, Hoffmann C, Boos J, Rosenbaum D. Physical activity and childhood cancer. *Pediatr Blood Cancer* [Internet]. 2010;54(4):501–10. Available from: <http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L358373434>
15. Schepers SA, Sint SM, Lotte N, Michel H, Schouten AYN, Margreet VM, et al. Real - world implementation of electronic patient - reported outcomes in outpatient pediatric cancer care. 2016;(July):1–9.
16. Haverman L, Oers HA Van, Limperg PF, Hijmans CT, Schepers SA, Nicolaas SMS, et al. Implementation of Electronic Patient Reported Outcomes in Pediatric Daily Clinical Practice: The KLIK Experience. 2014;2(1):50–67.
17. Engelen V, Haentjens MM, Detmar SB, Koopman HM, Grootenhuis MA. Health related quality of life of Dutch children: psychometric properties of the PedsQL in the Netherlands. 2009;8:1–8.
18. Field A. *Discovering statistics using IBM SPSS statistics*. 2013.
19. Halinski H.S.; Feldt L.S. The Selection of Variables in Multiple Regression Analysis. *J Educ Meas*. 1970;7(3):151–7.
20. de Vocht A. *Basishandboek SPSS 22*. 2014.
21. Kiel C. *G * Power 3: A flexible statistical power analysis program for the social , behavioral , and biomedical sciences*. 2007;39(2):175–91.
22. Ochs JJ. Neurotoxicity Due to Central Nervous System Therapy for Childhood Leukemia. *Am J Pediatr Hematol Oncol*. 1989;11(1):93–105.
23. Harila-Saari AH, Huuskonen UEJ, Tolonen U, Vainionpa LK, Md ÈÈ, Lanning BM. Motor Nervous Pathway Function Is Impaired After Treatment of Childhood Acute Lymphoblastic Leukemia: A Study With Motor Evoked Potentials. *Med Pediatr Oncol*. 2001;36:345–51.
24. Sander SG, Tobin W, Henderson ES. Vincristine-induced neuropathy A clinical study of fifty leukemic patients.
25. Ness KK, Mertens AC, Hudson MM, Wall MM, Leisenring WM, Oeffinger KC, et al. *Annals of Internal Medicine* Article Limitations on Physical Performance and Daily Activities among Long-Term Survivors of Childhood Cancer. 2017;639–48.
26. Bianco A, Patti A, Thomas E, Palma R, Maggio MC, Paoli A, et al. transplantation. 2014;385–9.
27. Hartman A, Hop W, Takken T, Pieters R, Heuvel-eibrink M Van Den. Motor Performance and Functional Exercise Capacity in Survivors of Pediatric Acute Lymphoblastic Leukemia. 2013;(June 2012):494–9.
28. Warner JT, Bell W, Webb DKH, Gregory JW, Park H, Cardi V. Relationship between cardiopulmonary response to exercise and adiposity in survivors of childhood

