Surviving childhood cancer : quality of life, course of life, and coping

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Quality of life, course of life, and coping

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Surviving childhood cancer
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1 Introduction

The treatment of patients with childhood cancer has enormously improved in recent decades. Many patients who may previously have had a limited life expectancy are now growing up with childhood cancer and surviving into adulthood. A five-year period from diagnosis is usually considered the defining criterion for long-term survival (1). The enormous increase in the number of survivors of childhood cancer reaching adulthood has intensified the need to investigate the consequences of childhood cancer for survivors and their families. The diagnosis and treatment of childhood cancer is a dramatic event that could influence physical and psychosocial functioning long after treatment has been terminated (2-5). Survivors and their parents have to live with the uncertainty about recurrence of the disease and possible long-term negative side effects.

Increasing numbers of studies have been directed at assessing Health Related Quality of Life (HRQOL) and psychosocial adjustment in survivors of childhood cancer, and considerable literature has been devoted to the emotional reactions and coping of paediatric patients, their parents or both during cancer treatment (2;6;7). Less is known about what happens in the first few years after successful treatment, in the period leading up to survivorship, and relatively little attention has been directed at psychosocial predictors of (long-term) adjustment to the cancer experience. The course of patients' adjustment to survivorship over time and their adjustment in young adulthood are the main subjects of this thesis, which focuses on psychosocial factors that are predictive of adjustment. This introductory section describes the background of the study; medical aspects of childhood cancer, the concept of HRQoL and the design of the VOLG (Vragenlijsten kinderOncologie Late Gevolgen; in English, Questionnaire on Late Effects of Childhood Cancer) study. Although a five-year period from diagnosis is commonly considered a criterion for survival, we decided to consider the patients in the VOLG-study survivors because they were in progression towards long-term survivorship.

2 Medical aspects

2.1 Diagnosis

Cancer is a rare disease in children. Nevertheless, it is the second leading cause of death in children and the primary cause of death from diseases (8). Approximately 400 children up to the age of fifteen are diagnosed with cancer in the Netherlands every year, accounting for 0.6 percent of the total cancer incidence in the Netherlands (9). Approximately two of every thousand young adults in the Netherlands have suffered from childhood cancer at some time (10).

Cancer is defined as the uncontrolled and unrestrained proliferation of cells, which can occur anywhere in the body. The characteristics of childhood cancer differ from those of cancer in adults in type, histology and anatomic location. Leukaemia, central nervous system tumours (CNS-tumours) and lymphoma are the most common in children, representing approximately about one-third, one-fourth and one-tenth of the incidence of childhood cancer, respectively. The incidence of several cancer diagnoses varies across age groups and

gender. The incidence of some childhood cancer diagnoses (e.g. acute lymphocytic leukaemia (ALL), CNS-tumour, neuroblastoma,Wilms's tumour) decreases with age, while the incidence of other diagnoses (e.g. Hodgkin's disease and bone tumour) increases with age. Leukaemia and lymphoma are found more frequently in boys than in girls (8;10;11).

2.2 Treatment

In the Netherlands, most children suspected of having cancer are referred to one of the paediatric oncology centres. In some cases, part of the treatment can be performed in another hospital that is closer to the patient's home than the paediatric oncology centre. Patients are treated according to treatment protocols that have been developed through international cooperation and research. All healthcare providers specialised in child oncology in the Netherlands are members of the Dutch Childhood Oncology Group (Stichting Kinderoncologie Nederland; SKION). Surgery, chemotherapy and radiotherapy are the major modalities of cancer therapy. Standard practice usually involves a combination of treatment modalities. Leukaemia is currently treated with chemotherapy alone and, solid tumours are usually treated with surgery combined with chemotherapy and/or radiotherapy. The length and type of treatment depend on a number of factors, including the type of cancer, location and stage of the disease. Children with ALL, the most frequently occuring diagnosis of leukaemia, undergo a two-year chemotherapeutic protocol, which also includes repeated lumbar punctures and bone-marrow punctures (12). Solid tumours (e.g. bone tumours, nephroblastoma and brain tumours) are treated according to their location, size and nature. In some cases, surgical removal without further treatment is sufficient; in many cases, however, chemotherapy, radiotherapy or both may be necessary after (or before) surgery.

Unfortunately, cancer treatment and related medical procedures cause pain and distress. Although the development of more effective and targeted treatments has reduced the side effects to some extent, they are still present. The severity of the side effects depends on the type and location of cancer, the age of the child and the intensity of treatment. Side effects of treatment can occur within days or weeks of initial treatment (early side effects), or even months to years after the end of treatment (late side effects). Late side effects are discussed in Section 2.4.

Surgery is performed in order to diagnose the cancer, determine tumour response after therapy, or remove (part of) the tumour. It is usually preceded or followed by chemotherapy, radiotherapy or both (13). The use of surgery increases the risk of adhesion. The negative impact of surgical procedures depends on the location and the extent of the surgery. Amputation of an arm or a leg is a surgical procedure that is sometimes used in the treatment of bone tumours. Advances in diagnostic imaging and the use of pre-surgical chemotherapy have led to the development of more limb-sparing procedures for children with bone tumours (14).

Chemotherapy concerns the oral or intravenous administration of cytostatica which affect all rapidly dividing cells, including normal cells. This can cause such side effects as hair loss, nausea and vomiting, mouth sores, diarrhoea and bone-marrow depression, which can lead to anaemia, leukopaenia and thrombocytopenia (15).

Radiotherapy destroys tumour tissue but it can also damage nearby normal tissue. Damage to normal tissue can cause side effects such as burns, skin discoloration or weakness of the skin, usually related to the treated area (16).

2.3 Survival

Cure and long-term survival rates are usually based on five-year survival from diagnosis (1). Before the introduction of chemotherapy and radiotherapy, in the 1960s, childhood cancer was fatal in most cases. The introduction of modern therapies has resulted in enormous increases in survival rates. More recently, centralisation of care, treatment protocols and large successful clinical trials have contributed to further improvement in survival rates.

The overall five-year survival rate for children diagnosed with cancer in Europe is currently more than 70%, as compared to 30% in the 1960s (1;17-19). Survival rates depend on both diagnostic and prognostic factors. The survival chances for some types of cancer are high. For example the survival chances for Wilms' tumour and Hodgkin's disease are between 80% and 90%. On the other hand, the prognosis for some other cancers (e.g. neuroblastoma) is much lower (17). Although the majority of the childhood cancer patients can be considered cured five years after diagnosis, 10% of such patients die of disease recurrence or treatment-related causes within ten years (17).

2.4 Late effects and aftercare

As more and more children with cancer survive and enter adulthood, the importance of monitoring the late effects (both physical and psychosocial) of disease and treatment has been gaining recognition. In 1996 the long-term follow-up clinic at the Emma Children's Hospital/Academic Medical Centre in Amsterdam was established to monitor the long-term sequelae of childhood cancer and its treatment. Survivors become eligible for transfer from active-treatment clinics to the follow-up clinic if they have successfully completed their cancer treatment at least five years earlier. Survivors are evaluated annually in the clinic by a paediatric oncologist (survivors younger than 18 years of age) or by an internist-oncologist (survivors 18 years of age or older) for late medical effects. From two years after the end of treatment patients receive psychosocial screening from a psychologist of the Emma Children's Hospital AMC in addition to their regular control visits with the paediatric oncologist.

Studies indicate that between 60% and 75% of all long-term childhood cancer survivors develop one or more adverse events due to the disease or treatment, and approximately one-third of these events are classified as either moderate or severe (5;20-24). The health problems can be categorised into ten main groups, according to the classification developed by Stevens et al.(4): endocrine, organ toxicity, mobility/orthopaedic, fertility, sensory, cosmetic, fatigue, subsequent neoplasm, psychosocial/cognitive and neurological.

Studies in childhood cancer survivors performed during the past 25 years have found little evidence of serious maladjustment based on standardised psychological tests (25). Research on specific areas of psychosocial adjustment, however, has found that between 25% and 30% of survivors and their family members have experienced personal, family or social difficulties that have affected their academic achievement, employment, interpersonal relationships or self-esteem (23). Considering the adverse effects of many treatments, there is need for research that addresses the psychosocial impact of late physical effects on the lives of (long-term) survivors (26). The research literature about late psychosocial consequences of childhood cancer is reviewed in Chapters 2 and 7 of this thesis.

Survivors have an increased risk of developing subsequent neoplasms, which are probably the most feared late effect. Second malignancies can result from chemotherapy or

radiotherapy, but predisposition could also be a explanatory factor (27-29). The cumulative risk of developing second malignant tumours among survivors varies from 3.7% to 12% within 25 years after treatment of a first cancer in childhood (30). Subsequent benign or malignant neoplasms were diagnosed in one out of every twenty adult survivors at the PLEK (29).

In the light of the foregoing discussion, it is questionable whether children who have been treated for cancer can ever be considered cured. Experts in paediatric oncology from fifteen countries in Europe and North America discussed this issue and wrote in the Erice Statement (31): "We define "cure" as cure from the original cancer, regardless of any potential for, or presence of remaining disabilities or side effects of treatment. The term "cured" should be used when discussing the survivors' status in society. The term "long-term survivor" will continue to be used in scientific research and related literature to alert professionals to sequelae which require care and attention."

3 Health-Related Quality of life

3.1 The concept of Health-Related Quality of life

The increased survival rates of paediatric diseases, especially childhood cancer, have led to a call for new outcome measures that reflect more than the quantity of survival. The quality of survival – in other words, the quality of life (QoL) – is becoming more and more important (2;32).

There is no universally accepted definition of QoL, as it is depends on the specific social, cultural, spiritual and historical circumstances in which we find ourselves. The World Health Organisation defines QoL as "individuals' perceptions of their position in life in the context of the culture and value systems in which they live, and in relation to their goals, expectations, standards and concerns". The medical approach to QoL emerged in response to advances in medical care. The concept of Health-Related QoL (HRQoL) refers to the impact of health and illness on an individual's QoL (2;32). While HRQoL focuses on the health concept and the field of health outcomes, QoL includes all aspects of life, including the environment or externalities outside the context of healthcare (33).

It is generally accepted that HRQoL is a multidimensional construct incorporating at least three broad domains: physical, psychological and social functioning. Physical functioning refers to activities of daily living, as well as to physical symptoms resulting from disease or treatment. Psychological functioning ranges from severe psychological distress to a positive sense of well-being, and it may encompass cognitive functioning. Social functioning refers to social relationships and interactions, and to societal integration. Beyond this core set of HRQoL domains, additional issues may be relevant for specific groups of patients, depending on the functional domains affected by the disease or treatment. In addition, there is consensus that HRQoL also entails an overall judgement of health and/or quality of life (34).

3.2 Assessment of Health-Related Quality of life

Measuring HRQoL is complicated, given the breadth of the construct and the fact that it cannot be assessed directly. In the past, measurements of HRQoL were often limited to physical functioning or health status, without taking into account the patients' evaluations

of their health status. This can be considered improper use of the HRQoL concept because 'real' HRQoL is characterised by weighting health status problems by the impact of the health status problems on the well-being of patients. The latter is important, as it offers patients the possibility of differentiating between their functioning and the way they feel about it, which could yield clinically relevant information for healthcare providers. The availability of 'real' HRQoL instruments is increasing. Examples include the Dutch TAPQOL, TACQOL and TAAQOL questionnaires, which have also been translated into English and several other languages (35-39). Most of the items in these questionnaires comprise two questions linked to one another. The first question concerns the frequency of the health status problem in the past few weeks. The second question rates the possible negative emotional responses to the problems. The items are clustered into multi-item scales covering all HRQoL domains: physical, psychological, and social functioning (see also Section 3.3). This type of instruments is still sparse and has yet to receive wide acceptance, but the availability of multidimensional HRQoL instruments that cover the basic HRQoL domains is increasing.

The instruments used in research may be either generic, disease-specific or domain-specific (34), depending on the nature of the research questions and on the availability of the preferred instruments. Most HRQoL instruments are self-report questionnaires.

Generic instruments are intended for use across a wide range of (patient) populations. They are usually composed of a number of subscales, each of which assesses a different dimension of HRQoL. The major advantage of generic instruments is that they allow for comparison across different populations, including healthy populations. Such instruments are less appropriate for assessing specific problems arising from specific diseases (e.g. disease symptoms and treatment side effects). Most generic instruments are therefore insufficiently responsive to allow the assessment of disease-related changes in HRQoL (32;34).

Disease-specific instruments include domains designed to be valid only for specific patient populations, as they assess disease-related aspects of HRQoL (e.g. side-effects of chemotherapy among cancer patients). Disease-specific instruments are more responsive to disease-related changes in HRQoL over time and to differences within disease groups than are generic instruments, but they are not suitable for comparisons across disease groups (32;34).

Domain-specific instruments address one specific aspect of HRQoL (e.g. pain or depression) in greater detail. These instruments are usually not disease-specific (34). Batteries of domain-specific instruments are sometimes used for cases in which no comprehensive measure of HRQoL is available.

3.3 Measuring Health-related Quality of life in children

The evaluation of adult HRQoL is well established and the use of reliable and valid measures of HRQoL is included in many clinical trials. From an historical perspective, the measurement of HRQoL in children has received less attention than it has in adults.

Increases in the survival rates for paediatric diseases have intensified the need to assess HRQoL among children. Early efforts to describe HRQoL in children were focused on health status and functional status, and most relied on assessments made by clinicians (32). In contrast, HRQoL is now considered to be a multidimensional concept that includes at least physical functioning (e.g. physical complaints, motor functioning), psychological functioning (e.g. cognitive and emotional functioning) and social functioning (e.g. contacts with peers).

Nonetheless, few instruments explicitly allow differentiations between children's functioning and the way they feel about it, as do the TAPQOL, TACQOL and TAAQOL. These questionnaires are generic Dutch instruments for different age groups, and they measure health status problems weighted by the impact of the health status problems on well-being. The TNO-AZL Preschool Quality of Life questionnaire (TAPQOL) is intended for children between the ages of one to five (36;40), the Parent Form of the TNO-AZL Children's Quality of Life questionnaire (TACQOL-PF) is intended for children between the ages of six to fifteen (38) and the Child Form (TACQOL-CF) is intended for children between the ages of eight and fifteen (37;39). Finally, the TNO-AZL Adult's Quality of Life questionnaire (TAAQOL) is intended for people sixteen years of age and older (35) (see also Section 3.2).

In recent years, increasing numbers of disease-specific HRQoL instruments have been developed for use with children with several chronic diseases. These instruments have been validated and translated into Dutch. Examples include the Kidscreen and the Disabkids (41), and the cancer-specific module of the PedsQL (42). The latter focuses on HRQoL during treatment and is not appropriate for performing assessments after termination of active treatment.

Assessing HRQoL in children is difficult, because different questionnaires are needed for different age groups. Comparisons of HRQoL outcomes in children from different age groups or over time are thus complicated as well. It is important to consider the use of *proxy ratings* as substitutes for ratings made by children themselves. A case in point would be when children are either too young or too ill to complete the questionnaires themselves. Proxy ratings can also provide important complementary information about children (32). It is becoming increasingly acknowledged that the children's perspectives differ from those of their parents, although they are not less valid. This is an argument for obtaining information from both parents and children whenever possible (43).

The results of a systematic review by Eiser and Morse (43) showed that child scores and parent scores for observable aspects of HRQoL (e.g. physical functioning) were in closer agreement than they were for non-observable aspects of HRQoL (e.g. emotional functioning). There was also better agreement between the scores of parents and chronically ill children than there was between parents and their healthy children, although the agreement may be dependent on the HRQoL measure employed.

Theunissen et al. (44) investigated agreement between child-reported and parent-reported HRQoL assessed with the TACQOL, one of the HRQoL instruments used in this thesis. They found that the levels of HRQoL reported by children from the general Dutch population with regard to physical complaints, motor functioning, autonomy, cognitive functioning and positive emotions, were significantly lower than those reported by their parents. Furthermore, agreement on all scales seemed to be related to the magnitude of the HRQoL score (i.e. child scores were less extreme than the parent scores were). When parents were very pessimistic, children seemed to say "It's not so bad", and when parents were very optimistic, children seemed to say "It's not that good".

3.4 Clinical relevance

Although HRQoL is assessed in many clinical trials in adult medicine, the interpretation of HRQoL data remains difficult. When are changes in HRQoL over time clinically meaningful? Although changes in HRQoL may be statistically significant, the clinical relevance of these

changes may be difficult to interpret. According to Lydeck and Epstein (45) "Results from 'objective' tests are seen to be 'clinically meaningful' only because of the historical context. The problem with defining clinical significance of HRQoL change has nothing to do with any innate inferiority of HRQoL as a type measure. It is merely a reflection on the newness of these measures and our inexperience with them. As all parties involved gain increased familiarity with these measures, their clinical significance will become more obvious and less problematic."

The clinical meaningfulness of group change scores on HRQoL questionnaires has been receiving increasing attention (43;46). Lydick and Epstein (34;45;47) distinguished two approaches to establishing clinical meaningfulness: distribution-based and anchor-based. Distribution-based approaches are based on statistical characteristics of the study sample. The magnitude of the effect is expressed in terms of the variability of the results: statistical significance, effect size or standard error of measurement (48). Effect size, as defined by Cohen (49), is used widely. Effect sizes (d) are calculated by dividing the difference in mean score between the patients and the norm group by the standard deviation of the scores in the norm group. According to Cohen, effect sizes up to 0.2 are considered small, effect sizes of about 0.5 are considered medium, and effect sizes of about 0.8 are considered large.

Anchor-based approaches compare the HRQoL scores to an independent standard or anchor that is more easy interpretable than the HRQoL instrument is, and is at least moderately correlated with the HRQoL instrument used (50). This type of approach allows changes in HRQoL to be linked to a meaningful external anchor. The use of 'global ratings of change' is one of the most commonly used anchor-based approaches for establishing clinically meaningful change in longitudinal studies (48). In a 'subjective significance questionnaire', patients can indicate whether their global HRQoL improved, decreased or remained unchanged during a specific period. The 'global rating of change' can be used as a standard against which to compare actual changes in HRQoL (i.e. the scores on the HRQoL questionnaire) (46). The smallest difference in score in the HRQoL domain of interest that patients perceive as change (worse or better) is called the Minimal Clinically Important Difference (MCID) (45;50). The threshold of discrimination for changes in HRQoL among adult patients appears to be approximately half of one standard deviation (51). To date, however, MCID has not been assessed for HRQoL in children.

4 VOLG-study

This thesis reports the results of the VOLG (Vragenlijsten kinderOncologie Late Gevolgen; in English, Questionnaire on Late Effects of Childhood Cancer) study, which investigated 'quality of life, course of life and coping in childhood cancer survivors'. The VOLG-study, which was financed by the Dutch Cancer Society, was conducted by the Psychosocial Department of the Emma Children's Hospital AMC between 2000 and 2006.

The study focuses on (1) the psychosocial adjustment of children and adolescents growing up with childhood cancer, and the emotional adjustment of their parents, in the first three to five years after successful treatment in the run-up to survivorship (longitudinal part VOLG-

study), and (2) the psychosocial adjustment of young adult survivors of childhood cancer (cross-sectional part of the VOLG-study).

The VOLG-study is part of the research line of the paediatric psychology program in the Emma Children's Hospital AMC, which focuses on studying the consequences of growing up with chronic disease for patients as well as for their parents.

4.1 Purpose

The number of children and adolescents surviving cancer and reaching adulthood has increased enormously in recent decades due to advances in cancer treatment. As a result, healthcare providers are increasingly likely to be confronted with survivors who have grown up with childhood cancer. In order to provide optimal support to survivors and parents, more insight is needed into the process of psychosocial adjustment to childhood cancer.

The VOLG-study aimed to (1) assess HRQoL in paediatric survivors of childhood cancer over time in comparison with normative data, and HRQoL in young adult survivors in cross-sectional comparison with a reference group, (2) identify predictors of HRQoL in survivors of childhood cancer, focusing on course of life, coping, social support, family functioning and medical variables, and (3) assess emotional adjustment in parents over time.

4.2 Research questions

The goal of the VOLG-study was to answer the following research questions.

The primary questions of the *longitudinal study* are as follows:

1. How does the HRQoL of children with cancer following the end of successful treatment compare with normative data over time?
2. Which characteristics (e.g. coping, family functioning and medical variables) are predictors of HRQoL over time in childhood cancer survivors?
3. How do parents adjust emotionally over time following the end of successful treatment of their children with cancer?

The primary questions of the *cross-sectional study* are as follows:

1. How does the HRQoL of young adult survivors of childhood cancer compare to that of a reference group?
2. How does the course of life of young adult survivors of childhood cancer compare to that of a reference group?
3. What is the relationship between medical variables (e.g. diagnosis, treatment, age at diagnosis) and the course of life of young adult survivors of childhood cancer?
4. Which characteristics (e.g. course of life, coping, and medical variables) are predictors of HRQoL in young adult survivors of childhood cancer?

4.3 Theoretical background and research model

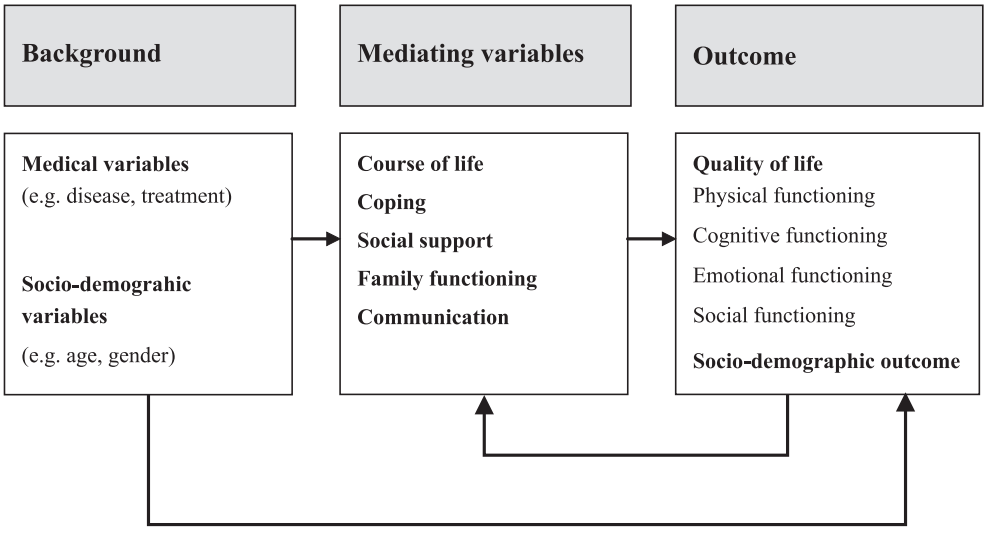
Diagnoses of childhood cancer have an enormous impact on the affected children and their families. They are confronted with a life-threatening disease that usually implies extensive treatment with negative side effects and the risk of negative long-term consequences. Though psychopathological disturbances are rarely found in either children with cancer or their parents (6;7), a growing body of evidence suggests that a considerable proportion of the long-term survivors are adversely affected in specific areas of psychosocial functioning. This

evidence emphasises the need for more insight into the process of psychosocial adjustment to childhood cancer (23;25).

Insight is needed into protective and risk factors associated with adjustment to the experience of childhood cancer. Although previous reviews have traced several predictors of adjustment in survivors of childhood cancer, it is not clear whether the adjustment of cancer survivors is associated with cancer-related medical factors or with such psychosocial factors as coping and family functioning (6;7).

Equivalent to other conceptual frameworks used to explain adjustment in paediatric patients (52) and adult patients (53), we presume that adjustment in survivors of childhood cancer (operationalised as HRQoL) is an outcome of a longitudinal process that is influenced by characteristics of the situation and the disease, and by personal and psychosocial factors (e.g. course of life, coping, social support, family functioning and communication about the disease). The VOLG-study focuses specifically on psychosocial factors, as they play an important role in paediatric psychology and are assumed susceptible to change. Our assumptions about the process of adjustment to cancer are reflected in the research model (Figure 1). The concepts require some explanation (see below). The concept of HRQoL has already been discussed in Section 3.

Figure 1: Research model



4.3.1 Course of life

The developmental consequences of growing up with or after childhood cancer may have consequences in adulthood. The fulfilling of age-specific developmental tasks in childhood is of great importance to the adjustment in adult life (54;55). The developmental tasks and the resulting developmental milestones that are necessary in the development of a child are referred to as the 'course of life'. The normal developmental tasks of childhood and adolescence involve the attainment of social and academic competence, the development of peer relationships and increasing independence from the parents (56).

The burden of cancer, treatment, hospitalisation and long-term medical sequelae interfere with the course of life. Suffering from childhood cancer and the subsequent treatment often increases the dependence of juvenile patients on their parents and other adults, and decreases participation in peer and school-based activities (57-60). This could pose a threat to the accomplishment of developmental tasks, resulting in a hampered course of life. Cognitive problems and non-attendance at school as a result of the disease and treatment may result in lower educational achievement levels (61;62). In addition, the achievement of identity might be problematic for adolescent cancer survivors (63).

From a developmental psychological point of view, risk behaviour is also relevant. To a certain extent, displaying risk behaviour – in terms of trying out – is part of the development from being a teenager to becoming an adult. Survivors of childhood cancer may display less risk behaviour than do their healthy peers, because they are keenly aware of the vulnerability of their health (64-66). Moreover, increased parental involvement as a result of the paediatric cancer experience (67) may limit children's opportunities to have unsupervised time with peers, which may decrease their opportunities to engage in risk activities with peers. On the other hand, we could possibly expect to observe more risk behaviour among survivors, in compensation for the limitations that were imposed upon them by disease in their youth. Previous studies have shown inconsistent results on this matter (68-71).

Some aspects of course of life (e.g. social functioning in school-aged cancer patients or survivors) have already been investigated. Little is known, however, about either the impact of medical determinants on the course of life of childhood cancer survivors or the impact of the course of life during childhood and adolescence on functioning in young adulthood. Knowledge about possible gaps in the course of life could be useful in clinical practice, as it could enable healthcare providers to aim for the most favourable course of life for patients with childhood cancer, both during and after treatment.

4.3.2 Appraisal, coping and stress

According to the model of stress and coping developed by Lazarus and Folkman (72), coping consists of actions, behaviours and thoughts aimed at dealing with the demands of events and situations that are appraised as stressful. Lazarus and Folkman (72) define the coping process as "cognitive and behavioural efforts to manage specific external and/or internal demands that are appraised as taxing or exceeding the resources of a person". Coping therefore mediates the effect of stress on the well-being of individuals. Perceptions, or cognitive appraisals of the stressful situation, are an important element in regulating stress (emotion-focused coping) or managing problems that cause stress (problem-focused coping).

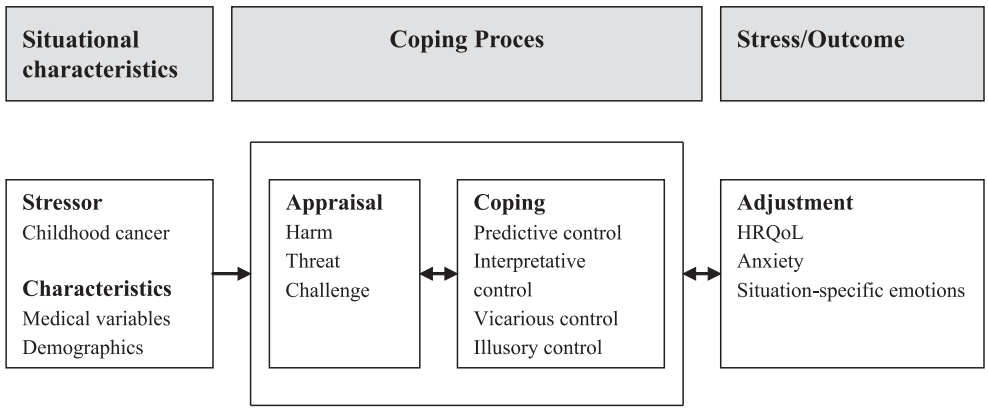
Cancer can be considered an uncontrollable stressor, as there is little that patients can do to cure the disease, and they are dependent on physicians. Our model of coping in survivors of childhood cancer (Figure 2) is based on Rothbaum's concept of primary- and secondary control (73). Rothbaum's theory is related to the problem-focused and emotion-focused coping described by Lazarus and Folkman (72). All of the actions involved in problem-focused coping can be seen as primary control. If stressors (e.g. childhood cancer) are perceived as uncontrollable, primary control fails and people will try to adjust to the situation. This process is known as secondary or cognitive control. Rothbaum et al. (73) distinguish four

control strategies: predictive control, vicarious control, interpretative control and illusory control.

In the context of coping with life-threatening illness the following disease-related cognitive control strategies were found to be relevant (74). *Predictive control* refers to attempts to predict events in order to create a feeling of control over the situation. Having positive expectations helps patients to deal with the consequences of disease. *Vicarious control* concerns the attribution of special power to others. In the case of cancer patients, power may be attributed to the doctors on whom they are dependent and on whom they focus all of their hopes. Because patients are unable to alter the course of the disease, a belief in powerful others can be adaptive. *Interpretative control* refers to the search for meaning and understanding. Using information to help understand emotional reactions or reduce uncertainty is an example of an interpretative control strategy. Finally, *illusory control* refers to attempts associated with chance, such as hoping for a miracle or wishful thinking.

Increased understanding about disease-related coping and the relation of coping with psychosocial functioning and HRQoL can enable healthcare providers to help patients cope with the consequences of their disease. It is difficult, however, to determine whether coping is associated with survivors' functioning or with their HRQoL because most studies have focused on coping as an outcome variable rather than as a predictor (7).

Figure 2: Model of appraisal, coping and stress



4.3.3 Social support

Social support refers to the perceived availability of friends and family to help a person cope with stress (75). For children with cancer, social support also contributes to personality and social development. Social support is a multi-dimensional construct that involves the type of relationship, the type and frequency of supportive behaviours and the quality of support (76).

In terms of coping, social support can be considered a coping resource, as social resources contribute to the (re)interpretation of the meaning of stressful situations. For example, social support can cause the situation to be perceived as less threatening. In this way, social support affects individual's well-being indirectly by alleviating the consequences of stressful life events. Social support may also influence the use of other coping strategies.

Positive social relations are considered to improve the HRQoL of individuals in general and to protect or buffer them from stressful life events, such as cancer (76). Childhood cancer is an extremely stressful event. Despite the importance of investigating social support in childhood cancer, research in this area remains sparse. Previous studies have indicated that social support is positively related to the emotional adjustment of survivors (77-79) and that it can protect parents from stress caused by their children's disease and treatment (80-82).

4.3.4 Family functioning

Because childhood cancer affects the life of the entire family of which the patient is a part, it is appropriate to consider the whole family system when studying adjustment to the cancer experience. According to the family-system perspective, the functioning of parents and the family influences the functioning of children, and vice versa. In several studies on childhood cancer, parental distress was found to be correlated with the emotional functioning of the children, but it is difficult to determine the direction of the correlation (7).

Family adjustment to chronic paediatric diseases has been often investigated by means of cohesion and adaptability, two dimensions of the Circumplex model of marital and family systems, described by Olson (83). Adaptability refers to the extent to which a family adapts its power structure, role definitions and rules according to internal and external demands. Cohesion refers to mutual connectedness among family members. In this theoretical framework moderate levels of cohesion and adaptability are considered related to the most favourable adjustment outcome in families faced with stress, whereas extreme levels of adaptation and cohesion are related to less adaptive functioning. Other, more recent, studies have indicated that high scores on cohesion and adaptability are related to more functional family relationships (84).

Most investigators report that the functioning of families experiencing childhood cancer is within normal limits (85-89), although some indicate that the parents of survivors are overly protective (90) and that they are more rigid and less flexible than are the parents of children who do not have a disease (91). A few studies report that the quality of family communication, cohesion and adaptability is positively related tot psychosocial outcomes in survivors (67;78;79;92).

Life events other than the cancer are also likely to explain adjustment in survivors of childhood cancer (7). A greater number of stressful or negative life events was found to be predictive of increased psychological distress and behavioural problems in childhood cancer survivors (93;94).

4.3.5 Communication

Communication has the function of transmitting information (informational function). It also serves to define, maintain or alter the relationship with the other person (relational function). Communication is related to coping, as it can change the appraisal of the stressful situation, and it can enhance primary control (problem-focused coping) and secondary control (emotion-focused coping). Information exchange about the disease enables those involved to define the problem and to attempt to solve it (primary control). Communication directed at secondary control of the situation promotes understanding and acceptance of the disease, and aims to reduce negative emotions and strengthen positive emotions. Communication

is of the utmost importance in stressful situations, as information can reduce uncertainty about situations that are perceived as threatening.

Openly informing the child about the disease and its implications appeared to be positively related to the child's emotional experience (95). It can help both the child and the parent to understand their situation and to gain psychological control of their situations. It is important to realise, however, that communication about the disease does not only involve the exchange of information about the disease; it also involves the exchange of emotions evoked by the situation. Open communication seems to be the best strategy as long as the facts about the illness are involved. Avoidance of communication about the seriousness of the illness or the emotional experience of the illness reflects a common defensive reaction to painful events; such avoidance could be a protective mechanism (96). For example, Van Veldhuizen and Last (97) found that children and parents use a specific type of protective coping strategy, which they called the phenomenon of double protection. Both children and their parents avoid communication about the emotional experience of cancer, not only to protect themselves against disease-related stress, but also to guard against painful confrontations with the unpleasant emotions of the other. An area of tension always exists between the need to control the situation by double protection and the need to share emotions with the other person. If the threatening stimuli and the emotions are too strong to be denied, the need for sympathy and support becomes dominant.

4.4 Study design

The VOLG-study consists of a longitudinal and a cross-sectional component.

A *longitudinal study* was conducted among 134 children or adolescents (between one and eighteen years of age at inclusion), from the end of treatment until three to five years thereafter, depending on the moment of inclusion. Children eight years of age or older completed the questionnaires themselves; these annual questionnaires concerned their HRQoL and coping. For children under the age of eight, parents completed proxy measures about their children's HRQoL. Parents also completed questionnaires about their own emotional adjustment and coping with the illness of their children. The scores of children and parents were compared with normative data, changes over time were analysed, and predictors of HRQoL were examined.

A *cross-sectional study* was conducted among 353 young adult survivors of childhood cancer, between the ages of eighteen and thirty years. All of these survivors had been diagnosed before the age of sixteen, and they had been screened at the long-term follow-up clinic at The Emma Children's Hospital AMC (PLEK). They completed questionnaires about HRQoL, course of life (retrospectively) and coping. The HRQoL and the course of life of the survivors were compared to that of a reference group, and predictors of HRQoL and course of life were investigated.

The questionnaires that were used in the VOLG-study are presented in Table 1 and Table 2.

Table 1: Questionnaires Longitudinal VOLG-study

Patients	
HRQoL	TNO-AZL Preschool Quality of Life questionnaire, for children aged 1 to 5 years (TAPQOL) (36;40).
	TNO-AZL Children's Quality of Life questionnaire; Parent Form for children aged 6 to 15 years (TACQOL-PF) (38) and Child Form for children aged 8 to 15 years (TACQOL-CF), (37;39).
	TNO-AZL Adult's Quality of Life questionnaire (TAAQOL) (35).
	Dutch Children's AZL/TNO Quality of life Questionnaire (DUCATQOL) (98).
Anxiety	State-Trait Anxiety Inventory (STAI), ZBV DY-2 (99;100).
	State-Trait Anxiety Inventory for Children (STAI-C), the ZBV-K (101;102).
Course of life	Course of life questionnaire (103-105).
Generic coping	Utrecht Coping List for Adolesents (106).
Disease-related cognitive coping	Cognitive Control Strategies Scale for patients (74;107-109).
Family functioning	Family Adaptability and Cohesion Evaluation Scales (FACES) (110-113).
Communication disease-related emotions	Exchange of Emotions Questionnaire (EEQ); developed for the VOLG-study, Psychosocial Department of the Emma Children's Hospital AMC
Parents	
Emotional distress	General Health Questionnaire (GHQ-30) (114;115).
Disease-related emotions	Situation-Specific Emotional Reaction Questionnaire (116).
Generic coping	Utrecht Coping List (UCL) (117).
Disease-related cognitive coping	Cognitive Control Strategies Scale for parents (CCSS) (74;107).
Family functioning	Family Adaptability and Cohesion Evaluation Scales (FACES) (110-113).
Social Support	Social Support Questionnaire for Transactions (118-120).
Communication disease-related emotions	Exchange of Emotions Questionnaire (EEQ); developed for the VOLG-study, Psychosocial Department of the Emma Children's Hospital AMC.

Table 2: Questionnaires Cross-sectional VOLG-study

HRQoL	RAND-36 (121;122)
Emotional distress	General Health Questionnaire (GHQ-30) (114;115)
Course of life	Course of life questionnaire (103-105)
Generic coping	Utrecht Coping List (UCL) (117)
Disease-related cognitive coping	Cognitive Control Strategies Scale for patients (CCSS) (74;107-109).
Social support	Social Support Questionnaire for Transactions (SSQT) (118-120)
Healthcare needs	Health-Care-Needs-Questionnaire (HCN-Q); developed for the VOLG-study, Psychosocial Department of the Emma Children's Hospital AMC

4.5 Outline of the thesis

This thesis focuses on answering the research questions described in Section 4.2.

In *Part I* the results of the longitudinal component of the VOLG-study are reported. It starts with the state of the art by summarising the research literature about social and emotional adjustment in young survivors of childhood cancer (Chapter 1). The subsequent two chapters focus on the adjustment of childhood cancer patients and their parents a few months after the end of successful treatment, in terms of the HRQoL of the children and the emotional adjustment of their parents (Chapter 2) and predictors of the HRQoL of the children (Chapter 3). Subsequently, the adjustment in the first few years after the end of successful cancer treatment is reported over time, including possible predictive factors: HRQoL in preschool children (Chapter 4) and in school-aged children (Chapter 5). Parental emotional adjustment over time and possible predictive factors are reported in Chapter 6.

In *Part II* the results of the cross-sectional component of the VOLG-study are reported. It starts with the state of the art by summarising the research literature about HRQoL in young adult survivors of childhood cancer (Chapter 7). Subsequent discussions address HRQoL and coping (Chapter 8), Course of life (Chapter 9), and Course of life as predictor of HRQoL (Chapter 10). Finally, all the information described in Part II is integrated by testing the entire VOLG research model (Chapter 11).

This thesis closes with a summary and discussion of the results of the preceding chapters (General discussion).

REFERENCES

(1) Novakovic B. U.S. Childhood cancer survival, 1973-1987. Med Pediatr Oncol 1994;23:480-6.

(2) Eiser C. Children with cancer. The quality of life. Mahwah, New Jersey, Londen: Lawrence Erlbaum Associates Publishers, 2004.

(3) Eiser C. Practitioner Review: long-term consequences of childhood cancer. Journal of Child Psychology and Psychiatry 1998;39(5):621-33.

(4) Stevens MCG, Mahler H, Parkes S. The health status of adult survivors of cancer in childhood. Eur J Cancer 1998;34(5):694-8.

(5) Oeffinger KC, Mertens AC, Sklar CA, Kawashima MS, Hudson MM, Meadows AT, et al. Chronic health conditions in adult survivors of childhood cancer. The New England Journal of Medicine 2006;355(15):1572-82.

(6) Langeveld NE, Stam H, Grootenhuis MA, Last BF. Quality of life in young adult survivors of childhood cancer (review). Support Care Cancer 2002;10:579-600.

(7) Stam H, Grootenhuis MA, Last BF. Social and emotional adjustment in young survivors of childhood cancer (review). Support Care Cancer 2001;9:489-513.

(8) Smith MA, Gloeckler LA, Ries LA. Childhood cancer: incidence, survival, and mortality. In: Pizzo P.A., Poplack D., eds. Principles and Practices of Pediatric Oncology.Philadelphia: Lippincott, Williams & Wilkins, 2002.

(9) Visser O, Siesling S, van Dijck JAAM. Incidence of cancer in the Netherlands 1999/2000 (digital publication). Utrecht: Association of Comprehensive Cancer Centres; 2003.

(10) Paulides J, Kamps WA, Caron H. Childhood cancer in the Netherlands 1989-1997. Utrecht, the Netherlands: Association of Comprehensive Cancer Centres; 2000.

(11) Stiller CA, Draper GJ. The epidemiology of cancer in children. In: Voûte PA, Barret A, Stevens MCG, Caron HN, eds. Cancer in children: clinical management. fifth edition ed. Oxford: Oxford University Press, 2005. p. 1-16.

(12) van den Berg H. Leukemie en myelodysplasie [Leukaemia and myelodysplasia]. In: Behrendt H., van den Berg H., van de Wetering M.D., eds. Kinderen en kanker [Children and cancer]. Amsterdam: Boom, 2002. p. 99-116.

(13) Heij HA. Chirurgie [Surgery]. In: Behrendt H., van den Berg H., van de Wetering M.D., eds. Kinderen en kanker [Children and cancer].Amsterdam: Boom, 2002. p. 42-6.

(14) Schaap GR, van den Berg H. Bottumoren [Bone tumours]. In: Behrendt H., van den Berg H., van de Wetering M.D., eds. Kinderen en kanker [Children and cancer].Amsterdam: Boom, 2002. p. 180-92.

(15) Verschuur AC. Chemotherapy. In: Behrendt H., van den Berg H., van de Wetering M.D., eds. Kinderen en kanker [Children and cancer].Amsterdam: Boom, 2002. p. 24-41.

(16) Oldenburger F. Radiotherapie bij kinderen [Radiotherapy in children]. In: Behrendt H., van den Berg H., van de Wetering M.D., eds. Kinderen en kanker [Children and cancer].Amsterdam: Boom, 2002. p. 47-58.

(17) Stiller CA, Draper GJ. The epidemiology of cancer in children. In: Voûte PA, Kalifa C, Barrett A, eds. Cancer in children: clinical management. fourth edition ed. Oxford: Oxford University Press, 1998.

(18) Magnani C, Pastore G, Coebergh J, Viscomi S, Spix C, Steliarova-Foucher E. Trends in survival after childhood cancer in Europe, 1978-1997: Report from the Automated Childhood Cancer Information system project (AGGIS). Eur J Cancer 2006;42(13):1981-2005.

(19) Sankila R, Martos Jiménez MC, Miljus D, Pritchard-Jones K, Steliarova-Foucher E, Stiller C. Geographical comparison of cancer survival in European children (1988-1997): Report from the Automated Childhood Cancer Information System project. Eur J Cancer 2006;42(13):1972-80.

(20) Lackner H, Benesch M, Schagerl S, Kerbl R, Schwinger W, Urban C. Prospective evaluation of late effects after childhood cancer therapy with a follow-up over 9 years. Eur J Pediatr 2000;159:750-8.

(21) Oeffinger KC, Eshelman DA, Tomlinson GE, Buchanan GR, Foster BM. Grading of late effects in young adults survivors of childhood cancer followed in an ambulatory adult setting. Cancer 2000;88:1687-95.

(22) Oeffinger KC, Hudson MM. Long-term complications following childhood and adolescent cancer: foundations for providing risk-based health care for survivors. CA Cancer J Clin 2004;54:208-36.

(23) Friedman DL, Freyer DR, Levitt GA. Models of care for survivors of childhood cancer. Pediatric Blood Cancer 2006;46:159-68.

(24) Geenen MM, Cardous-Ubbink MC, Kremer LCM, van den Bos C, van der Pal HJH, Heinen RC, et al. Medical assessment of adverse health outcomes in long-term survivors of childhood cancer. JAMA 2007;292(24):2705-15.

(25) Patenaude AF, Kupst MJ. Psychosocial functioning in pediatric cancer. J Pediatr Psychol 2005;30(1):9-27.

(26) Patenaude AF, Kupst MJ. Introduction to the special issue: surviving pediatric cancer: research gains and goals. J Pediatr Psychol 2005 Jan;30(1):5-8.

(27) Shusterman S, Meadows AT. Long term survivors of childhood cancer. Curr Opin Hematol 2000;7:217-22.

(28) Behrendt H, van den Bos C. Kankerbehandeling bij kinderen: late gevolgen [Cancer treatment of children: late consequences]. In: Behrendt H., van den Berg H., van de Wetering M.D., eds. Kinderen en kanker [Children and cancer]. 3th ed. Amsterdam: Boom, 2002. p. 233-45.

(29) van den Bos C, Langeveld NE, Geenen MM, Sukel M, Heinen RC, Jaspers MWM, et al. Follow-up of long-term survivors of childhood cancer: 6 years experience with a specialised care and screening programme. Cured of cancer: from childhood to adulthood, quality of survival.Amsterdam: Thela Thesis, 2003. p. 17-32.

(30) Lemerle J, Oberlin O, de Vathaire F, Pein F, Aubier F. Late and very late effectsof therapy - towards lifetime follow-up of cured patients. Cancer in children: clinical management. Oxford: Oxford University Press, 1998. p. 84-98.

(31) Haupt R, Spinetta JJ, Ban I, Barr RD, Beck JD, Byrne J, et al. Long term survivors of childhood cancer: cure and care. The Eric Statement. Eur J Cancer 2007;(in press; published online).

(32) Eiser C, Morse R. Quality-of-life measures in chronic diseases of childhood. Health Technol Assess 2001;5(4).

(33) Patrick DL. Patient-reported outcomes (PRO's): an organizing tool for concepts, measures, and applications. QoL Newsletter 2003;(31):1-5.

(34) Sprangers MAG, Aaronson NK, . Quality of life assessment in oncology. Acta Oncol 2002;41(3):229-37.

(35) Bruil J, Fekkes M, Vogels T, Verrips GHW. TAAQOL Manual. Leiden, The Netherlands: Leiden Center for Child Health and Pediatrics LUMC-TNO, 2004.

(36) Fekkes M, Bruil J, Vogels T. TAPQOL-manual. Leiden: Leiden Center for Child Health and Pediatrics LUMC-TNO; 2004.

(37) Verrips GHW, Vogels TGC, Koopman HM, Theunissen NCM, Kamphuis RP, Fekkes M, et al. Measuring health-related quality of life in a child population. European Journal of Public Health 1999;9(114):119.

(38) Vogels AGC, Verrips GHW, Fekkes M, Kamphuis RP, Koopman HM, Theunissen NCM, et al. Measuring health-related quality of life in children: the development of the TACQOL parent form. Qual Life Res 1998;7:457-69.

(39) Vogels T, Bruil J, Koopman H, Fekkes M, Verrips GHW. TACQOL CF 12-15 Manual. Leiden: TNO Prevention and Health; 2004.

(40) Fekkes M, Theunissen NCM, Brugman E, Veen S, Verrips E, Koopman HM, et al. Development and psychometric evaluation of the TAPQOL: A health-related quality of life instrument for 1-5-year-old children. Qual Life Res 2000;9:961-72.

(41) Ravens-Sieberer U, Erhart M, Bullinger M, European Kidscreen and Disabkids Groups. The Kidscreen and Disabkids Questionnaire - Two new measures for childrens' and adolescents' Health-Related Quality of Life. Patient Reported Outcomes 37, 9-11. 2006.

(42) Varni JW, Seid M, Rode CA. The PedsQL: Measurement model for the Pediatric Quality of Life Inventory. Med Care 1999;37:126-39.

(43) Eiser C, Morse R. Can parents rate their child's health-related quality of life? Results of a systematic review. Qual Life Res 2001;10:347-57.

(44) Theunissen NCM, Vogels TGC, Koopman HM, Verrips GHW, Zwinderman KAH, Verloove-Vanhorick SP, et al. The proxy problem: child report versus parent report in health-related quality of life research. Qual Life Res 1998;7:387-97.

(45) Lydick E, Epstein RS. Interpretation of quality of life changes. Qual Life Res 1993;2:221-6.

(46) Cella D, Hahn A, Dineen K. Meaningful change in cancer-specific quality of life scores: differences between inmporvement and worsening. Qual Life Res 2002;11(3):207-21.

(47) Sprangers MAG, Moinpour CM, Moynihan TJ, Patrick DL, Revicki DA, Clinical Significance Consensus Meeting Group. Assessing meaningful change in quality of life over time: a user's guide for clinicians. Med Pediatr Oncol 2002;77:561-71.

(48) Crosby RD, Kolotkin RL, Williams GR. Defining clinically meaningful change in health-related quality of life. J Clin Epidemiol 2003;56:395-407.

(49) Cohen J. Statistical power analysis for the behavioral sciences. New York: Academy Press, 1988.

(50) Guyatt GH, Osoba D, Wu AW, Wyrwich KW, Norman GR, the Clinical Significance Consensus Meeting Group. Methods to explain the clinical significance of health status measures. Mayo Clin Proc 2002;77:371-83.

(51) Norman GR, Sloan JA, Wyrwich KW. Interpretation of changes in health-related quality of life. The remarkable universality of half a standard deviation. Med Care 2003;41(5):582-92.

(52) Wallander JL, Varni JW. Effects of pediatric chronic physical disorders on child and family adjustment. Journal of Child Psychology and Psychiatry 1998;39(1):29-46.

(53) Wilson IB, Cleary PD. Linking clinical variables with health-related Quality of life. A conceptual model of patient outcomes. JAMA 1995;273(1):59-65.

(54) Garber J. Classification of childhood psychopathology: a developmental perspective. Child Dev 1984;55:30-48.

(55) Lewis M, Miller SM. Handbook of developmental psychopathology. New York: Plenum Press, 1990.

(56) Goudena PP. Ontwikkelingsopgaven en opvoedingopgaven [Developmental tasks and pedagogic tasks]. In: Rippens J., Goudena P.P., Groenendaal J.J.M., eds. Preventie van psychosociale problemen bij kinderen en jeugdigen [Prevention of psychosocial problems in children].Houten: Bohn Stafleu Van Lochem, 1994. p. 59-70.

(57) Pendley JS, Dahlquist LM, Dreyer Z. Body image and psychosocial adjustment in adolescent cancer survivors. J Pediatr Psychol 1997;22(1):29-43.

(58) Spirito A, Stark LJ, Cobiella C, Drigan R, Androkites A, Hewett K. Social adjustment of children succesfully treated for cancer. J Pediatr Psychol 1990;15(3):359-71.

(59) Vannatta K, Gartstein MA, Short A, Noll RB. A controlled study of peer relationships of children surviving brain tumors: teacher, peer, and self ratings. J Pediatr Psychol 1998;23(5):279-87.

(60) Vannatta K, Zeller M, Noll RB, Koontz K. Social functioning of children surviving bone marrow transplantation. J Pediatr Psychol 1998;23(3):169-78.

(61) Charlton A, Larcombe IJ, Meller ST, Morris Jones PH, Mott MG, Potton MW, et al. Absence from school related to cancer and other chronic conditions. Arch Dis Child 1991;66:1217-22.

(62) Eiser C. Chronic childhood disease. An introduction to psychological theory and research. Cambrigde: Cambrigde University Press, 1990.

(63) Madan-Swain A, Brown RT, Foster MA, Vega R, Byars K, Rodenberg W, et al. Identity in adolescent survivors of childhood cancer. J Pediatr Psychol 2000;25(2):105-15.

(64) Tyc VL, Hadley W, Crockett G. Predictors of intentions to use tobacco among adolescent survivors of cancer. J Pediatr Psychol 2001;26(2):117-21.

(65) Tyc VL, Hudson MM, Hinds P. Health promotion interventions for adolescent cancer survivors. Cognitive and behavioral practice 1999;6(2):128-36.

(66) Weinstein ND. Testing four competing theories of health-protective behavior. Health Psychol 1993;12(4):324-33.

(67) Rait DS, Ostroff JS, Smith K, Cella DF, Tan C, Lesko LM. Lives in balance: perceived family functioning and the psychosocial adjustment of adolescent cancer survivors. Fam Process 1992;31:383-97.

(68) Haupt R, Byrne J, Connelly RR, Mostow EN, Austin DF, Holmes GR, et al. Smoking habits in survivors of childhood and adolescent cancer. Med Pediatr Oncol 1992;20:301-6.

(69) Hollen PJ, Hobbie WL. Decision making and risk behaviors of cancer-surviving adolescents and their peers. J Pediatr Oncol Nurs 1996;13(3):121-34.

(70) Tao ML, Guo MD, Weiss R, Byrne J, Mills JL, Robinson LL, et al. Smoking in adult survivors of childhood Acute Lymphoblastic Leukemia. J Natl Cancer Inst 1998;90(3):219-25.

(71) Verrill JR, Schafer J, Vannatta K, Noll RB. Agression, antisocial behavior, and substance abuse in survivors of pediatric cancer: possible protective effect of cancer an its treatment. J Pediatr Psychol 2000;25(7):493-502.

(72) Lazarus RS, Folkman S. Stress, appraisal, and coping. New York: Springer Publishing Company, 1984.

(73) Rothbaum F, Weisz JR, Snyder SS. Changing the world and changing the self: a two-process model of perceived control. J Pers Soc Psychol 1982;42:5-37.

(74) Grootenhuis MA, Last BF, de Graaf-Nijkerk JH, van der Wel M. Secondary control strategies used by parents of children with cancer. Psychooncology 1996;5(2):91-102.

(75) Overholser JFG. The impact of childhood cancer on the family. Journal of psychosocial oncology 1990;8:71-85.

(76) Woodgate RL. The importance of being there: perspectives of social support by adolescents with cancer. J Pediatr Oncol Nurs 2006 May;23(3):122-34.

(77) Fritz GK, Williams JR, Amylon M. After treatment ends: psychosocial sequelae in pediatric cancer survivors. Am J Orthopsychiatry 1988;58:552-61.

(78) Kazak AE, Barakat LP, Meeske K, Christakis D, Meadows AT, Penati B, et al. Posttraumatic stress, family functioning, and social support in survivors of childhood leukemia and their mothers and fathers. J Consult Clin Psychol 1997;65(1):120-9.

(79) Kazak AE. Posttraumatic distress in childhood cancer survivors and their parents. Medical and Pediatric Oncology Supplement 1998;1:60-8.

(80) Dockerty JD, Williams SM, McGee R, Skegg DCG. Impact of childhood cancer on the mental health of parents. Med Pediatr Oncol 2000;35:475-83.

(81) Hoekstra-Weebers JEHM, Jaspers JPC, Kamps WA, Klip EC. Psychological Adaptation and social support for parents of pediatric cancer patients: a prospective longitudinal study. J Pediatr Psychol 2001;26(4):225-35.

(82) Kazak AE, Stuber ML, Barakat LP, Meeske K, Guthrie D, Meadows AT. Predicting posttraumatic stress symptoms in mothers and fathers of survivors of childhood cancers. Journal of the American Academy of Child and Adolescence Psychiatry 1998;37(8):823-31.

(83) Olson DH, Russell CS, Sprenkle DD. Circumplex model of marital and family systems: VI. Theoretical Update. Fam Process 1983;22:69-83.

(84) Olson DH. Commentary: three-dimensional (3-D) circumplex model and revised scoring of FACES III. Fam Process 1991;30:74-9.

(85) Greenberg HS, Kazak AE, Meadows AT. Psychologic functioning in 8- to 16-year-old cancer survivors and their parents. The Journal of Pediatrics 1989;114(3):488-93.

(86) Kazak AE, Meadows AT. Families of young adolescents who have survived cancer: social-emotional adjustment, adaptability, and social support. J Pediatr Psychol 1989;14:175-91.

(87) Kazak AE, Christakis D, Alderfer M, Coiro MJ. Young adolescent cancer survivors and their parents: adjustment, learning problems, and gender. Journal of Family Psychology 1994;8(1):74-84.

(88) Olson AL, Boyle WE, Evans MW, Zug LA. Overall function in rural childhood cancer survivors: the role of social competence and emotional health. Clin Pediatr (Phila) 1993;32(6):334-42.

(89) Sloper T, Larcombe IJ, Charlton A. Psychosocial adjustment of five-year survivors of childhood cancer. J Cancer Educ 1994;9(3):163-9.

(90) Pelcovitz D, Goldenberg LA, Mandel F, Kaplan S, Weinblatt M, Septimus A. Posttraumatic stress disorder and family functioning in adolescent cancer. J Trauma Stress 1998;11(2):205-21.

(91) Madan-Swain A, Brown RT, Sexson SB, Baldwin K, Pais R, Ragab A. Adolescent cancer survivors: psychosocial and familial adaptation. Psychosomatics 1994;35(5):453-9.

(92) Lesko LM. Surviving hematological malignancies: stress responses and predicting psychological adjustment. The Biology of Hematopoiesis.New York: Wiley-Liss. Inc, 1990. p. 423-37.

(93) Carlson-Green B, Morris RD, Krawiecki N. Family and illness predictors of outcome in pediatric brain tumors. J Pediatr Psychol 1995;20(6):769-84.

(94) Varni JW, Katz ER, Colegrove R, Dolgin M. Perceived stress and adjustment of long-term survivors of childhood cancer. Journal of psychosocial oncology 1994;12(3):1-16.

(95) Last BF, Van Veldhuizen AMH. Information about the diagnosis and prognosis related to anxiety and depression in children with cancer aged 8-16 years. Eur J Cancer 1996;32a(2):290-4.

(96) Last BF. The phenomenon of double protection. In: Last B.F., Van Veldhuizen A.M.H., eds. Developments in pediatric psychosocial oncology.Amsterdam / Lisse: Swets & Zeitlinger B.V., 1992. p. 39-52.

(97) Van Veldhuizen AMH, Last BF. Children with cancer. Communication and emotions. Amsterdam/Lisse: Swets & Zeitlinger, 1991.

(98) Koopman HM. Dutch Children's AZL/TNO Quality of life Questionnaire (DUCATQOL). The Netherlands; 1995.

(99) van der Ploeg HM, Defares PB, Spielberger CD. Handleiding bij de Zelf-beoordelings Vragenlijst ZBV. Een Nederlandstalige bewerking van de Spielberger State-Trait Anxiety Inventory STAI-DY. Swets & Zeitlinger B.V.; 1981.

(100) Spielberger C.D., Gorsuch R.L., Lushene R.E. STAI Manual for the State-Trait Personality Inventory. Palo Alto, California: Consulting Psychologists Press, 1973.

(101) Bakker FC, van Wieringen PCW, van der Ploeg HM, Spielberger CD. Handleiding bij de Zelf-beoordelings Vragenlijst voor Kinderen (ZBV-K). Een Nederlandse bewerking van de State-Trait-Anxiety Inventory for Children (STAI-C) van Spielberger et al. [Manual of the Dutch version of the STAI-C]. Lisse: Swets Test Services; 1989.

(102) Spielberger C. The State-Trait Anxiety Inventory for Children. Palo Alto, California: Consulting Psychologists Press, 1970.

(103) Last BF, Grootenhuis MA, Destrée-Vonk A, Heymans HSA. De ontwikkeling van een levensloopvragenlijst voor jong-volwassenen (LVJV) [Development of a course of life questionnaire for young adults]. Gedrag & Gezondheid 2000;8(1):22-30.

(104) Grootenhuis MA, Stam H, Destrée-Vonk A, Heijmans HSA, Last BF. Levensloop Vragenlijst voor Jong-Volwassenen [Course of life questionnaire for young adults]. Gedrag & Gezondheid 2003;31(5):336-50.

(105) Stam H, Grootenhuis MA, Last BF. The course of life of survivors of childhood cancer. Psychooncology 2005;14:227-38.

(106) Bijstra JO, Jackson S, Bosma HA. De Utrechtse Coping Lijst voor Adolescenten. Kind en Adolescent 15[2], 98-109. 1994.

(107) Grootenhuis MA, Last BF. Children with cancer with different survival perspectives: defensiveness, control strategies, and psychological adjustment. Psychooncology 2001;10:305-14.

(108) Loonen HJ, Grootenhuis MA, Last BF, Koopman HM, Derkx HHF. Quality of life in peadiatric inflammatory bowel disease measured by a generic and disease-specific questionnaire. Acta Paediatr 2002;91:341-54.

(109) Houtzager BA, Oort FJ, Hoekstra-Weebers JEHM, Caron HN, Grootenhuis MA, Last BF. Coping and family functioning predict longitudinal psychological adaptation of siblings of childhood cancer patients. J Pediatr Psychol 2004;29(8):591-605.

(110) Buurmeijer FA, Hermans PC. Gezins Dimensie Schalen - Handleiding [Dutch version of the Family Adaptability and Cohesion Evaluation Scales (FACES)]. Lisse, The Netherlands: Swets & Zeitlinger, 1988.

(111) Olson DH, Bell RQ, Porter J. FACES: Family adaptability and cohesion evaluation scales. St. Paul: Family Social Science, University of Minnesota, 1978.

(112) Olson DH, Portner J, Bell B. FACES II: Family adaptability and cohesion evaluation scales. St. Paul: Family Social Science, University of Minnesota, 1982.

(113) Olson DH, Porter J, Bell B. FACES III: Family adaptability and cohesion evaluation scales. St. Paul: Family Social Science, University of Minnesota, 1985.

(114) Goldberg DP, Williams P. A user's guide to the General Health Questionnaire. Windsor: NFER-Nelson, 1988.

(115) Koeter MWJ, Ormel J. General Health Questionnaire: The Dutch application. Amsterdam: Swets Test Services, 1991.

(116) Grootenhuis MA, Last BF. Parents' emotional reactions related to different survival perspectives of their children with cancer. Journal of psychosocial oncology 1997;15:43-62.

(117) Schreurs PJ, Willige G, Brosschot JF, Tellegen B, Graus GMH. De Utrechtse Coping Lijst: UCL herziene handleiding [The Utrecht Coping List: UCL-Manual]. Lisse, the Netherlands: Swets & Zeitlinger; 1993.

(118) Suurmeijer ThPBM, Doeglas DM, Briancon S, Krijnen W, Krol B, Sanderman R, et al. The measurement of social support in the "European research on incapacitating disease and social support": the development of the Social Support Questionnaire for Transactions (SSQT). Soc Sci Med 1995;40:1221-9.

(119) Doeglas D, Suurmeijer T, Briancon S, Moum T, Krol B, Bjelle A, et al. An international study on measuring social support: interactions and satisfaction. Soc Sci Med 1996;43(9):1389-97.

(120) van Sonderen E. Het meten van sociale steun met de Sociale Steun Lijst-Interacties (SSL-i) en Sociale Seun Lijst Discrepanties (SSL-d): een handleiding [Measurement of social support with the Social Support Questionnaire - Interactions and the Social Support Questionnaire - Discrepancies: manual]. Groningen: Noordelijk Centrum voor Gezondheidsvraagstukken. Rijksuniversiteit Groningen, 2004.

(121) Aaronson NK, Muller M, Cohen PDA, Essink-Bot M, Fekkes M, Sanderman R, et al. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. J Clin Epidemiol 1998;51(11):1055-68.

(122) van der Zee KI, Sanderman R. Het meten van de algemene gezondheidstoestand met de RAND-36. Een handleiding. [Measuring general health status with the RAND-36. A guide.]. Groningen, the Netherlands: Noordelijk Centrum voor Gezondheidsvraagstukken. Rijksuniversiteit Groningen, 2003.

Part I

Chapter 1

Social and emotional adjustment in young survivors of childhood cancer (review)

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ABSTRACT

An overview is given of the social and emotional adjustment in young survivors of childhood cancer. The results are described in terms of self-esteem, anxiety, depression and posttraumatic stress (emotional adjustment), and in terms of behavioral functioning, social competence and school performance (socio-behavioral adjustment). Furthermore, factors related to survivors' adjustment are reported: demographics, illness- and treatment-related factors, coping and social support, and family and parental functioning. Limitations of the studies and consequences for future research are discussed.

On the whole, the adjustment of young cancer survivors as a group was reasonably good, but the findings with respect to the emotional and social adjustment were inconsistent. This might be attributed to limitations of the study designs and the fact that the studies were not all directly comparable. In order to gain more insight into the predictors of adjustment, longitudinal studies are recommended, which should include control groups or standardized instruments with norm data, and use cancer-specific measures in addition to generic measures.

INTRODUCTION

Since the introduction of modern therapies (around 1980) more children with cancer have survived their illness. As a result of this, interest in the degree of adjustment achieved by cancer survivors has increased. There is now a considerable literature devoted to physical health and cognitive functioning in childhood cancer survivors. Far less attention is paid to the implications for social and emotional functioning, although an increasing number of studies is focused on these themes (1;2). The present review summarizes specifically the literature dealing with these aspects of adjustment in young survivors of childhood cancer. The purpose of this article is to give investigators and other persons involved in childhood cancer care an overview of the research that has been conducted in this field. We report what is known and discuss the limitations and the implications for future research.

Studies published (in English) since 1985 in journals and books in the field of social sciences, pediatrics and nursing were identified using computer-based searches in Medline and PsycINFO. The following keywords were used: cancer/neoplasms, survivors, late effects/long-term effects, adolescence/childhood, psychology/psychiatry. In addition, references cited in the studies identified were searched for relevant information.

Because the present review is focused particularly on social and emotional adjustment, results relating to physical, neuropsychological or intellectual functioning of the cancer survivors are not reported, and studies dealing exclusively with functioning in these domains were excluded. This review is concerned with functioning in survivors, so that parent and family functioning are only reported in connection with survivors' functioning.

Studies focusing on survivors of childhood cancer are very diverse, differing in age of patients at diagnosis and during study, in time since the termination of treatment, and in type of cancer. Our review is focused on young survivors, which means 18 years of age or younger at the time of study. Study populations with mainly adult survivors, aged over 18 at the time of assessment, have been excluded because these studies include many patients who were treated before the introduction of modern therapies. All types of cancer have been included, and we used no strict criterion for survival of childhood cancer. Although a 5-year period without treatment can be considered a criterion of survival of childhood cancer, several investigators also regard children who have been off treatment for shorter periods than this as survivors. This is partly due to the different survival perspectives for different diagnoses in childhood cancer.

Ideally there is a substantial study sample including a control group of healthy peers, and standardized instruments are used. Because insistence on all these criteria would have resulted in too few studies, we decided to include studies in which standardized instruments were used and the sample was made up of at least 20 survivors.

The results of the studies examined are summarized in Table 1. The following information is displayed: (1) literature reference and objective of the study; (2) method and sample characteristics; (3) measures, and (4) results. Articles referring to the same population are described together, if possible. All abbreviations used are explained at the beginning of Table 1. The present review is divided into four sections. Firstly *emotional* adjustment is described, including, self-esteem, anxiety, depression, and posttraumatic stress (PTS). The second section summarizes the results relating to *socio-behavioral* adjustment, such as behavioral functioning, social competence and school performance. The third section describes factors

related to the *survivors' adjustment*. Demographics, illness- and treatment-related factors, coping and social support, and family and parental functioning are discussed, these being factors that might influence adjustment. In the final section the conclusions and implications for further research are discussed.

EMOTIONAL ADJUSTMENT

Many different instruments have been used to investigate the emotional adjustment of childhood cancer survivors. In this section childhood cancer survivors are described in terms of overall emotional functioning, self-esteem, anxiety and depression, and PTS symptoms. In most studies adjustment of the survivors has been compared with adjustment in a control group of healthy peers or with normative data.

Overall and global emotional functioning

Based on standardized questionnaires or interviews, many researchers found that the overall emotional adjustment of the survivors as a group was within normal limits and did not differ from that in healthy peers. No overt psychological dysfunctioning was found; nor was there any evidence of significant psychopathology. When there were pathologic profiles, the number of survivors exceeding clinical cut-off scores was consistent with published norms (3-7). Lesko (8) reported more global psychological distress and less robust overall mental health in survivors than in normative samples, but this did not reach psychopathological levels. Various aspects of emotional adjustment are described below.

Self-esteem

The instruments mostly used to assess self-esteem, self-concept, self-worth or perceived competence in survivors were the Piers-Harris Children's Self-concept scale, the Self-Perception Profile for Children, and the Self- Perception Profile for Adolescents. These (child-report) questionnaires measure global/general self-worth and also perceived competence in such specific areas as behavior, intellectual and school status, physical appearance, athletic performance, social acceptance, popularity and close friendship, satisfaction and happiness.

When they used the Piers-Harris Children's Self-concept Scale, Anholt et al. (9) and Olson et al. (10) found no difference in global self-concept between survivors and healthy children, and the scores were within normal limits. In comparison with healthy children, cancer survivors even felt significantly better about their intellectual and school status, behavior, and overall happiness and satisfaction (9). Greenberg et al. (11) reported poorer self-concept (total scale and with reference to intellectual and school status, happiness and popularity) in survivors than in the control group but these children were nonetheless functioning within normal limits. In contrast, Fritz et al. (12) found better self-image in survivors than in the normative sample.

Radcliffe et al. (7), Spirito et al. (13) and Van Dongen-Melman (14) used the Self-Perception Profile for Children to investigate self-worth in childhood cancer survivors compared with healthy children and/or normative values. With respect to general self-worth they did not

find any differences, but according to Radcliffe et al. (7) brain tumor survivors felt they had less athletic competence than the normative sample. Van Dongen-Melman also (14) reported less athletic competence in survivors than in the control group, but higher scores on physical appearance.

The Self-Perception Profile for Adolescents was used by Kazak et al. (15;16), Madan-Swain et al. (17) and Sloper et al. (18), none of whom found any differences in global self-worth between survivors and controls or normative samples. Bauld et al. (4) also reported no differences between survivors and controls when they used the Possible Selves Inventory.

The Swedish study of Von Essen et al. (19) in contrast, showed lower total self-esteem and lower scores on the subscales psychological well-being and physical self-esteem in survivors than in healthy children and adolescents. The investigators used the "I think I am," a Swedish self-report scale for measuring self-esteem, standardized on a Swedish sample of children aged 8–16 years. Arvidson et al. (20) used the same instrument and found that survivors did not differ from the Swedish children.

Pendley et al. (21) and Madan-Swain et al. (17) investigated body image among adolescent cancer survivors. Madan-Swain et al. (17) reported that body comfort, measured with the Millon Adolescent Personality Inventory, was more problematic in children who had survived cancer than in controls. Pendley et al. (21), on the other hand, could not confirm their hypothesis that adolescents with cancer had a more negative perception of their bodies than controls. They based their conclusions on several instruments assessing body image. In addition, on objective ratings of attractiveness no differences were found between cancer survivors and healthy peers.

Anxiety and depression

Anxiety was measured with the Revised Children's Manifest Anxiety Scale and the State-Trait Anxiety Inventory. The results of these child-reports were a little conflicting. Barakat et al. (22) found no differences in anxiety between survivors and controls assessed with both the RCMAS and the State-Trait Anxiety Index (STAI). Sloper et al. (18), who compared survivors with school peers, also did not report any differences. The same is also true of the study of Von Essen et al. (19) after correction for age. In contrast, Bauld et al. (4) found higher state anxiety levels (according to STAI) in survivors than in peers, as did Kazak et al. (23) on the basis of the RCMAS.

Referring to normative values, Kazak et al. (24) and Radcliffe et al. (7) reported that survivors were less anxious, whereas in another study conducted by Kazak's group (16) this was true for the male subjects.

Various standardized measures were used to explore depression in childhood cancer survivors, all based on self-reports of the survivors. Fritz et al. (12;25) used the Children's Depression Rating Scale. They found the percentage of survivors who were depressed was no higher than the percentage in the general population. Based on the Children's Depression Scale, Van Dongen-Melman (14) reported no differences between survivors and controls; Greenberg et al. (11) and Von Essen et al. (19) used the Children's Depression Inventory and also found no differences. On the other hand, Radcliffe et al. (7) found that brain tumor survivors were less depressed than their normative counterparts and Kazak et al. (16) reported feelings of hopelessness about the future were below the norm.

Posttraumatic stress

Because cancer and the intrusive treatment is often a life-threatening experience, childhood cancer survivors could suffer from PTS symptoms. Barakat et al. (22), Kazak et al. (23;26) and Stuber et al. (27-29) used the Posttraumatic Stress Disorder Reaction Index to investigate PTS symptoms among survivors of childhood cancer. Stuber et al. (27;28) found that 17% of survivors had moderate symptoms and 30%, mild symptoms. In another study of Stuber et al. (29), 12.5% of the survivors were categorized in the 'severe' range for PTS, which is higher than the prevalence (1–9%) in the general population. In comparison with healthy controls the survivors did not report more symptoms (22;23;26). In addition, compared with other traumatized groups survivors had lower PTS symptoms (23;26).

Measured with the Posttraumatic Stress Disorder Symptom Scale, completed by parents about their children, the incidence of PTS disorder (PTSD) was no greater in survivors of cancer than in the general population (30). Pelcovitz et al. (31) used the Structured Clinical Interview for DSM-PTSD. They found no higher prevalence of current PTSD than in a control group, but 35% of adolescent cancer subjects met the criteria for lifetime PTSD, as against only 7% of abused adolescents and 4% of the control group.

SOCIO-BEHAVIORAL ADJUSTMENT

Socio-behavioral functioning concerns behavioral reactions, school-related problems, social competence and identity. The Child Behavior Checklist (CBCL) is the instrument that is most widely used to investigate the socio- behavioral consequences of childhood cancer. The CBCL measures behavior problems and competence (social, school, activity) and consists of the Parent Report Form, the Teacher Report Form (TRF) and the Youth Self Report (YSR).

Sawyer et al., using the CBCL, conducted two longitudinal studies with a control group to examine the consequences of childhood cancer. In the first study (32;33), 5.7 years after their diagnosis leukemia survivors had more behavioral problems and less social competence, particularly in school-related activities, than the control group and their siblings. Almost 10 years after diagnosis the differences between survivors and control group had narrowed. Survivors were performing worse at school than the matched controls, but there were no differences in behavior ratings. In another study (34-36), Sawyer et al. measured the socio-behavioral problems of cancer patients immediately after diagnosis (T1) and then annually for the next 4 years. At T1 survivors scored higher on the CBCL Behavior Problems scales (Internalizing and Total) than the control group. Their scores were intermediate between the scores reported in the community and in mental health clinics. At the subsequent measures (T2–T5) the survivors' scores were generally consistent with the control groups' scores, which mean a decrease across time for the survivors.

The CBCL was used in many other studies besides the longitudinal studies, mostly being completed by the parents. Anderson et al. (3), Kazak et al. (15), Madan- Swain et al. (17), and Van Dongen-Melman (14) compared survivors' CBCL scores with those of healthy age-matched controls. The first investigators reported that survivors scored within normative limits and/or did not differ from the control group in these scores. According to Van Dongen-Melman (14) the majority of survivors adjust well, but there were serious adjustment problems

(Total problems scale) in some, especially boys. Among the male survivors 27% had serious adjustment problems, as opposed to 10% of their healthy peers. The survivors were more withdrawn and introverted, and they had more somatic complaints and social problems than controls.

Other researchers compared survivors' CBCL scores with normative samples. They did not agree on this subject. According to Kazak et al. (16), Levin Newby et al. (37), Noll et al. (6), and Lesko (8), survivors' behavior was generally similar to instrument norms. Carlson et al. (38) noted slightly elevated rates of problem behavior, as did Mulhern et al. (39), who found that more survivors had deficiencies in social competence and more behavior problems than found in the general population, especially in terms of school performance and somatic complaints. The findings in other studies (22;40) showed that brain tumor survivors and other survivors exhibited an abnormally high prevalence of social and behavioral problems.

The results of teacher and parent CBCL reports were not always consistent. In a study conducted by Olson et al. (10) both parents and teachers reported poorer social competence among survivors than among classroom peers, but parents reported more behavior problems whereas teachers noted poorer school performance. In another study mothers rated their children who had survived childhood cancer lower than normative peers in overall social and scholastic competence, whereas the teachers reported no such differences (7).

Levin Newby et al. (37) and Sloper et al. (18) used the Rutter Behavioural Scale to measure behavioral adjustment. Survivors scored lower than controls on both teacher- and parent-rated measures of behavioral adjustment. The proportion at risk according to the Rutter Scale A and B was higher in the cancer survivors. With respect to school-related problems the teacher ratings indicated less concentration, less academic progress, and lower popularity with peers than for control school peers. In contrast, Glaser et al. (41) found no lowering of the level of overall school behavior compared with controls. The scores on the Deasy-Spinetta Behavioral Questionnaire, a school behavior questionnaire, showed a normal willingness to attend school among survivors and no difficulties with school work or concentration. In the study of Spirito et al. (13) survivors obtained even more positive teacher ratings on the school behavior scales: willingness, attendance, and school social situations.

Pendley et al. (21), Spirito et al. (13) and Vannatta et al. (42;43) focused on the social functioning and peer relations of childhood cancer survivors. For that purpose Spirito et al. (13) developed the Social Skills Questionnaire for children. Their study showed that fewer survivors than controls had friends of the same age and more survivors spent time by themselves. However, no differences were found in social skills. According to the study of Pendley et al. (21) survivors participated in fewer social (peer) activities than controls but they did not differ in social anxiety and loneliness. On the basis of the Revised Class Play and the Liking Rating scales Vannatta et al. (42;43) concluded that brain tumor survivors and survivors of bone marrow transplantation were more socially isolated than classmates and had fewer friends. Their classmates described them as less physically attractive and not so good at athletics (43).

Levin Newby et al. (37) investigated social skills in survivors by means of the Social Skills Rating Scale Parent and Teacher Forms (SSRS-P and SSRS-T). This instrument assesses social skills in the pre-school, elementary school and secondary school periods: prosocial skills, social competence, adaptive functioning (SSRS-P), and cooperation, assertion, and self

control (SSRS-T). The survivors were generally found to have normal social skills when their results were compared with normative data recorded in their healthy Swedish peers.

Madan-Swain et al. (44) have investigated identity in adolescent survivors of childhood cancer, using the Extended Objective Measure of Ego Identity Status-2 for this purpose. This instrument classifies individuals into four identity states: diffusion (no exploration, no commitment), foreclosure (no exploration, commitment), moratorium (exploration, no commitment), and achievement (exploration, commitment). More cancer survivors than healthy controls had the foreclosed identity status. This result suggests that the foreclosure identity status, which involves adopting the views of significant others, may serve a protective function in assisting survivors to cope with the stressors inherent in the cancer experience.

FACTORS RELATED TO SURVIVORS' ADJUSTMENT

In the preceding sections the psychosocial consequences of childhood cancer have been discussed. This section is concerned with the factors related to functioning in childhood cancer survivors. Some studies focus on these factors (e.g.,(38;45)) but predictors of psychosocial adjustment are discussed in almost all studies to some degree. The following types of predictors can be distinguished: (1) demographic factors, (2) illness- and treatment-related factors, (3) coping, (4) family and parental functioning, (5) other related factors.

Demographics

With respect to the gender of the survivors Stuber et al. (45) reported more PTS symptoms in women than in men, whereas others found male survivors to be more depressed and anxious than female survivors (5;16), and also less socially competent (40). Van Dongen-Melman (14) reported serious behavioral problems especially in boys.

In several studies older age at the time of the study appeared to be associated with worse adjustment. Older survivors had more PTS symptoms (30), more psychological distress (4;8;46), and more socio-behavioral problems (39) than younger ones. In addition, Van Dongen-Melman (14) found that boys aged at least 11 years were more at risk than younger boys.

Another demographic factor is living in a single- or a two-parent home. Carlson et al. (38) concluded that living in a single-parent home was related to more behavioral problems in pediatric brain tumor survivors. Mulhern et al. (39) also found that a single-parent home was one of the factors associated with more behavioral problems, and children living in two-parent families scored higher on psychological well-being (19).

Only Carlson et al. (38) found an effect of social class. He concluded that higher socioeconomic status was associated with more adaptive functioning.

Several researchers (18;22;23;26;41;47) did not find any association between demographics and adjustment in survivors of childhood cancer.

Illness- and treatment-related factors

Age at diagnosis is often investigated in relation to the adjustment of childhood cancer survivors. Some authors reported that older age at diagnosis was related to more psychological

distress (8), more behavioral problems (40), more PTS symptoms (29), or that boys who were older (≥5 years) at the time of diagnosis were at risk for socio-behavioral problems (14). Carlson et al. (38), on the other hand, found that survivors who were younger at the time of diagnosis had more behavioral problems, and Bauld et al. (4) reported a less negative view of now and the future and higher scores on the school concept in survivors who were older at diagnosis. Von Essen et al. (19) also found a relation between age at diagnosis and psychological adjustment. The survivors who were 10–14 years old when diagnosed showed higher levels of depression and anxiety than those who were diagnosed when younger (1–6 years) or older (15–17 years).

Not only age at diagnosis, but also time off treatment, appeared to be a strong predictor of psychological outcome. Survivors who were longer off treatment had more behavioral problems, lower self-worth, and more negatively body image, and they were more socially anxious than the other survivors (9;21;40). More behavioural problems were also found in male survivors who had been off treatment for at least 5 years than in the male survivors who had been off treatment for shorter periods (14). In line with this, shorter time since diagnosis was associated with more adaptive functioning in brain tumor survivors (38). In contrast, Stuber et al. (45) reported a negative relation between PTS symptoms and months off treatment, and Levin Newby et al. (37) found that time off treatment and behavioral problems were negatively associated.

Cranial irradiation is the treatment that has most frequently been investigated versus other therapies. Cranially irradiated survivors were more socially isolated (43), had more socio-behavioral problems (39), scored lower on the school scale of the CBCL, had more attentional and social problems, and were more anxious/depressed and withdrawn (3) than the children who had undergone other therapies. Van Dongen-Melman (14) reported cranial irradiation in male survivors as a risk factor for psychosocial maladjustment. Arvidson et al. (20) found that CNS treatment intensity was positively correlated with degree of behavioral problems and negatively with social competence.

Stuber et al. (27;29;45) examined predictors of PTS in survivors and their parents. They concluded that the intensity of the treatment was an important predictor. Appraisal of treatment intensity by the survivors or their parents was positively correlated with PTS symptoms. Apart from that, the oncologist's assessment of treatment intensity did not contribute to PTS symptoms.

Varni et al. (46) used the diagnosis as a predictor of adjustment in survivors. They found that children with leukemia suffered from greater distress than survivors with other diagnoses. According to Carpentieri et al. (40) brain tumor survivors displayed more problems with social competence than other survivors (mainly survivors of leukemia) but they had fewer behavioral (internalizing) problems.

In general, severe late medical effects led to a poorer self-concept and more depressive symptoms (11). Physical disability or functional impairment in particular were associated with depression (25), with less positive feelings about physical appearance, an aspect of self-concept (9), and with more socio-behavioral problems (39;40). Physical attractiveness and athletic ability were also positively correlated with the social competence of BMT survivors (43).

In several studies (6;7;17;18;22;23;26;41;47) no effects of illness and treatment factors on adjustment in childhood cancer survivors were reported.

Coping resources

The way of coping with the consequences of a life-threatening disease such as cancer can be regarded as an important mediating factor in adaptation to the cancer experience and thus to the survivor's (long-term) adjustment. Apart from social support, hardly any studies on coping strategies in childhood cancer survivors have been found.

Madan-Swain et al. (17) used the Coping Strategies Inventory to describe coping in survivors and their families. They found normal overall coping among survivors. According to Bauld et al. (4), survivors tended to apply more avoidance strategies, measured with the Adolescent Coping Scale (ACS), than a healthy control group.

Kazak et al. (15;16) examined social support among survivors, measuring it with the Social Support Rating Scale. In general survivors scored within normative limits and did not differ from controls with respect to social support. Changes over time suggested a decline in the available social support for survivors and their families (15). Social support from family members was rated higher than was the support from friends and school staff (16). In a study among 130 leukemia survivors who had been off treatment for an average of 5.8 years, Kazak et al. (23;26) found that social support was negatively associated with anxiety and PTS outcomes. According to Fritz et al. (25), the availability of peer support during treatment was predictive of psychosocial outcome.

Although in many studies parental coping strategies are examined a few studies focus on coping in relation to adjustment in childhood cancer survivors. Madan-Swain et al. (17) used the Coping Strategies Inventory to describe coping in survivors' families. In comparison with a small sample of mothers of nondiseased children, survivors' mothers used more social withdrawal as a coping strategy.

Carlson et al. (38) examined family predictors of outcome in pediatric brain tumor survivors on average of 44 months after diagnosis. They concluded that fewer maternal coping resources, measured with the Coping Health Inventory for Parents, were related to better adaptive functioning in survivors. That means that survivors whose mothers reported reliance on fewer family resources and social and medical resources had better adaptive functioning.

Sloper et al. (18) asked parents about the strategies they had used to deal with problems at the time of their child's illness and currently. The interview was derived from work on parental coping with child-related problems. They found that lower use of direct action both at the time of the study and at the time of the illness, and higher use of positive thinking at the time of the study were associated with more behavioral problems.

Family and parental functioning

Of course childhood cancer causes emotional reactions in the family. The emotional adjustment of the parents, and family communication and structure may be factors influencing survivors' adaptation and functioning. In several studies these factors have been investigated. The findings concerning the relation between family/parental functioning and the survivor's adjustment are discussed below.

Parental emotional adjustment

It is likely that emotional functioning in parents influences the functioning in their children, but the converse could also be true. It is difficult to determine the direction of the influence, in addition to which the findings were not consistent.

Kazak et al. (24), who collected data during treatment and again 6 months or longer after treatment, examined the correlation between parental distress and the emotional adjustment in 29 children with leukemia. They found that during treatment the emotional distress in children with cancer was related to maternal PTS symptoms and state anxiety. After completion of treatment maternal PTS symptoms during treatment were no longer associated with child distress (anxiety). Barakat et al. (22) mentioned that survivors' symptoms ≥1 year after treatment were associated with their parents' symptoms.

On the basis of a 2-year longitudinal study Sawyer et al. (36) reported that greater maternal psychopathology (measured with the General Health Questionnaire) immediately after diagnosis was associated with a greater number of childhood emotional and behavioral problems 2 years after diagnosis. The findings of Sloper et al. (18) were in line with this: behavioral adjustment 5 years after diagnosis was negatively correlated with parents' psychological distress.

Pelcovitz et al. (31) studied PTS symptoms in survivors and their parents 0–11 years after active treatment. PTS disorder (PTSD) status in survivors was related to their mothers' PTSD status, but not to mothers' overall adjustment as measured with the Symptom Checklist. Stuber et al. (29) also reported that children's PTS scores were correlated with the PTS scores of their mothers.

Family functioning

The idea that family functioning influences survivors' adjustment is plausible. Although most studies have been focused on family functioning as an outcome variable, this review underscores the findings with respect to family functioning as a predictor of survivors' adjustment.

The Family Environment Scale (FES) and the Family Adaptation and Cohesion Scale (FACES) are the two most widely used measures of family functioning. The FES is composed of ten dimensions grouped into three underlying domains of family functioning: relationships, personal growth, and systems maintenance. The ten domains are: cohesion, expression, conflict, independence, organization, control, activity-recreational orientation, moral-religious emphasis, achievement orientation, and intellectual / cultural orientation.

Carlson et al. (38), Greenberg et al. (11) and Olson et al. (10) used the FES. Their findings showed that in general the family functioning of the survivors' families did not differ from control or normative samples. Sloper et al. (18) found no association between behavioral adjustment scores and family cohesion and expression. Levin Newby et al. (37) concluded that more family cohesiveness was associated with more behavioral problems. According to Madan-Swain et al. (44), family functioning characterized by greater levels of conflict was positively associated with foreclosed identity status, which is an identity state of commitment to goals and beliefs without having experienced a period of questioning or reflection.

Other investigators used the FACES. This instrument distinguishes four levels of cohesion (disengaged, separated, connected, and enmeshed) and four levels of adaptability (rigid,

structural, flexible, and chaotic). Cohesion and adaptability were combined into types of families useful in differentiating functional and dysfunctional families.

Kazak et al. (15;16;23;26) reported that in general family functioning was within normal limits and not different from functioning in the families of healthy controls. Family cohesion and adaptability reported by survivors and parents were developmentally appropriate. Madan-Swain et al. (17) found no major difficulties in family communication among cancer survivors, although mothers in cancer families designated themselves as more rigid and less flexible than the mothers of children in the nondiseased control group. Pelcovitz et al. (31), however, concluded that survivors' parents were overly protective and highly caring, fitting into the 'affectionate constraint' category. And he found survivors' PTSD status was related to their perception of the family as chaotic. In another study (47) survivors reported lower levels of cohesion than a normative sample but no differences in adaptability.

Kazak et al. (23;26), Lesko (8) and Rait et al. (47) found that family functioning was associated with psychosocial outcomes in survivors. According to Kazak et al., family functioning was negatively associated with anxiety and PTS outcomes. Lesko also found that the quality of family communication, and family cohesion and adaptability, were related to the mental health of the survivors. In line with these observations, Rait et al. (47) reported that family cohesion was strongly (positively) related to psychological adjustment: overall mental health, self-esteem and global competence.

Other factors related to survivors' adjustment

Dealing with childhood cancer is a dramatic event that could influence psychosocial functioning. Other life events are also likely to explain adjustment problems in cancer survivors and their families. Carlson et al. (38) examined family stressors in relation to survivors' behavior. He used the Family Inventory of Life Events (FILE), which measures normative and nonnormative (family) life events experienced over the preceding 12 months. The instrument provides a weighted score for total family stress. Carlson et al. concluded that fewer negative life events caused fewer behavioral problems. In line with this, Varni et al. (46) reported that a greater number of stressful events predicted increased psychological distress and lower general self-esteem. They used the Adolescent Perceived Events Scale, which measures the number and intensity of negative, stressful events representative of those experienced during adolescence, and refers to events that have occurred within the last 6 months.

