Care for consequences in children treated for leukemia or brain tumor
Aukema, Eline

Citation for published version (APA):
Aukema, E. J. (2013). Care for consequences in children treated for leukemia or brain tumor

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
CHAPTER 7

GENERAL DISCUSSION
Aims

This thesis focuses on long-term consequences for survivors of a childhood brain tumor or childhood leukemia. The consequences after successful medical treatment are described from different points of view. The subsequent chapters describe the late effects and need for aftercare from the parents’ perspective and the quality of life from the children’s perspective. Furthermore, white matter damage as a pathophysiological substitute for neurocognitive decline, and finally options for interventions for survivors suffering from neurocognitive late effects are described.

Main findings

An overview of the studies presented in this thesis is provided in Table 1. This paragraph describes the main findings.

Chapter 2, in which the long-term consequences for CBTS are described from their parents’ perspectives, reveals that the majority of the CBTS (n=42, mean age=14.7 yrs., mean time since end of treatment=6.2 yrs.) experience several types of late effects: physical effects (90%), neurocognitive effects (74%), emotional effects (64%), and social effects (57%). One-third of the parents reported parenting problems. A comparable need for aftercare for these domains was found in both CBTS treated with adjuvant therapy and CBTS who were treated with surgery only. Failure to identify late effects as well as self-referral in proper time was frequently reported, especially for psychosocial problems. Furthermore, parental knowledge of aftercare school services was lacking. We conclude that although professional aftercare providers respond appropriately to physical health problems, increased awareness and a more timely response is needed for neurocognitive, psychosocial and parenting problems.

Chapter 3 demonstrates that HRQOL scores in CBTS (n=34, mean age=14.7 yrs., mean time since end of treatment=6.4 yrs.) were significantly lower compared with the norm population in the domains of “physical well-being and psychosocial well-being” and “peers and social support”. The risk for impaired HRQOL in the domains of “physical well-being”, “moods and emotions”, “peers and social support” and “bullying” was 35 to 53% compared with 16% in the norm group. Similar high percentages were found in CBTS treated with and without adjuvant therapy. These findings lead to the conclusion that although in some domains HRQOL appears to be similar to the Dutch norm population, a considerable number of CBTS are at risk for impaired physical well-being, negative moods and impaired social functioning, regardless of the therapy applied.
Chapter 4, in which white matter is mapped out using white matter fractional anisotropy (WMFA) with Diffusion Tensor Imaging (DTI) on a 3.0-T MRI scanner, shows white matter damage in brain tumor and leukemia survivors (n=17, mean age=14.0 yrs., mean time since end of treatment=8.4 yrs.). Significant lower WMFA in parts of the corpus callosum and right inferior fronto-occipital fascilicus were found especially in medulloblastoma survivors, but also in ALL survivors treated with high doses of MTX compared with peers. This low WMFA was positively correlated with information processing speed and fine motor speed, which supports the idea that a higher integrity of white matter tracts facilitates more and faster processing of information.

These findings indicate a correlation between white matter damage and neurocognitive late effects. We conclude that DTI on a 3.0 T MRI is sensitive for the detection of region-specific changes in white matter integrity and correlates with slow information processing speed in CBTS.

Chapter 5 describes the feasibility of neurofeedback training (NFT) as a neurocognitive intervention for CBTS who experience neurocognitive late effects. Based on the personal quantitative electroencephalogram (QEEG) it was possible to make individualized NFT protocols for the participating CBTS (n=9, mean age=17.0 yrs., time since end of treatment=8.6 yrs.). The participants completed the 30 NFT sessions and no negative side effects were reported. Negative comments only concerned the amount of time needed for the intervention (30 x 1 hour of training). The training was evaluated as being enjoyable and recommendable for other survivors. Based on the neuropsychological test scores, some preliminary indications were found of improved information processing speed, and in daily life these improvements were also mentioned by some participants post-NFT. These first experiences are helpful to optimize future study designs to investigate the efficacy of NFT.
<table>
<thead>
<tr>
<th>Study ID</th>
<th>Overview of the studies presented in this thesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1</td>
<td>Methodology and implementation details</td>
</tr>
<tr>
<td>S2</td>
<td>Data collection and analysis</td>
</tr>
<tr>
<td>S3</td>
<td>Results and discussion</td>
</tr>
<tr>
<td>S4</td>
<td>Conclusion and future work</td>
</tr>
</tbody>
</table>