- malignancy. 1997;298–303.
29. Zeltzer LK, Recklitis C, Buchbinder D, Zebrack B, Casillas J, Tsao JCI, et al. Psychological status in childhood cancer survivors: a report from the Childhood Cancer Survivor Study. *J Clin Oncol*. 2009 May;27(14):2396–404.
 30. Johnston CA. Parent and Child Reporting of Negative Life Events: Discrepancy and Agreement across Pediatric Samples. *J Pediatr Psychol* [Internet]. 2003 Dec 1 [cited 2016 May 16];28(8):579–88. Available from: <http://jpepsy.oxfordjournals.org/content/28/8/579.abstract>
 31. Jurbergs N, Long A, Hudson M, Phipps S. Self-report of somatic symptoms in survivors of childhood cancer: effects of adaptive style. *Pediatr Blood Cancer* [Internet]. 2007 Jul [cited 2016 May 16];49(1):84–9. Available from: <http://www.ncbi.nlm.nih.gov/pubmed/16847928>
 32. Sprangers MA., Schwartz CE. Integrating response shift into health-related quality of life research: a theoretical model. *Soc Sci Med* [Internet]. 1999;48(11):1507–15. Available from: <http://www.sciencedirect.com/science/article/pii/S0277953699000453>
 33. Maurice-stam H, Oort FJ, Last BF, Brons PPT, Caron HN, Grootenhuis MA. Longitudinal Assessment of Health-Related Quality of Life in Preschool Children With Non-CNS Cancer After the End of Successful Treatment. 2008;1047–51.
 34. Eiser C, Vance YH, Horne B, Glaser A, Galvin H. The value of the PedsQLTM in assessing quality of life in survivors of childhood cancer. 2003;(March):95–102.
 35. Eiser C, Eiser JR, Greco V. *Surviving Childhood Cancer*: 1998;
 36. Meeske K, Katz ER, Palmer SN, Burwinkle T, Varni JW. Parent proxy-reported health-related quality of life and fatigue in pediatric patients diagnosed with brain tumors and acute lymphoblastic leukemia. *Cancer*. 2004 Nov;101(9):2116–25.
 37. Meeske KA, Patel SK, Palmer SN, Nelson MB, Parow AM. Factors Associated With Health-Related Quality of Life in Pediatric Cancer Survivors. 2007;(February 2006):298–305.
 38. Sung L, Klaassen RJ, Dix D, Pritchard S, Yanofsky R, Dzolganovski B, et al. Identification of paediatric cancer patients with poor quality of life. 2009;82–8.
 39. Wu E, Robison LL, Jenney MEM, Rockwood TH, Feusner J, Friedman D, et al. Assessment of Health-Related Quality of Life of Adolescent Cancer Patients Using the Minneapolis-Manchester Quality of Life Adolescent Questionnaire. 2007;678–86.

APPENDIX I INFORMED CONSENT - DUTCH

[Akkoordverklaring voor op KLIK site](#)

Wanneer? Zodra ouders zich hebben aangemeld, en voor de eerste keer inloggen met het wachtwoord, komen ze eerst op deze akkoordverklaring pagina. Eenmalig

Akkoordverklaring

Beste ouder(s)/verzorger(s),

Welkom op de KLIK website. Voor deelname aan KLIK is het van belang dat u de voorwaarden heeft gelezen en begrepen. Voor meer informatie, zie onder de knop [voorwaarden](#) onderaan deze pagina. U heeft eerder uw e-mailadres doorgegeven op de site. Uw e-mailadres wordt uitsluitend gebruikt in het kader van het KLIK project. Informatie hierover vindt u onder de kopjes 'vertrouwelijkheid' en 'privacy'.

Ik verklaar dat ik de voorwaarden op de KLIK website heb gelezen en begrepen.

U kunt toestemming geven voor het gebruik van uw gegevens, verzameld via KLIK, voor wetenschappelijk onderzoek binnen het ziekenhuis. Uw behandelcentrum wil graag te weten komen hoe het met kinderen met een (chronische) ziekte of aandoening gaat en hoe ze zich voelen. Daarom wordt gevraagd of de informatie die u invult op de KLIK website gebruikt mag worden voor wetenschappelijk onderzoek naar de Kwaliteit van Leven en het psychosociaal functioneren van kinderen en eventueel hun ouders binnen het ziekenhuis of binnen multicenter onderzoek van Nederlandse zorginstellingen. Dit is geheel vrijwillig. Uw beslissing zal geen enkele invloed hebben op de gebruikelijke begeleiding of medische zorg. Wij zouden alleen wel willen benadrukken dat het doen van wetenschappelijk onderzoek met gegevens van grote groepen kinderen en ouders voor ons van groot belang is om de toekomstige zorg voor kinderen met een chronische ziekte te verbeteren. Wij hopen dan ook van harte dat u hiervoor toestemming geeft. Voor meer informatie over het gebruik van de gegevens voor wetenschappelijk onderzoek klikt u [hier](#). De gegevens zullen vertrouwelijk en anoniem worden behandeld.

Ik ga akkoord met het gebruik van de door mij ingevulde antwoorden op de vragenlijsten voor wetenschappelijk onderzoek.

Met vriendelijke groet,

Lotte Haverman
Psycholoog / projectleider KLIK

Aanmelding [versturen](#)

Mensen kunnen alleen de aanmelding versturen als ze het eerste vinkje hebben aangevinkt. Het tweede vinkje is optioneel.