Barakat et al. (22) stated that the objective aspects of the cancer and its treatment were not related to PTS symptoms in childhood cancer survivors, but that it was much more the past perceived threat to life that contributed to PTS symptoms in survivors. With the Assessment of Life Threat and Treatment Intensity Questionnaire (ALTTIQ) constructed for their study, Barakat et al. addressed the extent to which the cancer and its treatment were believed to be intense and life threatening.

Finally, Levin Newby et al. (37) investigated whether academic functioning was related to social skills and adjustment. Their findings confirmed a positive association between academic functioning and social skills and adjustment.

CONCLUSIONS AND DISCUSSION

Although young cancer survivors adjust reasonably well, the findings with respect to their emotional and social adjustment are inconsistent. In this section the results are summarized and discussed with a view to future research. Firstly the limitations of the studies come up for discussion; subsequently the survivors' adjustment, the role of predictors, and the impact of conclusions drawn so far on future research will be discussed.

Study designs

The inconsistent findings can be attributed to several underlying problems, which concern the comparability of the studies. Firstly, the concepts measured are very wide, as are the instruments used. Most instruments are generic measures and not all are appropriate to assessment of the specific problems arising out of childhood cancer. Secondly, the study populations are very diverse. Patients who had different cancer diagnoses and underwent different treatments are included, and there were also differences in age, in time since diagnosis, and in time since termination of treatment. In many studies survivors of a brain tumor have been excluded or the study has been directed exclusively at survivors of brain tumors (7;38;41;42). Other studies have been conducted exclusively among survivors of leukemia (3;4;6;23;24;26;29;32;33).

Another difficulty is that the information has been gathered from different kinds of informants, varying from parents, teachers, and oncologists to the cancer survivors themselves. Even when measured with the same instrument, e.g., the CBCL, the parents' and teachers' reports differ (e.g. (7;10)).

The inconsistent findings can also be due to the often small sample sizes. Less than a third of the studies have sample sizes over 50 survivors. Especially in combination with diverse populations of survivors, the power of the studies will be low, resulting in small chance of finding differences between survivors and healthy controls. Furthermore, many studies included many outcome measures with no control for type I errors despite the small sample sizes.

Finally, in some studies there was no control group or comparisons with population norms were limited.

Survivors' adjustment

With the aforementioned limitations in mind, we conclude that on the whole the prevalence of psychosocial problems experienced by children treated for cancer does not differ from that found in children in the general population. The majority of investigators found that the overall emotional adjustment of the survivors as a group was within normal limits, not differing from that in their healthy peers. While there were pathologic profiles, the number of survivors exceeding clinical cutoff scores was consistent with published norms. Consideration of different aspects of emotional functioning in survivors of childhood cancer reveals that the results are not consistent, but in most studies the survivors' self-esteem, anxiety and depression did not differ from healthy controls or the normative population. In addition, in most samples of survivors the prevalence of PTS symptoms was no greater than

in healthy samples. However, one third of the adolescent survivors met criteria for lifetime PTSD, which is a higher percentage than in the general population (31).

It is difficult to summarize the results with respect to socio-behavioral functioning, because the studies and results vary widely. The findings in the longitudinal studies (32-36) indicated that survivors had more behavioral problems and less social competence than matched peers but the problems decreased across time to the same level as in the control group. With respect to peer relations there is agreement. All studies (13;21;42;43) showed that survivors had fewer friends than healthy peers and that they took less part in peer activities. Identity achievement in adolescent cancer survivors could be problematic. According to Madan-Swain et al. (44), more adolescent survivors than healthy controls were in the foreclosed identity status. This finding suggests that adopting the views of significant others may be a (protective) way of coping with the stressors of the cancer experience.

As described above, most survivors are functioning reasonably well socially and emotionally. This is not what would be expected considering the stressful experience of childhood cancer and their treatment. It could be partly attributable to the instruments used. Perhaps more highly cancer-specific instruments are needed to assess the impact of cancer. The good adjustment could also be the result of adequate (family) coping with the stresses of childhood cancer. The use of denial as a coping strategy is often assumed to be harmful, but in the case of cancer denial can be adaptive (48). Possibly patients maintain a high degree of optimism, which may be viewed as denial, but it can also be viewed from a cognitive viewpoint as 'selective cognitive processing' or can be considered as healthy denial (49). Another possible explanation could be 'response shift,' which means that the experience with cancer has changed children's conceptualization of problems. As a result of this response shift, problems are being underreported. Response shift has also been described in adults with cancer (50). In addition, sample bias could be an explanatory factor. Perhaps families of children who had been more severely affected had chosen not to participate because they wished to avoid confronting the difficulties experienced by themselves and their children. Conversely, the respondents might be those with the more difficult problems, using the study as an opportunity to make their difficulties known to the study personnel.

Predictors of adjustment

It is likely that not all children and adolescents with cancer suffer from adjustment problems, some being more vulnerable to maladjustment than others. It is therefore important to identify factors that predict successful psychosocial adaptation. Nevertheless, few factors that are predictive for survivors' adjustment have been identified. In a considerable number of studies no predictors were reported, while the results of others were not consistent. In addition, most study designs are cross-sectional, so that causality between factors and adjustment cannot be established. What can be concluded is that older age at diagnosis, longer time off treatment, irradiation therapy, and severe medical late effects are disease-related factors that were associated with adjustment problems.

Another, probably important, predictor of adjustment is coping. Because many studies have been focused on coping as an outcome variable, rather than a predictor, it is difficult to conclude whether these factors are associated with adjustment in childhood cancer survivors. Moreover, hardly any studies on coping in childhood cancer survivors have been found.

Parental and family functioning influences the functioning in children and vice versa. Although most investigators reported that family functioning was within normal limits (10;11;15;16;18;44) some found that survivors' parents were overly protective (31) and also more rigid and less flexible than the parents of nondiseased children (17). A few investigators reported that the quality of family communication, cohesion and adaptability were related to psychosocial outcome in survivors (8;23;26;47).

It is important that future studies clarify whether cancer survivors' problems are associated with the cancer or with other factors, such as coping, family functioning, and survivors' functioning at diagnosis. For example, Carpentieri et al. (40) found that the social competence and behavioral problems shortly after diagnosis were strong predictors of psychosocial adjustment in survivors. Self-esteem would also be an interesting mediating variable, as well as an outcome variable, as in this review. Longitudinal investigation of childhood cancer survivors will allow more insight into predictors of psychosocial adjustment, such as coping, illness- and treatment-related factors, and family functioning.

Future research

On the basis of the findings and problems described above the following implications for future research can be formulated. More insight is needed into the predictors of adjustment among young survivors of childhood cancer, to enable detection of the survivors at risk. Apart from illness- and treatment-related factors, the role of coping, family functioning and survivors' functioning at diagnosis are variables that it will be important to investigate in relation to adjustment.

Cancer and its treatment are a potential threat to the accomplishment of developmental tasks, because they increase dependence on adults and decrease participation in peer and school-based activities, at least temporarily. Failing to meet developmental tasks in growing up increases the risk of adjustment problems later in life. Yet the influence of childhood cancer on the course of children's lives has hardly been studied. For this reason it is not known to what degree children with cancer meet their developmental tasks in comparison with healthy peers. More insight is therefore needed into the correlation between course of life and adjustment. The age at diagnosis has been found to be one factor that predicts adaptation, maybe because developmental tasks of infancy are less disrupted by cancer than the developmental tasks of adolescence. Thus, it is interesting to determine whether the course of life / development of the young survivors mediates between the direct consequences of cancer – e.g. dependence on adults – and the adjustment of the survivors.

This review has addressed the social and emotional adjustment of survivors of childhood cancer, two aspects of quality of life (QoL). Although QoL in adults has received a great deal of attention, QoL in children is a relatively new field of research (51). The current consensus on the assessment of QoL is that it is a multidimensional concept including at least four domains: physical, cognitive, social, and emotional. However, the majority of the studies in the field of children focus on only a few aspects of QoL. The use of standardized QoL instruments that comply with appropriate psychometric requirements (52), is recommended to increase the comparability and completeness of the studies.

Investigating the predictors of survivors' adjustment requires a longitudinal research design (preferably from diagnosis until survivorship), a substantial sample size because of the statistical power, and the use of a control group or the use of standardized instruments with

available norm data. To increase the sensibility cancer-specific measures are recommended, as well as generic measures to allow for comparison between survivors and control group or the general population.

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REFERENCES

(1) Eiser C, Havermans T. Long term social adjustment after treatment for childhood cancer. Arch Dis Child 1994;70:66-70.

(2) Eiser C, Hill JJ, Vance YH. Examining the psychosocial consequences of surviving childhood cancer: Systematic review as a research method in pediatric psychology. J Pediatr Psychol 2000;25(6):49-60.

(3) Anderson V, Smibert E, Ekert H, Godber T. Intellectual, educational, and behavioral sequelae after cranial irradiation and chemotherapy. Arch Dis Child 1994;70:476-83.

(4) Bauld C, Anderson V, Arnold J. Psychosocial aspects of adolescent cancer survival. J Paediatr Child Health 1998;34:120-6.

(5) Chang P, Nesbit ME, Youngren R, Robison LL. Personality characteristics and psychosocial adjustment of long-term survivors of childhood cancer. J Psychosoc Oncol 1988;5(4):43-58.

(6) Noll RB, MacLean WEJr, Whitt JK, Kaleita TA, Stehbens JA, Waskerwitz MJ, et al. Behavioral adjustment and social functioning of long-term survivors of childhood leukemia: parent and teacher reports. J Pediatr Psychol 1997;22(6):827-41.

(7) Radcliffe J, Bennett D, Kazak AE, Foley B, Phillips PC. Adjustment in childhood brain tumor survival: child, mother and teacher report. J Pediatr Psychol 1996;21(4):529-39.

(8) Lesko LM. Surviving hematological malignancies: stress responses and predicting psychological adjustment. The Biology of Hematopoiesis. Wiley-Liss. Inc, 1990. p. 423-37.

(9) Anholt UV, Fritz GK, Keener M. Self-concept in survivors of childhood and adolescent cancer. J Psychosoc Oncol 1993;11(1):1-17.

(10) Olson AL, Boyle WE, Evans MW, Zug LA. Overall function in rural childhood cancer survivors: the role of social competence and emotional health. Clin Pediatr (Phila) 1993;32(6):334-42.

(11) Greenberg HS, Kazak AE, Meadows AT. Psychologic functioning in 8- to 16-year-old cancer survivors and their parents. J Pediatr 1989;114(3):488-93.

(12) Fritz GK, Williams JR. Issues of adolescent development for survivors of childhood cancer. J Am Child Adolesc Psychiatry 1988;27(6):712-5.

(13) Spirito A, Stark LJ, Cobiella C, Drigan R, Androkites A, Hewett K. Social adjustment of children succesfully treated for cancer. J Pediatr Psychol 1990;15(3):359-71.

(14) Van Dongen-Melman JEWM. On surviving childhood cancer. Rotterdam: Dissertation Academisch Ziekenhuis Rotterdam / Erasmus Universiteit Rotterdam, 1995.

(15) Kazak AE, Meadows AT. Families of young adolescents who have survived cancer: social-emotional adjustment, adaptability, and social support. J Pediatr Psychol 1989;14:175-91.

(16) Kazak AE, Christakis D, Alderfer M, Coiro MJ. Young adolescent cancer survivors and their parents: adjustment, learning problems, and gender. J Fam Psychol 1994;8(1):74-84.

(17) Madan-Swain A, Brown RT, Sexson SB, Baldwin K, Pais R, Ragab A. Adolescent cancer survivors: psychosocial and familial adaptation. Psychosomatics 1994;35(5):453-9.

(18) Sloper T, Larcombe IJ, Charlton A. Psychosocial adjustment of five-year survivors of childhood cancer. J Cancer Educ 1994;9(3):163-9.

(19) Von Essen L, Enskär K, Kreuger A, Larsson B, Sjöden PO. Self-esteem, depression and anxiety among Swedish children and adolescents on and off cancer treatment. Acta Paediatr 2000;89:229-36.

(20) Arvidson J, Larsson B, Lönnerholm G. A long-term follow-up study of psychosocial functioning after autologous bone marrow transplantation in childhood. Psychooncology 1999;8:123-34.

(21) Pendley JS, Dahlquist LM, Dreyer Z. Body image and psychosocial adjustment in adolescent cancer survivors. J Pediatr Psychol 1997;22(1):29-43.

(22) Barakat LP, Kazak AE, Meadows AT, Casey R, Meeske K, Stuber ML. Families surviving childhood cancer: a comparison of posttraumatic stress symptoms with families of healthy children. J Pediatr Psychol 1997;22(6):843-59.

(23) Kazak AE, Barakat LP, Meeske K, Christakis D, Meadows AT, Penati B, et al. Posttraumatic stress, family functioning, and social support in survivors of childhood leukemia and their mothers and fathers. J Consult Clin Psychol 1997;65(1):120-9.

(24) Kazak AE, Barakat LP. Brief report: Parenting stress and quality of life during treatment for childhood leukemia predicts child and parent adjustment after treatment ends. J Pediatr Psychol 1997;22:249-758.

(25) Fritz GK, Williams JR, Amylon M. After treatment ends: psychosocial sequelae in pediatric cancer survivors. Am J Orthopsychiatry 1988;58:552-61.

(26) Kazak AE. Posttraumatic distress in childhood cancer survivors and their parents. Med Pediatr Oncol Suppl 1998;1:60-8.

(27) Stuber ML, Meeske K, Gonzalez S, Houskamp BM, Pynoos R. Post-traumatic stress after childhood cancer I: the role of appraisal. Psychooncology 1994;3:305-12.

(28) Stuber ML, Gonzalez S, Meeske K, Guthrie D, Houskamp BM, Pynoos R, et al. Post-traumatic stress after childhood cancer II: a family model. Psychooncology 1994;3:313-9.

(29) Stuber ML, Christakis DA, Houskamp B, Kazak AE. Posttrauma symptoms in childhood leukemia survivors and their parents. Psychosomatics 1996;37:254-61.

(30) Butler RW, Rizzi LP, Handwerger BA. Brief report: the assessment of posttraumatic stress disorder in pediatric cancer patients and survivors. J Pediatr Psychol 1996;21(4):499-504.

(31) Pelcovitz D, Goldenberg LA, Mandel F, Kaplan S, Weinblatt M, Septimus A. Posttraumatic stress disorder and family functioning in adolescent cancer. J Trauma Stress 1998;11(2):205-21.

(32) Sawyer M, Crettenden A, Toogood I. Psychological adjustment of families of children and adolescents treated for leukemia. Am J Pediatr Hematol Oncol 1986;8(3):200-7.

(33) Sawyer MG, Toogood I, Rice M, Haskell C, Baghurst P. School Performance and psychological adjustment of children treated for leukemia. Am J Pediatr Hematol Oncol 1989;11(2):146-52.

(34) Sawyer M, Antoniou G, Toogood I, Rice M. Childhood cancer: A two year prospective study of the psychological adjustment of children and parents. J Am Acad Child Adolesc Psychiatry 1997;36(12):1736-43.

(35) Sawyer M, Antoniou G, Toogood I, Rice M, Baghurst P. Childhood cancer: a 4-year prospective study of the psychological adjustment of children and parents. J Pediatr Hematol Oncol 2000;22(3):214-20.

(36) Sawyer MG, Streiner DL, Antoniou G, Toogood I, Rice M. Influence of parental and family adjustment on the later psychological adjustment of children treated for cancer. J Am Acad Child Adolesc Psychiatry 1998;37(8):815-22.

(37) Levin Newby W, Brown RT, Pawletko TM, Gold SH, Whitt JK. Social skills and psychological adjustment of child and adolescent cancer survivors. Psychooncology 2000;9(2):113-26.

(38) Carlson-Green B, Morris RD, Krawiecki N. Family and illness predictors of outcome in pediatric brain tumors. J Pediatr Psychol 1995;20(6):769-84.

(39) Mulhern RK, Wasserman AL, Friedman AG, Fairclough D. Social competence and behavioral adjustment of children who are long-term survivors of cancer. Pediatrics 1989;83(1):18-25.

(40) Carpentieri SC, Mulhern RK, Douglas S, Hanna S, Fairclough DL. Behavioral resiliency among children surviving brain tumors: a longitudinal study. J Clin Child Psychol 1993;22(2):236-46.

(41) Glaser AW, Nik Abdul Rashid NF, Walker UCL, Walker DA. School behavior and health status after central nervous system tumours in childhood. Br J Cancer 1997;76(5):643-50.

(42) Vannatta K, Gartstein MA, Short A, Noll RB. A controlled study of peer relationships of children surviving brain tumors: teacher, peer, and self ratings. J Pediatr Psychol 1998;23(5):279-87.

(43) Vannatta K, Zeller M, Noll RB, Koontz K. Social functioning of children surviving bone marrow transplantation. J Pediatr Psychol 1998;23(3):169-78.

(44) Madan-Swain A, Brown RT, Foster MA, Vega R, Byars K, Rodenberg W, et al. Identity in adolescent survivors of childhood cancer. J Pediatr Psychol 2000;25(2):105-15.

(45) Stuber ML, Kazak AE, Meeske K, Barakat L, Guthrie D, Garnier H, et al. Predictors of posttraumatic stress symptoms in childhood cancer survivors. Pediatrics 1997;100(6):958-64.

(46) Varni JW, Katz ER, Colegrove R, Dolgin M. Perceived stress and adjustment of long-term survivors of childhood cancer. J Psychosoc Oncol 1994;12(3):1-16.

(47) Rait DS, Ostroff JS, Smith K, Cella DF, Tan C, Lesko LM. Lives in balance: perceived family functioning and the psychosocial adjustment of adolescent cancer survivors. Fam Process 1992;31:383-97.

(48) Lazarus RS, Lazarus BN. Passion and reaction: making sense of our emotions. New York Oxford: Oxford University Press; 1994.

(49) Druss RG, Douglas CJ. Adaptive responses to illness and disability. Healthy denial. Gen Hosp Psychiatry 1988;10:163-8.

(50) Sprangers MAG, Schwartz CE. Integrating response shift into health-related quality of life research: a theoretical model. Soc Sci Med 1999;48:1507-15.

(51) Calaminus G, Kiebert G. Studies on health-related quality of life in childhood cancer in the European setting: an overview. Int J Cancer 1999;Supplement 12:83-6.

(52) Eiser C, Morse R. A review of measures of quality of life for children with chronic diseases. Arch Dis Child 2001;84:205-11.

Table 1 Studies on emotional or social adjustment in young survivors of childhood cancer.
(M mean, Med median, SD standard deviation, yrs years, ALL acute lymphatic leukemia, ANLL acute nonlymphatic leukemia, HL Hodgkin lymphoma, NHL non-Hodgkin lymphoma, BMT bone marrow transplantation, CNS central nervous system, PTS(D) posttraumatic stress (disorder), SES socioeconomic status, c child or adolescent survivor, p parent, t teacher, ph physician, o other).

Reference: study objective	Method / sample characteristics	Measures	Results
(3): Intellectual, educational and behavioral sequelae after cranial irradiation and chemotherapy	Survivors N=100: age at study 7–16 yrs (M=12.1), 45% boys, 55% girls, leukemia treated with chemotherapy + cranial irradiation. Survivors N=50: age at study 7–16 yrs (M=11.7), 50% boys, 50% girls, mixed diagnosis, chemotherapy only. Control group N=100: healthy children, age at study 12.0 yrs (M), 48% boys, 52% girls	Wechsler Intelligence Scale for Children – Revised (WISC-R), Wide Range Achievement Test – Revised (WRAT-R) (c), Child Behavior Checklist (CBCL) (p)	CBCL scores of both clinical groups fell within the average band, with no evidence of significant psychopathology. There were no differences between the two clinical groups on the overall behavior scale, the activity scale or the social scale. Cranially irradiated survivors scored lower on the school scale than the survivors receiving chemotherapy only. In addition, they were more anxious/depressed and withdrawn, and they had more attentional and social problems.
(9): Self-concept of survivors of childhood and adolescent cancer compared with healthy children. Physical, psychological, and social impact of cancer on children's self-concept	Survivors N=62: age at study 7–18 yrs (M=13.5), age at diagnosis ≤14 yrs, off treatment ≤6 months or ≥2 yrs (M=20 months), 64.5% boys, 35.5% girls, mixed diagnosis, brain tumors excluded. Control group N=120: healthy children, aged 6–17 yrs (M=11.0), 46.7% boys, 53.3% girls	Piers-Harris Children's Self-concept Scale (c), Oncologist Rating Form (ph), Physical Impairment Rating Scale (o)	Global self-concept was similar and within normal limits in both groups. Survivors felt better about the self-concept aspects of their intellectual and school status, behavior, and overall happiness and satisfaction than healthy children. Physical appearance aspect of self-concept was the only aspect affected by disease and treatment factors: greater physical impairment and longer time since end of treatment was associated with less positive feelings about physical appearance
(20): Psychosocial functioning after autologous bone marrow transplantation (ABMT) in childhood	Survivors N=26: age at study 6.9–24.7 yrs (Med=16.1), age at diagnosis 1.5–16.2 (Med=4.8), time since diagnosis 3.7–16.1 yrs (Med=9.6), age at ABMT 1.9–17.9 (Med=9.6), time	I think I am (ITIA) (c), CBCL (p), CBCL Teacher Report Form (TRF), Rutter teacher questionnaire (t)	With respect to self-esteem the survivors did not differ from healthy Swedish children. Parents reported higher scores for behavioral problems (total behavior and internalizing) and

	since ABMT 2.0–9.9 yrs (Med=7.0), 69% boys, 31% girls, leukemia and lymphoma. No control group		lower levels of social competence (total and school competence) in survivors than in the normative sample. Teachers also reported more behavioral problems (Total and subscale Neurotic). The CNS treatment intensity correlated positively with the magnitude of behavior problems and negatively with social competence
(22): Comparison of posttraumatic stress symptoms between families in which survival of childhood cancer has taken place and families of healthy children	Survivors N=309 (and parents): age at study 8–20 yrs (M=13.5), age at diagnosis 1–17 yrs (M=5.8), off treatment ≥1 year (M=5.9), 50% girls, 50% boys, mixed diagnosis. 309 mothers, mean age 41.7 yrs; 213 fathers, mean age 43.8 yrs. Controls N=219 (and parents): healthy children, age at study 8–20 yrs (M=12.3), 56% girls, 44% boys. 211 mothers, mean age 42.3 yrs; 114 fathers, mean age 44.4 yrs	Revised Children's Manifest Anxiety Scale (RCMAS), Trauma Symptom Checklist for Children (TSC) (c), Impact of Event Scale (IES), Posttraumatic Stress Disorder Reaction Index (PTSD-RI), Assessment of Life Threat and Treatment Intensity Questionnaire (ALTTIQ) (c, p), State-Trait Anxiety Inventory (STAI), Family Adaptability and Cohesion Evaluation Scale IIIA (FACES IIIA), Social Network Reciprocity and Dimensionality Assessment Tool (SNRDAT) (p)	Survivors did not differ from the control group. Past perceived threat to life contributed to PTS symptoms in survivors. Survivors' reports of symptoms associated with their parents' report of symptoms. Demographic characteristics and objective aspects of the cancer and its treatment were not related to reports of PTS symptoms
(4): Psychosocial status of adolescent cancer survivors compared with healthy peers	Survivors N=32: age at study 12–17 yrs (M=14.9), age at diagnosis 7.5 yrs (M), off treatment 8.0 yrs (M), 40.6% boys, 59.4% girls, ALL Control group N=34: healthy children, aged 12–17 yrs (M=14.8), 32.4% boys, 67.6% girls	STAI, Adolescent Coping Scale (ACS) (M), Self Description Questionnaire II (SDQ II), Possible Selves Inventory (PSI) (c)	No overt psychological dysfunctioning in cancer survivors. No differences between survivors and controls in total-self-concept. Survivors had higher state anxiety levels than peers (trait anxiety scores were equivalent) and tended to employ more avoidance strategies (coping). Survivors aged 15–17 years worried more than 12- to 14-years-olds. Older age at diagnosis was associated with a less negative view of present and future, and positively related to the school concept

(30): Posttraumatic stress disorder in pediatric cancer patients and survivors	Survivors N=42: survivors' mean age at study 8.8 yrs (SD=4.0) No control group[b]	PSS, modified version, CBCL, Personality Inventory for Children (PIC) (p)	Among off-treatment pediatric cancer survivors, the incidence of PTSD was not higher than in the general population. PTS symptoms were associated with behavioral problems: withdrawn, social problems, somatic complaints, being anxious/depressed, attentional problems. Increased intensity of stress symptoms was significantly predicted by a combination of higher age and being on treatment
(38): Family and illness predictors of outcome in pediatric brain tumors	Survivors N=63 (and mothers): age at diagnosis 2–16 yrs (M=7.0), time between diagnosis and testing 1–123 months (M=44), 75% boys, 43% girls, brain tumors Family data at T1: at diagnosis Child data at T2: 3–56 months later (M=24). No control group	Stanford-Binet Intelligence Scale, 4th edn., WRAT-R (c), CBCL Parent Report Form (PRF), Vineland Adaptive Behavior Scale, Coping Health Inventory for Parents (CHIP), Family Inventory of Life Events (FILE), Family Environment Scale (FES) (p)	Cognitive and behavioral outcomes were different from normative samples. Academic achievement at low end of average range, and Stanford-Binet Composite standard score fell in average range. Slightly elevated rates of problem behavior, and adaptive functioning 1 SD below norms. Family measures did not differ from those in normative samples. Family and demographic variables were best predictors of behavior problems and adaptive behavior: higher SES, shorter time since diagnosis, fewer maternal coping resources (= use of family, social and medical resources) related to better adaptive functioning. Single-parent homes and more negative life events were associated with more behavioral problems. Best predictors of achievement were illness and demographic variables: more severe treatment, longer time since diagnosis, lower SES and younger age at diagnosis were correlated with poorer achievement

(40): Behavioral resilience among children surviving brain tumors	Survivors N=40: age at study 4–16 yrs, age at diagnosis 8.8 yrs (M) (SD=3.0), time since diagnosis 2.1 yrs (M) (SD=0.3), 67.5% boys, 35.5% girls, brain tumors Survivors N=40 (control group): age at study 4–16 yrs, age at diagnosis 7.3 yrs (M) (SD=4.5), time since diagnosis 2.1 yrs (M) (SD=0.3), 52.5% boys, 47.5% girls, mixed diagnosis without a history of CNS disease	WISC-R (c), CBCL (p), (cosmetic and functional impairment rated by psychologists as none, mild, moderate, severe)	Brain tumor survivors and other survivors exhibited an abnormally high prevalence of social and behavioral problems. Overall 51% of the brain tumor group and 49% of the control group had increased problems on one or more CBCL scales. Survivors had more problems with respect to social competence (Total, Activities, School) than the general population. Increased problems were also evident on the scales: Total behavior, Internalizing, Externalizing, Somatic complaints. Survivors in the brain tumor group displayed more problems in the Social competence scales (Total, Activities, School) but they had fewer behavioral problems (Internalizing) than the other survivors. Social competence and behavioral problems shortly after diagnosis were strong predictors of the outcome in survivors of brain tumors. In addition, their social competence was positively associated with mother's age at diagnosis (Activity subscale), with younger age at diagnosis (<9 yrs), being female (School subscale), and negatively with functional impairment (Total). Time since diagnosis was positively correlated with behavioral problems (Somatic complaints and Total) in brain tumor survivors. In addition, those who were older at diagnosis had more somatic complaints
(5): Psychosocial adjustment of long-term survivors of childhood cancer	Survivors N=42: age at study 11–25 yrs (M=17.2), age at diagnosis 2–18 yrs (M=9.7), 59.5% boys, 40.5% girls, mixed	Minnesota Multiphasic Personality Inventory (MMPI), PIC (p), structured interview about educational,	Emotional adjustment of survivors as a group was within normal limits. One-third of the survivors had

	diagnoses, mostly ALL. No control group	-occupational and behavioral adjustment (c or p)	pathologic MMPI social profiles – incidence no different from that in general population. Most frequent problems were hypomania and alcoholism. PIC profiles reported by the parents were also within normal limits, suggesting absence of psychopathology. Male survivors more depressed and anxious and less active then female. Survivors' social, educational, and occupational adjustment warranted concern
(12): Adolescent development in survivors of childhood cancer. Part of the larger study by same group [16]	Survivors N=41: age at study 13–21 yrs (M=17.3), age at diagnosis 11.0 yrs (M), age at treatment 13.6 yrs (M), 47% boys, 53% girls, mixed diagnoses, brain tumors excluded. No control group	Piers-Harris Children's Self-concept Scale (c), Children's Depression Rating Scale (CDRS) (c, p, o), Global Adjustment Rating, designed for this study (o)	Global functioning / adjustment among survivors good or excellent in 61%, satisfactory or average in 22%, marginal to poor in 7%, very poor 10%. Depression: 81% not depressed, 12% possibly depressed, 7% depressed (general population 8% depressed). Survivors reported a higher self-image than the normative sample: 75% of them had a high self-image
(25): Antecedents of psychosocial adjustment in pediatric cancer survivors	Survivors N=52: age at study 7–21 yrs (M=15.9), age at diagnosis 9.7 yrs (M), off treatment 2–7 yrs (M=3.7), mixed diagnosis, brain tumors excluded. No control group	CDRS (c, p, o), Global Adjustment Rating, designed for this study (o)	Most survivors functioning well: 61% excellent or good global adjustment, 26% average, 14% marginal or poor. Serious psychosocial problems were relatively rare: 80% were not depressed, 14% possibly depressed and 6% depressed (general population 8% depressed). Most illness-related variables were not predictive of psychosocial outcome, only residual physical handicap. Psychosocial variables, especially communication patterns and availability of peer support during treatment were predictive of psychosocial outcome

(41): School behavior and health status after central nervous system tumors in childhood	Survivors N=27 (and parents): age at study 6–17 yrs (M=10.8), age at diagnosis 1–13 yrs (M=6.1), time since diagnosis 1–10 yrs (M=4.8), off treatment ≥1 yr, 40.8% boys, 59.2% girls, CNS tumors. Control group N=25 (and parents): sex- and age-matched controls (21 school-age siblings and controls)	Health utilities Index, Marks II and III (c, t, p) Lansky play performance scale, Deasy-Spinetta Behavioral Questionnaire (t), self-esteem question (not standardized) (c)	No lower overall level of school behavior than in controls: normal willingness to attend school and normal concentration, and no difficulties with school work or concentration. Reduced ability: more pain and worry, lower cognitive scores, impaired emotion. Less likely to participate in organized activities; worse self-esteem but their confidence in future was similar to that of their peers. Scores not affected by exposure to chemotherapy, radiotherapy, age at diagnosis or sex
(11): Psychological functioning in 8- to 16-year-old childhood cancer survivors and their parents	Survivors N=138 (and mothers): age at study 8–16 yrs (M=12.5), age at diagnosis 2 months to 9 yrs (M=3.6 yrs), time since diagnosis 5.0–16.3 yrs (M=8.8), off treatment ≥2 yrs, 56% boys, 44% girls, mixed diagnoses. Control group N=92 (and mothers): healthy children, matched for age, sex and race, 45% boys, 55% girls	Piers-Harris Self-Concept Scale, Nowicki-Strickland Locus of Control Scale, Children's Depression Inventory (c), FES, Derogatis Stress Profile (p)	Although survivors had poorer self-concepts (Total and subscales Intellectual and School status, Anxiety, Happiness, Behavior and Popularity) than the controls, their functioning was within normative limits. No difference with respect to depression. Survivors had a more external locus of control. Children with severe medical late effects had a poorer total self-concept, more depressive symptoms and more external locus of control than those with no or mild to moderate late effects
(23;26): PTS, family functioning, and social support in survivors of childhood leukemia and their parents	Survivors N=130 (and 130 mothers, 96 fathers): age at study 8–19 yrs (M=13.5), age at diagnosis 1–16 yrs (M=4.8), off treatment ≥1 yr (M=5.8), 50.8% boys, 49.2% girls, ALL and ANLL.	RCMAS, TSC (c), Impact of Event Scale (IES), PTSD-RI (c, p), STAI, FACES-IIIA, SNRDAT (p)	Overall and on PTSD Reaction Index and IES survivors and controls did not differ. Survivors had more anxiety. Generally survivors and their parents reported significantly lower posttraumatic stress symptoms than reported for stressed and traumatized groups. No differences between the

	Control group N=155 (and 148 mothers, 80 fathers): healthy children, aged 8–20 yrs (M=12.3), 45.8% boys, 54.2% girls		groups with regard to family functioning and social support although they were negatively associated with anxiety and posttraumatic stress outcomes. Current child age, age at diagnosis and months off treatment not correlated with outcome
(24): Child and parent adjustment during treatment and after treatment ends	Longitudinal study: T1 at treatment (first remission), T2 off treatment ≥ 6 months. Survivors N=29: age at T1 7.64 yrs (M), age at T2 9.79 yrs (M), 45% boys, 55% girls, ANLL, ALL	RCMAS (c), PSI (short form), Pediatric Oncology Quality of Life Scale (POQOLS), PTSD-RI, STAI (p)	Survivors scored lower than normative values on anxiety. During treatment (T1) survivors had a higher QoL than normative sample for the POQOLS. Parent-rated child QoL during treatment (T1) was associated with later adjustment for mothers and children. Child's total QoL (at T1) was associated with mother's off treatment posttraumatic stress symptoms and her state anxiety. The emotional distress subscale of the POQOLS (at T1) was related to maternal posttraumatic stress symptoms and her state anxiety during treatment (T1) and to child anxiety after treatment. Parenting stress scores (T1) were not associated with child anxiety off treatment
(15): Families of young adolescent cancer survivors: social emotional adjustment, adaptability and social support.	Longitudinal study: T1, T2 six months later. Survivors N=35 at T1, N=25 at T2 (and parents): age at study 10–15 yrs (M=12.2); age at diagnosis 3.7 yrs (M), off treatment ≥5 yrs (at T1), ALL, ANL, NHL. Control group N=13 at T1, N=9 at T2 (and parents): healthy children recruited by asking survivors' families to identify friends/neighbours who have children of the same age	Self Perception Profile for Adolescents, Social Support Rating Scale (SSRS) (c), Family Adaptability and Cohesion Evaluation Scales-Version II (FACES-II) (c, p), Langner Symptom Checklist (LSC); Child Behavior Checklist (CBCL) (p)	In general survivors scored within normative limits and did not differ from controls with respect to perceived self-competence, social support, child behavior, parental distress and family adaptability and cohesion. At T1 survivors rated their families as 'structured', whereas the controls as 'flexible'. At T2 survivors reported lower levels of competence and less help and guidance from friends than controls.

			Changes over time suggest a decline of available social support for survivors and their families. Survivors reported at T2 less emotional support from family, teachers and other adults, and less help and guidance from friends. They also had a decline in perceived competence related to athletic abilities and their fathers reported lower levels of behavioral problems. At T2 mothers rated their families less adaptable and cohesive than at T1 and less adaptable than the controls
(16): Young adolescent cancer survivors and their parents: adjustment, learning problems and gender	Longitudinal study: T1, T2 1 year later. Survivors N=74 at T1, N=59 at T2 (and their families): age at T1 10–15 yrs (M=12.3), age at diagnosis 3.7 yrs (M), time since diagnosis at T1 96.2 months (M), off treatment at T1 ≥5 yrs (M=70.8 months), at T1 60% boys, 40% girls, at T2 40% boys, 60% girls, mixed diagnosis. No control group	Self Perception Profile for Adolescents, Social Support Rating Scale (SSRS), State-Trait Anxiety Inventory for Children (STAIC), Hopelessness Scale for Children (HSC), Children's Social Desirability Questionnaire (CSD) (c), FACES-III (c, p), Langner Symptom Checklist (LSC), CBCL (p)	Survivors' adjustment was within normal limits. Little change over the year (T1-T2). Self perception and anxiety was comparable to normative values, but males scored lower than the norms on anxiety. Hopelessness was also below the norms (70–73% low hopelessness, 6–8% high hopelessness). Parents' report of survivor's behavior were consistent with normative values. Family cohesion and adaptability, reported by survivors and parents, developmentally appropriate. Social support from family was rated higher than was support from friends and school staff. (Normative data not available)
(8): Stress responses and predicting psychological adjustment in survivors of hematological malignancies	Survivors N=58[c]: current age M=16 (SD=2), age at diagnosis M=9 (SD=4), ≥1 yr off treatment, 26% girls, 74% boys, hematological malignancies (ALL, HL, NHL). No control group	Brief Symptom Inventory, IES, Social Adjustment Scale (SAS), CBCL Youth Self Report (YSR), Derogatis Sexual Functioning Inventory, FACES (c)	Adolescent survivors reported more global psychological distress and less overall mental health than normative samples (but not of psychopathological proportions). They did not differ on social competence, problem behavior, or school achievement.

			Quality of family communication and family cohesion and adaptability were positively correlated with mental health of survivors. Survivors who were older at the time of diagnosis and at time of assessment, and who were more recently off treatment reported heightened psychological distress. Neither diagnosis nor type of treatment (BMT versus conventional chemotherapy) was associated with psychosocial difficulties
(37): Social skills and psychological adjustment of cancer survivors	Survivors N=42: age at study 6–18 yrs (M=13.1), age at diagnosis 0.0–12.3 yrs (M=4.8), off treatment 2.5–17.5 yrs (M=6.8), 50% girls, 50% boys, mixed diagnosis except brain tumors. No control group	CBCL, SSRS – Parent, FES (p), CBCL Teacher Report Form (TRF), SSRS – Teacher (t).	Survivors generally showed normal social skills and few internalizing or externalizing behavioral problems compared with normative data. Social skills as reported by parents and teachers were positively correlated with academic functioning. Better academic functioning was also correlated with less (teacher reported) behavioral problems, but more family cohesiveness was associated with more behavioral problems as rated by teachers. Longer time off therapy was related to fewer behavioral problems (reported by parents)
(17): Psychosocial and familial adaptation in adolescent cancer survivors and their families	Survivors N=25: age at study 12–18 yrs (M=15.6), age at diagnosis 5.1 yrs (M), off treatment ≥5 yrs, boys 48%, girls 52%, mixed diagnosis. Control group N=16: non-diseased children, aged 15.4 yrs (M), boys 43.8%, girls 56.2%, matched for age, gender and race	Self-Perception Profile for Adolescents (SPPA), Millon Adolescent Personality Inventory (MAPI) (c), Coping Strategies Inventory (CSI), FACES-III, Inventory of Parent-Adolescent Communication (IPAC) (c, p), CBCL Teacher Rating Scale (TRS) (t)	No major difficulties in social competence, overall coping, and family communication among cancer survivors. School teachers reported no symptoms of psychopathology. Survivors reported body image disturbances and adjustment difficulties. Survivors reported body comfort as more problematic and unresolved than controls,

			and as a major concern. Survivors had less self-criticism than controls but similar global self-worth. No differences found on the adolescents' FACES-III ratings, but survivors' mothers used more social withdrawal (coping) than controls' mothers, and designated themselves as more rigid and less flexible. No correlations between disease and disability parameters and the outcome measures
(44): Identity in adolescent survivors of childhood cancer	Survivors N=52: age at study 12–23 yrs, age at diagnosis 1.1–18.5 yrs (M=9.4), age off therapy 3.1–19.5 yrs (M=11.4), off treatment 1.0–14.3 yrs (M=5.8), 82.7% continuous remission, 11.5% one relapse, 5.8% two relapses, mixed diagnosis, brain tumors excluded. Control group N=42: healthy adolescents, aged 12–23 yrs, 43% boys, 57% girls, recruited from youth clubs, activity centers, schools and universities, matched for age, gender, socio-economic background and economic dependence in the family	Extended Objective Measure of Ego Identity Status-2 (EOMEIS-2), PTSD-RI, Adolescent Inventory of Life Events and Changes (A-FILE), Perceived Social Support-Family and Perceived Social Support – Friend (PSS-Fa & PSS-Fr) (c), PSDI, FILE, FES (p)	A greater frequency of survivors than of their healthy peers was found within the foreclosed identity status (17 versus 9). Factors positively associated with the fore-closed identity status in survivors were: age, cancer, symptoms of PTSD, and family functioning characterized by greater levels of conflict
(39): Social competence and behavioral adjustment of children who are long-term survivors of cancer	Survivors N=183: age at study 7.0–15.9 yrs (med=12.2), age at diagnosis 0.1–9.7 yrs (med=2.7), time since diagnosis 5.0–15.2 yrs (med=8.6), off treatment 2.1–14.8 yrs (med=6.9), boys 58.5% girls 41.5%, mixed diagnosis. No control group	CBCL (p)	In comparison with the general population more survivors had deficiencies in social competence and increased behavior problems, especially school performance and somatic complaints. Functional impairment, physical disability, treatment of leukemia with cranial radiation, age ≥12 yrs at time of study and living in a single-parent household were associated with social competence or/and behavioral problems. No correlations between

			outcome and gender of the patient, SES, duration of therapy, disease recurrence
(6): Behavioral adjustment and social functioning of survivors of childhood leukemia	Survivors N=126 parent reports (teacher reports N=78): age at study 5–18 yrs (M=8.7), age at diagnosis M=4.8 yrs (SD=3.1), time since diagnosis ≥4 yrs (M=4.3), ALL intermediate prognosis. No control group	CBCL (p, t), PIC (p)	Results indicate minimal psychosocial morbidity. The scores of the survivors were generally similar to instrument norms. Parents, but not teachers, reported heightened child somatic concerns. The number of survivors exceeding clinical cut-off scores for behavior problems and competence was consistent with published norms. There was no effect of radiotherapy or chemotherapy regimen on behavioral adjustment and school functioning. Intensity of therapy not related to behavioral outcomes
(10): Social and emotional functioning of childhood cancer survivors	Survivors N=20: age at study 6–16 yrs (M=9.7), age at diagnosis 1.5–7.0 yrs (M=3.1), off treatment 1–6 yrs (M=2.4), length of treatment 2.1 yrs (M), boys 65%, girls 35%, mixed diagnosis. Control group N=40: classroom peers, aged 6–17 yrs (M=9.5), boys 65%, girls 35%, matched on gender and age	Health Locus of Control, Piers-Harris Child's Self-Concept Scale (c), Revised Vineland Adaptive Behavior scales, FES, Functional Status II(r) Measure (p), CBCL (p, t), Health Resources Inventory (HRI) (t)	Cancer survivors and controls had similar attitudes about self-esteem, family conflicts, physical functioning, social skills, independence, and sense of control over health. Survivors had high levels of somatic complaints but no different from controls. Both parents and teachers noted poorer social competence among survivors, but parents reported more behaviour problems whereas teachers reported poorer school performance
(31): PTSD and family functioning in adolescents with a history of cancer	Survivors N=23: age at study 14–23 yrs (M=17.6), age at diagnosis 2–18 yrs (M=10.5), age off treatment 5–19 yrs (M=12.5), off treatment 0–11 yrs (M=3.3), 48% boys, 52% girls, mixed diagnosis. Abused adolescents N=23:	Parental Bonding Instrument (PBI), FACES III (c), Structured Clinical Interview for DSM-PTSD (SCID-PTSD) (c, p), Symptom Checklist 90 Global Severity Index (SCL-90-R GSI) (p)	Higher lifetime prevalence of PTSD in survivors (34.8%) than in physically abused children (7%) and control group (4%). No differences on current PTSD. Survivors' parents were more protective than the others. They were overly protective and highly caring, fitting into the

	aged 15.1 yrs (M), 41% boys, 59% girls. Control group N=27: aged 16.1 yrs (M), 48% boys, 52% girls		'affectionate constraint' category. No differences found in perceived family adaptability and cohesion. PTSD status in survivors was related to mothers' PTSD status and to survivors' perception of family as chaotic. Overall adjustment of the mothers was not related to survivors' PTSD
(21): Body image and psychosocial adjustment in adolescent cancer survivors	Survivors N=21: age at study 11–21 yrs, age at diagnosis 12.2 yrs (M), off treatment 0.5–2.5 yrs, length 19.5 months, 57.1% boys, 42.9% girls, mixed diagnosis. Control group N=21: matched for age, sex and ethnicity	Self-Image Questionnaire for Young Adolescents (SIQYA), Body Cathexis Scale (BCS), Self-Report Likert Rating of Body Image, Body Image Avoidant Questionnaire (BIAQ), Situational Inventory of Body Image Distress (SIBID), Peer Interaction Record (PIR), Loneliness Questionnaire, Social Anxiety Scale for Children-Revised (SASC-R), Self-Perception Profile for Adolescents (SPPA) (c), School Attendance (c, p) Objective Ratings of Attractiveness (o)	Survivors took part in fewer social (peer) activities than controls, but no differences found for social anxiety, loneliness, body image scores or school truancy. Survivors longer off treatment had lower self-worth, more social anxiety and more negative body image than other survivors. They did not differ in ratings of attractiveness
(7): Adjustment in childhood brain tumor survivors and their mothers	Survivors N=38 (and mothers): age at study 6–18 yrs (M=11.4), time since diagnosis 2–5 yrs, 65.8% boys, 34.2% girls, brain tumors. No control group	Children's Depression Inventory (CDI), Children's Manifest Anxiety Scale-Revised (CMAS-R), Self-Perception for children (SPCC) (c), CBCL (p, t), Vineland Adaptive Behavior Scale (VABS), Beck Depression Inventory (BDI), STAI, and PSI – Short Form (p)	In general the (brain tumor) survivors reported psychological adjustment within normal limits. They felt less athletically competent but also less anxious and depressed than their normative counterparts. Mothers rated them lower in overall social scholastic competence than normative peers, and reported they had greater difficulties in communication skills and in mother-child interaction. Teachers reported no differences. No effect of radiation treatment on adjustment
(47): Family functioning and the relationship with psychological adjustment of adolescent cancer	Survivors N=88: age at study 12–19 yrs (M=15.6), age at diagnosis 4–17 yrs (M=10.6), off	FACES-III, Rand Mental Health Inventory, Rosenberg Self-Esteem Scale, CBCL YSR (c),	Survivors reported lower levels of family cohesion than a normative sample but no difference in

survivors	treatment ≥3 months (M=37.4), treatment duration 23 months (M), 66% boys, 34% girls, ALL, HL, NHL. No control group		family adaptability. Family cohesion was strongly (positively) correlated with psychological adjustment: overall mental health, self-esteem and global competence. Not related: current age, age at diagnosis, gender, time off treatment
(32;33): Psychological adjustment of children and adolescents treated for leukemia	Longitudinal study: T1 5.7 yrs (M) after diagnosis, T2 9.7 yrs (M) after diagnosis. Survivors N=42 at T1: age at study 4–16 yrs (M=10.4), time since diagnosis 5.7 yrs (M), 54.8% boys, 45.2% girls, ALL. N=32 at T2: age at study 13.4 yrs (M), time since diagnosis 9.7 yrs (M), 53.1% boys, 46.9% girls. Control group N=42 at T1: healthy children, aged 10.3 yrs (M), 54.8% boys, 45.2% girls, matched at age, sex and school class. Control group N=32 at T2: aged 13.5 yrs (M), 59.4% boys, 40.6% girls. Survivors' siblings N=56 at T1: aged 11.1 yrs (M), 55.4% boys, 44.6% girls. Survivors siblings N=33 at T2: aged 12.5 yrs (M), 63.6% boys, 36.4% girls. Control siblings N=54 at T1: aged 10.4 yrs (M), 59.3% boys, 40.7% girls. Control siblings N=39 at T2: aged 13.4 yrs (M), 69.2% boys, 30.8% girls	CBCL (YSR) (only at T2) (c), Family Concept Inventory (FCI) (p, c), CBCL PRF, TRF (p, t), Rutter B2 Behavioural Scale for Teachers (t)	T1: Survivors had more behavioural problems and less social competence, particularly in school-related activities, than the control group and their siblings. There was a tendency for survivors to have a more disturbed profile than the controls. No differences between the two groups of siblings, or between the survivors' and control families. T2: Range of differences between survivors and control group was less than at T1 (4 yrs before). Survivors were performing worse at school than the matched controls. No differences on ratings of behavior. Differences between survivors and their siblings no longer present
(34-36) Psychological adjustment of children and parents to childhood cancer[a]	Longitudinal study: T1 immediately after diagnosis, then annually for the next 4 yrs. Survivors N=39 at T5 (4 yrs after diagnosis): age at T1 5.2 yrs (M), age	CBCL, General Functioning Scale (GFS) of the Family Assessment Device (FAD), 28-item General Health Questionnaire (GHQ-28) (p)	Immediately after diagnosis (T1) the survivors scored higher on the CBCL Total Behavior Problems and on CBCL Internalizing than the control group.

	at diagnosis 2–12 yrs, 51% boys, 49% girls, mixed diagnosis, most ALL. Control group N=49 (at T5): general community (children selected from preschool, primary school and preschool health clinic), aged 5.1 yrs at T1 (M), 49% boys, 51% girls		The survivors' scores were intermediate between the scores reported in the community and mental health clinics. At the subsequent measures (T2-T5) the scores were generally consistent with those in the control group, i.e. there was a decrease in scores across time for the survivors. Psychological adjustment of families did not vary greatly across the five assessments and between the groups. Greater maternal psychopathology immediately after diagnosis (T1), more child emotional and behavioral problems at T1, and worse family adjustment were associated with a greater number of childhood emotional and behavioral problems 2 yrs after diagnosis
(18): Psychosocial adjustment of five-year survivors of childhood cancer	Survivors N=31 (and parents): age at study 9–18 yrs (M=12.3), time since diagnosis 5 yrs, 58.1% boys, 41.9% girls, leukemia or solid tumors, 54.8% have had relapses. Control group N=31 (and parents): school peers, aged 8–18 yrs (M=12.2), 58.1% boys, 41.9% girls	RMCAS, SPPA (c), Malaise Inventory, FES, Rutter Scale A, open-ended coping interview (p), Rutter Scale B, teacher ratings of children's social, academic and behavioral conduct at school (t)	No differences in anxiety and self-esteem between survivors and controls. Survivors scored lower on both teacher- and parent rated measures of behavioral adjustment than controls. The proportion at risk (on basis of Rutter Scale A and B) was higher in the cancer-survivor group. Teachers gave survivors significantly lower scores for concentration, academic progress and popularity with peers than they gave to controls. Behavioral adjustment of the survivors is negatively correlated with parents' psychological distress, and positively with children's perception of their scholastic competence and their relationships with peers. Behavioral adjustment was also correlated with parental coping

			strategies: lower-level use of direct action at time of study and during the illness, and more use of wishful thinking during study were associated with more behavioral problems. No association between behavioral adjustment scores and family cohesion and expression. No associations between behavioral adjustment and illness variables (relapses and type of cancer), social class or age and gender
(13): Social adjustment, peer relations and social skills development of young survivors of cancer	Survivors N=56: age at study 5–12 yrs (M=9.2), age at treatment 2–5 yrs, off treatment 1/2 –5 yrs (M=41.6 months), 53.8% boys, 48.2% girls, mixed diagnosis. Control group N=52: healthy children, aged 5–12 yrs (M=8.8), 53.8% boys, 46.2% girls	SPPC, Social Skills Questionnaire (developed for this study) (c), Taxonomy of Problem Situations (TOPS – Parent Form), Parent Interview Questions (developed for this study) (p), TOPS, Deasy-Spinetta Behavioral Questionnaire (DSBQ) (t)	Fewer survivors than controls had friends of the same age, and more survivors spent time by themselves. No differences in social skills and self-perception. Few differences between survivors and controls rated by teachers and parent. Survivors obtained more positive teacher ratings on school behavior (willingness, attendance, school social situations)
(29): Posttraumatic symptoms in childhood leukemia survivors and their parents	Survivors N=64 (and parents): age at study 7–19 yrs (M=14.0), age at diagnosis 1–13 yrs (M=4.6), off treatment ≥2 yrs (M=6.7), 50% boys, 50% girls, leukemia. No control group	PTSD-RI, self-report form (c, p)	Prevalence of PTS: 12.5% of the survivors were within the severe range of PTS, which is higher than in the general population (1–9%). Child PTS scores were (positively) correlated with age at diagnosis and with maternal PTS scores. No association between child PTS and years off treatment
(27;28): PTS in childhood cancer survivors and their parents	Survivors N=30: age at study 8–19 yrs (M=13.8), age at diagnosis 1–15 yrs (M=6.7), off treatment since 22–128 months (M=61.5), duration of treatment 1–77 months (M=22.7), 47% boys, 53% girls, mixed diagnosis.	Six-item questionnaire to measure appraisal of life threat and treatment intensity, Post-Traumatic Stress Disorder Reaction Index (PTSD-RI), self-report version adapted for use with cancer patients) (c, p), State Trait Inventory (STAI) (p)	Prevalence of PTS symptoms among survivors: 17% moderate, 30% mild symptoms. Appraisal of treatment was correlated with PTS symptoms, appraisal of life threat was not. Duration of treatment intensity was correlated with appraisal of

	30 mothers, aged 33–51 yrs (M=42.2), 17 fathers aged 36–59 yrs (M=43.4). No control group		treatment intensity. Neither diagnosis nor time off treatment were related to appraisal of treatment intensity and life threat, or to survivor's traumatic stress symptoms. Among children aged ≤6 yrs at treatment the intensity of treatment was positively correlated with PTS symptoms. In the older group (>6 yrs) duration of treatment was positively correlated with PTS symptoms. Appraisal of life threat was not related to PTS symptoms. Survivors PTS symptoms were not directly correlated with any parent variable
(45): Predictors of posttraumatic stress symptoms in childhood cancer survivors	Survivors N=186 (and mothers): age at study 8–20 yrs (M=13.4), age at diagnosis 1–16 yrs (M=6), off treatment 13–220 months (M= 66.1), length of treatment 1–67 months (M=16.4), 50% boys, 50% girls, mixed diagnosis, brain tumors excluded. No control group	Revised Children's Manifest Anxiety Scale, (RCMAS), Social Support Rating Scale (SSRS), Posttraumatic Stress Disorder Reaction Index (PTSD-RI) (c), Assessment of Life Threat and Treatment Intensity Questionnaire (ALTTIQ), constructed for this study (c, p), Treatment Intensity Rating, Severity of Medical Late Effects (ph), stress history (checklist).	Female gender, perception of life threat and treatment intensity, stressful life events, and how upsetting the survivors found the responses of the people in the support network were positively related to survivors' PTS symptoms. Time (months) off treatment was negatively correlated with PTS symptoms. Mothers' perceptions of treatment were indirectly correlated with the stress symptoms, via child anxiety and child appraisal of life threat and treatment intensity. Oncologist's assessment of treatment intensity, age at diagnosis and relapse did not contribute to anxiety, appraisal of life threat and treatment intensity, or to PTS symptoms
(14): Psychosocial functioning in children surviving cancer during middle childhood	Survivors N=95: age at study 8.3–13.7 yrs (median=10.3), age at diagnosis 0.7–12.0 yrs (median=4.7), duration of treatment 39% <2 yrs, 46% 2–3 yrs, 15% > 3 yrs, time off treatment 32% <2 yrs,	Self-Perception Profile for Children (SPPC), Amsterdam Biographic Questionnaire for Children (ABV-K), Children's Depression Scale (CDS) (c), Child Behavior Checklist	Survivors were more withdrawn and introverted, and had more somatic complaints and social problems, than controls. Survivors scored lower on athletic competence and higher

	42% 2–5 yrs, 26% >5 yrs, 7% relapse, 38% girls, 62% boys, mixed diagnosis. Controls N=90: healthy peers from local elementary schools, matched for age and gender	(CBCL) (p)	on physical appearance. Male survivors had more psychosocial problems than male controls. Girl survivors did not differ from girls in the control group. The majority of the survivors adjust well, but serious adjustment problems (CBCL Total problems) were found especially in boys: 27% male survivors as compared to 10% healthy peers. Risk factors in psychosocial adjustment of male survivors: – age at diagnosis ≥5 yrs – prognosis ≤50% – duration of treatment ≥3 yrs – cranial irradiation – time off treatment ≥5 yrs – age at investigation ≥11 yrs – concurrent stresses. Risk factors in psychosocial adjustment of female survivors: – overweight
(42): Peer relationships of children surviving brain tumors	Survivors N=28: age at study M=11.2 yrs (SD=2.8), time since diagnosis 1.5–5.2 yrs (M=3), 46.4% girls, 53.6% boys, brain tumors. Control group N=28: closest date of birth classmate, same gender, nonchronically ill	Revised Class Play (RCP) (c, t, o), Liking Rating Scale (c, o), (choose three best friends)	Brain tumor survivors were described by teacher, peer and self-report as more socially isolated than the controls and they were nominated less often as best friend by peers. Peers nominated the survivors more often roles related to illness, fatigue and missing school. There were no differences between subgroups of survivors
(43): Social functioning in children surviving BMT	Survivors N=48: age at study 11.7 yrs (M), time since BMT 9 months to 8 yrs (M=3.6 yrs), 56% boys, 44% girls, 27% autologous BMT, 73% allogeneic BMT, mixed tumors mostly leukemia. Controls N=48: same-gender classmates	RRCP (c, t, o), Liking Rating Scale (c, o), (choose three best friends)	BMT survivors had fewer friends than control classmates and were described by peers as more socially isolated. Teachers nominated survivors less often for aggressive-disruptive roles. Peers described the survivors as less physically attractive and athletically skillful. Physical attractiveness and athletic ability (negatively) and earlier

			treatment with cranial irradiation (positively) mediated the social difficulties of BMT survivors. Social functioning was not correlated with time since BMT
(46): Stress and adjustment of long-term childhood cancer survivors	Survivors N=39: age at study 13–24 yrs (M=17.4), age at diagnosis 0–15 yrs (M=8.3), time since diagnosis 5–17 yrs (M=8.9), 51.3% boys, 48.7% girls, mixed diagnosis. No control group	Adolescent Perceived Events Scale (APES), Symptom Checklist 90-Revised (SCL-90), Global Severity Index (GSI), SPPA (c)	Higher perceived stress predicted increased psychological distress and lower general self-esteem. Psychological distress was correlated with age and diagnosis: children of older age and with leukemia reported greater distress
(19): Self-esteem, depression and anxiety among Swedish children and adolescents on and off cancer treatment	Children/adolescents off treatment N=35: age at study 8–18 yrs (M=12.6), age at diagnosis 1–7 yrs (M=9.3), time since diagnosis 1–106 months (M=39.4), 51% boys, 49% girls, mixed diagnosis. Children/adolescents on treatment N=16: age at study 8–18 yrs (M=13.3), age at diagnosis 1–7 yrs (M=12.9), time since diagnosis 5.3 months (M), 69% boys, 31% girls, mixed diagnosis. Control group: healthy Swedish children	ITIA, Children's Depression Inventory (Swedish translation of the CDI), Revised Children's Manifest Anxiety Scale (Swedish translation of the RCMAS) (c)	Adolescents (10–18 yrs) off treatment scored lower on self-esteem (ITIA Total and ITIA subscales, Physical components and Psychological well-being) than healthy Swedish children. The children aged 8–9 yrs did not differ. With respect to depression and anxiety the children/adolescents off treatment did not differ from the healthy children after correction for age. No differences in self-esteem, depression and anxiety were found between children and adolescents on and off treatment. Children (aged 10–18 yrs) off treatment and living in two-parent families scored higher on the ITIA subscale Psychological well-being. Age at diagnosis was related to depression and anxiety: those who were 10–14 yrs old when diagnosed showed higher levels of depression and anxiety than those who were diagnosed when younger (1–6 yrs) or older (15–17 yrs)

[a] The results presented were mainly based on the last publication;
[b] Results of 30 pediatric cancer patients were not reported because they were not off treatment
[c] Results of another 70 survivors are not reported here because they were adults.

Chapter 2

Health-Related Quality of life in children and emotional reactions of parents following completion of cancer treatment

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ABSTRACT

Background: Completing therapy is one of the major transitions in care in the practice of pediatric oncology and therefore deserves special consideration. The purpose of the study was to investigate Health-related Quality of life (HRQOL) of pediatric patients, and emotional reactions of their parents, shortly after the end of successful treatment.

Methods: HRQOL of 126 patients, aged 1-15 years, on average two months after the end of successful treatment, was assessed with the TNO-AZL Preschool Quality of life Questionnaire and the TNO-AZL Children's Quality of life Questionnaire. Emotional adjustment of 124 mothers and 111 fathers was assessed with the General Health Questionnaire and the Situation Specific Emotional Reaction Questionnaire. The outcomes of the patients and parents were compared with norm data by means of one sample t-tests, one sample sign-tests or binomial tests.

Results: All age groups, except patients aged 8-11 years, experienced worse HRQOL than the norm with respect to motor functioning. In addition, preschool patients were rated worse on Sleeping, Appetite, Stomach, Skin, Problem Behavior, Anxiety and Liveliness, and patients aged 6-7 years on Autonomy and Cognitive functioning. Parents reported more psychological distress than the norm. Compared to parents whose children were one to five years after cancer treatment, they suffered more from feelings of loneliness, helplessness and uncertainty.

Conclusions: A few months after the end of successful cancer treatment, both patients and parents appeared to experience worse well-being than the norm to a clinically relevant extent. Supporting patients and parents should not stop when treatment ends.

INTRODUCTION

Approximately 400 children are diagnosed with cancer in the Netherlands every year (1). The diagnosis of childhood cancer has an enormous impact on the child and his family. They are confronted with a life-threatening disease mostly implying extensive treatment with negative side-effects and the risk of negative long-term consequences. Considerable literature has been devoted to the long-term adjustment of the child (2-4). It can be concluded that dealing with childhood cancer is a dramatic event that could influence physical and psychosocial functioning long time after termination of the treatment (2;5;6). In addition, posttraumatic stress symptoms appeared to be common in families of childhood cancer; among survivors of childhood cancer, as well as among their parents (7-10). Nevertheless, many long-term survivors of childhood cancer turned out to function well (11;12)(see reviews by Langeveld et al.(3) and Stam et al. (4)). This appeared also to be true for their parents; overall, most of them did not experience more emotional disturbances than healthy controls (13-16). However, if illness related concerns were taken into account, parents of survivors of childhood cancer seemed to experience feelings of uncertainty and loneliness (17;18).

Less is known about what happens in the years immediately after successful treatment. During treatment, patients and their families may have struggled for life, living day by day, supported intensively by the medical staff and social support networks. After termination of treatment, concerns about the further course of the disease as well as the child's education and employment can take the place of treatment-related worries (2). The social and emotional support also often decrease when active treatment ends. Families have to integrate their experiences in normal daily life and have to face future challenges relating to issues surrounding the diagnosis and treatment of cancer. These first years following the end of treatment can be considered as an important phase of adjustment to the cancer experience. A longitudinal study was designed in order to gain insight into this process of adjustment.

The results presented here concern the first assessment of the longitudinal study among the childhood cancer patients and their parents, two months after the termination of the cancer treatment. We considered this moment of assessment to be interesting because it represents the transition from active treatment to 'normal daily life'. The aims of the current study are the assessment of (1) Health-Related Quality of Life (HRQOL) 2 months after the end of treatment, using comprehensive instruments that measure physical, cognitive, social as well as emotional aspects of HRQOL, and (2) the emotional adjustment of the parents 2 months after the end of treatment of their child.

PATIENTS AND METHODS

Procedure

The results presented here concern the first measurement of the longitudinal VOLG-study (Vragenlijsten kinderOncologie Latere Gevolgen), a Dutch study on the late psychosocial consequences of cancer in childhood. It started in 2000 and will end in 2006. The respondents of the VOLG-study were recruited from the The Emma Children's Hospital/Academic Medical Center in Amsterdam (from March 2000 until the end of 2002) and the Radboud University

Nijmegen Medical Center (from June 2002 until the end of 2002). Inclusion criteria were: (1) aged 1-18 years, (2) complete first remission, (3) end of successful treatment at most two months before, and (4) being able to complete Dutch questionnaires.

Parents of children with cancer, and children with cancer aged eight years or older were informed about the VOLG-study by letter. After informed consent was obtained, the parents were telephoned and an appointment was made for completion of questionnaires anonymously in the hospital or at home. The children and parents were instructed to complete the questionnaires independently. The assistance of the researcher was restricted to reading questions out loud and to explaining the meaning of difficult words. Some parents and some patients aged 15 years or older filled in the questionnaires without the assistance of the researcher, at home. The respondents were asked to complete the questionnaires, yearly, four to six times, depending on the year of inclusion. The results of the first assessment were used in this study. The self reports of the patients aged 16 years or older were not included in this paper because of the small number of eight patients in this age group. A unique patient number made it possible to gather medical information, from the respondents as well as from the non-respondents. The Medical Ethic Committee of the Academic Medical Center in Amsterdam and the Radboud University Nijmegen Medical Center has approved the study protocol.

Measures

Health-related quality of life

HRQoL of the childhood cancer patients was assessed with the *TNO-AZL Preschool Quality of Life* questionnaire for children aged 1 to 5 years (TAPQOL) (19;20), and with the *TNO-AZL Children's Quality of Life questionnaire*; Parent Form for children aged 6 to 11 years (TACQOL-PF) (21) and Child Form for children aged 8 to 15 years (TACQOL-CF), (22;23). These questionnaires are generic Dutch instruments that measure health status problems weighted by the impact of the health status problems on well-being. It offers the respondent the possibility of differentiating between their functioning and the way they feel about it. Most of the items consist of two questions linked to one another. On the first one the respondent can rate whether or not a specific problem occurred in the past few weeks. The second one is about the possible negative emotional responses to the problems. The respondent can indicate how he (or his child) felt about this problem on a four point Likert scale: fine, not so good, quite bad, bad. The items are clustered into multi-item scales with higher scores indicating better quality of life. Norm data from the general Dutch population were available. The instruments measure HRQOL on group level in a reliable and valid way (19-24).

The *TAPQOL* assesses the child's functioning on 12 domains: sleeping, appetite, lungs, stomach, skin, motor functioning, social functioning, problem behavior, communication, anxiety, positive mood, liveliness. The raw scales scores of the TAPQOL are converted to a 0-100 scale. The Cronbach's alphas in our study population were moderate to good. Norm data were collected via a sample from the general population of children visiting well-baby clinics in the Netherlands in 1997. Periodically, almost all children aged 0-5 years in the Netherlands visit well-baby clinics (19).

The *TACQOL* for children aged *6-11* years (PF) or aged *8-11* years (CF), assesses functioning on seven domains: physical complaints, motor functioning, autonomy, cognitive functioning,

social functioning (in relation to parents and peers), positive emotions and negative emotions. The *TACQOL* for adolescents, aged *12-15* years, assesses functioning on six domains: physical complaints, motor functioning, cognitive functioning, social functioning (in relation to peers), positive emotions and negative emotions. The Cronbach's alphas in our study population were moderate to good. Norm data were collected via the Centers for Preventive Youth Health Care all over The Netherlands, via stratified random sampling (21-23;25).

Medical data

Medical data were obtained from the medical record of the ill child. Prognosis was based on the oncologist's rating of the child's survival chances at diagnosis, that is, <25%, 25-75%, >75%.

Parental distress

Parental distress was measured with the *General Health Questionnaire-30* (GHQ-30)(26;27), a 30-item self-report measure. The raw total scale score can be used as an overall index of psychological distress, ranging from 0 to 30 with higher scores indicating more distress. According to Goldberg et al. (26), scores ≥5 indicate clinically elevated levels of psychological distress. The validity of the 30-item version is well documented and internal reliability is highly satisfactory (26). Cronbach's alpha in the current study is high (α=0.92).

Parental situation-specific emotional reactions. Parental situation-specific emotional reactions were assessed with the *Situation Specific Emotional Reaction Questionnaire* (SSERQ). This is a Dutch questionnaire that consists of 30 items, divided in four subscales, which describe feelings that can be considered situation-specific for parents of children with cancer. It concerns feeling of (1) loneliness, 11 items, for example, "I have the feeling that nobody understands what I am going through", (2) helplessness, 7 items, for example, "I feel helpless that I can't do anything about the situation", (3) uncertainty, 6 items, for example, "I am uncertain about the course of the disease", and (4) positive feelings, 6 items, for example, "I have the feeling that I can enjoy small things more tremendously". Parents were asked to indicate whether they experienced an emotional reaction on a 4-point scale: never, sometimes, often, almost all the time. The higher the scores the more often parents experienced the emotional reactions. The validity and reliability turned out to be satisfactory in former studies (28). The Cronbach's alphas in the current study were also satisfactory, ranging from α=0.71 to α=0.85.

Statistical analyses

The Statistical Package for Social Sciences (SPSS), Windows version 11.5, was used for all analyses. Before conducting the final analyses several preparation analyses were conducted. First, scales were constructed and missing data imputed on the basis of the guidelines of the questionnaires used. Second, the reliability of these scales was calculated. Third, descriptive statistics were used to describe the demographic and medical characteristics of the participants. Finally, binomial tests were performed in order to test whether the distribution by gender in the several patient groups (1-5, 6-7, 8-11 and 12-15 years) differed from that in the age-matched norm groups.

HRQOL of the childhood cancer patients

One sample t-tests, or, if the sample size was smaller than 20, non-parametric equivalents (one sample sign-test or binomial test), were performed to test whether the mean score, the median or the binomial distribution of the several HRQOL-scales scores of the childhood cancer patients differed from the norm data available. A significance level of $p < 0.005$ was used in order to compensate for multiple testing. Effect sizes (d) were calculated by dividing the difference in mean score between the childhood cancer patients and the norm group by the standard deviation of the scores in the norm group. According to Cohen, effect sizes of up to 0.2 were considered to be small, effect sizes of about 0.5 to be moderate and effect sizes of about 0.8 to be large (29).

Patients' self-reports were used for analysis unless the self-report was not available due to the young age of the patient. Separate analyses were conducted for (1) patients aged 1-5 years, using the TAPQOL, (2) patients aged 6-7 years, using the TACQOL-PF, (3) patients aged 8-11 years, using the TACQOL-CF for children, and (4) patients aged 12-15 years, using the TACQOL-CF for adolescents.

Separate analyses by gender were performed in the age group 8-11 years because the distribution of gender in this patient group differed from that in the norm group. This was not the case in the other age groups.

Parental emotional reactions

Parental psychological distress was compared with the Dutch norm by conducting one sample *t*-tests on the mean total GHQ-score, and binomial testing on the percentage "clinically elevated levels of psychological distress", that is, GHQ-scores ≥5. Analyses were performed for mothers and fathers separately. Effect sizes could not be calculated because the standard deviations of the mean scores among the norm group were not available. The mean items scores on the subscales of the SSERQ, computed for mother and fathers separately, were compared to the mean items scores of mothers and fathers of children who were off cancer treatment for 1 – 5 years (28). One-sample *t*-tests were conducted and effect sizes were calculated.

RESULTS

Participants

A total of 164 consecutive childhood cancer patients who completed treatment successfully at most two months before, and their parents, were approached for the longitudinal part of the VOLG-study; 150 patients from the Emma Children's Hospital AMC and 14 patients from the Radboud University Nijmegen Medical Center. The response rate was 81.7 per cent (N=134). Of the 30 families who did not participate, 9 did not want to be confronted with cancer any longer, 8 did not return the informed consent form and 5 did not return the questionnaires. Other reasons of refusal were: recurrence of the disease (N=3), multiple family problems (N=3), not being able to complete Dutch questionnaires (N=2). No significant differences were found ($p < 0.1$ at *t*-tests or χ^2-tests) between the participants and non-participants with respect to age, gender, and several medical variables (Table 1).

Table 1: Socio-demographic and medical characteristics of the participant and non-participant patients.

	Participants				Non-participants			
	M	**SD**	**Range**	**N**	**M**	**SD**	**Range**	**N**
Age at study (years)	8.3	4.6	1.1-18.2	134	8.4	4.9	1.7-17.7	30
Age at first diagnosis (years)	7.1	4.7	0.3-17.2	134	7.8	5.2	0.6-17.2	30
Time since first diagnosis (months)	13.6	8.3	2.0-29.7	134				
Time since end of last treatment (months)	2.2	1.0	0.1-5.7	134				
Duration of treatment (months)	11.4	8.3	0.6-26.0	134	12.5	9.5	0.5-26.1	29
Days of admission in Emma Children's hospital	44.9	30.2	2-141	120	45.7	30.6	5-127	27
	%		**N**		**%**		**N**	
Age categories								
1-5 years	40.3		54		40.0		12	
6-11 years	33.6		45		26.7		8	
12-15 years	20.1		27		26.7		8	
16-18 years[1]	6.0		8		6.7		2	
Gender female	43.3		58		38.7		12	
Native country The Netherlands	96.2		128					
Diagnosis								
leukemia/lymphoma	47.8		64		53.3		16	
solid tumor	47.8		64		40.0		12	
brain tumor	4.5		6		6.7		2	
Treatment [2]								
chemotherapy	95.5		128		89.7		26	
radiotherapy	18.7		25		17.2		5	
surgery	47.0		63		44.8		13	
autologous bone marrow transplantation	2.2		3		3.4		1	
other	2.2		3		3.4		1	
Prognosis								
< 25%	5.2		7		6.9		2	
25 – 75%	41.0		55		31.0		9	
> 75%	53.7		72		62.1		18	
Visible consequences of the disease[2]								
none	68.8		86					
amputation	4.8		6					
moon-faced	6.5		8					
bald	37.1		46					
scars	21.8		27					
wheelchair	4.0		5					
other	27.2		34					

[1] The self reports of this patients were not included in the present paper.
[2] More than one answer is possible per patient

The final study sample of the VOLG-study consisted of 134 patients, 124 mothers and 111 fathers. Their socio-demographic and medical characteristics were presented in Tables 1 and 2. A total of 60 patients were old enough to complete questionnaires themselves. The self reports of eight patients aged 16 years or older were not included in this paper. The 52 patients aged 8-15 years filled in the TACQOL-CF; 25 patients aged 8-11 years, and 27 patients

Table 2: Socio-demographic characteristics of the participating parents.

	M	SD	Range	N
Age mother (years)	37.8	5.0	26.0-50.0	124
Age father (years)	39.8	5.2	29.0-54.0	108
	%		N	
Family				
father and mother, and child(ren)	94.0		125	
father or mother, and child(ren)	4.5		6	
other	1.5		2	
Eductional level[1] father				
low	21.8		24	
middle	34.6		38	
high	43.6		48	
Educational level[1] mother				
low	43.1		53	
middle	30.8		38	
high	26.0		32	

[1] Highest level completed: Low: Primary Education, Technical and Vocational Training, Lower and Middle General Secondary Education; Middle: Middle Vocational Education, Higher General Secondary Education, Pre-university Education; High: Higher Vocational Education, University.

aged 12-15 years. The researchers assigned the parent-form of the HRQOL-questionnaires at random to the father or the mother of the patients aged 1-7 years. The TAPQOL for children aged 1-5 years was completed by 35 mothers and 19 fathers. A total of nine mothers and nine fathers of children aged 6-7 years filled in the TACQOL-PF. All parents filled in the questionnaires about their own emotional well-being.

Health-related Quality of life of childhood cancer patients off treatment

Patients aged 1-5 years

The HRQOL of the preschool patients appeared to be significantly worse ($p<0.005$) than the HRQOL of age-matched children from the general Dutch population, on eight out of the twelve scales of the TAPQOL: sleeping $T(1,53) = -4.4$, appetite $T(1,52) = -4.2$, stomach $T(1,53) = -6.2$, skin $T(1,53) = -3.0$, motor functioning $T(1,50) = -6.1$, problem behavior $T(1,53) = -3.4$, anxiety $T(1,52) = -6.5$, liveliness $T(1,52) = -3.6$. These differences were moderate to large: effect sizes (d) ranged from $d = 0.4$ for skin to $d = 3.7$ for motor functioning. No significant differences were found on the following scales: lungs, social functioning, communication, positive mood (Table 3).

Patients aged 6-7 years

According to the results of non-parametric testing, the parent-reported HRQOL of the patients aged 6-7 years was significantly worse ($p < 0.005$) than that of age-matched children from the general Dutch population with respect to motor functioning, autonomy, and cognitive functioning. The differences were large: effect size (d) = 3.2 for motor functioning, $d = 2.7$ for autonomy, and $d = 1.0$ for cognitive functioning. The patients did not differ from the general population on the other TACQOL-PF scales: physical complaints, social functioning, positive emotions, and negative emotions (Table 4).

Table 3: Mean (M) and standard deviation (SD) of the scores[1] on the TAPQOL-PF, childhood cancer patients aged 1-5 years versus the norm[2]

	Cancer patients 1 – 5 years			Norm	Effect size
Parent report	**M**	**SD**	**N**	**M**	**d**
Sleeping	67.9*	24.1	54	82.3	0.8
Appetite	74.7*	17.1	53	84.6	0.8
Lungs	94.0	14.6	53	93.6	0.0
Stomach	72.4*	23.2	54	91.9	1.4
Skin	87.5*	10.5	54	91.8	0.4
Motor functioning	81.9*	19.5	51	98.5	3.7
Social functioning	84.7	24.0	50	91.3	0.4
Problem behavior	55.6*	26.1	54	67.7	0.8
Communication	92.9	14.3	50	91.7	0.1
Anxiety	55.0*	26.1	53	78.3	1.3
Positive mood	92.1	17.2	53	98.7	1.0
Liveliness	87.4*	21.2	53	98.0	1.3

* $p < 0.005$ at one sample t-test: cancer patients versus norm

1 Scores range from 0 – 100, higher scores representing better HRQOL.

2 General Dutch population of children aged 1 – 5 years (19).

Table 4: Mean (M)[1] and standard deviation (SD) of the raw scores[2] on the TACQOL-PF, childhood cancer patients aged 6-7 years versus the norm[3]

	Cancer patients 6 – 7 years			Norm	Effect size
Parent report	**M**	**SD**	**N**	**M**	**d**
Physical complaints	25.2 (78.8)	4.9	18	27.5	0.6
Motor functioning	24.0* (75.0)	6.6	18	31.0	3.2
Autonomy	25.6* (80.1)	6.2	18	31.0	2.7
Cognitive functioning	26.0* (81.3)	5.7	15	29.6	1.0
Social functioning	28.7 (89.6)	2.8	18	30.2	0.7
Positive emotions	14.4 (89.9)	2.4	18	15.0	0.3
Negative emotions	11.0 (68.8)	2.5	18	11.4	0.2

* $p < 0.005$ at non-parametric testing (sign-test or binomial test): cancer patients versus norm.

1 Higher scores represent better HRQOL: range 0 – 32 for physical, motor, cognitive, social, autonomy; range 0 – 16 for positive and negative emotions.

2 Transformed scores (0 – 100) are put between brackets.

3 General Dutch population of children aged 6 – 7 years (25).

Patients aged 8-11 years

On the basis of the TACQOL self-reports, the patients aged 8-11 years seemed not to differ from the general Dutch population of 8-11 aged children, at a significance level of $p < 0.005$ (Table 5). However, the cancer patients tended to score worse than the general population on motor functioning ($T(1,23) = -2.3$; $p = 0.03$) and autonomy ($T(1,22) = -2.2$; $p = 0.04$). The effect sizes were moderate to large: $d = 0.7$ and $d = 0.9$ for motor functioning and autonomy, respectively. The non-parametric analysis by gender revealed no significant differences between the cancer patients and the general population, although the cancer patients scored worse on all scales of the TACQOL-CF.

Table 5: Mean (M)[1] and standard deviation (SD) of the raw scores[2] on the TACQOL-CF, childhood cancer patients aged 8-11 years versus the norm[3], 12-15 years versus the norm[4]

	Cancer patients 8 – 11 years			Norm	Effect size	Cancer patients 12 – 15 years			Norm	Effect size
Child report	**M**	**SD**	**N**	**M**	**d**	**M**	**SD**	**N**	**M**	**d**
Physical complaints	26.4 (82.6)	5.3	24	24.9	0.3	22.7 (71.0)	4.8	25	23.7	0.2
Motor functioning	27.7* (86.5)	4.8	24	29.8	0.7	25.0** (78.3)	5.4	25	29.8	1.5
Autonomy	29.5* (92.1)	3.7	23	31.2	0.9	-	-	-	-	-
Cognitive functioning	28.5 (89.1)	3.2	23	28.4	0.0	28.6 (89.3)	3.3	26	27.6	0.2
Social functioning	29.8 (93.0)	3.5	24	29.7	0.0	30.8 (96.4)	2.6	26	31.1	0.1
Positive emotions	12.5 (78.3)	3.1	24	13.5	0.4	12.9 (81.2)	3.6	26	13.0	0.0
Negative emotions	11.3 (70.3)	2.6	24	11.6	0.1	11.2 (70.2)	2.9	26	11.6	0.2

* $p < 0.05$ at one sample t-test: cancer patients versus norm.
**$p < 0.005$ at one sample t-test: cancer patients versus norm.
[1] Higher scores represent better HRQOL: range 0 – 32 for physical, motor, cognitive, social, autonomy; range 0 – 16 for positive and negative emotions.
[2] Transformed scores (0 – 100) are put between brackets.
[3] General Dutch population of children aged 8 – 11 years (25).
[4] General Dutch population of children aged 12 – 15 years (23).

Patients aged 12-15 years

The cancer patients aged 12-15 years appeared to score significantly worse than the general population on motor functioning: $T(1,24) = -1.0$, $p < 0.005$, which is considered a large effect ($d = 1.5$). No significant differences were found on the other scales, and the corresponding effect sizes were small (Table 5).

Emotional reactions of parents of childhood cancer patients off treatment

Parental psychological distress

Mothers as well as fathers reported significantly more psychological distress ($p < 0.001$) than the general Dutch population: $T(114) = 10.5$ and $T(107) = 7.3$ for mothers and fathers, respectively. The mean level of distress of the mothers ($M = 10.1$) as well as that of the fathers ($M = 8.2$) was in the clinical range, that is, GHQ-total score ≥5. Moreover, the percentage of mothers and fathers who reported a clinically elevated level of psychological distress was significantly higher ($p < 0.001$) than the percentage in the general population. Almost

Table 6: Psychological distress in parents of childhood cancer patients versus the norm[1]: Mean (M) and standard deviation (SD) of the GHQ-30 total scores, and percentage clinically elevated levels of psychological distress

	GHQ-total score [2]			GHQ-total score ≥5 [3]	
	M	**SD**	**Norm (M)**	**%**	**Norm (%)**
Mothers (N = 121)	10.1*	7.5	3.0	72*	24
Fathers (N = 108)	8.2*	7.2	3.1	60*	22

* $p < 0.001$ at one sample t-test or binomial test: parents versus norm.
[1] General Dutch population (27).
[2] Score range 0 – 30; higher scores indicate higher levels of psychological distress.
[3] Scores ≥5 indicate a clinically elevated level.

three fourths of the mothers (72%) fell in the clinical range versus 24% of the female Dutch population. Among the fathers we found 60% to be in the clinical range versus 22% of the male Dutch population (Table 6).

Parental situation-specific emotional reactions

The results in Table 7 indicated that a considerable part of the mothers as well as of the fathers often experience feelings of helplessness, on average 2 months after the end of successful treatment of their child. However, they also often experience positive feelings. Feelings of uncertainty appeared to be experienced sometimes, while feelings of loneliness were reported less frequently.

Compared to parents whose children were 1 – 5 years after cancer treatment (28), the parents in our study turned out to suffer significantly more often from feelings of loneliness, helplessness and uncertainty, mothers (T(120) = 2.1, T(121) = 3.1, T(121) = 6.7) as well as fathers (T(108) = 3.0, T(108) = 8.5, T(108) = 6.7). Moreover, the mothers reported less positive feelings on average 2 months after termination of treatment than the mothers a few years after that: T(120) = -3.5.

Table 7: Situation-specific emotional reactions of parents of childhood cancer patients on average two months after termination of successful treatment, versus parents of childhood cancer patients one to five years after termination of succesful treatment: mean items score[2] on the SSERQ.

	Mothers				Fathers			
	M (SD)	**N**	**M [1]**	**Effect Size (d)**	**M (SD)**	**N**	**M [1]**	**Effect Size (d)**
Loneliness	1.47 (0.38)*	120	1.40	0.2	1.33 (0.35)**	109	1.23	0.4
Helplessness	2.30 (0.56)**	121	2.16	0.2	2.27 (0.49)***	109	1.87	0.6
Uncertainty	2.03 (0.53)***	121	1.72	0.7	1.88 (0.47)***	109	1.58	0.8
Positive feelings	2.54 (0.52)***	120	2.71	0.4	2.40 (0.50)	109	2.38	0.0

* p<0.05
**p<0.01
*** p<0.001 at one sample t-test.
[1] Parents of childhood cancer patients 1 – 5 years after termination of succesful treatment (28). 2 Item scores: 1 = never; 2 = sometimes; 3 = often; 4 = almost all the time.

DISCUSSION

This study focuses on well-being of children and parents at the transition from active treatment to normal daily life. As far as we know, multidimensional HRQOL of pre-school patients of childhood cancer, shortly after termination of succesful treatment, has never been assessed before. The patients with childhood cancer appeared to experience worse HRQOL in the physical domain, namely motor functioning. A considerable part of the patients in almost all age groups reported difficulty with activities such as walking, running and endurance. The youngest patients, aged 1 – 5 years, were also rated worse HRQOL on other physical scales than motor functioning: sleeping, appetite, lungs, stomach and skin. These physical aspects were measured more globally among the older patients very likely because the TACQOL take

the complaints together in one scale. The older patients seemed not to differ from the norm on this scale of physical complaints.

Among the older children, very few psychosocial differences were found between patients and the normal control group. Patients appeared to function well emotionally in contrast to their parents who reported high levels of distress. It is imaginable that the pediatric patients look less into the future than their parents, whose treatment-related worries will be replaced by the uncertainty about the future course of the disease and concerns about their child's education and employment (2). Another explanation could be that older pediatric patients would be able to understand what has happened. This could lead to feelings of happiness to have survived the disease and treatment. These positive feelings could result in under-reporting of problems and in improving of HRQOL. This phenomenon, already described among adults, is called "response shift". It means that the experience with cancer changes the internal standards of patients, resulting in changes in the meaning of their self-evaluation and hence in a possibly different experience of problems (30). Data about pre-cancer perceptions are needed to assess response shift.

It is reasonable to question whether patients really functioned psychosocially as well as the norm group or whether that there were methodological explanations. Perhaps more differences between the patients and the norm group would have been observed if an instrument could have been used that assesses pediatric social and emotional HRQOL in a more sensitive or cancer specific way than the TAPQOL and the TACQOL do. However, HRQOL-questionnaires translated and normed for young Dutch children, other than the TAPQOL and the TACQOL, were not available at the start of the VOLG-study. Unfortunately, the reliability of the social functioning scale of the TACQOL was moderate. This is a very interesting domain in our opinion, because recent research revealed that the social development of young adult long-term survivors of childhood cancer was hampered (31).

Finally, the "proxy problem" should be taken into account, because the HRQOL in the younger patients was assessed by their parents while the HRQOL of the patients aged 8-15 years was assessed by self-report. Previous research on the correlation between the parent-reported and the child-reported HRQOL showed that, on average, children reported significantly lower HRQOL than their parents on five out of the seven scales of the TACQOL including the positive emotions scale (32). The comparison of the parent report and the child report in the current study revealed no systematic difference (internal report). Based on those data, we believe that there is no indication of a serious "proxy problem" in our study.

The parents experienced more psychological distress than the general Dutch population, and they appeared to suffer from feelings of loneliness, helplessness and uncertainty. This is not surprising given the enormous transition from active treatment to the "coming off treatment" period. The parents have to get used to live with the uncertainty about recurrence of the disease and possible long-term side-effects. Many parents report that they feel uncertain without the protection of the medical treatment and support from the hospital. However, the experience of cancer is not necessarily in negative direction. We found that the parents often experience positive feelings, such as "I have the feeling that I can appreciate things more". The results of research by Greenberg and Meadows (17) were in the same direction, which showed negative parental comments as well as positive outcomes including the acquisition of new values and attitudes, improved marital adjustment, and social support.

There are some limitations in the present study that should be mentioned. First, the conclusions are based on relatively small subgroups of patients, because different age groups need different questionnaires. Second, the HRQOL questionnaires used had some limitations, though the TAPQOL and TACQOL are acceptable and the best available at the start of the study. Third, it can not be concluded definitely that the worse HRQOL of the patients was due to cancer or having any chronic disease, because of the lack of data about pre-cancer functioning.

In spite of the limitations of the study, we can conclude that a few months after the end of successful cancer treatment, both patients and parents experienced worse well-being than the general Dutch population to a clinically relevant extent. The effect sizes found on the HRQOL of the young children with cancer in comparison with the norm groups were large according to Cohen (29).

The results emphasize that supporting patients and parents should not stop when treatment ends. Completing therapy is one of the major transitions in care in the practice of pediatric oncology and, therefore, deserves special consideration (33). It is of importance to identify patients and parents at risk for adjustment problems. This called for longitudinal research directed at the predictors of patient's and parental adjustment in order to enable health care providers to trace and support patients and parents at risk.