Table 1: Overview of the studies presented in this thesis.
Chapter 6 describes the effect of growth-hormone (GH) therapy (during a period of 24 months) on neurocognitive functioning in ALL survivors (n=20, mean age=23.7 yrs., mean time since end of treatment=15.0 yrs.), most of whom were treated with CRT. Our study reveals that GH has variable effects on memory and attention test scores. At baseline assessment, a surprisingly high level of intelligence and also intact neurocognitive functions were found. Insulin-like growth factor (IGF-I) levels were used to express neuro-endocrine effects of GH treatment. Although the mean IGF-I level increased during the first year of GH treatment, it decreased in the second year, but remained higher than at baseline. The increase of IGF-I appeared to have a negative relation with verbal short-term and long-term memory scores. Sustained attention and visual spatial memory scores improved after the first and second year of GH treatment. It would seem that especially the speed and quality of visuomotor and visual perceptual performance were related to the IGF-I increase in the first year. We conclude that while GH treatment has some positive effects on visual-spatial long-term memory and attention, it has negative effects on verbal memory functions. Optimal dosing of GH in relation to cognitive outcome requires further study.

Reflections on the main findings

High prevalence of late effects: Cured but not healed
Increased survival rates of CBTS come at a cost. CBTS suffer from many adverse effects from cancer and its treatment [1, 2]. This thesis demonstrates a high prevalence of late effects, experienced by the CBTS, and reported by their parents (Chapters 2, 3, 4 and 5).

High prevalence of physical health problems
A high incidence of physical problems was seen in long-term CBTS. Physical problems were reported by 90% of the parents (Chapter 2). These physical problems consist of poor motor function, low energy level, hormone dysfunction, visual problems, epilepsy and hearing loss. Of the survivors, 41% reported impaired physical well-being, revealing a low level of physical activity, poor health, energy and fitness (Chapter 3). These results are comparable with the outcome of former publications that describe the increased risk of many severe health problems in survivors [1, 2].

Neurocognitive late effects, especially slow information processing speed
Of the parents, 74% reported neurocognitive deficits in their child, which mostly consist of attention problems, slow information processing speed, decreased fine motor skills, and memory problems (Chapter 2). Neuropsychological test results showed below-average intelligence scores (<-1SD) and deficits in reaction time, information processing speed, attention problems and slow motor speed (Chapters 4
Impaired information processing speed seems to be the core deficit in CBTS and hinders the acquisition of new skills and knowledge [3-6]. A child who slowly processes information may be able to pay attention adequately, but generally needs more time and repetition to memorize the information, which leads to fatigue and/or frustration. Fatigue, in turn, negatively influences neurocognitive functioning. Specialized educational services were often required (for 61% of the CBTS) and one-third of the CBTS needed a transition to a special education school (Chapter 2), which is tenfold more compared with the Dutch population (3%). Neurocognitive late effects also occur in 20-40% of the ALL survivors and have been associated with CRT [7]. However, methotrexate (MTX) chemotherapy, replacing CRT as CNS prophylaxis, has also been related to neurocognitive problems in some studies [8, 9]. Subtle problems with attention [10, 11], complex fine motor skills [12], speed of information processing and working memory [13, 14] have been described. In this thesis mean intelligence scores in long-term ALL survivors treated with and without CRT were within average level (Chapters 4 and 6). However, subtle neurocognitive problems may be present which are not identified by intelligence tests. Contrary to what we expected, we did not find neurocognitive problems in long-term ALL survivors after CRT (mean time since diagnosis 15 yrs.) and we found test scores to be within the normal range (Chapter 5). In ALL survivors treated with MTX we only found subtle problems with fine motor speed and complex fine motor skills, which corresponds with previous findings [12] (Chapter 4).