APPENDIX II PEDSQL GCS 4.0 – Dutch version

Hoezeer heb je in de **AFGELOPEN MAAND** een probleem gehad met...

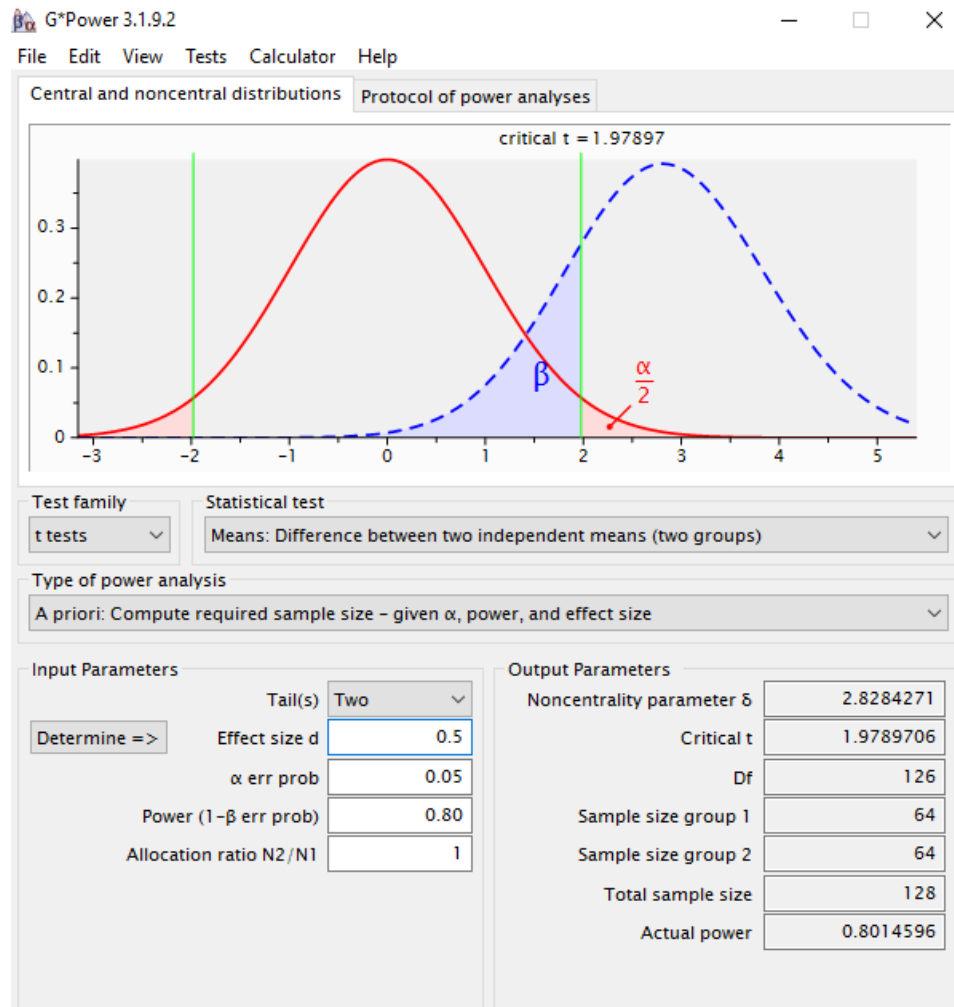
Over mijn gezondheid en activiteiten (<i>problemen met...</i>)	Nooit	Bijna Nooit	Soms	Vaak	Bijna Altijd
1. Het is voor mij moeilijk om meer dan 100 meter lopen	0	1	2	3	4
2. Het is voor mij moeilijk om te rennen	0	1	2	3	4
3. Het is voor mij moeilijk om te sporten of lichamelijke oefeningen te doen	0	1	2	3	4
4. Het is voor mij moeilijk om iets zwaars op te tillen	0	1	2	3	4
5. Het is voor mij moeilijk om zonder hulp in bad te gaan of te douchen	0	1	2	3	4
6. Het is voor mij moeilijk om karweitjes in en rond het huis doen	0	1	2	3	4
7. Ik heb pijn	0	1	2	3	4
8. Ik heb weinig energie	0	1	2	3	4