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REFERENCES

(1) Visser O, Siesling S, van Dijck JAAM. Incidence of cancer in the Netherlands 1999/2000 (digital publication). Utrecht: Association of Comprehensive Cancer Centres; 2003.

(2) Eiser C. Children with cancer. The quality of life. Lawrence Erlbaum Associates Publishers: Mahwah, New Jersey, 2004.

(3) Langeveld NE, Stam H, Grootenhuis MA, Last BF. Quality of life in young adult survivors of childhood cancer (review article). Support Care Cancer 2002;10:579-600.

(4) Stam H, Grootenhuis MA, Last BF. Social and emotional adjustment in young survivors of childhood cancer (review article). Support Care Cancer 2001;9:489-513.

(5) Eiser C. Practitioner Review: long-term consequences of childhood cancer. J Child Psychol Psychiatry 1998;39(5):621-33.

(6) Stevens MCG, Mahler H, Parkes S. The health status of adult survivors of cancer in childhood. Eur J Cancer 1998;34(5):694-8.

(7) Kazak AE, Alderfer M, Rourke MT, et al. Posttraumatic stress disorder (PTSD) and posttraumatic stress symptoms (PTSS) in families of adolescent childhood cancer survivors. J Pediatr Psychol 2004;29(3): 211-219.

(8) Brown RT, Madan-Swain A, Lambert R. Posttraumatic stress symptoms in adolescent survivors of childhood cancer and their mothers. J Trauma Stress 2003;16(4):309-18.

(9) Hobbie WL, Stuber M, Meeske K, et al. Symptoms of posttraumatic stress in young adult survivors of childhood cancer. J Clin Oncol 2000;18(24):4060-6.

(10) Erickson SJ, Steiner H. Trauma spectrum adaptation. Somatic symptoms in long-term cancer survivors. Psychosomatics 2000;41(4):339-46.

(11) Zebrack BJ, Zeltzer LK, Whitton J, et al. Psychological outcomes in long-term survivors of childhood leukemia, Hodgkin's disease, and Non-Hodgkin's lymphoma: a report from the childhood cancer survivor study. Pediatr 2002;110(1):42-52.

(12) Zebrack BJ, Gurney JG, Oeffinger K, et al. Psychological outcomes in long-term survivors of childhood brain cancer: a report from the Childhood Cancer Survivors Study. J Clin Oncol 2004;22(6):999-1006.

(13) Greenberg HS, Kazak AE, Meadows AT. Psychologic functioning in 8- to 16-year-old cancer survivors and their parents. J Pediatr 1989;114(3):488-93.

(14) Kazak AE, Meadows AT. Families of young adolescents who have survived cancer: social-emotional adjustment, adaptability, and social support. J Pediatr Psychol 1989;14:175-91.

(15) Speechley KN, Noh S. Surviving childhood cancer, social support, and parents' psychological adjustment. J Pediatr Psychol 1992;17(1):15-31.

(16) Grootenhuis MA, Last BF. Adjustment and coping by parents of children with cancer: a review of het literature. Support Care Cancer 1997;5:466-84.

(17) Greenberg HS, Meadows AT. Psychosocial impact of cancer survival on school-age children and their parents. J Psychosoc Oncol 1991;9(4):43-57.

(18) Van Dongen-Melman JE, Pruyn JFADG., Koot HM, et al. Late psychosocial consequences for parents of children who survived cancer. J Pediatr Psychol 1995;20:567-86.

(19) Fekkes M, Bruil J, Vogels T. TAPQOL-manual. Leiden: TNO Prevention and Health; 2003.

(20) Fekkes M, Theunissen NCM, Brugman E, et al. Development and psychometric evaluation of the TAPQOL: A health-related quality of life instrument for 1-5-year-old children. Qual Life Res 2000;9:961-72.

(21) Vogels T, Verrips GHW, Verloove-Vanhorick SP, et al. Measuring health-related quality of life in children: the development of the TACQOL parent form. Qual Life Res 1998;7:457-69.

(22) Verrips GHW, Vogels TGC, Koopman HM, et al. Measuring health-related quality of life in a child population. Eur J of Public Health 1999;9(114):119.

(23) Vogels T, Bruil J, Koopman H, et al. TACQOL CF 12-15 Manual. Leiden: TNO Prevention and Health; 2004.

(24) Verrips G.H.W., Vogels T.G.C., Verloove-Vanhorick S.P., Fekkes M, Koopman H.M., Kamphuis R.P., et al. Health-related quality of life measure for children - the TACQOL. Journal of Applied Therapeutics 1998;1(357):360.

(25) Vogels T, Verrips GHW, Koopman HM, et al. TACQOL Manual. Parent Form and Child Form. Leiden: Leiden Center for Child Health and LUMC-TNO; 2000.

(26) Goldberg DP, Williams P. A user's guide to the General Health Questionnaire. Windsor: NFER-Nelson, 1988.

(27) Koeter MWJ, Ormel J. General Health Questionnaire: The Dutch application. Amsterdam: Swets Test Services, 1991.

(28) Grootenhuis MA, Last BF. Parents' emotional reactions related to different survival perspectives of their children with cancer. J Psychosoc Oncol 15, 43-62. 1997.

(29) Cohen J. Statistical power analysis for the behavioral sciences. New York: Academy Press, 1988.

(30) Sprangers MAG, Schwartz CE. Integrating response shift into health-related quality of life research: a theoretical model. Soc Sci Med 1999;48:1507-15.

(31) Stam H, Grootenhuis MA, Last BF. The course of life of survivors of childhood cancer. Psychooncology 2005;14:227-38.

(32) Theunissen NCM, Vogels TGC, Koopman HM, et al. The proxy problem: child report versus parent report in health-related quality of life research. Qual Life Res 1998;7:387-97.

(33) Nagel K, Eves M, Waterhouse L, et al. The development of an off-therapy needs questionnaire and protocol for surivors of childhood cancer. J Pediatr Oncol Nurs 2002;19(6):229-33.

Chapter 3

Psychosocial indicators of HRQoL in children with cancer two months after the end of treatment

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ABSTRACT

The purpose of the study was to identify psychosocial correlates of Health-Related Quality of Life (HRQoL) in pediatric cancer patients following completion of cancer treatment. Multiple regression analyses were performed to predict self-reported HRQoL of 52 patients aged 8-15 years, and parent-reported HRQoL of 54 patients aged 1-5 years. Cognitive coping, family functioning, parental emotional reactions, communication about the disease, and several medical variables were included in the regression models.

Better HRQoL was especially associated with more positive expectations of the further course of the disease and less frequent parental asking after disease-related emotions of the child. Interventions should include 'positive thinking' as a coping strategy. Several other psychosocial variables were indicative of better HRQoL but further research is needed to confirm and to understand the relationship between psychosocial variables and HRQoL.

INTRODUCTION

Dealing with childhood cancer is a dramatic event that could influence psychosocial functioning for a long time. An increasing number of studies have been directed at assessing Health-Related Quality of Life (HRQoL) in long-term survivors of childhood cancer because of the enormous increase in the number of survivors of childhood cancer reaching adulthood over the last decades (1-3). Much less attention has been paid to HRQoL of young patients and to patients' functioning in the time surrounding coming off treatment, which is a very difficult and anxious time for both patients and parents. Families have to integrate their experiences in normal daily life and have to get used to living with the uncertainty about the recurrence of the disease and possible long-term side-effects. Recently, the authors found that two months after the end of successful cancer treatment, pediatric patients aged 1-15 years and their parents experienced worse HRQoL than the general population to a clinically relevant extent (4). The next logical step is to investigate which patients are at risk for worse HRQoL. Coming off therapy is one of the major transitions in care in the practice of pediatric oncology and therefore deserves special consideration (5). Health care providers should understand the emotional reactions and ways of adjustment of the patients in order provide optimal support.

Little is known about determinants of HRQoL in pediatric cancer patients shortly after the end of treatment. However, older age at diagnosis, longer time off treatment, irradation therapy, and severe medical late effects turned out to be associated with worse HRQoL in pediatric long-term survivors of childhood cancer (see review of Stam et al. (3).)

The predictors of HRQoL mentioned before concern medical and demographic factors. However, we are most interested in psychosocial predictors of HRQoL because these factors could be susceptible to modification. In imitation of conceptual frameworks used to explain adjustment in pediatric patients (6), we presume that HRQoL is the outcome of a process over time that is influenced by demographic and medical variables and by psychosocial variables such as coping and family functioning. The psychosocial variables mediate the effect of the disease (the stressor) on an individual's well-being (Figure 1). The psychosocial variables from the model are discussed below: coping, family functioning, parental emotional functioning and communication.

According to the model of stress and coping developed by Lazarus and Folkman (7), *coping* consists of actions, behaviors and thoughts aimed at dealing with the demands of events and situations that are appraised as stressful. In the context of coping with cancer Grootenhuis et al. (8) found the following cognitive control strategies to be relevant in the medical setting: expectations of the further course of the disease (predictive coping), relying on powerful others such as doctors (vicarious control), associating with chance, such as hoping for a miracle or wishful thinking (illusory control), and searching for information (interpretative control). Positive expectations about the further course of the disease (predictive coping) proved to be correlated with better quality of life, independent of the health status of the survivors (9). Landolt et al. (10) found that pediatric patients tend to prefer strategies that include cognitive and behavioral activities of avoidance. Similar results were found among pediatric cancer patients in remission (11) and among survivors of childhood cancer (12). According to Phipps et al. (13) children at cancer diagnosis showed a higher incidence of a repressive adaptive style than healthy children, and the incidence remained stable over

time. Inconsistent results were reported about the impact of avoidant coping on survivors' adjustment.

According to the family system theories, parental and family functioning influences the functioning in children and vice versa. Several studies on childhood cancer reported that *parental emotional functioning* was correlated with that of pediatric patients but it was difficult to determine the direction of the correlation. In addition, the time points of the assessment varied from shortly after diagnosis to long time after termination of treatment *(3). Family adjustment* to chronic pediatric diseases has often been investigated by means of cohesion and adaptability, two dimensions of the Circumplex model of marital and family systems (14). In this theoretical framework moderate levels of cohesion and adaptability are considered to be related to the most favorable adjustment outcome in families faced with stress, whereas extreme levels of adaptation and cohesion were related to less adaptive functioning. More recent research by Olson indicated that high scores on cohesion and adaptability are related to more functional family relationships (15). Although most studies on childhood cancer indicated that family functioning was within normal limits (16-21), some found that survivors' parents were overly protective (22) and also less flexible than the parents of healthy children (19). Other studies reported that the quality of family cohesion and adaptability were positively related to psychosocial outcome in survivors (23-27).

Communication about the disease is another aspect of dealing with cancer. It involves the exchange of information about the disease, but also the exchange of emotions evoked by the situation. Open communication seemed to be the best policy as long as the facts about the illness are involved. Openly informing the child about the disease and the implications appeared to be related positively to the child's psychosocial adjustment (28-30). Avoidance of communication about the seriousness of the illness and about the emotional experience of the illness reflects a common defense reaction to a painful event, that could be a protective mechanism (31). Van Veldhuizen and Last (32) found that children and parents used a typical, protective coping strategy, which they called the phenomenon of *double protection*. Children as well as their parents avoid communication about the emotional experience of cancer, not only to protect themselves against disease-related stress, but also against painful confrontations with the unpleasant emotions in the other. An area of tension always exists between the need to control the situation by double protection and the need to share emotions with the other person.

The aim of this paper is to investigate to what extent psychosocial factors as shown in Figure 1 are associated with HRQoL in childhood cancer patients a few months after the end of successful cancer treatment. Identification of these factors will enable care-providers to provide optimal support to patients and their parents. The associations between the independent psychosocial variables and HRQoL outcomes (dependent variables) were controlled for effects of age, gender, medical variables and stressful family events other than the cancer. We hypothesized that having more positive expectations of the further course of the disease (predictive coping), and better parental emotional functioning were correlated with better HRQoL. Furthermore, we explored the relation between HRQoL and (1) cognitive coping strategies other than predictive coping, (2) family functioning, and (3) the exchange of disease-related emotions (communication).

METHODS

Procedure

The results presented here concern the first measurement of the longitudinal VOLG-study (Vragenlijsten kinderOncologie Latere Gevolgen), a Dutch study on the late psychosocial consequences of cancer in childhood. It started in 2000 and ended in 2006. The respondents were recruited from the The Emma Children's Hospital/Academic Medical Center in Amsterdam (from March 2000 until the end of 2002) and the Radboud University Nijmegen Medical Center (from June 2002 until the end of 2002). All consecutive patients who met the inclusion criteria were approached for the VOLG-study. Inclusion criteria were: (1) aged 1-18 years, (2) complete remission, (3) end of successful treatment at most two months before, and (4) being able to complete Dutch questionnaires.

Parents of children with cancer and children with cancer aged eight years or older were informed about the VOLG-study by letter. After informed consent was obtained, the parents were telephoned and an appointment was made for completion of questionnaires anonymously in the hospital or at home. The researcher assigned the questionnaire about HRQoL of preschool patients at random to the father or the mother. The parent to whom the questionnaire was assigned completed the questionnaire at each measurement occasion. The children and parents were instructed to complete the questionnaires independently. The assistance of the researcher was restricted to reading out questions aloud and to explaining the meaning of difficult words. Some parents and some patients aged 15 years or older filled in the questionnaires at home, without the assistance of the researcher. The respondents were asked to complete the questionnaires yearly, four to six times, depending on the year of inclusion. The results of the first assessment were used in this paper. Neither the self-reports of the patients aged 16 years or older, nor the parent reports of patients aged 6-7 years were included in this paper because of the small number of patients in these age groups.

It was possible to gather medical information from the respondents as well as from the non-respondents. The Medical Ethics Committee of the Academic Medical Center in Amsterdam and the Radboud University Nijmegen Medical Center has approved the study protocol.

Measures

Dependent Variables: Health-Related Quality of life (Figure 1)

The *TNO-AZL Preschool Quality of Life* questionnaire for children aged 1 to 5 years (TAPQOL) (33;34), and the *TNO-AZL Children's Quality of Life questionnaire* Child Form for children aged 8 to 15 years (TACQOL) (35;36) are generic Dutch instruments that measure HRQoL on group level in a reliable and valid way (33-39). The questionnaires measure health status problems weighted by the impact of the problems on well-being. Most of the items consist of two questions linked to one another. The first one is about the frequency of the problem in the past few weeks. The second one rates the possible negative emotional responses to the problems on a four-point Likert scale. The items are clustered into multi-item scales with higher scores indicating better HRQoL. Norm data from the general Dutch population are available.

The *TAPQOL* assesses the child's functioning on 12 domains: sleeping, appetite, lungs, stomach, skin, motor functioning, social functioning, problem behavior, communication,

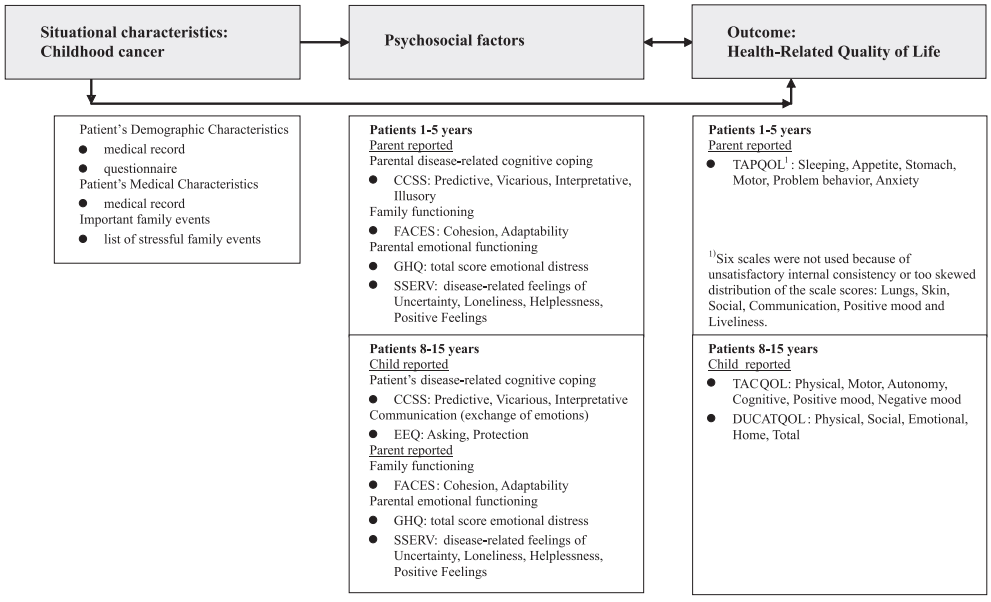
anxiety, positive mood and liveliness. The Cronbach's alphas in our study population were moderate to good (0.67-0.97) with the exception of Skin (Cronbach's alpha <0.60). This scale was not used in the analyses. The *TACQOL* assesses functioning on seven domains: physical complaints, motor functioning, autonomy, cognitive functioning, social functioning, positive emotions and negative emotions. The Cronbach's alphas in our study population were moderate to good (0.66-0.85) with the exception of Social Functioning (Cronbach's alpha <0.60). This scale was not used in the analyses.

The *Dutch Children's AZL/TNO Quality of life Questionnaire* (DUCATQOL) (40) measures *quality of daily functioning*, an aspect of HRQoL, in patient aged 8-15 years. The 25 items, scored on a five-point Likert scale are clustered into a total score and four domains: family functioning, bodily functioning, emotional functioning and social functioning. Higher scores represent better HRQoL. The *DUCATQOL* is reported to be internally consistent and reproducible (40;41). The Cronbach's alphas in the present study were satisfactory, ranging from 0.73 to 0.92.

Independent Variables: Psychosocial Factors (Figure 1)

Disease-related cognitive coping was assessed with the *Cognitive Control Strategies Scale* (CCSS) for parents (PF) and patients (CF). The instrument, based on the model of Rothbaum et al. (42), was developed at the Psychosocial Department of the Emma Children's Hospital/ AMC. It assesses to what extent respondents try to gain sense of control over the illness by using cognitive coping strategies, measured on a four-point Likert scale. Higher scores represent a stronger reliance upon the control strategy. Scales were composed by means of principal component factor analysis with varimax rotation and reliability. The questionnaire proved to be useful in earlier studies (4;8;41;43;44). The 25 items of the *CCSS-PF* were grouped into four scales: predictive control (being optimistic about the course of the disease), vicarious

Figure 1. Research model with the domains of the questionnaires used



control (attributing power to medical care-givers and treatment), interpretative control (searching for information in order to better understand emotional reactions and to gain insight into the situation), and illusory control (attempts to influence the chance-determined outcome). The Cronbach's alphas in the present study were satisfactory, ranging from 0.63 to 0.83. The 22 items of the *CCSS-CF* were grouped into three scales: predictive, vicarious and interpretative control. The Cronbach's alphas in the present study were satisfactory, ranging from 0.69 to 0.83.

Family functioning as perceived by the parents was measured with the Dutch version of the *Family Adaptability and Cohesion Evaluation Scales* (FACES) (45) developed by Olson et al. (46-48). The Adaptation scale (13 items) refers to the level to which a family adapts its power structure, role definitions, and rules according to internal and external demands. The Cohesion scale (23 items) refers to mutual connectedness among family members. Items are scored on a four-point Likert scale. Internal consistency of the Dutch version is good though in the present study Cronbach's alphas were moderate, ranging from 0.57 to 0.69.

Parental emotional functioning was measured with the *General Health Questionnaire-30 (GHQ-30)* and the *Situation Specific Emotional Reaction Questionnaire* (SSERQ). The *GHQ* (49;50) is a 30-item self-report measure. The raw total scale score can be used as an overall index of psychological distress with higher scores indicating more distress. The validity of the 30-item version is well documented and internal consistency is highly satisfactory (49). Cronbach's alpha in the current study was high (α=0.92).

The *SSERQ*, developed at the Psychosocial Department of the Emma Children's Hospital/ AMC (51), consists of 30 items divided in four subscales which describe feelings that can be considered situation-specific for parents of children with cancer (51). It concerns feeling of loneliness, helplessness, uncertainty and positive feelings, which are assessed on a four-point Likert scale. The higher the scores the more often parents experienced the emotional reactions. The validity and reliability turned out to be satisfactory in former studies (41;51). The Cronbach's alphas in the current study were also satisfactory, ranging from 0.71 to 0.85.

Communication about the disease was measured with the *Exchange of Emotions Questionnaire* (EEQ)₁ recently developed at the Psychosocial Department of the Emma Children's Hospital/AMC. It is a questionnaire for children (CF) and parents (PF) that consists of two scales. The Child Form was used in the current study. The scale Asking contains three items about the frequency the parent asks after disease-related emotions of their child, e.g. "How often did your father or mother ask whether you were sad about your disease". The scale Protection (PF) contains six items about the frequency of masking disease-related emotions, e.g. "I tried to keep a firm attitude with my father or mother" or "When I was worried about my disease, I tried not to show that to my father or mother". The answers are scored on four-point Likert scale. Higher scale scores indicate more exchange of disease-related emotions. The internal consistency of the scales was satisfactory in the present study; Cronbach's alpha 0.81 and 0.80 for Asking and Protection respectively.

Independent Variables: Situational Characteristics (Figure 1)

Important family events that occurred in the last year were rated by the parents on a list of 19 stressful family events, such as: birth of a child, parental divorce, moving, death of a family member or friend, decline in financial means, change of school, change of job. A total

score of family events was computed. The scores were then dichotomized based on presence or absence of at least two life events.

Medical data were obtained from the medical record of the patient. Prognosis was based on the survival chances at diagnosis as rated by each patient's oncologist, i.e. < 25%, 25-75%, > 75%. The patients and parents were asked to rate their perception of the intensiveness of the treatment for childhood cancer on a Visual Analogue Scale, from 'totally non-intensive' (0, left end of line) to 'very intensive' (10, right end of line). The parents were also asked to assess the visible consequences of the disease. Their answers were dichotomized to 'presence' or 'absence' of visible consequences.

Statistical analyses

The Statistical Package for Social Sciences (SPSS), Windows version 11.5, was used for all analyses. Before conducting the final analyses, dichotomizing of some variables was needed because of the small number of patients in one or more of the categories (see Table 1). Diagnosis, treatment and prognosis were dichotomized as follows: leukemia/lymphoma (yes or no), chemotherapy and radiotherapy with/without surgery (yes or no), prognosis > 75% (yes or no).

Multiple regression analyses were performed to predict HRQoL as expressed by the scores on the TAPQOL (patients aged 1-5 years), the TACQOL and the DUCATQOL (patients aged 8-15 years) (Figure 1). Linear regression models of the Social scale of the TACQOL, and Lungs, Skin, Social, Communication, Positive mood and Liveliness of the TAPQOL could not be fitted because of unsatisfactory internal consistency or too skewed distribution of the scale scores (strong ceiling effect). Due to the limited sample size we had to select independent variables beforehand. For the final regression analyses we selected variables that proved to be associated with HRQoL ($p < 0.15$) in one of the following regression models: (1) age and gender; (2) diagnosis, treatment, prognosis; (3) duration of treatment, time since end of treatment, perceived treatment intensity, visible consequences of disease and treatment; (4) cognitive coping strategies, (5) family functioning, important family events, parental emotional distress, exchange of disease-related emotions (only in patients aged 8-15 years), and (6) parental disease-related emotional reactions. Age at diagnosis was left out of analyses because it appeared to correlate too strongly with age at study. Figure 1 shows how variables were assessed in whom.

Because of the strong explorative nature of our study, priority is given to find phenomena that exist (avoiding type I errors) rather than correcting for multiple testing (avoiding type II errors). Therefore, a significance level $p< 0.05$ was used in combination with effect sizes of the standardized regression coefficients (β) > 0.25. According to Cohen (52) correlations of 0.1 were considered small, 0.3 medium and 0.5 large.

RESULTS

Participants

A total of 164 consecutive childhood cancer patients were approached for the longitudinal part of the VOLG-study; 150 patients from The Emma Children's Hospital AMC and 14 patients from the Radboud University Nijmegen Medical Center. The response rate was

Table 1. Demographic and Medical Characteristics VOLG-study

	Participants				Non-participants			
	M	**SD**	**Range**	**N**	**M**	**SD**	**Range**	**N**
Age at study (years)	7.9	4.5	1.1-15.9	106	7.9	4.7	1.7-15.0	25
Age at first diagnosis (years)	6.7	4.6	0.3-15.2	106	7.5	5.2	0.6-14.7	24
Time since first diagnosis (months)	13.7	8.2	2.0-29.7	106				
Time since end treatment (months)	2.2	1.0	0.1-5.7	106				
Duration of treatment (months)	11.5	8.4	1.2-25.9	106	10.6	8.6	0.5-25.9	24
		%		**N**		**%**		**N**
Age categories								
1-5 years		50.9		54		48.0		12
8-15 years		49.1		52		52.0		3
Gender (female)		42.5		45		36.0		9
Diagnosis								
Leukemia/lymphoma		45.3		48		44.0		11
Solid tumor		50.9		54		48.0		12
Brain tumor		3.8		4		8.0		2
Prognosis								
< 25%		5.7		6		8.3		2
25 – 75%		40.6		43		29.2		7
> 75%		53.8		57		62.5		15
Treatment [1]								
Chemotherapy		95.3		101		87.5		21
Radiotherapy		21.7		23		20.8		5
Surgery		47.2		50		54.2		13
Autologous bone marrow transplantation		1.9		2		4.2		1
Other		2.8		3		4.2		1

[1]More than one answer was possible per patient.

81.7 per cent (n = 134). Of the 30 families who did not participate, 9 did not want to be confronted with cancer any longer, 8 did not return the informed consent form and 5 did not return the questionnaires. Other reasons of refusal were: recurrence of the disease (n = 3), multiple family problems (n = 3), not being able to complete Dutch questionnaires (n = 2). No significant differences were found ($p < 0.1$ at t-tests or χ^2-tests) between the participants and non-participants with respect to age, gender and several medical variables (Table 1).

A total of 52 patients aged 8-15 years and 54 patients aged 1-5 years, represented by 35 mothers and 19 fathers, were included in the present study.

Psychosocial Indicators of HRQoL in Patients aged 1-5 years

The TAPQOL scale scores were explained reasonably well by the regression models, except Stomach and Problem behavior. The explained variances of the other scales ranged from 0.30 (Anxiety) to 0.52 (Appetite) (Table 2). Parents who used more interpretative coping strategies reported less problem behavior in their child ($\beta = 0.27$, $p < 0.05$). Higher scores on family adaptability and cohesion appeared to be associated with worse appetite and more anxiety, respectively ($\beta = -0.28$, $p < 0.05$; $\beta = -0.44$, $p < 0.01$). Finally, parents who experienced more disease-related positive feelings reported more problems related to their child's appetite and motor functioning ($\beta = -0.59$, $\beta = -0.49$; $p < 0.001$).

Table 2. Standardized Regression Coefficients ß for the Relation between HRQoL (TAPQOL)[1] of Patients Aged 1-5 years and Psychosocial variables[2], corrected for Demographic and Medical Variables

	Sleeping ß	Appetite ß	Stomach ß	Motor ß	Problem behavior ß	Anxiety ß
Age	0.36**	-	0.19	-	-	-
Chemo+radio with/without surgery	-0.17	0.27*	-	-	-	-
Prognosis > 75%	-	0.15	-	-	- 0.29*	-
Duration of treatment (months)	-	-	-	- 0.32*	-	-
Time since end treatment (months)	0.31*	-	0.30*	-	-	0.29*
Perceived treatment intensity	-0.16	-0.19	-	-	-	-
Parent reported						
Predictive control	-	-	-	0.17	-	-
Interpretative control	-	-	-	-	0.27*	-
Family functioning: adaptability	-0.19	-0.28*	-	-	-	-
Family functioning: cohesion	-	-	-	-	-	-0.44**
Emotional distress parent	-	-0.11	-	-	-	-
Disease-related feelings uncertainty	-	-0.20	-	-	-	-
Disease-related positive feelings	-	-0.59***	-	-0.49***	-	-
Disease-related feelings loneliness	-	-	-	-	-0.22	-
Df	5,40	7,37	2,50	3,44	3,49	2,46
R^2	0.35**	0.52***	0.13*	0.35***	0.22**	0.30***

[1]Higher scores represent less problems, so better HRQoL. [2]Not selected from pre-analyses: Gender, Leukaemia/ lymphoma, Visible consequences, Important family events, Vicarious and Illusory control, parental disease-related feelings of Helplessness. *p < 0.05. ** p < 0.01. *** p < 0.001.

Psychosocial Indicators of HRQoL in Patients aged 8-15 years

Self-reported HRQoL of the patients aged 8-15 years was predicted reasonably well by the regression models, except Cognitive functioning. The explained variance of the other scales ranged from 0.28 (Negative mood) to 0.56 (Physical daily functioning). HRQoL as measured with the TACQOL is presented in Table 3. Patients who reported that their parents asked more after their disease-related emotions experienced worse physical and cognitive functioning and stronger negative mood ($\beta = -0.26$, $\beta = -0.34$, $\beta = -0.33$; $p < 0.05$, respectively). In addition, patients of parents who reported more emotional distress, reported more physical problems ($\beta = -0.26$, $p < 0.05$). Child-reported cognitive coping strategies appeared not to be associated significantly with TACQOL-scores.

Quality of daily functioning (DUCATQOL) is presented in Table 4. Patients who relied more on predictive control strategies reported better physical and emotional daily functioning ($\beta = 0.33$, $p < 0.05$; $\beta = 0.39$, $p < 0.01$), and those who used more vicarious control strategies reported better social functioning ($\beta = 0.31$, $p < 0.05$). Stronger cohesion in the family was found to correlate with more positive appraisal of the patient's functioning at home ($\beta = 0.40$, $p < 0.01$).

Table 3. Standardized Regression Coefficients ß for the Relation between HRQoL (TACQOL)[1] of Patients aged 8-15 years and Psychosocial variables[2], corrected for Demographic and Medical Variables

	Physical ß	Motor ß	Autonomy ß	Cognitive ß	Pos. mood ß	Neg. mood ß
Age	-0.32*	-0.22	-	-	-	-
Gender (female)	-0.17	-	-	-	-	-
Chemo+radio with/without surgery	-	0.24	0.23	-	-	-
Prognosis >75%	-	0.16	0.37*	-	-	-
Duration of treatment (months)	-	0.06	-0.10	-	-	-
Perceived treatment intensity	-	-	-	-	0.50**	-
No visible consequences	-	-	0.15	-	0.40*	-
Important family events (≥ 2)	-0.22	-0.20	-	-	- 0.30*	-
Child reported						
Predictive control	-	-	-	-	0.07	0.26
Vicarious control	-	-	-	-	-0.19	-0.24
Interpretative control	-	-0.17	-0.21	-	-	-
Exchange of emotions: asking[3]	-0.26*	-0.16	-	-0.34*	-	-0.33*
Exchange of emotions: protection[3]	-	-	-	-	0.24	-
Parent reported						
Emotional distress parent	-0.26*	-	-	-	-	-
Disease-related positive feelings	-	-0.12	-	-	-	-
Disease-related feelings loneliness	-	-	-0.17	-	-	-0.18
Df	5,40	8,35	6,37	1,46	6,33	4,40
R^2	0.41**	0.34*	0.32*	0.12*	0.45**	0.28*

[1]Higher scores represent less problems, so better HRQoL. [2]Not selected from pre-analyses: Leukaemia/lymphoma, Time since end of treatment, Family adaptability, Family cohesion, parental disease-related feelings of Uncertainty and Helplessness. [3]Higher scores indicate more exchange of disease-related emotions, so less Protection and more Asking. * $p < 0.05$. ** $p < 0.01$.

Table 4. Standardized Regression Coefficients ß for the Relation between Daily Functioning (DUCATQOL)[1] of Patients aged 8-15 years and Psychosocial variables[2], corrected for Demographic and Medical Variables

	Physical ß	Social ß	Emotional ß	Home ß	Total ß
Age	-0.55***	-0.47***	-0.37**	-0.23	-0.51***
Gender (female)	-0.07	-	-	-0.11	-0.05
Important family events (≥ 2)	-	-	-	-	-
Child reported					
Predictive control	0.33*	-	0.39**	0.21	0.35**
Vicarious control	0.01	0.31*	-	-	-
Exchange of emotions: asking3	-0.09	-	-	-	-
Parent reported					
Family functioning: cohesion	0.07	0.17	-	0.40**	0.18
Df	6,39	3,42	2,45	4,41	4,41
R^2	0.56***	0.49***	0.33***	0.35**	0.53***

[1]Higher scores represent higher quality of daily functioning, so better HRQoL

[2]Not selected from pre-analyses: all medical variables, Interpretative control, Exchange of emotions (Protection), Family adaptability, Parental emotional distress, all Parental disease-related feelings.

[3]Higher scores indicate more exchange of disease-related emotions, so more Asking. * $p < 0.05$. ** $p < 0.01$. *** $p < 0.001$.

DISCUSSION

The present study was focused on psychosocial indicators of HRQoL in pediatric cancer patients shortly after termination of successful treatment. This period of coming off therapy is understudied and, as far as we know, psychosocial correlates of HRQoL in preschool children have hardly been studied before. Psychosocial indicators of pediatric HRQoL were investigated on average two months after the end of treatment, i.e. at the transition from active treatment to 'normal daily life'.

Predictive *coping*, which means being optimistic about the further course of the disease, was hypothesized to correlate positively with HRQoL. This hypothesis was partly confirmed. The more optimistic patients (8-15 years) were about the further course of the disease the better they felt in daily life, in general, emotionally and with respect to their body. These findings were in line with the results among young adult long-term survivors of childhood cancer (9). However, the question of causality "does optimism lead to better HRQoL, or vice versa" can not be answered. Positive thinking could incline to avoidant coping. The impact of the latter coping style is not clear yet because inconsistent findings were reported. An avoidant coping style, consisting of distraction, blaming others, and wishful thinking was found to correlate positively with child depression and anxiety (53). Phipps et al. (54;55), on the contrary, reported that pediatric oncology patients scored significantly lower on depression, anxiety and PTSS, as well as higher on repressive coping.

Parental predictive coping appeared not to be associated with HRQoL in preschool patients, but parental interpretative coping did correlate with problem behavior in these patients. Probably parents who relied strongly on interpretative coping are inclined to either explain their child's behavior as a natural emotional reaction to the cancer experience, or search for information because of the problem behavior of their child. Furthermore, patient's vicarious coping appeared to be correlated to positive feelings about others (Social scale DUCATQOL).

Positive as well as negative correlations were found between *family functioning* and HRQoL. Patients (aged 8-15 years) from cohesive families seemed to feel better at home and about their parents than patients from less cohesive families. However, more cohesion appeared to correlate with greater anxiety in preschool patients. This result could suggest that the stronger mutual involvement the more transmission of parental worries to the child, or, inversely, that patient's anxiety could put parents up to stronger connectedness with their child. Furthermore, stronger adaptability was correlated with less appetite, which could mean that preschool patients had less eating problems as family structure was more stable. This seems especially reasonable in the context of young children.

The impact of *parental emotional adjustment* on patient's HRQoL seemed limited. According to our hypothesis, we found parental emotional distress to be related negatively to physical HRQoL as reported by patients aged 8-15 years. It is plausible to assume that the more the child suffers from physical complaints the more distress the parent experiences. On the other hand, parents with high levels of distress could be inclined to evaluate the health status of their child negative. Furthermore, parents who derived more positive feelings from the cancer experience reported worse appetite and worse motor functioning in their young child. Maybe the worse HRQoL of their child the more the parents need to derive positive feelings from the disease to keep it up. It is known that stressful events could generate positive

affect, for instance labelling ordinary events with positive meaning and appraising stressful situations as challenges which can generate feelings of mastery and control (56).

In several studies on childhood cancer, parental distress was found to be correlated with adjustment of the child (3). However, most studies are not truly comparable with the present one because these concern patient's emotional adjustment instead of HRQoL and differed on the time of assessment (21;22;57-59).

Interesting correlations were found between *parental asking after their child's disease-related emotions*, physical and cognitive functioning and negative mood. Again, it is not possible to determine the direction of the correlation. Suffering from observable complaints, physically or emotionally, could stimulate parents to ask whether he or she feels. Inversely, children whose parents ask more often after their disease-related emotions will become more aware of their disease and the consequences, which could lead to a more negative evaluation of their health. We did not find any significant correlation between masking of disease-related emotions and HRQoL. This finding could indicate that masking disease-related emotions did not influence patients' well-being. Additional research should further explore the way children and parents communicate about disease-related facts and the degree to which it is predictive of HRQoL.

Although it was not the focus of the present study to investigate the impact of medical variables on HRQoL we should mention the following: Medical variables seemed not to correlate with patient's affective evaluation of their daily functioning as measured with the DUCATQOL (feelings about them, their parents and friends, and feelings about daily routines at home and at school), while typical health-related outcomes as measured with the TACQOL, such as complaints and limitations that patients experience, seemed not to correlate with cognitive coping. Comparable results were found among long-term survivors of childhood cancer, in whom the independent impact of cognitive coping on physical HRQoL was considerably lower than on the mental HRQoL (9).

Limitations

This study revealed useful information about psychosocial indicators of HRQoL in pediatric cancer patients a few months after termination of successful treatment, though causality could not be established. Strength of the study was the inclusion of a large number of psychosocial variables, including cognitive coping, family functioning, parental emotional functioning, and exchange of disease-related emotions. A disadvantage of the large number of variables was that pre-selection of variables for the final regression analysis was necessary. Furthermore, though children with a bad prognosis (< 25%) or brain tumor were included, their number was too small to assess the impact of bad prognosis and brain tumor reliably.

Another issue for discussion concerns the model of coping used in the present study. Our model of coping was based on the models of Lazarus and Folkman (7) and Rothbaum et al. (42), whose theoretical framework was developed for adults. In the area of childhood cancer developmental considerations should be taken into account, because with growing cognitive ability children will employ other coping strategies. Though several studies indicated that cognitive coping is relevant to children (43;60-62) it is also known that behavioral and problem-solving strategies are more predominant in younger children (11;63).

Another limitation concerns the measures used. First, the present study focused on HRQoL but of course there are other interesting aspects of patients' functioning, for instance post

traumatic stress, social skills and educational achievement. It would be of utmost importance to investigate indicators of social functioning very thoroughly because previous studies indicated that pediatric survivors suffered from clinically significant social anxiety, had less friends and participated less in peer and school activities than controls (64-68). Moreover, social development of young adult survivors of childhood cancer seemed to be hampered (69). On the contrary, Reiter-Purtill et al. (70) concluded that patients did not exhibit more social difficulties than their peers two years after diagnosis. Second, unfortunately, not all HRQoL scales could be used because of insufficient internal consistency or too skewed distribution of the scale scores. The latter indicates that the instruments are not sensitive and cancer specific. However, HRQoL-questionnaires translated and validated for young Dutch children, other than the TAPQOL, TACQOL and DUCATQOL, were not available at the start of the VOLG-study. Third, the 'proxy problem' in the assessment of HRQoL in the preschool patients should be mentioned. Because the parents evaluated the child's HRQoL as well as their own adjustment, the correlations we found did not represent the clear impact of parental emotional adjustment on patients' HRQoL. We were not able to differentiate between the impact of parental emotions on parental perception of their child's HRQoL and the impact on 'real' patient's HRQoL. Finally, although the explained variances of the regression models of HRQoL were satisfactory, undoubtedly there were several potential predictors of patients' HRQoL we did not assess in the present study, such as parental post traumatic stress (57;71-74).

Nevertheless, the present study revealed several interesting psychosocial indicators of patients' HRQoL. Following patients over time is necessary in order to be able to predict long-term HRQoL to the cancer experience, and to test whether psychosocial variables really mediate the effect of cancer on HRQoL. These are the main purposes of the ongoing VOLG-study.

Clinical implications

Though clear predictors of HRQoL can not be established, some consistent correlations of medium to large effect sizes according to Cohen (52) were found between psychosocial factors and HRQoL. Positive expectations of the further course of the disease, less frequent parental asking after disease-related emotions of the child, and lower levels of family adaptability could be considered psychosocial indicators of a favorable HRQoL. These indicators of HRQoL could be useful in clinical practice. Interventions should preferably include 'positive thinking' because being hopeful could protect patients and parents from negative emotions. In addition, giving attention to strengths of the patients, which survivors of childhood cancer undoubtedly have, can generate feelings of mastery and control. Psycho-educational support groups could be helpful because a group intervention offers possibilities for sharing of emotions and experiences, and for supporting and helping each other to deal with the cancer experience. The group could also be used for practising skills and developing positive cognitions that these patients need to integrate their experiences in normal daily life, e.g. what to tell friends about the disease, how to deal with physical limitations in relation to activities with peers. Overall, there is evidence of effectiveness for psycho-educational interventions for children with chronic disease incorporating cognitive-behavioural techniques on variables such as self-efficacy and psychosocial well-being (75;76). A pilot study on the effects of a social-skills training group among children treated for brain tumors showed improvements (77). As far as we know, other

effective group interventions directed at pediatric survivors of childhood cancer have not been published yet (78) but group interventions focused on long-term adolescent and adult survivors and/or the whole family, appeared to be promising (79;80).

Interventions to improve HRQoL of pediatric patients should also be directed at the parents. Psycho-educational support groups as described above could also be helpful for parents. Support groups could help parents to integrate their experiences in normal daily life and facilitate living with the uncertainty about the recurrence of the disease and possible long-term side-effects. Furthermore, support groups could be useful to educate parents about the various aspects of openness in communication about the disease, such as the phenomenon of *double protection*, which has already been discussed in the Introduction. Previous research revealed high levels of emotional distress in parents shortly after the end of their child's cancer (4). However, further research is needed in order to generate specific instructions to improve the well-being of the child by supporting the parents.

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REFERENCES

(1) Eiser C. Children with cancer. The quality of life. Mahwah, New Jersey, Londen: Lawrence Erlbaum Associates Publishers, 2004.

(2) Langeveld NE, Stam H, Grootenhuis MA, Last BF. Quality of life in young adult survivors of childhood cancer (review). Support Care Cancer 2002;10:579-600.

(3) Stam H, Grootenhuis MA, Last BF. Social and emotional adjustment in young survivors of childhood cancer (review). Support Care Cancer 2001;9:489-513.

(4) Stam H, Grootenhuis MA, Brons PTT, Caron HN, Last BF. Health-related Quality of life in children and emotional reactions of parents following completion of cancer treatment. Pediatric Blood & Cancer 2006;47:312-9.

(5) Nagel K, Eves M, Waterhouse L, Alyman C, Posgate S, Jamieson J, et al. The development of an off-therapy needs questionnaire and protocol for surivors of childhood cancer. J Pediatr Oncol Nurs 2002;19(6):229-33.

(6) Wallander JL, Varni JW. Effects of pediatric chronic physical disorders on child and family adjustment. Journal of Child Psychology and Psychiatry 1998;39(1):29-46.

(7) Lazarus RS, Folkman S. Stress, appraisal, and coping. New York: Springer Publishing Company, 1984.

(8) Grootenhuis MA, Last BF, de Graaf-Nijkerk JH, van der Wel M. Secondary control strategies used by parents of children with cancer. Psychooncology 1996;5(2):91-102.

(9) Stam H, Grootenhuis MA, Last BF. Quality of life and coping in young adult survivors of childhood cancer: positive expectations about the further course of the disease were correlated with better quality of life. Psychooncology 2006;15(1):31-43.

(10) Landolt MA, Vollrath M, Ribi K. Predictors of coping strategy selection in paediatric patients. Acta Paediatr 2002;91(9):954-60.

(11) Bull BA, Drotar D. Coping with cancer in remission: stressors and strategies reported by children and adolescents. J Pediatr Psychol 1991;16:767-82.

(12) Bauld C, Anderson V, Arnold J. Psychosocial aspects of adolescent cancer survival. Journal of Paediatric Child Health 1998;34:120-6.

(13) Phipps S, Steele RG, Hall K, Leigh L. Repressive adaptation in children with cancer: a replication and extension. Health Psychol 2001;20(6):445-51.

(14) Olson DH, Russell CS, Sprenkle DD. Circumplex model of marital and family systems: VI. Theoretical Update. Fam Process 1983;22:69-83.

(15) Olson DH. Commentary: three-dimensional (3-D) circumplex model and revised scoring of FACES III. Fam Process 1991;30:74-9.

(16) Greenberg HS, Kazak AE, Meadows AT. Psychologic functioning in 8- to 16-year-old cancer survivors and their parents. The Journal of Pediatrics 1989;114(3):488-93.

(17) Kazak AE, Meadows AT. Families of young adolescents who have survived cancer: social-emotional adjustment, adaptability, and social support. J Pediatr Psychol 1989;14:175-91.

(18) Kazak AE, Christakis D, Alderfer M, Coiro MJ. Young adolescent cancer survivors and their parents: adjustment, learning problems, and gender. J Fam Psychol 1994;8(1):74-84.

(19) Madan-Swain A, Brown RT, Sexson SB, Baldwin K, Pais R, Ragab A. Adolescent cancer survivors: psychosocial and familial adaptation. Psychosomatics 1994;35(5):453-9.

(20) Olson AL, Boyle WE, Evans MW, Zug LA. Overall function in rural childhood cancer survivors: the role of social competence and emotional health. Clin Pediatr (Phila) 1993;32(6):334-42.

(21) Sloper T, Larcombe IJ, Charlton A. Psychosocial adjustment of five-year survivors of childhood cancer. J Cancer Educ 1994;9(3):163-9.

(22) Pelcovitz D, Goldenberg LA, Mandel F, Kaplan S, Weinblatt M, Septimus A. Posttraumatic stress disorder and family functioning in adolescent cancer. J Trauma Stress 1998;11(2):205-21.

(23) Lesko LM. Surviving hematological malignancies: stress responses and predicting psychological adjustment. The Biology of Hematopoiesis. Wiley-Liss. Inc, New York: 1990. p. 423-37.

(24) Rait DS, Ostroff JS, Smith K, Cella DF, Tan C, Lesko LM. Lives in balance: perceived family functioning and the psychosocial adjustment of adolescent cancer survivors. Fam Process 1992;31:383-97.

(25) Kazak AE, Barakat LP, Meeske K, Christakis D, Meadows AT, Penati B, et al. Posttraumatic stress, family functioning, and social support in survivors of childhood leukemia and their mothers and fathers. J Consult Clin Psychol 1997;65(1):120-9.

(26) Kazak AE. Posttraumatic distress in childhood cancer survivors and their parents. Medical and Pediatric Oncology Supplement 1998;1:60-8.

(27) Sloper P. Predictors of distress in parents of children with cancer: a prospective study. J Pediatr Psychol 2000;25(2):79-91.

(28) Last BF, Van Veldhuizen AMH. Information about the diagnosis and prognosis related to anxiety and depression in children with cancer aged 8-16 years. Eur J Cancer 1996;32a(2):290-4.

(29) Clarke S-A, Davies H, Jenney M, Glaser A, Eiser C. Parental communication and children's behaviour following diagnosis of childhood leukaemia. Psychooncology 2005;14(4):274-81.

(30) Slavin L, O'Malley JE, Koocher GP, Foster DJ. Communication of the cancer diagnosis to pediatric patiënts: impact on long-term adjustment. Am J Psychiatry 1982;139:179-83.

(31) Last BF. The phenomenon of double protection. In: Last B.F., Van Veldhuizen A.M.H., eds. Developments in pediatric psychosocial oncology.Amsterdam / Lisse: Swets & Zeitlinger B.V., 1992. p. 39-52.

(32) Van Veldhuizen AMH, Last BF. Children with cancer. Communication and emotions. Amsterdam/Lisse: Swets & Zeitlinger, 1991.

(33) Fekkes M, Bruil J, Vogels T. TAPQOL-manual. Leiden: Leiden Center for Child Health and Pediatrics LUMC-TNO; 2004.

(34) Fekkes M, Theunissen NCM, Brugman E, Veen S, Verrips E, Koopman HM, et al. Development and psychometric evaluation of the TAPQOL: A health-related quality of life instrument for 1-5-year-old children. Qual Life Res 2000;9:961-72.

(35) Verrips GHW, Vogels TGC, Koopman HM, Theunissen NCM, Kamphuis RP, Fekkes M, et al. Measuring health-related quality of life in a child population. European Journal of Public Health 1999;9(114):119.

(36) Vogels T, Bruil J, Koopman H, Fekkes M, Verrips GHW. TACQOL CF 12-15 Manual. Leiden: TNO Prevention and Health; 2004.

(37) Vogels AGC, Verrips GHW, Fekkes M, Kamphuis RP, Koopman HM, Theunissen NCM, et al. Measuring health-related quality of life in children: the development of the TACQOL parent form. Qual Life Res 1998;7:457-69.

(38) Verrips GHW, Vogels TGC, Verloove-Vanhorick SP, Fekkes M, Koopman HM, Kamphuis RP, et al. Health-Related Quality of Life measure for children - the TACQOL. Journal of Applied Therapeutics 1998;1(357):360.

(39) Bunge EM, Essink-Bot M-L, Kobussen MPHM, Suijlekom-Smit LWA, Moll HA, Raat H. Reliability and validity of health status measurement by the TAPQOL. Arch Dis Child 2005;90(351):358.

(40) Kolsteren MMP, Koopman HM, Schalekamp G, Mearin ML. Health -related quality of life in children with celiac disease. The Journal of Pediatrics 2001;138(4):593-5.

(41) Houtzager BA, Oort FJ, Hoekstra-Weebers JEHM, Caron HN, Grootenhuis MA, Last BF. Coping and family functioning predict longitudinal psychological adaptation of siblings of childhood cancer patients. J Pediatr Psychol 2004;29(8):591-605.

(42) Rothbaum F, Weisz JR, Snyder SS. Changing the world and changing the self: a two-process model of perceived control. J Pers Soc Psychol 1982;42:5-37.

(43) Grootenhuis MA, Last BF. Children with cancer with different survival perspectives: defensiveness, control strategies, and psychological adjustment. Psychooncology 2001;10:305-14.

(44) Loonen HJ, Grootenhuis MA, Last BF, Koopman HM, Derkx HHF. Quality of life in peadiatric inflammatory bowel disease measured by a generic and disease-specific questionnaire. Acta Paediatr 2002;91:341-54.

(45) Buurmeijer FA, Hermans PC. Gezins Dimensie Schalen - Handleiding [Dutch version of the Family Adaptability and Cohesion Evaluation Scales (FACES)]. Lisse, The Netherlands: Swets & Zeitlinger, 1988.

(46) Olson DH, Bell RQ, Porter J. FACES: Family adaptability and cohesion evaluation scales. St. Paul: Family Social Science, University of Minnesota, 1978.

(47) Olson DH, Portner J, Bell B. FACES II: Family adaptability and cohesion evaluation scales. St. Paul: Family Social Science, University of Minnesota, 1982.

(48) Olson DH, Porter J, Bell B. FACES III: Family adaptability and cohesion evaluation scales. St. Paul: Family Social Science, University of Minnesota, 1985.

(49) Goldberg DP, Williams P. A user's guide to the General Health Questionnaire. Windsor: NFER-Nelson, 1988.

(50) Koeter MWJ, Ormel J. General Health Questionnaire: The Dutch application. Amsterdam: Swets Test Services, 1991.

(51) Grootenhuis MA, Last BF. Parents' emotional reactions related to different survival perspectives of their children with cancer. Journal of psychosocial oncology 1997;15:43-62.

(52) Cohen J. Statistical power analysis for the behavioral sciences. New York: Academy Press, 1988.

(53) Frank NC, Blount RL, Brown RT. Attribution, coping, and adjustment in children with cancer. J Pediatr Psychol 1997;22(4):563-76.

(54) Phipps S, Srivastava DK. Repressive adaptation in children with cancer. Health Psychol 1997;16(6):521-8.

(55) Phipps S, Larson S, Long A, Rai SN. Adaptive style and symptoms of posttraumatic stress in children with cancer and their parents. J Pediatr Psychol 2006;30(1):1-12.

(56) Folkman S. Positive psychological states and coping with severe stress. Soc Sci Med 1997;45(8):1207-21.

(57) Barakat LP, Kazak AE, Meadows AT, Casey R, Meeske K, Stuber ML. Families surviving childhood cancer: a comparison of posttraumatic stress symptoms with families of healthy children. J Pediatr Psychol 1997;22(6):843-59.

(58) Sawyer MG, Streiner DL, Antoniou G, Toogood I, Rice M. Influence of parental and family adjustment on the later psychological adjustment of children treated for cancer. Journal of the American Academy of Child Adolescence Psychiatry 1998;37(8):815-22.

(59) Kazak AE, Barakat LP. Brief report: Parenting stress and quality of life during treatment for childhood leukemia predicts child and parent adjustment after treatment ends. J Pediatr Psychol 1997;22:249-758.

(60) Petersen C, Schmidt S, Bullinger M. Brief report: development and pilot testing of a coping questionnaire for children and adolescents with chronic health conditions. J Pediatr Psychol 2004;29(8):635-40.

(61) Sandler IN, Tein J-Y, West SG. Coping, stress, and the psychological symptoms of children of divorce: A cross-sectional and longitudinal study. Child Dev 1994;65:1744-63.

(62) Ayers TS, Sandler IN, West SG, Roosa MW. A dispositional and situational assessment of children's coping: testing alternative models of coping. J Pers 1996;64(4):923-58.

(63) Schmidt S, Petersen C, Bullinger M. Coping with chronic disease from the perspective of children and adolescents - a conceptual framework and its implications for participation. Child Care Health Dev 2003;29(1):63-75.

(64) Bessell AG. Children surviving cancer: psychosocial adjustment, quality of life, and school experiences. Except Child 2001;67(3):345-59.

(65) Pendley JS, Dahlquist LM, Dreyer Z. Body image and psychosocial adjustment in adolescent cancer survivors. J Pediatr Psychol 1997;22(1):29-43.

(66) Spirito A, Stark LJ, Cobiella C, Drigan R, Androkites A, Hewett K. Social adjustment of children succesfully treated for cancer. J Pediatr Psychol 1990;15(3):359-71.

(67) Vannatta K, Gartstein MA, Short A, Noll RB. A controlled study of peer relationships of children surviving brain tumors: teacher, peer, and self ratings. J Pediatr Psychol 1998;23(5):279-87.

(68) Vannatta K, Zeller M, Noll RB, Koontz K. Social functioning of children surviving bone marrow transplantation. J Pediatr Psychol 1998;23(3):169-78.

(69) Stam H, Grootenhuis MA, Last BF. The course of life of survivors of childhood cancer. Psychooncology 2005;14:227-38.

(70) Reiter-Purtill J, Vannatta K, Gerhardt CA, Correll J, Noll RB. A controlled longitudinal study of social functioning of children who completed treatment of cancer. J Pediatr Hematol Oncol 2003;25(6):467-73.

(71) Kazak AE, Alderfer M, Rourke MT, Simms S, Streisand R, Grossman JR. Posttraumatic stress disorder (PTSD) and posttraumatic stress symptoms (PTSS) in families of adolescent childhood cancer survivors. J Pediatr Psychol 2004;29(3):211-9.

(72) Pelcovitz D, Goldenberg B, Kaplan S, Weinblatt M, Mandel F, Meyers B, et al. Posttraumatic Stress Disorder in mothers of pediatric cancer survivors. Psychosomatics 1996;37:116-26.

(73) Stuber ML, Christakis DA, Houskamp B, Kazak AE. Posttrauma symptoms in childhood leukemia survivors and their parents. Psychosomatics 1996;37:254-61.

(74) Stuber ML, Kazak AE, Meeske K, Barakat L, Guthrie D, Garnier H, et al. Predictors of posttraumatic stress symptoms in childhood cancer survivors. Pediatrics 1997;100(6):958-64.

(75) Barlow JH, Ellard DR. Psycho-educational interventions for children with chronic disease, parents and siblings: an overview of the research evidence based. Child: Care, Health & Development 2004;30(6):637-45.

(76) Plante WA, Lobato D, Engel R. Review of group interventions for pediatric chronic conditions. J Pediatr Psychol 2001;26(7):435-53.

(77) Barakat LP, Hetzke JD, Foley B, Carey ME, Gyato K, Phillips PC. Evaluation of a social-skills training group intervention with children treated for brain tumours: a pilot study. J Pediatr Psychol 2003;28(5):299-307.

(78) Kazak AE. Evidence-based interventions for survivors of childhood cancer and their families. J Pediatr Psychol 2005;30(1):29-39.

(79) Kazak AE, Simms S, Barakat L, Hobbie W, Foley B, Golomb V, et al. Surviving Cancer Competently Intervention Program (SCCIP): A cognitive-behavioral and family therapy intervention for adolescent survivors of childhood cancer and their families. Fam Process 1999;38(2):175-91.

(80) Zampini K, Ostroff JS. The post-treatment resource program: portrait of a program for cancer survivors. Psychooncology 1993;2:1-9.

Chapter 4

Longitudinal assessment of Health-Related Quality of Life in preschool children with non-CNS cancer after the end of successful treatment

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ABSTRACT

BACKGROUND The aim of the study was to access Health-Related Quality of Life (HRQoL) in preschool cancer survivors during the first three years of continuous remission after the end of successful treatment, and to identify predictors of HRQoL.

PROCEDURE Parent-reported HRQoL was assessed in 53 preschool children treated successfully for cancer, using the TAPQOL and compared with norm data. Longitudinal mixed models analyses were performed to investigate to what extent demographic and medical variables and parental psychological distress were predictive of HRQoL over time.

RESULTS Two months after the end of successful cancer treatment, survivors showed significantly ($p<0.01$) more problem behavior and anxiety, and scored significantly worse ($p<0.01$) on sleeping, motor functioning, positive mood and liveliness than the norm. One year after the end of treatment survivors still showed significantly ($p<0.01$) more anxiety and worse motor functioning. The level of HRQoL in survivors had normalised two and three years after the end of treatment. Longer duration of treatment, bad prognosis and greater parental psychological distress were associated with worse scores on the Physical Component Score of the TAPQOL. Medical variables and parental psychological distress were not associated with the Mental Component Score.

CONCLUSIONS Survivors adjusted well to the cancer experience; HRQoL improved with time. Despite overall resilience in survivors over time, physical as well as psychosocial monitoring in follow-up is recommended. Standard aftercare should preferably include psychosocial screening, education and counselling directed at both survivors and parents.

INTRODUCTION

The diagnosis and treatment of childhood cancer is a dramatic event that affects the daily life and emotional well-being of all family members (1-3). The enormous increase in survival (4-8) has heightened the need to investigate the consequences of childhood cancer. An increasing number of studies has been directed at assessing Health Related Quality of Life (HRQoL) in long-term survivors, and considerable literature has been devoted to the pediatric patients and their parents during cancer treatment (1;9;10). Less is known about what happens in the first few years after treatment in the run-up to long-term survivorship. Longitudinal studies are sparse, especially among preschool patients, whereas the number of children with cancer in this age group is relatively high.

The first few years following the end of successful treatment are considered as an important phase in the adjustment to the cancer experience. Coming off therapy is one of the major transitions in care in the practice of pediatric oncology (11). A longitudinal study was focused on answering the following questions: (1) How is the course of HRQoL of preschool survivors during the first three years of continuous remission following the completion of treatment for cancer? (2) To what extent are demographic and medical variables and parental psychological distress associated with HRQoL of preschool survivors during the first three years of continuous remission following the completion of treatment for cancer? Although a 5-year period without treatment is commonly considered a criterion of survival, the patients in our study were called 'survivors' because they were in continuous remission in the period approaching long-term survivorship.

METHODS

Procedure

The results presented here are taken from the VOLG-study, a Dutch study on the psychosocial consequences of cancer in childhood, which started in 2000 and ended in 2006. From 2000 to 2002, survivors and their parents were recruited from the Emma Children's Hospital at the Academic Medical Center in Amsterdam and the Radboud University Nijmegen Medical Center. The Medical Ethics Committee of the two Dutch hospitals has approved the study protocol.

The inclusion criteria were: (1) age of the survivors 1-18 years, (2) complete remission, (3) end of successful treatment at most two months before, and (4) ability to complete Dutch questionnaires. The data of survivors aged 1-5 years ('preschool survivors') with leukaemia, lymphoma or solid tumours were used in this paper.

Once informed consent had been obtained, the researcher assigned the questionnaire about HRQoL of preschool survivors at random to the father or the mother. The assigned parents completed the questionnaires four to six times depending on the year of inclusion. The first four assessments were used for analyses; approximately two months (M1), one year (M2), two years (M3), and three years (M4) after the end of treatment. The data for survivors who relapsed were excluded from analysis from the moment of the relapse.

Measures

HRQoL was assessed with the *TNO-AZL Preschool Quality of Life* questionnaire for children aged 1 to 5 years (TAPQOL), which assesses the child's functioning on 12 domains: sleeping, appetite, lungs, stomach, skin, motor functioning, social functioning, problem behaviour, communication, anxiety, positive mood, liveliness. Higher scores indicate better HRQoL (12;13). Following the method of Ware et al. (14) we used Principal Components Analysis (oblique rotation) at M1 to aggregate all TAPQOL scale scores into two summary scales: Mental Component Scale (MCS) and Physical Component Scale (PCS).

Parental psychological distress was measured using the General Health Questionnaire-30 (GHQ-30). The raw total scale score can be used as an overall index of psychological distress, where higher scores indicate greater distress. (15;16).

Medical data were obtained from the survivor's medical record. The prognosis was based on the survival chances at diagnosis as rated by each survivor's oncologist, viz. <25%, 25-75%, or >75%. After the end of treatment (M1), the parents rated their perception of the intensiveness of their child's treatment on a Visual Analogue Scale, from 'totally non-intensive' (0, left end of line) to 'very intensive' (10, right end of line). They were also asked to assess the visible consequences of the disease. Their answers were dichotomized to 'presence' or 'absence' of visible consequences.

Important family events (other than the cancer of the child) during the past year were scored by the parents on a list of 19 such events, including the birth of a child, parental divorce, moving, death of a family member or friend, and decline in financial means. The total score of important family events was dichotomized to 'less than two' and 'two or more'.

Statistical analyses

SPSS version 12.0 was used for all analyses. One sample t-tests or non-parametric equivalents were performed to test whether the TAPQOL scores of the preschool survivors differed from those in the norm population, at a significance level of 0.01. The seven TAPQOL scales with sufficient internal consistency at every measurement occasion were used for these analyses: problem behavior, anxiety, positive mood, communication, liveliness, sleeping, and motor functioning.

Linear mixed model analysis (17) was performed to examine the course of HRQoL and to what extent demographics, medical variables and parental psychological distress were predictive of HRQoL (PCS and MCS) over time, while controlling for important family events. Measurement occasions were treated as fixed because growth-curve models were not appropriate for these data. Because of the large number of predictor variables in relation to the sample size, pre-selection was necessary. The initial model consisted of the random intercept M1 and the fixed parameters for measurement occasions M2 to M4. Predictor variables were entered one by one into the initial model. If significant at least at 0.15, variables were selected for the final model. Compound symmetry appeared the best longitudinal covariance structure for PCS, where for MCS an autoregressive structure was more appropriate. We found that it was not necessary to add any first-order interaction effect of measurement occasion with the other predictor variables, at Bonferroni adjusted level of significance.

To facilitate interpretation of regression coefficients, continuous scores were transformed into standard normal scores, expressing deviations from the mean at M1. We considered

standardised regression coefficients of 0.1 as small, 0.3 as medium and 0.5 as large after Cohen (18). For binary coded predictor variables, regression coefficients of 0.2 can be considered small, 0.5 medium and 0.8 large.

RESULTS

Participants

The parents of 66 consecutive preschool children whose cancer treatment had successfully been ended, were invited to participate in the VOLG-study. The response rate was 81.8 per cent (N=54); 34 mothers and 20 fathers. The 12 survivors whose parents did not participate, did not differ from participating survivors with respect to demographic and medical variables ($p<0.1$ in t-tests or χ^2-tests). One survivor was excluded from analyses because she had a brain tumor.

TAPQOL data of 53 survivors were available at M1, 38 at M2 (71.7%), 23 at M3 (43.4), 17 (32.1%) at M4. For 36 survivors TAPQOL data were not available up to M4 ('incomplete data'). The main reason for incomplete data was that if a survivor reached the age of 6 years (N=26, 49.1%), the TAPQOL could not be filled in any longer. Dropout because of non-response was 7.5% (N=4). Furthermore, if a patient suffered from a relapse, the corresponding data from subsequent measurement occasions were excluded from analyses (N=6, 11.3%).

At M1, survivors with incomplete data did not differ ($p<0.1$) from survivors with data up to M4 ('complete data'), except on one scale: survivors with incomplete data showed less sleeping problems at M1 than those with complete data. As a result of the limited age range of the TAPQOL, differences between incomplete and complete data were found in age and age-related medical variables (Table I).

HRQoL over time

Two months after treatment (M1), survivors scored significantly ($p<0.001$) worse than the norm on six out of the seven TAPQOL scales we used in the analyses (Figure 1). The differences were large. Compared to the norm, survivors scored worse on problem behavior (M=56.9, d=0.7), anxiety (M=55.8, d=1.3), motor functioning (M=82.4, d=3.6), positive mood (M=92.9, d=0.9), liveliness (M=88.8, d=1.1) and sleeping (M=66.9, d=0.9).

One year after treatment (M2), HRQoL scores have improved though significant differences with the norm were still present on anxiety (M= 69.7, d=0.4, $p<0.01$) and motor functioning (M=91.9, d=2.6, $p<0.001$). Survivor's level of HRQoL was normalized two and three years after treatment (M3 and M4). Survivors did not differ from the norm on the Communication scale at any measurement occasion.

Predictors of HRQoL

Parameter estimates from the longitudinal mixed models analyses of survivor's HRQoL are shown in Table II. Apart from the contribution of measurement occasion, Physical HRQoL (PCS) was explained significantly by duration of treatment, prognosis and parental psychological distress. Longer duration of treatment, poor prognosis (< 25%) and greater parental psychological distress were associated with worse PCS. Apart from measurement

Table I. Characteristics of the survivors

	M1 2 months	M2 1 year	M3 2 years	M4 3 years
N	**53**	**38**	**23**	**17**
Gender: N (%)				
Girls	27 (50.9)	19 (50.0)	13 (56.5)	10 (58.8)
Boys	26 (49.1)	19 (50.0)	10 (43.5)	7 (41.2)
*Age**				
M (SD)	3.9 (1.4)	4.1 (1.3)	4.3 (0.8)	4.8 (0.7)
Range	1.1 – 5.9	2.0 – 5.9	2.9 – 5.6	3.5 – 5.8
*Age at diagnosis**				
M (SD)	2.6 (1.4)	2.1 (1.3)	1.4 (0.9)	1.1 (0.6)
Range at M1:	0.3 – 5.3	0.3 – 4.5	0.3 – 3.4	0.3 – 2.3
Time since diagnosis (months)				
M (SD)	14.7 (9.1)	25.3 (9.1)	34.8 (8.3)	46.3 (7.5)
Range	2.8 – 29.7	14.1 – 40.8	26.8 – 49.9	38.3 – 61.2
Duration of treatment (months)				
M (SD)	12.6 (9.3)	12.4 (9.2)	10.6 (8.3)	10.3 (7.6)
Range	1.5 – 25.9	2.1 – 25.9	2.3 – 25.5	2.5 – 25.3
Diagnosis: N (%)*				
Leukaemia/lymphoma	24 (45.3)	15 (39.5)	7 (30.4)	4 (23.5)
Solid tumour	29 (54.7)	23 (60.5)	16 (69.6)	13 (76.5)
Treatment: N (%)*				
Chemotherapy	51 (96.2)	36 (94.7)	21 (91.3)	15 (88.2)
Radiotherapy	11 (20.8)	8 (21.1)	6 (26.1)	6 (35.3)
Surgery	26 (49.1)	21 (55.3)	14 (60.9)	11 (64.7)
Autologous Bone Marrow Transplantation	2 (3.8)	2 (5.3)	2 (8.7)	2 (11.8)
Other	2 (3.8)	2 (5.3)	2 (8.7)	2 (11.8)
Prognosis at diagnosis: N (%)*				
< 25%	4 (7.5)	4 (10.5)	4 (17.4)	4 (23.5)
25-75%	20 (37.7)	13 (34.2)	10 (43.5)	8 (47.1)
> 75%	29 (54.7)	21 (55.3)	9 (39.1)	5 (29.4)
Relapse: N	0	0	0	0
Respondent: N (%)				
Mother	34 (64.2)	26 (68.4)	18 (78.3)	14 (82.4)
Father	19 (35.8)	12 (31.6)	5 (21.7)	3 (17.6)

* Significant differences at < 0.1 between survivors with and without TAPQOL data up to M4.

occasion, no other variables appeared to be associated significantly with mental HRQoL (MCS). The effects of measurement occasion and prognosis were medium to large, while the effects of duration of treatment and parental psychological distress were small.

DISCUSSION

Preschool survivors adjusted well to the cancer experience; as time from end of treatment increased HRQoL improved. Longer duration of treatment and poor prognosis seemed to

Table II. Parameter estimates for longitudinal regression models of HRQoL in survivors aged 1-5 years predicted by measurement occasion, demographic and medical characteristics, and parental psychological distress

	Physical Component Score (TAPQOL)	Mental Component Score (TAPQOL)
FIXED EFFECTS		
Measurement (deviation from end of treatment; M1)		
One year (M2)	0.41*	0.41*
Two years (M3)	0.48	0.72**
Three years (M4)	0.52	0.77*
PERCENTAGE OF EXPLAINED VARIANCE BY FIXED EFFECTS	0.09	0.11
Medical and demographic characteristics		
Gender survivor	-	-
Age survivor	0.02	- 0.21
Age at diagnosis	0.04	0.09
Time since end of treatment	-	-
Duration of treatment	- 0.13*	0.02
Leukeamia or lymphoma (versus solid tumours)	-	-
Radio-and chemotherapy	-	-
Prognosis < 25%	- 0.53*	- 0.20
Perceived treatment intensity	-	-
Visible consequences	-	-
PERCENTAGE OF EXPLAINED VARIANCE BY FIXED EFFECTS	0.24	0.14
Parental data		
Age	-	-
Gender	-	-
Parental psychological distress (GHQ)	- 0.13*	- 0.12
Important family events (≥ 2)	-	-
PERCENTAGE OF EXPLAINED VARIANCE BY FIXED EFFECTS	0.16	0.27
TOTAL NUMBER OF OBSERVATIONS	115	115

* p<0.05 p<0.01

affect physical HRQoL negatively. Survivors with poor prognoses have been treated more intensively which could result in more physical complaints. The greater psychological distress the parents experienced, the worse HRQoL they reported in their child. This finding is in line with results from previous studies on childhood cancer but the direction of the relationship could not be determined (19-22). We were not able to differentiate between the impact of parental emotions on parental perception of their child's HRQoL and the impact on 'real' survivor's HRQoL, because the parents evaluated the HRQoL of their children as well as their own adjustment.

Overall, the variables in the model explained only 26 and 16 per cent of the variance for physical HRQoL (PCS) and mental HRQoL (MCS) respectively. This is not surprising, given the fact that the medical variables were assessed rather roughly and because it was too short after termination of treatment to find late effects of treatment. The limited impact of medical variables on HRQoL has been found in many studies among survivors of childhood cancer (9;10).

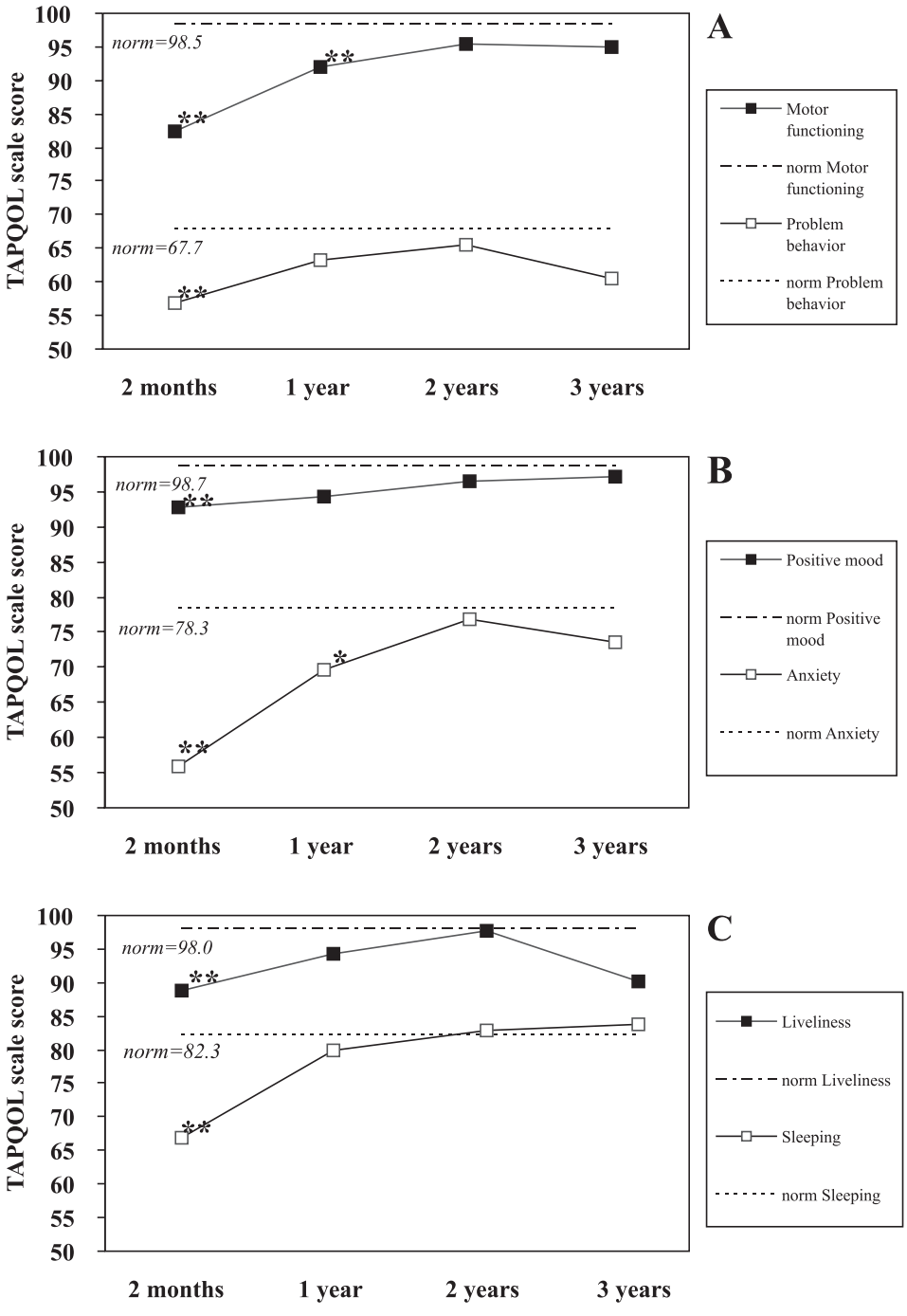

Fig. 1. HRQoL in preschool survivors over measurements occasions: Motor functioning and Problem behavior (A), Positive mood and Anxiety (B), Liveliness and Sleeping (C).
Mean TAPQOL scale scores, ranging from 0-100 with higher scores representing better HRQoL, that differ significantly from the norm in the general Dutch population of children aged 1-5 years(13) are marked:
* $p<0.01$, ** $p<0.001$.

There would be other psychosocial factors than assessed in the present study that affect survivors's HRQoL, for example the interaction between the parent and their children. If parents perceive their children's health as very vulnerable, this could lead to overprotection and failing to set age-appropriate limits on the children's behavior, which might have adverse effects for the children (23;24). Further research is needed to explore these findings, especially because parents of survivors are faced with uncertainty about the further course of the disease, which might influence their perceptions of their children's vulnerability.

Limitations and implications

The problem of small sample size is inherent to research on children, especially when children are studied longitudinally, as different age groups need different, age-specific questionnaires. Low power due to small sample size could have contributed to the fact that few variables were found to be predictive of HRQoL. Furthermore, it was necessary to pre-select variables for the final analyses. As a result of this, several medical variables were excluded in the final models which could have led to underestimation of the explained variance of the models. Despite the small sample size at the last measurement occasion, longitudinal analyses were possible because linear mixed models analyses incorporates all available data into analysis, including data from survivors that missed one or more measurement occasions.

Another limitation concerns the HRQoL instruments. We used generic HRQoL measures because we wanted to compare the survivors with the general population. The use of cancer-specific instruments is recommended for longitudinal assessments because this kind of instruments is more sensitive to change. Unfortunately, HRQoL instruments translated and validated for Dutch preschool children are not available.

Though most survivors regained a good HRQoL two years after the end of successful cancer treatment, there is no reason to lean back because of the known late effects of many treatments (25-29). Survivors should be followed longer to be able to assess the impact of the late effects on the survivor's HRQoL, physical as well as psychosocial. It is satisfying that monitoring and screening survivors have become standard aftercare in many hospitals in the last decade. Standard aftercare should preferably include psychosocial screening, education and counselling directed at both survivors and parents. Providing psychosocial information on the effects of the disease and treatment, and assisting parents in treating the survivors as normally as possible could prevent late psychosocial problems by enhancing re-entry into normal life.

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REFERENCES

(1) Eiser C. Children with cancer. The quality of life. Mahwah, New Jersey, Londen: Lawrence Erlbaum Associates Publishers, 2004.

(2) Eiser C. Practitioner Review: long-term consequences of childhood cancer. J Child Psychol and Psychiatry 1998;39(5):621-33.

(3) Stevens MCG, Mahler H, Parkes S. The health status of adult survivors of cancer in childhood. Eur J Cancer 1998;34(5):694-8.

(4) Novakovic B. U.S. Childhood cancer survival, 1973-1987. Med Pediatr Oncol 1994;23:480-6.

(5) Stiller CA, Draper GJ. The epidemiology of cancer in children. In: Voûte PA, Kalifa C, Barrett A, eds. Cancer in children: clinical management. fourth edition ed. Oxford: Oxford University Press, 1998.

(6) Stiller CA, Draper GJ. The epidemiology of cancer in children. In: Voûte PA, Barret A, Stevens MCG, Caron HN, eds. Cancer in children: clinical management. fifth edition ed. Oxford: Oxford University Press, 2005. p. 1-16.

(7) Magnani C, Pastore G, Coebergh J, Viscomi S, Spix C, Steliarova-Foucher E. Trends in survival after childhood cancer in Europe, 1978-1997: Report from the Automated Childhood Cancer Information system project (AGGIS). Eur J Cancer 2006;42(13):1981-2005.

(8) Sankila R, Martos Jiménez MC, Miljus D, Pritchard-Jones K, Steliarova-Foucher E, Stiller C. Geographical comparison of cancer survival in European children (1988-1997): Report from the Automated Childhood Cancer Information System project. Eur J Cancer 2006; 42(13):1972-1980.

(9) Langeveld NE, Stam H, Grootenhuis MA, Last BF. Quality of life in young adult survivors of childhood cancer (review). Support Care Cancer 2002;10:579-600.

(10) Stam H, Grootenhuis MA, Last BF. Social and emotional adjustment in young survivors of childhood cancer (review). Support Care Cancer 2001;9:489-513.

(11) Nagel K, Eves M, Waterhouse L, Alyman C, Posgate S, Jamieson J, et al. The development of an off-therapy needs questionnaire and protocol for surivors of childhood cancer. J Pediatr Oncol Nurs 2002;19(6):229-33.

(12) Fekkes M, Theunissen NCM, Brugman E, Veen S, Verrips E, Koopman HM, et al. Development and psychometric evaluation of the TAPQOL: A health-related quality of life instrument for 1-5-year-old children. Qual Life Res 2000;9:961-72.

(13) Fekkes M, Bruil J, Vogels T. TAPQOL-manual. Leiden: Leiden Center for Child Health and Pediatrics LUMC-TNO; 2004.

(14) Ware JE, Kosinski M. Interpreting SF-36 summary health measures: a response. Qual Life Res 2001;10:405-13.

(15) Goldberg DP, Williams P. A user's guide to the General Health Questionnaire. Windsor: NFER-Nelson, 1988.

(16) Koeter MWJ, Ormel J. General Health Questionnaire: The Dutch application. Amsterdam: Swets Test Services, 1991.

(17) Snijders FAB, Bosker RJ. Multilevel Analysis. An introduction to basic and advanced multilevel modeling. London: SAGE Publications Ltd, 2004.

(18) Cohen J. Statistical power analysis for the behavioral sciences. New York: Academy Press, 1988.

(19) Barakat LP, Kazak AE, Meadows AT, Casey R, Meeske K, Stuber ML. Families surviving childhood cancer: a comparison of posttraumatic stress symptoms with families of healthy children. J Pediatr Psychol 1997;22(6):843-59.

(20) Kazak AE, Barakat LP. Brief report: Parenting stress and quality of life during treatment for childhood leukemia predicts child and parent adjustment after treatment ends. J Pediatr Psychol 1997;22:249-758.

(21) Sawyer MG, Streiner DL, Antoniou G, Toogood I, Rice M. Influence of parental and family adjustment on the later psychological adjustment of children treated for cancer. J Am Acad Child Adolesc Psychiatry 1998;37(8):815-22.

(22) Sloper T, Larcombe IJ, Charlton A. Psychosocial adjustment of five-year survivors of childhood cancer. J Cancer Educ 1994;9(3):163-9.

(23) Estroff DB, Yando R, Burke K, Snyder D. Perceptions of preschoolers' vulnerability by mothers who had delivered preterm. J Pediatr Psychol 1994 Dec;19(6):709-21.

(24) Stern M, Karraker K, McIntosh B, Moritzen S, Olexa M. Prematurity stereotyping and mothers' interactions with their premature and full-term infants during the first year. J Pediatr Psychol 2006 Jul;31(6):597-607.

(25) Lackner H, Benesch M, Schagerl S, Kerbl R, Schwinger W, Urban C. Prospective evaluation of late effects after childhood cancer therapy with a follow-up over 9 years. Eur J Pediatr 2000;159:750-8.

(26) Oeffinger KC, Eshelman DA, Tomlinson GE, Buchanan GR, Foster BM. Grading of late effects in young adults survivors of childhood cancer followed in an ambulatory adult setting. Cancer 2000;88:1687-95.

(27) Oeffinger KC, Hudson MM. Long-term complications following childhood and adolescent cancer: foundations for providing risk-based health care for survivors. CA Cancer J Clin 2004;54:208-36.

(28) Friedman DL, Freyer DR, Levitt GA. Models of care for survivors of childhood cancer. Pediatr Blood Cancer 2006;46:159-68.

(29) Oeffinger KC, Mertens AC, Sklar CA, Kawashima MS, Hudson MM, Meadows AT, et al. Chronic health conditions in adult survivors of childhood cancer. N Eng J Med 2006;355(15):1572-82.

Chapter 5

School-aged children after the end of successful treatment of non-CNS cancer: Longitudinal assessment of Health-Related Quality of Life, anxiety and coping

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Submitted

ABSTRACT

Introduction: The aim of the study was to investigate 1) the course of HRQoL and anxiety in school-aged cancer survivors during the first four years of continuous remission after the end of successful treatment and 2) correlations of disease-related coping with HRQoL and anxiety.

Material and Methods: Survivors of childhood cancer aged 8-15 years completed questionnaires about HRQoL, anxiety and disease-related cognitive coping. The child-reported HRQoL of the survivors was compared with norm data, two months, one year, two years, three years and four years after termination of successful treatment. Through longitudinal mixed models analyses it was investigated to what extent disease-related cognitive coping was associated with HRQoL and anxiety over time, independent of the impact of demographic and medical variables.

Results: Survivors reported worse Motor functioning (HRQoL) two months after the end of treatment but from one year after treatment they did no longer differ from the norm population.
Lower levels of anxiety were associated with male gender, being more optimistic about the further course of the disease (predictive control) and less searching for information about the disease (interpretative control). Stronger reliance on the physician (vicarious control) was associated with better mental HRQoL.

Conclusions: As a group, survivors regained good HRQoL from one year after treatment. Monitoring and screening survivors are necessary to be able to trace the survivors at risk of worse HRQoL.

INTRODUCTION

The treatment of patients with childhood cancer has enormously improved in recent decades. Many patients who may previously have had a limited life expectancy are now growing up with childhood cancer and surviving into adulthood. The overall 5-year survival rate for children diagnosed with cancer in Europe is currently more than 70% compared with 30% in the 1960's (1;2).

The diagnosis and treatment of childhood cancer is a dramatic event that affects the daily life and emotional well-being of all family members (3). An increasing number of studies have been directed at assessing Health Related Quality of Life (HRQOL) and emotional adjustment in long-term survivors of childhood cancer. Less is known about the first few years after treatment in the run-up to long-term survivorship, and longitudinal studies are sparse. Sawyer and colleagues (4) found that patients had behavioural-emotional problems immediately after diagnosis but in the next four years the scores were generally consistent with those in the control group. Others (5-7) reported that survivors did not show elevated levels of anxiety in comparison with the norm in the first years after termination of treatment. Recently, we found that two months after the end of successful cancer treatment, paediatric patients and their parents experienced worse HRQoL than the general population to a clinically relevant extent (8).

Demographic and medical factors related to the HRQoL and emotional functioning of paediatric survivors have been discussed to some extent in many studies. The results, however, were not consistent and most study designs were cross-sectional so that causality can not be established. What can be concluded is that older age at diagnosis, longer time off treatment, irradation therapy, and severe medical late effects were associated with worse psychosocial functioning in paediatric long-term survivors of childhood cancer (see review of Stam et al. (9)).

The role of coping is important in relation to the adjustment to childhood cancer (10). Coping consists of actions, behaviours and thoughts aimed at dealing with the demands of events and situations that are appraised as stressful (11). So, coping mediates the effect of a stressor on an individual's well-being. In the context of coping with a life-threatening illness the following disease-related cognitive control strategies were found to be relevant (12). *Predictive control* means that patients attempt to predict events in order to create the feeling that they are able to control the situation. Having positive expectations helps patients to deal with the consequences of disease. *Vicarious control* strategies concern the attribution of special power to others, in the case of cancer patients to the doctors, on whom they are dependent and all hope is focused. Because one can not alter the course of the disease, belief in powerful others can be adaptive. *Interpretative control* refers to the search for meaning and understanding. Using information to help to understand emotional reactions or to reduce uncertainty are interpretative control strategies. Finally, with *illusory control* one attempts to associate with chance, such as hoping for a miracle or wishful thinking.

Some studies on coping strategies in paediatric survivors of cancer were found. Madan-Swain et al. (13) found that, overall, survivors used coping strategies which were comparable with the strategies used by controls. Others found that survivors tended to apply more avoidance strategies in stressful situations than a healthy control group (14), which is in line with the coping strategies found in paediatric cancer patients during treatment (15;16). It is

difficult, however, to conclude whether coping is associated with the patient's functioning because most studies have been focused on coping as an outcome variable, rather than a predictor. Moreover, the few studies on the impact of coping on surivors' functioning, showed inconsistent results (16).

The more we understand about disease-related coping and about the relation of coping with survivors' functioning the better health care providers will be able to help patients to live with the consequences of their disease. The present study was therefore directed at HRQoL and emotional functioning as well as disease-related coping. A longitudinal study was designed with the following research questions: (1) How are the course of HRQoL and anxiety of survivors during the first four years of continuous remission following the completion of treatment for cancer? (2) To what extent is disease-related cognitive coping associated with survivors' HRQoL and anxiety during the first four years of continuous remission following the completion of treatment for cancer? Although a 5-year period without treatment is commonly considered a criterion of survival, we decided to call the patients in our study 'survivors' because they were in continuous remission in the run-up to long-term survivorship.

MATERIAL AND METHODS

Procedure

The results presented here are taken from a Dutch study on the late psychosocial consequences of cancer in childhood, which started in 2000 and ended in 2006, the VOLG-study. From 2000 to 2002, survivors and their parents were recruited from two Dutch university hospitals, the Emma Children's Hospital at the Academic Medical Center in Amsterdam and the Radboud University Nijmegen Medical Center. The Medical Ethics Committees of the hospitals have approved the study protocol.

All consecutive survivors who met the inclusion criteria during these periods were invited to participate in the VOLG-study. The inclusion criteria were: (1) age of the survivors 1-18 years, (2) complete remission, (3) end of successful treatment at most two months before, and (4) ability to complete Dutch questionnaires. The self-reported data of survivors aged 8-15 years ('school-aged survivors') were used in the present study. This means that the data were included in the analyses at the measurement occasions that the respondent was aged 8-15 years.

Once informed consent had been obtained from both the survivors and their parents, the respondents completed several questionnaires, four to six times, depending on the year of inclusion. The first five assessments were used for analyses; approximately two months (M1), one year (M2), two years (M3), three years (M4) and four years (M5) after the end of treatment. Data of the sixth measurement occasion and data for survivors with CNS-tumours were not used because of too small numbers of respondents. Furthermore, the data for patients who relapsed were excluded from analysis from the moment of the relapse.