White matter damage
A DTI MRI technique visualizes changes in the integrity of white matter. We found decreased WMFA in medulloblastoma survivors, but also in ALL survivors treated with high doses of MTX (Chapter 4). In particular, lower WMFA in parts of the corpus callosum and right inferior fronto-occipital fasciculus were found compared with peers. Lower WMFA in these parts was correlated with impaired information processing speed and fine motor speed. This supports the idea that higher WMFA facilitates faster processing of information. WMFA in the frontal lobes in normal subjects are associated with attention, information processing speed and working memory, and especially the right frontal-parietal region contributes to the speed of visual-spatial searching [15]. Decreased WMFA has not only been found in medulloblastoma survivors but also in survivors of pilocytair astrocytoma treated with surgery only [16]. Law et al. [17] found delineated WMFA in cerebro-cerebellar connections in CBTS and this reduced WMFA was correlated with impaired working memory scores. In ALL survivors, Kesler et al. [18] found reduced WMFA in several regions of interest (bilateral caudate, left corpus callosum, thalamus, fornix and bilateral superior fronto-occipital fasciculus).
Porto et al. [19] found that reduced WMFA in adult survivors of ALL was more severe in survivors treated with chemotherapy and CRT, but that it was also present in survivors treated with chemotherapy only. White matter damage seems to be a pathophysiologic explanation for neurocognitive deficits [3, 20]. There is a high need for more knowledge of the development of white matter in healthy children and adolescents in order to obtain normal values for DTI as an imaging technique for detecting and monitoring white matter damage in CBTS and ALL survivors.

Psychosocial late effects
Both emotional and social late effects were reported by the CBTS themselves as well as their parents. Almost half of the CBTS felt socially isolated and different from their peers (Chapters 2 and 3). They lacked social support, spent less time with other children and felt rejected by others. These results are in line with the findings of others who found that CBTS appear to be more at risk for isolation from peers, and show social competency deficits [21, 22].

Internalizing problems, such as depressive moods and emotions, stressful feelings, and problems regarding the illness experience, were described by 44% of the CBTS and by 64% of the parents (Chapters 2 and 3).

Survivors with physical difficulties are restricted in their peer contact (in sport clubs, getting along at school, or playing outside after school), and in combination with neurocognitive deficits (e.g., a slow information processing speed) this may result in poorer social functioning and interaction with peers [21, 23, 24], which leads to internalizing problems. Especially low energy and fatigue can have a negative effect on daily functioning. In a study of Meeske et al. [25], for example, fatigue was found to be the most powerful predictor of physical and psychosocial HRQOL, especially in CBTS.

Most of the CBTS studied in this thesis were adolescents. Normal expectations and challenges in this period of development, such as increasing independence from parents and focusing on the peer group may be more difficult for CBTS. These challenges could also cause depressive feelings. Limited possibilities for young adult CBTS to achieve the normal milestones of adulthood, including graduating from college, being financially independent and getting married were described [26-29].

Despite the presence of several late effects, CBTS also reported positive emotions, satisfaction with life and positive self image (Chapter 3). This is in line with prior findings in survivors of cancer and could point to resilience and positive adjustment to late effects [28, 30-32].

Unrecognized late effects: Special attention is required for survivors who were treated with surgery only
Neurocognitive [33, 34] and psychosocial problems [35, 36] have been widely
documented in CBTS. Especially those CBTS treated with surgery and adjuvant therapy (CRT and/or chemotherapy) are at risk for these late effects and survivors who were treated with surgery only were supposed to be at minimal risk [20].

In the present study an equal number of late effects (in three domains) and an equal risk for impaired HRQOL were reported in CBTS who were treated with surgery only compared with those who were additionally treated with adjuvant therapy (Chapter 2 and 3). In studying HRQOL we found that more than one-third of the survivors treated with surgery only are at risk for impaired HRQOL for physical well-being, negative moods or social functioning.

From clinical experience we know that these survivors received less aftercare in an oncology/outpatient clinic. Only survivors with obvious late effects and problems were referred to psychosocial and neurocognitive assessments. It could be that these survivors struggle with subtle, unrecognized late effects, for instance neurocognitive deficits, leading to learning difficulties, negative moods and feeling different than peers. Without a standardized aftercare program in which all domains of functioning are monitored, subtle late effects may go unrecognized, and without recognition survivors may not receive the aftercare they need. This stresses the need for routine medical, but also psychosocial and neurocognitive aftercare for survivors who were treated with surgery only [33].