Over mijn gevoelens (<i>problemen met...</i>)	Nooit	Bijna Nooit	Soms	Vaak	Bijna Altijd
1. Ik voel me angstig of bang	0	1	2	3	4
2. Ik voel me verdrietig	0	1	2	3	4
3. Ik voel me boos	0	1	2	3	4
4. Ik heb moeite met slapen	0	1	2	3	4
5. Ik maak me zorgen over wat mij zal overkomen	0	1	2	3	4

Hoe ik met anderen op kan schieten (<i>problemen met...</i>)	Nooit	Bijna Nooit	Soms	Vaak	Bijna Altijd
1. Ik heb moeite om met andere tieners op te schieten	0	1	2	3	4
2. Andere tieners willen mijn vriend(in) niet zijn	0	1	2	3	4
3. Andere tieners pesten mij	0	1	2	3	4
4. Ik kan dingen niet die andere tieners van mijn leeftijd wel kunnen	0	1	2	3	4
5. Het is moeilijk om mee te blijven doen met tiener van mijn leeftijd	0	1	2	3	4

Over school (<i>problemen met...</i>)	Nooit	Bijna Nooit	Soms	Vaak	Bijna Altijd
1. Het is moeilijk op te letten tijdens de les	0	1	2	3	4
2. Ik vergeet dingen	0	1	2	3	4
3. Ik heb moeite om bij te blijven met schoolwerk (waaronder huiswerk)	0	1	2	3	4
4. Ik ga niet naar school gaan, omdat ik me niet lekker voel	0	1	2	3	4
5. Ik ga niet naar school, omdat ik naar de dokter of het ziekenhuis moet	0	1	2	3	4

APPENDIX III SAMPLE SIZE CALCULATION



SAMENVATTING

Doelstelling: Kanker is één van de meest voorkomende ziektes voor kinderen wereldwijd. De overlevingskans voor kinderen met kanker is drastisch toegenomen over de jaren. Echter is deze toegenomen overlevingskans een gevolg van de meer rigoureuze behandelingen. Dit kan de kwaliteit van leven beïnvloeden vanwege late bijwerkingen van de behandeling. Hierdoor is de vraag naar studies met subjectieve maten zoals kwaliteit van leven toegenomen. Het meten van deze uitkomsten tijdens de klinische remissie fase is van belang, omdat dit vaak het moment is dat de patiënt weer terug zal keren in de maatschappij. Het doel van dit onderzoek is het objectiveren van de mate van fysiek, sociaal en school functioneren van kinderen in de vroege klinische remissie van kanker vergeleken met normwaardes.

Methode: Voor dit cross-sectionele onderzoek zijn kinderen (5-18 jaar) gerekruteerd uit het Prinses Maxima Centrum tijdens de vroege klinische remissie fase. Fysiek, sociaal en school functioneren is gemeten met behulp van de Nederlandse versie van de Pediatric Quality of Life Inventory Generic Core Scales vragenlijst. Kinderen (5-7 jaar) of ouders (8-18 jaar) werden gevraagd om de vragenlijst online thuis in te vullen. De sub scores op fysiek, sociaal en school functioneren zijn vergeleken met normwaardes.

Resultaten: In totaal zijn 64 patiënten geïncludeerd voor deze studie. Kinderen van 5-7 jaar oud tijdens de vroege klinische remissie van kanker scoorden significant lager op fysiek ($p < 0.001$), sociaal ($p = 0.017$) en school functioneren ($p = 0.004$) vergeleken met gezonde kinderen. Geen significante verschillen werden gevonden tussen de oudere kinderen (8-18 jaar oud) tijdens de vroege klinische remissie van kanker en gezonde kinderen.

Conclusie: Jonge kinderen (5-7 jaar) tijdens de vroege klinische remissie van kanker kunnen een verminderd fysiek, sociaal en school functioneren ervaren. Mogelijk hebben deze kinderen baat bij interventies gericht op fysiek en sociaal functioneren om deze uitkomsten te verbeteren. Fysiotherapeuten en maatschappelijk werkers zouden hierin een rol kunnen spelen.