Measures

Dependent Variables: Health-Related Quality of life and anxiety

The *TNO-AZL Children's Quality of Life questionnaire* for children aged 8 to 15 years (TACQOL-CF) (17;18) was used. This is a generic Dutch instrument that measures HRQoL on group level in a reliable and valid way. Norm data from the general Dutch population are available (17;19;20). The questionnaire measures health status problems weighted by the impact of the problems on well-being. Most of the items consist of two questions linked to one another. The first one is about the frequency of the problem in the past few weeks. The second one rates the possible negative emotional responses to the problems on a four-point Likert scale. The items are clustered into seven multi-item scales with higher scores indicating better HRQoL: Physical complaints, Motor functioning, Autonomy, Cognitive functioning, Social functioning, Positive emotions and Negative emotions. Following the method of Ware et al. (21) we used PCA to aggregate all TACQOL scale scores into two summary scales: the Mental Component Scale (MCS) and the Physical Component Scale (PCS). The relative contribution of each scale to MCS and PCS was derived from PCA at M1, oblique rotation (Oblimin).

Anxiety was measured with the Dutch version of the *State-Trait Inventory for Children* (STAI-C), the ZBV-K (22). The 'trait' version was used to assess the tendency to respond with anxiety in a stressful situation. This version is more appropriate to measure the overall level of anxiety a child experiences than the 'state' version that measures conditional anxiety at the very moment of assessment. Higher scores indicate higher levels of anxiety. The norm data from the general Dutch population of school-aged children (22) could not be used because only gender-specific norm data were available, which resulted into too small subgroups of survivors at the several measurement occasions.

Independent Variables: disease-related cognitive control and medical variables

Disease-related cognitive coping was assessed with the *Cognitive Control Strategies Scale* for patients (CCSS). The instrument, based on the model of Rothbaum et al. (23), was developed at the Psychosocial Department of the Emma Children's Hospital/AMC. It assesses to what extent respondents try to gain sense of control over the illness by using cognitive coping strategies, measured on a four-point Likert scale. Higher scores represent a stronger reliance upon the control strategy. The questionnaire proved to be reliable and useful in earlier studies (7;8;24). The items of the *CCSS-CF* were grouped into four scales, as described in the Introduction section: predictive, vicarious, interpretative and illusory control. The Illusory control scale was not used in analyses because of insufficient internal consistency.

Medical data were obtained from the survivor's medical record. The prognosis was based on the survival chances at diagnosis as rated by each survivor's oncologist, viz. <25%, 25-75%, or >75%. After the end of treatment (M1), the parents were asked to rate their perception of the intensiveness of their child's treatment on a Visual Analogue Scale, from 'totally non-intensive' (0, left end of line) to 'very intensive' (10, right end of line). They were also asked to assess the visible consequences of the disease. Their answers were dichotomized to 'presence' or 'absence' of visible consequences.

Statistical analyses

SPSS version 12.0 was used for all analyses. Survivors' HRQoL over time was compared with norm data for the general Dutch population of children aged 8-11 years and 12-15 years, with respect to the four TACQOL scales with sufficient internal consistency at each measurement occasion: Motor functioning, Cognitive functioning, Positive emotions and Negative emotions. One sample t-tests or non-parametric equivalents (one sample sign-test or binomial test) were performed to test (at $p<0.05$, two-sided) whether the mean score, the median or the binomial distribution of the scales scores in the childhood cancer survivors differed from that in the norm population.

Linear mixed model analysis (25) was performed to examine the course of HRQoL and anxiety and to explore to what extent disease-related cognitive coping was predictive of HRQoL (PCS and MCS) and anxiety, while controlling for demographic and medical variables. To account of repeated measures within respondents, linear mixed models were fitted to the data. These models can also be characterised as multilevel models for longitudinal data, with measurement occasions as first level units of analysis and respondents as second level units. The major advantage of linear mixed model analysis is that all available data are incorporated into the analysis, including data from survivors who missed one or more measurement occasions. Changes in the numbers of subjects from occasion to occasion do not harm the analysis, other than that the statistical power to find deviations from baseline decreases with higher attrition.

To facilitate interpretation of regression coefficients, all continuous scores were transformed into standard normal scores, expressing deviations from the mean at M1. We considered standardized regression coefficients of 0.1 as small, 0.3 as medium and 0.5 as large after Cohen (26). For binary coded predictor variables, regression coefficients of 0.2 can be considered small, 0.5 medium and 0.8 large.

Measurement occasions were treated as fixed because growth-curve models were not appropriate for these data. The intercept was considered random with its mean equal to the standardized mean outcome at M1, thus taking the outcome at M1 as reference point. In this way, parameter estimates for M2 through M5 can be interpreted as deviations from baseline (M1). The deviations were treated as fixed parameters after checking for random parameters, using Akaike's information criterion.

Models were fitted for PCS, MCS and anxiety. Because of the large number of predictor variables in relation to the sample size, pre-selection was necessary. The initial model consisted of the random intercept (M1) and the fixed parameters for measurement occasions M2 to M5. Demographic and medical predictor variables were entered one by one into the initial model. If significant at least at 0.3, the demographic and medical variables were selected for the final model. All three variables concerning cognitive coping were included. The final model thus consisted of the random intercept (M1), the fixed regression coefficients for M2 through M5 and the three coping variables, completed with the demographic and medical predictor variables that remained after pre-selection. For one outcome, anxiety, there appeared to be no intercept variance. The final model for this outcome was therefore fitted with a fixed intercept. Percentages of total explained variance were calculated.

For each model, we checked whether the longitudinal covariance structure was best described by compound symmetry or by an autoregressive structure, with reference to Akaike's information criterion. Compound symmetry appeared to give the best fit for all

models. Furthermore, we checked whether first-order interaction effects of measurement occasion with the other predictor variables should be added to the model. To prevent too many findings occurring by chance, these tests were carried out at Bonferroni adjusted level of significance. We concluded that it was not necessary to add any of the first-order interaction effects.

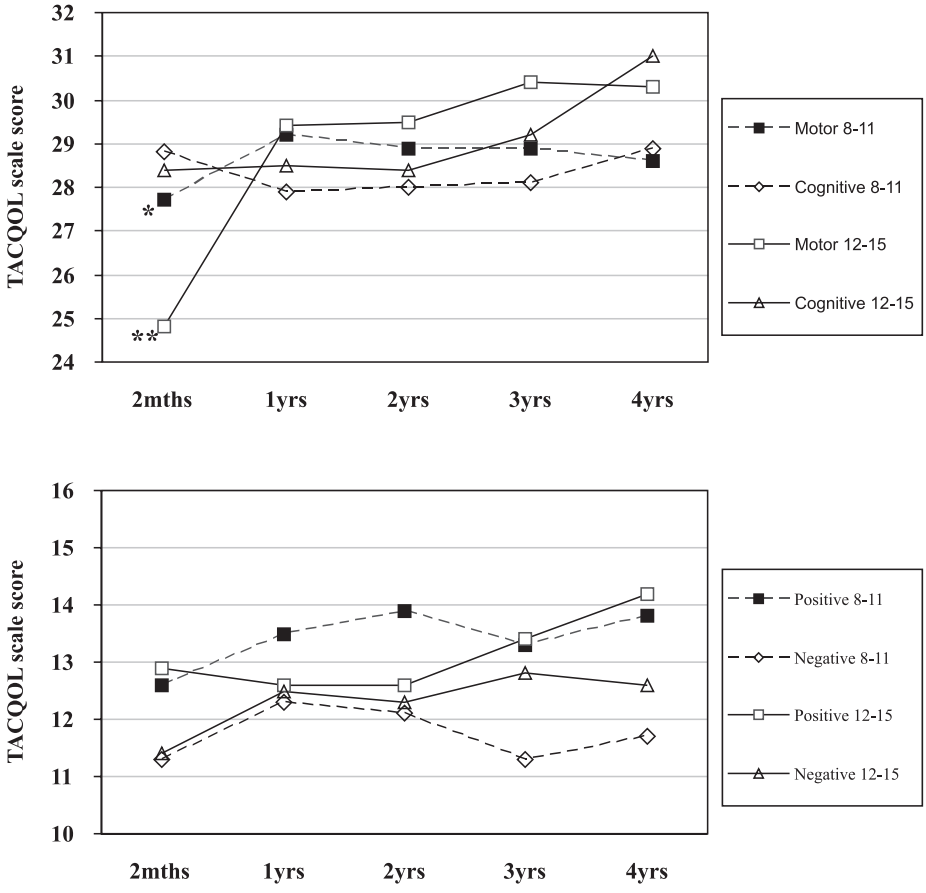

Figure 1: HRQoL in survivors aged 8-11 and 12-15 years over measurement occasions; mean TACQOL scale scores[1] compared with the norm[2].

Legend:

* Scale score differed significantly from the norm at p<0.05 (two-sided) at one sample t-test.

** Scale score differed significantly from the norm at p<0.001 (two-sided) at one sample t-test.

1 Higher scores represent better HRQOL; Range Motor and Cognitive functioning = 0–32, Range Positive and Negative feelings = 0-16.

2 General Dutch population of children aged 8-11 years (44) and 12-15 years (18).

Table 1: Characteristics of the survivors

Measurement time since end of treatment		**M1 2 months**	**M2 1 year**	**M3 2 years**	**M4 3 years**	**M5 4 years**
N		**49**	**41**	**41**	**42**	**27**
Gender: N (%)	Females	17 (34.7)	15 (36.6)	13 (31.7)	15 (35.7)	5 (18.5)
Age: Mean (SD)	(range at M1: 8.1 – 15.9)	12.1 (2.3)	11.8 (2.5)	11.5 (2.5)	11.5 (2.4)	10.9 (2.2)*
Age category: N (%)	8 – 11 years	23 (46.9)	19 (46.3)	25 (61.0)	25 (59.5)	21 (77.8)
	12 – 15 years	26 (53.1)	22 (53.7)	16 (39.0)	17 (40.5)	6 (22.2)
Age at diagnosis: Mean (SD)	(range at M1: 6.4 – 15.2)	11.0 (2.4)	9.9 (2.5)*	8.6 (2.6)*	7.5 (2.7)*	5.7 (2.4)*
Time since diagnosis (months): Mean (SD)	(range at M1: 2.0 – 28.0)	13.2 (7.2)	23.7 (7.1)	35.2 (7.9)	48.3 (8.9)	62.4 (10.4)
Duration of treatment (months): Mean (SD)	(range at M1: 1.2 – 25.7)	10.9 (7.3)	10.7 (6.9)	10.9 (7.7)	12.1 (8.6)	14.3 (10.3)
Diagnosis: N (%)	Leukaemia/ lymphoma	24 (49.0)	18 (43.9)	20 (48.8)	22 (52.4)	20 (74.1)
	Solid tumour	25 (51.0)	23 (56.1)	21 (51.2)	20 (47.6)	7 (25.9)
Treatment: N (%)	Chemotherapy	48 (98.0)	41 (100)	41 (100)	42 (100)	27 (100)
	Radiotherapy	8 (16.3)	6 (14.6)	4 (9.8)	4 (9.5)	0 *
	Surgery	21 (42.9)	21 (51.2)	20 (48.8)	20 (47.6)	10 (37.0)
	ABMT	0	0	0	0	0
	Other	1 (2.0)	0	0	0	0
Prognosis at diagnosis: N (%)	< 25%	1 (2.0)	0	0	0	0
	25-75%	21 (42.9)	15 (36.6)	13 (31.7)	11 (26.2)	5 (18.5)
	> 75%	27 (55.1)	26 (63.4)	28 (68.3)	31 (73.8)	22 (81.5)*
Native country: N (%)	The Netherlands	48 (98.0)	41 (100)	40 (97.6)	41 (97.6)	26 (96.3)

* Survivors differed significantly from the survivors at M1, $p < 0.05$ (two-sided).

RESULTS

Participants

A total of 164 consecutive survivors whose cancer treatment had successfully ended, were invited to participate in the longitudinal part of the VOLG-study. The response rate was 81.7 per cent (N=134). The 30 families who did not participate, did not differ from participating families with respect to demographic and medical variables ($p<0.1$ at t-tests or χ^2-tests).

A total of 76 survivors were included in the present study, who were aged 8-15 years at one or more measurement occasions: 49 survivors at M1, 41 at M2, 41 at M3, 42 at M4 and 27 at M5. Characteristics of survivors are presented in Table 1. Dropout because of non-response was 2.6% (N = 2). Furthermore, after recurrence of the childhood cancer, data of subsequent measurement occasions were excluded from analyses (N = 8, 10.5%). So, it depends on the moment of relapse how many measurement occasions were included. Data at M5 were not available in 19 (25.0%) survivors because of the finite follow-up period of the VOLG-study. The survivors included at M2, M3, M4 and M5 did not differ significantly ($p < 0.05$) from the survivors at M1 with respect to their demographic and medical characteristics, except for age at diagnosis. The survivors at M1 were older at diagnosis than the survivors at the other measurement occasions. Furthermore, some differences were found between survivors at

M5 and those at M1, as shown in Table 1. Finally, participants did not differ from the non-participants at the several measurement occasions with respect to their outcome scores at T1.

Health-Related Quality of Life and Anxiety over time

On average two months after the end of successful treatment (M1), survivors aged 8-11 years scored significantly worse on Motor functioning ($p < 0.05$) than the general Dutch population: M = 27.7 (SD = 4.6) versus M = 29.8 (SD = 3.2). At M1, also survivors aged 12-15 years reported significantly worse Motor functioning ($p < 0.001$) than the general Dutch population: M = 24.8 (SD = 5.4) versus M = 29.8 (SD = 3.3). The differences were large, d = - 0.7 and d = - 1.6 respectively. One (M2), two (M3), three (M4) and four years (M5) after the end of

Table 2: Parameter estimates for longitudinal regression models of HRQoL (TACQOL) in survivors aged 8-15 years predicted by measurement occasion, demographic and medical characteristics and disease-related cognitive coping.

	Physical Component Scale (TACQOL)	**Mental Component Scale (TACQOL)**
FIXED EFFECTS		
Measurement (deviation from end of treatment; M1)		
One year (M2)	0.36**	0.36º
Two years (M3)	0.32*	0.54º
Three years (M4)	0.33*	0.61
Four years (M5)	0.44**	0.86
PERCENTAGE OF EXPLAINED VARIANCE		
BY FIXED EFFECTS	0.06	0.01
Medical and demographic characteristics		
Gender (female)	-	- 0.32
Age	-	- 0.22
Age at diagnosis	-	0.34
Duration of treatment	- 0.10	-
Leukeamia or lymphoma (versus solid tumours)	-	-
Radio-and chemotherapy	-	-
Chemotherapy without radiotherapy	-	-
Prognosis > 75%	0.16	- 0.35º
Perceived treatment intensity	-	-
Visible consequences	-	-
PERCENTAGE OF EXPLAINED VARIANCE		
BY FIXED EFFECTS	0.10	0.07
Disease-related cognitive coping (CCSS)		
Predictive control	0.02	0.04
Interpretative control	- 0.10º	- 0.13º
Vicarious control	0.04	0.13*
PERCENTAGE OF EXPLAINED VARIANCE		
BY FIXED EFFECTS	0.13	0.09
TOTAL NUMBER OF OBSERVATIONS	177	177

Notes. The higher the score is, the better the HRQoL. Dashes (-) mean that the variables were not included in the model. Medical and demographic variables that were not correlated significantly at $p < 0.3$ with PCS and/or MCS in the initial models were not selected for the final models. º $p<0.10$ * $p<0.05$ ** $p< 0.01$

treatment, survivor's level of Motor functioning was normalized in both aged groups. Neither the survivors aged 8-11 years nor the survivors aged 12-15 years differed from the general population with respect to Cognitive functioning, Positive emotions and Negative emotions at any measurement occasion (Figure 1a and 1b).

Predictors of Health-Related Quality of Life

Parameter estimates from the longitudinal mixed models analyses of survivor's HRQoL are shown in Table 2. Survivors reported significant higher scores on PCS one to four years after the end of treatment than at two months. The effects of time were small to medium. PCS was not predicted significantly ($p<0.05$) by any demographic, medical or coping variable. Interpretative control, however, was associated negatively with PCS at $p = 0.08$ ($\beta = -0.10$).

Table 3: Parameter estimates for longitudinal regression models of Anxiety (STAI-C) in survivors aged 8-15 years predicted by measurement occasion, demographic and medical characteristics and disease-related cognitive coping.

	Anxiety (STAI-C)
FIXED EFFECTS	
Measurement (deviation from end of treatment; M1)	
One year (M2)	- 0.18
Two years (M3)	- 0.28
Three years (M4)	- 0.16
Four years (M5)	- 0.21
PERCENTAGE OF EXPLAINED VARIANCE	
BY FIXED EFFECTS	0.004
Medical and demographic characteristics	
Gender (female)	0.60**
Age	0.11
Age at diagnosis	- 0.23
Duration of treatment	-
Leukeamia or lymphoma (versus solid tumours)	-
Radio-and chemotherapy	-
Chemotherapy without radiotherapy	0.51º
Prognosis > 75%	-
Perceived treatment intensity	-
Visible consequences	- 0.13
PERCENTAGE OF EXPLAINED VARIANCE	
BY FIXED EFFECTS	0.12
Disease-related cognitive coping (CCSS)	
Predictive control	- 0.18*
Interpretative control	0.18*
Vicarious control	0.00
PERCENTAGE OF EXPLAINED VARIANCE	
BY FIXED EFFECTS	0.21
TOTAL NUMBER OF OBSERVATIONS	190

Notes. The higher the score is, the higher the level of anxiety. Dashes (-) mean that the variables were not included in the model. Medical and demographic variables that were not correlated significantly at $p < 0.3$ with anxiety in the initial models were not selected for the final model. º $p<0.10$ * $p<0.05$ ** $p<0.01$

MCS, in contrast with PCS, was not associated significantly ($p < 0.05$) with measurement occasion, though at M2 and M3 survivors tended to report better MCS than at the first measurement occasion; $\beta = 0.36$, $p = 0.06$ and $\beta = 0.54$, $p = 0.08$ respectively. Furthermore, a small positive effect was found for vicarious control ($\beta = 0.13$, $p < 0.05$). Good prognosis tended to be associated negatively with MCS ($\beta = -0.35$, $p = 0.07$), as did interpretative control ($\beta = -0.13$, $p = 0.053$).

Predictors of anxiety

Parameter estimates from the longitudinal mixed models analyses of survivor's level of anxiety are shown in Table 3. Measurement occasion did not contribute significantly to the model, where gender and coping were associated significantly with anxiety. Females reported higher levels of anxiety than males ($\beta = 0.60$, $p < 0.001$), which was a medium to large effect. Higher scores on predictive control were associated with lower levels of anxiety ($\beta = -0.18$, $p < 0.05$) but higher scores on interpretative control were associated with higher levels of anxiety ($\beta = 0.18$, $p < 0.05$). The effects of cognitive coping were small to medium. Finally, survivors who were treated with chemotherapy without radiotherapy tended to report a higher level of anxiety ($\beta = 0.51$, $p = 0.08$) than the other survivors.

DISCUSSION

Unlike cross-sectional studies, the present longitudinal study on HRQoL, anxiety and disease-related coping of school-aged survivors yielded insight into the process of adjustment over time. The first few years of continuous remission after the end of treatment were investigated, in view of the importance of this phase in the run-up to long-term survivorship. The results indicate that, in general, school-aged survivors adjusted well to the cancer experience. Compared to norm data from the general Dutch population, survivors showed worse HRQoL only with respect to motor functioning on average two months after the end of treatment. From one year after treatment, however, survivors did no longer differ from the norm population. We should realize that - on purpose - the data for patients who relapsed were excluded from analysis from the moment of the relapse. Furthermore, survivors having been treated for CNS-cancer were not included in the present study.

Our results were in line with the majority of studies among long-term survivors of childhood cancer, in which was found that their overall emotional adjustment as a group was within normal limits (9). This is not what would be expected considering the stressful experience of childhood cancer and its treatment. It could be partly attributable to the instruments we used. We decided to use generic HRQoL instruments in order to be able to compare the survivors to the general population. The use of cancer-specific instruments, however, is recommended for measuring the impact of childhood cancer longitudinally because this kind of instruments is more sensitive to change. Unfortunately, cancer-specific instruments translated and validated for Dutch school-aged children are not available yet.

Another possible explanation could be 'response shift,' which has been described in adults with cancer (27). The experience with cancer can have changed children's conceptualization of

problems, so that fewer problems are being experienced. The good adjustment could also be the result of adequate (family) coping with the stresses of childhood cancer, as is discussed below.

It is important to identify factors that were associated with HRQoL and anxiety so that survivors who are more vulnerable to maladjustment can be traced. None of the medical variables appeared to be associated significantly with HRQoL or anxiety. Female survivors, however, reported higher levels of anxiety which is common in the general population. Some correlations were found between disease-related coping and the outcomes. Firstly, survivors who relied more strongly on the expertise of their physician and attributed power to the cancer treatment (*vicarious control*) reported better mental HRQoL (MCS). It is well known that physicians play a role in diminishing disease-related feelings of uncertainty. Secondly, survivors who were more optimistic about the further course of the disease (*predictive control*) experienced lower levels of anxiety, while those who searched more for information about the disease (*interpretative control*) reported higher levels of anxiety. Causality can not be established but is reasonable to assume that being more optimistic about the further course of the disease can result in lower levels of anxiety. The correlation between interpretative control and anxiety is less clear. On the one hand, survivors who feel insecure and anxious may be more in need of information about the disease. On the other hand, the gathered information could reinforce anxiety.

Overall, the variables in the model explained only 13, 9 and 21 per cent of the variance for PCS, MCS and anxiety respectively. The limited variance explained by the medical variables is not surprising because these variables were assessed rather roughly and it was too short after termination of treatment for the manifestation of late effects of treatment. Besides, the limited impact of medical variables on HRQoL has been found in many studies among survivors of childhood cancer (9;28). Undoubtedly, there are other psychosocial variables than the coping variables we assessed in the present study that affect survivors' HRQoL and anxiety, for example family functioning (29-31) and pre-cancer functioning of the survivor.

Limitations and implications

The present study has several limitations that are common in psychosocial research among children. Longitudinal research on children is sparse because different age groups need different, age-specific questionnaires resulting in small sample size. Low power due to small sample size could have contributed to the fact that few variables were found to be predictive of HRQoL and anxiety. Furthermore, because pre-selection of variables for the final analyses was necessary, several medical variables were excluded in the final models which could have led to underestimation of the explained variance of the models. Another disadvantage of the small sample size was that comparison of survivors' anxiety with that of the norm was not possible. In addition, survivors of CNS-cancer were not included because these children are underrepresented in the longitudinal VOLG-study for logistical reasons.

Despite the small sample size at the last measurement occasion, longitudinal analyses were possible because linear mixed models analyses incorporate all available data into analysis, including data from survivors that missed one or more measurement occasion. Although only 27 observations were available at M5, these observations could still be used to increase the precision of the parameter estimates that are not specific to M5, such as the fixed effects of coping. The attrition of survivors who reached the age of 16 (because of the limited age

range of the TACQOL) did probably not bias the results seriously. Firstly, participants did not differ from the non-participants at the several measurement occasions with respect to their outcome scores at T1. Secondly, the impact of age and medical variables on HRQoL and anxiety was limited in the present study.

Another limitation concerns the outcomes of the study; HRQoL and anxiety. Of course there are other interesting aspects of survivors' functioning, for instance posttraumatic stress, social functioning and educational achievement. It would be of utmost importance to investigate indicators of social functioning because previous studies revealed that school-aged survivors suffered from clinically significant social anxiety, had less friends and participated less in peer and school activities than controls (32-35). On the contrary, Reiter and colleagues (36) concluded that, two years after diagnosis, survivors did not exhibit more social difficulties than peers.

In conclusion, as a group survivors regained good HRQoL after the end of successful cancer treatment in the run-up to survivorship. No doubt, this is an important finding that speaks well for the resilience of the survivors and their parents. However, there is no reason to lean back because of the known (long-term) late effects of many treatments (37;38), whose relationship with survivors' well-being is not clear yet. Though there is little evidence of serious maladjustment, research on more specific paediatric psycho-oncology outcomes demonstrated that there is consistently a group of children and family members (estimated 25-30%) who do not cope well with the cancer or who have personal, family, and social difficulties (39). The development of sensitive, cancer-related instruments is of utmost importance to be used in psychosocial screening, since few clear medical risk factors for worse psychosocial functioning could be traced until now (39). It is satisfying that monitoring and screening survivors have become standard aftercare in many hospitals in the last decade. Apart from physical and psychosocial screening, the standard aftercare should preferably include education and counselling directed at both survivors and their parents. Providing psychosocial information on the effects of the disease and treatment, and assisting parents in treating the survivors as normally as possible could prevent late psychosocial problems by enhancing re-entry into normal life.

Giving attention to the cognitive coping strategies of the survivors might be useful when a survivor experiences psychosocial problems. Although the longitudinal analyses in the present study yielded stronger evidence of the presence of causal correlations than do traditional analytic procedures, they can not offer definitive proof of causality between coping and outcomes. This requires an intervention study intended to influence coping. There is evidence of effectiveness for psycho-educational interventions for children with a chronic disease incorporating cognitive-behavioural techniques (40-43). Further steps in the direction of evidence-based interventions for survivors will be important in the years to come.

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REFERENCES

(1) Stiller CA, Draper GJ. The epidemiology of cancer in children. In: Voûte PA, Barret A, Stevens MCG, Caron HN, eds. Cancer in children: clinical management. fifth edition ed. Oxford: Oxford University Press, 2005. p. 1-16.

(2) Magnani C, Pastore G, Coebergh J, Viscomi S, Spix C, Steliarova-Foucher E. Trends in survival after childhood cancer in Europe, 1978-1997: Report from the Automated Childhood Cancer Information system project (AGGIS). Eur J Cancer 2006;42(13):1981-2005.

(3) Eiser C. Children with cancer. The quality of life. Mahwah, New Jersey, Londen: Lawrence Erlbaum Associates Publishers, 2004.

(4) Sawyer M, Antoniou G, Toogood I, Rice M, Baghurst P. Childhood cancer: a 4-year prospective study of the psychological adjustment of children and parents. J Pediatr Hematol Oncol 2000;22(3):214-20.

(5) Kazak AE, Christakis D, Alderfer M, Coiro MJ. Young adolescent cancer survivors and their parents: adjustment, learning problems, and gender. Journal of Family Psychology 1994;8(1):74-84.

(6) Radcliffe J, Bennett D, Kazak AE, Foley B, Phillips PC. Adjustment in childhood brain tumor survival: child, mother and teacher report. J Pediatr Psychol 1996;21(4):529-39.

(7) Grootenhuis MA, Last BF. Children with cancer with different survival perspectives: defensiveness, control strategies, and psychological adjustment. Psychooncology 2001;10:305-14.

(8) Stam H, Grootenhuis MA, Brons PPT, Caron HN, Last BF. Health-related Quality of life in children and emotional reactions of parents following completion of cancer treatment. Pediatr Blood Cancer 2006;47:312-9.

(9) Stam H, Grootenhuis MA, Last BF. Social and emotional adjustment in young survivors of childhood cancer (review). Support Care Cancer 2001;9:489-513.

(10) Last BF, Grootenhuis MA. Emotions, coping and the need for support in families of children with cancer: a model for psychosocial care. Patient Educ Couns 1998;33(2):169-79.

(11) Lazarus RS, Folkman S. Stress, appraisal, and coping. New York: Springer Publishing Company, 1984.

(12) Grootenhuis MA, Last BF, de Graaf-Nijkerk JH, van der Wel M. Secondary control strategies used by parents of children with cancer. Psychooncology 1996;5(2):91-102.

(13) Madan-Swain A, Brown RT, Sexson SB, Baldwin K, Pais R, Ragab A. Adolescent cancer survivors: psychosocial and familial adaptation. Psychosomatics 1994;35(5):453-9.

(14) Bauld C, Anderson V, Arnold J. Psychosocial aspects of adolescent cancer survival. J Paediatr Child Health 1998;34:120-6.

(15) Landolt MA, Vollrath M, Ribi K. Predictors of coping strategy selection in paediatric patients. Acta Paediatr 2002;91(9):954-60.

(16) Phipps S, Steele RG, Hall K, Leigh L. Repressive adaptation in children with cancer: a replication and extension. Health Psychol 2001;20(6):445-51.

(17) Verrips GHW, Vogels TGC, Koopman HM, Theunissen NCM, Kamphuis RP, Fekkes M, et al. Measuring health-related quality of life in a child population. Eur J Publ Health 1999;9(114):119.

(18) Vogels T, Bruil J, Koopman H, Fekkes M, Verrips GHW. TACQOL CF 12-15 Manual. Leiden: TNO Prevention and Health; 2004.

(19) Vogels AGC, Verrips GHW, Fekkes M, Kamphuis RP, Koopman HM, Theunissen NCM, et al. Measuring health-related quality of life in children: the development of the TACQOL parent form. Qual Life Res 1998;7:457-69.

(20) Verrips GHW, Vogels TGC, Verloove-Vanhorick SP, Fekkes M, Koopman HM, Kamphuis RP, et al. Health-Related Quality of Life measure for children - the TACQOL. Journal of Applied Therapeutics 1998;1(357):360.

(21) Ware JE, Kosinski M. Interpreting SF-36 summary health measures: a response. Qual Life Res 2001;10:405-13.

(22) Bakker FC, van Wieringen PCW, van der Ploeg HM, Spielberger CD. Handleiding bij de Zelf-beoordelings Vragenlijst voor Kinderen (ZBV-K). Een Nederlandse bewerking van de State-Trait-Anxiety Inventory for Children (STAI-C) van Spielberger et al. [Manual of the Dutch version of the STAI-C]. Lisse: Swets Test Services; 1989.

(23) Rothbaum F, Weisz JR, Snyder SS. Changing the world and changing the self: a two-process model of perceived control. J Pers Soc Psychol 1982;42:5-37.

(24) Loonen HJ, Grootenhuis MA, Last BF, Koopman HM, Derkx HHF. Quality of life in peadiatric inflammatory bowel disease measured by a generic and disease-specific questionnaire. Acta Paediatr 2002;91:341-54.

(25) Snijders FAB, Bosker RJ. Multilevel Analysis. An introduction to basic and advanced multilevel modeling. London: SAGE Publications Ltd, 2004.

(26) Cohen J. Statistical power analysis for the behavioral sciences. New York: Academy Press, 1988.

(27) Sprangers MAG, Schwartz CE. Integrating response shift into health-related quality of life research: a theoretical model. Soc Sci Med 1999;48:1507-15.

(28) Langeveld NE, Stam H, Grootenhuis MA, Last BF. Quality of life in young adult survivors of childhood cancer (review). Support Care Cancer 2002;10:579-600.

(29) Kazak AE, Barakat LP, Meeske K, Christakis D, Meadows AT, Penati B, et al. Posttraumatic stress, family functioning, and social support in survivors of childhood leukemia and their mothers and fathers. J Consult Clin Psychol 1997;65(1):120-9.

(30) Lesko LM. Surviving hematological malignancies: stress responses and predicting psychological adjustment. The Biology of Hematopoiesis.New York: Wiley-Liss. Inc, 1990. p. 423-37.

(31) Rait DS, Ostroff JS, Smith K, Cella DF, Tan C, Lesko LM. Lives in balance: perceived family functioning and the psychosocial adjustment of adolescent cancer survivors. Fam Process 1992;31:383-97.

(32) Bessell AG. Children surviving cancer: psychosocial adjustment, quality of life, and school experiences. Except Child 2001;67(3):345-59.

(33) Pendley JS, Dahlquist LM, Dreyer Z. Body image and psychosocial adjustment in adolescent cancer survivors. J Pediatr Psychol 1997;22(1):29-43.

(34) Spirito A, Stark LJ, Cobiella C, Drigan R, Androkites A, Hewett K. Social adjustment of children succesfully treated for cancer. J Pediatr Psychol 1990;15(3):359-71.

(35) Stam H, Grootenhuis MA, Last BF. The course of life of survivors of childhood cancer. Psychooncology 2005;14:227-38.

(36) Reiter-Purtill J, Vannatta K, Gerhardt CA, Correll J, Noll RB. A controlled longitudinal study of social functioning of children who completed treatment of cancer. J Pediatr Hematol Oncol 2003;25(6):467-73.

(37) Geenen MM, Cardous-Ubbink MC, Kremer LCM, van den Bos C, van der Pal HJH, Heinen RC, et al. Medical assessment of adverse health outcomes in long-term survivors of childhood cancer. JAMA 2007;(in press).

(38) Oeffinger KC, Mertens AC, Sklar CA, Kawashima MS, Hudson MM, Meadows AT, et al. Chronic health conditions in adult survivors of childhood cancer. N Eng J Med 2006;355(15):1572-82.

(39) Patenaude AF, Kupst MJ. Psychosocial functioning in pediatric cancer. J Pediatr Psychol 2005;30(1):9-27.

(40) Barlow JH, Ellard DR. Psycho-educational interventions for children with chronic disease, parents and siblings: an overview of the research evidence based. Child: Care, Health & Development 2004;30(6):637-45.

(41) Plante WA, Lobato D, Engel R. Review of group interventions for pediatric chronic conditions. J Pediatr Psychol 2001;26(7):435-53.

(42) Vannatta K, Gartstein MA, Short A, Noll RB. A controlled study of peer relationships of children surviving brain tumors: teacher, peer, and self ratings. J Pediatr Psychol 1998;23(5):279-87.

(43) Last BF, Stam H, Onland-van Nieuwenhuizen A-M, Grootenhuis MA. Positive effects of a psycho-educational group intervention for children with a chronic disease: first results. Patient Educ Couns 2007;65:101-12.

(44) Vogels T, Verrips GHW, Koopman HM, Theunissen NCM, Fekkes M, Kamphuis RP. TACQOL Manual. Parent Form and Child Form 6-11 years. Leiden: Leiden Center for Child Health and Pediatric LUMC-TNO; 2004.

Chapter 6

Emotional functioning of parents of children with cancer: the first five years of continuous remission after the end of treatment

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ABSTRACT

Objectives The aim of this study was to investigate parental emotional functioning during the first five years of continuous remission after the end of their child's treatment and to identify predictors of parental emotional functioning.

Methods Psychological distress and situation-specific emotional reactions were assessed in 122 mothers and 109 fathers from 130 families. Longitudinal mixed models analyses were performed to investigate to what extent generic and disease-related coping, family functioning and social support were predictive of parental emotional functioning over time.

Results Initial elevated levels of distress, disease-related feelings of uncertainty and helplessness returned to normal levels during the first two years after the end of treatment. Being more optimistic about the further course of the child's disease (predictive control) was correlated with lower psychological distress and less negative disease-related feelings, while more passive reaction patterns were correlated with higher psychological distress and more negative disease-related feelings.

Conclusions Though in general the parents of children with successfully treated cancer showed adequate emotional resilience, support for these parents should not stop when treatment ends. Parents in need of help can be identified on the basis of their coping abilities.

INTRODUCTION

As a result of advances in the treatment of childhood cancer, the number of successfully treated patients has increased enormously in the last decades. The overall 5-years survival rate for children diagnosed with cancer in Europe is currently more than 70% compared with 30% in the 1960's [1; 2]. Childhood cancer is a dramatic event that affects the daily life and emotional well-being of all family members. The results of longitudinal studies showed that, although many parents adjust well to the paediatric cancer experience, a considerable percentage of parents continue to suffer problems such as psychological distress, anxiety and post-traumatic-stress symptoms after termination of their child's cancer treatment [3-7]. More affirmative reactions to the cancer experience have also been observed, however. Cognitive strategies used to cope with stressful events can generate positive affect, for instance labelling ordinary events with positive meaning and appraising stressful situations as challenges rather than burdens, which can generate feelings of mastery and control [8; 9].

The authors recently found that parents experienced considerably more emotional distress than the general Dutch population two months after end of their child's successful treatment for cancer [9]. This is not surprising, since coming off therapy is one of the major transitions in care in the practice of paediatric oncology [10]. It is a very difficult and anxious time for both patients and parents[11; 12], while there is a tendency for social and emotional support to decrease when treatment ends [13], even though the family is just starting to come to terms with what has happened.

In the present study, a process-oriented approach was applied to investigate parental emotional adjustment to childhood cancer. We presume that parental emotional functioning is the outcome of a process over time that is influenced by situational characteristics, such as demographic and medical variables, and by psychosocial factors such as coping, social support and family functioning. These psychosocial factors are important because those can be approached in intervention.

Previous research revealed highly diverse demographic and medical variables that were predictive of parental maladjustment to the cancer experience [14], among others: being a mother, low socio-economic status, recurrence of the disease in the child and worse health status of the child [5; 15-18].

The ways in which parents cope with the consequences of childhood cancer, can be regarded as an important factor in their adaptation to the cancer experience. According to the model of stress and coping developed by Lazarus and Folkman [19], coping consists of actions, behaviours and thoughts aimed at dealing with the demands of events and situations that are appraised as stressful. In the context of coping with cancer, Grootenhuis et al. [20] found the following cognitive control strategies to be relevant in the medical setting: expectations of the further course of the disease (predictive coping), reliance on powerful others such as doctors (vicarious control), attempts to influence the chance-determined outcome, such as hoping for a miracle or wishful thinking (illusory control), and searching for information (interpretative control). Previous research revealed that parents who were optimistic about the further course of their child's disease reported fewer emotional problems [16]. Others reported that higher scores for the 'social support-seeking' generic coping style resulted in lower distress levels one year after the diagnosis of cancer [17].

Several studies indicate that social support can protect parents from the stress caused by their child's disease and treatment [13; 21-23]. In families of a child with cancer, higher scores on family cohesion and adaptability were found to be correlated with lower parental anxiety and fewer parental post-traumatic-stress symptoms [22]. In addition, Sloper et al. [24] found that stronger family cohesion was associated with lower distress levels in mothers.

The first few years following the end of treatment are considered as an important phase in the adjustment to the cancer experience. A longitudinal study was designed in order to gain insight into the process of parental adjustment during this phase. The main research questions were: (1) How do mothers and fathers adjust emotionally during the first five years of continuous remission following the completion of treatment for childhood cancer? (2) To what extent are coping, family functioning and social support associated with parental emotional functioning during the first five years of continuous remission following the completion of treatment for childhood cancer? The associations between the psychosocial variables (independent variables) and parental emotional outcomes (dependent variables) were controlled for demographic and medical variables.

METHODS

Procedure

The results presented here concern the longitudinal VOLG-study (*Vragenlijsten kinder-Oncologie Latere Gevolgen* = Questionnaires on childhood cancer late sequelae), a Dutch study on the late psychosocial consequences of cancer in childhood, which started in 2000 and ended in 2006. Patients and their parents were recruited from two Dutch university hospitals, the Emma Children's Hospital at the Academic Medical Center in Amsterdam (from March 2000 until the end of 2002) and the Radboud University Nijmegen Medical Center (from June 2002 until the end of 2002). The Medical Ethics Committee of the hospitals have approved the study protocol.

All consecutive patients who met the inclusion criteria during these periods were invited to participate in the VOLG-study. The inclusion criteria were: (1) age of the patients 1-18 years, (2) complete remission, (3) end of successful treatment at most two months before, and (4) being able to complete Dutch questionnaires.

Parents were informed about the VOLG study by letter. Once informed consent had been obtained, the parents were telephoned and an appointment was made to fill in the questionnaires at the hospital or at home. The parents completed the questionnaires, four to six times, depending on the year of inclusion. The assessments took place approximately two months (M1), one year (M2), two years (M3), three years (M4), four years (M5) and five years (M6) after the end of successful treatment. The data for parents whose child relapsed were excluded from analysis from the moment of the relapse.

Measures

Dependent variables: parental emotional outcomes

Parental psychological distress was measured using the *General Health Questionnaire-30 (GHQ-30)* [25; 26]. The raw total scale score can be used as an overall index of psychological

distress, where higher scores indicate greater distress. According to Goldberg et al. [25] scores of 5 or more indicate clinically elevated levels of psychological distress. The validity of the 30-item version is well documented and its internal consistency is highly satisfactory [25; 26].

Parental situation-specific emotional reactions were assessed using the *Situation-Specific Emotional Reaction Questionnaire* (SSERQ) developed at the Psychosocial Department of the Emma Children's Hospital/AMC [27]. It consists of four scales, which describe feelings that can be considered situation-specific for parents of children with cancer, during and after treatment [27], namely disease-related feelings of loneliness, helplessness, uncertainty and positive feelings. The higher the scores the more often parents experienced the emotional reactions in question. The validity and internal consistency is satisfactory [27; 28].

Independent variables: situational characteristics

Medical data were obtained from the patient's medical record. The prognosis was based on the survival chances at diagnosis as rated by each patient's oncologist, viz. <25, 25-75 or >75%. After the end of treatment (M1), the parents were asked to rate their perception of the intensiveness of their child's treatment on a Visual Analogue Scale, from 'totally non-intensive' (0, left end of line) to 'very intensive' (10, right end of line). They were also asked to assess the visible consequences of the disease. Their answers were dichotomized to 'presence' or 'absence' of visible consequences.

Important family events during the past year were scored by the parents on a list of 19 such events, including the birth of a child, parental divorce, moving, death of a family member or friend, decline in financial means, change of school, and change of job. The total score of important family events was dichotomized to 'less than two' and 'two or more'.

Independent variables: psychosocial factors

Generic coping was measured with the *Utrecht Coping List* (UCL) [29], a questionnaire about coping with stressful or problematic situations. The UCL covers seven coping styles: active problem-focusing, palliative reaction pattern, avoidance behavior, seeking social support, passive reaction pattern, expression of emotions, comforting cognitions. A higher scale score means more use of the coping style. The internal consistency and validity are satisfactory [29; 30].

Disease-related cognitive coping was assessed using the *Cognitive Control Strategies Scale* for Parents (CCSS-PF). The instrument, based on the model of Rothbaum et al. [31], was developed at the Psychosocial Department of the Emma Children's Hospital/AMC [20]. It assesses the extent to which respondents try to gain sense of control over the illness by using four cognitive coping strategies: predictive control (being optimistic about the course of the disease), vicarious control (attributing power to medical-care givers and treatment), interpretative control (searching for information in order to better understand emotional reactions and to gain insight into the situation), and illusory control (attempts to influence the chance-determined outcome). Higher scores represent a stronger reliance upon the control strategy in question. The questionnaire proved to be useful, valid and reliable in the context of cancer and Inflammatory Bowel Disease [20; 28; 32-34] }.

Family functioning was measured with the Dutch version of the *Family Adaptability and Cohesion Evaluation Scales* (FACES) [35], developed by Olson and colleagues [36-38]. The

Adaptability scale indicates the extent to which a family adapts its power structure, role definitions, and rules to meet internal and external demands. The Cohesion scale indicates the degree of mutual connectedness between family members. Higher scale scores mean greater adaptability and cohesion. The validity and internal consistency of the Dutch version are good [35].

The amount of *social support* the respondent indicated that he received from the social network was assessed using the *Social Support Questionnaire for Transactions* (SSQT), developed by Suurmeijer and colleagues [39-41]. The SSQT measures the frequency of supportive interactions on seven different scales, together with a total score. The psychometric properties of the SSQT have proved to be good [39; 41]. The SSQT total score was used in the present study.

Statistical analyses

The Statistical Package for Social Sciences (SPSS), Windows version 12.0, was used for all analyses. Missing values were handled according to the guidelines given in the manuals for the relevant questionnaires and, after that, through the Expectation-Maximization estimation method [42]. Analyses were carried out for mothers and fathers separately.

In order to describe parental emotional functioning over time, mean scores of psychological distress (*GHQ-30*) and situation-specific emotional reactions (*SSERQ)* were depicted in Figure 1 and 2. For each outcome, we fitted a linear mixed model with a random intercept representing the baseline at the first measurement occasion and fixed slopes representing the deviations from baseline at the other measurement occasions. In addition, parental levels of psychological distress were compared with norm data of the general Dutch population at each measurement occasion, using one-sample t-tests and binomial tests at each measurement occasion.

Linear mixed model analysis was further carried out to examine to what extent psychosocial factors over time were predictive of parental emotional functioning over time, while controlling for demographic and medical characteristics. Measurement occasions were treated as nested within respondents. The major advantage of this method is that all available data are incorporated into the analysis, including data from parents who missed one or more measurement occasions. Efficient estimates can be obtained through maximum likelihood estimation procedures if dropout is random (conditionally on the non-missing data)[43]. Hence, changes in the numbers of subjects from occasion to occasion do not harm the analysis, other than that the statistical power to find deviations from baseline decreases with higher attrition.

To facilitate interpretation of regression coefficients, all continuous scores on dependent (outcome) variables and independent (predictor) variables were transformed into standard normal scores, expressing deviations from the mean at M1. We followed Cohen [44] in considering standardized regression coefficients of 0.1 as small, 0.3 as medium and 0.5 as large. For binary coded variables, regression coefficients of 0.2 can be considered small, 0.5 medium and 0.8 large.

Measurement occasions were treated as fixed because growth curve models did not fit the data. The intercept was considered random with its mean fixed at the standardized mean outcome at M1, thus taking the outcome at M1 as reference point. In this way, parameter estimates for M2 through M6 can be interpreted as deviations from baseline (M1). The deviations were treated as fixed parameters as indicated by Akaike's information criterion.

Models were fitted for each of the five outcomes (parental psychological distress and the four situation-specific emotional reactions). Because of the large number of predictor variables, pre-selection was necessary. The initial model consisted of the random intercept (M1) and the fixed parameters for measurement occasions M2 to M6. Predictor variables were subsequently entered in four steps into the initial model, if significant at least at 0.20: (1) demographic and medical variables, (2) disease-related coping, (3) generic coping, (4) family functioning and social support. Once selected, the variables remained in the model, even if they turned out to be non-significant in later steps. The final models thus consisted of the random intercept (M1) and the fixed regression coefficients for M2 to M6, completed with the predictor variables that were selected in the stepwise procedure. For one outcome, positive feelings, there appeared to be no intercept variance. The final model for this outcome, both for mothers and fathers, was therefore fitted with a fixed intercept. Percentages of total explained variance were calculated after each step.

For each model, we checked whether the longitudinal covariance structure was best described by compound symmetry or by an autoregressive structure, with reference to Akaike's information criterion. Compound symmetry appeared to give the best fit for all models except that for parental psychological distress, where an autoregressive structure was more appropriate.

We checked whether first-order interaction effects of measurement occasion with medical variables, disease-related coping and social support should be added to the model. To prevent too many findings occurring by chance, these tests were carried out at a Bonferroni adjusted level of significance. The conclusion under these conditions was that none of the first-order interaction effects considered needed to be added to the model.

RESULTS

Participants

A total of 164 consecutive childhood cancer patients who completed treatment successfully at most two months before, and their parents, were invited to participate in the longitudinal part of the VOLG-study; 150 patients from The Emma Children's Hospital AMC and 14 patients from the Radboud University Nijmegen Medical Center. The response rate was 81.7 per cent (N=134). The 30 families who did not participate, did not differ from participating families with respect to demographic and medical variables ($p<0.1$ at t-tests or χ^2-tests).

Data about emotional functioning of mothers and/or fathers from 130 (of the 134) families were available: 129[1] families at M1 (99.2%), 109 at M2 (83.4%), 105 at M3 (80.8), 97 (74.7%) at M4, 55 at M5 (42.3%) and 25 (19.2%) at M6. Dropout because of non-response was 8.5% (N=11). Furthermore, the data for parents whose children had relapsed were excluded from analysis from the moment of the relapse (N=25, 19.2%). Hence, it depends on the moment of relapse how many measurement occasions were included. Finally, data at M5 and M6 were not available in, respectively, 57 (43.8%) and 91 families (70%) because of the finite follow-up period of the VOLG-study.

1 Parental data from one family were not available at M1. Data at subsequent measurement occasions were included.

Only a few significant differences were found between the parents with data until M6 ('complete data') and the parents whose data did not include M6 ('incomplete data'). Firstly, the parents with incomplete data were on average one to two years younger than the parents with complete data. Secondly, incomplete data include fewer parents of patients with a good prognosis (survival chance at diagnosis > 75%) than complete data. This is not surprising because families were excluded from analysis from the moment of a relapse. No other differences in demographic and medical variables were found at a significance level of 0.10. We also compared mean parental outcomes at M1 for parents with incomplete data with that of parents with complete data, and found no difference. Characteristics of patients and parents are presented in Table 1.

Table 1: Characteristics of the patients and their parents at M1 (2 months since end of treatment)

	N	**M**	**SD**	**Range**
Parents				
Age mothers (years)	122	37.9	5.0	
Age fathers (years)	109	39.7	5.1	
Patients				
Age at study (years)	129	8.0	4.4	1.1-18.2
Age at diagnosis (years)	129	6.8	4.5	0.3-17.2
Time since diagnosis (months)	129	13.7	8.4	2.0-29.7
Duration of treatment (months)	129	11.5	8.4	0.6-26.0
	%		**N**	
Age category (years)				
1-5	41.9		54	
6-11	34.1		44	
12-15	20.9		27	
≥ 16	3.1		4	
Gender				
female	41.9		54	
male	58.1		75	
Diagnosis				
Leukemia/lymphoma	48.1		62	
Solid tumor	47.3		61	
Brain tumor	4.7		6	
Prognosis				
< 25%	5.4		7	
25 – 75%	39.5		51	
> 75%	55.0		71	
Treatment [1]				
Chemotherapy	95.3		123	
Surgery	46.5		60	
Radiotherapy	18.6		24	
Autologous bone marrow transplantation	2.3		3	
Other	2.3		3	

[1]More than one answer was possible per patient.
NOTE Number of mothers and fathers at M2-M6: Mothers 103 (M2), 98 (M3), 92 (M4), 52 (M5), 24 (M6) Fathers 91 (M2), 87 (M3), 78 (M4), 46 (M5), 19 (M6)

Emotional functioning over time

Psychological distress

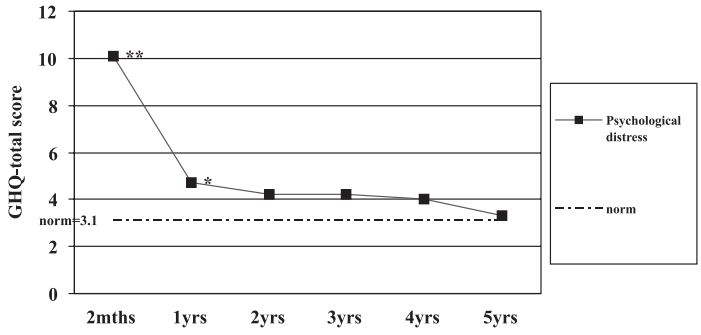
Two months after the end of treatment, about two-third of the mothers (72%) and fathers (60%) reported clinically elevated levels of psychological distress, which was much higher than the percentage in the general population (24% and 22% for females and males respectively). One year after the end of treatment, elevated levels were found in 34% of the mothers and 36% of the fathers, still significantly different from the norm. From two years after treatment, mothers and fathers reported normal levels of psychological distress.

Elevated levels of psychological distress were also expressed by the mean GHQ-total scores (Figure 1). Two months after the end of successful treatment, mothers as well as fathers had a significantly higher mean total score than the norm: $T(120)=10.3$, $p<0.0001$ and $T(107)=7.5$, $p<0.001$, for mothers and fathers respectively. The distress scores decreased over time. Both mothers and fathers reached a normal level of psychological distress at two years. At one year, their scores were still higher than the norm: $T(102)=2.5$, $p<0.05$ and $T(90)=2.4$, $p<0.05$, for mothers and fathers respectively.

Situation-specific emotional reactions

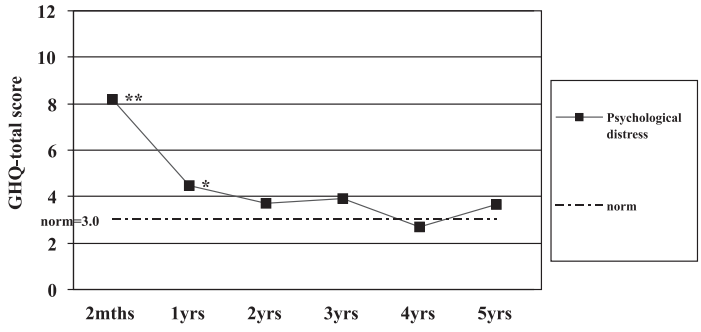
The frequency of disease-related feelings of loneliness ($p<0.05$), helplessness ($p<0.001$) and uncertainty ($p<0.001$) decreased significantly in mothers during the first year after the end of

Figure 1a: Psychological distress (GHQ-total scores) in mothers over measurements occasions, compared with the norm[1].



* GHQ-total score differed significantly from the norm at 0.05
** GHQ-total score differed significantly from the norm at 0.001
[1] General Dutch population (37)

Figure 1b: Psychological distress (GHQ-total scores) in fathers over measurements occasions, compared with the norm[1].



* GHQ-total score differed significantly from the norm at 0.05
** GHQ-total score differed significantly from the norm at 0.001
[1] General Dutch population (37)

treatment (M2), and remained low at subsequent measurement occasions. The frequency of disease-related positive feelings was constant over time (Figure 2).

The frequency of feelings of helplessness ($p<0.001$) and uncertainty ($p<0.001$) decreased significantly also in fathers during the first year after the end of treatment (M2), and remained low at subsequent measurement occasions. The frequency of positive feelings and feelings of loneliness was stable over time, with the exception of M4, where fathers reported fewer positive feelings than at M1 ($p<0.05$), and M5, where they reported fewer feelings of loneliness compared to M1 ($p<0.01$).

Predictors of emotional functioning

The fixed effects derived from the longitudinal mixed models analyses of parental emotional functioning are shown in Table 2 (mothers) and Table 3 (fathers), as well as the total explained variance after each step in the analysis.

Parental emotional functioning was explained well by the longitudinal mixed models. The total explained variance was more than 40%, except for positive feelings. In general, the amount of variance explained by the medical effects was much smaller than that explained by coping. Disease-related feelings of uncertainty were explained particularly well by coping, 42.9 and 55.1% in mothers and fathers respectively. It is notable that – apart from the contribution of the time of measurement – parental feelings of helplessness were explained

Figure 2a: Situation-specific emotional reactions (SSERQ) in mothers over measurements occasions.
* 1 = never 2 = sometimes 3 = often 4 = almost all the time

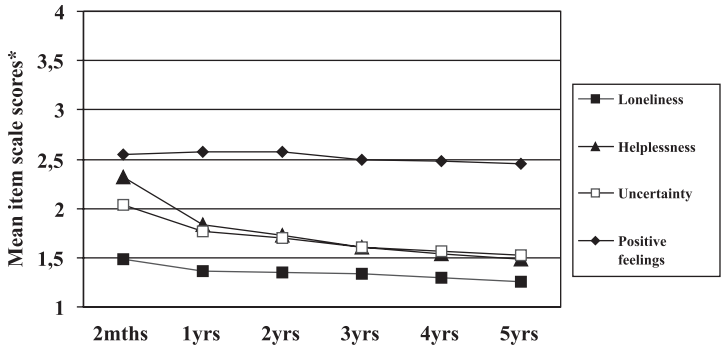
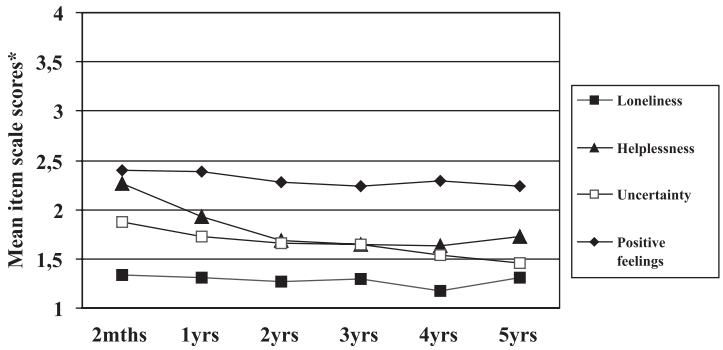


Figure 2b: Situation-specific emotional reactions (SSERQ) in fathers over measurements occasions.
* 1 = never 2 = sometimes 3 = often 4 = almost all the time



mainly by disease-related coping. Positive feelings, on the other hand, were explained much more by generic coping than by disease-related coping.

Apart from that, most fixed effects were small [44]. Medium-sized effects were found for the effect of predictive control (disease-related coping) and passive reaction pattern (generic coping). The predictors of emotional functioning in both mother and fathers are presented in greater detail in Table 2 and Table 3, and are described below.

Psychological distress

Both mothers and fathers reported that longer duration of treatment and greater optimism about the further course of the disease (predictive control) were associated with lower levels of psychological distress. Having a more passive reaction pattern was associated with higher levels of distress. In mothers, we also found that older age and stronger family cohesion was associated with lower levels of distress, while mothers who reported the occurrence of two or more important family events during the past year and mothers who perceived treatment as being more intensive had higher levels of distress. Fathers who had more palliative reaction patterns experienced lower levels of distress.

Situation-specific emotional reactions

More use of predictive control strategies was correlated with less disease-related *loneliness* in both mothers and fathers, while higher scores on passive reaction patterns and family adaptability were related to more loneliness. In addition, mothers who used more illusory control strategies reported more loneliness, while mothers who reported higher scores on family cohesion experienced less loneliness. Fathers who reported less supportive interactions (social support) experienced more loneliness.

If the children did not exhibit visible consequences of the disease and treatment, their mothers and fathers reported less disease-related feelings of *helplessness*. Predictive control in mothers and fathers was also associated with less helplessness. Higher scores on illusory control, palliative and passive reaction patterns were related to greater feelings of helplessness in both mothers and fathers, as were higher scores on interpretative control, family cohesion and adaptability in fathers.

Mothers and fathers who used more predictive control strategies reported less disease-related feelings of *uncertainty*, while higher scores on palliative and passive reaction patterns and family adaptability were associated with more uncertainty. In mothers, we also found that the use of more illusory control strategies and higher scores on family adaptability were associated with more uncertainty, while older age was associated with less uncertainty. If the children did not show visible consequences of the disease and treatment, the fathers reported less uncertainty. In addition, more active problem focusing was associated with less uncertainty in fathers.

Disease-related *positive feelings* were positively correlated with active problem focusing and comforting cognitions, in both mothers and fathers. In addition, illusory control was positively correlated with positive feelings in mothers, and mothers who had reported more family cohesion and the occurrence of two or more important family events during the past year experienced more positive feelings. Fathers who perceived the treatment as being more intensive, fathers who reported more supportive interactions and fathers who had

more palliative reaction patterns experienced more positive feelings. Finally, expression of emotions was associated with less positive feelings in fathers.

Table 2: Parameter estimates for longitudinal regression models of emotional functioning in mothers predicted by measurement occasion, demographic and medical characteristics, coping, family functioning and social support.

	Psychological distress (GHQ)	**Loneliness (SSERQ)**	**Helplessness (SSERQ)**	**Uncertainty (SSERQ)**	**Positive feelings (SSERQ)**
FIXED EFFECTS					
Measurement					
(deviation from end of treatment; M1)					
One year (M2)	- 0.57**	- 0.13	- 0.66**	- 0.34**	0.13
Two years (M3)	- 0.48**	- 0.03	- 0.74**	- 0.33**	0.19*
Three years (M4)	- 0.49**	- 0.06	- 0.95**	- 0.48**	0.08
Four years (M5)	- 0.50**	- 0.08	- 0.99**	- 0.52**	0.44*
Five years (M6)	- 0.36*	0.06	- 1.08**	- 0.42**	0.03
PERCENTAGE OF EXPLAINED VARIANCE BY FIXED EFFECTS	12.8	2.6	21.1	11.4	0.6
Medical and demographic characteristics					
Age mother	- 0.12*	- 0.11	- 0.09	- 0.11*	- 0.07
Age patient			0.09		
Time since end of treatment					
Duration of treatment	- 0.14**				
Leukeamia or lymphoma					
Radio-and chemotherapy					
Prognosis > 75%					
Perceived treatment intensity	0.10*				
No visible consequences			- 0.26**		
PERCENTAGE OF EXPLAINED VARIANCE BY FIXED EFFECTS	19.6	7.1	25.4	14.6	0.8
Disease-related coping (CCSS)					
Predictive control	- 0.17**	- 0.19**	- 0.32**	- 0.33**	
Illusory control		0.14**	0.18**	0.10**	0.19**
Interpretative control			0.06		0.03
Vicarious control					
PERCENTAGE OF EXPLAINED VARIANCE BY FIXED EFFECTS	27.2	24.6	39.6	37.8	8.6
Generic coping (UCL)					
Active problem focusing				- 0.06	0.18**
Expression of emotions			- 0.08		- 0.06
Palliative reaction pattern			0.13**	0.10**	
Passive reaction pattern	0.36**	0.37**	0.20**	0.36**	
Comforting cognitions			0.08		0.21**
Seeking social support		- 0.05			
Avoidance behaviour		0.07			
PERCENTAGE OF EXPLAINED VARIANCE BY FIXED EFFECTS	41.0	40.3	43.4	57.5	27.5

Table 2 continued

	Psychological distress (GHQ)	Loneliness (SSERQ)	Helplessness (SSERQ)	Uncertainty (SSERQ)	Positive feelings (SSERQ)
FIXED EFFECTS					
Family functioning and Social support					
Adaptability (GDS)		0.14**		0.09*	
Cohesion (GDS)	- 0.10*	- 0.09*	0.07		0.09*
Supportive interactions (SSL)		- 0.08			0.10
≥ 2 important family events (last year)	0.16*				0.15*
PERCENTAGE OF EXPLAINED VARIANCE BY FIXED EFFECTS	42.9	42.9	44.1	58.1	30.5
TOTAL NUMBER OF OBSERVATIONS	421	489	480	489	442

* p<0.05, ** p <0.01

DISCUSSION

The first five years of continuous remission after the end of treatment were investigated, in view of the importance of this phase for parental adjustment in the run-up to long-term survivorship of their children with cancer. The present study indicates that on the whole, parents adjust well to the experience of childhood cancer in their family. The findings illustrate that psychosocial variables are stronger indicators of emotional functioning than medical variables.

Parental levels of distress and disease-related negative feelings returned to normal levels in the first two years after the completion of treatment. This finding is not in line with the results of most other studies, in which elevated levels of distress where found during the first years after the end of treatment [3; 4; 6; 22; 27; 45-48]. It should be realized that the favourable outcomes presented in the VOLG-study could not be extrapolated to the parents of children who suffered a relapse. If these parents are included in the analysis, higher levels of psychological distress and more disease-related negative feelings are found. In addition, patients with brain tumours were underrepresented in the longitudinal VOLG-study for logistical reasons.

While the findings in the present study indicate that, on the whole, parents adjusted well over time to the experience of childhood cancer in their family, early identification of parents who are at risk of developing adjustment problems is important so that appropriate support can be offered at an early state. The results of our longitudinal mixed models analysis showed that both disease-related and generic coping and family functioning were predictive of emotional functioning, independent of the impact of demographic and medical factors. These results are discussed in greater detail below, followed by discussion of the limitations and clinical implications of the present study.

With respect to *disease-related cognitive coping*, it can be concluded that the more optimistic the parents were about the further course of the disease (*predictive* control), the less emotional distress and the fewer disease-related negative feelings they reported. Although the present study does not answer the question of causality, it is plausible to suppose that

optimism about the further course of the disease leads to less emotional distress and fewer disease-related feelings of loneliness, uncertainty and helplessness. In other words, being hopeful could protect parents from negative emotions. The protective impact of a positive view on adjustment to stressful events has been previously reported [49; 50] and is in line with previous research on the parents of children with cancer [16].

Table 3: Parameter estimates for longitudinal regression models of emotional functioning in *fathers* predicted by measurement occasion, demographic and medical characteristics, coping, family functioning and social support.

	Psychological distress (GHQ)	**Loneliness (SSERQ)**	**Helplessness (SSERQ)**	**Uncertainty (SSERQ)**	**Positive feelings (SSERQ)**
FIXED EFFECTS					
Measurement (deviation from end of treatment; M1)					
One year (M2)	- 0.38**	0.13	- 0.36**	- 0.11	0.12
Two years (M3)	- 0.41**	0.16	- 0.71**	- 0.09	- 0.10
Three years (M4)	- 0.43**	0.16	- 0.70**	- 0.16	- 0.07
Four years (M5)	- 0.48**	0.03	- 0.69**	- 0.21*	- 0.08
Five years (M6)	- 0.27	0.47**	- 0.36	- 0.22	- 0.22
PERCENTAGE OF EXPLAINED VARIANCE BY FIXED EFFECTS	9.2	1.2	15.5	5.6	1.7
Medical and demographic characteristics					
Age father		- 0.10			
Age patient					
Time since end of treatment					
Duration of treatment	- 0.12**				
Leukeamia or lymphoma					
Radio-and chemotherapy					0.35
Prognosis > 75%					0.30
Perceived treatment intensity			0.01		0.18*
No visible consequences	- 0.10		- 0.28**	- 0.14*	
PERCENTAGE OF EXPLAINED VARIANCE BY FIXED EFFECTS	13.0	3.8	17.6	6.7	4.9
Disease-related coping (CCSS)					
Predictive control	- 0.11**	- 0.14**	- 0.34**	- 0.30**	
Illusory control	0.06		0.18**	0.07	
Interpretative control			0.14**		0.10
Vicarious control					0.06
PERCENTAGE OF EXPLAINED VARIANCE BY FIXED EFFECTS	23.3	18.4	41.1	35.2	9.0
Generic coping (UCL)					
Active problem focusing			- 0.10	- 0.13**	0.21**
Expression of emotions	0.08				- 0.20**
Palliative reaction pattern	- 0.08*		0.10*	0.08*	0.13*
Passive reaction pattern	0.41**	0.33**	0.17**	0.38**	
Comforting cognitions	0.05	0.06			0.12*
Seeking social support					
Avoidance behaviour		0.03			
PERCENTAGE OF EXPLAINED VARIANCE BY FIXED EFFECTS	45.7	39.4	47.6	61.8	19.4

Table 3 continued

	Psychological distress (GHQ)	Loneliness (SSERQ)	Helplessness (SSERQ)	Uncertainty (SSERQ)	Positive feelings (SSERQ)
FIXED EFFECTS					
Family functioning and Social support					
Adaptability (GDS)		0.09*	0.12*	0.09*	
Cohesion (GDS)			0.23**		
Supportive interactions (SSL)		- 0.18**			0.12*
≥ 2 important family events (last year)					
PERCENTAGE OF EXPLAINED VARIANCE BY FIXED EFFECTS	45.7	45.0	51.3	61.8	22.5
TOTAL NUMBER OF OBSERVATIONS	421	426	353	421	357

* p<0.05, ** p <0.01

Illusory control is found to have a negative association with parental emotional functioning, especially in mothers. This assocation was also reported by Grootenhuis et al. [16] and studies on care giving for diseased adults showed also that wishful thinking was negatively associated to adjustment. Once again, we cannot establish causality, but it seems plausible that parents who feel lonely, uncertain and helpless about the disease may come to rely on wishful thinking [51; 52].

Five out of the seven *generic coping* styles were associated with parental emotional functioning. The passive reaction pattern was the strongest predictor of emotional functioning in both mothers and fathers. Goal-oriented parents who faced the situation calmly (active problem focusing) reported better emotional functioning than parents who coped with stress by taking a passive standpoint and allowing themselves to be totally immersed in the problem (passive reaction pattern) and parents who engaged in distracting activities and tried to relax (palliative reaction pattern). These correlates are not surprising, since passive coping is related to the concept of 'learned helplessness' and active coping to feelings of control over events [53]. The findings in the present study agree with those of other investigations of parents of children with cancer [53; 54] and other life-threatening diseases [55; 56].

With regard to *family functioning*, we found a cohesive family structure to be particularly important for mothers. Mothers who reported more family cohesion were less distressed and lonely, and they reported more positive feelings. This finding is not surprising, as many parents mentioned that the experience of childhood cancer led to stronger family bonding [11; 57]. Other studies have indicated that stronger family cohesion is related to lower levels of parental distress 18 months post diagnosis, and to less post-traumatic stress at least one year after the end of successful treatment [3; 22].

Higher levels of family adaptability appeared to be associated with stronger feelings of loneliness, helplessness and uncertainty. In the Circumplex model of marital and family systems, the theoretical framework proposed by Olson, Russell & Sprenkle [58], moderate levels of cohesion and adaptability are considered to be related to the most favourable adjustment outcomes in families faced with stress, whereas extreme levels of adaptation ('chaotic' family systems) and cohesion ('enmeshed' family systems) are related to less adaptive functioning. Inspection of our data, however, did not demonstrate extreme high levels of

adaptability and cohesion in the families under study. Previous studies showed inconsistent results on this point [46; 59-62].

More *supportive interactions* were found to be associated with lower levels of loneliness and more positive feelings. Correlations of social support with psychological distress, helplessness and uncertainty, however, were found in neither fathers nor mothers. Other studies [13; 21; 22] showed positive correlations between parental emotional functioning and social support but these findings concern a shorter period after diagnosis than in the present study.

Limitations and practical implications

Data were as far as possible collected from all parents two months, and one, two and three years after the end of treatment (i.e. at measurement points M1, M2, M3 and M4 respectively). Due to the long inclusion period and the finite follow-up period of the VOLG-study, a considerable proportion of the parents did not complete the questionnaires four and five years after treatment (M5 and M6). As a result, sample sizes were relatively small on these two last occasions. The observations at M5 and M6, however, can be used to increase the precision of the parameter estimates that are not specific to M5 and M6. Our investigations showed that parents with incomplete data did not differ from parents with complete data with respect to their scores on the outcome variables at M1, so that, probably, the incomplete data led to no bias in the results. The small sample sizes at M5 and M6 did however result in lower power, and the scores at M5 and M6 carried less weight than those at previous measurement occasions.

Meaningful conclusions cannot be drawn for the parents of children with brain tumours because these children are underrepresented in the longitudinal VOLG-study. Furthermore, as mentioned above, the generalisability of the results is – on purpose – limited to parents of children who did not suffer a relapse. This is also a strength of this study.

Another strength of this study is that it includes both mothers and fathers, and a large number of psychosocial variables as possible predictors of parental emotional functioning. A disadvantage of the large number of variables chosen was that it was necessary to pre-select variables for the final analyses, though the sample size was fairly large compared with other studies into paediatric cancer.

Another restriction lies in the variables of the research model chosen. Firstly, the present study focused on a limited number of outcomes, namely psychological distress and situation-specific emotional reactions. Other interesting aspects indicative of parental emotional (mal)adjustment, such as post-traumatic stress symptoms, could also be taken into account [6; 22; 46-48]. Secondly, we assessed neither previous parental emotional functioning (such as a history of psychiatric problems), nor socio-economic variables (such as income and employment) – factors that have been shown in previous studies to have an impact on parental functioning [14; 17]. Intrapersonal factors such as personality and temperament may also affect adjustment [63]. These were partly expressed in the personal coping styles investigated in our study.

In conclusion, despite the overall resilience in parents over time found in this study, there are good reasons why support for parents should not stop when treatment ends. Firstly, continued support for families might relieve psychological distress in the first couple of years after the cessation of treatment, and help parents to get back to normal daily life. Secondly,

certain subgroups of parents appeared to be at greater risk of worse emotional malfunction. If parents are still experiencing high levels of distress and disease-related negative feelings of helplessness and uncertainty one to two years after the end of treatment, they may suffer adjustment problems. Particular attention should be paid to parents who are less optimistic about the further course of the disease, and parents who have a passive coping style.

Oncologists could play a part in tracing adjustment problems in parents. If they observe that parents continue to report higher levels of distress than called for by the health of the child, psychosocial support may be appropriate. Screening parents in an early stage would make sense, since we did not find any interaction of time with psychosocial predictor variables, which means that the correlations with the outcome are applicable to each measurement occasion. It is important for care givers to understand emotional and behavioural reactions as outcomes of a coping process, so as to be able to respond to them more appropriately. Providing information on the psychosocial consequences of their child's condition, and helping them to treat their child as normally as possible could prevent late psychosocial problems by enhancing re-entry into normal life.

The results could yield points of departure for interventions aimed at improving parental emotional functioning. In this perspective, we should consider the question of causality and changeability of the psychosocial factors found to be associated with parental emotional functioning. These questions can not be answered definitely, but there were some indications that interventions on coping could improve well-being [64]. The results of a pilot study into reducing distress and improving family functioning by means of cognitive behavioural and family therapy for adolescent survivors and their families (the Surviving Cancer Competently Intervention Program – SCCIP) are promising [65; 66].

Above all, the aftercare for the survivors should also be directed at the parents, in order to be able to support parents optimally and to trace parents at risk of adjustment problems. Increasingly, computer-scored individual measurement of HRQoL is used in clinical practice to inform the physician about the patients HRQoL. Computer-scored measurement of emotional well-being in parents is also recommended.

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REFERENCES

(1) Stiller CA, Draper GJ. The epidemiology of cancer in children. In: Voûte PA, Barret A, Stevens MCG, Caron HN, eds. Cancer in children: clinical management. fifth edition ed. Oxford: Oxford University Press, 2005. p. 1-16.

(2) Magnani C, Pastore G, Coebergh J, Viscomi S, Spix C, Steliarova-Foucher E. Trends in survival after childhood cancer in Europe, 1978-1997: Report from the Automated Childhood Cancer Information system project (AGGIS). Eur J Cancer 2006;42(13):1981-2005.

(3) Sloper P. Predictors of distress in parents of children with cancer: a prospective study. J Pediatr Psychol 2000;25(2):79-91.

(4) Van Dongen-Melman JE, Pruyn JFADG, Koot HM, Hahlen K, Verhulst FC. Late psychosocial consequences for parents of children who survived cancer. J Pediatr Psychol 1995;20:567-86.

(5) Wijnberg-Williams BJ, Kamps WA, Klop EC, Hoekstra-Weebers JEHM. Psychological adjustment of parents of pediatric cancer patients revisited: five years later. Psychooncology 2006;15(1):1-8.

(6) Kazak AE, Alderfer M, Rourke MT, Simms S, Streisand R, Grossman JR. Posttraumatic stress disorder (PTSD) and posttraumatic stress symptoms (PTSS) in families of adolescent childhood cancer survivors. J Pediatr Psychol 2004;29(3):211-9.

(7) Brown RT, Madan-Swain A, Lambert R. Posttraumatic stress symptoms in adolescent survivors of childhood cancer and their mothers. J Trauma Stress 2003;16(4):309-18.

(8) Folkman S. Positive psychological states and coping with severe stress. Soc Sci Med 1997;45(8):1207-21.

(9) Stam H, Grootenhuis MA, Brons PPT, Caron HN, Last BF. Health-related Quality of life in children and emotional reactions of parents following completion of cancer treatment. Pediatr Blood Cancer 2006;47:312-9.

(10) Nagel K, Eves M, Waterhouse L, Alyman C, Posgate S, Jamieson J, et al. The development of an off-therapy needs questionnaire and protocol for surivors of childhood cancer. J Pediatr Oncol Nurs 2002;19(6):229-33.

(11) Quin S. The long-term psychosocial effects of cancer diagnosis and treatment on children and their families. Soc Work Health Care 2004;39:129-49.

(12) Eiser C. Children with cancer. The quality of life. Mahwah, New Jersey, Londen: Lawrence Erlbaum Associates Publishers, 2004.

(13) Hoekstra-Weebers JEHM, Jaspers JPC, Kamps WA, Klip EC. Psychological Adaptation and social support for parents of pediatric cancer patients: a prospective longitudinal study. J Pediatr Psychol 2001;26(4):225-35.

(14) Grootenhuis MA, Last BF. Adjustment and coping by parents of children with cancer: a review of het literature. Support Care Cancer 1997;5:466-84.

(15) Dahlquist LM, Czyzewiski DI, Jones CL. Parents of children with cancer: a longitudinal study of emotional distress, coping style, and marital adjustment two and twenty months after diagnosis. J Pediatr Psychol 1996;21(4):541-54.

(16) Grootenhuis MA, Last BF. Predictors of parental emotional adjustment to childhood cancer. Psychooncology 1997;6:115-28.

(17) Hoekstra-Weebers JEHM, Jaspers JPC, Kamps WA, Klip CE. Risk factors for psychological maladjustment of parents of children with cancer. J Am Acad Child Adolesc Psychiatry 1999;38(12):1526-35.

(18) Van Dongen-Melman JEWM, De Groot A, Van Dongen JJM, Verhulst FC, Hählen K. Cranial irradation is the major cause of learning problems in children treated for leukemia and lymphoma: a comparative study. Leukemia 1997;11:1197-200.

(19) Lazarus RS, Folkman S. Stress, appraisal, and coping. New York: Springer Publishing Company, 1984.

(20) Grootenhuis MA, Last BF, de Graaf-Nijkerk JH, van der Wel M. Secondary control strategies used by parents of children with cancer. Psychooncology 1996;5(2):91-102.

(21) Dockerty JD, Williams SM, McGee R, Skegg DCG. Impact of childhood cancer on the mental health of parents. Med Pediatr Oncol 2000;35:475-83.

(22) Kazak AE, Stuber ML, Barakat LP, Meeske K, Guthrie D, Meadows AT. Predicting posttraumatic stress symptoms in mothers and fathers of survivors of childhood cancers. J Am Acad Child Adolesc Psychiatry 1998;37(8):823-31.

(23) Lindahl Norberg AL, Lindblad F, Boman KK. Support-seeking, perceived support, and anxiety in mothers and fathers after children's cancer treatment. Psychooncology 2006 Apr;15(4):335-43.

(24) Sloper T, Larcombe IJ, Charlton A. Psychosocial adjustment of five-year survivors of childhood cancer. J Cancer Educ 1994;9(3):163-9.

(25) Goldberg DP, Williams P. A user's guide to the General Health Questionnaire. Windsor: NFER-Nelson, 1988.

(26) Koeter MWJ, Ormel J. General Health Questionnaire: The Dutch application. Amsterdam: Swets Test Services, 1991.

(27) Grootenhuis MA, Last BF. Parents' emotional reactions related to different survival perspectives of their children with cancer. Journal of Psychosocial Oncology 1997;15:43-62.

(28) Houtzager BA, Oort FJ, Hoekstra-Weebers JEHM, Caron HN, Grootenhuis MA, Last BF. Coping and family functioning predict longitudinal psychological adaptation of siblings of childhood cancer patients. J Pediatr Psychol 2004;29(8):591-605.

(29) Schreurs PJ, Willige G, Brosschot JF, Tellegen B, Graus GMH. De Utrechtse Coping Lijst: UCL herziene handleiding [The Utrecht Coping List: UCL-Manual]. Lisse, the Netherlands: Swets & Zeitlinger; 1993.

(30) Oldehinkel AJ, Koeter MWJ, Ormel J, Van den Brink W. Omgaan met problematische situaties [Coping with problematic situations]. Gedrag en Gezondheid 1992;20(5):236-44.

(31) Rothbaum F, Weisz JR, Snyder SS. Changing the world and changing the self: a two-process model of perceived control. J Pers Soc Psychol 1982;42:5-37.

(32) Grootenhuis MA, Last BF. Children with cancer with different survival perspectives: defensiveness, control strategies, and psychological adjustment. Psychooncology 2001;10:305-14.

(33) Loonen HJ, Grootenhuis MA, Last BF, Koopman HM, Derkx HHF. Quality of life in peadiatric inflammatory bowel disease measured by a generic and disease-specific questionnaire. Acta Paediatr 2002;91:341-54.

(34) Stam H, Grootenhuis MA, Last BF. Quality of life and coping in young adult survivors of childhood cancer: positive expectations about the further course of the disease were correlated with better quality of life. Psychooncology 2006;15(1):31-43.

(35) Buurmeijer FA, Hermans PC. Gezins Dimensie Schalen - Handleiding [Dutch version of the Family Adaptability and Cohesion Evaluation Scales (FACES)]. Lisse, The Netherlands: Swets & Zeitlinger, 1988.

(36) Olson DH, Bell RQ, Porter J. FACES: Family adaptability and cohesion evaluation scales. St. Paul: Family Social Science, University of Minnesota, 1978.

(37) Olson DH, Portner J, Bell B. FACES II: Family adaptability and cohesion evaluation scales. St. Paul: Family Social Science, University of Minnesota, 1982.

(38) Olson DH, Porter J, Bell B. FACES III: Family adaptability and cohesion evaluation scales. St. Paul: Family Social Science, University of Minnesota, 1985.

(39) Doeglas D, Suurmeijer T, Briancon S, Moum T, Krol B, Bjelle A, et al. An international study on measuring social support: interactions and satisfaction. Soc Sci Med 1996;43(9):1389-97.

(40) Suurmeijer ThPBM, Doeglas DM, Briancon S, Krijnen W, Krol B, Sanderman R, et al. The measurement of social support in the "European research on incapacitating disease and social support": the development of the Social Support Questionnaire for Transactions (SSQT). Soc Sci Med 1995;40:1221-9.

(41) van Sonderen E. Het meten van sociale steun met de Sociale Steun Lijst-Interacties (SSL-i) en Sociale Seun Lijst Discrepanties (SSL-d): een handleiding [Measurement of social support with the Social Support Questionnaire - Interactions and the Social Support Questionnaire - Discrepancies: manual]. Groningen: Noordelijk Centrum voor Gezondheidsvraagstukken. Rijksuniversiteit Groningen, 2004.

(42) SPSS 11.5 Syntax Reference Guide: base system, advanced models, regression models. Chicago, IL: SPSS Inc; 2002.

(43) Snijders FAB, Bosker RJ. Multilevel Analysis. An introduction to basic and advanced multilevel modeling. London: SAGE Publications Ltd, 2004.

(44) Cohen J. Statistical power analysis for the behavioral sciences. New York: Academy Press, 1988.

(45) Boman K, Lindahl A, Björk O. Disease-related distress in parents of children with cancer at various stages after the time of diagnosis. Acta Oncol 2003;42(2):137-46.

(46) Kazak AE, Barakat LP, Meeske K, Christakis D, Meadows AT, Penati B, et al. Posttraumatic stress, family functioning, and social support in survivors of childhood leukemia and their mothers and fathers. J Consult Clin Psychol 1997;65(1):120-9.

(47) Kazak AE. Posttraumatic distress in childhood cancer survivors and their parents. Medical and Pediatric Oncology Supplement 1998;1:60-8.

(48) Kazak AE, Barakat LP, Alderfer M, Rourke MT, Meeske K, Gallagher PR, et al. Posttraumatic stress in survivors of childhood cancer and mothers: development and validation of the Impact of Traumatic Stressors Interview Schedule (ITSIS). J Clin Psychol Med Set 2001;8(4):307-23.

(49) Taylor SE, Brown JD. Illusion and well-being: a social psychological perspective on mental health. Psychol Bull 1988;103(2):193-210.

(50) Taylor SE, Armor DA. Positive illusion and coping with adversity. J Pers 1996;64(4):873-98.

(51) Pakenham KI. Application of a stress and coping model to caregiving in multiple sclerosis. Psychology, Health & Medicine 2001;6(1):13-27.

(52) Pakenham KI, Bursnall S. Relations between social support, appraisal and coping and both positive and negative outcomes for children of a parent with multiple sclerosis and comparisons with children of healthy parents. Clin Rehabil 2006 Aug;20(8):709-23.

(53) Lindahl Norberg A, Lindblad F, Boman KK. Coping strategies in parents of children with cancer. Soc Sci Med 2005;60:965-75.

(54) Hoekstra-Weebers JE, Jaspers JP, Kamps WA, Klip EC. Gender differences in psychologcial adaptation and coping in parents of pediatric cancer patients. Psychooncology 1998;7:26-36.

(55) Thompson RJ, Jr., Gil KM, Burbach DJ, Keith BR, Kinney TR. Psychological adjustment of mothers of children and adolescents with sickle cell disease: the role of stress, coping methods, and family functioning. J Pediatr Psychol 1993 Oct;18(5):549-59.

(56) Thompson RJ, Jr., Gil KM, Gustafson KE, George LK, Keith BR, Spock A, et al. Stability and change in the psychological adjustment of mothers of children and adolescents with cystic fibrosis and sickle cell disease. J Pediatr Psychol 1994 Apr;19(2):171-88.

(57) Greenberg HS, Meadows AT. Psychosocial impact of cancer survival on school-age children and their parents. Journal of Psychosocial Oncology 1991;9(4):43-57.

(58) Olson DH, Russell CS, Sprenkle DD. Circumplex model of marital and family systems: VI. Theoretical Update. Fam Process 1983;22:69-83.

(59) Kazak AE, Meadows AT. Families of young adolescents who have survived cancer: social-emotional adjustment, adaptability, and social support. J Pediatr Psychol 1989;14:175-91.

(60) Madan-Swain A, Brown RT, Sexson SB, Baldwin K, Pais R, Ragab A. Adolescent cancer survivors: psychosocial and familial adaptation. Psychosomatics 1994;35(5):453-9.

(61) Pelcovitz D, Goldenberg LA, Mandel F, Kaplan S, Weinblatt M, Septimus A. Posttraumatic stress disorder and family functioning in adolescent cancer. J Trauma Stress 1998;11(2):205-21.

(62) Rait DS, Ostroff JS, Smith K, Cella DF, Tan C, Lesko LM. Lives in balance: perceived family functioning and the psychosocial adjustment of adolescent cancer survivors. Fam Process 1992;31:383-97.

(63) Wallander JL, Varni JW. Effects of pediatric chronic physical disorders on child and family adjustment. J Child Psychol Psychiatry 1998;39(1):29-46.

(64) de Ridder D, Schreurs K. Developing interventions for chronically ill patients: is coping a helpful concept? Clin Psychol Rev 2001;21(2):205-40.

(65) Kazak AE, Simms S, Barakat L, Hobbie W, Foley B, Golomb V, et al. Surviving Cancer Competently Intervention Program (SCCIP): A cognitive-behavioral and family therapy intervention for adolescent survivors of childhood cancer and their families. Fam Process 1999;38(2):175-91.

(66) Kazak AE. Evidence-based interventions for survivors of childhood cancer and their families. J Pediatr Psychol 2005;30(1):29-39.

Part II

Chapter 7

Quality of life in young adult survivors of childhood cancer (review article)

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ABSTRACT

In recent years the necessity of measuring quality of life in childhood cancer survivors has been stressed. This paper gives an overview of the results of studies into the quality of life (QL) of young adult survivors of childhood cancer and suggest areas for future research.
A literature search of studies published up to 2001 was conducted using the data bases of MEDLINE, CINAHL , EMBASE and PsychINFO.

The review located 30 empirical studies published up to 2001. The results are described in terms of the following quality-of-life dimensions: physical functioning (general health), psychological functioning (overall emotional functioning, depression and anxiety, self-esteem), social functioning (education, employment, insurance, living situation, marital status and family), and sexual functioning. Factors related to survivors' QL are reported: demographics and illness- and treatment related variables. Although the literature yields some inconsistent findings, a number of clear trends can be identified: a) most survivors reported to be in good health, with the exception of some bone tumour survivors; b) most survivors function well psychologically; c) survivors of CNS tumours and survivors of acute lymphoblastic leukaemia (ALL) are at risk for educational deficits; d) job discrimination, difficulties in obtaining work and problems in obtaining health and life insurance's were reported; e) survivors have lower rates of marriage and parenthood; f) survivors worry about their reproductive capacity and/or about future health problems their children might experience as a result of their cancer history.

There is a need for methodological studies that measure QL among survivors of childhood cancer more precisely by taking into account the effects of the severity of the cancer and the long-term impact of different treatments. Additional data are needed to help us understand the needs of survivors and to identify those subgroups of survivors who are at greatest risk for the adverse sequelae of the disease and its treatment.

INTRODUCTION

As a result of more effective treatment, improved supportive care and centralisation of care, the long-term survival rate of childhood cancer patients has risen dramatically during the past few decades. More than 70% of children newly diagnosed with acute lymphocytic leukaemia will be in continuous remissions 5 years following their initial diagnosis, and the majority of these patients are probably cured of their disease. Survival has also increased for children with solid tumours: 93% of children with Hodgkin's disease, 84% of children with Wilms' tumour and 73% of children with non-Hodgkin's lymphoma will be alive 5 years after diagnosis (1).

The same treatments as have enabled long-term survival, however, can also cause potentially debilitating deficits, ranging from disruptions in day-to-day activities to such late effects as second primary cancers (2-4).While numerous long-term physical effects of childhood cancer have been documented, the impact of such sequelae on patients' quality of life (QL) is much less understood. Although a growing number of studies have documented the considerable impact of cancer diagnosis and treatment on QL in short-term survivors, less attention has focused on QL in long-term young adult survivors, partly because the rise in survival rates is relatively recent.

It is evident that long-term effects in young adults may differ from those experienced in childhood or adolescence. New issues may come up that were not of concern earlier on. For example, worries about fertility and health of offspring may not emerge until the survivor has reached a certain age and is in a stable relationship and both partners would really want to have children. Some of the late physical effects of childhood cancer treatment, such as those resulting from the cardiotoxic effects of some chemotherapeutic agents, are only just being identified, and how these sequelae may affect the survivors' QL is not known.