Unmet needs during aftercare: The importance of adequate information and timely referral for specialized aftercare

Aftercare needs
The need for aftercare was met for physical late effects. However, unaddressed neurocognitive and psychosocial needs during the years after treatment were reported (Chapter 2). One-third of the parents reported parenting problems, which remained unnoticed by hospital staff. Parents complained about late responses to the need for aftercare and the lack of support in finding the proper aftercare services. In addition, parents complained about insufficient psycho-education on possible late effects, a lack of information on available aftercare services and delays in referral for psychosocial problems. The need for earlier identification of parental needs and subsequent better access to psychosocial aftercare is in line with prior findings [37, 38].

Although these unmet needs could be more or less explained by several barriers in communication or inadequate aftercare possibilities, more intrapersonal barriers such as positive denial of the need for care could also be present [39]. After treatment for a brain tumor it could be too hard for parents to face the negative consequences of the tumor and the treatment in the daily functioning of their child. Rather than facing the consequences and communicating about these consequences, they could choose not to communicate about the problems in order to maintain a high degree of optimism and gratefulness for their child being cured. This behavior can
be conceived as self-protective and has been described as positive denial [39-41]. Avoiding communication about the disease and its possible consequences can also be characterized by this self-protective strategy which has been referred to by Van Veldhuizen & Last (1991) as the phenomenon of double protection [42]. Children and/or parents often choose not to talk about the negative implications of the disease because this will evoke distress and negative emotions.

Hoven et al. found that unmet needs for follow-up care have negative consequences for the family [38] and therefore early identification of CBTS’ and parents’ needs is an important goal for oncology health care teams. In addition to healthcare providers having good communication skills, a multidisciplinary approach are needed to screen these aftercare needs.

Needs for interventions for neurocognitive late effects

The need for effective interventions is considerable and more attention has been paid to the development of neurocognitive rehabilitation programs and pharmacological therapy in the past decades. Reducing neurocognitive problems could improve learning possibilities and psychosocial functioning in CBTS.

In this thesis we explored the feasibility of neurofeedback training in a pilot study, an intervention often used in children with ADHD (Chapter 5). The training was found to be feasible for CBTS and some indications were found for faster information processing speed, both objectively and subjectively, although the small sample size and variable results withhold us from drawing conclusions about its efficacy.

We studied the effect of growth hormone (GH) therapy on neurocognitive functioning (Chapter 6) in ALL survivors treated with CRT. GH does indeed seem to influence neurocognitive functioning; especially the level of IGF-I (insulin-like growth factor which is a serum substitute level for GH status) is associated with the neurocognitive. We found some positive effects on visual spatial memory and attention, but negative effects on verbal memory functions. Arwert et al. [43] found positive links between IGF-I and different cognitive functions in healthy adults. Results from other studies also suggest that higher levels of both GH and IGF-I influence memory functioning [44]. In an intervention study in adult patients with traumatic brain injury with cognitive disorders, GH treatment was found to significantly improve several cognitive test results [45]. But no link between cognitive improvement and IGF-I rise was found in this study.

So far, the effect of GH treatment on neurocognitive functioning in CBTS has not been studied. Since many CBTS are treated with GH, awareness of the possible correlation between neurocognitive functioning and IGF-I levels is needed during GH treatment until more insight is gained into the relationship between GH, IGF-I and neurocognitive functioning.
Limitations

The findings of this thesis must be considered in the light of some overall limitations.

Participants

Small sample size

An important limitation of the studies within this thesis is the small sample size and the heterogeneity of the participants in the different studies. Childhood brain tumors are rare, and because of our single-institute study, the available sample size was relatively small, with a variety in age at diagnosis, type of tumor and treatment modalities. Given our small study group, we were not able to analyze the role of different medical and demographic variables on HRQOL and neurocognitive functioning. However, we could study differences between CBTS treated with and without adjuvant therapy as being relevant based on the professional literature and clinical experience of the need for aftercare in that group. These small sample sizes and heterogeneity of CBTS are common in CBTS research and collaboration between research centers is therefore needed [21, 46].

