CHAPTER 10

Summary

Childhood cancer and its treatment negatively affect physical and most often psychosocial functioning of a child. Some negative effects are permanent, but others are reversible. The assessment of late effects after childhood cancer and its treatment is increasingly important since there is an increasing number of childhood cancer patients that survive the disease. Current estimates indicate that 77% of the children who are diagnosed with cancer will be alive five year post-diagnosis. Mortality rates in childhood cancer survivors are increased compared to the general population and studies on morbidity after childhood cancer showed that approximately 75% of the 5-years childhood cancer survivors had one or more (severe) chronic health-outcomes. Given the increased risk for future health problems it is important to develop interventions both to prevent organ damage as well as to promote healthy behavior.

The primary aim of this thesis was to assess whether it was possible to improve physical fitness and health-related quality of life through a 12-week combined physical exercise and psychosocial training program for children with cancer (Quality of Life in Motion [QLIM]), provided during or within the first 12-months after cessation of treatment. In addition, the cost-effectiveness of this intervention was evaluated to assess if health care providers should incorporate the QLIM intervention in general practice.

In **chapter 2**, we investigated the cardiorespiratory fitness, physical activity and sedentary behavior as well as factors associated with these outcomes in children during or shortly after cancer treatment. Baseline study data were used to determine cardiorespiratory fitness, obtained by the cardiopulmonary-exercise-test, and physical activity and sedentary behavior data as measured by an accelerometer. It appeared that the peak oxygen uptake of children with cancer was low; in 32 out of 60 children the peak oxygen uptake was even 2 standard deviation below the predicted value. We found a significant association between cardiorespiratory fitness and physical activity and sedentary behavior: each additional activity count per min resulted in a 0.05 $ml \cdot kg^{-1} \cdot min^{-1}$ peak oxygen uptake increase and each additional min sedentary reduced the peak oxygen uptake with 0.06 $ml \cdot kg^{-1} \cdot min^{-1}$. A significant association was found between a decreased activity level and higher age, being fatigued and being during childhood cancer treatment or having a higher percentage of fat mass. In line with these results we could conclude that there was need for children with cancer to increase their physical fitness.

In **chapter 3** the results of a Cochrane review on physical fitness interventions for children with cancer are presented. In this review only randomized controlled trials and clinical controlled trials were included. The aim of eligible studies was to improve physical fitness (cardiorespiratory fitness or muscle strength), body composition, health-related quality of life, or self-perception, or to decrease fatigue, or anxiety and depression in children with cancer. Study participants needed to be less than 19 years of age, could be diagnosed with any type of childhood cancer and were during the first

five years after diagnosis. Studies that were included needed to compare a physical exercise training intervention with a control group receiving care as usual.
Six articles were included in this review: five randomized controlled trials (14, 14, 28, 40, and 51 participants) and one clinical controlled trial (24 participants). All included children were treated for childhood acute lymphoblastic leukemia and all study interventions were implemented during chemotherapy treatment. The training time per session ranged from 15 to 60 min and the duration of the intervention from ten weeks to two years. In all included studies the control group received care as usual. The six included studies showed some positive intervention effects on cardiorespiratory fitness, muscle strength, body composition, health-related quality of life and flexibility, and but not on the level of daily activity, and fatigue.
In **chapter 4** the design of the planned multi-center randomized controlled trial was provided. The QLIM study intervention, a 12-week combined physical exercise and psychosocial training program, was provided to children who were during or within the first year after childhood cancer treatment. This study intervention was compared with usual care (control group).
The physical intervention included a combination of both cardiorespiratory and muscle strength training (twice a week for 45 min) and was provided by pediatric physical therapists at a local physical therapy (sports) center according to an instruction manual. The psychosocial intervention included cognitive-behavior techniques and psycho-education and was provided by an experienced pediatric psychologist (once every 2-weeks for 60 min) at the childhood oncology treatment center of the child. Two parent sessions were added to increase awareness of inactivity and cancer-related problems (at the start) and to evaluate the process and effects of the QLIM intervention (final session).
The study primarily aimed to assess effects on cardiorespiratory fitness, and muscle strength (physical fitness), but also to investigate many additional outcomes, such as body composition (bone density and fat mass), fatigue, psychosocial functioning and health-related quality of life. For most outcomes the gold-standard method or a comparable solid and validated assessment tool was used.
Chapter 5 provides the short and long-term results of the QLIM intervention. In total, 68 children (mean age 13.2 years (SD: 3.1); 54% male) were included; 30 in the intervention and 38 in the 'usual-care' control group. Effects on physical fitness and other physical outcomes directly after the intervention were absent. However, after 12-months, a significant beneficial intervention effect was found for lower body muscle strength. Unfortunately, but in line with the other outcomes, no significant intervention effects were found for psychosocial wellbeing.
We, furthermore, were interested in effects on the end score of health-related quality of life. More specifically, we were interested if the relation between receiving the QLIM intervention and end-score health-related quality of life was mediated by both physi-