The research on QL in young adult survivors of childhood cancer is reviewed in this paper. The purpose of this article is to give investigators and other persons involved in childhood cancer care an overview of the research that has been conducted in this field. On the basis of the literature, limitations of the studies and methodological difficulties are described. Finally, suggestions for future research are given.

The concept of quality of life

Assessment of QL is complicated by the fact that there is no universally accepted definition for it. In the past, most researchers measured only one dimension, such as physical function, economic concern, or sexual function. More recently, researchers have attempted further definition of QL. The World Health Organization defines QL as "individuals' perceptions of their position in life in the context of the culture and value system in which they live and in relation to their goals, standards, and concerns" (5). The definition includes six broad domains: physical health, psychological state, levels of independence, social relationships, environmental features, and spiritual concerns. The importance of this definition to childhood cancer survivors lies in the inclusion of both emotional and social dimensions of health in addition to physical aspects. While many survivors have no physical evidence of disease and appear to have made full recoveries, others have to come to terms with the chronic, debilitating, or delayed effects of therapy. All remain at risk of the development of late sequelae of the former disease and/

or treatment and of second malignancies. Furthermore, in most cases the life-threatening experience of cancer is never forgotten. In many ways, survival enhances appreciation for life, while at the same time reminding survivors of their vulnerability. The metaphor of the Damocles syndrome illustrates this dichotomy and the way individual survivors interpret this metaphor for life will influence the quality of their survival (6).

METHODS

A literature search of studies published up to 2001 was conducted using the data bases of MEDLINE (National Library of Medicine), CINAHL (Cumulative Index to Nursing and Allied Health Literature), EMBASE and PsychINFO. The keywords 'childhood cancer', '(long-term) survivors', and 'late effects' were combined with dimensions that are often included as components of QL, including psychological/social adjustment, employment/health insurance, schools/learning, and quality of life/health status. Relevant articles were then hand-searched for further pertinent references. Studies published in English were included in the review. This review has been performed according to the methodological criteria defined by Eiser and colleagues (7) for the inclusion of studies in the field of psychosocial paediatric oncology. These standards are: 1) well-validated and reliable measures, 2) well-matched control group, or comparison with culturally appropriate measurement norms, 3) information about demographics and about illness and treatment factors (at least cancer diagnosis and time since diagnosis), 4) respondent rate, and 5) use of appropriate rigorous statistical tests. Additional selection criteria applied included: 6) survivors as the primary source of QL information, either by means of interviews or by completion of self-report questionnaires (studies with no more than 20% proxies as primary source of information were also included in this review), 7) original diagnoses of survivors made before they were 20 years of age, and 8) at least 5 year's survival after completion of therapy. Some studies, however, included survivors of 5 or more years after completion of therapy along with respondents who were closer to completion of therapy. We decided to include these studies as well because in most cases the mean or median time since completion of therapy ranged from 6 to 15 years. In addition, there is no consensus in the paediatric oncology literature about the definition of a survivor. Some authors define a survivor as a child or adolescent who has been disease-free for at least 5 years, while others use disease-free survival for 2 years or more as their criterion. This may be partly due to the different survival perspectives for the different diagnoses in childhood cancer. We intended to limit this review to studies of survivors who were at least 18 years old at the time of investigation. However, a number of studies included survivors both under and over the age of 18 years. Studies of QL that included patients with very wide age ranges were excluded on the grounds that in these studies it is not possible to distinguish the impact of cancer on children from that on older adults. Studies in which results for the long-term survivors, or time since completion of therapy were reported separately are included. In most study reports, however, this was not the case.

Initially, the studies featured in this review were selected by two reviewers on the basis of the above methodological criteria. However, we found that in most studies survivors' social functioning (e.g. education, employment) was not measured with the aid of standardised,

well-validated instruments. Because we did not want to exclude the social aspects of survivors' QL we decided to include these studies in the review as well, while being aware of the methodological limitations. At the same time, these limitations meant that there was no possibility of doing a systematic review.

A total of 30 empirical studies that met the inclusion criteria were found. We found the results of one study in two different journals, and we have combined these findings in our review (8;9). The studies are summarised in Table 1. In this table, the following information is provided for each study: a) the first author and year of publication; b) type of cancer; c) number and sex of survivors; d) age at evaluation; e) age at diagnosis and time since completion of therapy; f) number, sex and age of subjects in control group; g) instruments/measures used; and h) results/outcome. These parameters are reviewed and summarised in the following five sections. The first section describes physical functioning, including QL and general health. The second section summarises the results relating to psychological functioning: overall emotional functioning, depression and anxiety, and self-esteem. No studies were found about the cognitive or neuropsychological aspects of psychological functioning in childhood cancer survivors. The third section describes social functioning, including education, employment, insurance, living situation, marital status and family. Sexual functioning is the topic of the fourth section, and in the fifth section factors related to survivors' functioning are summarised: demographics, and illness- and treatment related factors.

RESULTS

Of the 30 studies, 17 involved survivors of different cancers and did not attempt to distinguish between diagnostic groups in terms of outcome (9-25). Three of these studies excluded survivors of a CNS tumour (10;20;23). Six studies focused specifically on leukaemia survivors (26-31), and Mackie and colleagues (32) included survivors who had been treated for acute lymphoblastic leukaemia (ALL) and Wilms' tumour. Four studies examined survivors treated for a bone tumour (33-36); one study investigated Hodgkin's disease survivors (37); and one study was found in which survivors treated for solid tumours, except for CNS tumors, were investigated (38).

The majority of the studies in this review were conducted in the United States (9;11;13;15-26;30;31;34;35;37;39). Three studies were conducted in Finland (10;29;38), 2 in the United Kingdom (14;32), 2 in the Netherlands (27;36), 1 in Norway (28), 1 in Austria (33), and 1 in Israel (12). Sample sizes varied from 30 (29) to 10425 (22). Survivors differed in age at the time of evaluation (range from 10[1] (35;37) to 55 years (19), age at diagnosis, and time since completion of therapy. Twelve investigators used time since diagnosis as a criterion. Most investigators (n = 22) compared the results in survivors with those in sex- and age-matched siblings, peers or healthy controls. Seven studies included comparison with population norms (13;15;22;33;36-38), and 1 study included both population norms and a control group of survivors with a different cancer diagnosis (31). The instruments used in most of the studies were a mixture of standardised questionnaires and tests (see Table 2). In the remainder the

[1] As mentioned in the methods section, a number of studies included both survivors under the age of 18 years as survivors above the age of 18 years

instruments were mostly newly developed questionnaires with no information given on reliability and validity, or authors used less highly structured interviews.

Physical functioning

Four investigations asked survivors for a general evaluation of their health. The majority of the survivors (89%) in the study by Meadows and colleagues (21) reported being in good to excellent health. Nicholson and colleagues (34) investigated 111 bone tumour survivors, and 80% of osteosarcoma and 100% of Ewing's sarcoma survivors classified their health as good or excellent. Similar findings of apparently good health when compared to siblings were reported by Novakovic and colleagues (35), who studied 89 survivors of Ewing's sarcoma family tumors. However, the osteosarcoma suvivors in the study by Nicholson and colleagues (34) were more likely than their siblings to perceive their health as fair or poor; this was neither explained by an excess of chronic health condition nor related to amputation status. When Dolgin and colleagues (12) asked participants to rate their current health status on a five point scale, survivors rated their health as poorer than controls.

However, the QL of the survivors and their controls was explored by use of the SF-12 in the study by Moe and colleagues (28) and with the Rand Health Insurance study General Well-being measure by Tebbi and colleagues (23). Neither of these studies found any statistical differences between the groups with respect to physical health and QL. However, Moe and colleagues (28) found that the somatisation score on the General Health Questionnaire with items closely related to fatigue demonstrated a significantly higher score for acute lymphoblastic leukaemia (ALL) survivors than for controls. Fatigue was also mentioned in the study by Wasserman and colleagues (37). One of the physical residual effects, as reported by 5% of the Hodgkin's disease survivors, was easy fatigability. Nevertheless, the study by Zeltzer and colleagues (30) showed no difference between the POMS Fatigue subscale score of 552 ALL survivors and 394 sibling controls.

Apajasalo and colleagues (10) used the 15D (a 15-dimensional questionnaire) to examine the health-related QL of 168 survivors with a range of different malignancies and 129 controls. They found that the QL score of the survivors was significantly better than that of the controls; survivors reported better levels of vitality, distress, depression, discomfort, elimination and sleeping dimensions. There were no differences in QL between survivors with different malignancies, but it should be noted that the numbers in each diagnostic group were small.

Three studies attempted to measure physical functioning in bone tumour survivors. Two studies used a study-specific questionnaire (34;36), and the Karnofsky performance scale was used in the other study (35). In all studies there is evidence that the bone tumour group had poorer physical functioning than their controls. These included specific difficulties with climbing stairs (34), and "general physical functioning" (35;36).

Psychological functioning

With respect to psychological functioning, we found that most studies focused on emotional aspects, using many different instruments. Most authors employed standardised measures with the availability of norms and comparison groups. In this section, emotional functioning is described in terms of overall emotional functioning, depression and anxiety, and self-esteem.

Table 2. Standardised instruments used in quality of life studies of survivors of childhood cancer

Instrument	Studies using instrument
Physical functioning	
15 D (15-dimensional questionnaire)*	Apajasalo et al., 1996
Items EORTC QLQ-BR23	Veenstra et al., 2000
Items EORTC QLQ-C30	Veenstra et al., 2000
General Health Questionnaire*	Moe et al., 1997
Karnofsky performance scale	Novakovic et al., 1997
Physical Abilities Battery (PAB)	Tebbi et al., 1989
Profile of Mood States (POMS) fatigue subscale*	Zeltzer et al., 1997
SF-12*	Moe et al., 1997
SF-36	Veenstra et al., 2000
The Rand Health Insurance Study Functional Limitations Battery (FLB)	Tebbi et al., 1989
The Rand Health Insurance Study General Well-Being measure*	Tebbi et al., 1989
Psychological functioning	
Overall emotional functioning	
15 D (15-dimensional questionnaire)*	Apajasalo et al., 1996
General Health Questionnaire*	Moe et al., 1997
Mental Health Inventory	Dolgin et al., 1999
Multi-dimensional Personality Questionnaire (MPQ) Well-Being and Stress Reaction Scales	Zevon et al., 1990
Profile of Mood States (POMS)*	Gray et al., 1992; Zeltzer et al., 1997
Questionnaire on Subjective Well-Being	Felder-Puig et al., 1998
SF-12*	Moe et al., 1997
Symptom Checklist-90 Revised	Elkin et al., 1997
The Rand Health Insurance Study General Well-Being measure*	Tebbi et al., 1989
Depression and anxiety	
Diagnostic and Statistical Manual of Mental Disorders (DSM)	Wasserman et al., 1987
General Health Questionnaire*	Moe et al., 1997
Mental Health Inventory*	Dolgin et al., 1999
Profile of Mood States (POMS)*	Zeltzer et al., 1997
Schedule for Affective Disorder and Schizophrenia lifetime (SADS-L)	Teta et al., 1986; Mackie et al. 2000
State-Trait-Anxiety Inventory	Felder-Puig et al., 1998
Symptom Checklist-90 Revised	Elkin et al., 1997
Self-esteem	
Frankfurt Self-Concept Scales	Felder-Puig et al., 1998
Rosenberg Self-Esteem Scale	Gray et al., 1992
Oxford Psychologists Press adult self-esteem Questionnaire	Evans & Radford, 1995
Other	
Control Belief Scale	Gray et al., 1992
Desirability of Control Scale	Gray et al., 1992
Eyseneck's short scale of the EPQ-R	Moe et al., 1997
Impact of Event Scale	Gray et al., 1992
Locus of Control Scale	Gray et al., 1992
Minnesota Satisfaction Questionnaire-Short Form (MSQ)	Zevon et al., 1990
Questionnaire on Life Goals and Satisfaction with Life	Felder-Puig et al. 1998
Raven's standards progressive matrices	Mackie et al., 2000
Social functioning	
Adult Personality Functioning	Mackie et al., 2000
Long-term Follow-up Questionnaire (LFQ)	Zevon et al., 1990
Social Support List-Interactions and Social Support List-Discrepancies	Veenstra et al., 2000
Sexual functioning	
No instruments	

* Questionnaire consisting of both physical and psychological items.

Overall emotional functioning

All investigations assessing the overall emotional or mental functioning of the survivors used standardised measures containing various dimensions of emotional well-being. In general, survivors seemed to be well adjusted. Most researchers found no difference in functioning between survivors and healthy peers and/or normative samples, based on the scores at the Rand Health Insurance Study General Well-Being measure (23), Multidimensional Personality Questionnaire Well-Being and Stress Reaction Scales (31), Profile of Mood States (9), SF-12 and General Health Questionnaire (28), Symptom Checklist-90-Revised (SCL-90-R) (13), Questionnaire on Subjective Well-Being (33), and Mental Health Inventory (12). For the small percentage of survivors who did display one or more clinical elevations on the SCL-90-R, three factors were identified which were associated with increased risk of maladjustment: older age at follow-up, greater number of relapses, and presence of severe functional impairment (13). Survivors of bone tumors diagnosed in adolescence had more problems than survivors who became ill during childhood or early adulthood (33).

In two studies survivors appeared to be less well adjusted emotionally than their healthy peers or the general population. Lansky and colleagues (20), who used a structured interview to assess overall psychologic adjustment, reported a higher prevalence rate of episodes of treated depression, alcoholism and/or suicide attempts in survivors than in the general population. Both Gray and colleagues (9) and Zeltzer and colleagues (30) measured overall psychologic adaptation with the Profile of Mood States (POMS). While the first authors reported that 62 survivors with a range of diagnoses were similar to their 51 healthy age-matched peers, the 580 ALL survivors in the study by Zeltzer and colleagues had a greater negative mood, more tension, depression, anger and confusion than their 396 sex-matched siblings. The female survivors reported the highest mood disturbance. However, their scores were not as high as were found in a psychiatric sample. Finally, Elkin and colleagues (13) found that survivors' scores on the SCL-90-R subscales Anxiety, Psychoticism, Global Severity index, and Total Positive Symptoms were below normative values, suggesting that this group of survivors must be healthier than would be expected according to normative data.

Depression and anxiety

In some studies depression and anxiety were measured with a subscale of a standardised instrument measuring overall emotional adjustment. In most studies (9;12;13;25;28), no increased rates of depression and/or anxiety were reported. Zeltzer and colleagues (30), however, reported more depression among ALL survivors than among their siblings, and Lansky and colleagues (20) found that the prevalence of treated depression was higher in survivors than in the general population. Moreover, female survivors of ALL experienced more anxiety in stressful situations than the sex-appropriate norms, in contrast to males, who scored below the norms (31). Felder-Puig and colleagues (33) used the scale "trait-anxiety" from the State-Trait-Anxiety Inventory in their study. No increased anxiety was found for the 26 survivors of bone tumors relative to the norm group.

In three studies, the Diagnostic and Statistical Manual of Mental Disorder (DSM) criteria were used to assess the frequency of affective disorders in survivors. Teta and colleagues (25) used the Schedule for Affective Disorder and Schizophrenia (SADS-L) and found that the prevalence of lifetime major depression in 450 survivors (with a variety of cancers) did not

differ from that of their 587 sex-matched siblings. It was also similar to those reported in the literature for the general population. More recently, similar findings were reported by Mackie and colleagues (32), who found no increased rates of minor depression in 169 survivors of ALL or Wilms' tumors relative to 102 healthy age- and sex-matched controls. Finally, Wasserman and colleagues (37), who included a DSM psychiatric assessment in the interviews with 40 survivors of Hodgkin's disease, reported that the frequency of psychiatric diagnoses in the sample was basically no different from that found in community studies.

Self-esteem

In three studies assessing self-esteem with (a part of) a standardised instrument, no differences between survivors and control groups and/or normative groups were found. More specifically, the 60 bone tumour survivors in the study by Felder-Puig and colleagues (33) scored within normal ranges on the Frankfurt Self-Concept Scales, as did the 62 survivors on the Rosenberg Self-Esteem Scale (9). The survivors in the latter study did not differ from their healthy peers. Finally, overall self-esteem of 48 survivors with a range of diagnoses was as high as that of their healthy siblings, as measured with the Oxford Psychologists Press adult self-esteem questionnaire (14).

Social functioning

Across studies, social functioning has been operationalised in a variety of ways, covering such issues as education, employment, insurance cover, living situation, marital status, and fertility, including reproductive capacity and family planning. Most investigations used (semi-) structured interviews with author-developed questionnaires.

Education

With respect to education, many research studies have demonstrated that survivors of childhood cancer, as a whole, did not differ much from controls or from the general population (12;14;16;19-21;28;33;35;37;38), although there were exceptions in certain subgroups of survivors. Kelaghan and colleagues (19) investigated the level of education in 2283 survivors and compared the results with those of 3261 sibling controls. The survivors of CNS tumors diagnosed before age 15 were significantly less likely than their controls to complete the eight grade of school. CNS tumour survivors who did complete secondary school were also less likely to enter college. The deficit was more severe in survivors who were treated with radiation therapy than those who underwent surgery alone. They also found that an early age at diagnosis was associated with a larger educational deficit than late age at diagnosis. Another study (16) reported that although 91% of the CNS tumour survivors had completed high school, only 10% had received a bachelor's or equivalent degree, as against 98% and 25%, respectively, in the non-CNS tumour group. Two studies evaluated the impact of treatment on scholastic performance in survivors of ALL (26;27). Significantly more survivors than controls were placed in a special educational programme (26;27), or a learning disabled programme (26). In the study by Kingma and colleagues (27) in ALL survivors with cranial radiotherapy (CRT) a significant difference in the level of secondary education was found for all survivor/sibling comparisons except in the case of survivors aged over 7 years at the time of diagnosis, when mean level of education no longer differed from that of their siblings.

Younger age at diagnosis was also associated with referrals. The researchers found no effect of gender or irradiation dose on referral to special schools or on level of secondary education. In contrast, Haupt and colleagues (26) reported that the risk associated with special education and learning-disabled programmes increased with increasing dose of CRT. Survivors treated with 24 Gy and those diagnosed before 6 years of age were less likely to enter college.

Finally, Evans & Radford (14) concluded from their study of 48 survivors with various tumours that there was no significant difference between survivors and siblings in qualifications at 16 years. However, survivors were significantly less likely to go on to higher education (16 years onwards) than their siblings. Many survivors (67%) felt that their education had suffered as a result of their disease. This percentage was higher than that found in the study by Dolgin and colleagues (12), in which 45% of the survivors reported that their illness had impacted on their educational achievement to a (very) great extent. In contrast, 77% of survivors in another study said that cancer had had no effect on their educational achievement (21).

Employment

The employment problems of cancer survivors have been of increasing interest during the last decades. Zeltzer and colleagues (30) studied 580 young adult survivors of ALL and found that significantly more survivors than sibling controls who had not enjoyed higher education were unemployed or were working less than half-time. This finding agrees partly with the study by Green and colleagues (15), who compared 227 former paediatric cancer patients with population norms. They found that the percentage of unemployed male survivors did not differ from population norms. The percentage of unemployed female suvivors, however, was slightly higher than that of the U.S. population in general. Other studies found that survivors and controls did not differ with respect to employment status (12;14;16;20;23;28;31;35) and that the majority of long-term survivors old enough to be in the work force were employed in a range of professional, clerical, and skilled labour positions (23;33). Two studies looked specifically at survivors of bone tumors. Nicholson and colleagues (34) studied 111 survivors treated for Ewing's sarcoma and osteosarcoma and found that, in spite of a greater likelihood of having ever been disabled, their employment status did not differ from that of their siblings. Felder-Puig and colleagues (33), however, noted that many survivors treated for a bone tumour reported major difficulties in obtaining work.

In 1987, Mellette & Franco (40) reviewed the literature relating to employment of survivors of childhood cancer. They noted that, whereas in studies of a decade ago various forms of discrimination were reported, recent studies had been unable to document many of such problems. Nevertheless, Green and colleagues (15) found evidence of employment-related discrimination in 11% of 227 childhood cancer survivors who were treated between 1960 and 1985. Almost 30% of the male survivors were rejected for military service. However, these frequencies were lower than those reported by Teta and colleagues (25) and Wasserman and colleagues (37) in 1986 and 1987, respectively. Teta and colleagues reported in their study of 450 survivors and their 587 siblings that there was significantly more rejection of survivors (85%) than of their siblings (18%) by the military and other prospective employers (survivors 32%, siblings 21%). In the study by Wasserman and colleagues of 40 survivors of childhood and adolescent Hodgkin's disease, 20% reported that they had experienced job discrimination. In a recent study by Dolgin and colleagues (12), 46% of the Israeli survivors reported that their illness had impacted on their employment histories "to a great extent"

or "to a very great extent". Forty-five percent of the survivors had been rejected from a workplace, compared with 19% of the controls. Approximately half of these survivors felt that their workplace rejection was due to their cancer history. They also found that 55% of the survivors had difficulty being accepted into the military service. Rejection for the military has also been reported in another investigation (16).

Six studies have assessed the level of income. Dolgin and colleagues (12) and Hays (16) found that survivors reported less annual income than the controls, however, in the latter study this difference was not significant. Interestingly, the survivors in the study by Tebbi and colleagues (23) reported a higher mean income than controls. The other studies found no differences (14;33;34).

Insurance

Obtaining adequate health and life insurance has been a recurring problem for survivors of cancer. Although the differences were not significant, male and female survivors reported they were turned down for life and health insurance more frequently than their siblings (25). A report of insurance problems among 100 survivors who were treated during the years 1945-1975 showed that 24% had difficulty in securing health insurance and 15% had no health insurance at the time of the survey, versus 0% and 7%, respectively, in these categories among controls (17). Difficulty in obtaining life insurance was noted by 44% of survivors and by only 2% of matched controls. Tebbi and colleagues (23) found that many survivors had difficulty in obtaining health, life, or disability insurance. Green and colleagues (15) found that the percentages of survivors who had life insurance and company-offered health insurance were lower than those reported for the general U.S. population. Twenty-four percent of those with life insurance had had difficulty in obtaining it. Although a small percentage (7%) of survivors in the study by Hays and colleagues (16) had been denied employment-related health insurance at some time and another 8% had at some time had health insurance cover that excluded cancer, most survivors were covered by health insurance policies without cancer-related restrictions. There were no differences from the controls. Evidence of both past and current discrimination in obtaining affordable life insurance on the basis of a cancer history was clearly recognisable. However, the majority of survivors who desired life insurance were insured and at standard rates. Novakovic and colleagues (35) found no difference in health care insurance status, but more problems in getting job-related health insurance. Finally, Jacobson Vann and colleagues (18) assessed the effects of having a cancer diagnosis on the subsequent acquisition of health insurance cover for young adults diagnosed as children in North Carolina. They found that survivors were turned down for health insurance cover more often than their siblings, this was due, according to the survivors, to their cancer history and related medical history. Survivors were also more likely than their siblings to have health insurance policies with clauses excluding cover for pre-existing health conditions. When participants were asked whether they had had problems in obtaining health insurance coverage, 24% survivors answered "yes", as apposed to 2% of the responding siblings. Furthermore, survivors were 4.3 times as likely to be covered by their parents' health insurance policies.

Living situation, marital status and family

Only two investigations have specifically addressed the living situation of young adult survivors. In a pilot study of 39 survivors Lansky and colleagues (20) found that survivors did not significantly differ from the sibling group on living arrangements (with parents versus other); however, the survivors left home at a slightly older age (21 versus 19 years). The survivors in Felder-Puig's study (33) also seemed to stay at home longer after reaching adulthood than controls of a similar age.

Two studies have focused solely on marriage issues among childhood cancer survivors, and several studies of the late effects on cancer treatment have included data on marital status as an indicator of social competence. The largest and most comprehensive study of marriage, which compared 10425 survivors with a broad range of diagnoses with U.S. population norms, was published by Rauck and colleagues in 1999 (22). They found that the percentage of survivors who had ever been married was lower than that in the general U.S. population within similar age groups. In particular, compared with their age-matched counterparts in the general population, women and whites were less likely to have married, whereas black survivors were more likely to have married. Comparison of childhood tumour types showed that survivors with a diagnosis of CNS tumors, particularly males, were less likely to have married than those with other diagnoses or the general population. In the second largest study of marriage, which compared 2170 survivors with sibling controls, Byrne and colleagues (11) also found that, as a group, survivors were less likely to be married and that the differences were greatest among male survivors of CNS tumors. Similar findings were reported in some smaller studies. Zevon and colleagues (31) found a decreased frequency of marriage for both men and women relative to the U.S. population in a group of 46 survivors with ALL. These conclusions were supported in a study of 227 survivors, including few with a diagnosis of CNS tumour by Green and colleagues (15) and in two other studies with survivors of bone cancer (33;35). Green and colleagues (15) also found that marital status was not affected by age at diagnosis, gender, history of disease recurrence and diagnosis. Teeter and colleagues (24) reported data collected by the University of Kansas on marital status among 263 survivors and 369 controls. Twenty-five percent of the survivors and 16 percent of the controls had never married. Makipernaa (38) studied survivors diagnosed with solid tumors (excluding CNS tumours) and found that fewer of the women and as many of the men were married as in the general population. Finally, in a study of 95 survivors, Meadows and colleagues (21) found that survivors were less likely to be married than members of the sibling control group. However, the authors stated that this was probably a biased comparison, because the siblings as a group were older than the survivors.

In contrast, other studies have suggested that there are no significant differences among survivor/control comparisons with respect to marital status. For example, Nicholson and colleagues (39) found no marriage relative to controls in a population of 111 survivors of bone cancer. Hays and colleagues (16) reported marriage statistics from two centres, which showed no difference between survivors with a variety of diagnoses and the general U.S. population when CNS tumors were excluded. Wasserman and colleagues (37) studied 40 survivors of childhood and adolescent Hodgkin's disease and also found that the overall proportions of marriage in the survivors were not different from the general population statistics. Four other studies yielded similar results (12;14;20;30).

Some studies provide data on specific reasons for not marrying. All the participants in the study by Teeter and colleagues (24), were asked whether they had refrained from marrying for medical or health reasons. Twenty-one survivor (31%) and one control (2%) said that they had not married for health reasons. Green and colleagues (15) found that among the survivors who had never married or lived as married (n=96), almost 16% reported that their history of childhood cancer had influenced their decisions on marriage. In Makipernaa's study (38) 5 survivors reported that it was expressly the cancer treatment that had made them decide to remain single. One woman emphasised that knowing she had had a hysterectomy had prevented her marriage. Four others felt that the cancer and its treatment had so impaired their appearance that it hampered their personal contacts. Most single survivors in the study by Meadows and colleagues (21) indicated that having had cancer had no impact on their desires or opportunities for marriage. However, 21% said that having had cancer sometimes affected their ability to meet others, and 38% reported that their history of cancer sometimes scares others.

There was no significant difference in the overall frequency of separation or divorce in the study by Green and colleagues (15). However, a more detailed analysis of the separation and divorce data revealed that the percentage of divorced women aged 35-44 was significantly greater relative to that in the normative group. Zevon and colleagues (31) also reported an elevated frequency of divorce in women compared with the rates for the general population. In contrast, separate analysis of the men in the study of Wasserman and colleagues (37) showed a significantly higher rate of divorce than in age- and race-specific statistics. Survivors of bone tumors were also found to be more likely to have divorced in the study by Novakovic and colleagues (35). One study found that, in general, the proportion of survivors who were divorced or separated was lower than that of the U.S. population (22). Men, however, were more likely to have divorced or separated than their age-matched counterparts in the general population, and women less likely. Survivors with the diagnosis of CNS tumour were also more often divorced or separated than those with other diagnoses or the general population. The latter finding was confirmed by Hays and colleagues (16) who found that in the CNS group 23% survivors had been divorced, versus 8% in the non-CNS tumour category. Byrne and colleagues (11) also reported that first marriages of male survivors of CNS tumors who were diagnosed before age 10 years were three times as likely to end than those of controls. They also found that male survivors of retinoblastoma had higher divorce rates than male controls.

The effect of a history of childhood cancer on divorce was addressed in one study (15). For those survivors who were separated or divorced, 20% (n=5) reported that their history of childhood cancer had been a contributing factor to the dissolution of their relationships.

The issue of fertility has been investigated by several investigators. Nicholson and colleagues (34) found that although deficits in crude fertility rates were significant when all former bone cancer survivors were compared against all controls, these differences were non-significant after controlling for sex. According to Moe and colleagues (28) men once diagnosed with ALL had significantly fewer offspring than the men in the control group, whereas the women in the ALL group had slightly more children than their controls. Three other studies reported that the percentage of survivors with children was lower than the percentage of controls (16;24;35). Among the survivors who had ever been married or lived as married in the study by Green and colleagues (15), 10% indicated that their history of childhood cancer influenced their decision to limit the number of children they had to a moderate or greater degree. For an

additional 10%, their medical history was a factor that contributed to their decision to have no children. Worries about reproductive capacity were reported in three studies. Gray and colleagues (9) found that survivors were more likely than a matched control group of peers to report worrying about being able to conceive a child. When Wasserman and colleagues (37) conducted open-ended interviews in 40 adult survivors of Hodgkin's disease, they found that female survivors often reported concerns about fertility, whereas male survivors did so much less often. Forty-six percent of the female ALL survivors and 29% of the male ALL survivors in the study by Zevon and colleagues (31) reported being concerned about possible future health problems their children might experience as a result of their cancer history.

Sexual functioning

So far, not many studies provide data on sexual functioning. Veenstra and colleagues (36) assessed body image and sexual functioning in 33 bone tumour survivors with a rotation plasty. Almost half of the survivors felt slightly to very limited in initiating intimate relationships as a result of the rotation plasty. While 19 survivors reported that they did not feel physically unattractive as a result of the rotation plasty during the week prior to the assessment, 10 reported feeling a little unattractive and 4 reported feeling quite a bit to very unattractive. Of the survivors who were sexually active (n=21), 10 survivors reported that they were limited in their sexual activities to a small (n=8) or moderate (n=2) degree as a result of the surgery.

Puukko and colleagues (29) investigated possible changes in sexual identity, sexual attitudes, and sexual behavior of 30 female survivors diagnosed with acute leukaemia as compared with healthy age-matched controls. They found that survivors did not differ from controls with respect to the following aspects of sexual behavior: age at which dating began, onset and frequency of sexual intercourse, and opinions on sexual behavior. They also found that there were significant differences in behavior: survivors were less likely to have experienced sexual intercourse, less likely to have initiated intercourse, less likely to masturbate and less likely to have talked with friends about sexual topics. With regard to inner sexuality, survivors also differed from controls. Their images of sexuality were more restrictive, and their attitudes, especially those concerning sexual pleasure, were more negative than those of the controls. Finally, sexual identity among the survivors was less often feminine and more often infantile than among controls.

Factors related to survivors' functioning

Fortunately, not all young adult survivors of childhood cancer seem to suffer from the late sequelae of their disease and/or treatment. So it is very important to identify factors that predict good QL and to trace risk factors. In most studies factors related to survivors' function have been discussed to some extent. Predictors can be divided into demographics, and illness- and treatment related factors.

Demographics

In several studies gender has been investigated in relation to survivors' functioning. Especially female survivors seemed to be at risk for psychological problems. According to Zevon and colleagues (31) female ALL survivors had an increased tendency to experience

anxiety in stressful situations, and in the study by Zeltzer and colleagues (30) female ALL survivors reported the greatest total mood disturbance. With respect to marriage, the percentage of married female survivors was lower (15;22), but according to Rauck and colleagues (22) female survivors were less likely to divorce/separate. However, Green and colleagues (15) found that a subgroup of female survivors (aged 35-44) had a significantly higher frequency of divorce than age-specific group norms. Male gender was positively related to employment (15). In contrast with these findings, Apajasalo and colleagues (10), Elkin and colleagues (13) and Kingma and colleagues (27) reported that gender was not associated with survivors' functioning respectively with QL, maladjustment according to the SCL-90-R, and educational status.

In five studies, age at study has been analysed in relation to outcome. Age was found to be negatively related to psychological functioning. Younger survivors reported a better QL (10), and older survivors scored higher on the Symptom Checklist (13). Older survivors were also more likely never to have married than younger survivors (30), but they were more likely to be employed (15). The sexual identity of the survivors seemed not to be associated with age according to Puukko and colleagues (29).

Two studies reported results about minority survivors. Minority survivors of ALL showed the highest mood disturbance (30). Black survivors were generally found to be more likely to have married, but also more likely to have divorced/separated once married than the general US population (22).

Illness and treatment related factors

Age at diagnosis is one of the factors that has been most frequently investigated in relation to survivors' functioning. Survivors diagnosed at a younger age were at higher risk for poor educational performance (19;26;27). Felder-Puig (33) concluded that survivors of bone tumors diagnosed in adolescence had more problems (especially less social well-being) than those diagnosed in childhood or early adulthood. In contrast, in seven other studies age at diagnosis appeared to be not associated with outcome, and/or not to be related to emotional functioning (8), depression (25), maladjustment in terms of the SCL-90 (13), poor close relationships (32), sexual identity (29), educational level (21), or marriage, divorce, employment and insurance (15).

With respect to the diagnosis (type of cancer), especially CNS tumors versus other diagnoses is the comparison that has been most intensively investigated. It was found that survivors of CNS tumors were more seriously affected. Their educational level was lower (9;16;19), and they were less likely to be married (11;16). Moreover, they were more likely to have divorced and their rates of parenthood were also lower (16). Elkin and colleagues (13), who studied survivors with a range of diagnoses, found no relation between type of cancer and QL. Similar findings were reported by Apajasalo and colleagues (10), who excluded survivors with CNS tumors.

With respect to type of treatment, radiation therapy appeared to be a risk factor. First, survivors who were treated with cranial irradiation showed less well-being than the other ALL survivors (31). Second, treatment with radiation therapy versus surgery alone (19), and a higher dose of cranial irradiation (26) seemed to be risk factors for poor educational performance. However, among the ALL survivors in the study by Kingma and colleagues (27), the cranial irradiation was not associated with educational level.

In a sample of survivors with a range of diagnoses (except CNS tumours) survivors of bone marrow transplantation has a slightly lower QL than the other survivors (10). In three other samples with a variety of diagnoses no association was found between the type of treatment and outcome: emotional functioning according to the SCL-90 (13), depression (25), educational level (21). Moreover, Puukko and colleagues (29) concluded that the sexual identity of ALL survivors was not predicted by the type of treatment and Novakovic and colleagues (35) found that the treatment protocol of bone tumour survivors was not related to marriage and having children.

According to Mackie and colleagues (32) longer duration of treatment in survivors of ALL and Wilms' tumour was related to poor close relationships. In the same study this was also found in survivors whose illness was more recent. In three studies in which time since diagnosis or time since end of treatment was investigated no association with outcome was found (9;10;29).

Only three studies looked at the effect of recurrence of the disease. While Elkin and colleagues (13) concluded that disease relapse was a risk factor for emotional maladjustment, the opposite was found in the study by Gray and colleagues (8). Green and colleagues (15) also found no evidence that recurrence of cancer was related to survivors' functioning, specifically it was not related to marriage, divorce, employment and insurance.

Medical and functional late effects were investigated in two samples of survivors of bone tumors. Nicholson and colleagues (39) reported that amputation status was not associated with health perception and Felder-Puig and colleagues (33) found no correlation between emotional functioning with physical or functional sequelae. In line with these results, disability, which was reported by survivors with different tumours, was not related to emotional functioning (8). In contrast, Elkin and colleagues (13) concluded that severe functional impairment was a risk factor for maladjustment, while cosmetic status was not.

Conclusion and future directions

The purpose of this review was to give an overview of the research about QL in young adult survivors of childhood cancer populations during the last two decades. This review identified a wide variety of studies. Studies are characterised by a high degree of heterogeneity with respect to: the patients samples investigated (e.g. survivors with different cancers who had undergone a variety of treatments), the comparison groups selected, the QL dimensions assessed and the instruments employed. Additionally, age at time of evaluation, age at diagnosis, and time elapsed since completion of therapy varied widely. Moreover, the majority of the studies reviewed suffered from at least one of the following methodological weaknesses: small samples, nonstandardised, study-specific instruments, and cross-sectional rather than prospective designs. Given all of these differences between studies, perhaps it is not surprising that outcomes of studies differ and that the QL reported by survivors also varies, making it impossible at this time to come to firm conclusions about the magnitude and nature of long-term consequences for childhood cancer survivors.

However, despite the heterogeneity in study procedures and the methodological shortcomings, some clear trends emerge from this review. Although some inconsistent data have been reported across studies, the results suggest the following.

Physical functioning

1) The majority of survivors reported they were in apparently good health, with the exception of bone tumour survivors, who were more likely to perceive their health as fair or poor. Bone tumour survivors also had poorer physical functioning than their controls. Difficulties in climbing stairs and poor "general physical functioning" were reported.
2) Some studies mentioned fatigue as a residual effect of treatment.

Psychological functioning

1) Most long-term survivors functioned well psychologically and did not have significant more emotional problems than controls. The subgroup of survivors who reported problems mentioned depression, mood disturbances, tension, anger, confusion and anxiety. Female gender, older age at follow-up, greater number of relapses, presence of severe functional impairment, cranial irradiation and minority survivors were associated with an increased risk for emotional problems in some studies.

Social functioning

1) Survivors of CNS tumours and survivors of ALL seemed to be at risk for educational deficits. Cranial irradiation and an early age at diagnosis was associated with educational deficits. Many survivors reported that their education had suffered as a result of their disease.
2) The majority of survivors old enough to be in the workforce were employed. Although in almost all research survivors did not differ from controls with respect to employment status, some survivors experienced some form of job discrimination and difficulties in obtaining work. Problems in obtaining health and life insurance were also reported.
3) Survivors seem to stay at home longer after reaching adulthood and leave home at an older age than their controls.
4) There is a lower prevalence of marriage among survivors, particularly in male survivors with a diagnosis of CNS tumors. The survivors reported that the history of childhood cancer, the consequences of treatment and problems with health as specific reasons for not marrying.
5) The percentage of survivors with children seems lower. The survivors indicated that the medical history is a factor that contributes to the decision to have no children. Many survivors reported worrying about their reproductive capacity and/or about possible future health problems their children might experience as a result of their cancer history.

Childhood cancer was almost always a fatal disease in the not-too-distant past. Over the last decades significant treatment advances have been made, and long-term survival is now a reality. With the increasing number of long-term childhood cancer survivors, the need to assess their QL is becoming more important and meaningful. This article has summarised what is known about the long-term effects of disease and treatment on the QL of survivors. Where do we go from here?

It is evident that additional research is needed. Although the low incidence of childhood cancer, the variety of diseases and treatments and the wide range in ages pose methodological problems in QL assessment, we need well-designed studies. Since not many institutions have a sufficient number of patients to control for the numerous patient-specific and therapy-specific variables involved, multi-institutional collaboration is recommended. At the least, account must be taken of the age of the child at diagnosis and treatment, the length of time since completion of therapy, and the differences in severity of the cancer and its treatment, and thus the treatment era. The QL dimensions of interest, and therefore the outcome measures of the study, must be clearly defined. This will enhance the possibility of comparing international studies and to conducting systematic reviews. Researchers should attempt to use prospective study designs with sufficiently large sample sizes, choose instruments appropriate to their goals and establish the methodological properties of the instruments they use in keeping with that goal. However, in this still-evolving area of research, it is wise for investigators to include an opportunity for survivors to report additional concerns not covered in standardised QL scales wherever possible. Naturally, one or another is dependent on the question of whether the main objective is measurement of differences between patients at one particular point in time or longitudinal change within patients over time.

As Gotay & Muraoka (41) stated in their review on QL in adult-onset cancer survivors, there is a need to understand the long-term impact of different treatment on QL. It is important to document how varying therapeutic modalities can give rise to different long-term effects. Such information can establish whether there are any residual effects of one treatment but not another and whether there are treatment-related decrements in QL that vary in the short term and long term. Further, little is known about the impact of persistent effects of cancer treatment on survivors' QL. Survivors may learn to live with and adjust to their possible limitations, they may continue to experience problems to the same degree as during short-term survival, or their tolerance of disability may decline with the passage of time (i.e., an enhanced QL, an unchanged QL, or a worsened QL, respectively) (41). It is also important to identify the subgroups of survivors who have problems rather than evaluating only differences between survivors as a whole and their controls.

Many of the studies reported to date are based on North-American samples; this seems to be an area of research in which North American researchers have taken a lead. However, there are many cultural differences between the United States and European countries, in addition to dissimilarities in their health care systems, particularly with respect to health care insurance. No studies were found for this review from anywhere outside the United States and Europe, and this raises questions about the functioning of childhood cancer survivors in other countries. The increasing cultural/ethnic diversity of people within the borders of all countries and the growing communication network around the globe underscore the relevance of cross-cultural comparisons (42). It is known that there are many differences in adjustment to cancer across cultures. The cultural distinctions between and within national boundaries provide an unique opportunity to examine differences in the meaning of survivorship, as well as values and behaviours, in different groups.

Future research efforts should also be directed at the intermediate factors of QL that have received relatively little attention in previous studies, including the role of coping and adaptation, social relationships and family variables. Considering that many survivors are functioning reasonably well and that not much difference is found between results in survivors

and their peers, it would be interesting and advisable to investigate the role of denial and response-shift. It would also be interesting to know if survivors meet developmental tasks in growing up. More insight is therefore needed into the relation between the survivors' course of life and their functioning in later life. The need for future studies applies for other aspects as well, such as posttraumatic stress, body image and spiritual dimensions. Although these concepts are investigated in younger survivors, we did not find any studies in which these topics had been measured with standardised questionnaires and compared with norms in young adults. It is also remarkable that no studies about cognitive functioning in (young) adult survivors of childhood cancer were found, in contrast with the large number of studies done in children. As Kingma (43) has mentioned, it is not yet known what may happen to maturing brains long after exposure to CRT and/or chemotherapy in childhood. Furthermore, in the adult cancer literature it is suggested that more research is needed because neuropsychologic symptoms, particularly problems with memory and concentration, are frequently reported by cancer patients treated with chemotherapy, even years after completion of treatment (44).

As we learn more about the challenges associated with long-term childhood cancer survival, interventions will be needed to address the problems identified. It is possible that some problems can be prevented and others remediated if appropriate care is provided. However, it is critical to determine the kind of support desired by long-term survivors and to identify who is most in need of and likely to benefit from such interventions (45;46). Therefore, it is critical to ask survivors what they need and what they want, for example by means of focus groups. Interventions to reduce psychological morbidity or improving QL, such as patient education, coping skills management, and support groups deserve continued attention. Studies are needed to identify the extent to which these interventions improve QL.

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REFERENCES

(1) Stiller CA. Population based survival rates for childhood cancer in Britain 1980-1991. British Medical Journal 309, 1612-1616. 1994.

(2) Hawkins MM, Stevens MC. The long-term survivors. British Medical Bulletin 52, 898-923. 1996.

(3) Hobbie W, Ruccione K, Moore IK, Truesdell S. Late effects in long-term survivors. In: Foley GV, Fochtman D, Mooney KH, eds. Nursing Care of the Child with Cancer.Orlando, Florida: W.B. Saunders Company, 1993. p. 466-96.

(4) Schwartz CL, Hobbie WL, Constine LS, Ruccione KS. Survivors of Childhood Cancer: Assessment and Management. St. Louis, Missouri: Mosby-Year Book, Inc, 1994.

(5) World Health Organization DoMH. WHO-QOL Study protocol: The development of the World Health Organization quality of life assessment instrument. Geneva, Switzerland; 1993.

(6) Leigh SA, Stovall EL. Cancer Survivorship. Quality of Life. In: King CR, Hinds PS, eds. Quality of Life. From Nursing and Patient Perspectives.Sudbury, Massachusetts: Jones and Bartlett Publishers, 1998. p. 287-300.

(7) Eiser C, Hill JJ, Vance YH. Examining the psychosocial consequences of surviving childhood cancer: Systematic review as a research method in pediatric psychology. J Pediatr Psychol 2000;25(6):449-60.

(8) Gray RE, Doan BD, Shermer P, Vatter Fitzgerald AV, Berry MP, Jenkin D, et al. Surviving childhood cancer: a descriptive approach to understanding the impact of life-threatening illness. Psychooncology 1992;1:235-45.

(9) Gray RE, Doan BD, Shermer P, Vatter Fitzgerald AV, Berry MP, Jenkin D, et al. Psychologic adaptation of survivors of childhood cancer. Cancer 1992;70:2713-21.

(10) Apajasalo M, Sintonen H, Siimes MA, Hovi L, Holmberg C, Boyd H, et al. Health-related Quality of life of Adults Surviving Malignancies in Childhood. Eur J Cancer 1996;32A(8):1354-8.

(11) Byrne J, Fears TR, Steinhorn SC, Mulvihill JJ, Connelly RR, Austin DF, et al. Marriage and divorce after childhood and adolescent cancer. JAMA 1989;262(19):2693-9.

(12) Dolgin MJ, Somer E, Buchvald E, Zaizov R. Quality of life in adult survivors of childhood cancer. Soc Work Health Care 1999;28(4):31-43.

(13) Elkin TD, Phipps S, Mulhern RK, Fairclough D. Psychological functioning of adolescent and young adult survivors of pediatric malignancy. Med Pediatr Oncol 1997;29:582-8.

(14) Evans SE, Radford M. Current lifestyle of young adults treated for cancer in childhood. Arch Dis Child 1995;72:423-6.

(15) Green DM, Zevon MA, Hall B. Achievement of life goals by adult survivors of modern treatment for childhood cancer. Cancer 1991;67:206-13.

(16) Hays DM, Landsverk J, Sallan SE, Hewett KD, Farkas Patenaude A, Schoonover D, et al. Educational, occupational, and insurance status of childhood cancer survivors in their fourth and fifth decades of life. J Clin Oncol 1992;10(9):1397-406.

(17) Holmes GE, Baker A, Hassanein RS, Bovee EC, Mulvihill JJ, Myers MH, et al. The availability of insurance in long-time survivors of childhood cancer. Cancer 1986;57:190-3.

(18) Jacobson VJC, Biddle AD, Daeschner CW, Chaffee S, Gold SH. Health insurance access to young adult survivors of childhood cancer in North Carolina. Med Pediatr Oncol 1995;25:389-95.

(19) Kelaghan J, Myers MH, Mulvihill JJ, Byrne J, Connelly RR, Austin DF, et al. Educational achievement of long-term survivors of childhood and adolescent cancer. Med Pediatr Oncol 1988;16:320-6.

(20) Lansky SB, LIst MA, Ritter-Sterr C. Psychosocial consequences of cure. Cancer 1986;58:529-33.

(21) Meadows AT, McKee L, Kazak AE. Psychosocial status of young adult survivors of childhood cancer: a survey. Med Pediatr Oncol 1989;17:466-70.

(22) Rauck AM, Green DM, Yasui Y, Mertens A, Robinson LL. Marriage in the survivors of childhood cancer: a preliminary description from childhood cancer survivor study. Med Pediatr Oncol 1999;33:60-3.

(23) Tebbi CK, Bromberg C, Piedmonte M. Long-term vocational adjustment of cancer patients diagnosed during adolescence. Cancer 1989;63:213-8.

(24) Teeter MA, Holmes GE, Holmes FF, Baker AB. Decisions about marriage and family among survivors of childhood cancer. Journal of psychosocial oncology 1987;5(4):59-68.

(25) Teta MJ, Del PMC, Kasl SV, Meigs JW, Myers MH, Mulvihill JJ. Psychosocial consequences of childhood and adolescent cancer survival. Journal of Chronic Disease 1986;39(9):751-9.

(26) Haupt R, Fears TR, Robison LL, Mills JL, Nicholson HS, Zeltzer LK, et al. Educational attainment in long-term surivors of childhood acute lymphoblastic leukemia. JAMA 1994;272(18):1427-32.

(27) Kingma A, Rammeloo LAJ, Van der Does-Van den Berg A, Rekers-Mombarg L, Postma A. Academic career after treatment for acute lymphoblastic leukaemia. Arch Dis Child 2000;82:353-7.

(28) Moe PJ, Holen A, Glomstein A, Madsen B, Hellebostad M, Stokland T, et al. Long-term survival and quality of life in patients treated with a national all protocol 15-20 years earlier: IDM/HDM and late effect? Pediatr Hematol Oncol 1997;14:513-24.

(29) Puukko LM, Hirvonen E, Aalberg V, Hovi L, Rautonen J, Siimes MA. Sexuality of young women surviving leukaemia. Arch Dis Child 1997;76:197-202.

(30) Zeltzer LK, Chen E, Weiss R, Guo MD, Robinson LL, Meadows AT, et al. Comparison of psychologic outcome in adult survivors of childhood acute lymphoblastic leukemia versus sibling controls: a cooperative children's cancer group and national institutes of health study. J Clin Oncol 1997;15(2):547-56.

(31) Zevon MA, Neubauer NA, Green DM. Adjustment and vocational satisfaction of patients treated during childhood or adolescence for acute lymphoblastic leukemia. The American Journal of Pediatric Hematology/Oncology 1990;12(4):454-61.

(32) Mackie E, Hill J, Kondryn H, McNally R. Adult psychosocial outcomes in long-term survivors of acute lymphoblastic leukaemia and Wilms' tumour: a controlled study. Lancet 2000;355:1310-4.

(33) Felder-Puig R, Formann AK, Mildner A, Bretschneider W, Bucher B, Windhager R, et al. Quality of life and psychosocial adjustment of young patients after treatment of bone cancer. Cancer 1998;83(1):69-75.

(34) Nicholson HS, Mulvihill JJ, Byrne J. Late effects of therapy in adult survivors of osteosarcoma and Ewing's sarcoma. Med Pediatr Oncol 1992;20:6-12.

(35) Novakovic B., Fears T.R., Horowitz M.E., Tucker M.A., Wexler L.H. Late effects of therapy in survivors of Ewing's Sarcoma Family Tumors. J Pediatr Hematol Oncol 1997;19(3):220-5.

(36) Veenstra KM, Sprangers MAG, Van der Eyken J, Taminiau AHM. Quality of life in survivors with a Van Ness-Borggreve rotationplasty after bone marrow tumour resection. J Surg Oncol 2000;73:192-7.

(37) Wasserman AL, Thompson EI, Wilimas JA, Fairclough DL. The psychological status of survivors of childhood/adolescent Hodgkin's Disease. Am J Dis Child 1987;141:626-31.

(38) Mäkipernaa A. Long-term quality of life and psychosocial coping after treatment of solid tumours in childhood: a population-based study of 94 patients 11-28 years after their diagnosis. Acta Paediatr 1989;78:728-35.

(39) Nicholson HS, Byrne J. Fertility and pregnancy after treatment for cancer during childhood or adolescence. Cancer 1993;71:3392-9.

(40) Mellette SJ, Franco PC. Psychosocial barriers to employment of the cancer survivor. Journal of psychosocial oncology 1987;5(4):97-115.

(41) Gotay CC, Muraoka MY. Quality of life in long-term survivors of adult-onset cancers. J Natl Cancer Inst 1998 May 6;90(9):656-67.

(42) Padilla GV, Kagawa-Singer M. Quality of life and culture. In: King CR, Hinds PS, eds. Quality of life from nursing and patient perspectives: theory, research, practice.Sudbury, Massachusetts: Jones and Barlett Publishers, 1998. p. 74-92.

(43) Kingma A. Neuropsychological late effects of leukemia treatment in children. Thesis. The Netherlands: Groningen Rijksuniversiteit; 2001.

(44) Schagen SB, van Dam FSAM, Muller MJ, Boogerd W, Lindeboom J, Bruning PF. Cognitive deficits after postoperative adjuvant chemotherapy for breast carcinoma. Cancer 1999;85(3):640-50.

(45) Rose JH. Social support and cancer: adult patients' desire for support from family, friends, and health professionals. Am J Community Psychol 1990;18:439-64.

(46) Worden JW, Weisman AD. Do cancer patients really want counseling? Gen Hosp Psychiatry 1980;2(100):103.

Table 1. Summary of selected studies in young adult survivors of childhood cancer

Study (yr)	Type of cancer	Number and sex of survivors	Age at evaluation (yr)	Age at diagnosis and time since completion of therapy (yr)
Holmes et al., 1986 (17)	Mixed	100 58% men 42% women	21 + mean age 33 median age 32	range 0 - 19 ; 5+ since diagnosis
Lansky et al., 1986 (20)	mixed (excluding CNS tumors)	39 49% men 51% women	mean age 23 age range 16 - 33	mean 13 range 10 - 18; 5+ since diagnosis mean 7 range 0 - 18
Teta et al., 1986 (25)	mixed	450 48% men 52% women	21 +	< 19; 5+ since diagnosis
Teeter et al., 1987 (24)	mixed	263 52% men 48% women	21 + mean age 33 age range 23 - 54	< 20; 5+ since diagnosis
Wasserman et al., 1987 (37)	Hodgkin's Disease	40 55% men 45% women	mean age 25 age range 10 -38	< 20 mean 13 range 12 - 19; 5+ since diagnosis mean 12 range 7 - 19
Kelaghan et al., 1988 (19)	mixed	2283 50% men 50% women	> 21 mean age 31 age range 21 - 55	< 20 range <5 - 19; 5+ since diagnosis

Number, sex and age of control group	Instruments/measures	Results/outcome
100 sex-matched siblings: mean age 33 median age 32	structured interview in person or by telephone about life and health insurance	Survivors had significantly more difficulty in obtaining life insurance and in obtaining health insurance because of health reasons. Survivors were significantly less likely than siblings to be covered by health insurance
siblings	structured interview in person or by telephone about family demograp-hics, past and present medical problems, acade-mic and career achieve-ments, disease impact, issues related to separa-tion, overall psychologi-cal adjustment	No significant difference in marital status, living arrangements, academic and career attainment. A higher prevalence rate in episodes of treated depression, alcoholism, and/or suicide attempts in survivors compared with that in the general population. Almost half reported that academic plans were altered, and 38% had made changes in their career goals because of the illness
587 sex-matched siblings: 47% men 53% women age >19	structured interview in person or by telephone: Addendum at NCI questionnaire about depression, difficulties in obtaining entrance to armed forces or access to educational and employ-ment opportunities, health and life insurance	No significant difference in depression between survivors and siblings, frequency was similar to the general population. No differences in reported frequencies of suicide attempts, running away or psychiatric hospitalisations. Survivors experienced significantly more jobdiscrimination, more rejection from the armed forces and had more difficulty obtaining health and life insurance than their siblings. Depression was not associated with: age at diagnosis, year of diagnosis and type of treatment
369 sex-matched siblings: 47 % men 53% women mean age 33 age range 20 - 59	structured interview in person or by telephone: Part of NCI questionnaire including decisions about marriage and family planning, outcome of pregnancy	Survivors were less likely to marry. More survivors than controls were not married for health reasons. More survivors than controls reported that they never have been pregnant and having no offspring. No significant difference was found between frequency of birth defects among the offspring of both survivors and controls
no control group, population norms available	structured interview in person about perceptions about their cancer, reactions of family and friends, risk-taking behavior, perceived benefits, education, employment, current medical problems; standardised question-naire: Diagnostic and Statistical Manual of Mental Disorders	Survivors educational levels exceeded those expected in sex-age- and state-matched populations. Overall proportions of marriage and divorce did not differ from general population statistics. Male survivors had a higher rate of divorce compared with age- and race-specific statistics. Frequency of psychiatric diagnoses were not different from that found in the community
3261 sex-matched siblings: 49% men 51% women mean age 33 age range 19 - 70	structured interview in person or by telephone about demographic characteristics, medical and reproductive history, social characteristics, including highest educa-tional level achieved	No significant differences in educational achievement were found for survivors of non-CNS cancers. Survivors of CNS tumors were significantly less likely than controls to complete eight grades of school or, if they completed high school, to enter college. Educational deficit of brain tumour survivors was especially striking for tumors of the ventricles or cerebral hemispheres and the deficit was more severe for those who were younger at diagnosis and those treated with radiation therapy than by surgery alone

Tebbi et al., 1989 (23)	mixed (excluding CNS tumors)	40 40% men 60% women	mean age 26 age range 18 - 35	mean 16 range 13 - 19; 5+ since diagnosis mean 10
Byrne et al., 1989 (11)	mixed	2170 sex not given	> 21 mean age 31	< 20; 5+ since diagnosis
Meadows et al., 1989 (21)	mixed	95 53% men 47% women	> 18 mean age 24 median age 22 age range 18 - 35	< 16 mean 6; 5+ since diagnosis
Mäkipernaa, 1989 (38)	solid tumors (excluding CNS tumors)	94 51% men 49% women	median age 23 age range 11 - 15	median 3 range 0 - 18
Zevon et al., 1990 (31)	ALL	46 52% men 48% women	mean age 23 age range 18 - 34	< 20 mean 7 range 2 - 18; 5+ since diagnosis mean 15
Green et al., 1991 (15)	mixed	227 54% men 46% women	median age 27 age range 18 - 44	< 20 median 11 range 1 - 19; 5+ since diagnosis

40 healthy sex- and age-matched controls: 38% men 63% women mean age 26 age range 18 - 35	semi-structured interview by telephone with standardised question-naires: The Rand Health Insuran-ce Study Functional Limi-tations Battery (FLB), Physical Abilities Battery (PAB), vocational, insu-rance, social status, The Rand Health Insurance study General Well-Being measure	No differences with regard to overall general well-being, although survivors were more concerned about their health and reported lower general spirits. Survivor's health limited their ability to engage in vigorous activities. Survivors reported disease-related discrimination in hiring, induction into military service, and obtaining health, life, and disability insurance. Survivors did not differ with respect to employment status but they reported a higher average income than controls
3138 sex-matched siblings: sex not given mean age 33	structured interview in person or by telephone about demographic characteristics, personal medical history, marriage, divorce, pregnancies, offspring, fertility	Survivors were less likely to be married. Men treated for CNS tumors were the most serious affected. Not only were they less likely to be married, their first marriages were shorter and they were older at first marriage. Increased divorce rate in male survivors of retinoblastoma
number of siblings not given median age 25	structured interview by telephone about educatio-nal achievement, occupa-tional status, interpersonal relation-ships, including marital status and pro-geny, benefits and insu-rance concerns, medical and health behaviours	Good overall functioning. No difference in the amount of education between survivors and their siblings. Siblings were significantly more likely to be married. Many survivors worried about recurrence of cancer. History of cancer sometimes affected their relationships. Age at diagnosis and the type of treatment was not related to education level
no control group, population norms available	semi-structured interview in person about educa-tion, occupation, social security, interests, marital status, disease-related opinions	Most survivors had good adjustment, some are at risk of developing emotional and social problems. Education level was similar, or slightly above population level. Some males were rejected for military service because of the history of cancer. Fewer of the females and as many of the males were married as in the general population
population norms available control group with survivors with HD + NHL	standardised question-naires in person or by mail: Multi-dimensional Personality Questionnaire (MPQ) Well-Being and Stress Reaction Scales, Minnesota Satisfaction Questionnaire-Short Form (MSQ), Long-Term Follow-Up Questionnaire (LFQ) (medical, employ-ment, marital, and family history), occupational status	ALL survivors appeared to be well-adjusted. Female survivors, however, had an increased tendency to experience anxiety in stressful situations. ALL survivors were marrying at a somewhat lower rate than the overall population. Vocational satisfaction did not differ from population norms. Vocational discrimination did not appear to be a problem. Cranial irradiation was negatively associated with well-being
no control group, population norms available	self-report questionnaire in person or by mail about marital status, employ-ment history, current occupation and job duties, health and life insurance status, reproductive history, family history	The percentage of employed survivors was not different from US norms. Percentages of life and health insurances were lower than US population. The percentages of married men and women were significantly lower than US norms, especially women aged 20-24. Women aged 35-44 had a significantly higher frequency of divorce compared with age-specific group norms. Male gender and age at study was positively associated with employment. Diagnosis, age at diagnosis and disease recurrence were not related to employment, marriage, divorce and insurance

Hays et al., 1992 (16)	mixed	219 sex not given	30+	< 19; 2+ since diagnosis
Gray et al., 1992 (9 Gray et al., 1992 (8)	mixed	62 65% men 35% women	> 18 mean age 26 age range 18 - 37	< 18 mean 11 range 1 - 18; 2+ since diagnosis mean 15 range 2 - 33
Nicholson et al., 1992 (34)	osteosarcoma + Ewing's sarcoma	111 50% men 50% women	> 21 mean age 33 age range 21 - 51	< 20 mean 15 range 3 - 19; 5+ since diagnosis mean 18
Haupt et al., 1994 (26)	ALL	593 51% men 49% women	> 18 mean age 23 age range 18 - 33	< 20 median 10 range 0 - 20; 2+ since diagnosis
Evans & Radford, 1995 (14)	mixed	48 54% men 46% women	mean age 20 age range 16 - 30	information about age at diagnosis not given < 5 (16 survivors) 5 + (32 survivors)
Jacobson Vann et al., 1995 (18)	mixed	187 47% men 53% women	age range 19 - 39	< 19; 5+ since diagnosis

	190 sex-matched siblings or friends	structured interview by telephone or mail about insurance coverage, demographic questions on race and ethnicity, occupation, education, employment, income	No differences in education, employment and insurance between non-CNS survivors and controls. Survivors of CNS tumors had limited educational achievements and lower rates of marriage and parenthood
	51 healthy age-matched peers: 45% men 55% women mean age 26	standardised question-naires in person: Profile of Mood States, Desirability of Control Scale, Control Belief Scale, Locus of Control Scale, Rosenberg Self-Esteem Scale, Impact of Event Scale, projective story-telling technique, screening questionnaire (demographic factors, presence or absence of health-risk behaviours), experience-sampling technique	Survivors were similar to their peers in overall psychologic adaptation, both within normal ranges. Survivors reported more positive affect, less negative affect, higher intimacy motivation, more perceived personal control and greater satisfaction with control in life situations. Survivors, especially CNS survivors, were more likely to have repeated school grades. Further, survivors worried more about issues of fertility and expressed more dissatis-faction with important relationships. No effects of time since illness, age at diagnosis, presence of recurrence and report of disability
	151 sex- and age-matched siblings: 44% men 56% women mean age 33 age range 21 - 66	structured interview in person or by telephone about health status, activities of daily living, education, employment and disability, marriage, fertility, pregnancy, health of their offspring	Osteosarcoma survivors were more likely than their siblings to perceive their health as poor. Survivors were more likely than controls to have some difficulty climbing stairs and to have had employment disability. Marriage rate, fertility, employment status and annual income were similar. Amputation status was not associated with health perception
	409 sex-matched siblings: 46% men 54% women mean age 25 age range 18 - 42	structured interview by telephone about educa-tion (highest level of schooling, average grades during high school, enrollment into special programs	On average, survivors had lower grades, were more likely to enter a special education or a learning disabled program and spent longer time in these programs. Survivors were at higher risk of missing school for long periods and/or repeating 1 year of school. Most survivors have rates of high school graduation, college entry, and college graduation that are similar to their siblings. Survivors treated with 24 Gy of CRT and those diagnosed at a preschool age were at higher risk for poor educational performance
	38 siblings: mean age 21 age range 16 - 30	unstructured interview in person about their experiences of cancer; structured interview: questions about their illness and current lifestyle; standardised questionnaire: Oxford Psychologists Press adult self-esteem questionnaire	No significant difference in their educational achievements, employment status and salary earned, driving test achievements, establishing relationships, partaking in societies and competitive sports. Survivors were less likely to go on to higher education. Survivors overall self-esteem was as high as their siblings
	108 siblings: 43% men 57% women age range 19 - 39	questionnaire by mail about health insurance	Survivors were found to be more likely to be denied health insurance because of their cancer history and related medical history than their siblings. Survivors also had health insurance policies that excluded care for pre-existing medical conditions more often. Survivors repor-ted more problems obtaining health insurance coverage, were more likely to be covered by their parents' health insurance policies and had been turned down for a job more often because of their cancer history

Apajasalo et al. 1996 (10)	mixed (excluding CNS tumors)	168 63% men 37% women	mean age 23 age range 16 - 35	information about age at diagnosis not given 1+ since diagnosis median 12
Puukko et al., 1997 (29)	Acute Leukaemia	30 100% women	> 16 mean age 20	mean 9; 1+ since diagnosis mean 8
Moe et al., 1997 (28)	ALL (without CRT)	94 55% men 45% women	not given	mean 5; 15+ since diagnosis
Zeltzer et al., 1997 (30)	ALL	580 51% men 49% women	mean age 23 median age 22 age range 18 - 33	< 20; 2+ since diagnosis
Elkin et al., 1997 (13)	mixed	161 53% men 47% women	> 15 median age 19 range 15 - 31	median 10 range 0 - 21; 2+ since diagnosis median 7 range 2 - 15

129 persons general population : 47% men 53% women age range 17 - 35	standardised question-naire by mail: 15-dimensional question-naire (15D) (mobility, vision, hearing, breathing, sleeping, eating, speech, elimination, usual activities, mental function, discomfort and symptoms, depression, distress, vitality and sexual activity)	Survivors QL was significantly better than that of controls. Both the survivors and the controls reported good levels of physical dimensions, sensory dimen-sions, usual activities and mental func-tion. Although emotional dimensions (depression, distress, vitality, sleeping and discomfort) were less satisfactory in both groups, survivors reported less problems than the controls. Younger survivors reported a better QL. BMT survivors reported a slightly lower QL. Type of cancer, follow-up time and gender were not associated with QL
50 healthy age-matched controls: 100% women mean age 20	self-report questionnaire, semi-structured interview, psychiatric evaluation, psychological tests in person about sexual attitudes, fears and behaviours, family and peer relationships, sexual experiences, health and illness concerns, ideals and expectations from life	The age at initiation of dating and sexual activity, the frequency of sexual intercourse, and opinions on sexual behavior were similar. Survivors differed significantly from controls with regard to inner sexuality; images of sexuality more restrictive, attitudes (concerning sexual pleasure) more negative. Sexual identity less often feminine and more often infantile in survivors. Sexual identity was not associated with age at study, age at diagnosis, type of treatment and follow-up time
90 sex-matched siblings/cousins: 59% men 41% women	standardised question-naires by mail: SF-12 (physical and mental health), General Health Questionnaire (depression, anxiety, fatigue, social dysfunc-tion), Eysenck's short scale of the EPQ-R (pos-sible late effects on personality); author-developed questionnaire: demographic data, number of offspring, learning problems, level of athletic perfor-mance, education and work status	No statistical difference with respect to physical and mental health and QL. The somatization score on the GHQ invol-ving items closely related to fatigue demonstrated a significantly higher score for the ALL survivors. No significant differences with regard to performances issues, such as academic skills, level of education, work status and level of physical exercise. Male survivors had significant fewer offspring than their male controls
396 sex-matched siblings: 46% men 54% women mean age 25 median age 25 age range 18 - 41	structured interview by telephone about educa-tion, marital status, employment status, health, fertility, offspring, risk behaviours; standardised questionnaire: Profile of Mood States (POMS) (tension, anxiety, depres-sion, anger, confusion, vigor, fatigue)	Marital differences between survivors and controls were not significant, however, older survivors were more likely to never have married. Survivors were more likely to be unemployed or working less than half-time. Survivors had a greater negative mood, reported more tension, depression, anger and confusion than controls, however, scores were not as high as those found in a psychiatric sample. No differences on the vigor and fatigue subscale scores. Female, minority, and unemployed survivors reported highest total mood disturbance
no control group, population norms available	standardised question-naire in person: Symptom Checklist-90 Revised (SCL-90-R) (somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, psychoticism, distress, cosmetic and functional impairments)	Mean scores on all subscales of SCL-90-R were lower than those of the standardisation sample, distributions of scores on the anxiety, psychotism, Global severity index, and positive symptom total scores were significantly below normative values. Survivors appear significantly healthier than age- and gender matched norms for the general population. Older age, disease relapse and functional impairment were risk factors for maladjustment. Not associated were diagnosis, age at diagnosis, type of treatment, cosmetic status, gender and socioeconomic status

Novakovic et al., 1997 (35)	Ewing's sarcoma family tumors	89 54% men 46% women	mean age 29 age range 10 - 48	mean 15 range 4 - 34; mean 13 since diagnosis range 2 - 29
Felder(Puig et al., 1998 (33)	osteosarcoma + Ewing's sarcoma	60 43% men 57% women	mean age 24 age range 15 - 30	mean 15 range 0 – 25; 1+ since diagnosis mean 8 range 1 - 21
Dolgin et al., 1999 (12)	mixed	64 47% men 53% women	> 18 mean age 24 age range 18 - 35	< 18 mean 12 range 1 - 17; 3+ since diagnosis mean 10 range 3 - 21
Rauck et al., 1999 (22)	mixed	10425 54% men 46% women	median age 26 range 15 - 48	< 21 median 7 range 0 - 21; 5+ since diagnosis
Veenstra et al., 2000 (36)	bone tumor	33 55% men 45% women	> 16 mean age 25 range 16 - 50	Information about age at diagnosis not given; 1+ since diagnosis mean 6 range 1 - 11

	97 sex- and age-matched siblings: 47% men 53% women mean age 31 age range 10 - 57	questionnaire by mail about education, job history, marital status, fertility, health status, diet, exercise habits, health insurance, health care needs; standardised instrument: Karnofsky performance scale (current functional status)	No difference in educational achieve-ment. Survivors were less likely to be employed full-time, to be married and to have children. Survivors were more likely to have divorced than their siblings. No difference in self-rating of health status or in health care insurance status, but more problems in getting job-related health insurance. Functional status was adversely affected in survivors, they scored significantly worse than sibling controls. Having children was not related to treatment-related factors. Marriage was not associated with the treatment protocol and body irradiation
	no control group, population norms available	standardised question-naires in person: Questionnaire on Subjec-tive Well-Being (positive attitudes towards life, depressive mood, joy of life), State-Trait-Anxiety Inventory (trait-anxiety), Frankfurt Self-Concept Scales, Questionnaire on Life Goals and Satisfac-tion with Life; semi-structured interview about socioeconomic issues, life-style, problems and limitations due to disease and its consequences, overall quality of life	Survivors did not show a higher rate of serious personality disturbances or psychosocial problems then controls. Many, however, dealt with problems such as restricted mobility, catching up at school, changing jobs or job orientation. Survivors appeared to be married at a lower rate and seemed to live at home longer. Levels of education and income were similar. Survivors diagnosed in adolescence had more problems (especially social well-being) than those diagnosed in childhood or early adulthood. Physical or functional sequelae and disease-related variables were not associated with psychosocial adjustment
	51 age- and sex-matched controls: 53% men 47% women mean age 23 age range 18 - 32	structured interview in person about level of functioning and achieve-ment in the domains of education, employment, military service, social/family status, health status; standardised questionnaire: Mental Health Inventory (anxiety, depression, loss of control, general positive feeling, positive relationships)	No differences in education, employment, marital status and relation-ships with significant others. No evidence of increased psychological impairment or pathology. Survivors experienced military recruitment difficulties, lower income levels and higher rates of workplace rejection. Almost half reported feelings that their illness experience had impaired their achievement in education, social and family goals
	no control group, population norms available	questionnaire by mail about marital status	Survivors, especially females and whites, were less likely to have ever married, but, once married, were less likely to divorce/separate. Black survivors were generally found to be more likely to have married, with males and blacks more likely to divorce/separate once married. Survivors of CNS tumors, particularly males, were less likely to have ever married and more likely to divorce/separate compared to those with other diagnoses and the general US population
	no control group, population norms available	standardised question-naires by mail: 2 items EORTC-QLQ-C30, SF-36, shortened version Social Support List-Interactions and Social Support List-Discrepancies, items from EORTC QLQ-BR23, physical functioning and prosthesis, negative and positive effects of surgery	Survivors physical functioning was poorer than that of healthy peers but better than chronically ill patients. Levels of psychosocial functioning, general QL and social support were highly comparable with healthy peers

Kingma et al., 2000 (27)	ALL (with CRT)	94 43% men 57% women	median age 20 range 15 - 32	median 5 range 1 - 15 mean 15
Mackie et al., 2000 (32)	ALL + Wilms tumour	102 56% men 44% women	mean age 26 range 20 - 31	< 16 mean 5 range 0 - 15; 5+ since diagnosis mean 16 range 5 - 29

	134 siblings: 49% men 51% women median age 19 age range 14 - 32	questionnaire by mail about school career	Significantly more survivors than siblings were placed in special educational programmes. Survivors had also a lower level of secondary educa-tion. Younger age at diagnosis was negatively related to educational level. Gender and cranial irradiation dose were not associated with educational level
	102 healthy age- and sex-matched controls: 56% men 45% women mean age 26 age range 20 - 31	standardised question-naires in person; Schedule for Affective Disorder and Schizo-phrenia lifetime (SADS-L) with DSM-III-R, Adult Personality Functioning Assessment (APFA), Raven's standard progressive matrices	No increased rates of psychiatric disorder for survivors. Mean scores of survivors were significantly higher (indicating poorer functioning) than controls for love/sex relationships, friendships, non-specific social contacts and day-to-day coping. Mean overall work and educational performance scores did not differ between groups. Poor close relationship was related to longer duration of treatment and more recent illness, while age at diagnosis was not associated

Chapter 8

Quality of life and current coping in young adult survivors of childhood cancer: positive expectations about the further course of the disease were correlated with better quality of life

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ABSTRACT

Objectives: As a result of advances in the treatment of childhood cancer many patients who may previously have had a limited life expectancy, are now surviving into adulthood. More insight is needed into the long-term adjustment of young adult survivors of childhood cancer. The purpose of this study was to (1) assess HRQoL, and (2) to explore the role of cognitive coping in relation to HRQoL.

Methods: HRQoL of 353 Dutch young adult survivors of childhood cancer was compared with HRQoL of 507 peers. Linear regression analyses predicted survivors' HRQoL by cognitive coping, independent of the impact of demographics and medical variables.

Results: Survivors reported a lower HRQoL than their peers. Health status was the best predictor of the Physical Component Scale of the RAND-36; health status and cognitive coping contributed almost equally well to the Mental Component Scale. The explanatory value of cognitive coping could mainly be attributed to the use of predictive control strategies.

Conclusions: Because current coping seemed to be an important predictor of HRQoL, interventions directed at the coping strategies of survivors should be useful. The strong association between predictive coping and HRQoL stresses the importance of focusing at having positive expectations about the further course of the disease.

INTRODUCTION

As a result of advances in the treatment of childhood cancer, the number of survivors reaching adulthood has increased enormously in the last decades. With the increasing number of long-term survivors of childhood cancer, the need to assess their quality of life (QoL) becomes more and more important. The concept of health-related QoL (HRQoL) refers to the impact of health and illness on the individual's QoL (1;2). Numerous long-term physical effects of childhood cancer have been documented, but the impact of such sequelae on the HRQoL of patients is much less well understood. Reviews about the HRQoL of young adult survivors of childhood cancer mention a wide variety of studies with contradictory results (3;4). The contradictory results are due to several causes. The assessment of HRQoL is complex because there is not yet an universally accepted definition for it. The current consensus is that it should include at least four domains: physical, cognitive, social and emotional functioning. Furthermore, HRQoL studies are characterised by a high degree of heterogeneity with respect to: the patient samples (e.g. survivors with different cancers who have undergone a variety of treatments), the comparison groups selected, the HRQoL dimensions assessed, and the instruments employed (4).

As we learn more about the challenges associated with long-term survival of childhood cancer, more insight is needed into the predictors of adjustment of young adult survivors to enable us to detect the survivors at risk for adjustment problems. Factors related to the functioning of survivors, especially demographics and medical variables, have been discussed to some extent in many studies of HRQoL (5-9)(see also: review of Langeveld et al. (4)). Although inconsistent data have been reported across studies, the results suggest the following. Firstly, an increased risk for emotional problems proved to be associated with female gender, older age at follow-up, a greater number of relapses, the presence of severe functional impairment, cranial irradiation, and belonging to a minority. Secondly, survivors of CNS tumors and subsets of survivors of acute lymphatic leukaemia (ALL) seemed to be at risk for educational deficits; the same is true for cranial irradiation and early age at diagnosis. Thirdly, survivors of bone tumors were more likely to perceive their health as fair or poor, and also reported lower physical functioning than their controls. The demographics and medical variables described above only explain variations in HRQoL to a limited extent.

Apart from medical variables, more insight is needed into other predictors of adjustment among survivors of childhood cancer, such as coping and family functioning, in order to enable health care providers to detect and help survivors at risk.

The role of coping seems to be important in relation to the adjustment of children with cancer (10). The more we know about disease-specific coping and about the relation between coping and HRQoL the better health care providers will be able to help patients to cope with the consequences of their disease. However, in the literature no former studies were found about the young adults' coping with the long-term consequences of childhood cancer. Therefore, the current study was directed at this topic.

According to the model of stress and coping developed by Lazarus and Folkman (11), coping consists of actions, behaviors and thoughts aimed at dealing with the demands of events and situations that are appraised as stressful. So, coping mediates the effect of stress on an individual's well-being. Two main types of coping can be distinguished: problem-focused coping and emotion-focused coping. Problem-focused coping involves direct effort to modify

the problem causing the distress, whereas emotion-focused coping is directed at regulating affects surrounding a stressful experience.

Rothbaum's concept of primary- and secondary control (12) is related to problem-focused and emotion-focused coping. All the actions of problem-focused coping can be seen as primary control. If stressors are perceived as uncontrollable, primary control fails, and people will try to adjust to the situation, which is called secondary or cognitive control. Rothbaum et al. (12) distinguish four control strategies: predictive control, vicarious control, illusory control, and interpretative control.

It is reasonable to say that cancer is an uncontrollable stressor because patients can't solve the problem and are dependent on physicians. So, patients have to rely predominately on emotion-focused coping or, in other words, secondary or cognitive control, the main topic of this paper. In the context of coping with a life-threatening illness the following disease-related cognitive control strategies are relevant (13). *Predictive control* means that one attempts to predict events in order to create the feeling that one is able to control the situation. Having positive expectations helps patients to deal with the consequences of disease. *Vicarious control* strategies concern the attribution of special power to others, in the case of cancer patients to the doctors, on whom all hope is focused. Because one can not alter the course of the disease, belief in powerful others can be adaptive. With *illusory control* one attempts to associate with chance, such as hoping for a miracle or wishful thinking. Finally, *interpretative control* refers to the search for meaning and understanding. Using information to help to understand emotional reactions or to reduce uncertainty are interpretative control strategies.

The purpose of the present study was (1) to assess the HRQoL of young adult survivors of childhood cancer in comparison with the HRQoL of peers without a history of childhood cancer, and (2) to explore the role of cognitive coping in relation to HRQoL, independent of the impact of medical variables. With respect to the first purpose we hypothesize that survivors report worse HRQoL than peers. Furthermore, we expected that cognitive coping is correlated with HRQoL.

PATIENTS AND METHODS

Procedure

The results presented here concern the cross-sectional part of the VOLG-study, a Dutch study on the late psychosocial consequences of cancer in childhood. The respondents for this part of the study were recruited from the long-term follow-up clinic at The Emma Children's Hospital/ Academic Medical Center in Amsterdam, established in 1996 to monitor long-term sequelae of childhood cancer and its treatment. Patients become eligible for transfer from active-treatment clinics to the follow-up clinic when they had successfully completed their cancer treatment at least 5 years earlier. Survivors are evaluated annually in the clinic by a paediatric oncologist (patients aged < 18 years) or by an internist-oncologist (patients aged > 18 years) for late medical effects, as well as a research nurse or psychologist for psychosocial effects.

In 2001 and 2002, the survivors of childhood cancer, aged between 18 and 30 years, who attended the long-term follow-up clinic were asked (by letter or by a psychologist) to fill in anonymously questionnaires about HRQoL, course of life, and coping with the disease. After

having completed the questionnaires at home, they could return them in a stamped addressed return envelope. After a month, all eligible survivors received a reminder letter together with the same questionnaires. The inclusion criteria were: (1) age at study 18-30 years, (2) end of successful treatment at least five years before, (3) age at cancer diagnosis < 18 years, and (4) being able to understand Dutch questionnaires.

At the end of 2000 and 2001 an age-matched and sex-matched control group was formed with the help of the general practitioners (GPs) of the survivors. The GPs were asked to select ten patients from their registry lists, whose surnames started with a given letter from the alphabet, and who had a given sex and age. The inclusion criteria for the comparison group were: (1) age at study 18-30 years, (2) no history of cancer, and (3) being able to understand Dutch questionnaires. The GPs had to send a packet containing the questionnaires, information about the VOLG-study, and a stamped addressed return envelope to the ten randomly selected patients. Two weeks after the original mailing date, the GPs had to send another packet with the same content and a reminder letter.

The Medical Ethic Committee of the Academic Medical Center in Amsterdam has approved the study protocol.

Measures

Health-related quality of life (HRQoL) was assessed with the RAND-36 and the Cognitive Control Strategies Scale (CCSS) was used for measuring current cognitive coping with a disease.

The *RAND-36* is a Dutch version of the MOS-SF-36 Health Survey and almost identical to the Dutch SF-36 (14). The RAND-36 is composed of 36 items with standardized response choices, clustered into eight multi-item scales: Physical Functioning (PF), Social Functioning (SF), Role limitations due to Physical health problems (RP), Role limitations due to Emotional problems (RE), general Mental Health (MH), vitality (VT), Bodily Pain (BP), and General Health perceptions (GH). All raw scale scores are converted to a 0-100 scale, with higher scores indicating higher levels of functioning or well-being. The validity and reliability of the RAND scales are satisfactory (15). In the present study we found Cronbach's alpha's in the range 0.74 – 0.90 among survivors and 0.74 – 0.89 in the comparison group.

Overall physical and overall mental health were assessed by aggregation of all scale scores according to the algorithm described by Ware et al. (16), which leads to the so-called Physical Component Scale (PCS) and Mental Component Scale (MCS). The relative contribution of each scale to PCS and MCS was derived from principal components analysis, non-orthogonal rotation (Oblimin), based on the assumption that physical health and mental health are interdependent. This is contrary to the analysis of Ware et al. (16), who conducted an orthogonal rotation.

The *Cognitive Control Strategies Scale* (CCSS) was used to measure coping with the disease in now-healthy survivors. The CCSS is an instrument of disease-related cognitive coping, based on the model of Rothbaum et al. (12) and developed at the Psychosocial Department of The Emma Children's Hospital/AMC. Although the validity of this instrument has not yet been published formally, the questionnaire proved to be useful in earlier studies (13;17;18). The CCSS consists of 22 items, and may be applied to children, adolescents and young adults with any chronic disease. In this questionnaire respondents are asked to indicate whether

they agree with a given statement on a 4-point scale: totally agree, agree, disagree, totally disagree. Higher scores on a subscale represent a stronger reliance upon the control strategy.

The items of the CCSS were grouped into three subscales: predictive control (being optimistic about the course of the illness), vicarious control (attributing power to medical-care givers and treatment), and interpretative control (searching for meaning and information in order to better understand emotional reactions and to gain insight into the situation). Because in validity studies the subscale assessing illusory control failed to show sufficient internal consistency (Cronbach's alpha of 0.45), this subscale is not included in the instrument as we use it. Items composing a subscale were selected after a principal component factor analysis with varimax rotation, and after inspection of the psychometric features of the items. Inclusion of items in the subscales was based on (1) factor loadings higher than 0.40, (2) no reduction in the Cronbach's alpha coefficient of the subscale, (3) a considerable correlation with the other items of the subscale. Test-retest reliability was tested in a population of 21 adolescents with Familial Hypocholesterolemia (FH), a chronic stable disease (19). The adolescents completed the questionnaire twice within 2 weeks. Test-retest reliability was analysed calculating the intra-class correlation coefficient (ICC). ICCs for the three subscales exceeded 0.60: predictive control 0.64; vicarious control 0.73; and interpretative control 0.88.

The Cronbach's alpha's in the present study were satisfactory: predictive control 0.74 (3 items); vicarious control 0.78 (8 items); interpretative control 0.80 (4 items). The use of the three control strategies were related to each other. Vicarious control was positively related to predictive control ($r = 0.30$, $p<0.01$) and to interpretative control ($r = 0.16$, $p<0.05$). There was no significant correlation between predictive control and interpretative control.

Medical data, concerning diagnosis, treatment and health problems, were obtained from the registry of the long-term follow-up clinic at The Emma Children's Hospital/Academic Medical Center in Amsterdam. The registry of health problems is based on the information the oncologist receives at the annual evaluation; the oncologist also noted down whether the patient reported psychosocial or cognitive problems. The health problems were categorised into ten groups, based on Stevens et al. (20): i.e. endocrine, organ toxicity, mobility/orthopaedic, infertility, sensory, cosmetic, fatigue, subsequent neoplasm, psychosocial/cognitive, and neurological. Apart from the registration at the long-term follow-up clinic all respondents were asked to fill in whether they had experienced health complaints in the last four weeks and whether they suffered from a chronic disease.

Statistical analysis

The Statistical Package for Social Sciences (SPSS), Windows version 11.5, was used for all analyses. Before conducting the final analyses several preparation analyses were conducted. Firstly, (sub)scales were constructed, on the basis of the guidelines of the questionnaires used, and the reliability of these (sub)scales was calculated. Secondly, we created three medical variables. We formed two dummy variables and took the first category of each dummy as reference for the analysis: *diagnosis*: leukaemia/lymphoma, solid tumours, brain tumours; *treatment*: surgery only, chemotherapy with or without surgery, radiotherapy with or without surgery, chemotherapy and radiotherapy with or without surgery. Survivors' *health problems* as registered (at any time) by the long-term follow-up clinic were divided into two variables: physical problems (yes or no) and psychosocial/cognitive/neurologic problems (yes

or no). Thirdly, missing data were imputed at (sub)scale level. If less than half of the items of a (sub)scale was missing, the (sub)scale score was calculated on the basis of the items the respondent had completed. The percentage imputed RAND-scalescore ranged from 0.0 to 6.7 and the percentage imputed scalescore on the CCSS ranged from 0.7 to 4.7. Finally, we compared survivors and comparisons with respect to their demographic characteristics in order to detect confounders. Therefore, we used Student's t-test and χ^2-tests.

After these preparation analyses, multivariate analysis of variance (MANOVA) and univariate analysis of variance (ANOVA) were conducted to test group differences on the RAND-36, corrected for age, sex and, if needed, other confounders. Effect sizes (*d*) were calculated by dividing the difference in mean score between survivors and comparisons by the standard deviation of the scores in the comparison group. We considered effect sizes up to 0.2 to be small, effect sizes about 0.5 to be moderate, and effect sizes about 0.8 to be large (21).

To get an impression of the meaning of the scores on the subscales of the CCSS, the mean scores on the subscales were divided by the number of items of the subscale. This resulted in the mean item scores for the three cognitive control strategies. The higher the mean item score the more agreement with the statements, that is, the stronger the reliance on the cognitive control strategies. A mean item score 1 means total disagreement and a mean item score 4 means total agreement with all the items of the subscale.

We performed multiple linear regression analyses to investigate the predictive value of cognitive coping in relation to the RAND scores, and we corrected for (1) demographics, i.e. age and gender, (2) medical variables, i.e. diagnosis, treatment, age at first diagnosis, duration of treatment, and relapse or second malignancy, and (3) health status, i.e. current health complaints/disease, and health problems as registered (at any time) by the long-term follow-up clinic at The Emma Children's Hospital/Academic Medical Center in Amsterdam. The medical variables 'time since diagnosis' and 'time since end of treatment' were not entered into the model because of multicollinearity. These variables could be predicted by 'age', 'age at first diagnosis', and 'duration of treatment', variables which are represented in the model.

We limited the regression analysis to the two summary scales of the RAND-36 in order to minimize the number of statistical tests. All variables were presented in the final regression model for the physical summary score (PCS) and the mental summary score (MCS) of the RAND-36. In order to compare the strength of the association between the summary scores and the various groups of independent variables, we entered the variables stepwise into the regression model: (1) demographics, (2) medical variables, (3) health status, and (4) cognitive coping. After each step, the total variance explained by the included variables (R-square) was assessed, so that an increase in explained variance could be contributed to the added variables.

RESULTS

Participants

Survivors

A total of 499 consecutive young adult survivors were asked to take part in the cross-sectional part of the VOLG-study, 262 men (52.5%) and 237 women (47.5%). Three hundred and fifty-five questionnaires were returned (response 71.0%), two questionnaires could not be

used for analysis because of not being filled in by the patient herself (n = 1) or returned too late (n = 1). Of the 144 survivors who did not complete the questionnaires 18 returned the non-response form. Most of these non-respondents reported that they did not have enough time or didn't feel like taking part in the study (n = 10). Two non-respondents did not complete the questionnaire because they did not want to be confronted with cancer again; the other six refused for other reasons.

The data of 353 survivors could be used for the analyses: 175 (49.6%) men, 178 (50.4%) women. Their mean age was 24.3 years (SD=4.0; range=17.7-31.1) and the median age was 24.5 years (Table 1).