Representativeness

Questions may arise about the representativeness of our study group. CBTS who refused to participate were most often treated for a low-grade tumor leading to some selection bias. Reasons for not willing to participate were lack of interest or too much time or effort required for the questionnaires or intervention. However, our sample of CBTS includes all different types of brain tumors and reflects the general population of brain tumor patients (50% high-grade and 50% low-grade tumors).

In addition, the broad time span (patients who had completed treatment between 1990 and 2006 were invited to participate) in which survivors were treated could have influenced the functional outcome of survivors, due to changed treatment strategies and differences in time which had elapsed since treatment. Furthermore, of the 160 children diagnosed in the inclusion period in our database, only 57 met the inclusion criteria; the other 103 were not eligible. A database or tracking system was still in the process of being set up at our hospital and was one of the reasons that we could not include more patients.

Questions may also arise about representativeness of the ALL survivor group because of the high intelligence scores we found in these irradiated survivors compared with the expectations [20, 47].
Single-center study
Furthermore, because all CBTS were recruited from a single center, generalization of our evaluation of aftercare (described in Chapter 2) to other centers is limited. Our center does, however, have a long tradition of providing psychosocial aftercare to childhood cancer survivors which could be indicative for a relatively well-organized aftercare process [29].

Methodology

Explorative nature
Due to the explorative nature of the different pilot studies (Chapters 4 and 5), only limited conclusions can be drawn. Pilot and explorative studies are, however, an important step for future research. Further research within larger samples of CBTS is needed to optimize the studies and designs set out in this thesis. Meanwhile, the pilot study neurofeedback resulted in a double blind placebo randomized controlled trial currently running.

Non-standardized questionnaires
Some studies were limited given the lack of standardized questionnaires, e.g., the survey used to evaluate the late effects and follow-up care, but also the interview to evaluate the effect of neurofeedback on daily life. However, at the time of our research, questionnaires such as the Behaviour Rating Inventory Executive Functioning (BRIEF [48]), were not yet available in The Netherlands.

Nature of pilot designs
Due to the lack of a placebo control group in our intervention studies, we were not able to determine whether placebo effects were present. The use of standardized neurocognitive tests enabled us, however, to compare participants’ test results with normative data and to prevent test-retest effects by using reliable change index scores or comparable versions of the tests. Furthermore, CBTS are known to decline in neurocognitive functioning in time, therefore improvements on objective standardized neurocognitive tests are not expected to be a result of placebo effects. However, placebo effects should be considered in these pilot designs. Since limited improvements on neurocognitive tests are common in cognitive intervention research [49], incorporation of standardized questionnaires such as the BRIEF and monitoring school results could have added to the objective effects of the intervention.

Notwithstanding these limitations, the studies in this thesis describe the late effects in survivors from different points of view using new methods and exploring new interventions for neurocognitive problems. We provide a comprehensive view of late effects from the parents’ perspectives and from the survivors’ perspectives. We
have identified a considerable need for aftercare for different domains of functioning and delays in identifying these late effects. These delays were identified despite the fact that CBTS are known to be at risk for late effects. By using KIDSCREEN, a standardized QOL questionnaire, we found that a substantial number of CBTS are at risk for impaired QOL. We found a high percentage of CBTS to be at risk for impaired social relationships and social acceptance. These late effects described by both parents and CBTS were reported in all CBTS, regardless of the treatment applied.

By using WMFA MRI technique we were able to visualize white matter damage and explored the pathophysiology of neurocognitive problems in cancer survivors. Furthermore, we found that neurofeedback is a feasible intervention for CBTS with neurocognitive late effects, and that growth hormone therapy has variable effects on memory and attention functions in ALL survivors. Both interventions require further examination in childhood cancer survivors.

The present findings provide several suggestions for future research.

**Recommendations for future research**

Recommendations for future research are categorized by the high prevalence of late effects and the unmet needs during after care. These recommendations are applicable to all CBTS, regardless of the treatment applied.