cal and psychosocial outcomes. These regression paths were investigated through mediation analysis. We found no significant mediation effect by physical or psychosocial short term intervention effects on health-related quality of life. However, we found a positive relation between four psychosocial outcomes (depressive symptoms, athletic competence, global self-worth and behavior problems) measured directly after the intervention and the final score on general health-related quality of life. This indicated that the intervention could have had positive effects on health-related quality of life.

In **chapter 6** we described differences between children who wanted to participate in the QLIM study and those who did not wanted to participate in the study. Over a period of four years a total of 174 children were eligible for the study, of which 106 (61%) did not participate. All these 106 children were asked whether they were willing to fill in a one-time survey. This survey included a form to report their reason for study-refusal and many of the same questionnaires as the participants had to fill in at baseline. Sixty-one out of the 106 (58%) completed and returned the questionnaires. The main reason for not willing to participate was that the study was too time consuming, and that (especially) parents thought the intervention was too demanding for their child. The participant versus non-participant comparison showed no difference between participants and non-participants on characteristics such as age, sports participation, body mass index, health-related quality of life, school-type and own report on their health. We showed that children with more travel distance (home-treating hospital) were significantly less willing to participate in the study. In addition, we showed that the non-participants rated their physical fitness, on a 10-point scale, with a higher score than participants, and participants (11–18 years old) significantly reported more (in particular internalizing) behavioral problems. From these results it seemed that the QLIM study included a somewhat selected group of participants that were in need for additional care.

In **chapter 7** the costs of the intervention and provided health care were assessed over the total study period of 12-months. At 12-months follow-up, no significant differences in costs and effects were observed between the intervention and control group. On average, but not significantly, societal costs were € 497 per child higher in the intervention group than in the control group and non-cancer treatment medication costs were € 2000 higher in the control-group than in the intervention group.

The probability of the intervention to be cost-effective on the outcome s 'quality adjusted life-years' (QALYs) and 'lower body muscle strength' increased up to 75-80 percent at willingness-to-pay values of € 100,000 per gained QALY and € 600 per increased Newton (strength). For two other outcomes (cardiorespiratory fitness and upper body muscle strength), the maximum probabilities of cost-effectiveness were low at all willingness-to-pay values and therefore would never become cost-effective.

Sensitivity analyses did not show changes in outcomes, indicating that the results were relatively robust.
With these results we showed that the intervention was not cost effective and should not be implemented as part of standard care in its current form.
In **chapter 8** a comparison was made between the results of the gold-standard gas-analysis using cardiopulmonary exercise test and the Steep Ramp Test to measure/estimate peak oxygen uptake. Short and easy testing is generally preferred, but this is especially suitable for children with cancer who already have to face many inconvenient assessments and intensive treatment. Compared to the cardiopulmonary exercise test, the Steep Ramp Test has a relatively short duration and can be performed without gas-analysis. Not needing gas-analysis increases the implementation possibilities to less specialized clinics, or local physical therapy center. Sixty-one children performed both the cardiopulmonary exercise test and the Steep Ramp Test on the same day at baseline of the study. The test results were compared.
The test results correlated significantly. However, the cardiopulmonary exercise test was more demanding for the cardiovascular system than the Steep Ramp Test. This was especially shown by the lower peak oxygen uptake (L/min), peak ventilation and peak heart rate values during the Steep Ramp Test. The duration of the Steep Ramp Test was shorter; as was also shown by our results. The cardiopulmonary exercise test had a median duration of 6.5 min (IQR: 5-8 min) whereas the Steep Ramp Test had a median duration of 1.5 min (IQR: 1-2 min). Apart from these differences we found that the Steep Ramp Test can validly be used to estimate the peak oxygen uptake through an equation to provide a valid impression of the child's cardiorespiratory fitness.
In conclusion, the Steep Ramp Test can be used in children with cancer to get an indication of their cardiorespiratory fitness. This can be done without gas-analysis and in a local hospital or physical therapy center, making the test less invasive.
Finally, in chaper 9, the main findings were discussed and interpreted, and recommendations for research and practice were presented.