The respondents were older than the non-respondents at study (M=23.2 years; SD=3.9; range=18.0-30.8) and at diagnosis (M=6.3 yrs; SD=4.7; range 0.0-17.0) ($p < 0.05$), and there was a higher percentage of women among the respondents than among the non-respondents (50.4% versus 40.4%, $p < 0.01$). No significant differences were found in diagnosis and treatment, time since first diagnosis, time since end of treatment, duration of treatment, having had a relapse or second malignancy, and health problems as registrered at the long-term follow-up clinic.

Comparison group

A total of 264 General Practitioners (GPs) were asked to recruit ten patients from their practice for the comparison group; 96 (36.4%) GPs agreed to take part in the study. From 82 general practices one ore more completed questionnaires were returned. So we concluded that in the end 82 GP's (31.0%) had participated in the study, whom we assumed to have recruited 820 patients. The investigators received 517 questionnaires (response rate 63.0%), of which 10 could not be used because of: the age of the patients at study being younger than 18 years or older than 30 years (n=5), unknown age (n = 1), history of cancer (n = 2), RAND-36 not being completed (n = 2). So the final comparison group consisted of 507 respondents, 239 men (47.1%) and 268 women (52.9%), mean age 24.2 years (SD 3.8, range 18.0-30.9), median age 23.8.

Of the 303 non-respondents 50 returned the non-response form. They reported that they had no time (n = 13) or no interest (n = 8) to take part in the study. Ten possible respondents did not complete the questionnaires because they misunderstood the informative letter and supposed that they should have a history of cancer themselves. Eight questionnaires proved to be undeliverable, and the remaining 11 non-response forms mentioned other reasons. More men (70%) than women (30%) refused. Because the recruitment by the GPs was strictly anonymous, we could not trace other characteristics of the non-response group, or the reasons for refusal.

Survivors versus comparison group

The characteristics of the survivors and the comparison group are listed in Table 1. No significant differences were found with respect to age, gender, native country, nationality, and religion.

Quality of life (RAND-36): survivors versus comparison group

The multivariate analysis of variance (MANOVA) for the RAND scales as a function of group, gender and age showed multivariate main effects for group ($F(8,835) = 2.8$, $p <$

Table 1: Demographic and medical characteristics of the survivors and the comparison group

	Survivors (n = 353)			Comparison group (n=507)		
	M	**SD**	**Range**	**M**	**SD**	**Range**
Age at study (years)	24.3	4.0	17.7-31.1	24.2	3.8	18.0-30.9
Age at first diagnosis (years)	7.3	4.7	0.0-17.0			
Time since first diagnosis (years)	17.0	6.0	6.2-30.7			
Time since end of last treatment (years)	15.5	5.5	4.9-30.3			
Duration of treatment (months)	12.5	10.5	0.0-72.5			

	n	**%**	**n**	**%**
Gender				
female	178	50.4	268	52.9
male	175	49.6	239	47.1
Native country				
The Netherlands	338	96.6	487	96.1
Other	12	3.4	20	4.0
Religion				
yes	164	47.1	218	43.2
no	184	52.9	287	56.8
Diagnosis				
leukaemia/lymphoma	176	49.9		
solid tumor	152	43.1		
brain tumor	25	7.1		
Treatment				
Chemotherapy (with/without surgery)	199	56.4		
Radiotherapy (with/without surgery)	14	4.0		
surgery alone	26	7.4		
combination therapie (chemo+ radio, with/ without surgery)	114	32.3		
Health problems				
no problems	45	12.7		
physical	299	84.7		
psychosocial / cognitive / neurological	114	32.3		
Relapse or second malignancy				
yes	43	12.2		
no	310	87.8		

0.01) and gender ($F(8,835) = 8.4$, $p < 0.001$). The results of the univariate F-tests according to MANOVA showed worse HRQoL among survivors than among the comparison group with respect to: Physical Functioning ($F(1,842) = 7.6$, $p < 0.01$), Social Functioning ($F(1,842) = 5.9$, $p < 0.05$), and Role limitations due to Physical problems ($F(1,842) = 8.3$, $p < 0.01$) (Table 2). ANOVA for the Physical Summary Scale confirmed these findings (Table 3): survivors scored significantly lower $F(1,842) = 4.4$, $p < 0.05$ than the comparison group. All significant differences between survivors and comparisons were small: effect sizes ranged from 0.15 for PCS to 0.22 for Role limitations due to Physical problems.

Table 2: Mean scores, SD's and differences between survivors and comparison group on the eight scales of the RAND-36, as a function of Group by Gender[a]

	Survivors			Comparison group			Effect size (d)
	Males n = 144	Females n = 150	Total n = 294	Males n = 238	Females n = 262	Total n = 500	Total
PF							
Mean	94.6	86.8	90.2[c]	94.6	91.7	93.1	0.21
SD	13.3	19.7	17.2	12.7	15.1	14.1	
SF							
Mean	90.4	78.2	84.2[b]	89.6	85.5	87.4	0.17
SD	16.9	24.0	21.6	17.1	19.4	18.4	
RP							
Mean	87.2	75.0	81.0[c]	90.4	83.7	86.9	0.22
SD	28.7	37.1	33.7	23.0	30.0	27.0	
RE							
Mean	89.6	79.5	84.5	89.5	85.5	87.4	0.10
SD	26.7	36.1	32.2	27.0	30.1	28.7	
MH							
Mean	77.6	71.2	74.4	77.3	74.8	76.0	0.11
SD	14.0	17.2	16.0	15.0	15.3	15.2	
VT							
Mean	69.2	58.4	63.7	67.5	63.1	65.2	0.09
SD	18.4	18.7	19.3	16.6	16.8	16.8	
BP							
Mean	93.4	81.4	87.3	91.4	82.5	86.8	0.03
SD	13.3	21.0	18.6	14.6	21.4	18.9	
GH							
Mean	77.6	70.9	74.2	76.1	74.4	75.2	0.06
SD	19.0	21.3	20.5	16.4	18.1	17.3	

[a] Multivariate effects were found on group ($p < 0.01$) and gender ($p < 0.001$). [b] $p < 0.05$: difference between survivors and comparison group (based on univariate F-tests according to MANOVA, RAND-scales by group, gender, age).[c] $p < 0.01$: difference between survivors and comparison group (based on univariate F-tests according to MANOVA, RAND-scales by group, gender, age).

PF: physical functioning; SF: social functioning; RP: role limitations due to physical problems; RE: role limitations due to emotional problems; MH: mental health; VT: vitality; BP: bodily pain; GH: general health perceptions.

Table 3: Mean scores, SD's and differences between survivors and comparison group on the PCS and the MCS of the RAND-36, as a function of Group by Gender[a]

	Survivors			Comparison group			Effect size (d)
	Males n = 170	Females n = 174	Total n = 334	Males n = 238	Females n = 264	Total n = 502	Total
PCS							
Mean	51.9	45.4	48.6[b]	51.7	48.6	50.1	0.15
SD	8.8	13.2	11.7	7.7	11.4	9.9	
MCS							
Mean	51.8	46.0	48.9	51.2	49.1	50.1	0.12
SD	9.5	11.6	11.0	9.5	10.2	9.9	

[a] Univariate effects were found on group (PCS, $p < 0.05$) and gender (PCS and MCS, $p < 0.001$) [b] $p < 0.05$: difference between survivors and comparison group.

PCS: Physical Component Scale; MCS: Mental Component Scale.

Cognitive coping and HRQoL of survivors

The scores on the subscales of the CCSS are presented in Table 4: predictive control, vicarious control, and interpretative control strategies. The scores in Table 4 indicate agreement with many statements of the three cognitive control strategies.

Table 4: Mean scores, SD's, ranges, and mean item scores on the subscales of CCSS

	N	Mean	SD	Range	Mean Item score
Predictive control (3 items)	351	9.5	1.6	4 – 12	3.2
Vicarious control (8 items)	351	22.5	3.2	10 – 32	2.8
Interpretative control (4 items)	352	12.0	2.3	5 – 16	3.0

The results of the multiple regression analyses are presented in Table 5, including the total variance explained (R^2) after each step, so that the increase in R^2 represents the contribution of the variables added at that step.

Both PCS (R^2 = 0.40; $p < 0.001$) and MCS (R^2 = 0.39; $p < 0.001$) were reasonably well predicted by the regression model. Health status (step 3) was the best predictor of the PCS: it explained half (20%) of the total variance explained (40%). Health status (step 3) and cognitive coping (step 4) together contributed almost equally to MCS, 12% and 14% of the total R^2 (39%), respectively.

Age and gender (step 1) explained 10% (PCS) and 8% (MCS) of the regression model, which was mainly due to gender. The mean HRQoL of women was worse than that of men; for both PCS and MCS β = -0.13 ($p < 0.01$). In step 2, i.e. the entrance of the medical variables, there was a small increase in R^2, i.e. 3% for PCS, and 5% for MCS. As shown in Table 5, the age of the survivor at diagnosis was negatively related to HRQoL: the older at diagnosis, the worse PCS and MCS (β = -0.16; $p < 0.01$ and β = -0.19; $p < 0.001$ respectively). Survivors who had been treated otherwise than with surgery alone reported better mental HRQoL (MCS) than survivors treated with surgery alone. Diagnosis, duration of treatment and the occurence of a relapse did not contribute to HRQoL. With regard to step 3, survivors with psychosocial/cognitive/neurological problems registered (at any time) at the long-term follow-up clinic had lower scores on PCS (β = -0.19; $p < 0.001$) and MCS (β = -0.18; $p < 0.001$) than survivors without these problems. Physical problems registered (at any time) at the long-term follow-up clinic did not contribute to the model. Current health problems (experienced health complaints in the last four weeks) were negatively associated with PCS (β = -0.33; $p < 0.001$) and MCS (β = -0.21; $p < 0.001$). Step 4, cognitive coping, showed that the more use of predictive control strategies, the better HRQoL, including the PCS (β = 0.23; $p < 0.001$) and the MCS (β = 0.39; $p < 0.001$). In contrast, more use of interpretative control strategies was associated with worse physical HRQoL (PCS: β = -0.12; $p < 0.01$). Reliance on vicarious control was not related to HRQoL.

Table 5: Standardized regression coefficients ß for the relationship between cognitive coping (CCSS) and HRQoL (RAND-36), corrected for demographics and medical variables

	Physical Component Scale	Mental Component Scale
	ß	ß
Age	-0.04	0.00
Gender (female)	-0.13 [a]	-0.13 [a]
DF	2,341	2,341
total R^2	0.10 [b]	0.08 [b]
Diagnosis (leukaemie/lymphoma = reference)		
solid tumour	-0.10	-0.09
brain tumour	0.01	0.04
Treatments (surgery only = reference)		
chemo (with/without surgery)	0.05	0.31 [a]
radio (with/without surgery)	0.06	0.19 [a]
chemo + radio (with/without surgery)	0.03	0.25 [a]
Age at first diagnosis (years)	-0.16 [a]	-0.19 [b]
Duration of treatment (months)	-0.03	-0.03
Relapse or second tumour	-0.09	0.02
DF	10,333	10,333
total R^2	0.13 [a]	0.13 [b]
Physical problems [c]	-0.00	0.01
Psychosocial / cognitive / neurological problems [c]	-0.19 [b]	-0.18 [b]
Current health complaints/disease [d]	-0.33 [b]	-0.21 [b]
DF	13,322	13,322
total R^2	0.33 [b]	0.27 [b]
Predictive control	0.23 [b]	0.39 [b]
Vicarous control	0.08	-0.02
Interpretative control	-0.12 [a]	-0.04
DF	16,316	16,316
total R^2	0.40 [b]	0.39 [b]

[a] $p < 0.01$; [b] $p < 0.001$

[c] Health problems as registered (at any time) by the long-term follow-up clinic at The Emma Children's Hospital/Academic Medical Center in Amsterdam

[d] Health complaints experienced in the last four weeks as reported by the respondents.

DISCUSSION

The purpose of this study was (1) to assess the HRQoL of young adult survivors of childhood cancer in comparison with the HRQoL of peers without a history of childhood cancer, and (2) to explore the role of cognitive coping in relation to HRQol, independent of the impact of medical variables.

With regard to the first purpose we conclude that the hypothesis has been confirmed: the HRQoL of the survivors in our sample group was worse than the HRQoL of the comparison group of peers without a history with cancer. The two groups differed significantly on the

physical component scale (PCS) of the RAND-36, and on the scales Physical Functioning, Social Functioning, and Role limitations due to Physical problems. However, the differences were small ($d \leq 0.22$) according to classification of Cohen (21). The findings of our present study are in accordance with the results of other recent studies on HRQoL and psychosocial outcome of young adult survivors of childhood cancer, in most of which small differences, or no differences at all, were found between survivors and healthy controls or normdata (5;8;9;22;23). However, this is not what we would have expected considering the stressful experience of childhood cancer and treatment.

The good adjustment we found could have been a result of the process of response shift, which has been described in adults with cancer (24). Response shift means that the experience with cancer changes the internal standards of survivors, resulting in changes in the meaning of their self-evaluation and hence in a possibly different experience of problems. It is plausible to suppose that the more severe disease and treatment are, the more this mechanism applies. This could explain why 'the surgery only survivors' in the current paper reported worse mental HRQoL than survivors having been treated with radiotherapy and/or chemotherapy.

The good adjustment of the survivors could also have been achieved as a result of personal growth or the availability of social support systems, or as a result of adequate coping with the stresses of the long-term consequences of childhood cancer. In the current study we explored the role of cognitive coping in relation to the adjustment of (now-healthy) survivors, the second purpose of the study. But first we looked at the impact of medical variables.

Although we traced several medical variables that were significantly associated with HRQoL (such as age at diagnosis), their contribution was not substantial, i.e. only a few per cent of the explained variance. That is not surprising, given the fact that the medical variables in the current study were limited to diagnosis and treatment, without taking into account the severity of the diagnosis and treatment. In contrast, health status explained a great part of the PCS and MCS: addition of the variables concerning health status caused a considerable increase in explained variance. As expected, current health complaints (e.g. influenza) decreased HRQoL. The psychosocial/cognitive/neurological problems registered by the long-term follow-up clinic were also negatively related to HRQoL. Physical problems appeared not to be associated with HRQoL. This could be a consequence of taking together all physical problems in the analyses, regardless of the type and severity. When we introduced 'amputation' in the regression model this aspect of 'physical problems' turned out to be a predictor of the physical component of HRQoL. It was not the purpose of the study to investigate the impact of medical variables. However, that does not alter the fact that it would be relevant to investigate the impact of diagnosis and treatment more thoroughly than we did, in order to be able to trace risk factors and to improve the care during the treatment and afterwards. Anyway, the results indicate that, from a HRQoL point of view, clinicians should pay attention to psychosocial functioning of survivors, because psychosocial/cognitive/neurological problems' appeared to be significantly correlated with HRQoL, in contrast to 'physical problems'.

The finding that health status was the best predictor of the physical summary scale (PCS) of the RAND, explaining half of the total R^2, is not surprising. The independent impact of cognitive coping on physical HRQoL was considerably lower (7% of the 40% total variance explained); its impact on the mental summary scale (MCS) was almost equal to the contribution of health status, i.e. 12% and 14% of the total R^2 (39%) respectively.

The results show the influence of current cognitive coping independently of the health status of the survivors. Only a weak correlation was found between reliance on predictive coping and health status: survivors who reported no health problems tended to rely a little more on predictive coping than survivors suffering from one or more health problems (Pearson's correlation 0.12, $p < 0.05$).

The explanatory value of cognitive coping can mainly be attributed to the use of predictive control strategies. Survivors who were optimistic about the course of the disease (agreeing with statements such as: I am sure everything will work out right for me, and When I think about my illness I assume all will go well) at the time of the study were found to have a better HRQoL, especially better mental HRQoL. The positive relationship between predictive control strategies and a patient's adjustment was found in previous studies among adolescents with Inflammatory Bowel Disease (IBD) and among children with cancer (17;19). Another study about the role of optimistic beliefs and adaptation showed that positive outcome expectancies were specifically beneficial when (adult) patients suffered from a chronic disease that is uncontrollable to a considerable extent (25).

The current study does not answer the question of causality: does optimism lead to better HRQoL, or vice versa. In addition, we do not know to which extent a survivor's coping changed since the cancer diagnosis because only current coping strategies were measured. Although a longitudinal study design is needed to be able to answer these questions, results of previous studies suggested that cancer patients can, indeed, improve their HRQoL by cognitive behavior therapy (26). At risk of labouring the obvious, it should be stressed that this does not mean that cognitive behavior therapy can improve health. The results indicated that cognitive coping can change the patient's perception of health or the impact of the disease on the patient's emotional well-being.

Another question is whether the strong relationship between the cognitive coping style 'predictive control' and mental HRQoL is a matter of measuring the same concept, namely emotional functioning. We consider this not to be plausible because the items of the predictive control scale are formulated without the description of emotional functioning in the items, and are, therefore, not mixed up with outcome. Besides, we found predictive control also to be positively associated with physical HRQoL.

Interpretative control seemed to be negatively associated with physical HRQoL. This means that if survivors relied more on interpretative control strategies, they reported worse physical HRQoL. The question of causability is also under discussion here. It seems reasonable to assume that experiencing bad physical HRQoL brings someone to rely on interpretative control strategies, such as searching for meaning and information. On the other side, searching for information could imply focusing on threatening aspects of the disease, which in turn could lead to negative emotions and more negative evaluation of their social and physical functioning.

The small differences that we found between the HRQoL of the survivors and the HRQoL of their peers, can, we think, be partly attributed to methodological limitations. Firstly, more cancer-specific instruments are needed to assess the impact of childhood cancer. Secondly, survivors of brain tumors were under-represented in the current study, and survivors with serious cognitive problems were not represented at all because they were not able to fill in the questionnaires. Thirdly, the instrument used, the RAND-36, measures HRQoL roughly and is typically health-related. For example, the score on the domain Social Functioning does not

say anything about survivors' real social functioning (such as their social skills and number of friends), but refers to the respondents' perceived limitations in social activities due to health problems. Therefore, specific questionnaires are needed to investigate the functioning of survivors more thoroughly, which is of great interest. Furthermore, there are other important aspects of the functioning of survivors, concerning educational achievement, employment, marital status, and so on. Previous research concerning these aspects points out inconsistent differences between survivors and controls (4;6;7;9;23;27-35).

As far as we know, this is the first study describing the association between styles of disease-related cognitive coping and HRQoL of survivors of childhood cancer. Cognitive coping seems to play an important role in relation to HRQoL because it increases the explained variance of HRQoL considerably. The strong association between predictive coping and HRQoL stresses the importance of having positive expectations with respect to the course of the disease. We feel that the knowledge of this association could be useful in clinical practice because coping can be considered as a relative stable but changeable characteristic, responsive to intervention. Health care providers who know more about disease-related coping are better able to help patients to cope with the consequences of their disease. It is important that health-care providers understand emotional and behavioral reactions as an outcome of a coping process, so that they are able to respond more appropriately (10). For instance, the oncologist's attitude about the course of the disease may influence a patient's expectations. Furthermore, interventions for survivors focusing at positive thinking could be useful. A review of 35 studies on the impact of interventions aimed at improving coping on the QoL of adult chronically ill patients showed positive results (36). De Ridder (36) argued that greater and more explicit consideration should be given to the potential of the coping concept for intervention in the chronically ill. In our opinion, cognitive coping is also a useful concept for psychosocial interventions for survivors of childhood cancer but more insight is needed into the way individual coping styles can be improved by interventions.

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REFERENCES

(1) Eiser C, Morse R. Quality-of-life measures in chronic diseases of childhood. Health Technol Assess 2001;5(4).

(2) Eiser C. Children with cancer. The quality of life. Mahwah, New Jersey, Londen: Lawrence Erlbaum Associates Publishers, 2004.

(3) Eiser C, Hill JJ, Vance YH. Examining the psychosocial consequences of surviving childhood cancer: Systematic review as a research method in pediatric psychology. J Pediatr Psychol 2000;25(6):49-60.

(4) Langeveld NE, Stam H, Grootenhuis MA, Last BF. Quality of life in young adult survivors of childhood cancer (review). Support Care Cancer 2002;10:579-600.

(5) Zebrack BJ, Chesler MA. Quality of life in childhood cancer survivors. Psychooncology 2002;11:132-41.

(6) Langeveld NE, Ubbink MC, Last BF, Grootenhuis MA, Voûte PA, de Haan RJ. Educational achievement, employment and living situation in long-term young adult survivors of childhood cancer in the Netherlands. Psychooncology 2003;12(3):213-25.

(7) Pui C-H, Cheng C., Leung W, Rai SN, Rivera GK, Sandlund JT, et al. Extended follow-up of long-term survivors of childhood acute lymphoblastic leukemia. N Engl J Med 2003;349(7):640-9.

(8) Zebrack BJ, Gurney JG, Oeffinger K, Whitton J, Packer RJ, Mertens A, et al. Psychological outcomes in long-term survivors of childhood brain cancer: a report from the Childhood Cancer Survivors Study. J Clin Oncol 2004;22(6):999-1006.

(9) Pastore G, Mosso ML, Magnani C, Luzzatto L, Bianchi M, Terracini B. Physical impairment and social life goals among adult long-term survivors of childhood cancer: a population-based study from the childhood cancer registry of Piedmont, Italy. Tumori 2001;87:372-8.

(10) Last BF, Grootenhuis MA. Emotions, coping and the need for support in families of children with cancer: a model for psychosocial care. Patient Educ Couns 1998;33(2):169-79.

(11) Lazarus RS, Folkman S. Stress, appraisal, and coping. New York: Springer Publishing Company, 1984.

(12) Rothbaum F, Weisz JR, Snyder SS. Changing the world and changing the self: a two-process model of perceived control. J Pers Soc Psychol 1982;42:5-37.

(13) Grootenhuis MA, Last BF, de Graaf-Nijkerk JH, van der Wel M. Secondary control strategies used by parents of children with cancer. Psychooncology 1996;5(2):91-102.

(14) Aaronson NK, Muller M, Cohen PDA, Essink-Bot M, Fekkes M, Sanderman R, et al. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. J Clin Epidemiol 1998;51(11):1055-68.

(15) van der Zee KI, Sanderman R. Het meten van de algemene gezondheidstoestand met de RAND-36. Een handleiding. [Measuring general health status with the RAND-36. A guide.]. Groningen, the Netherlands: Noordelijk Centrum voor Gezondheidsvraagstukken. Rijksuniversiteit Groningen, 2003.

(16) Ware JE, Kosinski M. Interpreting SF-36 summary health measures: a response. Qual Life Res 2001;10:405-13.

(17) Grootenhuis MA, Last BF. Children with cancer with different survival perspectives: defensiveness, control strategies, and psychological adjustment. Psychooncology 2001;10:305-14.

(18) Loonen HJ, Grootenhuis MA, Last BF, Koopman HM, Derkx HHF. Quality of life in peadiatric inflammatory bowel disease measured by a generic and disease-specific questionnaire. Acta Paediatr 2002;91:341-54.

(19) van der Zaag-Loonen HJ, Grootenhuis MA, Last BF, Derkx HHF. Coping strategies and quality of life of adolescents with inflammatory bowel disease. Qual Life Res 2003;13(5):1011-9.

(20) Stevens MCG, Mahler H, Parkes S. The health status of adult survivors of cancer in childhood. Eur J Cancer 1998;34(5):694-8.

(21) Cohen J. Statistical power analysis for the behavioral sciences. New York: Academy Press, 1988.

(22) Veenstra KM, Sprangers MAG, Van der Eyken J, Taminiau AHM. Quality of life in survivors with a Van Ness-Borggreve rotationplasty after bone marrow tumour resection. J Surg Oncol 2000;73:192-7.

(23) Zebrack BJ, Zeltzer LK, Whitton J, Mertens AC, Odom L, Berkow R, et al. Psychological outcomes in long-term survivors of childhood leukemia, Hodgkin's disease, and Non-Hodgkin's lymphoma: a report from the childhood cancer survivor study. Pediatrics 2002;110(1):42-52.

(24) Sprangers MAG, Schwartz CE. Integrating response shift into health-related quality of life research: a theoretical model. Soc Sci Med 1999;48:1507-15.

(25) Fournier M, de Ridder D, Bensing J. How optimism contributes to the adaptation of chronic illness. A prospective study into the enduring effects of optimism on adaptation moderated by the controllability of chronic illness. Pers Individ Differ 2002;33:1163-83.

(26) Edelman S, Kidman AD. Application of cognitive behaviour therapy to patients who have advanced cancer. Behav Change 2000;17(2):103-10.

(27) Byrne J, Fears TR, Steinhorn SC, Mulvihill JJ, Connelly RR, Austin DF, et al. Marriage and divorce after childhood and adolescent cancer. JAMA 1989;262(19):2693-9.

(28) Green DM, Zevon MA, Hall B. Achievement of life goals by adult survivors of modern treatment for childhood cancer. Cancer 1991;67:206-13.

(29) Mäkipernaa A. Long-term quality of life and psychosocial coping after treatment of solid tumours in childhood: a population-based study of 94 patients 11-28 years after their diagnosis. Acta Paediatr 1989;78:728-35.

(30) Rauck AM, Green DM, Yasui Y, Mertens A, Robinson LL. Marriage in the survivors of childhood cancer: a preliminary description from childhood cancer survivor study. Med Pediatr Oncol 1999;33:60-3.

(31) Zevon MA, Neubauer NA, Green DM. Adjustment and vocational satisfaction of patients treated during childhood or adolescence for acute lymphoblastic leukemia. Am J Pediatr Hematol Oncol 1990;12(4):454-61.

(32) Allen A, Malpas JS, Kingston JE. Educational achievements of survivors of childhood cancer. Pediatr Hematol Oncol 1990;7:339-45.

(33) Nagarajan R, Nelgia JP, Clohisy DR, Yasui Y, Greenberg M, Hudson M, et al. Education, employment, insurance, and marital status among 694 survivors of pediatric lower extremity bone tumors. Cancer 2003;97:2554-64.

(34) Kingma A, Rammeloo LAJ, Van der Does-Van den Berg A, Rekers-Mombarg L, Postma A. Academic career after treatment for acute lymphoblastic leukaemia. Arch Dis Child 2000;82:353-7.

(35) Stam H, Grootenhuis MA, Last BF. The course of life of survivors of childhood cancer. Psychooncology 2005;14:227-38.

(36) de Ridder D, Schreurs K. Developing interventions for chronically ill patients: is coping a helpful concept? Clin Psychol Rev 2001;21(2):205-40.

Chapter 9

The course of life of survivors of childhood cancer

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ABSTRACT

The developmental consequences in adulthood of growing up with childhood cancer are not well understood. The Course of life questionnaire was developed to assess the attainment of developmental milestones retrospectively and socio-demographic outcomes in young adulthood. The aim of this study was to assess the course of life and socio-demographic outcomes in young adult survivors of childhood cancer. Knowledge about possible gaps in the course of life could enable health care providers to aim for the most favourable course of life.

A total of 353 Dutch survivors and a comparison group of 508 peers without a history of cancer, all aged between 18 and 30, filled in the Course of life questionnaire.

The course of life of the survivors was found to be hampered. The young adult survivors of childhood cancer in the Netherlands turned out to have achieved fewer milestones than their peers with respect to autonomy development, social development, and psycho-sexual development, or to have achieved the milestones when they were older than their peers. In addition, survivors displayed less risk behaviour than the comparison group. The survivors and the comparison group also differed on some socio-demographic issues. A considerably lower percentage of survivors than peers in the comparison group were married or living together, and/or employed. Their educational level, on the other hand, was as high as that of their peers.

INTRODUCTION

As a result of advances in the treatment of childhood cancer many patients who may previously have had a limited life expectancy, are now surviving into adulthood. Therefore, it has become more important to investigate the consequences of the disease and the treatment. Numerous long-term physical effects of childhood cancer have been documented, but the impact of the psycho-social sequelae are less well known. Reviews about the Quality of Life (QoL) of young adult survivors of childhood cancer mention a wide variety of studies with contradictory results (1;2). Apart from QoL, a number of socio-demographic issues have also been investigated. Although inconsistent data have been reported across studies, the results suggest the following: the majority of survivors proved to function well physically and emotionally, and in almost all studies survivors did not differ from the control groups with respect to employment status. But after reaching adulthood, survivors seemed to live with their parents longer than their peers, and there was a lower prevalence of marriage and parenthood among survivors. Finally, survivors of CNS tumours and ALL were at risk of educational deficits (2-7)

The developmental consequences of growing up with or after childhood cancer may have consequences in adulthood. The fulfilling of age-specific developmental tasks in childhood are of great importance to the adjustment in adult life (8;9). The developmental tasks and the resulting developmental milestones that are necessary in the development of a child are referred to as the 'course of life'.

Although it is known that children with cancer report adjustment problems during their treatment (10), what the consequences are for the achievement of the developmental milestones is not known. Suffering from childhood cancer and the subsequent treatment often increases the child's dependence on his or her parents and other adults, and decreases participation in peer and school-based activities (11-14). This could be a threat to the accomplishment of developmental tasks, resulting in a hampered course of life. Cognitive problems and non-attendance at school as a result of the disease and treatment may result in lower educational achievement levels (15;16). Identity achievement in adolescent cancer survivors might also be problematic (17).

From a developmental psychological point of view, risk behaviour is also relevant because displaying risk behaviour – in terms of trying out – is, to a certain extent, part of the development from being a teenager to becoming an adult. It is conceivable that survivors of childhood cancer display less risk behaviour than healthy peers because they are aware of just how vulnerable their health is (18-20). Moreover, increased parental involvement as a result of the paediatric cancer experience (21) may limit a child's opportunities for unsupervised time with peers, which may decrease a child's opportunities to engage in risk activities with peers. On the other hand, we could possibly expect there to be more risk behaviour among survivors in order to compensate for the limitations posed on them by the disease in their youth. Previous studies showed inconsistent results on this matter (22-25).

The aim of this study is to assess the course of life and socio-demographic outcomes in young adult survivors of childhood cancer compared with peers without a history of childhood cancer. Firstly, we hypothesize that the course of life of young adult survivors of childhood cancer is hampered. This means that we expect survivors to have achieved fewer developmental tasks and milestones, or to have reached the milestones when they were older

than their peers, manifested by lower scores for the domains covered by the Course of life questionnaire. In addition, we expect differences in the domains of risk behaviour, but we have no hypothesis about the direction of the differences.

Secondly, we hypothesize that the educational level of the survivors will be lower than that of their age matched peers without a history of cancer, and that their employment status and living situation will be different from that of their peers (i.e. lower percentage employed, higher percentage living with their parents or without a partner).

PATIENTS AND METHODS

Procedure

The results presented here involve the cross-sectional part of the VOLG study, a Dutch study on the late psychosocial consequences of cancer in childhood. The respondents for this part of the study were recruited from the long-term follow-up clinic at The Emma Children's Hospital/Academic Medical Center in Amsterdam, which was established in 1996 to monitor the long-term sequelae of childhood cancer and its treatment. Patients become eligible for transfer from active-treatment clinics to the follow-up clinic when they have successfully completed their cancer treatment at least 5 years earlier. Survivors are evaluated annually in the clinic by a paediatric oncologist (patients aged < 18 years) or by an internist-oncologist (patients aged > 18 years) for late medical effects, as well as by a research nurse or psychologist for any psychosocial effects.

In 2001 and 2002, the survivors of childhood cancer aged between 18 and 30, who attended the long-term follow-up clinic, were asked (by letter or by a psychologist) to fill in questionnaires anonymously. After having completed the questionnaires at home, they could return them in the stamped addressed envelope provided. After a month a reminder letter was sent together with the same questionnaire. The inclusion criteria were: (1) age at study 18-30 years, (2) end of successful treatment at least five years beforehand, (3) age at cancer diagnosis < 18 years, and (4) ability to understand questionnaires in the Dutch language.

At the end of 2000 and 2001 an age-matched and sex-matched control group was formed with the help of the general practitioners (GPs) of the survivors. The GPs were asked to select ten patients from their lists whose surnames started with a given letter of the alphabet, and who were of a given sex and age. The inclusion criteria for the comparison group were: (1) age at study 18-30 years, (2) no history of cancer, and (3) ability to understand questionnaires in Dutch. The GPs were asked to send a package containing the questionnaires, information about the VOLG study, and a stamped addressed envelope to the ten randomly selected patients. Two weeks after the original mailing date, the GPs were again asked to send another package with the same content and a reminder letter.

Measures

The *Course of life questionnaire*, a Dutch questionnaire, was used to assess the achievement of developmental milestones retrospectively. Because of the lack of appropriate instruments, the Psychosocial Department of the Emma Children's hospital/Academic Medical Center recently developed the *Course of life questionnaire* in order to be able to investigate the course

of life of young adults, aged 18-30, who have grown up with a chronic or life threatening disease, and to facilitate comparison with the course of life of peers without a history of disease (26). The items, based on the literature and clinical experience, concern behaviours that are characteristic of certain age stages, developmental tasks, and the limitations children might encounter when they grow up with a chronic disease. Most questions ask retrospectively whether the respondent had achieved certain developmental milestones (yes, no) or at what age (category) the respondent achieved the milestones. The answers are dichotomised, if necessary, before being added up to the scale-score. The items are divided into five scales: (1) development of autonomy (6 items about autonomy at home and outside the home), (2) psycho-sexual development (4 items about love and sexual relations), (3) social development (12 items about social contacts with peers, at school and in leisure time), (4) anti-social behaviour (4 items about misbehaviour at school and outside it), (5) substance use and gambling (12 items about the use of alcohol, tobacco and drugs, and about gambling). The Results section shows the scale items.

A higher score on the first three scales indicates the accomplishment of more developmental milestones and therefore a more favourable course of life. Lower scores for Anti-social behaviour and on Substance use and gambling mean that the respondent displays less anti-social behaviour and less substance use and gambling, which are indicative of a deviant course of life. Apart from the five scales, the questionnaire measures socio-demographic outcomes in young adulthood, such as living situation, education, and employment. The questionnaire covers a total of 74 items.

The validity of the course-of-life-scales is good. Firstly, the items are based on the literature and clinical experience. Secondly, the scales seemed to measure distinct constructs because the Pearson's correlation between the scales is not high ($r < 0.30$) with the exception of the correlation between the scales for Anti-social behaviour and Substance use and gambling ($r = 0.49$). Thirdly, the results of the Course of life questionnaire proved to be in line with several datasets of the Dutch population (26).

The test-retest reliability is good (27) and the internal consistency of four out of the five scales developed beforehand is satisfactory (26). The reliability of the development of autonomy scale is moderate, probably because the items concern diverging aspects of autonomy (26). The Cronbach's alphas in the population under study were moderate to good: (1) development of autonomy (range 6-12): survivors 0.46, comparisons 0.49; (2) psychosexual development (range 4-8): survivors 0.79, comparisons 0.71; (3) social development (range 12-24): survivors 0.76, comparisons 0.71; (4) anti-social behaviour (range 4-8): survivors 0.49, comparisons 0.57; (5) substance use and gambling (range 12-24): survivors 0.79; comparisons 0.78. The use of scales with moderate internal consistency is acceptable for group comparisons because the internal consistency is an indication of random error and has nothing to do with systematic error (bias).

Medical data were obtained from the registry at the long-term follow-up clinic at The Emma Children's Hospital/Academic Medical Center in Amsterdam, and covered diagnosis, treatment, age at first diagnosis, duration of treatment, time since diagnosis, time since end of treatment, occurrence of relapse or second malignancy.

Statistical analysis

The Statistical Package for Social Sciences (SPSS) Windows version 11.5 was used for all the analyses. Several preparatory analyses were conducted before the final analyses were made.

Firstly, scales were constructed based on the guidelines of the questionnaires used, and the reliability of the scales was calculated. Secondly, by applying student's *T*-tests and χ^2-tests we compared survivors and comparisons with respect to their demographic characteristics in order to detect confounders. Because the survivors did not differ from the comparison group with respect to demographic characteristics, there was no need to correct for these characteristics.

After these preparatory analyses, multivariate analysis of variance (MANOVA) and univariate analysis of variance (ANOVA) were conducted to test group differences on the course-of-life-scales, and to assess the main effects of age and gender. In order to adjust for multiple testing a significance level of 0.01 was used.

Effect sizes (d) were calculated by dividing the difference in mean score between survivors and comparisons by the standard deviation of the scores in the comparison group. We considered effect sizes of up to 0.2 to be small, effect sizes of about 0.5 to be moderate and effect sizes of about 0.8 to be large (28). In order to be sure about the results, we also performed non-parametric Mann-Whitney *U*-tests because the distribution of the scores of the course of life scales was not quite normal. A significance level of 0.01 was used to compensate for the 5 tests that were conducted.

In order to gain a detailed insight into the course of life of the survivors, differences on item level between survivors and the comparison group were also calculated. Therefore, χ^2-tests were conducted at the frequency distributions of the individual (dichotomised) items. We used a significance level of $p < 0.01$ in order to compensate for multiple testing.

Student's *T*-tests were used to investigate the differences between the survivors and the comparison group with respect to the percentage of them who were employed, and χ^2-tests were conducted to trace differences in occupational status (employed or unemployed), educational level (low, middle, high[1]) and living situation (married/living together or single; living with their parents or not).

RESULTS

Participants

Survivors

A total of 499 young adult survivors were asked to take part in the cross-sectional part of the VOLG study - 262 men (52.5%) and 237 women (47.5%). 355 questionnaires were returned (response rate 71.0%), two questionnaires could not be used for analysis because one questionnaire had not been completed by the patient herself ($n = 1$), and the other one was returned too late ($n = 1$). Of the 144 survivors who did not complete the questionnaires, 18 returned the non-response form. Most of these non-respondents reported that they did not have enough time or did not feel like taking part in the study ($n = 10$). Two non-respondents did not complete the questionnaire because they did not want to be confronted again with cancer; the other six refused for other reasons.

The data from 353 survivors could be used for the analyses: 175 (49.6%) men, 178 (50.4%) women. Their mean age was 24.3 years (SD = 4.0; range = 17.7-31.1) and the median age was 24.5 years (Table 1).

Table 1. Demographic and medical characteristics of the survivors and the comparison group

	Survivors (n = 353)			Comparison group (n = 508)		
	M	**SD**	**Range**	**M**	**SD**	**Range**
Age at study (years)	24.3	4.0	17.7-31.1	24.2	3.8	18.0-30.9
Age at first diagnosis (years)	7.3	4.7	0.0-17.0			
Time since first diagnosis (years)	17.0	6.0	6.2-30.7			
Time since end of last treatment (years)	15.5	5.5	4.9-30.3			
Duration of treatment (months)	12.5	10.5	0.0-72.5			
	N		**%**	**N**		**%**
Gender						
Female	178		50.4	269		53.0
Male	175		49.6	239		47.0
Native country						
The Netherlands	338		96.6	487		96.1
Other	12		3.4	20		4.0
Religion						
Yes	164		47.1	218		43.2
No	184		52.9	287		56.8
Educational level parents						
Low	137		41.1	206		42.8
Middle	98		29.4	121		25.2
High	98		29.4	154		32.0
Diagnosis						
Leukemia/lymphoma	176		49.9			
Solid tumour	152		43.1			
Brain tumour	25		7.1			
Treatment						
Chemotherapy (with/without surgery)	199		56.4			
Radiotherapy (with/without surgery)	14		4.0			
Surgery alone	26		7.4			
Combination therapy (chemotherapy + radiotherapy, with/without surgery)	114		32.3			
Health problems (registered at the long-term follow-up clinic)						
no problems	45		12.7			
physical	299		84.7			
psycho-social / cognitive / neurological	114		32.3			
Relapse or second malignancy						
Yes	43		12.2			
No	310		87.8			

The respondents were older than the non-respondents at study (M = 23.2 years; SD = 3.9; range = 18.0-30.8) and at diagnosis (M = 6.3 yrs; SD = 4.7; range = 0.0-17.0) ($p < 0.05$), and there was a higher percentage of women among the respondents than among the non-respondents (50.4% versus 40.4%, $p < 0.01$). No significant differences were found in diagnosis and treatment, time since first diagnosis, time since the end of the last treatment, duration of treatment, having had a relapse or second malignancy, and health problems as recorded at the long-term follow-up clinic.

Comparison group

A total of 264 general practitioners (GPs) were asked to recruit ten patients from their practice for the comparison group; 96 GPs (36.4%) agreed to take part in the study. One or more completed questionnaires were returned from 82 general practices, so we concluded that in the end 82 GPs (31.0%) had participated in the study, whom we assumed to have recruited 820 patients. The investigators received 517 questionnaires (response rate 63.0%), of which nine could not be used because their age at study was either less than 18 years or over 30 years (n = 5), unknown age (n = 1), history of cancer (n = 2), Course of life questionnaire not being completed (n = 1). So the final comparison group consisted of 508 respondents, 239 men (47.0%) and 269 women (53.0%), mean age 24.2 years (SD 3.8, range 18.0-30.9), median age 23.8.

Of the 303 non-respondents, 50 returned the non-response form. They reported that they had no time (n = 13) or were not interested (n = 8) in taking part in the study. Ten possible respondents did not complete the questionnaires because they had misunderstood the informative letter and assumed that they should have a history of cancer themselves. Eight questionnaires proved to be undeliverable, and the remaining 11 non-response forms gave other reasons. More men (70%) than women (30%) refused. Because the recruitment by the GPs was strictly anonymous, we could not trace other characteristics of the non-response group, or the reasons for refusal.

Survivors versus comparison group

The characteristics of the survivors and the comparison group are listed in Table 1. No significant differences were found with respect to age, gender, native country, nationality or religion.

Table 2. Mean scores, SD's and differences between survivors and comparison group on the five scales of the Course of life questionnaire, as a function of Group by Gender[a]

	Survivors			Comparison group			Effect size (d)
	Males N = 148	Females N = 150	Total N = 298	Males N = 203	Females N = 246	Total N = 449	Total N = 747
Autonomy development							
Mean	9.25	9.07	9.16*	9.42	9.44	9.43	0.18
SD	1.52	1.51	1.52	1.50	1.45	1.47	
Psycho-sexual development							
Mean	6.49	6.82	6.65**	7.12	7.20	7.16	0.45
SD	1.39	1.43	1.42	1.17	1.12	1.14	
Social development							
Mean	20.33	19.89	20.11**	21.00	20.91	20.95	0.34
SD	2.97	2.84	2.91	2.32	2.55	2.45	
Anti-social development							
Mean	4.54	4.31	4.42**	5.05	4.44	4.72	0.30
SD	0.88	0.62	0.77	1.12	0.74	1.00	
Substance use & gambling							
Mean	14.86	13.55	14.20**	15.87	14.42	15.08	0.33
SD	2.57	2.00	2.39	2.79	2.31	2.64	

a Multivariate effects were found on group ($p < 0.0001$), gender ($p < 0.0001$) and age ($p < 0.0001$).
* $p < 0.01$; ** $p < 0.001$: differences between survivors and comparison group (based on univariate F-tests according to MANOVA, Course of life-scales by group, gender, age).

Scales of the Course of life questionnaire

The multivariate analysis of variance (MANOVA) for the course-of-life-scales as a function of group, gender and age showed multivariate main effects for group ($F(5,739) = 10.2$, $p < 0.001$), gender ($F(5,739) = 21.4$, $p < 0.001$), and age ($F(5,739) = 6.3$, $p < 0.001$). The results of the univariate *F*-tests in accordance with MANOVA showed the achievement of fewer developmental milestones among survivors than among the comparison group: Autonomy development ($F(1,743) = 6.9$, $p < 0.01$) and Psycho-sexual development ($F(1,743) = 27.8$, $p < 0.001$), Social development ($F(1,743) = 17.8$, $p < 0.001$). In addition, survivors reported less Anti-social behaviour ($F(1,743) = 23.5$, $p < 0.001$) and they scored lower on the scale Substance use and gambling scale ($F(1,743) = 25.9$, $p < 0.001$) (Table 2). The differences between survivors and their peers were small to moderate: effect sizes ranged from 0.18 for Autonomy development to 0.45 for Psycho-sexual development. The results of the univariate *F*-tests in accordance with MANOVA were confirmed by non-parametric Mann-Whitney *U*-tests, which showed significant differences ($p < 0.001$) for all scales.

Course of life on item level

The frequency tables of the individual (dichotomised) items of the scales of the Course of life questionnaire show the milestones for which survivors differed significantly from their peers; $p < 0.01$ at χ^2-tests (Table 3a - 3e).

With respect to Autonomy development, we found that a lower percentage of the survivors than of the comparison group had had a paid job during secondary school, and that a lower percentage of survivors than of comparisons had been on holiday without adults before they were 18 years old.

We found differences between the survivors and the comparison group on three out of the four items of Psycho-sexual development. The survivors were older than the comparison group when for the first time they: had a boyfriend or girlfriend, had sexual intimacy, and had sexual intercourse.

The survivors differed from the comparison group on four items of the Social development scale. Firstly, a lower percentage of survivors than of comparisons had been a member of a sports club for at least one year during primary school. The same also applied during secondary school. Furthermore, the number of friends that the survivors had during secondary school was lower than the number of friends that the comparison group had, and a lower percentage of the survivors than of the comparison group spent their leisure time mainly with friends.

With respect to risk behaviour, we found that a lower percentage of survivors than of comparisons had ever been refused admission to lessons during secondary school (Anti-social behaviour scale). In addition, the prevalence of substance use was lower among the survivors than among the comparison group. This was true for smoking, during and after finishing secondary school, and for the use of soft drugs during secondary school. Moreover, survivors drank alcohol less often than the comparison group during secondary school.

Socio-demographic outcomes

The socio-demographic outcomes of the Course of life questionnaire are presented in Table 4. Firstly, a lower percentage of survivors than comparisons (i.e. 30.9% versus 39.1%, $p < 0.05$) were married or living together, but the groups did not differ significantly with respect

Table 3.

	Survivors		Comparison group		
	%	N	%	N	
(a) Frequencies of the (dichotomised) items of the course-of-life-scale Autonomy development, survivors versus comparison group					
Regular job in your family, primary school					
yes	42.3	148	46.0	233	
no	57.7	202	54.0	273	
Paid jobs, primary school					
yes	30.5	107	33.6	170	
no	69.5	244	66.4	326	
Regular job in your family, secondary school					
yes	57.4	202	60.2	304	
no	42.6	150	39.8	201	
Paid jobs, secondary school					
at the age of 18 or younger	80.2	283	87.4	443	$p < 0.01$
at the age of 19 or older / never	19.8	70	12.6	64	
For the first time being on holiday without adults					
at the age of 17 or younger	43.0	151	52.9	268	$p < 0.01$
at the age of 18 or older / never	57.0	200	47.1	239	
Leaving your parents place					
not living with your parents	69.8	208	64.6	328	
still living with your parents	40.2	140	35.4	180	
(b) Frequencies of the (dichotomised) items of the course-of-life-scale Psycho-sexual development, survivors versus comparison group					
First girlfriend / boyfriend					
at the age of 17 or younger	61.8	217	80.4	407	$p < 0.001$
at the age of 18 or older / never	38.2	134	19.6	99	
For the first time falling in love					
at the age of 18 or younger	87.6	304	91.7	462	
at the age of 19 or older / never	12.4	43	8.3	42	
For the first time sexual intimacy					
at the age of 18 or younger	69.4	240	83.4	421	$p < 0.001$
at the age of 19 or older / never	30.6	106	16.6	84	
For the first time sexual intercourse					
at the age of 18 or younger	47.7	166	58.5	296	$p < 0.01$
at the age of 19 or older / never	52.3	182	41.5	210	
(c) Frequencies of the (dichotomised) items of the course-of-life-scale Social development, survivors versus comparison group					
At least one year of membership in a sports club, primary school					
yes	73.3	258	84.2	427	$p < 0.001$
no	26.7	94	15.8	80	
Number of friends in first-third grade, primary school					
less than 4	35.7	123	37.0	187	
4 or more	64.3	222	63.0	319	
Number of friends in fourth-sixth grade, primary school					
less than 4	35.0	123	30.9	156	
4 or more	65.0	228	69.1	349	

Table 3. (continued)

	Survivors		Comparison group		
	%	N	%	N	
Best friend, primary school					
yes	72.2	254	74.2	377	
no	27.8	98	25.8	131	
Most of the time playing with….., primary school					
friends	82.1	285	87.6	436	
brothers and/or sisters, parents, on your own	17.9	62	12.4	62	
At least one year of membership in a sports club, secondary school					
yes	61.2	216	73.6	373	$p < 0.001$
no	38.8	137	26.4	134	
Number of friends, secondary school					
less than 4	41.0	144	30.4	154	$p < 0.01$
4 or more	59.0	207	69.6	352	
Best friend, secondary school					
yes	66.9	236	73.5	372	
no	33.1	117	26.5	134	
Belonging to a group of friends, secondary school					
yes	75.7	265	80.6	403	
no	24.3	85	19.4	97	
Leisure time, mainly with ….., secondary school					
friends	77.8	270	85.1	430	$p < 0.01$
brothers and/or sisters, parents, on your own	22.2	77	14.9	75	
Going out to a bar or disco, secondary school					
sometimes / often	80.3	281	84.8	430	
never	19.7	69	15.2	77	
At least one year of membership in a sports club, after secondary school					
yes	41.3	142	48.9	243	
no	58.7	202	51.1	254	
(d) Frequencies of the (dichotomised) items of the course-of-life-scale Anti-social behaviour, survivors versus comparison group					
Ever been suspended because of misbehaviour at school, primary school					
yes	4.0	14	6.9	35	
no	96.0	338	93.1	473	
Get into trouble with the police or law, secondary school					
yes	11.1	39	16.6	84	
no	88.9	312	83.4	423	
Ever been suspended because of misbehaviour at school, secondary school					
yes	8.8	31	13.0	66	
no	91.2	322	87.0	441	
Ever been refused admission to lessons, secondary school					
yes	21.6	76	34.3	174	
no	78.4	276	65.7	333	

Table 3. (continued)

	Survivors		Comparison group		
	%	N	%	N	
(e) Frequencies of the (dichotomised) items of the course-of-life-scale Substance use and gambling, survivors versus comparison group					
Alcohol, secondary school					
never / occasionally	81.0	285	72.7	368	p < 0.01
often / very often	19.0	67	27.3	138	
Softdrugs, secondary school					
never	80.3	282	70.6	357	p < 0.01
occasionally / often / very often	19.7	69	29.4	149	
Psychedelic drugs, secondary school					
never	96.0	338	96.3	488	
occasionally / often / very often	4.0	14	3.7	19	
Harddrugs, secondary school					
never	98.3	347	98.0	497	
occasionally / often / very often	1.7	6	2.0	10	
Smoking, secondary school					
no	76.1	267	60.3	305	p < 0.001
yes	23.9	84	39.7	201	
Gambling, secondary school					
never	83.8	295	77.8	393	
occasionally / often / very often	16.2	57	22.2	112	
Alcohol, after secondary school					
never / occasionally	54.7	187	49.9	245	
often / very often	45.3	155	50.1	246	
Softdrugs, after secondary school					
never	77.0	265	70.8	352	
occasionally / often / very often	23.0	79	29.2	145	
Psychedelic drugs, after secondary school					
never	93.6	322	91.4	456	
occasionally / often / very often	6.4	22	8.6	43	
Harddrugs, after secondary school					
never	95.9	329	93.4	466	
occasionally / often / very often	4.1	14	6.6	33	
Smoking, after secondary school					
no	70.3	242	52.0	258	p < 0.001
yes	29.7	102	48.0	238	
Gambling, after secondary school					
never	68.6	236	61.8	308	
occasionally / often / very often	31.4	108	38.2	190	

to the percentage that were living with their parents. Secondly, the χ^2-test performed at 'highest educational level completed' yielded no significant difference between survivors and their peers. Thirdly, more survivors than comparisons were not employed (i.e. 16.6% versus 6.9%, $p < 0.001$), as was also true for men and women separately (i.e. males 11.7% versus 2.6%, $p < 0.01$; females 20.5% versus 10.9%, $p < 0.05$). Survivors and peers did not differ with respect to the percentage that were employed.

DISCUSSION

This is one of the first studies that considered the course of life of young adult survivors of childhood cancer. The aim of this paper was the assessment of the course of life and socio-demographic outcomes in young adult survivors of childhood cancer, in comparison with age-matched and sex-matched peers without a history of cancer. The first hypothesis was confirmed: the course of life of the survivors was found to be hampered. The young adult survivors of childhood cancer in the Netherlands proved to have achieved fewer milestones, or to have achieved the milestones when they were older than their peers, with respect to Autonomy development, Social development, and Psycho-sexual development. In addition, survivors displayed less risk behaviour than the comparison group. Although the latter finding is indicative of a deviant course of life, the displaying of less anti-social behaviour and less substance use and gambling are in themselves not unfavourable. In contrast, it could be indicative of protective health behaviour among the survivors.

The second hypothesis was partly confirmed: the survivors and the comparison group differed on some socio-demographic issues. A considerably lower percentage of survivors than comparisons were married or living together, and/or employed. Their educational level, on the other hand, was as high as the level of their peers. This favourable result, not confirmed in most studies among survivors of childhood cancer (see review: Langeveld et al., 2002) (2), could be due to the fact that, if needed, patients in the Netherlands receive education in the hospital or at home. Efforts are directed at continuing school, so that the effects of non-attendance are reduced to a minimum. Another explanation could be that survivors with serious cognitive problems have not been included in the VOLG study because they were unable to fill in the written questionnaires.

The differences in mean scores on the course-of-life-scales between survivors and their age-matched and sex-matched peers were found to be small to moderate. This means that there would be a number of survivors whose course of life was seriously hampered, although on the whole the majority of survivors would have had a favourable course of life. Therefore, it is important for future research to investigate the predictors of a hampered course of life, in order to be able to detect, at an early stage, the children and adolescents who are at risk.

Apart from the magnitude of the differences between survivors and peers, the most important question is: what is the significance of a hampered course of life. First of all, from a developmental psychological point of view, the fulfilling of age-specific developmental tasks in childhood are of great importance to adjustment in adult life (8;9). We would like to know which aspects of adjustment in young adult survivors of childhood cancer are affected by which aspects of the course of life. Does the course of life correlate with QoL and socio-demographic outcomes in adulthood? We hope to be able to answer these questions in a later phase of the VOLG study.

Knowledge about possible gaps in the course of life could be useful in clinical practice because it enables health care providers to aim for the most favourable course of life of patients with childhood cancer, both during and after treatment. The results of the current study indicate that it is important to encourage children with cancer to make friends and to participate in peer activities, such as sport, because the survivors have achieved fewer milestones with respect to social development than the comparison group. Moreover, social development seemed to be related to psychosexual development (Pearson's correlation 0.34,

Table 4. Percentages and differences between survivors and comparison group with respect to living situation, educational and employment status, by gender

	Survivors					
	Males		Females		Total	
	%	N	%	N	%	N
Living with their parents						
no	55.2	95	64.2	113	59.8	208
yes	44.8	77	35.8	63	40.2	140
Marital status						
married / living together	22.6	38	39.0	67	30.9*	105
single	77.4	130	61.0	105	69.1	235
Educational level[a]						
low	34.1	57	33.1	56	33.6	113
middle	46.7	78	53.8	91	50.3	169
high	19.2	32	13.0	22	16.1	54
Employment status[b]						
employed	88.3**	83	79.5*	93	83.4***	176
not employed	11.7	11	20.5	24	16.6	35
% employed (fte) [b]	98.2	82	88.6	90	93.2	172

$p < 0.01$), so that friendships in youth are probably important for later sexual relationships. Furthermore, the role of the survivors' parents comes into focus. It is known that parents of chronically ill children are inclined to overprotect their ill child (21) but this does not help the child to develop the personal skills needed to cope with the challenges of growing up with childhood cancer. Therefore, health care providers should help the parents to stimulate and encourage their child's independence.

As far as one is aware, the Course-of-life-questionnaire is the first (Dutch) questionnaire on this issue. It has appeared to be a useful instrument even though several limitations were encountered. Firstly, the psychometric characteristics of the scales are not optimal; for example, the floor effect of the Anti-social behaviour scale and the moderate internal consistency of Autonomy development. We think that is acceptable to use scales with low internal consistency for making group comparisons because the internal consistency is an indication of random error and has nothing to do with systematic error (bias). The disadvantage of using scales with low internal consistency is that detecting differences between groups is more difficult. Because we found significant differences between the groups in our study, this disadvantage did not apply. Secondly, the questionnaire does not pretend to be complete. The fact that the course of life is measured retrospectively limits the range of topics. In order to prevent bias caused by inadequate memory, the questions are factual and do not go further back than to primary school, but the occurrence of bias is not guaranteed. Thirdly, because the questionnaire should be filled in by the survivors themselves, another cause of bias arises. It is likely that survivors report having achieved more milestones than was actually the case in order to prove that they have succeeded in getting over their disease. However, if this bias occurred in the current study, it would only strengthen the results.

Comparison group					
Males		Females		Total	
%	N	%	N	%	N
59.2	138	70.7	190	64.6	328
42.3	101	29.4	79	35.4	180
30.9	71	46.6	121	39.1	192
69.1	159	53.6	140	60.9	299
32.7	74	26.5	69	29.4	143
46.0	104	54.6	142	50.6	246
21.2	48	18.8	49	20.0	97
97.4	148	89.1	147	93.1	295
2.6	4	10.9	18	6.9	22
99.2	146	88.5	139	94.0	285

* Significant difference between survivors and comparisons, $p < 0.05$ based on $\chi 2$-test.
** Significant difference between survivors and comparisons, $p < 0.01$ based on $\chi 2$-test.
*** Significant difference between survivors and comparisons, $p < 0.001$ based on $\chi 2$-test.
[a] Highest level completed: Low:Primary Education, Technical and Vocational Training, Lower and Middle General Secondary Education. Middle: Middle Vocational Education, Higher General Secondary Education, Pre-university Education. High: Higher Vocational Education, University.
[b] Students excluded.

Nevertheless, the current study has demonstrated the importance of the issue of course of life in childhood cancer survivors. It illustrated that young adult survivors of childhood cancer in the Netherlands have achieved fewer milestones (or achieved them when they were older) than their peers without a history of cancer. Therefore, further research would be worthwhile. The next steps would be to investigate: (1) which survivors are at risk of a hampered course of life when they are growing up with or after childhood cancer, and (2) whether the course of life of survivors correlates with their adjustment in adult life, for example their living situation, employment and educational status and their quality of life.

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NOTES

1. Low: Primary Education, Technical and Vocational Training, Lower General Secondary Education; Middle: Middle General Secondary Education, Higher General Secondary Education, Pre-university Education High: Higher Vocational Education, University

REFERENCES

(1) Eiser C., Hill J.J., Vance Y.H. Examining the psychosocial consequences of surviving childhood cancer: Systematic review as a research method in pediatric psychology. J Pediatr Psychol 2000;25(6):49-60.

(2) Langeveld N.E., Stam H., Grootenhuis M.A., Last B.F. Quality of life in young adult survivors of childhood cancer. Support Care Cancer 2002;10:579-600.

(3) Byrne J., Fears T.R., Steinhorn S.C., Mulvihill J.J., Connelly R.R., Austin D.F., et al. Marriage and divorce after childhood and adolescent cancer. JAMA 1989;262(19):2693-9.

(4) Langeveld N.E., Ubbink M.C., Last B.F., Grootenhuis M.A., Voûte P.A., de Haan R.J. Educational achievement, employment and living situation in long-term young adult survivors of childhood cancer in the Netherlands. Psycho-oncology 2003;12(3):213-25.

(5) Rauck A.M., Green D.M., Yasui Y., Mertens A., Robinson L.L. Marriage in the survivors of childhood cancer: a preliminary description from childhood cancer survivor study. Med Pediatr Oncol 1999;33:60-3.

(6) Teeter M.A., Holmes G.E., Holmes F.F., Baker A.B. Decisions about marriage and family among survivors of childhood cancer. J Psychosoc Oncol 1987;5(4):59-68.

(7) Zevon M.A., Neubauer N.A., Green D.M. Adjustment and vocational satisfaction of patients treated during childhood or adolescence for acute lymphoblastic leukemia. Am J Pediatr Hematol Oncol 1990;12(4):454-61.

(8) Garber J. Classification of childhood psychopathology: a developmental perspective. Child Dev 1984;55:30-48.

(9) Lewis M., Miller S.M. Handbook of developmental psychopathology. New York: Plenum Press, 1990.

(10) Eiser C. Psychological effects of chronic disease. J Child Psych Psychiatry 1990;31:85-98.

(11) Pendley J.S., Dahlquist L.M., Dreyer Z. Body image and psychosocial adjustment in adolescent cancer survivors. J Pediatr Psychol 1997;22(1):29-43.

(12) Spirito A., Stark L.J., Cobiella C., Drigan R., Androkites A., Hewett K. Social adjustment of children succesfully treated for cancer. J Pediatr Psychol 1990;15(3):359-71.

(13) Vannatta K., Gartstein M.A., Short A., Noll R.B. A controlled study of peer relationships of children surviving brain tumors: teacher, peer, and self ratings. J Pediatr Psychol 1998;23(5):279-87.

(14) Vannatta K., Zeller M., Noll R.B., Koontz K. Social functioning of children surviving bone marrow transplantation. J Pediatr Psychol 1998;23(3):169-78.

(15) Charlton A., Larcombe I.J., Meller S.T., Morris Jones P.H., Mott M.G., Potton M.W., et al. Absence from school related to cancer and other chronic conditions. Arch Dis Child 1991;66:1217-22.

(16) Eiser C. Chronic childhood disease. An introduction to psychological theory and research. Cambrigde: Cambrigde University Press, 1990.

(17) Madan-Swain A., Brown R.T., Foster M.A., Vega R., Byars K., Rodenberg W., et al. Identity in adolescent survivors of childhood cancer. J Pediatr Psychol 2000;25(2):105-15.

(18) Tyc V.L., Hadley W., Crockett G. Predictors of intentions to use tobacco among adolescent survivors of cancer. J Pediatr Psychol 2001;26(2):117-21.

(19) Tyc V.L., Hudson M.M., Hinds P. Health promotion interventions for adolescent cancer survivors. Cogn Behav Pract 1999;6(2):128-36.

(20) Weinstein N.D. Testing four competing theorues of health-protective behavior. Health Psychol 1993;12(4):324-33.

(21) Rait D.S., Ostroff J.S., Smith K., Cella D.F., Tan C., Lesko L.M. Lives in balance: perceived family functioning and the psychosocial adjustment of adolescent cancer survivors. Fam Process 1992;31:383-97.

(22) Haupt R., Byrne J., Connelly R.R., Mostow E.N., Austin D.F., Holmes G.R., et al. Smoking habits in survivors of childhood and adolescent cancer. Med Pediatr Oncol 1992;20:301-6.

(23) Hollen P.J., Hobbie W.L. Decision making and risk behaviors of cancer-surviving adolescents and their peers. J Pediatr Oncol Nurs 1996;13(3):121-34.

(24) Tao M.L., Guo M.D., Weiss R., Byrne J., Mills J.L., Robinson L.L.., et al. Smoking in adult survivors of childhood Acute Lymphoblastic Leukemia. J Natl Cancer Inst 1998;90(3):219-25.

(25) Verrill J.R., Schafer J., Vannatta K., Noll R.B. Agression, antisocial behavior, and substance abuse in survivors of pediatric cancer: possible protective effect of cancer an its treatment. J Pediatr Psychol 2000;25(7):493-502.

(26) Grootenhuis M.A., Stam H., Destrée-Vonk A., Heijmans H.S.A., Last B.F. Levensloop Vragenlijst voor Jong-Volwassenen [Course of life questionnaire for young adults]. Gedrag & Gezondheid 2003;31(5):336-50.

(27) Last B.F., Grootenhuis M.A., Destrée-Vonk A., Heymans H.S.A. De ontwikkeling van een levensloopvragenlijst voor jong-volwassenen (LVJV) [Development of a course of life questionnaire for young adults]. Gedrag & Gezondheid 2000;8(1):22-30.

(28) Cohen J. Statistical power analysis for the behavioral sciences. New York: Academy Press, 1988.

Chapter 10

Course of life of survivors of childhood cancer is related to Quality of Life in young adulthood

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ABSTRACT

The aims of this study were to assess the following (1) the impact of medical determinants on the course of life of survivors of childhood cancer, and (2) the impact of the course of life on Quality of life in young adulthood. A total of 353 Dutch cancer survivors, aged 18-30 years, completed the RAND-36 Health Survey and the Course of life questionnaire. Multiple linear regression analyses were performed.

Survivors of brain tumors and survivors having been treated with radiotherapy reported the achievement of significantly fewer milestones in the psycho-sexual and social domain than the other survivors. Survivors who achieved fewer milestones in the social domain scored worse on Quality of life. Health care providers should help to minimize the harm for children who grow up with cancer by encouraging social and psychosexual development. Children should be encouraged to make friends and to participate in peer activities.

INTRODUCTION

The dramatic increase in the number of survivors of childhood cancer reaching adulthood over the last decades has heightened the need to investigate the consequences of both the disease and its treatment. More and more physicians will be confronted with young adult survivors of childhood cancer. Optimal transition from pediatric to adult health care requires physicians with knowledge of the psychosocial history of growing up with childhood cancer.

It is widely known that growing up with childhood cancer may have consequences in adulthood, and an increasing number of studies have been directed at assessing Quality of Life (QoL) in survivors of the disease (see review of Langeveld et al.(1)). Much less is known about the predictors of QoL in these survivors. Although the impact of demographic and medical variables on QoL has been investigated (e.g. (2-4), their explanatory value seems limited (5). More insight is needed into the psychological variables that predict QoL later in life, as this could be helpful in directing interventions for childhood cancer survivors.

The course of life in the transition from childhood to adult life maybe an important mediator of later QoL. Fulfilling developmental tasks and achieving developmental milestones while growing up (such as search for contacts outside the family, or acquisition of independence) are referred to as the 'course of life'. It is generally recognized that the fulfilling of age-specific developmental tasks in childhood is of great importance to adjustment in adult life (6;7). The burden of cancer, treatment, hospitalization and longterm medical sequelae interfere with this process in children with cancer. Childhood cancer and its treatment often increase children's dependence on their parents and other adults, and decrease the participation in peer-based and school-based activities of these children (8-11). This could pose a threat to the accomplishment of developmental tasks or milestones, resulting in a delayed course of life. This, in turn, may affect QoL and socio-demographic outcomes in adulthood. For example, childhood cancer survivors were found to live with their parents longer after reaching adulthood than their peers, and a lower prevalence of marriage and parenthood was found among cancer survivors than among their peers (1;12-17). Furthermore, cognitive problems and non-attendance as a result of the disease and treatment appeared to result in less educational achievement (18;19). Finally, it has been reported that identity achievement in adolescent survivors of cancer may be problematic (20).

Recently, it was found that the course of life of young adult survivors of childhood cancer in The Netherlands was delayed (17). More specifically, the young adult survivors of childhood cancer turned out to have achieved fewer milestones than their peers with respect to Autonomy development, Social development, and Psycho-sexual development. Furthermore, it was found that childhood cancer survivors exhibited less anti-social behavior, and less substance use and gambling than the comparison group. In addition, the course of life of survivors of childhood cancer was found to be less favorable than the course of life of young adults grown up anorectal malformations, Hirschsprung's disease or oesophageal atresia (21).

The finding that the course of life of the Dutch survivors of childhood cancer was delayed, has fuelled the need to investigate the predictors and consequences of the course of life: which survivors are at risk of a delayed course of life while growing up, and what are the consequences of a delayed course of life for QoL in adulthood? The aim of the current study was to investigate (1) the impact of medical determinants on the course of life of survivors of childhood cancer, while growing up, and (2) the impact of the course of life while growing

up on QoL in young adulthood. Our first hypothesis was that medical determinants would be predictive of the achievement of developmental milestones, and hence of the course of life. Secondly, we hypothesized that a more favorable course of life would be correlated with better QoL.

METHODS

Procedure

The results presented here concern the cross-sectional part of the VOLG-study (Vragenlijsten kinderOncologie Latere Gevolgen), a Dutch study on late psychosocial consequences of cancer in childhood. The respondents participating in this part of the study were recruited from the long-term follow-up clinic at The Emma Children's Hospital/ Academic Medical Center Amsterdam, a clinic established in 1996 to monitor long-term sequelae of childhood cancer and its treatment. Patients become eligible for transfer from active-treatment clinics to the follow-up clinic at least five years after successfully completing their cancer treatment. Survivors are evaluated annually in the clinic by a pediatric oncologist (patients aged < 18 years) or by an internist-oncologist (patients aged > 18 years) for late medical effects, as well as by a research nurse or a psychologist for psychosocial effects.

In 2001 and 2002, the survivors of childhood cancer, aged between 18 and 30 years, who attended the long-term follow-up clinic were invited (in person by a psychologist) to fill in several questionnaires anonymously. After completing the questionnaires at home, they were requested to return them in a stamped addressed return envelope. After a month a reminder letter was sent with a copy of the same questionnaires. The inclusion criteria were: (1) age at study 18-30 years, (2) end of successful treatment at least five years before, (3) age at cancer diagnosis < 18 years, and (4) ability to understand Dutch questionnaires. An unique patient number made it possible to gather medical information, from the respondents as well as from the non-respondents.

The study protocol was approved by the Medical Ethic Committee of the Academic Medical Center Amsterdam.

Measures

Course of life

The Course of life questionnaire, a Dutch questionnaire developed by the Psychosocial Department of The Emma Children's hospital/Academic Medical Center, was used to retrospectively assess the achievement of developmental milestones in the survivors of childhood cancer. This instrument was developed in order to be able to investigate the course of life of young adults, aged 18-30, who grew up with a chronic or life-threatening disease, in comparison with the course of life of peers without a history of disease (22). The questionnaire was normed with a sample of 508 young adults from the general Dutch population. This normative sample appeared not to differ from the current study sample of survivors of childhood cancer with respect to gender, age, religion, and educational level of their parents (17).

The items of the Course of life questionnaire, based on the literature and on clinical experience, concern behaviours that are characteristic of certain age-stages, developmental tasks, and limitations children with a chronic illness might face. Most questions retrospectively ask whether the respondent has achieved factual developmental milestones (yes, no) or at which age (category) the respondents achieved the milestones. The questions do not go further back in time than primary school. The answers are dichotomised, where necessary, before being added to the scale-score. The items of three out of the five scales were used in the current study: (1) development of autonomy (6 items, autonomy at home and outside home; e.g. "regular job in your family during primary school"), (2) psycho-sexual development (4 items, love and sexual relations; e.g. "for the first time falling in love"), (3) social development (12 items, social contacts with peers, at school and in leisure time; e.g. "belonging to a group of friends during secondary school"). For the complete description of the scale-items please refer to Stam et al. (17). A higher score on the scales indicates the accomplishment of more developmental milestones and hence a more favorable course of life. The validity of the course-of-life-scales is satisfactory. First, the items are based on the literature and clinical experience. Second, the scales seemed to measure distinct constructs because the Pearson's correlation between the scales is not high ($r<0.30$). Third, the results of the Course of life questionnaire, completed by a normative population of 508 young adults from the general Dutch population, proved to be in line with several datasets of the Dutch population (17;22). The test-retest reliability is good; Pearson's correlations between the test and retest scale scores were ≥ 0.86 (23). The reliability of two of the three scales used was satisfactory. The reliability of the Development of autonomy scale is moderate, probably because the items concern diverging aspects of autonomy (17;22). The Cronbach's alphas (α) among the survivors under study were moderate to good: (1) development of autonomy, 6 items: $\alpha = 0.46$, (2) psychosexual development, 4 items: $\alpha = 0.79$, (3) social development, 12 items: $\alpha = 0.76$. The use of scales with moderate internal consistency is acceptable for group comparisons because the internal consistency is an indication of random error and has nothing to do with systematic error (bias).

Quality of life

QoL was assessed with the RAND-36. The RAND-36 is a Dutch version of the MOS-SF-36 Health Survey and almost identical to the Dutch SF-36 (24). The RAND-36 is composed of 36 items with standardized response choices, clustered into eight multi-item scales: Physical Functioning (PF), Social Functioning (SF), Role limitations due to Physical health problems (RP), Role limitations due to Emotional problems (RE), general Mental Health (MH), Vitality (VT), Bodily Pain (BP), and General Health perceptions (GH). All raw scale scores are converted to a 0-100 scale, with higher scores indicating higher levels of functioning or well-being. The validity and reliability of the RAND scales are satisfactory (25). We found Cronbach's alphas of 0.74 to 0.90 among the survivors. Overall physical and overall mental health was assessed by aggregation of all scale scores according to the algorithm described by Ware et al.(26), leading to the so-called Physical Component Scale (PCS) and to the Mental Component Scale (MCS). The relative contribution of each scale to PCS and MCS was derived from principal components analysis, non-orthogonal rotation (Oblimin), on the basis of the assumption that physical health and mental health are interdependent. This is contrary to the analysis of Ware et al.(26), who conducted an orthogonal rotation.

Medical data

The following medical data were obtained from the registry of the long-term follow-up clinic at The Emma Children's Hospital/Academic Medical Centre Amsterdam: diagnosis, treatment, age at first diagnosis, duration of treatment, time since diagnosis, time since end of treatment, and relapse or second malignancy.

Statistical Analysis

The Statistical Package for the Social Sciences (SPSS) Windows version 11.5 was used for all analyses. Before conducting the final analyses we performed several preparation analyses. First, scales were constructed on the basis of the guidelines of the questionnaires used in this research, and the reliability of the scales was calculated. Second, we formed dummy variables, i.e. *diagnosis*: leukemia/lymphoma, solid tumors, brain tumors; *treatment*: surgery only, chemotherapy with or without surgery, radiotherapy with or without surgery, chemotherapy and radiotherapy with or without surgery. We took the first category of each dummy as reference for the analysis. Third, missing data on the RAND-36 were imputed at scale level. If less than half the items of a scale was missing, the scale-score was calculated on the basis of the items the respondent had completed. The missing data on the Course of life questionnaire were not imputed.

Multiple linear regression analyses were performed to investigate the impact of medical determinants on the course of life, controlling for age and gender. The following medical determinants were entered in the regression models: diagnosis, treatment, age at first diagnosis, duration of treatment, and relapse or second malignancy. The variables 'time since diagnosis' and 'time since end of treatment' were not entered into the models because of multicollinearity, as they can be derived from the 'age', 'age at first diagnosis', and 'duration of treatment', variables which are represented in the models. By presenting the regression coefficients B belonging to the medical determinants, it will be possible to calculate differences between subgroups of survivors with respect to the number of milestones achieved.

To investigate the impact of the achievement of developmental milestones while growing up on QoL in young adulthood, multiple linear regression models were fitted for the scales of the RAND-36. These analyses enable us to determine the impact of the developmental milestones on QoL independent of medical and demographic variables. The following independent variables were entered in all the regression models: the scores on Autonomy development, Psycho-sexual development and Social development, and age, gender and medical determinants.

RESULTS

Survivors

A total of 499 young adult survivors were asked to take part in the VOLG-study, 262 men and 237 women. A total of 355 questionnaires were returned (response rate 71.0%). Two questionnaires could not be used for analysis because they had not been filled in by the patients themselves (N = 1) or because they had been returned too late (N = 1). Of the 144 survivors who did not complete the questionnaires 18 returned the non-response form.

Most of these non-respondents reported that they did not have enough time or did not feel like taking part in the study (N = 10). Two survivors refused because they did not want to be confronted with cancer again. The remaining six did not complete the questionnaires for other reasons.

The data of 353 survivors were used for analysis (Table I). Participants were older than non-participants at time of study (M = 24.3 yrs versus M=23.2 yrs; p<0.01) and at diagnosis

Table I. Demographic and Medical Characteristics of Participants and Non-Participants

	Participants (N = 353)			Non-participants (N = 146)		
	M	**SD**	**Range**	**M**	**SD**	**Range**
Age at study (years)	24.3**	4.0	17.7-31.1	23.2	3.9	18.0-30.8
Age at first diagnosis (years)	7.3*	4.7	0.0-17.0	6.3	4.7	0.0-17.0
Time since first diagnosis (years)	17.0	6.0	6.2-30.7	16.8	5.5	5.4-28.4
Time since end of last treatment (years)	15.5	5.5	4.9-30.3	15.6	5.4	4.8-28.2
Duration of treatment (months)	12.5	10.5	0.0-72.5	10.8	11.5	0.0-71.0
	N		**%**	**N**		**%**
Gender						
Female	178		50.4*	59		40.4
Male	175		49.6	87		59.6
Diagnosis						
Leukemia/lymphoma	176		49.9	64		43.8
Solid tumor	152		43.1	77		52.7
Brain tumor	25		7.1	5		3.4
Treatment						
Chemotherapy (with/without surgery)	199		56.4	79		54.5
Radiotherapy (with/without surgery)	14		4.0	8		5.5
Surgery alone	26		7.4	16		11.0
Combination therapy (chemotherapy + radiotherapy, with/without surgery)	114		32.3	42		29.0
Health problems						
No problems	45		12.7	54		9.6
Physical	299		84.7	122		83.6
Psychosocial / cognitive / neurological	114		32.3	54		37.0
Relapse or second malignancy						
Yes	43		12.2	18		12.3
No	310		87.8	128		87.7
Educational level parents [a]						
Low	137		41.1			
Middle	98		29.4			
High	98		29.4			
Native country						
The Netherlands	338		96.6			
Other	12		3.4			

[a] Highest level completed: Low = Primary Education, Technical and Vocational Training, Lower and Middle General Secondary Education; Middle = Middle Vocational Education, Higher General Secondary Education, Pre-university Education; High = Higher Vocational Education, University

*p < 0.05. **p < 0.01

(M = 7.3 versus M = 6.3 yrs; $p < 0.05$), and there was a higher percentage of women among the participants than among the non-participants (50.4% versus 40.4%, $p < 0.01$). No significant differences were found with regard to diagnosis and treatment, time since first diagnosis, time since end of last treatment, duration of treatment, relapse or second malignancy, and health problems as registered at the long-term follow-up clinic.

The study sample appeared to be representative of all 18-30 years old survivors who attended the long-term follow-up clinic of the Academic Medical Centre Amsterdam in 2001 and 2002, with the exception of the survivors suffering from serious cognitive sequelae of disease and treatment. These survivors were not represented because they were not able to fill in the questionnaires.

The Impact of Medical Determinants on Course of Life in Survivors

The impact of age, gender, and medical determinants on the course-of-life scales is shown in Table II. As we can see, age was positively related to Autonomy development ($B = 0.05$, $p < 0.05$): survivors older at study achieved more milestones with respect to autonomy. Several medical determinants appeared to be associated with the scores on the course-of-life scales. Survivors of brain tumors had a lower score on Psycho-sexual development ($B = -0.89$, $p < 0.05$) than survivors of leukemia/lymphoma: on average, they have fulfilled almost one milestone less with respect to Psycho-sexual development than the survivors of leukemia/lymphoma. Having been treated with radiotherapy (with or without surgery) was negatively related to Social development ($B = -3.12$, $p < 0.01$) and to Psycho-sexual development ($B = -1.14$, $p < 0.05$). So, radiotherapy was associated with the achievement of three milestones less on Social development and one milestone less on Psycho-sexual development than surgery alone. Combination therapy (i.e.

Table II. Unstandardized Regression Coefficients B for the Relation Between Medical Determinants and the Scores on the Course-of-Life Scales, Controlling for Age and Gender

	AUTO B	PSEX B	SOC B
Age (years)	0.05*	-0.10	-0.08
Gender (female)	-0.19	0.28	-0.26
Diagnosis (leukemia/lymphoma = reference)			
Solid tumor	0.07	-0.03	0.10
Brain tumor	-0.40	-0.89*	-0.81
Treatment (surgery only = reference)			
Chemotherapy (with/without surgery)	-0.18	-0.59	-0.12
Radiotherapy (with/without surgery)	-0.44	-1.14*	-3.12**
Chemotherapy + radiotherapy (with/without surgery)	-0.27	-1.21***	-1.32
Age at first diagnosis (years)	0.004	0.01	-.001
Duration of treatment (months)	-0.01	-0.003	-0.05 **
Relapse or second malignancy	-0.10	0.21	0.76
DF	10,332	10,331	10,305
total R^2	0.04	0.10***	0.15***

*$p < 0.05$. **$p < 0.01$. ***$p < 0.001$.

Note: AUTO = development of autonomy; SOC = social development; PSEX = psycho-sexual development

chemo- and radiotherapy with or without surgery) was also negatively associated with Psycho-sexual development (B = -1.21, p < 0.001). Finally, the duration of treatment appeared to be negatively related to Social development (B = -0.05, p < 0.01): the longer the duration of treatment the fewer milestones on Social development were reported by the survivors.

The Impact of the Course of Life on QoL in Young Adulthood

The results of the multiple regression analyses for the impact of the course of life on QoL in young adulhood are presented in Table III. The RAND-scales were correlated with the scores on Autonomy development, Social development, and Psycho-sexual development, independent of age, gender, and medical determinants. Having achieved more milestones on Social development were associated with better QoL, i.e. higher scores on Physical Functioning, Social Functioning, Role limitations due to Emotional problems, Mental Health, Vitality, and Bodily Pain. The effect of Social development was also found in the summary scores of the RAND; Physical Component Scale and Mental Component Scale. The study showed no significant effect of Autonomy development and Psycho-sexual development on the QoL of the young adult survivors of childhood cancer who participated in this study.

DISCUSSION

Optimal transition from pedatric to adult health care requires knowledge of the psychosocial history of patients grown up with childhood cancer. Recently, it was found that the course of life of young adult survivors of childhood cancer in The Netherlands was delayed (17). Because the fulfilment of age-specific developmental tasks in childhood is of great importance to adjustment in adult life (6;7), the current study was directed at investigating 1) the impact of medical determinants on the course of life of childhood cancer survivors, while growing up, and (2) the impact of the course of life on QoL in young adulthood.

With respect to the first aim, we found that the achievement of developmental milestones was influenced by both disease and treatment. Survivors of brain tumors and survivors having been treated with radiotherapy, with or without chemotherapy, scored lower on Psycho-sexual development than survivors of leukemia/lymphoma and survivors having been treated with surgery alone, respectively. Survivors who had been treated with radiotherapy without chemotherapy reported lower scores on Social development than survivors treated with surgery alone, and a longer duration of treatment was associated with the achievement of fewer milestones on Social development too. This leads us to the conclusion that especially survivors of brain tumors and survivors having been treated with radiotherapy are at risk of a delayed course of life. These results are supported by the findings of Carpentieri et al. (27), who reported that young survivors of brain tumors exhibited more problems with respect to social competence than other survivors, mainly survivors of leukemia. Results obtained by Mulhern et al. (28) and Vannatta et al. (10) were also in line with the findings of the current study. These authors reported that cranial-irradiated young survivors were more socially isolated than survivors who had been treated otherwise.

The hypothesis with respect to the second aim of the current study was also confirmed: a more favorable course of life among the Dutch survivors of childhood cancer proved to be

Table III. Standardized Regression Coefficient ß for the Relation Between the Scores on the Course-of-Life Scales and the Scores on the RAND-scales, Controlling for Age, Gender, and Medical Determinants

	PF β	SF β	RP β	RE β
Age (years)	-0.02	-0.02	-0.01	-0.03
Gender (female)	-0.19***	-0.27***	-0.24***	-0.16***
Diagnosis (leukemia/lymphoma = reference)				
Solid tumor	-0.12	-0.00	0.02	-0.03
Brain tumor	-0.11	-0.04	-0.04	-0.02
Treatments (surgery only = reference)				
Chemotherapy (with/without surgery)	-0.06	0.17	0.01	0.16
Radiotherapy (with/without surgery)	-0.05	0.11	0.05	0.10
Chemotherapy + radiotherapy (with/without surgery)	-0.11	0.05	-0.07	0.03
Age at first diagnosis (years)	-0.11	-0.06	-0.08	-0.11
Duration of treatment (months)	0.06	-0.00	-0.03	0.03
Relapse or second malignancy	-0.08	-0.00	-0.03	0.14*
Autonomy development	0.06	-0.06	-0.04	-0.04
Psycho-sexual development	0.05	-0.08	0.01	-0.09
Social development	0.16*	0.15*	0.07	0.14*
DF	13,289	13,289	13,288	13,287
total R^2	0.14***	0.14***	0.09*	0.10**

*p < 0.05. **p < 0.01. ***p < 0.001

correlated with better QoL in young adulthood. The achievement of more milestones on Social development was associated with higher scores on six out of the eight scales of the RAND-36, as well as on the physical and mental summary scale of the RAND-36. Participants from our study were more often still living at home, or living alone (17). We found associations between developmental milestones and these outcomes (Data not shown). As can be expected, those who had a slower psycho-sexual development were less often married, and those with a slower autonomy development were more often still living at home. Although this may be in an expectable direction, it is an indication of the importance of achieving developmental milestones in relation to socio-demographic outcomes late in life.

The current study, as far as we know the first study on the impact of the course of life on QoL of young adult survivors of childhood cancer, stresses the importance of giving attention to the achievement of developmental milestones in children growing up with childhood cancer. However, the study as it has been carried out here, has some limitations. First, the representativeness of the survivors under study was not optimal. Survivors suffering from serious cognitive sequelae of disease and treatment were not represented in the study as they were not able to complete questionnaires. Second, the concept 'course of life' is more comprehensive than the milestones covered by the Course of life questionnaire. The fact that the course of life is measured retrospectively limits the range of topics. In order to prevent bias caused by inadequate memory, the questions are factual and do not go further back than to primary school. The test-retest reliability proved to be satisfactory, so that we can conclude that the reporting about milestones is rather reliable (23). Third, although most items of the

MH β	VT β	BP β	GH β	PCS β	MCS β
0.04	0.04	- 0.04	0.03	-0.03	-0.00
-0.19***	-0.28***	-0.35***	-0.18**	-0.32***	-0.27***
-0.07	0.03	0.02	0.03	-0.02	-0.02
-0.01	-0.09	-0.04	0.02	-0.08	-0.04
0.26*	0.12	-0.13	0.11	-0.06	0.23
0.15*	0.10	0.02	0.10	0.01	0.15*
0.10	0.00	-0.19	-0.02	-0.14	0.07
-0.14*	-0.09	-0.06	-0.06	-0.09	-0.12
0.03	0.07	-0.01	0.10	0.03	0.05
0.01	0.02	-0.03	-0.16**	-0.09	0.05
0.02	0.00	-0.09	-0.01	-0.04	-0.06
-0.09	-0.10	-0.03	0.08	0.01	0.08
0.19**	0.20**	0.14*	0.09	0.13*	0.17**
13,287	13,287	13,288	13,287	13,283	13, 283
0.12***	0.16***	0.18***	0.09*	0.16***	0.17***

Course of life questionnaire preceded (in time) the QoL outcomes in young adulthood, this cannot be considered solid evidence of causality. This means that longitudinal research is needed to confirm the causality between the achievement of developmental milestones, while growing up, and QoL in young adulthood.

Although the explanatory value of course of life on the survivors' QoL is not very high it adds to our understanding of QoL in survivors of childhood cancer. The findings of the current study showed that a favorable social development during childhood is particularly important for children with cancer. Results of previous research (8-11;17) proved that survivors of childhood cancer had fewer friends than healthy peers, that they participated less in peer activities and spent more time on their own. Therefore, parents and health-care providers should encourage children with cancer to make friends and to participate in peer activities, such as sports events, and to maintain the social contacts they had before they became sick. Social development seemed to be related to psychosexual development (Pearson's correlation 0.34, $p < 0.01$), which means that friendships in youth are probably of importance for later sexual relationships. Peer relationships are important for social development and self-esteem especially in adolescents. Adolescents with chronic illnesses may become marginalized by peers, rejected for being different at a time when body image and identity so largely depend on conformity (29). Chronic illness may complicate the transition to adulthood, characterized by transition from family life to independent living and transition from education to employment, and closely related to positive social and emotional development earlier on (30).

Furthermore, the role of survivors' parents comes into focus. It is known that parents of chronically ill children tend to overprotect their sick child (31) but this does not help the child to develop the personal skills needed to cope with the challenges of growing up with childhood cancer. Health care providers should help parents stimulate the independence of their child. This, in turn, could be instrumental in encouraging the child to engage in peer activities. Moreover, physicians currently treating young adult survivors of childhood cancer should pay attention to the social and independent functioning of the survivors, especially during transition from childhood to adulthood. However, more is needed than the efforts of the patients and their direct surroundings. Society, schools and friends should make their contribution to the (re)integration of the survivors of childhood cancer.

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REFERENCES

(1) Langeveld NE, Stam H, Grootenhuis MA, Last BF. Quality of life in young adult survivors of childhood cancer. Support Care Cancer 2002;10:579-600.

(2) Zebrack BJ, Chesler MA. Quality of life in childhood cancer survivors. Psychooncology 2002;11:132-41.

(3) Zebrack BJ, Zeltzer LK, Whitton J, Mertens AC, Odom L, Berkow R, et al. Psychological outcomes in long-term survivors of childhood leukemia, Hodgkin's disease, and Non-Hodgkin's lymphoma: a report from the childhood cancer survivor study. Pediatrics 2002;110(1):42-52.

(4) Zebrack BJ, Gurney JG, Oeffinger K, Whitton J, Packer RJ, Mertens A, et al. Psychological outcomes in long-term survivors of childhood brain cancer: a report from the Childhood Cancer Survivors Study. J Clin Oncol 2004;22(6):999-1006.