**High prevalence of late effects**

*Longitudinal research*

Longitudinal study designs in CBTS and ALL survivors are needed to provide more insight into the onset and further course of the late effects in the different domains (i.e., physical, neurocognitive, social and emotional) of functioning. This knowledge is needed to identify which patients are at risk for different late effects and to develop preventive strategies. Newer therapeutic strategies, such as proton therapy and fractionated CRT might help to reduce toxicity [50-52]. Longitudinal research designs are necessary to study the toxicity of these newer therapeutic strategies.

*Unraveling the contributing factors in late effects*

The effect of slow information processing speed [6] and physical limitations (such as low energy and fatigue [25, 53]) on daily functioning and learning should be studied more thoroughly. It is logical to assume that survivors with physical disabilities are restricted in their peer contact and that slow information processing speed also has a negative effect on the quality of social functioning. Unraveling this interaction could aid in the development of more timely and specific interventions. Better differentiating measuring instruments should be developed, especially for information
processing speed and fatigue. With newer measuring instruments the understanding of the severity and functional impact of neurocognitive deficits in daily life could be improved [6].

Neurotoxicity and imaging
The high prevalence of late effects in survivors warrants the focus on finding ways to protect healthy tissue from toxic effects of therapy applied. Advances in the treatment should find a new balance between reducing the neurotoxicity while maintaining high survival rates [3, 14, 20]. In addition to developing less toxic treatments, the pathophysiology of white matter damage must be studied in more detail. The use of white matter imaging techniques from the start of the treatment, integrated with neurocognitive measures, could lead to a better understanding of the course of white matter damage and the effect on cognitive functioning. More understanding could ultimately result in a predictive model of neurotoxicity influencing neurocognitive functioning.

Unmet needs during follow-up care

Detect late effects and needs for aftercare more timely
Monitoring and screening psychosocial and neuropsychological functioning during aftercare could lead to a more timely identification of late effects and referral to aftercare services. Monitoring and screening tools should be examined for their effectiveness in meeting the needs of CBTS and their families.

Interventions for cognitive late effects
Ongoing effort should focus on developing and evaluating interventions to reduce cognitive problems [20]. The development of effective interventions starts with feasibility studies in which new interventions are explored [54, 55]. Effective interventions from other pediatric populations with comparable neurocognitive problems (e.g., ADHD, traumatic brain injury, learning disabilities, fatigue, epilepsy) need to be explored in terms of feasibility and effectiveness in CBTS as well. Future study design might include a waitlist group to correct for non-specific training and possible placebo effects.

Further NFT research is currently being conducted in a double blind randomized fashion, including a control group in our center (www.prismastudie.nl)[56]. Future studies could benefit from effective NFT protocols used in adults with traumatic brain injury [57] and in children with dyslexia [58]. Since reading and word spelling difficulties are also described in CBTS [5, 59] and an underlying automatization deficit could be responsible for these learning disabilities, further research to explore NFT protocols for dyslectic patients is needed.
The effect of GH treatment on the cognitive functioning of CBTS has not been studied yet and warrants further exploration.

*Improve coping with late effects*

Psychosocial interventions in learning how to cope with and accept the late effects should be the focus of future research. Last and Maurice-Stam found positive results concerning disease-related skills and social competence in a psycho-educational group intervention for childhood cancer survivors [53, 54]. This psycho-educational group intervention has been transformed into an online version as well and requires further examination [60].

Because of the high percentage of CBTS being bullied, social skills training on making friends and on how to manage bullying is recommended. In addition, newer psychological treatments, such as mindfulness or acceptance and commitment therapy (ACT) or meditation [61], could be helpful in learning to cope with the consequences of the disease.

**Barriers that need to be overcome**

*Collaboration and consensus*

The small sample sizes can be overcome through collaboration between multiple research centers. To be able to evaluate the late effects of new treatment techniques (e.g., proton therapy, fractionated CRT, high dose chemotherapy), collecting outcome data should be optimized [3]. Consensus is needed with respect to standard test batteries and definitions of impairment in order to optimize collaborative national and/or international follow-up trials.