(5) Stam H, Grootenhuis MA, Last BF. Quality of life and coping in young adult survivors of childhood cancer: positive expectations about the further course of the disease were correlated with better quality of life. Psychooncology 2006;15(1):31-43.

(6) Garber J. Classification of childhood psychopathology: a developmental perspective. Child Dev 1984;55:30-48.

(7) Lewis M, Miller SM. Handbook of developmental psychopathology. New York: Plenum Press, 1990.

(8) Pendley JS, Dahlquist LM, Dreyer Z. Body image and psychosocial adjustment in adolescent cancer survivors. J Pediatr Psychol 1997;22(1):29-43.

(9) Spirito A, Stark LJ, Cobiella C, Drigan R, Androkites A, Hewett K. Social adjustment of children succesfully treated for cancer. J Pediatr Psychol 1990;15(3):359-71.

(10) Vannatta K, Gartstein MA, Short A, Noll RB. A controlled study of peer relationships of children surviving brain tumors: teacher, peer, and self ratings. J Pediatr Psychol 1998;23(5):279-87.

(11) Vannatta K, Zeller M, Noll RB, Koontz K. Social functioning of children surviving bone marrow transplantation. J Pediatr Psychol 1998;23(3):169-78.

(12) Byrne J, Fears TR, Steinhorn SC, Mulvihill JJ, Connelly RR, Austin DF, et al. Marriage and divorce after childhood and adolescent cancer. JAMA 1989;262(19):2693-9.

(13) Langeveld NE, Ubbink MC, Last BF, Grootenhuis MA, Voûte PA, de Haan RJ. Educational achievement, employment and living situation in long-term young adult survivors of childhood cancer in the Netherlands. Psychooncology 2003;12(3):213-25.

(14) Rauck AM, Green DM, Yasui Y, Mertens A, Robinson LL. Marriage in the survivors of childhood cancer: a preliminary description from childhood cancer survivor study. Med Pediatr Oncol 1999;33:60-3.

(15) Teeter MA, Holmes GE, Holmes FF, Baker AB. Decisions about marriage and family among survivors of childhood cancer. Journal of psychosocial oncology 1987;5(4):59-68.

(16) Zevon MA, Neubauer NA, Green DM. Adjustment and vocational satisfaction of patients treated during childhood or adolescence for acute lymphoblastic leukemia. The American Journal of Pediatric Hematology/Oncology 1990;12(4):454-61.

(17) Stam H, Grootenhuis MA, Last BF. The course of life of survivors of childhood cancer. Psychooncology 2005;14:227-38.

(18) Charlton A, Larcombe IJ, Meller ST, Morris Jones PH, Mott MG, Potton MW, et al. Absence from school related to cancer and other chronic conditions. Arch Dis Child 1991;66:1217-22.

(19) Eiser C. Children with cancer. The quality of life. Mahwah, New Jersey, Londen: Lawrence Erlbaum Associates Publishers, 2004.

(20) Madan-Swain A, Brown RT, Foster MA, Vega R, Byars K, Rodenberg W, et al. Identity in adolescent survivors of childhood cancer. J Pediatr Psychol 2000;25(2):105-15.

(21) Stam H, Hartman EE, Deurloo JA, Groothoff JW, Grootenhuis MA. Young adult patients with a pediatric disease in history: impact on course of life and transition into adulthood. J Adolesc Health 2006; 39:4-13.

(22) Grootenhuis MA, Stam H, Destrée-Vonk A, Heijmans HSA, Last BF. Levensloop Vragenlijst voor Jong-Volwassenen [Course of life questionnaire for young adults]. Gedrag & Gezondheid 2003;31(5):336-50.

(23) Last BF, Grootenhuis MA, Destrée-Vonk A, Heymans HSA. De ontwikkeling van een levensloopvragenlijst voor jong-volwassenen (LVJV) [Development of a course of life questionnaire for young adults]. Gedrag & Gezondheid 2000;8(1):22-30.

(24) Aaronson NK, Muller M, Cohen PDA, Essink-Bot M, Fekkes M, Sanderman R, et al. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. J Clin Epidemiol 1998;51(11):1055-68.

(25) van der Zee KI, Sanderman R. Het meten van de algemene gezondheidstoestand met de RAND-36. Een handleiding. [Measuring general health status with the RAND-36. A guide.]. Groningen, the Netherlands: Noordelijk Centrum voor Gezondheidsvraagstukken. Rijksuniversiteit Groningen, 2003.

(26) Ware JE, Kosinski M. Interpreting SF-36 summary health measures: a response. Qual Life Res 2001;10:405-13.

(27) Carpentieri SC, Mulhern RK, Douglas S, Hanna S, Fairclough DL. Behavioral resiliency among children surviving brain tumors: a longitudinal study. J Clin Child Psychol 1993;22(2):236-46.

(28) Mulhern RK, Wasserman AL, Friedman AG, Fairclough D. Social competence and behavioral adjustment of children who are long-term survivors of cancer. Pediatrics 1989;83(1):18-25.

(29) DiNapoli PP, Murphy D. The marginalization of chronically ill adolescents. The Nursing clinics of North America 2002;37:565-72.

(30) Sinnema G. Youths with chronic illness and disabitlity on their way to social and economic participation: a health-care perspective. J Adolesc Health 1992;13:369-71.

(31) Rait DS, Ostroff JS, Smith K, Cella DF, Tan C, Lesko LM. Lives in balance: perceived family functioning and the psychosocial adjustment of adolescent cancer survivors. Fam Process 1992;31:383-97.

Chapter 11

A predictive model of Health-Related Quality of Life in young adult survivors of childhood cancer

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ABSTRACT

The aim of the study was to examine factors that affect survivors' HRQoL, using a theoretical model in which demographic and medical characteristics explain HRQoL mediated by course of life, coping and social support.

In a cross-sectional design, 353 survivors aged 18-30 years completed questionnaires. Structural Equation Modeling was performed to investigate the relationships among the variables in the model and to test whether the model fitted the data.

The model fitted the data closely CHISQ(14) = 21.61, p = 0.087; RMSEA = 0.039, 90% CI [0.00;0.070]. The effect of medical and demographic characteristics on HRQoL was mediated by coping. Survivors having been treated with both chemotherapy and radiotherapy were most at risk for worse HRQoL because they suffer more from current health complaints and were less inclined to predictive and active coping.

Screening survivors medically as well as psychosocially could help to identify patients with the greatest needs, and help to direct interventions by which the follow-up care could be improved.

INTRODUCTION

The introduction of the modern therapies has resulted in an enormous increase of survival in childhood cancer. Nowadays, overall, the 5-years survival was more than 70% among children diagnosed with cancer in Europe, compared to 30% in the 1960's (1-5). About two young adults from every 1000 ever suffered from childhood cancer in the Netherlands (6). The enormous increase in the number of survivors of childhood cancer reaching adulthood over the last decades has heightened the need to investigate the consequences of both the disease and its treatment. An increasing number of studies has been directed at assessing Health Related Quality of Life (HRQoL), as an indicator of adjustment to the consequences of childhood cancer. Many survivors appeared to experience good HRQoL but some were more vulnerable to maladjustment than others (7-9). It is therefore important to get insight in the process of adjustment and to identify factors that predict better or worse HRQoL.

The impact of demographic and medical variables on survivors' HRQoL has been discussed to some extent in many studies of HRQoL (see: review of Langeveld et al., 2002 (8)). An increased risk of worse HRQoL was found to be associated with female gender, older age at follow-up, a greater number of relapses, the presence of severe functional impairment and cranial irradiation. In addition, survivors of CNS tumors and subsets of survivors of acute lymphatic leukemia seemed to be at risk for educational deficits; the same is true for cranial irradiation and early age at diagnosis. However, the demographic and medical variables only explain variations in HRQoL to a limited extent (8;10-14). Insight into the psychosocial variables that predict HRQoL is important, as this could be helpful in directing interventions for survivors of childhood cancer. Previous studies indicated that, among others, coping (11;15;16), social support (17-20), and the achievement of developmental milestones while growing up with a history of cancer (21-23) are related to survivors' HRQoL.

Equivalent to other conceptual frameworks used to explain adjustment in pediatric patients (24) and adult patients (25), we presume that adjustment in survivors of childhood cancer (operationalised as HRQoL) is an outcome of a process over time that is influenced by demographic and medical variables mediated by psychosocial variables. In other words, demographic and medical variables affect HRQoL directly as well as indirectly via psychosocial variables, such as course of life, coping and social support. The present study is especially directed at the psychosocial factors because these play an important role in (pediatric) psychology and are assumed to be susceptible to change. Our assumptions about the process of adjustment to cancer are reflected in the conceptual model (Figure 1). Several parts of the model have been investigated separately (8;10;11;15-21;23) but to date, the entire model has not been tested yet. The aim of the present study was to examine the entire model, including direct and indirect effects, in order to test whether the theoretical, conceptual, model, fitted the process of adjustment to childhood cancer. Structural Equation Modeling (SEM) was used to test the conceptual model because, in contrast to traditional analytic procedures as linear regression analysis, SEM made it possible to distinguish between direct and indirect effects, and provided information on the degree of fit for the entire model. It was examined to which extent several demographic and medical variables explained HRQoL in young adult survivors of childhood cancer mediated by course of life, coping and social support. The results could demonstrate the importance of interpreting HRQoL as outcome

based on both medical and psychosocial factors. Subsequently, this could be helpful in tracing survivors at risk of worse HRQoL and in developing interventions for survivors of childhood cancer, by which the follow-up care could be improved.

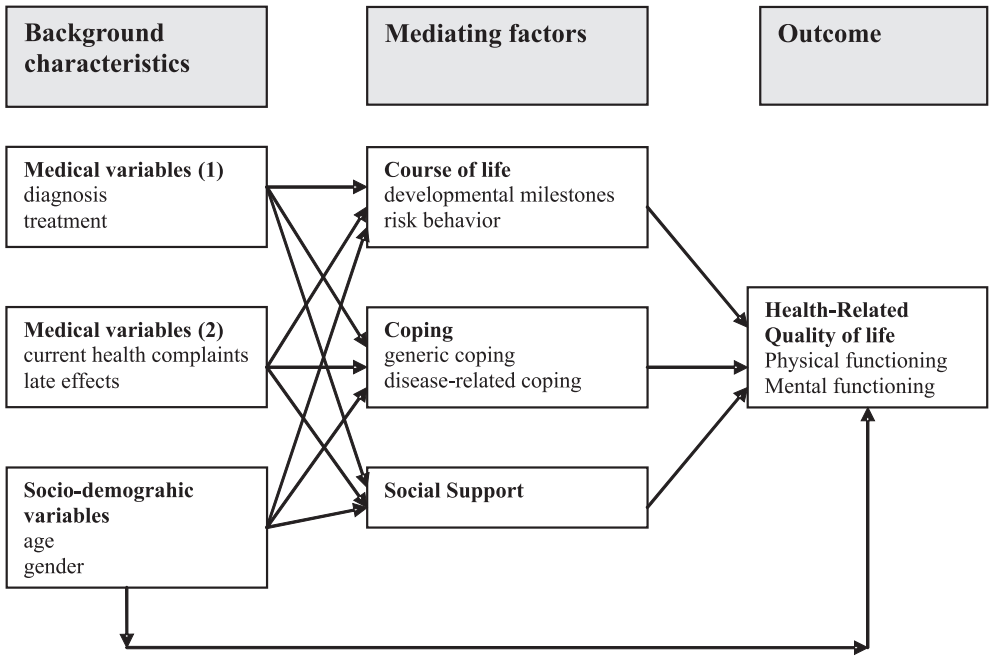

Figure 1: Conceptual model of the process of adjustment to childhood cancer: Background characteristics affecting HRQoL via Course of life, Coping and Social support.

METHODS

Procedure

In 2001 and 2002, the survivors of childhood cancer, aged between 18 and 30 years, who attended the long-term follow-up clinic at The Emma Children's Hospital/ Academic Medical Center Amsterdam, were invited (in person by a psychologist) to fill in several questionnaires anonymously. After completing the questionnaires at home, they were requested to return them in a stamped addressed return envelope. A reminder letter was sent with a copy of the same questionnaires after a month. The inclusion criteria were: (1) age at study 18-30 years, (2) end of successful treatment at least five years before, (3) age at cancer diagnosis < 18 years, and (4) ability to understand Dutch questionnaires.

An unique patient number made it possible to gather medical information, from the respondents as well as from the non-respondents. The study protocol was approved by the Medical Ethic Committee of the Academic Medical Center Amsterdam.

Measures

Background characteristics

Medical data concerning diagnosis, treatment and late effects were obtained from the registry of the long-term follow-up clinic at The Emma Children's Hospital/Academic Medical Center in Amsterdam. The registry is based on the medical information the oncologist receives at the annual evaluation; the oncologist also annotated whether the patient reported psychosocial or cognitive problems. The late effects were categorized into ten groups, based on Stevens et al. (26): i.e. endocrine, organ toxicity, mobility/orthopedic, infertility, sensory, cosmetic, fatigue, subsequent neoplasm, psychosocial/cognitive, and neurological. These health problems are clustered into two dichotomous variables: "physical late effects" (yes/no) and "psychosocial and/or cognitive and/or neurological late effects" (yes/no). Apart from the registration at the long-term follow-up clinic all respondents were asked to fill in whether they had experienced health complaints in the last four weeks (yes/no).

Mediating factors

Course of life, generic coping, disease-related coping and social support were the mediating factors in the present study.

Course of life was measured with the *Course of life questionnaire* (21;27) which assesses the achievement of developmental milestones. The items concern behavior characteristic of certain age-stages, developmental tasks, and the limitations children might face when they grow up with a chronic or life-threatening disease. The respondents are asked retrospectively whether they have achieved certain milestones or at what age they achieved the milestones. The answers are dichotomized, if necessary, before being added up to the scale-score. The items are divided into five scales: Autonomy development (6 items, autonomy at home and outside the home), Psycho-sexual development (4 items, love and sexual relations), Social development (12 items, contacts with peers), Anti-social behavior (4 items, misbehavior at school and outside it), Substance use and gambling (12 items). A higher score on the scales indicates the accomplishment of more developmental milestones or the displaying of more anti-social behavior and more substance use and gambling. For the complete description of the scale-items please refer to Stam et al. (21). The validity of the course-of-life-scales is satisfactory (21;27). The test-retest reliability is good (28) and the internal consistency is moderate to good (27).

For reasons of parsimony the five scales were aggregated into two summary scales: Developmental milestones and Risk behavior. The relative contribution of each scale to the summary scales was derived from Principal Components Analysis (PCA), oblique rotation (Oblimin).

Generic coping was measured with the *Utrecht Coping List* (UCL) (29), a questionnaire about coping with stressful or problematic situations. It consists of 47 questions with answers on a Likert-scale. The UCL covers seven coping styles: active problem-focusing, palliative reaction pattern, avoidance behavior, seeking social support, passive reaction pattern, expression of emotions, comforting emotions. A higher scale score means more use of the coping style. The internal consistency and validity is satisfactory (29;30).

For reasons of parsimony the seven scales were aggregated into three summary scales: Passive coping, Active coping, and Sharing emotions. The relative contribution of each scale to the summary scales was derived from PCA, oblique rotation (Oblimin).

Disease-related cognitive coping was assessed using the *Cognitive Control Strategies Scale* (CCSS). The instrument, based on the model of Rothbaum et al. (31), assesses on a Likert-scale to what extent respondents try to gain sense of control over the illness by using cognitive coping strategies. The items of the CCSS were grouped into three scales: predictive control (being optimistic about the course of the disease), vicarious control (attributing power to medical-care givers and treatment), interpretative control (searching for information in order to better understand emotional reactions and to gain insight into the situation). Higher scores represent a stronger reliance upon the control strategy. The internal consistency is satisfactory and the questionnaire proved to be useful in earlier studies (32-35).

The amount of *social support* the respondent indicates that he received from his social network was assessed with the *Social Support Questionnaire for Transactions* (SSQT) developed by Suurmeijer and colleagues (36-38). This questionnaire measures the frequency of 41 actual supportive transactions on a Likert-scale. The supportive transactions are categorized into seven subscales, and a total score is calculated by adding up the item scores: the more supportive transactions the higher the scores. The psychometric properties of the SSQT have proved to be good (36;38). The SSQT total score was used in the present study.

Outcome

Health-Related Quality of Life (HRQoL) was assessed with the *RAND-36*, the Dutch version of the MOS-SF-36 Health Survey and almost identical to the Dutch SF-36 (39). The RAND-36 is composed of 36 items with standardized response choices, clustered into eight multi-item scales: Physical Functioning, Social Functioning, Role limitations due to Physical health problems, Role limitations due to Emotional problems, general Mental Health, Vitality, Bodily Pain, and General Health perceptions. All raw scale scores are converted to a 0-100 scale, with higher scores indicating higher levels of functioning or well-being. The validity and reliability of the RAND-scales are satisfactory (40). Following the method of Ware et al. (41), we used PCA to aggregate the scale scores into two summary scales: Mental Component Scale (MCS) and Physical Component Scale (PCS). The relative contribution of each scale to MCS and PCS was derived from PCA, oblique rotation (Oblimin).

Statistical analyses

Missing values were handled according to the guidelines given in the manuals of the relevant questionnaires and, after that, through the Expectation-Maximization estimation method (42). A sample size of 353 remained available for analysis.

Structural Equation Modeling (SEM), using LISREL 8.30, was performed to investigate the relationships among the variables in the conceptual model and to test whether the conceptual model fitted the data. In SEM the covariance structure that follows from the proposed model is fitted to the observed covariances (43). The maximum likelihood estimate method yields estimates of the regression coefficients in the model, standard errors, and a χ^2-test of overall goodness-of-fit (44). An alternative fit measure is the root mean square error of approximation (RMSEA). According to a generally accepted rule of thumb (45) RMSEA

Table 1. Characteristics of the survivors

	Respondents (N = 353)			Non-respondents (N = 146)		
	M	**SD**	**Range**	**M**	**SD**	**Range**
Age at study (years)	24.3**	4.0	17.7-31.1	23.2	3.9	18.0-30.8
Age at first diagnosis (years)	7.3*	4.7	0.0-17.0	6.3	4.7	0.0-17.0
Time since first diagnosis (years)	17.0	6.0	6.2-30.7	16.8	5.5	5.4-28.4
Time since end of last treatment (years)	15.5	5.5	4.9-30.3	15.6	5.4	4.8-28.2
Duration of treatment (months)	12.5	10.5	0.0-72.5	10.8	11.5	0.0-71.0
	N		**%**	**N**		**%**
Gender						
Female	178		50.4*	59		40.4
Male	175		49.6	87		59.6
Diagnosis						
Leukemia/lymphoma	176		49.9	64		43.8
Solid tumor	152		43.1	77		52.7
Brain tumor	25		7.1	5		3.4
Treatment						
Chemotherapy (with/without surgery)	199		56.4	79		54.5
Radiotherapy (with/without surgery)	14		4.0	8		5.5
Surgery alone	26		7.4	16		11.0
Combination therapy (chemotherapy + radiotherapy, with/without surgery)	114		32.3	42		29.0
Late effects						
No problems	45		12.7	54		9.6
Physical	299		84.7	122		83.6
Psychosocial / cognitive / neurological	114		32.3	54		37.0
Relapse or second malignancy						
Yes	43		12.2	18		12.3
No	310		87.8	128		87.7
Educational level parents ‡						
Low	137		41.1			
Middle	98		29.4			
High	98		29.4			
Native country						
The Netherlands	338		96.6			
Other	12		3.4			

*$p < 0.05$ ** $p < 0.01$

‡ Highest level completed: Low = Primary Education, Technical and Vocational Training, Lower and Middle General Secondary Education; Middle = Middle Vocational Education, Higher General Secondary Education, Pre-university Education; High = Higher Vocational Education, University

values lower than 0.08 indicate satisfactory fit, and values lower than 0.05 indicate close fit. In addition to overall goodness-of-fit, component fit was evaluated by inspecting standardized discrepancies between observed and expected correlations, and LISREL's modification indices (44).

We used a significance level of $p < 0.05$ for the regression coefficients. Standardized regression coefficients of 0.1 were considered small, 0.3 medium and 0.5 large (46).

RESULTS

Survivors

A total of 499 young adult survivors were asked to take part in the VOLG-study, 262 men and 237 women. A total of 355 questionnaires were returned (response 71.0%), two questionnaires could not be used for analysis. Of the 144 survivors who did not complete the questionnaires 18 returned the non-response form. Most of these non-respondents reported that they did not have enough time or did not feel like taking part in the study (N = 10). Two survivors refused because they did not want to be confronted with cancer again. The remaining six did not complete the questionnaires for other reasons.

The data of 353 survivors could be used for analysis. Respondents were older than non-respondents at time of study and diagnosis, and there were a higher percentage of women among the participants than among the non-participants. No significant differences were found with regard to diagnosis and treatment, time since first diagnosis, time since end of last treatment, duration of treatment, relapse or second malignancy, and late effects as registered at the long-term follow-up clinic (Table 1).

The study sample appeared to be representative of all 18-30 years old survivors who attended the long-term follow-up clinic of the Academic Medical Centre Amsterdam in 2001 and 2002, with the exception of the survivors suffering from serious cognitive sequelae of disease and treatment. These survivors were not represented because they were not able to fill in the questionnaires.

Adjustment to childhood cancer

Model fit

The conceptual model (Fig.1) was fitted to the correlation matrix. The CHISQ measure of overall goodness-of-fit was 77.55 (CHISQ(22), p = 0.00) and the hypotheses of exact fit was rejected. The RMSEA was 0.085, and the 90% confidence interval (CI) ranged from 0.065 to 0.11, which indicated that the fit was not quite satisfactory. Inspection of component fit indices indicated several possible modifications. Firstly, the modification indices suggested direct effects of "current health complaints", "physical late effects" and "psychosocial/ cognitive/ neurological late effects" on HRQoL, which suggested to consider these factors as 'mediating factors' in stead of 'background characteristics'. Secondly, the modification indices suggested an additional direct effect of "relapse/second tumor" on HRQoL. These modifications were added stepwise to the model, resulting in a modified model with close fit: CHISQ(14) = 21.61, p = 0.087; RMSEA = 0.039, 90% CI [0.00;0.070] . The modified model explained 46% of the variance in MCS and 40% of the variance in PCS. Figure 2 gives a graphical display of the modified model, and Table 2 gives the parameter estimates.

The first part (1) of Table 2 presents the effects of demographic and medical variables (background characteristics) on the mediating factors, the second part (2) contains the direct effects of the background characteristics on HRQoL, and the third part (3) contains the effects of the mediating factors on HRQoL. The total effect of a variable on HRQoL can be calculated using the direct and indirect pathways in the modified model, as the following example illustrates. Table 2 shows that "brain tumor" has only indirect effects on HRQoL. Firstly, the diagnosis "brain tumor" compared to "leukemia/lymphoma" was associated with

an increase of 0.17 standard deviation in "psychosocial/cognitive/neurological late effects", and with a decrease of 0.13 standard deviation in "developmental milestones" and "risk behavior". Secondly, it is shown that the effect of "psychosocial/ cognitive/neurological late effects" on HRQoL was – 0.11 and – 0.15 for MCS and PCS, respectively. The significant (indirect) effects of "brain tumor" on MCS and PCS can be calculated as follows: 0.17 x – 0.11 = - 0.019 and 0.17 x – 0.15 = - 0.026, respectively. Apart from that, the other indirect effects of "brain tumor" on MCS and PCS were small and non-significant, so that the total effect remains small, - 0.05 and – 0.06, respectively.

Effects of the background characteristics

All significant regression coefficients of the demographic and medical variables were small to medium (46), ranging from β = - 0.13 (brain tumor) to β = - 0.34 (radio- and chemotherapy). Treatment variables appeared to affect the mediating factors most strongly.

Direct as well as indirect effects of gender on HRQoL were found. Being female had a negative impact on HRQoL, directly as well as indirectly via "current health complaints", "interpretative control", "predictive control", "passive coping" and "sharing emotions".

Survivors of brain tumors had worse HRQoL than survivors of leukemia/lymphoma, via "psychosocial/cognitive/neurological late effects". Survivors of solid tumors, on the contrary, reported better HRQoL via these late effects, but their HRQoL got worse via 'passive coping'. Survivors having been treated with chemotherapy with or without radiotherapy reported worse HRQoL than those treated with surgery only, mediated by "current health complaints". The negative effect of "radio-and chemotherapy" on HRQoL was also mediated by "predictive control" and "active coping".

It is interesting that "brain tumor", "radio-and chemotherapy" and "radiotherapy" were associated with the achievement of fewer developmental milestones. Furthermore, "female gender" and "brain tumor" were associated with less risk behavior. However, these mediating factors appeared not to affect HRQoL significantly.

Furthermore, "age at first diagnosis" and "duration of treatment" had a negative impact on HRQoL, mediated by "passive coping". Finally, a small direct negative effect of "relapse/ second tumor" on PCS was found.

Effects of the mediating factors

The significant effects of the mediating factors on HRQoL were small to medium, ranging from β = – 0.11 (psychosocial/cognitive/neurological late effects) to β = – 0.29 (passive coping).

Survivors with current health complaints or psychosocial/cognitive/neurological late effects reported worse HRQoL, mentally but especially physically. Both disease-related and generic coping affected HRQoL. The disease-related coping strategies "interpretative control" affected PCS negatively, while the effect of "predictive control" on MCS and PCS was positive. The generic coping style "passive coping" was associated negatively with MCS and PCS, as "sharing emotions" was with MCS. "Active coping", on the contrary, had a positive effect on MCS. No effects were found of the mediating factors "physical late effects", "developmental milestones", "risk behavior", "vicarious control" and "social support".

Table 2. Predictive model of Health-related Quality of life in young adult survivors of childhood cancer: standardized Regression Coefficients and Percentage of Explained Variance of the Modified Model*

	Age	Female gender	Brain tumor†	Solid tumor†	Radio Chemo therapy‡
1 Effects of demographic and medical variables on the mediating factors					
Morbidity					
Current health complaints	0.00	**0.23**	- 0.01	- 0.11	**0.23**
Physical late effects	0.03	0.08	0.00	**0.27**	0.17
Psych/cogn/neur. late effects	- 0.04	0.08	**0.17**	**- 0.16**	0.18
Course of life					
Develop. milestones	- 0.01	- 0.02	**- 0.13**	0.01	**- 0.34**
Risk behaviour	0.04	**- 0.24**	**- 0.13**	- 0.08	- 0.18
Disease-related coping					
Interpretative control	0.05	**0.19**	0.05	- 0.05	0.01
Vicarious control	0.06	- 0.04	- 0.10	- 0.06	- 0.10
Predictive control	- 0.07	**- 0.16**	- 0.05	0.01	**- 0.26**
Generic coping					
Passive coping	- 0.05	**0.23**	0.12	**0.22**	0.00
Active coping	0.11	- 0.07	- 0.02	0.01	**- 0.25**
Sharing emotions	0.08	**0.23**	0.04	- 0.06	- 0.19
Social support	- 0.03	**0.17**	0.04	**0.17**	- 0.04
2 Effects of demographic variables and Relapse/second tumour on HRQoL					
Mental functioning (MCS)	- 0.05	- 0.08			
Physical functioning (PCS)	- 0.08	**- 0.11**			

	Current health complaints	Physical late effects	Psych/cogn/ neurological late effects	Develop-mental milestones	Risk behaviour
3 Effects of mediating factors on HRQoL					
Mental functioning (MCS)	**- 0.12**	0.01	**- 0.11**	- 0.07	- 0.08
Physical functioning (PCS)	**- 0.28**	- 0.03	**- 0.15**	0.04	- 0.06

* N = 353; overall goodness of fit CHISQ(14) = 21.61, p = 0.087; RMSEA = 0.039, 90% confidence interval [0.0;0.070]. Bold regression coefficients differ significantly from zero at α = 0.05.
† "Leukemia/lymhoma" is reference. The variables were dichotomised as follows: brain tumor 1 vs leukemia/ lymphoma 0, solid tumor 1 vs leukemia/lymphoma 0
‡"Surgery only" is reference. The variables were dichotomised as follows: Radio- and chemotherapy with or without surgery 1 vs surgery only 0, radiotherapy with or without surgery 1 vs surgery only 0, chemotherapy with or without surgery 1 vs surgery only 0.
§ The model explains 46% and 40% of the variance of MCS and PCS, respectively

Radio therapy‡	Chemo therapy‡	Age first diagnosis	Duration treatment	Relapse Second tumor			
0.06	**0.28**	- 0.03	- 0.01	- 0.02			
- 0.02	- 0.09	0.09	**- 0.25**	0.07			
0.09	0.00	- 0.08	- 0.05	- 0.03			
- 0.20	- 0.13	0.01	- 0.12	0.06			
- 0.12	- 0.12	- 0.07	- 0.13	- 0.01			
0.07	0.02	- 0.04	- 0.01	- 0.09			
- 0.03	- 0.02	- 0.07	- 0.04	- 0.09			
- 0.08	- 0.09	- 0.04	0.10	- 0.02			
- 0.07	- 0.04	**0.21**	**0.15**	- 0.04			
- 0.09	- 0.04	0.00	0.01	0.11			
- 0.01	- 0.12	0.01	0.07	0.03			
0.02	0.10	0.01	0.13	0.02			
				0.02			
				- 0.08			
Interpret. control	Vicarious control	Predictive control	Passive coping	Active coping	Sharing emotions	Social support	*Explained Variance §*
- 0.07	- 0.03	**0.25**	**- 0.29**	**0.21**	**- 0.17**	0.07	*0.46*
- 0.13	0.05	**0.18**	**- 0.17**	0.07	- 0.01	0.00	*0.40*

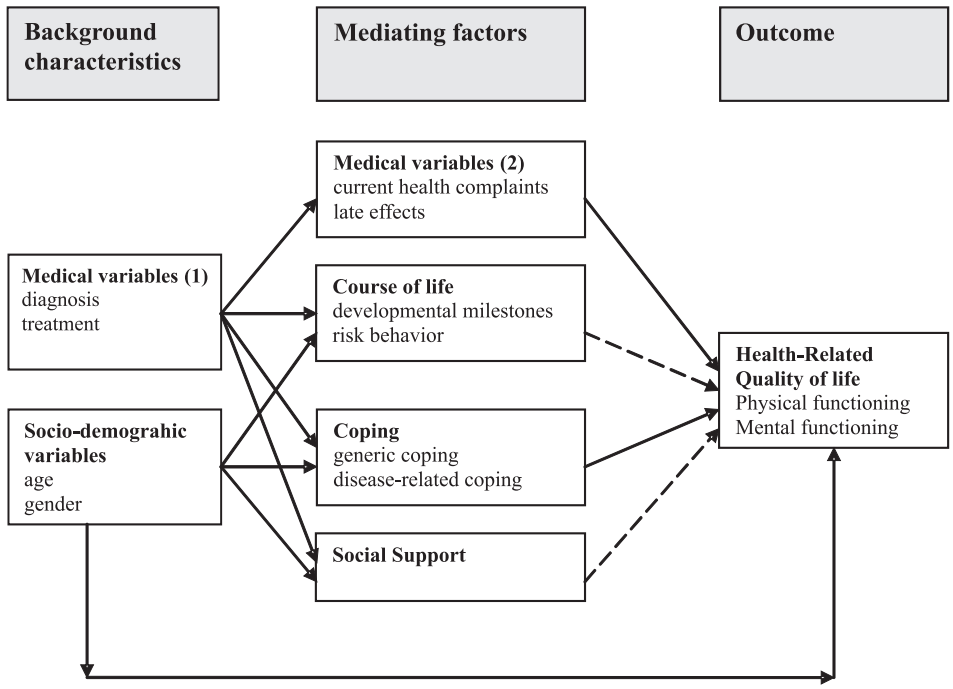

Figure 2: Modified, final, model of the process of adjustment to childhood cancer: Background characteristics affecting HRQoL via Medical variables, Course of Life, Coping and Social Support.

Note Non-significant paths (at 0.05) are marked with an interrupted arrow

DISCUSSION

The final, modified, model of adjustment to childhood cancer fitted the data closely and explained a substantial part of the variance of HRQoL of the survivors of childhood cancer (Figure 2, Table 2). The final model was somewhat different from our conceptual model (Fig.1). It seemed reasonable – data-driven as well as theoretically – to differentiate between characteristics of disease and treatment, and the late medical consequences. Diagnosis and treatment appeared to affect HRQoL via 'current health complaints' and 'psychosocial/ cognitive/neurological late effects', so that these variables were considered mediating factors instead of background characteristics. The paths in the model (Table 2) also showed that the medical and demographic characteristics were mediated by generic and disease-related coping. Course of life and social support had no significant (mediating) effects on HRQoL.

Gender is the factor that most frequently affected the mediating factors. In addition, a direct effect of gender on physical HRQoL was found. Female survivors reported more health complaints and worse HRQoL than male survivors, which finding has been reported frequently (39). Furthermore, female survivors reported less risk behavior which means that substance use and anti-social behavior was more prevalent among the male survivors. This gender effect

is also known among the general population (21). Apart from that, it is known that male as well as female survivors reported less risk behavior than their peers from the general Dutch population (21). The relation we found between gender and generic coping indicates that men and women have different styles of coping with general life stressors. Female survivors reported more passive coping, were more inclined to share emotions with others, and they reported more social support than the male survivors. These gender differences are in accordance with the results of several studies on generic coping in the general Dutch population (29). Gender effects were also found with respect to disease-related coping. Female survivors searched more for information about their disease (interpretative control), while men were more optimistic about the further course of their disease (predictive control).

Diagnosis and treatment were the medical characteristics that affected the mediating factors most strongly. Survivors having been treated with chemotherapy (with or without radiotherapy) were most at risk of health complaints, while survivors of a brain tumor were most at risk of psychosocial, cognitive or neurological late effects. In turn, these consequences of childhood cancer had a negative impact on both mental and physical functioning in young adulthood.

Survivors of a brain tumor and/or having been treated with radiotherapy had achieved fewer developmental milestones, and the survivors of a brain tumor reported also less risk behavior. Remarkably, these course-of-life-factors exerted no influence on survivors' HRQoL in contrast with previous results (22;47). Several explanations could be given. Firstly, coping was not included as predictor of HRQoL in the previous studies. In the present study, coping strategies revealed to be stronger predictors of HRQoL than the course of life, and coping and course of life were interrelated. Furthermore, we should realize that the instrument used, the RAND-36, measures generic HRQoL generally. Specific questionnaires are needed for the measurement of HRQoL of survivors more thoroughly. In addition, there are other important aspects of the well-being and functioning of survivors, such as educational achievement and marital status, which could be affected by the course of life. Although the mediating effect of the course of life on HRQoL has not been confirmed by our data, the achievement of developmental milestones while growing up is of great importance to adjustment in adult life (47-49).

Several medical variables affect coping. The results suggest that if the cancer was intrusive – indicated by "older age at diagnosis", "longer duration of treatment", "chemo- and radiotherapy" and "solid tumor" – patients were more inclined to a passive, avoidant coping style, and to less active and predictive strategies. However, we did not measure coping during treatment so we do not know whether the coping strategies during treatment were the same we found in the present study.

Coping mediated the effects of the background characteristics on HRQoL. Survivors who searched more for information about their disease (interpretative control) reported worse HRQoL, just as the survivors who had a passive reaction pattern and shared their emotions with others. An active, problem-focused coping style, on the contrary, had a positive impact on HRQoL, which was also true for being optimistic about the further course of the disease (predictive control). In other words, goal-oriented survivors who faced the situation calmly (active problem focusing) reported better emotional functioning than survivors who coped with stress by taking a passive standpoint and allowing themselves to be totally immersed in the problem (passive reaction pattern). These correlates are not surprising, since passive coping

is related to the concept of 'learned helplessness' and active coping to feelings of control over events (50). The results in the present study were in line with results in other studies about coping with general life stressors and about coping in disease-related situations (33;51).

In summary we conclude that our model explained the process of adjustment to childhood cancer reasonably well, as well as HRQoL as final outcome. Nevertheless, the explained variances in the model can probably be increased by adding factors and outcomes, found to be relevant in studies on adjustment to pediatric chronic physical disorders (24;52-54). Firstly, intrapersonal factors such as personality and temperament may affect adjustment (24). However, personality and temperament characteristics were expressed partly in the personal coping styles measured in our study. Secondly, social-ecological factors were not included in our model, such as family functioning and socio-economic factors. Thirdly, the concepts 'self-esteem' and 'mastery' could be predictive of adjustment (53;54). Finally, the present study focused on HRQoL outcomes but, of course, there are other interesting aspects indicative of patients' (mal)adjustment, for instance Posttraumatic Stress Symptoms (19;23;55-57) and socio-economic outcomes (58-60).

After all, one should realize that, overall, most survivors appear to cope well with the cancer experience and the late consequences of the disease and its treatment. Insight in the factors that affect HRQoL may alert clinicians to patients vulnerable to psychosocial problems. The model shows us that survivors having been treated with chemotherapy and radiotherapy are most at risk for worse HRQoL, because they suffer more from current health complaints and were less inclined to predictive and active coping. The model shows that it could be useful to give attention to survivors' way of coping with their disease and with general life stressors, because some coping strategies appeared to be more helpful than others.

By examining the entire model, the importance of monitoring survivors medically as well as psychosocially was stressed. In some hospitals, survivors are screened psychosocially by a psychologist during the annual evaluation at the long-term follow-up clinic. It would be useful to discuss coping strategies, especially if problems were reported. Giving attention to the achievement of developmental milestones is also recommended because several medical variables appeared to influence the achievement of the milestones unfavorably. Increasingly, computer-scored individually measurement of HRQoL is used in clinical practice, in order to inform the physician about the patient's HRQoL (59;61-64). The computer output – usually a graphical summary of HRQoL outcomes – assists the physician to focus at the HRQoL domains that correspond with patients needs. Utilizing HRQoL measurement can facilitate patient-physician communication and identifying patients with the greatest needs (62;63), so that referring to other health care providers is possible.

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REFERENCES

(1) Novakovic B. U.S. Childhood cancer survival, 1973-1987. Medical and Pediatric Oncology 1994;23:480-6.

(2) Stiller CA, Draper GJ. The epidemiology of cancer in children. In: Voûte PA, Kalifa C, Barrett A, eds. Cancer in children: clinical management. fourth edition ed. Oxford: Oxford University Press, 1998.

(3) Stiller CA, Draper GJ. The epidemiology of cancer in children. In: Voûte PA, Barret A, Stevens MCG, Caron HN, eds. Cancer in children: clinical management. fifth edition ed. Oxford: Oxford University Press, 2005. p. 1-16.

(4) Magnani C, Pastore G, Coebergh J, Viscomi S, Spix C, Steliarova-Foucher E. Trends in survival after childhood cancer in Europe, 1978-1997: Report from the Automated Childhood Cancer Information system project (AGGIS). European Journal of Cancer 2006;42(13):1981-2005.

(5) Sankila R, Martos Jiménez MC, Miljus D, Pritchard-Jones K, Steliarova-Foucher E, Stiller C. Geographical comparison of cancer survival in European children (1988-1997): Report from the Automated Childhood Cancer Information System project. European Journal of Cancer 2006;13(1972):1980.

(6) Paulides J, Kamps WA, Caron H. Childhood cancer in the Netherlands 1989-1997. Utrecht, the Netherlands: Association of Comprehensive Cancer Centres; 2000.

(7) Eiser C. Children with cancer. The quality of life. Mahwah, New Jersey, Londen: Lawrence Erlbaum Associates Publishers, 2004.

(8) Langeveld NE, Stam H, Grootenhuis MA, Last BF. Quality of life in young adult survivors of childhood cancer (review). Supportive Care in Cancer 2002;10:579-600.

(9) Stam H, Grootenhuis MA, Last BF. Social and emotional adjustment in young survivors of childhood cancer (review). Supportive Care in Cancer 2001;9:489-513.

(10) Langeveld NE, Grootenhuis MA, Voûte PA, de Haan RJ, van den Bos C. Quality of life, self-esteem and worries in young adult survivors of childhood cancer. Psycho-oncology 2004;13:867-81.

(11) Stam H, Grootenhuis MA, Last BF. Quality of life and coping in young adult survivors of childhood cancer: positive expectations about the further course of the disease were correlated with better quality of life. Psycho-oncology 2006;15(1):31-43.

(12) Zebrack BJ, Chesler MA. Quality of life in childhood cancer survivors. Psycho-oncology 2002;11:132-41.

(13) Zebrack BJ, Zeltzer LK, Whitton J, Mertens AC, Odom L, Berkow R, et al. Psychological outcomes in long-term survivors of childhood leukemia, Hodgkin's disease, and Non-Hodgkin's lymphoma: a report from the childhood cancer survivor study. Pediatrics 2002;110(1):42-52.

(14) Zebrack BJ, Gurney JG, Oeffinger K, Whitton J, Packer RJ, Mertens A, et al. Psychological outcomes in long-term survivors of childhood brain cancer: a report from the Childhood Cancer Survivors Study. Journal of Clinical Oncology 2004;22(6):999-1006.

(15) Phipps S, Srivastava DK. Repressive adaptation in children with cancer. Health Psychology 1997;16(6):521-8.

(16) Phipps S, Larson S, Long A, Rai SN. Adaptive style and symptoms of posttraumatic stress in children with cancer and their parents. Journal of Pediatric Psychology 2006;30(1):1-12.

(17) Fritz GK, Williams JR, Amylon M. After treatment ends: psychosocial sequelae in pediatric cancer survivors. American Journal of Orthopsychiatry 1988;58:552-61.

(18) Kazak AE, Barakat LP, Meeske K, Christakis D, Meadows AT, Penati B, et al. Posttraumatic stress, family functioning, and social support in survivors of childhood leukemia and their mothers and fathers. Journal of Consulting and Clinical Psychology 1997;65(1):120-9.

(19) Kazak AE. Posttraumatic distress in childhood cancer survivors and their parents. Medical and Pediatric Oncology Supplement 1998;1:60-8.

(20) Sloper T, Larcombe IJ, Charlton A. Psychosocial adjustment of five-year survivors of childhood cancer. Journal of Cancer Education 1994;9(3):163-9.

(21) Stam H, Grootenhuis MA, Last BF. The course of life of survivors of childhood cancer. Psycho-oncology 2005;14:227-38.

(22) Maurice-Stam H, Grootenhuis MA, Caron HN, Last BF. Course of life of survivors of childhood cancer is related to Quality of Life in young adulthood. Journal of psychosocial oncology 2007;25(3).

(23) Schwartz L, Drotar D. Posttraumatic stress and related impairment in survivors of childhood cancer in early adulthood compared to healthy peers. Journal of Pediatric Psychology 2006;31(4):356-66.

(24) Wallander JL, Varni JW. Effects of pediatric chronic physical disorders on child and family adjustment. Journal of Child Psychology and Psychiatry 1998;39(1):29-46.

(25) Wilson IB, Cleary PD. Linking clinical variables with health-related Quality of life. A conceptual model of patient outcomes. JAMA 1995;273(1):59-65.

(26) Stevens MCG, Mahler H, Parkes S. The health status of adult survivors of cancer in childhood. European Journal of Cancer 1998;34(5):694-8.

(27) Grootenhuis MA, Stam H, Destrée-Vonk A, Heijmans HSA, Last BF. Levensloop Vragenlijst voor Jong-Volwassenen [Course of life questionnaire for young adults]. Gedrag & Gezondheid 2003;31(5):336-50.

(28) Last BF, Grootenhuis MA, Destrée-Vonk A, Heymans HSA. De ontwikkeling van een levensloopvragenlijst voor jong-volwassenen (LVJV) [Development of a course of life questionnaire for young adults]. Gedrag & Gezondheid 2000;8(1):22-30.

(29) Schreurs PJ, Willige G, Brosschot JF, Tellegen B, Graus GMH. De Utrechtse Coping Lijst: UCL herziene handleiding [The Utrecht Coping List: UCL-Manual]. Lisse, the Netherlands: Swets & Zeitlinger; 1993.

(30) Oldehinkel AJ, Koeter MWJ, Ormel J, Van den Brink W. Omgaan met problematische situaties [Coping with problematic situations]. Gedrag en Gezondheid 1992;20(5):236-44.

(31) Rothbaum F, Weisz JR, Snyder SS. Changing the world and changing the self: a two-process model of perceived control. Journal of Personality and Social Psychology 1982;42:5-37.

(32) Houtzager BA, Oort FJ, Hoekstra-Weebers JEHM, Caron HN, Grootenhuis MA, Last BF. Coping and family functioning predict longitudinal psychological adaptation of siblings of childhood cancer patients. Journal of Pediatric Psychology 2004;29(8):591-605.

(33) Grootenhuis MA, Last BF, de Graaf-Nijkerk JH, van der Wel M. Secondary control strategies used by parents of children with cancer. Psycho-oncology 1996;5(2):91-102.

(34) Grootenhuis MA, Last BF. Children with cancer with different survival perspectives: defensiveness, control strategies, and psychological adjustment. Psycho-oncology 2001;10:305-14.

(35) Loonen HJ, Grootenhuis MA, Last BF, Koopman HM, Derkx HHF. Quality of life in peadiatric inflammatory bowel disease measured by a generic and disease-specific questionnaire. Acta Paediatrica 2002;91:341-54.

(36) Doeglas D, Suurmeijer T, Briancon S, Moum T, Krol B, Bjelle A, et al. An international study on measuring social support: interactions and satisfaction. Social Science and Medicine 1996;43(9):1389-97.

(37) Suurmeijer ThPBM, Doeglas DM, Briancon S, Krijnen W, Krol B, Sanderman R, et al. The measurement of social support in the "European research on incapacitating disease and social support": the development of the Social Support Questionnaire for Transactions (SSQT). Social Science and Medicine 1995;40:1221-9.

(38) van Sonderen E. Het meten van sociale steun met de Sociale Steun Lijst-Interacties (SSL-i) en Sociale Seun Lijst Discrepanties (SSL-d): een handleiding [Measurement of social support with the Social Support Questionnaire - Interactions and the Social Support Questionnaire - Discrepancies: manual]. Groningen: Noordelijk Centrum voor Gezondheidsvraagstukken. Rijksuniversiteit Groningen, 2004.

(39) Aaronson NK, Muller M, Cohen PDA, Essink-Bot M, Fekkes M, Sanderman R, et al. Translation, validation, and norming of the Dutch language version of the SF-36 Health Survey in community and chronic disease populations. Journal of Clinical Epidemiology 1998;51(11):1055-68.

(40) van der Zee KI, Sanderman R. Het meten van de algemene gezondheidstoestand met de RAND-36. Een handleiding. [Measuring general health status with the RAND-36. A guide.]. Groningen, the Netherlands: Noordelijk Centrum voor Gezondheidsvraagstukken. Rijksuniversiteit Groningen, 2003.

(41) Ware JE, Kosinski M. Interpreting SF-36 summary health measures: a response. Quality of Life Research 2001;10:405-13.

(42) SPSS 11.5 Syntax Reference Guide: base system, advanced models, regression models. Chicago, IL: SPSS Inc; 2002.

(43) Jöreskog KG, Sörbom D. LISREL 8 user's guide. Chicago IL: Scientific Software International, INC, 1996.

(44) Bollen KA. Structural equations with latent variables. New York: Wiley, 1989.

(45) Browne MW, Cudeck R. Alternative ways of assessing model fit. Sociological Methods Research 1992;21:230-58.

(46) Cohen J. Statistical power analysis for the behavioral sciences. New York: Academy Press, 1988.

(47) Grootenhuis MA, Stam H, Last BF, Groothoff JW. The impact of delayed development on the quality of life of adults with end-stage renal disease since childhood. Pediatric Nephrology 2006;21(4):538-44.

(48) Garber J. Classification of childhood psychopathology: a developmental perspective. Child Development 1984;55:30-48.

(49) Lewis M, Miller SM. Handbook of developmental psychopathology. New York: Plenum Press, 1990.

(50) Lindahl Norberg A, Lindblad F, Boman KK. Coping strategies in parents of children with cancer. Social Science and Medicine 2005;60:965-75.

(51) van der Zaag-Loonen HJ, Grootenhuis MA, Last BF, Derkx HHF. Coping strategies and quality of life of adolescents with inflammatory bowel disease. Quality of Life Research 2003;13(5):1011-9.

(52) Raina P, O'Donnell M, Schwellnus H, Rosenbaum P, King G, Brehaut J, et al. Caregiving process and caregiver burden: conceptual models to guide research and practice. BMC Pediatrics 2004;4:1-13.

(53) Raina P, O'Donnell M, Rosenbaum P, Brehaut J, Walter SD, Russell D, et al. The health and well-being of caregivers of children with cerebral palsy. Pediatrics 2005;115(6):e626-e636.

(54) Hartman EE, Oort FJ, Aronson DC, Hannekam MJG, van der Zee DC, Rieu PNMA, et al. Critical factors affecting quality of life of adult patients with anorectal malformations or Hirschsprung's disease. American Journal of Gastroenterology 2004;99(5):907-13.

(55) Hobbie WL, Stuber M, Meeske K, Wissler K, Rourke MT, Ruccione K, et al. Symptoms of posttraumatic stress in young adult survivors of childhood cancer. Journal of Clinical Oncology 2000;18(24):4060-6.

(56) Langeveld NE, Grootenhuis MA, Voûte PA, de Haan RJ. Posttraumatic stress symptoms in adult survivors of childhood cancer. Pediatric Blood Cancer 2004;42:604-10.

(57) Meeske KA, Ruccione K, Globe DR, Stuber ML. Posttraumatic stress, quality of life, and psychological distress in young adult survivors of childhood cancer. Oncology Nursing Forum 2001;28(3):481-9.

(58) Langeveld NE, Ubbink MC, Last BF, Grootenhuis MA, Voûte PA, de Haan RJ. Educational achievement, employment and living situation in long-term young adult survivors of childhood cancer in the Netherlands. Psycho-oncology 2003;12(3):213-25.

(59) Nagarajan R, Nelgia JP, Clohisy DR, Yasui Y, Greenberg M, Hudson M, et al. Education, employment, insurance, and marital status among 694 survivors of pediatric lower extremity bone tumors. Cancer 2003;97:2554-64.

(60) Pui C-H, Cheng C., Leung W, Rai SN, Rivera GK, Sandlund JT, et al. Extended follow-up of long-term survivors of childhood acute lymphoblastic leukemia. The New England Journal of Medicine 2003;349(7):640-9.

(61) Detmar SB, Muller MJ, Schornagel JH, Wever LDV, Aaronson NK. Health-Related Quality-of-Life assessment and patient-physician communication. A randomized controlled trial. JAMA 2002;288(23):3027-34.

(62) Detmar SM, Aaronson NK. Quality of life assessment in daily clinical oncology practice: a feasibility study. European Journal of Cancer 1998;34(8):1181-6.

(63) Varni JW, Burwinkle TM, Lane MM. Health-related quality of life measurement in pediatric clinical practice: An appraisal and precept for future research and application. Health and Quality of Life Outcomes 2005;3(34):1-9.

(64) Velikova G, Booth L, Smith AB, Brown PM, Lynch P, Brown JM, et al. Measuring Quality of Life in routine oncology practice improves communication and patient well-being: a randomized controlled trial. Journal of Clinical Oncology 2004;22(4):714-24.

General discussion

1 Introduction

The enormous increase in the number of survivors of childhood cancer who reach adulthood in recent decades has intensified the need to investigate the consequences of both the disease and its treatment. The ability to provide optimal support to survivors and parents depends on the development of more insight into the process of psychosocial adjustment to childhood cancer.

This thesis reports the results of the VOLG-study, which investigated 'quality of life, course of life and coping in childhood cancer survivors'. The goals of the study were as follows: (1) to assess Health-Related Quality of Life (HRQoL) of paediatric survivors of childhood cancer over time in comparison with normative data, and to assess the HRQoL of young adult survivors in cross-sectional comparison with a reference group; (2) to identify predictors of HRQoL among survivors of childhood cancer, focusing on course of life, coping, social support, family functioning and medical variables; and (3) to assess parental emotional adjustment over time.

This final section of the thesis provides a summary and discussion of the results. Firstly, the research questions of the VOLG-study are answered: the *longitudinal* component of the VOLG-study (paediatric patients in the run-up to survivorship[1] and their parents) is addressed in Paragraph 2, and the *cross-sectional* component of the VOLG-study (young adult survivors) is addressed in Paragraph 3. The longitudinal and cross-sectional results are integrated in Paragraph 4, which provides a discussion of the findings and a description of the strengths and limitations of the VOLG-study. This section closes with a discussion of clinical implications and recommendations for future research (Paragraph 5).

2 Longitudinal study

The longitudinal study was expected to provide answers to the following research questions:

1. How does the HRQoL of children with cancer following the end of successful treatment compare with normative data over time? (Section 2.1)
2. Which characteristics (e.g. coping, family functioning and medical variables) are predictors of HRQoL over time in childhood cancer survivors? (Section 2.2)
3. How do parents adjust emotionally over time following the end of successful treatment of their children with cancer? (Section 2.3)

The answers are presented below and summarised in Table 1.

2.1 Health-Related Quality of Life

The physical and psychosocial HRQoL of preschool survivors was considerably worse than the norm two months after the end of successful treatment. In most domains, HRQoL improved to normal levels during the first year after treatment; from two years after the end of treatment the survivors' HRQoL no longer differed from the normative population in any domain.

1 Although a 5-year period is commonly considered a criterion for survival, we decided to consider the patients in the VOLG-study survivors because they were progressing towards long-term survivorship.

Compared to normative data from the general Dutch population, school-aged survivors exhibited worse HRQoL with respect to motor functioning two months after the end of treatment. From one year after treatment, however, survivors no longer differed from the normative population, in either HRQoL or anxiety.

2.2 Predictors of Health-Related Quality of Life

Few medical variables were significantly associated with HRQoL. It is important to note, however, that survivors of brain tumours were excluded from the analyses, as were patients' data after they had experienced a recurrence of the childhood cancer.

For preschool survivors, longer duration of treatment and poor prognosis were associated with lower scores on physical HRQoL. For school-aged survivors (aged 8-15 years) none of the medical variables was significantly associated with either HRQoL or anxiety.

Several psychosocial variables were associated with HRQoL or anxiety. Parental distress was correlated negatively with HRQoL in preschool survivors. For school-aged survivors, disease-related cognitive coping was associated with both HRQOL and anxiety. Survivors who relied more heavily on physicians (*vicarious control*) reported better mental HRQoL. Survivors who were more optimistic about the further course of the disease (*predictive control*) experienced lower levels of anxiety, while those who searched more for information about the disease (*interpretative control*) reported higher levels of anxiety.

Unfortunately, internal reliability of the instrument in our sample was insufficient to allow us to assess the impact of (child-reported) family functioning on survivors' HRQoL over time. Data from the first measurement occasion (which took place an average of two months after the end of treatment) yielded inconsistent results with respect to the impact of family cohesion and family adaptability on HRQoL. The instrument we developed to assess openness in family communication about the disease proved relatively inapplicable from one year after the end of treatment. Results obtained an average of two months after the end of treatment indicated that less-frequent parental queries regarding disease-related emotions of the survivors was associated with better HRQoL.

In conclusion, as a group, survivors were strong and resilient; they regained good HRQoL between one and two years after the end of successful treatment. Nevertheless, survivors should be monitored and screened in order to identify survivors who are at risk of worse HRQoL or psychosocial problems.

2.3 Parental emotional adjustment

An average of two months after the end of successful treatment, parents showed elevated levels of psychological distress. Parental levels of distress and disease-related negative feelings then returned to normal levels during the first two years following the completion of treatment.

The results demonstrated that psychosocial variables were important indicators of emotional functioning, independent of disease and treatment. Being more optimistic about the further course of the child's disease (*predictive control*) was associated with better emotional functioning, while higher family adaptability scores, having a more passive and

palliative reaction pattern and the occurrence of stressful family events were associated with worse emotional functioning.

Although the parents of children with successfully treated cancer generally showed adequate emotional resilience, support for these parents should not stop when treatment ends. Parents in need of help can be identified according to their coping abilities and the occurrence of stressful family events.

Table1: Summary of the results of the *longitudinal* studies presented in this thesis: Growing up with childhood cancer.

Chapter	Purpose	Sample characteristics	Measures	Main results
1	Review article about social and emotional adjustment in paediatric survivors of childhood cancer	Studies N=40: Sample size > 20 Survivors ≤ 18 years at study[a] Mixed cancer diagnosis No strict criterion for survival[b] Healthy control group or norm data available	A literature search of studies in journals in the field of social sciences, paediatrics and nursing; published 1985-2001, in English; identified in MEDLINE and PsycINFO. Keywords: cancer/neoplasms, survivors, late effects/long-term effects, adolescence/childhood, psychology/psychiatry	Most survivors were functioning reasonably well socially and emotionally. However, consideration of different aspects of emotional functioning in survivors reveals that the results are not consistent. Few factors that predict successful psychosocial adaptation were identified.
2	Paediatric and parental adjustment shortly after completion of successful cancer treatment	Survivors N=134: Age at study: M=8.3 yrs (1.1-18.2) Age at diagnosis: M=7.1 yrs (0.3-17.2) Duration of treatment: M=11.4 months (0.6-26.0) Time since end treatment: M=2.2 months (0.1-5.7) Mixed diagnosis 43.3% girls / 56.7% boys Mothers N=124: Age at study: M=37.8 yrs (26.0-50.0) Fathers N=111: Age at study: M=39.8 yrs (29.0-54.0)	Survivors HRQoL: TNO-AZL Preschool Quality of Life questionnaire (TAPQOL), TNO-AZL Children's Quality of Life questionnaire – Parent Form and Child Form (TACQOL-PF, TACQOL-CF) Parents: General Health Questionnaire (GHQ), Situation Specific Emotional Reaction Questionnaire (SSERQ)	Survivors: All age groups, except survivors aged 8-11 years, experienced worse HRQOL than the norm with respect to motor functioning. In addition, preschool survivors were rated worse on Sleeping, Appetite, Stomach, Skin, Problem Behaviour, anxiety and Liveliness, and survivors aged 6-7 years on Autonomy and Cognitive functioning. The results of the survivors aged 16 years or older were not included because the small number of eight survivors in this age group. Parents: The parents reported more psychological distress than the norm. Compared to parents whose children were one to five years after cancer treatment, they suffered more from feelings of loneliness, helplessness and uncertainty.

Chapter	Purpose	Sample characteristics	Measures	Main results
3	Psychosocial indicators of paediatric HRQoL shortly after completion of successful cancer treatment	Survivors N=106: Age at study: M=7.9 yrs (1.1-15.9) Age at diagnosis: M=6.7 yrs (0.3-15.2) Duration of treatment: M=11.5 months (1.2-25.9) Time since end treatment: M=2.2 months (0.1-5.7) Mixed diagnosis: 45.3% leukaemia/lymphoma, 50.9% solid tumour, 3.8% brain tumours 42.5% girls / 57.5% boys The results of the survivors aged 6-7 years and the survivors aged 16 years or older were not included because the small number of eight survivors in this age group	Survivors HRQoL: TNO-AZL Preschool Quality of Life questionnaire (TAPQOL), TNO-AZL Children's Quality of Life questionnaire – Parent Form and Child Form (TACQOL-CF) Survivors and/or parents: Cognitive Control Strategies Scale (CCSS), Family Adaptability and Cohesion Evaluation Scale (FACES), Exchange of Emotions Questionnaire (EEQ) Parents: General Health Questionnaire (GHQ), Situation Specific Emotional Reaction Questionnaire (SSERQ), Questionnaire about important family events	Better HRQoL was especially associated with more positive expectations of the further course of the disease, less frequent parental asking after disease-related emotions of the child, and lower levels of family adaptability. Several other psychosocial variables were indicative of better HRQoL but further research is needed to confirm and to understand the relation between psychosocial variables and HRQoL. .
4	HRQoL in preschool survivors of non CNS-tumours: the first three years after successful treatment	Survivors N=53 at M1, N=38 at M2, N=23 at M3, N=17 at M4. Characteristics at M1: Age at study: M=3.9 yrs (1.1-5.9) Age at diagnosis: M=2.6 yrs (0.3-5.3) Duration of treatment: M=12.6 months (1.5-25.9) 45.3% Leukaemia/ lymphoma, 54.7% solid tumour 50.9% girls / 49.1% boys	Survivors HRQoL: TNO-AZL Preschool Quality of Life questionnaire (TAPQOL), Parents: General Health Questionnaire (GHQ), Questionnaire about important family events	Two months after the end of successful cancer treatment, survivors showed more problem behavior and anxiety, and scored worse on sleeping, motor functioning, positive mood and liveliness than the norm. One year after the end of treatment survivors still showed more anxiety and worse motor functioning. Two and three years after the end of treatment, survivor's level of HRQoL was normalized. Longer duration of treatment, bad prognosis and greater parental psychological distress were associated with worse scores on the Physical Component Score of the TAPQOL. Medical variables and parental psychological distress were not associated with the Mental Component Score.

Chapter	Purpose	Sample characteristics	Measures	Main results
5	HRQoL and anxiety in school-aged survivors of non CNS-cancer: the first four years after successful cancer treatment	Survivors N=49 at M1, N=41 at M2, N=41 at M3, N=42 at M4, N=27 at M5. Characteristics at M1: Age at study: M=12.1yrs (8.1-15.9) Age at diagnosis: M=11.0 yrs (6.4-15.2) Duration of treatment: M=10.9 months (1.2-25.7) 49.0% Leukaemia/ lymphoma, 51.0% solid tumour 34.7% girls / 65.3% boys	Survivors: TNO-AZL Children's Quality of Life questionnaire – Child Form (TACQOL-CF) State-Trait Inventory for Children (STAI-C) Cognitive Control Strategies Scale – Child Form (CCSS-CF).	Compared to norm data from the general Dutch population, survivors showed worse HRQoL with respect to motor functioning on average two months after the end of treatment but from one year after treatment survivors did no longer differ from the norm population, neither on HRQoL nor on anxiety. None of the medical variables were associated significantly with HRQoL or anxiety. Several psychosocial variables appeared to be associated with HRQoL or anxiety. Vicarious control strategies were associated with better mental HRQoL, and predictive control strategies were associated with lower levels of anxiety. Interpretative control strategies were related to higher levels of anxiety.
6	Parental emotional adjustment and coping: the first five years after successful cancer treatment of their child	Mothers N=122 at M1, N=103 at M2, N=98 at M3, N=92 at M4, N=52 at M5, N=24 at M6. Fathers N=109 at M1, N=91 at M2, N=87 at M3, N=78 at M4, N=46 at M5, N=19 at M6. Characteristics survivors at M1: Age at study: M=8.0 yrs (1.1-18.2) Age at diagnosis: M=6.8 yrs (0.3-17.2) Duration of treatment: M=11.5 months (0.6-26.0) 48.1% Leukaemia/ lymphoma, 47.3% solid tumour, 4.7% brain tumour 41.9% girls / 58.1% boys	General Health Questionnaire (GHQ), Situation Specific Emotional Reaction Questionnaire (SSERQ) Utrecht Coping List (UCL) Cognitive Control Strategies Scale – Parent Form (CCSS-PF). Family Adaptability and Cohesion Evaluation Scale (FACES)	Elevated levels of distress, disease-related feelings of uncertainty and helplessness shortly after the end of treatment, fell to normal levels during the first two years after the end of treatment. Being more optimistic about the further course of the child's disease were associated with better emotional functioning, while higher family adaptability scores and having a more passive and palliative reaction pattern was related to worse emotional functioning.

[a] Some studies also included survivors who were older than 18 years.

[b] Although a 5-year period without treatment can be considered a criterion of survival of childhood cancer, several investigators also regard children as survivors who have been off treatment for shorter periods. This is partly due to the different survival perspectives for different diagnoses in childhood cancer.

3 Cross-sectional study

The cross-sectional study was expected to provide answers to the following research questions:

1. How does the HRQoL of young adult survivors of childhood cancer compare to that of a reference group? (Section 3.1)
2. How does the course of life of young adult survivors of childhood cancer compare to that of a reference group? (Section 3.2)
3. What is the relationship between medical variables (e.g. diagnosis, treatment, age at diagnosis) and the course of life of young adult survivors of childhood cancer? (Section 3.2)
4. Which characteristics (e.g. course of life, coping, and medical variables) are predictors of HRQoL in young adult survivors of childhood cancer? (Section 3.3)

The answers are presented below and summarised in Table 2.

3.1 Health-Related Quality of Life

The HRQoL of the survivors differed from that of the comparison group, which consisted of peers from the general Dutch population, on three out of the eight scales of the *RAND-36*. Survivors reported lower levels of physical and social functioning, and they experienced more role limitations due to physical problems. In addition, the survivors scored less favourably on the summary scales of the RAND-36, i.e. the Physical Component scale and the Mental Component scale. The differences that we found between survivors and their peers can be considered minor, as they reflect small effect size according to Cohen's classification (1). No differences were found on the following scales of the RAND-36: Role limitations due to emotional problems, general mental health, vitality, bodily pain and general health perceptions.

3.2 Course of life

Survivors reported a less favourable course of life than their peers from the general Dutch population. They appeared to have achieved fewer milestones in the developmental domains that are included in the Course of life questionnaire (autonomy development, social development, psychosexual development), or to have achieved the milestones when they were older than their peers. The effect sizes of the differences that we found between survivors and their peers can be considered small to medium according to Cohen's classification (1). In addition, survivors displayed less risk behaviour (substance use and gambling, and anti-social behaviour) than their peers did. Survivors and peers also differed on a number of socio-demographic outcomes. A considerably lower percentage of survivors were married or living together, and/or employed than was observed among their peers in the general Dutch population. Their educational level of the survivors did not differ from that of their peers.

Medical variables appeared to be associated with course of life. Survivors of brain tumours and survivors who had been treated with radiotherapy reported having achieved fewer milestones in the psychosexual and social domains than did the other survivors.

3.3 Predictors of Health-Related Quality of Life

Medical and demographic characteristics were found to be associated with the survivors' HRQoL in young adulthood, as were psychosocial factors. Current health complaints and psychosocial/cognitive/neurological late effects of disease and treatment were negatively associated with physical and mental HRQoL. Female survivors and survivors who had been treated with both chemotherapy and radiotherapy were most at risk of worse HRQoL, as they suffered from current health complaints and were less inclined to either *predictive control* (disease-related cognitive coping) or *active coping* (generic coping).

Predictive control and active coping were found to enhance HRQoL. In contrast, *interpretative control* (disease-related cognitive coping) and *passive coping* (generic coping) were negatively associated with HRQoL.

Although survivors of brain tumours and survivors who had been treated with radiotherapy were at risk of an unfavourable course of life, it was not clear whether this decreased HRQoL. Testing the entire research model using Structural Equation Modelling (SEM) revealed no significant correlations between course of life and HRQoL, while results of traditional regression analyses of course of life and HRQoL showed that survivors who achieved fewer milestones in the social domain had lower scores on HRQoL. These inconsistent findings are discussed in Paragraph 4.

Table 2: Summary of the results of the *cross-sectional* studies presented in this thesis: Young adult survivors of childhood cancer.

Chapter	Purpose	Sample characteristics	Measures	Main results
7	Review article about HRQoL in young adult survivors of childhood cancer	Studies N=30: Sample size > 30 Survivors primary source of information[a] Survivors diagnosed before age of 20 years Survivors ≥ 18 years at study[b] Survivors at least 5 years after completion of therapyc Mixed cancer diagnosis Well-matched control group or norm data available	A literature search of studies published up to 2001, in English; identified in MEDLINE, CINAHL, EMBASE and PsycINFO. Keywords: childhood cancer, (longterm) survivors, late effects, psychological/ social adjustment, employment/health insurance, schools/ learning, QoL/health status.	Although the literature yielded some inconsistent findings, some clear trends were found: 1) Most survivors reported to be in good health, with the exception of bone tumour survivors. 2) Most survivors functioned well psychologically. 3) Survivors of CNS-tumours and survivors of ALL were at risk of educational deficits. 4) Job discrimination, difficulties in obtaining work and problems in obtaining health and life insurance. 5) Lower prevalence of marriage and parenthood among survivors.

Chapter	Purpose	Sample characteristics	Measures	Main results
8	HRQoL and coping in young adult survivors of childhood cancer	Survivors N=353: Age at study: M=24.3 yrs (17.7-31.1) Age at diagnosis: M=7.3 yrs (0.0-17.0) Time since first diagnosis: M=17.0 yrs (6.2-30.7) Duration of treatment: M=12.5 months (0.0-72.5) Time since end of last treatment: M=15.5 months (4.9-30.3) Mixed diagnosis Relapse/second tumour: 12.2% 50.4% female / 49.6% male Control group N=507: Peers without a history of cancer Age ate study: M=24.2 yrs (18.0-30.9) 52.9% female / 47.1% male	RAND-36 (Dutch version of the MOS-SF-36 Health Survey) Cognitive Control Strategies Scale (CCSS)	1) Survivors reported worse HRQoL than their peers. Small differences were found on Physical Functioning, Social functioning and Role limitations due to Physical problems, and on the Physical Component Scale and the Mental Component Scale. 2) Health status was the best predictor of the Physical Component Scale; health status and cognitive coping contributed almost equally well to the Mental Component Scale. The explanatory value of cognitive coping was mainly attributed to the use of predictive control strategies.
9	Course of life in in young adult survivors of childhood cancer	Survivors N=353: Age at study: M=24.3 yrs (17.7-31.1) Age at diagnosis: M=7.3 yrs (0.0-17.0) Time since first diagnosis: M=17.0 yrs (6.2-30.7) Duration of treatment: M=12.5 months (0.0-72.5) Time since end of last treatment: M=15.5 months (4.9-30.3) Mixed diagnosis Relapse/second tumour: 12.2% 50.4% female / 49.6% male Control group N=508: Peers without a history of cancer Age ate study: M=24.2 yrs (18.0-30.9) 53.0% female / 47.0% male	Course of life questionnaire	Survivors reported a less favourable course of life than their peers from the general population. They appeared to have achieved fewer milestones in all developmental domains, or to have achieved the milestones when they were older than their peers: autonomy development, social development and psychosexual development. In addition, survivors displayed less risk behaviour than their peers. Survivors and peers also differed on some socio-demographic issues: a considerably lower percentage of survivors than peers were married or living together, and/or employed. Their educational level was as high as that of their peers.

Chapter	Purpose	Sample characteristics	Measures	Main results
10	Course of life and HRQoL in young adult survivors of childhood cancer	Survivors N=353: Age at study: M=24.3 yrs (17.7-31.1) Age at diagnosis: M=7.3 yrs (0.0-17.0) Time since first diagnosis: M=17.0 yrs (6.2-30.7) Duration of treatment: M=12.5 months (0.0-72.5) Time since end of last treatment: M=15.5 months (4.9-30.3) Mixed diagnosis Relapse/second tumour: 12.2% 50.4% female / 49.6% male	RAND-36 (Dutch version of the MOS-SF-36 Health Survey) Course of life questionnaire	1) Several medical variables appeared to be correlated with Course of life. Survivors of brain tumours and survivors having been treated with radiotherapy reported the achievement of fewer milestones in the psychosexual and social domain, than the other survivors. 2) The achievement of developmental milestones was associated with HRQoL in young adulthood. Survivors who achieved fewer milestones in the social domain scored worse on HRQoL.

Chapter	Purpose	Sample characteristics	Measures	Main results
11	Theoretical predictive model of HRQoL in young adult survivors of childhood cancer	Survivors N=353: Age at study: M=24.3 yrs (17.7-31.1) Age at diagnosis: M=7.3 yrs (0.0-17.0) Time since first diagnosis: M=17.0 yrs (6.2-30.7) Duration of treatment: M=12.5 months (0.0-72.5) Time since end last treatment: M=15.5 months (4.9-30.3) Mixed diagnosis Relapse/second tumour: 12.2% 50.4% female / 49.6% male	RAND-36 (Dutch version of the MOS-SF-36 Health Survey) Course of life questionnaire Cognitive Control Strategies Scale (CCSS) Utrecht Coping List (UCL) Social Support Questionnaire for Transactions (SSQT)	1) The model fitted the data closely; the process of adjustment to experience of childhood cancer was explained well by the background variables (demographic and medical characteristics of the survivors) and the mediating factors (coping, course of life and social support). 2) The effect of medical and demographic characteristics on HRQoL was mediated by generic and disease-related cognitive coping. Course of life and social support had no significant mediating effect on HRQoL. Current health complaints and psychosocial/cognitive/neurological late effects were negatively related to HRQoL. Predictive and active coping were positively associated with HRQoL, while interpretative and passive coping as well as sharing emotions were found to be associated with HRQoL negatively. 3) Female survivors and survivors having been treated with both chemotherapy and radiotherapy were most at risk of worse HRQoL because they suffered from current health complaints and were less inclined to predictive and active coping. 4) Survivors of brain tumours and survivors having been treated with radiotherapy were at risk of an unfavourable course of life.

[a] Studies with no more than 20% proxies as primary source of information were included as well.

[b] Some studies also included survivors who were younger than 18 years.

[c] Although a 5-year period without treatment can be considered a criterion of survival of childhood cancer, several investigators also regard children as survivors who have been off treatment for shorter periods. This is partly due to the different survival perspectives for different diagnoses in childhood cancer.

4 Conclusions and critical review

4.1 Health-related Quality of Life

Shortly after the end of successful treatment, the HRQoL of the paediatric survivors was worse than was that of the reference groups, particularly in physical terms, but their HRQoL improved to normal levels during the first years after treatment. In young adulthood, the differences between the HRQoL of long-term survivors and that of their peers from the general Dutch population appeared to be small. These findings from the VOLG-study are in accordance with the results of other recent studies on HRQoL and psychosocial outcomes among young adult survivors of childhood cancer. Most of these studies report small, if any, differences between survivors and healthy controls-group subjects or normative data (2-6). Although overall mean adjustment in survivors, as measured by standardised psychological instruments, has been found to be near normal levels, a growing body of evidence suggests that more subtle or specific areas may be adversely affected in long-term survivors (7;8).

The results of the VOLG-study and previous studies (9;10) suggest that many survivors seem generally to cope well with the cancer experience. This is contrary to what would be expected considering the stressful experience of childhood cancer and the presence of long-term adverse physical effects in the majority of the survivors (11). Several explanations could be advanced. Firstly, the representativeness of the survivors in the VOLG-study was not optimal. The number of paediatric survivors with poor prognosis or with brain tumours was too small to allow a reliable assessment of the impact of these medical factors in the longitudinal component of the VOLG-study. In addition, young adult survivors suffering from serious cognitive sequelae of disease and treatment were not represented in the cross-sectional component of the VOLG-study, as they were not able to complete the questionnaires. The sample of young adult survivors was also limited to the survivors who attended the long-term follow-up clinic at the Emma Children's Hospital AMC Amsterdam in 2001 or 2002. We advise caution in extrapolating these findings to all long-term survivors, as treatments have been changed in recent decades.

A second possible explanation for the surprising results of the study is that the favourable adjustments that we found, could have resulted from the process of response shift, which has been observed in adults with cancer (12). The survivors' experiences with cancer could have changed their internal standards thereby causing changes in the meaning of their self-evaluation and, possibly, in the way they experienced problems. Similarly, a thirdly explanation could be that the survivors had achieved favourable adjustment through their own resilience and personal growth. The intrusive experience of the disease and treatment, combined with the uncertainty about the further course of the disease, are obviously sources of stress. Nonetheless, these experiences could generate feelings of personal strength and happiness to be alive, as well as to enhanced appreciation of life. The experience of coming face-to-face with their own mortality could have caused a positive shift in the perspectives and priorities of the survivors. People who have experienced traumas are sometimes able to apply positive interpretations to and find meaning in the traumatic events. This type of cognitive process could result in post-traumatic growth; in positive changes in one's self, in relationships and in philosophy of life. Barakat and colleagues (2006) found post-traumatic growth in the majority of adolescent survivors of childhood cancer (13). In the VOLG-study,

two thirds of the young adult survivors reported that the cancer had changed their lives. Of these survivors, 77% reported that these changes were positive.

Apart from processes of response shift and post-traumatic growth, which could be considered components of coping, a fourth explanation for the favourable adjustment that was found among the survivors in the VOLG-study was that adjustment could be the result of the survivors' use of adequate coping strategies and the availability of social support systems. Investigating this kind of psychosocial factors is useful, as these factors could be susceptible to change (see 4.3).

The methodological limitations of the VOLG-study should be taken into account. The conclusions about the HRQoL of paediatric survivors (longitudinal component of the VOLG-study) are based on relatively small subgroups of survivors, as different age groups needed different, age-specific questionnaires. The problem of small sample size is therefore inherent in research on children, especially when children are studied longitudinally. The comparison of paediatric data over time was further complicated in the VOLG-study by the 'proxy-problem'; for preschool children HRQoL could be assessed only by the parents.

Another limitation concerns the instruments that were used. In order to be able to compare the survivors to the general population, generic HRQoL measures were used. The use of cancer-specific instruments is recommended for measuring the impact of childhood cancer longitudinally, as this kind of instruments is more sensitive to change. In our case, however, no cancer-specific instruments that had been translated and validated for Dutch schoolchildren were available. Furthermore, specific questionnaires are needed to investigate the functioning of survivors more thoroughly. The VOLG-study focused on HRQoL and course of life; there are obviously other interesting aspects of survivors' functioning, including post-traumatic stress/growth and disease-related worries. Extensive investigation of social functioning and related concepts (e.g. self-esteem) is of great importance, as problems in social adjustment appeared to be a core issue for school-aged children surviving cancer (14-20).

In addition to the limitations mentioned above, the interpretation of HRQoL is difficult. For example, it is not always clear when differences between the survivors and the norm or changes in the HRQoL of survivors over time are meaningful. We used distribution-based approaches in the VOLG-study (i.e. significance and effect size) and we attempted to determine the 'Minimal Clinically Important Difference' (MCID) (21;22) for paediatric HRQoL, which is anchor-based approach. For this purpose we developed a *global rating of change questionnaire* for the TACQOL-PF. Because of the small sample size and moderate internal consistency of some of the TACQOL scales, however, it was not possible to calculate MCID in children.

4.2 Course of life

Knowledge about possible gaps in the course of life could be useful in clinical practice, as it could enable healthcare providers to educate parents in order to achieve the most favourable course of life for patients with childhood cancer, both during and after treatment. The results of the VOLG-study illustrate that young adult survivors of cancer in the Netherlands achieve fewer milestones – or achieve them at later ages – than do their peers who have no history of cancer. The milestones addressed in this study included autonomy, psychosexual and social development, as well as risk behaviour. Although the finding that the survivors exhibited

less risk behaviour than their peers could indicate a deviant course of life, it could also be indicative of protective health behaviour.

The differences between the mean scores of survivors on the course-of-life-scales and those of their age-matched and sex-matched peers were small to moderate. Although the course of life of a number of survivors was likely to have been seriously hampered, the majority of survivors are likely to have had a favourable course of life. In order to be able to trace and support childhood cancer patients who are at risk of an unfavourable course of life, factors associated with an unfavourable course of life were investigated. Survivors of brain tumours and those who had been treated with radiotherapy appeared particularly likely to be at risk of a unfavourable course of life in the social and psychosexual domain.

The findings that are described raises questions concerning the clinical relevance of an unfavourable course of life. From a developmental psychological point of view, the fulfillment of age-specific developmental tasks during childhood is of great importance to adjustment in adult life (23;24). A logical question, however, concerns whether a less favourable course of life affects the HRQoL of survivors. As mentioned earlier (4.1), the cancer experience could change the philosophy of life. It is conceivable that survivors set other life goals thereby avoiding any negative effects of unfavourable course of life on their HRQoL. We used two models to investigate whether course of life was correlated with HRQoL in adulthood. First we tested a model of course of life and HRQoL using traditional linear regression analysis. Second we tested the entire research model (Figure 1, General Introduction) using Structural Equation Modelling (SEM), including other psychosocial mediating factors in addition to course of life. The results of these two statistical approaches were inconsistent. When testing only part of the research model (i.e. the correlation between course of life and HRQoL), we found that the achievement of more milestones in the social domain was associated with better HRQoL (Chapter 10). Remarkably, when using SEM to test the entire model course of life had no effect on the HRQoL of survivors (Chapter 11). There are several possible explanations for the inconsistency of these results. Coping strategies were found to be stronger predictors of HRQoL than was the course of life, and there appeared to be interrelationships between coping and course of life. Specific questionnaires are needed to measure the functioning and well-being of young adult survivors more thoroughly than does the RAND-36, which is a more general measure of generic HRQoL.

In addition to the inconsistent findings, we must emphasise that it is not possible to prove causality between the achievement of milestones while growing up and HRQoL in young adulthood. The fact that most items in the Course of life questionnaire temporally preceded the HRQoL outcomes in young adulthood cannot be considered solid evidence of causality. Although SEM yielded stronger evidence of the presence of causal correlations than did the traditional analytic procedures, definitive proof requires a longitudinal design.

To the best of our knowledge, the Course of life questionnaire is the first (Dutch) questionnaire to address this issue. The instrument has proved useful, despite several limitations. First the psychometric characteristics of the scales (e.g. the floor effect of the anti-social behaviour scale and the moderate internal consistency of the autonomy-development scale) are not optimal. Nonetheless, we consider it acceptable to use scales with low internal consistency for making group comparisons, as the internal consistency is an indication of random error and has nothing to do with systematic error (bias). The disadvantage of using scales with low internal consistency is that it impedes the detection of differences between

groups. A second limitation of the Course of life questionnaire is that the retrospective measurement of course of life restricts the range of topics. In order to prevent bias caused by inadequate memory, the questions are factual and do not go further back than to primary school, but this does not guarantee that no bias will occur. Third the fact that the questionnaire is completed by the survivors themselves introduces another possible source of bias. In order to prove that they have succeeded in moving beyond their disease, survivors are likely to report having achieved more milestones than was actually the case. In the current study, however, any occurrence of this type of bias would only strengthen the results.

4.3 Psychosocial predictors of Health-Related Quality of Life

One of the main purposes of the VOLG-study was to identify psychosocial predictors of HRQoL, as these factors could be susceptible to change. The inclusion of a large number of psychosocial variables was one of the strengths of the VOLG-study. One disadvantage, however, was that the large number of variables sometimes made it necessary to pre-select variables for the (longitudinal) regression analyses, even though the sample size was fairly large in terms of the research into paediatric cancer.

4.3.1 Coping and social support

The results of the VOLG-study demonstrate that the use of coping strategies plays a role in adjustment to the cancer experience, for both paediatric survivors during the first years after the end of successful treatment and young adult long-term survivors. Coping explained a considerable portion of the variance in the HRQoL outcomes in young adulthood. The SEM of the cross-sectional data from the VOLG-study revealed that coping mediated the effect of medical variables in young adult long-term survivors. The fact that coping was also related to HRQoL in paediatric survivors during the first years after the end of treatment (longitudinal component of the VOLG-study) strengthens the conclusion that coping is a predictor of HRQoL. The role of disease-related *predictive control* should be mentioned in this context. Survivors who relied on cognitive efforts directed at maintaining positive expectations about the further course of the disease reported better HRQoL than did survivors who did not. The importance of reframing situations in a positive light (positive reappraisal) has already been stressed by Folkman and Moskowitz (25). A study about the role of optimistic beliefs and adaptation in adults showed that positive outcome expectations is specifically beneficial for patients suffering from chronic diseases that are largely uncontrollable (26).

The model of coping used in the present study raises an issue for discussion. Our model of disease-related cognitive coping is based on the models by Lazarus and Folkman (1984) (27) and by Rothbaum and colleagues (1982) (28), whose theoretical frameworks were developed for adults. In the area of childhood cancer, developmental considerations should be taken into account, as children are likely to employ other coping strategies as their cognitive ability increases. Although several studies have shown that cognitive coping is relevant to children (29-32), it is also known that behavioural and problem-solving strategies are more predominant in younger children (33;34). Unfortunately, at the start of the VOLG-study, no Dutch questionnaire was available for assessing problem-focused coping. We were therefore forced to limit our investigation of coping in survivors younger than 12 to disease-related cognitive coping.

Social support, which was measured cross-sectionally in the young adult long-term survivors of childhood cancer as the total number of supportive interactions, appeared not to be associated with HRQoL in young adult survivors. Analyses of HRQoL and the subscales of social support in further detail revealed a number of correlations between social support and HRQQoL. More daily emotional support appeared to be associated with better mental HRQoL, while more negative interactions were associated with worse physical and mental HRQoL. Earlier studies have indicated a positive relationship between social support and the emotional adjustment of survivors (35-37). In contrast to the VOLG-study, these studies did not measure social support in young adults. Moreover, other studies have suggested that support satisfaction is more relevant in explaining HRQoL than is the number of supportive interactions (38).

4.3.2 Family functioning and communication

Family functioning and communication about the disease was assessed longitudinally in paediatric survivors of childhood cancer. Unfortunately, the internal consistency of the Cohesion and Adaptability scale of the FACES was insufficient in our sample of paediatric survivors, except at the first measurement occasion. This is not surprising, considering the difficult wording of the items of the FACES. The results of the first measurement occasion, which took place an average of two months after the end of treatment, were not clear. Previous studies have also reported inconsistent results (36;39-42).

According to family systems theory, parental functioning influences the functioning of children and vice versa. Several studies on childhood cancer have reported correlations between parental emotional functioning and that of paediatric survivors, although the direction of the correlation was unclear (10). This is also true for the VOLG-study, which was further complicated by the 'proxy-problem' with regard to the assessment of HRQoL in preschool children. Because the parents evaluated the HRQoL of their preschool children as well as their own emotional adjustment, the correlations we found did not provide a clear represent of the impact of parental emotional adjustment on the HRQoL of the survivors. We were not able to differentiate between the impact of parental emotions on parental perceptions of their children's HRQoL and the impact on the 'actual' HRQoL of the survivors.

The instrument we developed to assess openness in family communication about the disease (Communication Questionnaire) yielded interesting results shortly after the end of treatment: less-frequent parental queries concerning the disease-related emotions of the survivors was associated with better HRQoL. This questionnaire, however, proved largely inapplicable one year or longer after the end of treatment. Attempts to improve the instrument would be worthwhile, as communication about the disease is an important tool for both children and their parents. Information and communications play an important role in reducing uncertainty (43). Moreover, in clinical practice, many parents mention that their children are reluctant to talk about their experiences with cancer. Parents are unsure whether their children do not want to talk about it because they truly have no problem with it or because they are hiding their emotional difficulties with the cancer.

4.4 Parental adjustment

Parental emotional adjustment was assessed longitudinally in a relatively large sample of mothers and fathers. The VOLG-study revealed an abundance of useful information on psychosocial indicators of emotional functioning in parents in the period leading up to the survivorship of their children with cancer.

Shortly after the end of treatment, parents showed elevated levels of psychological distress. This is not surprising, as 'coming off treatment' represents an enormous change for the survivors and their families. Parents must become accustomed to living with uncertainty about recurrence of the disease and possible long-term adverse effects. In paediatric oncology practice, many parents report that they feel uncertain without the protection of the medical treatment and support from the hospital. Parental levels of distress and negative feelings related to the disease subsequently returned to normal levels during the first two years after the completion of treatment. These findings provide strong evidence of the resilience of the parents. They are also in line with our findings from clinical practice, which suggest that it typically takes one to two years from the end of treatment for parents to feel relief and begin to believe that their children really will survive. We must emphasise that the favourable outcomes presented here cannot be extrapolated to the parents of children who suffered from relapses. The inclusion of these parents in the analysis yielded higher levels of psychological distress and more disease-related negative feelings (36;37;44-50).

Many parents reported quite stable positive feelings throughout the study. Although this could reflect a permanent change in parents' attitudes triggered by the intensive experience of childhood cancer, this hypothesis could not be tested, as we had no information on these parents' feelings before their children developed cancer. It should also be noted that while positive feelings are considered as outcomes in the VOLG-study, they could arguably be considered components of the psychosocial factor 'cognitive coping' as well. For example, the statements used in the SSERQ to test for positive feelings (e.g. "I have the feeling that I became more aware of life", "I have the feeling that I can enjoy small things more", "I am proud of myself for doing things I used to avoid") point in this direction, as do the significant correlation with the generic coping style 'comforting cognitions'.

While the findings in the present study indicate that the parents generally adjusted well over time to the experience of childhood cancer in their families, the early identification of parents who are at risk of developing adjustment problems is important so that appropriate support can be offered at an early state. The results of our longitudinal mixed models analysis showed that disease-related and generic coping were especially associated with parental emotional functioning. With respect to disease-related cognitive coping, we can conclude that the more optimistic the parents were about the further course of the disease (*predictive control*), the less emotional distress and the fewer disease-related negative feelings they reported. Although the present study does not answer the question of causality, it is conceivable that optimism about the further course of the disease leads to less emotional distress and fewer disease-related feelings of loneliness, uncertainty and helplessness. In other words, a hopeful attitude could protect parents from negative emotions. The protective impact that remaining a positive view has on adjustment to stressful events has been previously reported (51;52) and is in line with previous research on parents of children with cancer (53). The correlation between optimism and emotional adjustment, however, could reflect an underlying concept

(53;54). We may therefore question whether predictive control is a trait-like construct or a coping style that is susceptible to change. Further exploration is needed.