*5.3.2 Financial and tracking system resources*

To implement neurocognitive and psychosocial screening batteries, a comprehensive national tracking system is needed in order to know which survivors should be screened and when. Costs, time restraints and lack of tracking systems are barriers in the delivery of adequate aftercare [62]. These barriers require funding from health insurance companies and from national cancer societies (e.g., KWF and KIKA). New ICT techniques such as specifically designed websites and smartphone applications can prove helpful in efficiently improving aftercare. The development of a screening tool and care guidelines is a first step in delivering better aftercare, but it needs to be implemented properly in the daily practice. The initiative of a national oncology center for children in the Netherlands could be helpful in implementing guidelines.
Main recommendations and clinical implications

This thesis demonstrates that not only CBTS who were treated with surgery and adjuvant therapy, but also CBTS who were treated with surgery only can experience a wide range of late effects. Combined with our findings of a high need for aftercare for these late effects, this emphasizes the importance of routine multidisciplinary aftercare for all CBTS, regardless of the therapy applied [33]. Standardized aftercare after a childhood brain tumor should be used to inform, monitor, screen, and intervene where necessary. Multidisciplinary teams are needed. These teams should include doctors, nurses/nurse practitioners, neuropsychologists, social workers, child life specialists and hospital school teachers or school liaisons. The hospital school teacher or school liaison should bridge the gap in knowledge between the hospital and school and should play an important role in all aspects of aftercare. New ICT techniques such as specifically designed websites and smartphone applications could prove to be helpful for aftercare.

Inform: Provide information about possible late effects and specialized aftercare services

After successful treatment and regularly during the aftercare, psycho-education about the possible late effects and aftercare services should be provided to CBTS, parents and teachers. Information needs to be available on websites, smartphone applications and in leaflets [63]. The website www.skion.later.nl, which describes late effects of different treatment modalities, could be a useful source of information.

Monitor: Routinely monitor the neurocognitive and psychosocial functioning during aftercare care

The need for aftercare was met for physical impairments, but aftercare for neurocognitive and psychosocial late effects was inadequate. Internalizing problems (e.g., negative moods), difficulties relating to the illness experience and social problems (e.g., isolation and bullying) require more attention during medical aftercare visits. Parenting difficulties should also be given more attention. The use of patient reported outcomes (PROs) in daily clinical practice can be helpful to routinely monitor psychosocial functioning (HRQOL) and patients’ needs for aftercare [64, 65]. The use of PROs will increase awareness of, and communication about, psychosocial functioning and aftercare needs and could prevent delays in referral for aftercare services. Parenting difficulties and parents’ needs should also be monitored. Taking into account the possibility that children and parents may have trouble discussing their difficulties and are not always immediately motivated to seek help, health care workers need sufficiently adequate communication skills to discuss the possible late consequences of the disease with CBTS and their parents. Furthermore, school
results should also be closely monitored during aftercare in order to identify learning difficulties in time. Sufficient insight into a child's functioning before the diagnosis is required to identify a decline in functioning. We recommend collecting school results from before the diagnosis, and these results can be used as a baseline evaluation of a child's cognitive functioning.

**Screen: Identify survivors at risk for late effects and aftercare needs**

Screening can be helpful for the early identification of those survivors who are experiencing late effects and need aftercare [20, 59, 66]. Our recommendation is that all childhood cancer survivors at risk for neurocognitive difficulties should be examined regularly after treatment, even in the absence of overt problems [59]. Regular screening will enable timely referral or intervention where necessary. In collaboration with other Dutch centers a screening tool is currently being developed which incorporates psychosocial functioning (including HRQOL) and neurocognitive functioning. *During the first five years after diagnosis CBTS will be screened three times.* Neurocognitive instruments were chosen based on treatment protocols developed by the International Society of Pediatric Oncology (SIOP) and the Children's Oncology Group (COG). Neurocognitive assessments consist of a global estimate of intelligence, and assess domains of information processing speed, attention, complex visual motor skills and aspects of executive function [59, 67, 68]. The screening tool furthermore comprises questionnaires about executive functioning (BRIEF [69]), daily functioning (SDQ) and a screening list for traumatic brain injury (Brain injury alert [70]) filled in by parents and teachers. Part of the screening will be Internet-based, which makes it easier to conduct. Face-to-face contact with a psychologist is, however, needed to screen for potential difficulties and potential healthy denial of late effects. Protocols for screening more than *five years after diagnosis* have been developed by members of the Late Effects of Childhood Cancer task force of the Dutch Childhood Oncology Group (“DCOG LATER”). The neurocognitive and psychosocial guidelines comprise risk-based follow-up care with different intervals based on the treatment and depending on the age of the survivor (see [http://www.ski.on.nl/bestanden/richtlijn_follow-up_na_kinderkanker](http://www.ski.on.nl/bestanden/richtlijn_follow-up_na_kinderkanker)). The guidelines consist of a face-to-face contact with a psychologist screening for psychosocial functioning and assessment of neurocognitive functioning with a screening instrument, the Kaufman Neuropsychological Screening (K-SNAP). CBTS will be screened every three years when visiting the outpatient clinic. Based on the results of the screening tools, CBTS could be referred for aftercare services. Different options to intervene (see the following paragraph) or to comprehensively assess neurocognitive or psychosocial functioning are possible.
Intervene: If necessary, referral for aftercare services and suitable interventions should be considered for cognitive late effects or psychosocial late effects

Long-term consequences differ in intensity and level of impairment and warrant adjusted interventions. Different interventions can be distinguished, varying from more basic to more specialized aftercare and should be given based on the severity of the consequences, the level of basic learning skills and the needs of the survivors. Neuropsychologists might consider the following available options.

*Neurocognitive interventions*

**Basic interventions:** Remedial services at regular schools; comprehensive neurocognitive test assessment; general and specific educational and environment accommodations based on the neurocognitive profile; psycho-education of the strengths and weaknesses based on the neurocognitive profile.

**Specialized interventions:** Coaching parents and survivors based on the neurocognitive profile; using the BrainSTAR (Strategies for Teams and Reeducation for Students) program at school [71]; neurocognitive interventions: Amsterdam Training for Attention and Memory in Children (ATAG-K) [72]; Neurofeedback; Cogmed [73-75]; pharmacological interventions (Stimulantia [76-78]); transition to a special education school or rehabilitation setting; family interventions for example Brain Injury Family Intervention (BIFI) [79-81].

*Psychosocial interventions*

**Basic interventions:** Stimulate peer contact; Emma at Work (an employment agency for adolescents with a chronic disease); Psycho-educational group intervention (‘On track’ – Op Koers; face-to-face and web-based intervention-www.opkoersonline.nl) and fellow patient contact.

**Specialized interventions:** Social skills training; Coaching parents and survivors in coping with late effects; psychological therapy for instance focusing on social skills, acceptance and coping with the late effects, trauma-focused therapy.
Conclusions

This thesis includes exploratory studies of CBTS or ALL survivors within the broad scope of late effects and possible interventions for cognitive problems. Long-term survivors suffer from several late effects of their disease and their treatment many years after having been cured. This thesis demonstrates that not only survivors who were treated with surgery and adjuvant therapy, but also survivors who were treated with surgery only can experience a wide range of late effects. This stresses the need for routine multidisciplinary aftercare for all CBTS. Standardized aftercare after a childhood brain tumor should be used to inform CBTS and their parents about possible late effects and aftercare options, monitor functioning and needs of CBTS and their parents, screen and identify survivors at risk to be able to provide aftercare in time.

Take-home messages:

1. Late effects are commonly experienced by CBTS;
2. There is a considerable need for aftercare for the late effects, but this need is not always identified on time;
3. Special attention is required for survivors who were treated with surgery only in order to prevent underestimation of their late effects;
4. More than one-third of the CBTS are at risk for impaired HRQOL for physical well-being, psychological and social functioning;
5. White matter tracts show impairment in pediatric cancer survivors and correlate with the slow information processing speed in CBTS;
6. Neurofeedback training is a feasible intervention for CBTS who suffer from neurocognitive late effects;

Systematic aftercare is needed to:
- inform CBTS and their parents about late effects and to provide psycho-education
- monitor psychosocial functioning, school results and parents’ need
- identify survivors at risk for late effects and aftercare needs
- timely provide appropriate aftercare services and neurocognitive and/or psychosocial interventions.
References


44. Deijen JB, Arwert LI, Drent ML. The GH/IGF-I Axis and Cognitive Changes across a 4-Year Period in Healthy Adults. ISRN Endocrinol 2011: 249421.