Five out of the seven generic coping styles were associated with parental emotional functioning in the VOLG-study. *Passive reaction pattern* was the strongest predictor of emotional functioning in both mothers and fathers. Goal-oriented parents who faced the situation calmly (*active problem focusing*) reported better emotional functioning than did parents who coped with stress by taking a passive standpoint and allowing themselves to become totally immersed in the problem (passive reaction pattern) or parents who engaged in distracting activities and tried to relax (*palliative reaction pattern*). These correlations are not surprising, given that passive coping is related to the concept of 'learned helplessness', and active coping is related to feelings of control over events (53;55). The findings in the present study agree with those of other research on parents of children with cancer (53;55;56) and other life-threatening diseases (57;58).

With regard to family functioning, we found a *cohesive family structure* to be important. This finding is not surprising, as many parents mentioned that the experience of childhood cancer increased the strength of family bonding (59;60). On other hand, we found that stronger mutual connectedness among family members was associated with greater feelings of helplessness. The direction of this relationship cannot be determined. Stronger mutual involvement could increase the transmission of worries and distress among the family members. Alternatively, parents who feel more helpless might turn to other family members for comfort and support.

Higher levels of *family adaptability* appeared to be associated with stronger feelings of loneliness, helplessness and uncertainty. In the Circumplex model of marital and family systems, the theoretical framework proposed by Olson, Russell & Sprenkle (61), moderate levels of cohesion and adaptability are considered to be related to the most favourable adjustment outcomes in families that are facing stress, while extreme levels of adaptation ('chaotic' family systems) and cohesion ('enmeshed' family systems) are related to less adaptive functioning. Inspection of our data did not demonstrate extremely high levels of adaptability and cohesion in the families under study. Previous studies have reported inconsistent results on this point (36;39-42).

The association of more supportive interactions with lower levels of loneliness and more positive feelings is not surprising. We found no evidence that social support was associated with psychological distress, helplessness or uncertainty for either fathers or mothers. Although other studies (46;62;63) have reported positive correlations between parental emotional functioning and social support, their findings concern a shorter period after diagnosis than is addressed in the present study. Although it is conceivable that the impact of social support decreases inversely with time since the end of treatment, the results of the present study do not confirm this hypothesis.

A number of limitations to the VOLG-study merit discussion. No meaningful conclusions can be drawn for the parents of children with brain tumours, as these children are underrepresented in the longitudinal VOLG-study for logistical reasons. The results can also not be extrapolated to the parents of children who suffered from relapses. Another restriction lies in the variables that were included in the research model chosen. First the present study focused on a limited number of outcomes (i.e. psychological distress and situation-

specific emotional reactions). There are obviously other interesting aspects indicative of parental emotional (mal)adjustment, including post-traumatic stress symptoms (36;37;46-48). Second we assessed neither previous parental emotional functioning (e.g. a history of psychiatric problems) nor socio-economic variables (e.g. income and employment) – factors that have been shown in previous studies to have an impact on parental functioning (64;65). Personality, temperament and other intrapersonal factors may also affect adjustment (66). These factors were partly expressed in the personal coping styles that were investigated in the VOLG-study.

5 Clinical implications and future research

5.1 Clinical implications

5.1.1 Survivors

In general, most survivors appeared to cope well with the cancer experience and the (late) consequences of the disease and its treatment, although survivors growing up with childhood cancer seemed to be at risk of unfavourable course of life. On average, the differences between the HRQoL of the long-term survivors and that of their peers from the general Dutch population were small, with some survivors being more at risk of maladjustment than others were.

The results of the VOLG-study indicate that children and their parents are able to come through the stressful experience of childhood cancer well. It should therefore no longer be assumed that the general HRQoL of survivors is lower that of their peers. Nevertheless, a growing body of evidence suggests that more subtle or specific areas may be adversely affected in long-term survivors. Studies of paediatric psycho-oncological outcomes consistently identify a group of children and family members (estimated 25-30%) who do not cope well with the cancer or who have personal, family and social difficulties (7). This is in line with the experience of psychologists at the long-term follow-up clinic of the Emma Children's Hospital AMC (PLEK). In addition, a considerable proportion of the young adult survivors in the VOLG-study reported that the cancer experience had changed their lives negatively (23% of the two third of all respondents who reported that cancer had changed their lives). The VOLG-study identified several psychosocial factors that were correlated with better or worse adjustment. Insight into these factors may alert healthcare providers to survivors who are vulnerable to psychosocial problems and it may offer possibilities for intervention.

The results of the VOLG-study stress the importance of paying attention to the achievement of *developmental milestones* in children and adolescents growing up with childhood cancer. Social adjustment and interaction with peers require special attention (14;20;67). Peer relationships are important for social development and self-esteem, especially in adolescents. In addition, social development seems to be related to psychosexual development, suggesting that friendships in youth are important for later sexual relationships. Parents and healthcare providers should encourage children with cancer to make friends, participate in peer activities (e.g. sporting events) and maintain the social contacts that they had before they became ill. Adolescents with chronic illnesses may become marginalised by peers, facing

rejection for being different at a time when body image and identity largely depend on conformity (68). Psychologists should prepare survivors for interaction with their peers (e.g. what to tell friends about the disease and how to deal with physical limitations in relation to peers). The 'Educatieve Voorzieningen' (educational-facilities-services; Hospital School) in the Netherlands play an important role in informing the survivors' teachers about cancer and its consequences. Interventions can increase the chances that survivors will be accepted by their classmates. Furthermore, school interventions could be introduced. Interventions can stimulate the acceptance of children with cancer but may also contribute to changes in attitudes and cognitions in society.

The results of the VOLG-study also bring the role of the survivors' parents into focus. It is known that parents of chronically ill children tend to overprotect their sick children (42), although this does not help the children to develop the personal skills they need to cope with the challenges of growing up with cancer. Findings among parents of premature children indicate that parents who perceived their children's health as very vulnerable tend to be overprotective and often fail to set age-appropriate limits on their children's behaviour, with possible adverse consequences for the children (69;70). It is therefore important to support parents in treating survivor as normally as possible within the family (14). Providing psychosocial information on the late effects of disease and treatment could be helpful, with regard to understanding and handling any problematic behaviour that survivors may exhibit.

Growing up with childhood cancer may complicate the transition to adulthood, which is characterized by a transition from family life toward independent living and a transition from education to employment, and which is closely related to positive social and emotional development earlier on (71). Physicians should therefore pay attention to the social and independent functioning of survivors, especially during the transition from childhood to adulthood.

The results of the VOLG-study show that it could be helpful to pay attention to ways in which survivors *cope* with their disease and with general life stressors, as some coping strategies appear to be more helpful than others. It is important for healthcare providers to understand emotional and behavioural reactions as outcomes of a coping processes, in order to respond more appropriately (72). For example, the oncologist's attitude about the course of the disease may influence a survivor's expectations with regard to the further course of the disease.

Healthcare providers should determine whether survivors are gathering (medical) information without undermining their ability to maintain positive expectations about the disease and the future. Psychosocial intervention is indicated when the survivors are not able to control their emotions themselves (72). Analyses of the control strategies that are used could assist survivors in coping with the disease. For example, when survivors are very anxious about the course of the disease and depend largely upon interpretative control (using information) to reduce uncertainty, we should look critically at the information that they obtained about the disease and its long-term consequences.

Although causality could not be established, the results indicate that positive expectations about the course of the disease is related to better HRQoL, as it provides survivors with a sense of control. In general, paying attention to the strengths that survivors undoubtedly have can generate feelings of mastery and control. Coping can be considered as a relatively stable but changeable characteristic that is responsive to intervention. Interventions directed at

improving the coping skills of chronically ill adult patients showed positive effects on HRQoL (73). In our opinion, cognitive coping is also a useful concept for psychosocial interventions for survivors of childhood cancer (74), although additional insight is needed into the way individual coping styles can be improved through intervention.

5.1.2 Parents

Despite the overall resilience in parents over time that was found in this study, there are good reasons why support for parents should not stop when treatment ends. Continued support for families could relieve psychological distress during the first several years after the cessation of treatment, and it could help parents return to normal daily life. This is of utmost importance, as the emotional well-being of parents influences the well-being of survivors. Oncologists could play a role in tracking adjustment problems in parents. One logical step would be to screen parents at an early stage. Psychosocial support may be appropriate for cases in which oncologists observe that parents are continually reporting higher levels of distress than is justified by the health of the children.

It is important to understand that the emotional and behavioural reactions of parents are outcomes of a *coping* process in order to respond to these reactions more appropriately. Listening to parents and keeping them informed about the health status of their children and about the medical consequences of the disease and its treatment are important ways to diminish parental distress, uncertainty and helplessness. In addition, providing information on the psychosocial consequences of their children's condition and helping parents to treat their children as normally as possible within the family could prevent psychosocial problems by enhancing re-entry into normal life (see also 5.1.1). Interventions should also include training in 'positive thinking', as maintaining a hopeful attitude could protect parents from negative emotions. Cognitive coping strategies (e.g. learning to view stressful situations as challenges to be overcome) can generate feelings of mastery and control (75).

5.1.3 Psychosocial aftercare

The results of the VOLG-study showed that many survivors function well after the end of successful cancer treatment, during the period leading up to survivorship. This indisputably important finding attests to the resilience of the survivors. The known late effects of many treatments (8;76-79) suggest that much work remains to be done, however, as does growing body of evidence that a considerable proportion of all long-term survivors are adversely affected in specific areas of psychosocial functioning (7). Survivors should be followed longer to be able to assess the impact of the late effects on the survivors' HRQoL, both physically as psychosocially.

One satisfying development in recent decades is that the monitoring and screening of survivors, both medically and psychosocially, has become standard aftercare in many hospitals. Aftercare should be tailored to the needs of survivors and their parents, depending on the (developmental) age of the survivors as well as on the time since end of treatment. Standard aftercare should include psychosocial screening, education and counselling.

Psychosocial screening is needed, as few clear medical risk factors for diminished psychosocial functioning have been able to be traced until now (7), with the exception of CNS-tumours (18;80;81), bone tumours (9;82) and radiotherapy (81;83). Screening survivors

psychosocially by a psychologist is advisable. Such screenings could take place as part of the annual evaluations in the long-term follow-up clinic, in order to be able to trace problems in an early stage. Screening is particularly advisable at important developmental transitions, including the transition from kindergarten to primary school, the transition from primary to secondary school and at the end of secondary school. In addition, it is important to pay attention to the achievement of developmental milestones, given the finding from the VOLG-study that cancer and its treatment can lead to an unfavourable course of life.

Computer-scored individual measurements of HRQoL are being used increasingly in clinical practice, in order to inform the physician about the HRQoL of the patients (84-88). The computer output – usually a graphical summary of HRQoL outcomes – can help physicians to focus on the HRQoL domains that correspond to the needs of patients. Utilising HRQoL measurement can facilitate communication between patients and physicians, and it can assist in the identification of the patients with the greatest needs (85;87), so that they can be referred to other healthcare providers.

The provision of psychosocial information on the effects of the disease and treatment, and assisting parents in treating former patients as normally as possible could prevent late psychosocial problems by enhancing re-entry into normal life (see also 5.1.1 and 5.1.2). Psychologists could inform and support survivors and their parents, either individually or in groups. Psycho-educational support groups could be helpful, as group interventions offer possibilities for the sharing of emotions and experiences. Such interventions could also help both parents and survivors to integrate their experiences into their normal daily lives and to become accustomed to living with uncertainty concerning the recurrence of the disease and possible side effects. Group interventions could also be used for practising the skills and developing the cognitions that survivors need to integrate their experiences into their normal daily lives (e.g. what to tell friends about the disease, or how to deal with physical limitations in relation to activities with peers). It is important to note that attention should be given to the well-being of the siblings as well, given that cancer of a brother of sister can have a profound impact on the siblings (89-91).

General evidence suggests that psycho-educational interventions incorporating cognitive-behavioural techniques on such variables as self-efficacy and psychosocial well-being are effective for children with chronic disease (18;74;92;93). A pilot study on the effects of a social-skills training group among children treated for brain tumours showed improvements (94), as did a short intervention aimed at reducing Post-traumatic Stress Symptoms (PTSS) in adolescent survivors and their families (95). Group interventions focused on long-term adolescent and adult survivors and/or the entire family, appeared to be promising (67;96;97).

The psycho-educational interventions described above are intended to prevent adjustment problems in survivors and their families. If mild or serious adjustment problems are present, psychological intervention is indicated to facilitate adjustment and acceptance of the disease and the late medical effects, or adequate referral for problems not primarily associated with childhood cancer. Family therapy could also be advisable if functioning between parents and child or the family as a whole is affected (14).

5.1.4 Main recommendations

Supporting survivors and their parents should not stop when treatment ends. Standard aftercare should include psychosocial monitoring and screening, psycho-education and counselling:

- Psychosocial monitoring and screening are needed in order to trace problems in survivors and parents in an early stage, allowing appropriate support to be offered.
- Psycho-education and counselling are recommended, as providing psychosocial information on the effects of the disease and treatment, and assisting parents in treating former patients as normally as possible could prevent psychosocial problems by enhancing re-entry into normal daily life. Individual psycho-education and counselling or group-intervention is possible.
- Survivors of CNS-tumours and bone tumours deserve special attention, as do those who have been treated with radiotherapy.
- If mild or serious adjustment problems are present, psychological intervention is needed.

Guidelines for psychosocial monitoring and screening of survivors and their parents are summarised in Table 3. Important themes for psycho-education and counselling are presented in Table 4.

Table 3: Psychosocial monitoring and screening of survivors and their parents: guidelines.

Survivors	
• Regular screening of HRQoL: e.g. computer-scored individually measurement of HRQoL	• oncologist
• Regular assessment of developmental milestones	• psychologist [1]
• Regular assessment of psychosocial functioning	• psychologist [1]
Parents	
• Tracing adjustment problems: If parents continue to report higher levels of distress than called for by the health of the child, psychosocial support may be needed; referral to a psychologist is therefore recommended.	• oncologist
• Assessment of emotional functioning	• psychologist [1]

[1] or a social worker with expertise in psychosocial aspects of childhood cancer

Table 4: Psycho-education or counselling: important themes.

Survivors & parents	
• Course of life: Encourage survivors to participate in peer activities and maintain the social contacts they had before they became ill; avoid overprotection and treat survivors as normally as possible.	• oncologist
• Information about the disease and long-term consequences: Keep survivors and parents informed, but maintain a critical perspective on the information given; try not to undermine positive expectations of the further course of the disease.	• oncologist
• Realise that the oncologist's attitude may influence the expectations of both survivor and their parent concerning the further course of the disease.	• oncologist
Survivors	
• Social skills and cognitions needed to integrate the cancer experience in daily life: e.g. what to tell friends about the disease, how to deal with physical limitations in relation to activities with peers.	• psychologist [1]
• Cognitive coping strategies: positive thinking/expectations about the course of the disease, viewing stressful situations as challenges.	• psychologist [1]
• Information seeking about the disease: information sources, asking the oncologist.	• psychologist [1]
• Sharing emotions and experiences.	• psychologist [1]
Parents	
• Cognitive coping strategies: positive thinking/expectations of the course of the disease, viewing stressful situations as challenges.	• psychologist [1]
• Raising a child with childhood cancer: overprotection, impact of perceived vulnerability of the child's health, course of life of survivors (social contacts and autonomy).	• psychologist [1]
• Awareness of siblings	• psychologist [1]
• Communication about the disease	• psychologist [1]
• Sharing emotions and experiences	• psychologist [1]

[1] or a social worker with expertise in psychosocial aspects of childhood cancer

5.2 Future research

The VOLG-study was designed to gain insight into the process of adjusting to the cancer experience. To this end, children and adolescents were investigated longitudinally during the first several years following the end of successful treatment, and long-term consequences were investigated cross-sectionally in young adult survivors. The VOLG-study provided considerable information about the HRQoL of survivors over time and about factors that are probably predictive of HRQoL. The extensiveness of the VOLG-study could be considered both strength and weakness. Because it was impossible to study all aspects in depth, several recommendations for future research can be identified. The recommendations for future research are also based on the limitations described in the previous section (4.1-4.4).

5.2.1 Study design and study population

Considering the low incidence of childhood cancer, the sample size in the longitudinal component of the VOLG-study was reasonably large. The wide range of ages, however, caused methodological problems in the longitudinal assessment of survivors' HRQoL. Different age groups required different, age-specific questionnaires, thereby eliminating the possibility of the necessary subgroups analysis in some cases. For example, it was not possible to analyse the data from survivors 16 years of age or older longitudinally. Small sample size poses a number of additional limitations, including moderate statistical power and the necessity of pre-selection of the independent variables in the analyses. Multi-institutional collaboration is recommended to increase the sample size and to optimise the representativeness of the survivors in further studies.

The process of adjusting to cancer and the meaning of survivorship are known to differ across cultures. The increasing cultural and ethnic diversity of people in the Western countries underscores the importance of cross-cultural comparisons.

One of the main purposes of the VOLG-study was to identify predictors of HRQoL in survivors of childhood cancer. Although longitudinal analysis and SEM yielded stronger evidence of the presence of causal correlations than did traditional analytic procedures, they offered no definitive proof of causality between psychosocial factors (e.g. coping, course of life) and HRQoL. Randomised Clinical Trials (RCTs) in which hypothesised predictors of HRQoL (e.g. cognitive coping strategies) are influenced by intervention could yield stronger evidence of causality. Furthermore, the longitudinal assessment of the achievement of developmental milestones is of utmost importance. Additional longitudinal research is also needed to explain functioning of paediatric survivors and their parents in the period leading up to survivorship into adulthood, including a control group and data about pre-cancer functioning and functioning at diagnosis.

5.2.2 Measures and instruments

The limitations that were posed by the measures used in the VOLG-study (see Paragraph 4) yielded several recommendations for future research. In addition to the generic HRQoL measures used in the VOLG-study in order to allow comparison between the survivors and the general Dutch population, we recommend the use of cancer-specific instruments for measuring the impact of childhood cancer longitudinally, as this type of instrument is more sensitive to change. Although such instruments are currently not available in Dutch, increasing numbers of HRQoL instruments for children with several chronic diseases are being developed, validated and translated into Dutch. Examples include the Disabkids (98) and the cancer-specific module of the PedsQL (99). The latter instrument focuses at HRQoL during treatment and it is not appropriate for the period after active has treatment ended. Despite recent developments, the longitudinal assessment of HRQoL in children remains difficult. Efforts to compare HRQoL outcomes in children across various age groups would be very useful. Research on the so called 'Minimal Clinically Important Difference' (MCID) (21;22) for measures of HRQoL in children of differing age groups would be a first step. The VOLG-study employed distribution-based approaches (e.g. effect size and significance) to interpret the changes over time and differences between survivors and the norm, as the MCID has yet to be established for paediatric HRQoL. Unfortunately, the TACQOL data in

the VOLG-study appeared inappropriate for calculating the MCID of HRQoL in our study population.

Cancer-specific questionnaires are needed to investigate the functioning of survivors more thoroughly. In particular, we recommend extensive investigation of social functioning and such related concepts as self-esteem. In addition, insight into the process of adjustment (for survivors as well as their parents) is likely to be enhanced by the addition of factors and outcomes that have been found relevant in studies on adjustment to paediatric chronic physical disorders (66;100-102). Examples include such intrapersonal factors as personality and temperament (66), post-traumatic stress symptoms (37;103-106) and post-traumatic growth (13), as well as income, employment and other socio-economic variables (64;65), the vulnerability of the children's health as perceived by their parents, parent-child interaction and the burden of the disease on the parents.

The VOLG-study employed several relatively new instruments for measuring disease-related concepts: disease-related parental emotions (SSERQ), disease-related cognitive coping in survivors and parents (CCSS), communication about the disease (CQ) and the achievement of developmental milestones (Course of life questionnaire). To date, no other Dutch questionnaires are available for measuring these concepts; investigating and improving the psychometric characteristics of these instruments would therefore be useful.

5.2.3 Challenges

To summarise the points that have been made above, the following could be considered challenges for future research:

- Developing cancer-specific HRQoL measures appropriate for screening and monitoring patients in the period leading up to survivorship
- Developing a checklist of developmental milestones
- Establishing MCID for paediatric HRQoL
- RCTs to test intervention effects which could also yield stronger evidence of causality between psychosocial factors and HRQoL
- Longitudinal research on developmental milestones
- Research on the long-term psychosocial impact of physical late effects on the lives of adult survivors of childhood cancer.

The recent formation of a Paediatric Psycho-Oncology subcommittee of the *Societé Internationale Oncologie Pédiatrique* (SIOP PPO) is an important step forward that will stimulate psychosocial research in childhood cancer.

Finally, we must emphasise the following. In recent decades, psychosocial aftercare has become more and more extensive, and several interventions have been developed. The initial results of the effects of the interventions have been promising, and the interventions have apparently met the needs of survivors and their families (18;67;74;85;87;92-94;96;97;107). Further steps in the direction of evidence-based interventions for survivors and their families will be important in the years to come. To date, most interventions in paediatric oncology focus on psychosocial functioning. Interventions should also be developed to improve (neuro)cognitive functioning, which would subsequently improve future perspectives for survivors with cancer-related brain injury, cancer-related cognitive problems or both (108).

Considering the known adverse physical effects of many treatments (11) and the increased risk of second malignancies, there is a need for research that addresses the psychosocial impact of physical late effects on the lives of long-term survivors (109). It is important that survivors attend the long-term follow-up clinic so that they can be screened and informed about possible adverse effects and related health behaviour. Efforts should be directed at encouraging survivors to attend the follow-up clinic without stigmatising or frightening them. Insight into survivors' perceptions of risk is needed, as the communication of risks is difficult. Survivors should realise that they are "cured, but at risk". In other words, they are cured of the original cancer, but they are at risk of adverse effects and second malignancies. Life-long medical survey is therefore necessary (110).

REFERENCES

(1) Cohen J. Statistical power analysis for the behavioral sciences. New York: Academy Press, 1988.

(2) Veenstra KM, Sprangers MAG, Van der Eyken J, Taminiau AHM. Quality of life in survivors with a Van Ness-Borggreve rotationplasty after bone marrow tumour resection. J Surg Oncol 2000;73:192-7.

(3) Pastore G, Mosso ML, Magnani C, Luzzatto L, Bianchi M, Terracini B. Physical impairment and social life goals among adult long-term survivors of childhood cancer: a population-based study from the childhood cancer registry of Piedmont, Italy. Tumori 2001;87:372-8.

(4) Zebrack BJ, Chesler MA. Quality of life in childhood cancer survivors. Psychooncology 2002;11:132-41.

(5) Zebrack BJ, Zeltzer LK, Whitton J, Mertens AC, Odom L, Berkow R, et al. Psychological outcomes in long-term survivors of childhood leukemia, Hodgkin's disease, and Non-Hodgkin's lymphoma: a report from the childhood cancer survivor study. Pediatrics 2002;110(1):42-52.

(6) Zebrack BJ, Gurney JG, Oeffinger K, Whitton J, Packer RJ, Mertens A, et al. Psychological outcomes in long-term survivors of childhood brain cancer: a report from the Childhood Cancer Survivors Study. J Clin Oncol 2004;22(6):999-1006.

(7) Patenaude AF, Kupst MJ. Psychosocial functioning in pediatric cancer. J Pediatr Psychol 2005;30(1):9-27.

(8) Friedman DL, Freyer DR, Levitt GA. Models of care for survivors of childhood cancer. Pediatric Blood Cancer 2006;46:159-68.

(9) Langeveld NE, Stam H, Grootenhuis MA, Last BF. Quality of life in young adult survivors of childhood cancer (review). Support Care Cancer 2002;10:579-600.

(10) Stam H, Grootenhuis MA, Last BF. Social and emotional adjustment in young survivors of childhood cancer (review). Support Care Cancer 2001;9:489-513.

(11) Geenen MM, Cardous-Ubbink MC, Kremer LCM, van den Bos C, van der Pal HJH, Heinen RC, et al. Medical assessment of adverse health outcomes in long-term survivors of childhood cancer. JAMA 2007;292(24):2705-15.

(12) Sprangers MAG, Schwartz CE. Integrating response shift into health-related quality of life research: a theoretical model. Soc Sci Med 1999;48:1507-15.

(13) Barakat LP, Alderfer MA, Kazak AE. Posttraumatic growth in adolescent survivors of cancer and their mothers and fathers. J Pediatr Psychol 2006;31(4):413-9.

(14) Van Dongen-Melman JEWM. Developing psychosocial aftercare for children surviving cancer and their families. Acta Oncologica 39[1], 23-31. 2000.

(15) Bessell AG. Children surviving cancer: psychosocial adjustment, quality of life, and school experiences. Except Child 2001;67(3):345-59.

(16) Pendley JS, Dahlquist LM, Dreyer Z. Body image and psychosocial adjustment in adolescent cancer survivors. J Pediatr Psychol 1997;22(1):29-43.

(17) Spirito A, Stark LJ, Cobiella C, Drigan R, Androkites A, Hewett K. Social adjustment of children succesfully treated for cancer. J Pediatr Psychol 1990;15(3):359-71.

(18) Vannatta K, Gartstein MA, Short A, Noll RB. A controlled study of peer relationships of children surviving brain tumors: teacher, peer, and self ratings. J Pediatr Psychol 1998;23(5):279-87.

(19) Vannatta K, Zeller M, Noll RB, Koontz K. Social functioning of children surviving bone marrow transplantation. J Pediatr Psychol 1998;23(3):169-78.

(20) Stam H, Grootenhuis MA, Last BF. The course of life of survivors of childhood cancer. Psychooncology 2005;14:227-38.

(21) Lydick E, Epstein RS. Interpretation of quality of life changes. Qual Life Res 1993;2:221-6.

(22) Guyatt GH, Osoba D, Wu AW, Wyrwich KW, Norman GR, the Clinical Significance Consensus Meeting Group. Methods to explain the clinical significance of health status measures. Mayo Clin Proc 2002;77:371-83.

(23) Garber J. Classification of childhood psychopathology: a developmental perspective. Child Dev 1984;55:30-48.

(24) Lewis M, Miller SM. Handbook of developmental psychopathology. New York: Plenum Press, 1990.

(25) Folkman S, Moskowitz JT. Positive affect and the other side of coping. Am Psychol 2000;55(6):647-54.

(26) Fournier M, de Ridder D, Bensing J. How optimism contributes to the adaptation of chronic illness. A prospective study into the enduring effects of optimism on adaptation moderated by the controllability of chronic illness. Personality and individual differences 2002;33:1163-83.

(27) Lazarus RS, Folkman S. Stress, appraisal, and coping. New York: Springer Publishing Company, 1984.

(28) Rothbaum F, Weisz JR, Snyder SS. Changing the world and changing the self: a two-process model of perceived control. J Pers Soc Psychol 1982;42:5-37.

(29) Grootenhuis MA, Last BF. Children with cancer with different survival perspectives: defensiveness, control strategies, and psychological adjustment. Psychooncology 2001;10:305-14.

(30) Petersen C, Schmidt S, Bullinger M. Brief report: development and pilot testing of a coping questionnaire for children and adolescents with chronic health conditions. J Pediatr Psychol 2004;29(8):635-40.

(31) Sandler IN, Tein J-Y, West SG. Coping, stress, and the psychological symptoms of children of divorce: A cross-sectional and longitudinal study. Child Dev 1994;65:1744-63.

(32) Ayers TS, Sandler IN, West SG, Roosa MW. A dispositional and situational assessment of children's coping: testing alternative models of coping. J Pers 1996;64(4):923-58.

(33) Schmidt S, Petersen C, Bullinger M. Coping with chronic disease from the perspective of children and adolescents - a conceptual framework and its implications for participation. Child Care Health Dev 2003;29(1):63-75.

(34) Bull BA, Drotar D. Coping with cancer in remission: stressors and strategies reported by children and adolescents. J Pediatr Psychol 1991;16:767-82.

(35) Fritz GK, Williams JR, Amylon M. After treatment ends: psychosocial sequelae in pediatric cancer survivors. Am J Orthopsychiatry 1988;58:552-61.

(36) Kazak AE, Barakat LP, Meeske K, Christakis D, Meadows AT, Penati B, et al. Posttraumatic stress, family functioning, and social support in survivors of childhood leukemia and their mothers and fathers. J Consult Clin Psychol 1997;65(1):120-9.

(37) Kazak AE. Posttraumatic distress in childhood cancer survivors and their parents. Medical and Pediatric Oncology Supplement 1998;1:60-8.

(38) Doeglas D, Suurmeijer T, Briancon S, Moum T, Krol B, Bjelle A, et al. An international study on measuring social support: interactions and satisfaction. Soc Sci Med 1996;43(9):1389-97.

(39) Kazak AE, Meadows AT. Families of young adolescents who have survived cancer: social-emotional adjustment, adaptability, and social support. J Pediatr Psychol 1989;14:175-91.

(40) Madan-Swain A, Brown RT, Sexson SB, Baldwin K, Pais R, Ragab A. Adolescent cancer survivors: psychosocial and familial adaptation. Psychosomatics 1994;35(5):453-9.

(41) Pelcovitz D, Goldenberg LA, Mandel F, Kaplan S, Weinblatt M, Septimus A. Posttraumatic stress disorder and family functioning in adolescent cancer. J Trauma Stress 1998;11(2):205-21.

(42) Rait DS, Ostroff JS, Smith K, Cella DF, Tan C, Lesko LM. Lives in balance: perceived family functioning and the psychosocial adjustment of adolescent cancer survivors. Fam Process 1992;31:383-97.

(43) Grootenhuis MA, Last BF. Children with cancer. Recent Results in Cancer Research 168, 73-79. 2006.

(44) Boman K, Lindahl A, Björk O. Disease-related distress in parents of children with cancer at various stages after the time of diagnosis. Acta Oncol 2003;42(2):137-46.

(45) Grootenhuis MA, Last BF. Parents' emotional reactions related to different survival perspectives of their children with cancer. Journal of psychosocial oncology 1997;15:43-62.

(46) Kazak AE, Stuber ML, Barakat LP, Meeske K, Guthrie D, Meadows AT. Predicting posttraumatic stress symptoms in mothers and fathers of survivors of childhood cancers. Journal of the American Academy of Child and Adolescence Psychiatry 1998;37(8):823-31.

(47) Kazak AE, Barakat LP, Alderfer M, Rourke MT, Meeske K, Gallagher PR, et al. Posttraumatic stress in survivors of childhood cancer and mothers: development and validation of the Impact of Traumatic Stressors Interview Schedule (ITSIS). Journal of Clinical Psychology in Medical Settings 2001;8(4):307-23.

(48) Kazak AE, Alderfer M, Rourke MT, Simms S, Streisand R, Grossman JR. Posttraumatic stress disorder (PTSD) and posttraumatic stress symptoms (PTSS) in families of adolescent childhood cancer survivors. J Pediatr Psychol 2004;29(3):211-9.

(49) Sloper P. Predictors of distress in parents of children with cancer: a prospective study. J Pediatr Psychol 2000;25(2):79-91.

(50) Van Dongen-Melman JE, Pruyn JFADG, Koot HM, Hahlen K, Verhulst FC. Late psychosocial consequences for parents of children who survived cancer. J Pediatr Psychol 1995;20:567-86.

(51) Taylor SE, Brown JD. Illusion and well-being: a social psychological perspective on mental health. Psychol Bull 1988;103(2):193-210.

(52) Taylor SE, Armor DA. Positive illusion and coping with adversity. J Pers 1996;64(4):873-98.

(53) Grootenhuis MA, Last BF. Predictors of parental emotional adjustment to childhood cancer. Psychooncology 1997;6:115-28.

(54) Bedi G, Brown SL. Optimism, coping style and emotional well-being in cardiac patients. Br J Psychol 2005;10:57-70.

(55) Lindahl Norberg A, Lindblad F, Boman KK. Coping strategies in parents of children with cancer. Soc Sci Med 2005;60:965-75.

(56) Hoekstra-Weebers JE, Jaspers JP, Kamps WA, Klip EC. Gender differences in psychologcial adaptation and coping in parents of pediatric cancer patients. Psychooncology 1998;7:26-36.

(57) Thompson RJ, Jr., Gil KM, Burbach DJ, Keith BR, Kinney TR. Psychological adjustment of mothers of children and adolescents with sickle cell disease: the role of stress, coping methods, and family functioning. J Pediatr Psychol 1993 Oct;18(5):549-59.

(58) Thompson RJ, Jr., Gil KM, Gustafson KE, George LK, Keith BR, Spock A, et al. Stability and change in the psychological adjustment of mothers of children and adolescents with cystic fibrosis and sickle cell disease. J Pediatr Psychol 1994 Apr;19(2):171-88.

(59) Greenberg HS, Meadows AT. Psychosocial impact of cancer survival on school-age children and their parents. Journal of psychosocial oncology 1991;9(4):43-57.

(60) Quin S. The long-term psychosocial effects of cancer diagnosis and treatment on children and their families. Soc Work Health Care 2004;39:129-49.

(61) Olson DH, Russell CS, Sprenkle DD. Circumplex model of marital and family systems: VI. Theoretical Update. Fam Process 1983;22:69-83.

(62) Hoekstra-Weebers JEHM, Jaspers JPC, Kamps WA, Klip EC. Psychological Adaptation and social support for parents of pediatric cancer patients: a prospective longitudinal study. J Pediatr Psychol 2001;26(4):225-35.

(63) Dockerty JD, Williams SM, McGee R, Skegg DCG. Impact of childhood cancer on the mental health of parents. Med Pediatr Oncol 2000;35:475-83.

(64) Grootenhuis MA, Last BF. Adjustment and coping by parents of children with cancer: a review of het literature. Support Care Cancer 1997;5:466-84.

(65) Hoekstra-Weebers JEHM, Jaspers JPC, Kamps WA, Klip CE. Risk factors for psychological maladjustment of parents of children with cancer. Journal of American Academy of Child Adolescence Psychiatry 1999;38(12):1526-35.

(66) Wallander JL, Varni JW. Effects of pediatric chronic physical disorders on child and family adjustment. Journal of Child Psychology and Psychiatry 1998;39(1):29-46.

(67) Zebrack BJ, Oeffinger KCHR, Kaplan S. Advocacy skills training for young adult cancer survivors: the Young Adult Survivors Conference at Camp Mak-a-Dream. Support Care Cancer 2006;14(7):779-82.

(68) DiNapoli PP, Murphy D. The marginalization of chronically ill adolescents. The Nursing clinics of North America 2002;37:565-72.

(69) Estroff DB, Yando R, Burke K, Snyder D. Perceptions of preschoolers' vulnerability by mothers who had delivered preterm. J Pediatr Psychol 1994 Dec;19(6):709-21.

(70) Stern M, Karraker K, McIntosh B, Moritzen S, Olexa M. Prematurity stereotyping and mothers' interactions with their premature and full-term infants during the first year. J Pediatr Psychol 2006 Jul;31(6):597-607.

(71) Sinnema G. Youths with chronic illness and disabitlity on their way to social and economic participation: a health-care perspective. J Adolesc Health 1992;13:369-71.

(72) Last BF, Grootenhuis MA. Emotions, coping and the need for support in families of children with cancer: a model for psychosocial care. Patient Educ Couns 1998;33(2):169-79.

(73) de Ridder D, Schreurs K. Developing interventions for chronically ill patients: is coping a helpful concept? Clin Psychol Rev 2001;21(2):205-40.

(74) Last BF, Stam H, Onland-van Nieuwenhuizen A-M, Grootenhuis MA. Positive effects of a psycho-educational group intervention for children with a chronic disease: first results. Patient Educ Couns 2007;65:101-12.

(75) Folkman S. Positive psychological states and coping with severe stress. Soc Sci Med 1997;45(8):1207-21.

(76) Lackner H, Benesch M, Schagerl S, Kerbl R, Schwinger W, Urban C. Prospective evaluation of late effects after childhood cancer therapy with a follow-up over 9 years. Eur J Pediatr 2000;159:750-8.

(77) Oeffinger KC, Eshelman DA, Tomlinson GE, Buchanan GR, Foster BM. Grading of late effects in young adults survivors of childhood cancer followed in an ambulatory adult setting. Cancer 2000;88:1687-95.

(78) Oeffinger KC, Hudson MM. Long-term complications following childhood and adolescent cancer: foundations for providing risk-based health care for survivors. CA Cancer J Clin 2004;54:208-36.

(79) Oeffinger KC, Mertens AC, Sklar CA, Kawashima MS, Hudson MM, Meadows AT, et al. Chronic health conditions in adult survivors of childhood cancer. The New England Journal of Medicine 2006;355(15):1572-82.

(80) Boman K, Bodegard G. Long-term coping in childhood cancer survivors: influence of illness, treatment and demographic background factors. Acta Paediatr 2000;89:105-11.

(81) Maurice-Stam H, Grootenhuis MA, Caron HN, Last BF. Course of life of survivors of childhood cancer is related to Quality of Life in young adulthood. Journal of psychosocial oncology 2007;25(3).

(82) Eiser C. Practitioner Review: long-term consequences of childhood cancer. Journal of Child Psychology and Psychiatry 1998;39(5):621-33.

(83) Stam H, Grootenhuis MA, Last BF. Quality of life and coping in young adult survivors of childhood cancer: positive expectations about the further course of the disease were correlated with better quality of life. Psychooncology 2006;15(1):31-43.

(84) Detmar SB, Muller MJ, Schornagel JH, Wever LDV, Aaronson NK. Health-Related Quality-of-Life assessment and patient-physician communication. A randomized controlled trial. JAMA 2002;288(23):3027-34.

(85) Detmar SM, Aaronson NK. Quality of life assessment in daily clinical oncology practice: a feasibility study. Eur J Cancer 1998;34(8):1181-6.

(86) Nagarajan R, Nelgia JP, Clohisy DR, Yasui Y, Greenberg M, Hudson M, et al. Education, employment, insurance, and marital status among 694 survivors of pediatric lower extremity bone tumors. Cancer 2003;97:2554-64.

(87) Varni JW, Burwinkle TM, Lane MM. Health-related quality of life measurement in pediatric clinical practice: An appraisal and precept for future research and application. Health and Quality of Life Outcomes 2005;3(34):1-9.

(88) Velikova G, Booth L, Smith AB, Brown PM, Lynch P, Brown JM, et al. Measuring Quality of Life in routine oncology practice improves communication and patient well-being: a randomized controlled trial. J Clin Oncol 2004;22(4):714-24.

(89) Houtzager BA, Grootenhuis MA, Last BF. Adjustment of siblings to childhood cancer: a literature review. Support Care Cancer 1999;7:302-20.

(90) Houtzager BA, Grootenhuis M, Caron HN, Last BF. Quality of life and psychological adaptation in siblings of paediatric cancer patients, 2 years after diagnosis. Psychooncology 2004;13(8):499-511.

(91) Houtzager BA, Oort FJ, Hoekstra-Weebers JEHM, Caron HN, Grootenhuis MA, Last BF. Coping and family functioning predict longitudinal psychological adaptation of siblings of childhood cancer patients. J Pediatr Psychol 2004;29(8):591-605.

(92) Barlow JH, Ellard DR. Psycho-educational interventions for children with chronic disease, parents and siblings: an overview of the research evidence based. Child: Care, Health & Development 2004;30(6):637-45.

(93) Plante WA, Lobato D, Engel R. Review of group interventions for pediatric chronic conditions. J Pediatr Psychol 2001;26(7):435-53.

(94) Barakat LP, Hetzke JD, Foley B, Carey ME, Gyato K, Phillips PC. Evaluation of a social-skills training group intervention with children treated for brain tumours: a pilot study. J Pediatr Psychol 2003;28(5):299-307.

(95) Kazak AE, Alderfer MA, Streisand R, Simms S, Rourke MT, Barakat LP, et al. Treatment of posttraumatic stress symptoms in adolescent survivors of childhood cancer and their families: a randomized clinical trial. Journal of Family Psychology 2004;18(3):493-504.

(96) Kazak AE, Simms S, Barakat L, Hobbie W, Foley B, Golomb V, et al. Surviving Cancer Competently Intervention Program (SCCIP): A cognitive-behavioral and family therapy intervention for adolescent survivors of childhood cancer and their families. Fam Process 1999;38(2):175-91.

(97) Zampini K, Ostroff JS. The post-treatment resource program: portrait of a program for cancer survivors. Psychooncology 1993;2:1-9.

(98) Ravens-Sieberer U, Erhart M, Bullinger M, European Kidscreen and Disabkids Groups. The Kidscreen and Disabkids Questionnaire - Two new measures for childrens' and adolescents' Health-Related Quality of Life. Patient Reported Outcomes 37, 9-11. 2006.

(99) Varni JW, Seid M, Rode CA. The PedsQL: Measurement model for the Pediatric Quality of Life Inventory. Med Care 1999;37:126-39.

(100) Raina P, O'Donnell M, Schwellnus H, Rosenbaum P, King G, Brehaut J, et al. Caregiving process and caregiver burden: conceptual models to guide research and practice. BMC Pediatrics 2004;4:1-13.

(101) Raina P, O'Donnell M, Rosenbaum P, Brehaut J, Walter SD, Russell D, et al. The health and well-being of caregivers of children with cerebral palsy. Pediatrics 2005;115(6):e626-e636.

(102) Hartman EE, Oort FJ, Aronson DC, Hannekam MJG, van der Zee DC, Rieu PNMA, et al. Critical factors affecting quality of life of adult patients with anorectal malformations or Hirschsprung's disease. Am J Gastroenterol 2004;99(5):907-13.

(103) Hobbie WL, Stuber M, Meeske K, Wissler K, Rourke MT, Ruccione K, et al. Symptoms of posttraumatic stress in young adult survivors of childhood cancer. J Clin Oncol 2000;18(24):4060-6.

(104) Langeveld NE, Grootenhuis MA, Voûte PA, de Haan RJ. Posttraumatic stress symptoms in adult survivors of childhood cancer. Pediatric Blood Cancer 2004;42:604-10.

(105) Meeske KA, Ruccione K, Globe DR, Stuber ML. Posttraumatic stress, quality of life, and psychological distress in young adult survivors of childhood cancer. Oncol Nurs Forum 2001;28(3):481-9.

(106) Schwartz L, Drotar D. Posttraumatic stress and related impairment in survivors of childhood cancer in early adulthood compared to healthy peers. J Pediatr Psychol 2006;31(4):356-66.

(107) Kazak AE. Evidence-based interventions for survivors of childhood cancer and their families. J Pediatr Psychol 2005;30(1):29-39.

(108) Butler RW, Mulhern RK. Neurocognitive interventions for children and adolescents surviving cancer. J Pediatr Psychol 2005;30:65-78.

(109) Patenaude AF, Kupst MJ. Introduction to the special issue: surviving pediatric cancer: research gains and goals. J Pediatr Psychol 2005 Jan;30(1):5-8.

(110) Haupt R, Spinetta JJ, Ban I, Barr RD, Beck JD, Byrne J, et al. Long term survivors of childhood cancer: cure and care. The Eric Statement. Eur J Cancer 2007;(in press; published online).

Summary

Summary

The diagnosis and treatment of childhood cancer is a dramatic event that could influence physical and psychosocial functioning long time after treatment has been terminated. The treatment of patients with childhood cancer has enormously improved in recent decades. Many patients who may previously have had a limited life expectancy are now growing up with childhood cancer and surviving into adulthood. The enormous increase in the number of survivors of childhood cancer reaching adulthood over the last decades has intensified the need to investigate the consequences of childhood cancer for survivors and their families.

This thesis reports the results of the VOLG (Vragenlijsten kinderOncologie Late Gevolgen)-study, which investigated 'quality of life, course of life and coping in childhood cancer survivors'. The VOLG-study, which was financed by the Dutch Cancer Society, was conducted by the Psychosocial Department of the Emma Children's Hospital Academic Medical Center between 2000 and 2006. The course of patients' adjustment to survivorship over time and their adjustment in young adulthood are the main subjects of this thesis. The VOLG-study focuses on (1) the psychosocial adjustment of children and adolescents growing up with childhood cancer, and the emotional adjustment of their parents, in the first three to five years after successful treatment in the run-up to survivorship (longitudinal component of the VOLG-study) and (2) the psychosocial adjustment of young adult survivors of childhood cancer (cross-sectional component of the VOLG-study).

The VOLG-study is part of the research line of the paediatric psychology program in the Emma Children's Hospital AMC, which focuses on studying the consequences of growing up with chronic disease for both patients and their parents.

Although a 5-year period without treatment is commonly considered a criterion for survival, we decided to consider the patients in the VOLG-study survivors as they were progressing towards long-term survivorship.

This thesis consists of: General Introduction, Part I (longitudinal VOLG-study), Part II (cross-sectional VOLG-study) and General discussion.

The **General introduction** describes the background of the VOLG-study: medical aspects of childhood cancer, Health-related Quality of life (HRQoL) and the study design.

Cancer is a rare disease in children. Nevertheless, it is the second leading cause of death in children and the primary cause of death from diseases. Approximately 400 children up to the age of fifteen are diagnosed with cancer in the Netherlands every year, accounting for 0.6 percent of the total cancer incidence in the Netherlands. Approximately two of every thousand young adults in the Netherlands have suffered from childhood cancer at some time. Cure and long-term survival rates are usually based on 5-year survival. Before the introduction of chemotherapy and radiotherapy, in the 1960s, childhood cancer was fatal in most cases. Overall, the 5-years survival rate for children diagnosed with cancer in Europe is currently more than 70%, as compared to 30% in the 1960s. Surgery, chemotherapy and radiotherapy are the major modalities of cancer therapy. Standard practice usually involves a combination of treatment modalities. The length and type of treatment depend on a number of factors, including the type of cancer, location and stage of the disease. Although the development of more effective and targeted treatments has reduced the side effects to some extent, they are still present. Studies indicate that between 60% and 75% of all long-term childhood cancer

survivors develop one or more late effects due to the disease or treatment, and approximately one-third of these late effects are classified as either moderate or severe.

Increases in the survival rates for paediatric diseases, especially childhood cancer, have led to a call for new outcome measures that reflect more than the quantity of survival. The concept of HRQoL refers to the impact of health and illness on an individual's well-being. It is generally accepted that HRQoL is a multidimensional construct incorporating at least three broad domains: physical, psychological and social functioning.

The instruments used in HRQoL-research may either generic, disease-specific or domain-specific, depending on the nature of the research questions and on the availability of the preferred instruments. The evaluation of adult HRQoL is well established but HRQoL measurement in children is less routinely employed and cancer-specific instruments translated and validated for Dutch children are not available.

Equivalent to other conceptual frameworks used to explain adjustment in paediatric patients and adult patients, we presume that adjustment in survivors of childhood cancer (operationalised as HRQoL) is an outcome of a longitudinal process that is influenced by characteristics of the situation and the disease, and by personal and psychosocial factors (e.g. course of life, coping, social support, family functioning and communication about the disease). The VOLG-study focuses specifically on psychosocial factors, as they play an important role in paediatric psychology and are assumed susceptible to change.

Part I describes the results of the longitudinal component of the VOLG-study. From 2000-2006, paediatric cancer survivors from the Emma Children's Hospital AMC in Amsterdam and the Radboud University Nijmegen Medical Center, and their parents, were followed over time, three to five years after the end of successful cancer treatment.

Chapter 1 presents an overview of the research literature about social and emotional adjustment in paediatric survivors of cancer. The results are described in terms of self-esteem, anxiety, depression and post-traumatic stress (emotional adjustment) and in terms of behavioural functioning, social competence and school performance (socio-behavioural adjustment). Furthermore, factors related to survivors' adjustment are reported: demographics, illness- and treatment-related factors, coping and social support, family functioning and parental functioning. Limitations of the studies and consequences for future research are discussed.

In general, the adjustment of young cancer survivors as a group appeared to be reasonably good but the findings with respect to the emotional and social adjustment were inconsistent. This might be attributed to limitations of the study designs and the fact that the studies were not all comparable. In order to gain more insight into the predictors of adjustment, longitudinal studies are recommended which should include a control group or standardised instruments with normative data as well as cancer-specific measures in addition to generic measures.

Chapter 2 focuses on paediatric survivors of childhood cancer and their parents shortly after the end of successful treatment. Completing therapy is one of the major transitions in care in the practice of paediatric oncology and therefore deserves special consideration. HRQOL of 126 paediatric survivors and emotional reactions of 124 mothers and 111 fathers were studied two months after the end of successful treatment.

All age groups, except survivors aged 8–11 years, experienced worse HRQoL than the norm with respect to motor functioning. In addition, preschool survivors were rated worse on sleeping, appetite, stomach, skin, problem behaviour, anxiety and liveliness; survivors aged 6–7 years on autonomy and cognitive functioning. Parents reported more psychological distress than the norm. Compared to parents whose children were 1–5 years after cancer treatment, they suffered more from disease-related feelings of loneliness, helplessness and uncertainty. Supporting survivors and parents should not stop when treatment ends.

The purpose of **Chapter 3** is to identify psychosocial correlates of the HRQoL of paediatric cancer survivors shortly after completion of successful cancer treatment. In a cross-sectional study design, self-reported HRQoL of 52 survivors aged 8-15 years and parent-reported HRQoL of 54 survivors aged 1-5 years were predicted by cognitive coping, family functioning, parental emotional reactions, communication about the disease and several medical variables.

Better HRQoL was associated especially with more positive expectations of the further course of the disease, less-frequent parental queries regarding disease-related emotions of their children and lower levels of family adaptability. Several other psychosocial variables were indicative of better HRQoL but further research is needed to confirm and to understand the relation between psychosocial variables and HRQoL. Knowledge of psychosocial indicators of HRQoL could enable healthcare providers to give optimum support to the cancer survivors after the end of treatment.

In **Chapter 4**, we report about HRQoL in preschool survivors (aged 1-5 years) in the first three years after the end of successful treatment and about predictors of HRQoL. Parent-reported HRQoL was assessed in preschool children treated successfully for cancer and compared with normative data. Longitudinal analyses were performed to investigate to what extent demographic and medical variables and parental psychological distress were predictive of HRQoL over time. The data for patients who had relapsed were excluded from analysis from the moment of the relapse.

Compared to normative data, survivors exhibited worse HRQoL in several domains two months after the end of successful cancer treatment. They still showed more anxiety and worse motor functioning one year after the end of treatment. Two and three years after the end of treatment, however, survivors regained good HRQoL.

Longer duration of treatment, poor prognosis and greater parental psychological distress were associated with worse scores on physical HRQoL. Medical variables and parental psychological distress were not associated with mental HRQoL.

Chapter 5 focuses on HRQoL, anxiety and coping in school-aged survivors (aged 8-15 years) in the first four years after the end of successful treatment. Child-reported HRQoL of school-aged survivors was compared with normative data. Through longitudinal analyses it was investigated to what extent disease-related coping was associated with HRQoL and anxiety over time, controlled for demographic and medical variables. The data for patients who had relapsed were excluded from analysis from the moment of the relapse.

Compared to normative data, survivors reported only worse motor functioning (HRQoL) two months after the end of treatment. From one year after treatment, they no longer differed from the normative population in any HRQoL domain.

None of the medical variables appeared to be associated with HRQoL or anxiety. Female survivors reported higher levels of anxiety, which is common in the general population. Some correlations were found between cognitive coping and the outcomes. Firstly, survivors who

relied more heavily on the expertise of their physician and attributed power to the cancer treatment (vicarious control) reported better mental HRQoL. Secondly, survivors who were more optimistic about the further course of the disease (predictive control) experienced lower levels of anxiety, while those who searched more for information about the disease (interpretative control) reported higher levels of anxiety.

Chapter 6 describes parental emotional adjustment and coping in the first five years after the end of successful cancer treatment of their children. Psychological distress and situation-specific emotional reactions were assessed in mothers and fathers and compared with normative data. Longitudinal analyses were performed to investigate to what extent generic and disease-related coping, family functioning and social support were predictive of parental emotional functioning over time. The data for parents whose children had relapsed were excluded from analysis from the moment of the relapse.

Initial elevated levels of distress, disease-related feelings of uncertainty and helplessness returned to normal levels during the first two years after the end of treatment. Being more optimistic about the further course of the child's disease (*predictive control*) was associated with better emotional functioning, while higher family adaptability scores and having a more passive and palliative reaction pattern were related to worse emotional functioning.

Part II concerns the cross-sectional component of the VOLG-study. The survivors for this part of the study were recruited from the long-term follow-up clinic at the Emma Children's Hospital/Academic Medical Center in Amsterdam (PLEK), which was established in 1996 to monitor the long-term sequelae of childhood cancer and its treatment. In 2001 and 2002, the survivors of childhood cancer aged between 18 and 30, who attended the PLEK, were asked to complete questionnaires. An age-matched and sex-matched control group was formed with the help of the general practitioners of the survivors.

Chapter 7 presents an overview of the research literature about HRQoL in young adult survivors of childhood cancer. The results are described in terms of the following HRQoL dimensions: physical functioning and general health, psychological functioning (overall emotional functioning, depression and anxiety, self-esteem), social functioning (education, employment, insurance, living situation, marital status and family) and sexual functioning. Factors related to survivors' HRQoL are also reported: demographics and illness- and treatment related variables.

Although the literature yields some inconsistent findings, a number of clear trends can be identified: (a) most survivors reported being in good health, with the exception of some bone tumour survivors; (b) most survivors function well psychologically; (c) survivors of CNS-tumours and survivors of acute lymphoblastic leukaemia (ALL) are at risk for educational deficits; (d) job discrimination, difficulties in obtaining work and problems in obtaining health and life insurance were reported; (e) survivors have lower rates of marriage and parenthood; (f) survivors worry about their reproductive capacity and/or about future health problems their children might experience as a result of their cancer history.

There is a need for studies that measure HRQoL among survivors of childhood cancer more precisely by taking into account the effects of the severity of the cancer and the long-term impact of different treatments. Additional, psychosocial data are needed to help us understand the needs of survivors and to identify those subgroups of survivors who are at greatest risk for the adverse sequelae of the disease and its treatment.

Chapter 8 discusses HRQoL and coping in young adult survivors of childhood cancer. HRQoL of 353 Dutch young adult survivors of childhood cancer was compared with HRQoL of 507 peers without a history of cancer. In addition, survivors' HRQoL was predicted by cognitive coping, independent of the impact of demographics and medical variables.

The survivors reported lower HRQoL than their peers. Health status appeared to be the best predictor of the physical HRQoL, while survivors' health status and cognitive coping contributed almost equally strongly to the mental HRQoL. The explanatory value of cognitive coping was mainly attributed to the use of predictive control strategies; having positive expectations about the further course of the disease was related to better HRQoL. Because current coping seemed to be an important predictor of HRQoL, interventions directed at the coping strategies of survivors should be useful. The strong association between predictive coping and HRQoL stresses the importance of focusing at having positive expectations about the further course of the disease.

In **Chapter 9**, the achievement of milestones while growing up with childhood cancer is evaluated among 353 young adult survivors and compared with that of 508 peers without a history of cancer. The fulfilment of developmental tasks and achievement of developmental milestones while growing up, referred to as the 'course of life', are generally recognised to be of great importance to adjustment in adult life

The young adult survivors of childhood cancer turned out to have achieved fewer milestones with respect to autonomy development, social development, and psychosexual development, or to have achieved the milestones when they were older than their peers. In addition, survivors exhibited less risk behaviour. Survivors and peers also differed on a number of socio-demographic issues. A considerably lower percentage of survivors were married or living together and/or employed than was observed among their peers. Their educational level was as high as that of their peers. To conclude, knowledge about possible gaps in the course of life could enable healthcare providers to aim for the most favourable course of life. Moreover, optimal transition from paediatric to adult health care requires physicians with knowledge of the psychosocial history of growing up with childhood cancer.

Chapter 10 reports about the impact of medical factors on the course of life of survivors of childhood cancer and about the impact of the course of life, while growing up, on HRQoL in young adulthood.

From the data of 353 young adult survivors of childhood cancer it can be concluded that the survivors of brain tumours and survivors who had been treated with radiotherapy achieved fewer milestones in the psychosexual and social domains than did the other survivors, or reported having achieved the milestones when they were older. Survivors who had achieved fewer milestones in the social domain scored worse on HRQoL.

Healthcare providers should help to minimise the harm for children who grow up with cancer by encouraging social and psychosexual development. Children should be encouraged to make friends and to participate in peer activities.

In the final **Chapter 11**, all the information described in Part II is integrated into a model of determinants of HRQoL of young adult survivors of childhood cancer by testing the entire VOLG research model. A theoretical model is used in which demographic and medical characteristics explain HRQoL mediated by course of life, coping and social support.

Structural Equation Modeling (SEM) was performed to investigate the relationships among the variables and to test whether the model fitted the data.

The model proved to fit the data closely. The effect of medical and demographic characteristics on HRQoL appeared to be mediated by generic and disease-related coping. Course of life and social support had no significant mediating effects on HRQoL. Survivors who had been treated with both chemotherapy and radiotherapy were most at risk for worse HRQoL because they suffer more from current health complaints and were less inclined to predictive and active coping.

In conclusion, the results demonstrate the importance of interpreting HRQoL as outcomes based on both physical and psychosocial factors. The screening of survivors, both physically and psychosocially, could help to identify survivors with the greatest needs and to direct interventions by which the aftercare for survivors of childhood cancer could be improved.

The **General discussion** provides a summary and discussion of the results of the VOLG-study. The research questions are answered and salient findings are addressed, followed by a description of the strengths and limitations of the VOLG-study. This final section closes with a discussion of clinical implications and recommendations for future research.

The findings of the VOLG-study suggest that many survivors seem generally to cope well with the cancer experience and the (late) consequences of the disease and its treatment, although children growing up with childhood cancer seemed to be at risk of unfavourable course of life. On average, the differences between the HRQoL of the long-term survivors and that of their peers from the general Dutch population were small, with some survivors being more at risk of maladjustment than were others. The VOLG-study identified several psychosocial factors that were correlated with better or worse adjustment to the cancer experience. Insight into these factors may alert healthcare providers to survivors who are vulnerable to psychosocial problems and it may offer possibilities for intervention.

The results of the VOLG-study stress the importance of paying attention to the achievement of *developmental milestones*. For children and adolescents growing up with childhood cancer social adjustment and interaction with peers require special attention. The results of the VOLG-study show that it could be helpful to pay attention to ways in which survivors *cope* with their disease and with general life stressors, as some coping strategies appear to be more helpful than others. Interventions for survivors focusing on positive thinking could be useful because the results of the VOLG-study indicate that maintaining positive expectations about the further course of the disease is important.

Parental levels of distress and disease-related negative feelings appeared to return to normal levels during the first two years after the completion to treatment. This is in line with our findings from clinical practice, that it typically takes one to two years from the end of treatment for parents to feel relief and begin to believe that their children really will survive. Despite the overall resilience in parents over time found in the VOLG-study, continued support for parents is recommendable. It might relieve psychological distress in the first couple of years after the cessation of treatment and help parents to return to normal daily life. This is of utmost importance, as the emotional well-being of parents influences the well-being of survivors. It is important to understand that the emotional and behavioural reactions of parents are outcomes of a *coping* process in order to respond to these reactions more appropriately.

Although overall mean adjustment in survivors has been found to be near normal levels, a growing body of evidence suggests that more subtle or specific areas may be adversely affected in long-term survivors. Studies of paediatric psycho-oncological outcomes consistently identify a group of children and family members (estimated 25-30%) who do not cope well with the cancer or who have personal, family and social difficulties. Therefore, supporting survivors and their parents should not stop when treatment ends.

The monitoring and screening of survivors, both medically and psychosocially, has become standard aftercare in many hospitals in recent decades. Aftercare should be tailored to the needs of survivors and their parents, depending on the (developmental) age of the survivors as well as on the time since end of treatment. Standard aftercare should include psychosocial screening, education and counselling.

Psychosocial monitoring and screening is needed in order to trace problems in survivors and parents in an early stage, allowing appropriate support to be offered. It is important to pay attention to the achievement of developmental milestones, given the finding from the VOLG-study that cancer and its treatment can lead to an unfavourable course of life.

Psycho-education and counselling are recommended, as the provision of psychosocial information on the effects of the disease and treatment, and assisting parents in treating former patients as normally as possible could prevent psychosocial problems by enhancing re-entry into normal daily life. Psychologists could inform and support survivors and their parents, either individually or in groups. Psycho-educational support groups could be helpful, as group interventions offer possibilities for the sharing of emotions and experiences. Such interventions could also help both parents and survivors to integrate their experiences into their normal daily lives and to become accustomed to living with uncertainty concerning the recurrence of the disease and possible side effects. Group interventions could also be used for practising the skills and developing the cognitions that survivors need to integrate their experiences into their normal daily lives (e.g. what to tell friends about the disease, or how to deal with physical limitations in relation to activities with peers). It is important to note that attention should be given to the well-being of the siblings as well, given that cancer of a brother of sister can have a profound impact on the siblings. The effects of group interventions focused on long-term adolescent and adult survivors and/or the whole family have been promising but if mild or serious adjustment problems are present, psychological intervention is indicated.

The VOLG-study provided considerable information about the HRQoL of survivors over time and about factors that are probably predictive of HRQoL. The extensiveness of the VOLG-study could be considered both strength and weakness. Because it was impossible to study all aspects in depth several recommendations for future research can be identified: developing cancer-specific HRQoL measures appropriate for screening and monitoring patients in the period leading up to survivorship; developing a checklist of developmental milestones; establishing Minimal Clinically Important Difference (MCID) for paediatric HRQoL; Randomised Clinical Trials (RCTs) to test intervention effects which could also yield stronger evidence of causality of the correlations between psychosocial factors and HRQoL; longitudinal research on developmental milestones; research on the long-term psychosocial impact of physical late effects on the lives of adult survivors of childhood cancer.

Survivors should realize that they are "cured but at risk". They are cured from the original cancer but at risk of adverse effects and second malignancies. Life-long medical survey is therefore necessary. Efforts should be directed at encouraging survivors to attend the follow-up clinic without stigmatising or frightening them. Insight into survivors' perceptions of risk is needed. Finally, further steps in the direction of evidence-based interventions for survivors and their families are a challenge in the years to come.

Samenvatting

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Het krijgen van kanker op de kinderleeftijd (jeugdkanker) is een ingrijpende gebeurtenis die lange tijd na het einde van de behandeling nog fysieke en psychosociale gevolgen kan hebben. De behandeling van jeugdkanker is de afgelopen decennia ernorm verbeterd. Als gevolg hiervan bereiken veel patiënten de volwassenheid; patiënten die vroeger een beperkte levensverwachting hadden. Dit heeft geleid tot een sterke toename in het aantal overlevers en daarmee tot een toename van de noodzaak om onderzoek te doen naar de gevolgen van jeugdkanker.

De aanpassing aan de ziekte in de eerste jaren na het einde van de succesvolle behandeling, als ook de aanpassing in de jong-volwassenheid zijn de onderwerpen van dit proefschrift. Het beschrijft de resultaten van het VOLG (Vragenlijsten kinderOncologie Late Gevolgen)-onderzoek naar 'kwaliteit van leven, levensloop en coping van overlevers van jeugdkanker'. Het VOLG-onderzoek is in de jaren 2000-2006 uitgevoerd door de Psychosociale afdeling van het Emma Kinderziekenhuis AMC Amsterdam (EKZ AMC) met financiële steun van KWF Kankerbestrijding. Het VOLG-onderzoek is gericht op: 1) de psychosociale aanpassing van kinderen en adolescenten die opgroeien met jeugdkanker, en de emotionele aanpassing van hun ouders, in de eerste drie tot vijf jaar na het einde van de succesvolle behandeling 'op weg naar overleving' (longitudinaal deel van het VOLG-onderzoek), en 2) de psychosociale aanpassing van jong-volwassen overlevers van jeugdkanker (cross-sectioneel deel van het VOLG-onderzoek). Hoewel in het algemeen een periode van vijf jaar wordt beschouwd als criterium voor overleving, noemen wij de patiënten in het VOLG-onderzoek 'overlevers' omdat zij 'op weg zijn naar overleving'.

Het VOLG-onderzoek is onderdeel van de pediatrisch psychologische onderzoekslijn van het EKZ AMC, die is gericht op het bestuderen van de consequenties van het opgroeien met een chronische of levensbedreigende ziekte voor zowel de patiënten als hun ouders.

Dit proefschrift bestaat uit: Algemene Introductie, Deel I (longitudinale deel van het VOLG-onderzoek), Deel II (cross-sectionele deel van het VOLG-onderzoek), Algemene Discussie.

De **Algemene Introductie** beschrijft de achtergrond van het VOLG-onderzoek: medische aspecten van jeugdkanker, gezondheidgerelateerde kwaliteit van leven (GezKvL) en de opzet van het onderzoek.

Jeugdkanker is een zeldzame ziekte. Desalniettemin is het de tweede doodsoorzaak bij kinderen en de eerste doodsoorzaak door ziekte bij kinderen. Per jaar wordt in Nederland bij ongeveer 400 kinderen tot en met vijftien jaar kanker vastgesteld. Dat is 0.6 procent van de totale incidentie van kanker in Nederland. Van elke duizend volwassenen in Nederland hebben ongeveer twee personen kanker gehad in hun jeugd. Genezings- en overlevingscijfers zijn meestal gebaseerd op vijfjaarsoverleving. Voor de introductie van chemotherapie en radiotherapie, tussen 1960 en 1970, was jeugdkanker in de meeste gevallen dodelijk. De huidige vijfjaarsoverleving van jeugdkanker in Europa is meer dan 70% terwijl dat ongeveer 30% was tussen 1960 en 1970.

De meeste behandelingen bestaan uit chirurgie, chemotherapie of radiotherapie, of een combinatie hiervan. De aard van de behandeling hangt onder andere af van het type, de locatie en het stadium van de ziekte. Hoewel steeds effectievere en doelgerichtere behandelingen

mogelijk zijn, komen nadelige bijwerkingen op korte en lange termijn nog steeds veel voor. Onderzoek heeft uitgewezen dat 60 à 75% van de overlevers last heeft van late effecten van de ziekte en behandeling, die in ongeveer een derde van de gevallen kunnen worden aangemerkt als matig of ernstig.

De toenemende overlevingskansen voor kinderen met een ernstige ziekte heeft geleid tot een toenemende vraag naar uitkomstmaten die meer omvatten dan alleen kwantiteit van de overleving, zoals GezKvL. GezKvL heeft betrekking op de invloed van ziekte en gezondheid op het persoonlijk welzijn. Het is een multidimensioneel begrip dat tenminste de volgende domeinen omvat: fysiek, psychologisch en sociaal functioneren. Afhankelijk van de aard van de onderzoeksvraag en de beschikbare meetinstrumenten worden generieke, ziekte-specifieke of domeinspecifieke instrumenten gebruikt. Het meten van GezKvL is in de volwassenen oncologie zo langzamerhand gemeengoed geworden. GezKvL wordt bij kinderen minder vaak gebruikt als uitkomstmaat en er zijn nog geen kanker-specifieke meetinstrumenten voor kinderen beschikbaar die zijn gevalideerd en vertaald in het Nederlands.

In navolging van bestaande psychosociale verklaringsmodellen in de kindergeneeskunde en de geneeskunde voor volwassenen veronderstellen wij dat de aanpassing aan jeugdkanker (geoperationaliseerd als GezKvL) het resultaat is van een longitudinaal proces dat wordt beïnvloed door situationele- en ziektekenmerken, en door persoonlijke en psychosociale factoren (bijvoorbeeld levensloop, coping, sociale steun, familie functioneren en communicatie over de ziekte). Het VOLG-onderzoek richt zich vooral op de psychosociale factoren omdat wij veronderstellen dat deze veranderbaar zijn en een belangrijke rol spelen in de pediatrische psychologie.

Deel I beschrijft de resultaten van het longitudinale deel van het VOLG-onderzoek. In de jaren 2000 tot 2006 zijn overlevers van jeugdkanker uit het EKZ AMC en het UMC St Radboud Nijmegen, en hun ouders, drie tot vijf jaar gevolgd vanaf het einde van de succesvolle behandeling.

Hoofdstuk 1 geeft een overzicht van de literatuur over sociale en emotionele aanpassing van kinderen en adolescenten die opgroeien met jeugdkanker. De resultaten worden beschreven in termen van zelfwaardering, angst, depressie en posttraumatische stress (emotionele aanpassing), en gedragsmatig functioneren, sociale competentie en schoolfunctioneren (sociale en gedragsmatige aanpassing). Verder worden factoren beschreven die van invloed zijn op de aanpassing van overlevers: demografische kenmerken en ziekte- en behandelingskenmerken, coping en sociale steun, familie – en ouderlijk functioneren. Beperkingen van de studies en consequenties voor toekomstig onderzoek worden besproken.

Over het geheel genomen is de aanpassing van de jeugdige overlevers op groepsniveau goed te noemen maar de bevindingen zijn inconsistent. Dit zou kunnen worden toegeschreven aan beperkingen in de onderzoeksopzet en aan het feit dat de studies niet vergelijkbaar zijn. Longitudinale studies zijn nodig om meer inzicht te krijgen in factoren die van invloed zijn op de aanpassing aan de ziekte. Hierbij zijn controle groepen, gestandaardiseerde meetinstrumenten met normgegevens en kanker-specifieke meetinstrumenten als aanvulling op generieke instrumenten aanbevolen.

Hoofdstuk 2 beschrijft het welbevinden van 126 overlevers en hun ouders korte tijd na het einde van de succesvolle behandeling. Het einde van de behandeling wordt in de

kinderoncologie als een van de grootste overgangen in de zorg beschouwd. Daarom is speciale aandacht hiervoor op zijn plaats.

Alle leeftijdsgroepen ervaarden op motorisch gebied een slechtere GezKvL dan de norm, met uitzondering van de 8-11 jarige overlevers. De 6-7 jarigen scoorden bovendien slechter dan de norm in de domeinen autonomie en cognitief functioneren. De overlevers van 1-5 jaar scoorden slechter in de volgende domeinen: slaapproblemen, eetlust, maag- en buikklachten, huidproblemen, probleemgedrag, angst en levendigheid.

De ouders rapporteerden een slechter emotioneel welbevinden (psychological distress) dan de norm. Zij bleken ook meer last te hebben van ziekte-gerelateerde gevoelens van eenzaamheid, machteloosheid en onzekerheid dan ouders van kinderen 1-5 jaar na het einde van de behandeling voor jeugdkanker.

Het doel van **Hoofstuk 3** is het identificeren van psychosociale factoren die verband houden met de GezKvL van overlevers van jeugdkanker korte tijd na het einde van de succesvolle behandeling. In een cross-sectioneel design is de GezKvL van 52 overlevers in de leeftijd van 8-15 jaar en 54 overlevers in de leeftijd van 1-5 jaar voorspeld uit cognitieve coping, familie functioneren, ouderlijke emotionele reacties, communicatie over de ziekte en medische variabelen.

Een betere GezKvL bleek vooral samen te hangen met het hebben van positievere verwachtingen over het verdere verloop van de ziekte, het minder vaak vragen naar ziekte-gerelateerde emoties van het kind en met een lager niveau van family adaptability. Diverse andere psychosociale variabelen bleken ook samen te hangen met GezKvL maar verder onderzoek is nodig om deze bevindingen te bevestigen, en om de verbanden tussen de psychosociale variabelen en GezKvL beter te begrijpen. Kennis over psychosociale voorspellers van GezKvL stelt zorgverleners in staat overlevers en hun ouders optimaal te steunen.

Hoofstuk 4 beschrijft de GezKvL van 1-5 jarige overlevers in de eerste drie jaar na het einde van de succesvolle behandeling voor jeugdkanker, evenals de voorspellers van GezKvL. De GezKvL van 1-5 jarigen is vergeleken met normgegevens. Longitudinale analyses zijn uitgevoerd om te onderzoeken in welke mate demografische en medische variabelen, en ouderlijke emotioneel welbevinden (emotional distress) voorspellend zijn voor de GezKvL van de overlevers. De gegevens van kinderen die een recidief kregen tijdens het VOLG-onderzoek, zijn niet in de analyses betrokken vanaf het moment dat het recidief zich voordeed.

Twee maanden na het einde van de succesvolle behandeling hadden de overlevers op diverse gebieden een slechtere GezKvL. Een jaar na het einde van de behandeling was hun motorisch functioneren nog steeds slechter dan de norm en waren zij angstiger dan de normpopulatie. Echter, twee en drie jaar na het einde van de behandeling was hun GezKvL even goed als die van de norm.

Een slechte prognose, een langere behandelduur en slechter emotioneel welbevinden van de ouders hield verband met lagere scores op fysieke GezKvL. Medische variabelen en ouderlijk emotioneel welbevinden bleken geen verband te houden met mentale GezKvL.

In **Hoofdstuk 5** staan GezKvL, angst en coping van 8-15 jarige overlevers van jeugdkanker centraal. Hun GezKvL in de eerste vier jaar na het einde van de succesvolle behandeling is vergeleken met normgegevens. Longitudinale analyses zijn uitgevoerd om te onderzoeken in welke mate ziekte-gerelateerde coping voorspellend is voor GezKvL en angst, gecorrigeerd voor de invloed van medische en demografische variabelen. De gegevens van kinderen die

een recidief kregen tijdens het VOLG-onderzoek, zijn niet in de analyses betrokken vanaf het moment dat het recidief zich voordeed.

De overlevers rapporteerden twee maanden na het einde van de behandeling een slechtere GezKvL op motorisch gebied maar vanaf een jaar na het einde van de behandeling verschilden zij op geen enkel gebied meer van de normpopulatie.

Medische variabelen correleerden niet met GezKvL en angst. Vrouwelijke overlevers hadden hogere angstniveaus dan jongens, net zoals in de algemene bevolking. Enkele correlaties zijn gevonden tussen cognitieve coping en de uitkomsten. Ten eerste, naarmate overlevers een groter vertrouwen hadden in de arts en de behandeling (overgedragen beheersing) rapporteerden zij een betere GezKvL. Ten tweede, overlevers met positievere verwachtingen over het verdere verloop van de ziekte (predictieve beheersing) waren minder angstig, terwijl degenen die meer informatie zochten over de ziekte (interpretatieve beheersing) juist angstiger waren.

Hoofdstuk 6 beschrijft de emotionele aanpassing van de ouders in de eerste vijf jaar na het einde van de succesvolle behandeling van hun kind met kanker. Het emotioneel welbevinden (psychological distress) van de vaders en moeders en hun situatie-specifieke emotionele reacties zijn vergeleken met normdata. Longitudinale analyses zijn uitgevoerd om te onderzoeken in welke mate generieke en ziekte-gerelateerde coping, familie functioneren en sociale steun voorspellend zijn voor ouderlijk emotioneel functioneren. De gegevens van ouders wiens kind een recidief kreeg tijdens het VOLG-onderzoek, zijn niet in de analyses betrokken vanaf het moment dat het recidief zich voordeed.

De verhoogde niveaus van psychological distress en situatie-specifieke emotionele reacties die twee maanden na het einde van de succesvolle behandeling bestonden, daalden in de eerste twee jaar na het einde van de behandeling tot normale hoogte. Positievere verwachtingen over het verdere verloop van de ziekte (predictieve beheersing) was geassocieerd met beter emotioneel welbevinden, terwijl hogere scores op family adaptability, passieve en palliatieve reactiepatronen (generieke coping) geassocieerd waren met slechter emotioneel welbevinden.

Deel II betreft het cross-sectionele deel van het VOLG-onderzoek. De overlevers in dit deel van de studie zijn afkomstig van de Polikliniek Late Effecten Kindertumoren (PLEK) van het EKZ AMC, opgericht in 1996 met als doel de monitoring van lange termijn gevolgen (van de behandeling) van jeugdkanker. De PLEK-patiënten die in 2001 en 2002 18-30 jaar waren, zijn in die periode gevraagd vragenlijsten in het vullen in het kader van het VOLG-onderzoek. Dit is ook gevraagd aan een controle groep van leeftijdsgenoten, die via de huisartsen van de PLEK-patiënten zijn benaderd voor het VOLG-onderzoek.

Hoofstuk 7 geeft een overzicht van de literatuur over GezKvL van jong-volwassen overlevers van jeugdkanker. De resultaten worden beschreven in de volgende domeinen: fysiek functioneren en algemene gezondheid, psychologisch functioneren (algemeen emotioneel functioneren, depressie en angst, zelfwaardering), sociaal functioneren (opleiding, werk, verzekering, leefsituatie, burgerlijke staat) en seksueel functioneren. Verder worden factoren beschreven die van invloed zijn op de GezKvL van de jong-volwassen overlevers: demografische kenmerken en ziekte- en behandelingskenmerken.

Hoewel de literatuur enige inconsistente bevindingen laat zien, zijn de volgende trends aanwijsbaar: (a) de meeste overlevers hebben een goede gezondheid, met uitzondering

van overlevers van bottumoren; (b) het psychologisch functioneren van de meeste overlevers is goed; (c) overlevers van kanker in het centraal zenuwstelsel (CNS-kanker) en lymfatische leukemie (ALL) hebben een verhoogd risico op leerproblemen; (d) overlevers ervaren werkgerelateerde moeilijkheden zoals discriminatie, en problemen bij het afsluiten van levens- en ziektekostenverzekeringen; (e) huwelijk en ouderschap komt bij overlevers minder vaak voor dan in de algemene bevolking ; (f) overlevers maken zich zorgen over hun vruchtbaarheid en over mogelijke gezondheidsproblemen bij hun kinderen als gevolg van hun eigen geschiedenis van jeugdkanker.

Er is behoefte aan onderzoek dat GezKvL van jong-volwassen overlevers van jeugdkanker preciezer in kaart brengt dan tot dusver is gedaan. Hierbij dient ook de invloed van de ernst van de ziekte en de gevolgen van de behandeling op de lange termijn te worden onderzocht. Onderzoek naar de invloed van psychosociale factoren zou inzicht kunnen verschaffen in de behoeften van de overlevers en het mogelijk maken subgroepen van overlevers aan te wijzen met een vergroot risico op nadelige gevolgen van de ziekte en behandeling.

Hoofstuk 8 bespreekt GezKvL en coping van jong-volwassen overlevers van jeugdkanker. GezKvL van 353 overlevers in de leeftijd van 18-30 jaar is vergeleken met GezKvL van 507 leeftijdsgenoten die geen kanker hebben gehad. Daarnaast is de GezKvL van de overlevers voorspeld uit cognitieve coping, onafhankelijk van de invloed van demografische en medische factoren.

De overlevers rapporteerden een lagere GezKvL dan hun leeftijdsgenoten. Hun huidige gezondheid was de beste voorspeller van fysieke GezKvL. Aan hun mentale GezKvL droeg cognitieve coping evenveel bij als hun huidige gezondheid. De voorspellende waarde van cognitieve coping was vooral toe te schrijven aan het gebruik van predictieve beheersingsstrategieën; het hebben van positievere verwachtingen over het verdere verloop van de ziekte hing samen met een betere GezKvL. Gezien het positieve verband tussen predictieve beheersing en GezKvL lijken interventies gericht op het versterken van positieve verwachtingen over de ziekte zinvol.

In **Hoofdstuk 9** worden de ontwikkelingsmijlpalen die 353 jong-volwassen overlevers hebben bereikt terwijl zij opgroeiden met jeugdkanker, vergeleken met de mijlpalen van 508 leeftijdsgenoten zonder kanker in de voorgeschiedenis. Het vervullen van ontwikkelingstaken en bereiken van mijlpalen – levensloop genoemd – is van groot belang voor het welbevinden en voorkómen van aanpassingsproblemen in de volwassenheid.

De jong-volwassen overlevers van jeugdkanker bleken minder ontwikkelingsmijlpalen te hebben bereikt, of op latere leeftijd, dan hun leeftijdsgenoten. Zij scoorden lager in de domeinen van de zelfstandigheidsontwikkeling, sociale en psychoseksuele ontwikkeling. Zij vertoonden bovendien minder risicogedrag dan hun leeftijdsgenoten. Daarnaast verschilden zij op enkele socio-demografische uitkomsten. Een aanzienlijk kleiner percentage overlevers dan leeftijdsgenoten was getrouwd/samenwonend en/of had een betaalde baan. Hun opleidingsniveau was daarentegen niet lager dan dat van leeftijdsgenoten.

Kennis over mogelijke tekorten in de levensloop stelt zorgverleners beter in staat de levensloop van overlevers van jeugdkanker te stimuleren. Voor een goede overgang van de kindergeneeskunde naar de geneeskunde voor volwassenen is kennis wenselijk over de psychosociale voorgeschiedenis van patiënten die zijn opgegroeid met jeugdkanker.

Hoofdstuk 10 beschrijft de invloed van medische factoren op de levensloop van kinderen en adolescenten die opgroeien met kanker, en de invloed van de levensloop op GezKvL in de volwassenheid.

Uit de gegevens van 353 jong-volwassen overlevers van jeugdkanker is gebleken dat overlevers van hersentumoren en degenen die met radiotherapie zijn behandeld, minder sociale en psychoseksuele ontwikkelingsmijlpalen bereikten tijdens het opgroeien naar volwassenheid dan de andere overlevers. De overlevers die minder sociale mijlpalen in de ontwikkeling behaalden, rapporteerden als jong-volwassenen een minder goede GezKvL.

Zorgverleners zouden de nadelige invloed van jeugdkanker kunnen beperken door de sociale en psychoseksuele ontwikkeling te stimuleren. Kinderen en adolescenten die opgroeien met jeugdkanker, zouden moeten worden aangemoedigd te (blijven) deelnemen aan activiteiten met leeftijdsgenoten.

In **Hoofdstuk 11** wordt alle informatie die in Deel II van het VOLG-onderzoek is verzameld, geïntegreerd in één model van determinanten van GezKvL van jong-volwassen overlevers van jeugdkanker. De medische en demografische variabelen worden verondersteld van invloed te zijn op GezKvL via psychosociale factoren, namelijk levensloop, coping en sociale steun. Met behulp van Structural Equation Modeling (SEM) is getoetst of het VOLG-onderzoeksmodel past op de verzamelde data.

Het model bleek passend te zijn. Medische en demografische variabelen zijn via generieke en ziekte-gerelateerde coping van invloed op GezKvL. Levensloop en sociale steun hebben geen effect of GezKvL. Overlevers die zijn behandeld met zowel chemotherapie als radiotherapie lopen het grootste risico op een minder goede GezKvL omdat zij de meeste huidige gezondheidsklachten hebben en minder geneigd zijn tot predictieve beheersing en in mindere mate een actief reactiepatroon (generieke coping) hebben.

De resultaten benadrukken dat GezKvL moet worden gezien als het resultaat van zowel fysieke als psychosociale factoren. Het is daarom zinvol om overlevers zowel fysiek als psychosociaal te screenen zodat degenen bij wie een vergroot risico bestaat op een minder goede GezKvL, kunnen worden opgespoord en interventies kunnen worden ontwikkeld ter verbetering van de nazorg aan overlevers van jeugdkanker.

De **Algemene Discussie** vat de belangrijkste resultaten van het VOLG-onderzoek samen. Allereerst worden de onderzoeksvragen beantwoord en staan wij stil bij de belangrijkste resultaten. Daarna worden de sterke kanten en beperkingen van het VOLG-onderzoek besproken. De laatste paragraaf van dit proefschrift is gewijd aan de implicaties voor de klinische praktijk en aanbevelingen voor toekomstig onderzoek.

De resultaten laten zien dat overlevers van jeugdkanker over het algemeen goed kunnen omgaan met hun ziekte, de behandeling en de lange termijn gevolgen, hoewel zij een minder gunstige levensloop hebben dan hun leeftijdsgenoten. Op groepsniveau zijn de verschillen tussen de jong-volwassen overlevers en leeftijdsgenoten uit de algemene Nederlandse bevolking klein, waarbij sommige overlevers een grotere kans hebben op een minder goede GezKvL dan anderen. Het VOLG-onderzoek identificeerde diverse psychosociale factoren die geassocieerd zijn met GezkvL. Inzicht in die factoren kan zorgverleners attenderen op de overlevers met een vergroot risico op psychosociale problemen, en biedt aanknopingspunten voor interventies.

De resultaten van het VOLG-onderzoek benadrukken het belang van het bereiken van mijlpalen in de ontwikkeling. Voor kinderen en adolescenten die opgroeien met jeugdkanker zijn vooral sociale aanpassing en contacten met leeftijdsgenoten belangrijk. De resultaten laten ook zien dat het zinvol kan zijn om aandacht te besteden aan de manier waarop overlevers omgaan met hun ziekte (ziekte-gerelateerde coping) en met stressvolle situaties in het algemeen (generieke coping). Interventies gericht op het versterken van positief denken zijn aan te bevelen omdat het belangrijk is positieve verwachtingen te hebben over het verdere verloop van de ziekte.

Psychological distress en negatieve ziekte-gerelateerde gevoelens van de ouders daalden tot normale hoogte in de eerste twee jaar na het einde van de succesvolle behandeling van hun kind met kanker. Ondanks de veerkracht die wij bij de ouders in het VOLG-onderzoek hebben geconstateerd, is het zinvol hen te ondersteunen na het einde van de behandeling omdat het kan helpen het dagelijks leven weer op te pakken. Vermindering van ouderlijke psychological distress is van belang aangezien het emotioneel functioneren van ouders van invloed is op het welbevinden van kinderen. Om ouders goed te kunnen ondersteunen is het belangrijk dat zorgverleners de emotionele en gedragmatige reacties van de ouders begrijpen als uitkomsten van een coping proces.

Hoewel de algemene GezKvL van overlevers van jeugdkanker vrij goed is, worden er steeds meer aanwijzingen gevonden dat zij op specifieke gebieden wel degelijk nadeel ondervinden van het opgroeien met jeugdkanker. Uit studies in de pediatrische psycho-oncologie komt naar voren dat naar schatting 25-30% van de kinderen en hun familieleden problemen heeft als gevolg van de ervaring met jeugdkanker. Het betreft sociale problemen, persoonlijke – en gezinsproblemen. Ondersteuning en begeleiding van overlevers en hun gezin behoort daarom is niet te stoppen na het einde van de behandeling.

Screening en monitoring van overlevers, zowel fysiek als psychosociaal, is in de afgelopen decennia standaard nazorg geworden in veel ziekenhuizen. De nazorg moet zijn afgestemd op de behoeften van de overlevers en hun ouders, hetgeen afhankelijk is van de (ontwikkelings)leeftijd van de overlever als ook van de tijd die is verstreken sinds het einde van de behandeling. Nazorg omvat bij voorkeur psychosociale screening, psycho-educatie en counselling.

Door psychosociale screening en monitoring kunnen mogelijke problemen in een vroeg stadium worden opgespoord zodat passende hulp kan worden geboden aan de overlevers en/of het hele gezin. Hierbij is het van belang stil te staan bij de ontwikkelingsmijlpalen omdat het VOLG-onderzoek heeft uitgewezen dat opgroeien met jeugdkanker kan leiden tot een ongunstige levensloop.

Psycho-educatie en counselling kunnen de overgang naar het 'normale' dagelijks leven vergemakkelijken en daarmee psychosociale problemen voorkomen. Belangrijke elementen zijn het geven van psychosociale informatie over de mogelijke gevolgen van de ziekte en behandeling, en het helpen van de ouders om hun kind zo normaal mogelijk te behandelen in het gezin. Een psycholoog kan de informatie en ondersteuning zowel individueel of groepsgewijs geven. Groepsgewijze psycho-educatie heeft het voordeel van lotgenoten contact; uitwisseling van ervaringen en onderlinge steun. Het kan overlevers en ouders helpen hun ervaringen met de jeugdkanker te integreren in het dagelijks leven en te leren leven met de onzekerheden die de ziekte met zich meebrengt. Een groepsinterventie biedt ook mogelijkheden tot oefenen

van vaardigheden en ontwikkelen cognities. De effecten van interventies voor overlevers en/of het hele gezin zijn veelbelovend maar bij ernstige aanpassingsproblemen is psychologische hulp noodzakelijk.

Het VOLG-onderzoek heeft een enorme hoeveelheid informatie opgeleverd over overlevers die opgroeien met jeugdkanker, en hun ouders. De uitgebreidheid van het onderzoek kan zowel als een sterk als zwak punt van het VOLG-onderzoek worden aangemerkt. Het was onmogelijk om alle aspecten diepgaand te bestuderen zodat verscheidende aanbevelingen voor toekomstig onderzoek kunnen worden gegeven, waaronder: ontwikkeling van een kanker-specifiek GezKvL instrument dat geschikt is voor screening en monitoring van patiënten op weg naar overleving; ontwikkeling van een checklist van ontwikkelingsmijlpalen; het bepalen van Minimal Clinically Important Difference (MCID) voor GezKvL bij kinderen; Randimized Clinical Trials (RCTs) voor het vaststellen van de effecten van interventies voor overlevers en/of hun ouders, als ook voor het versterken van de bewijslast voor de causaliteit van verbanden tussen diverse psychosociale factoren en GezKvL; longitudinaal onderzoek naar ontwikkelingsmijlpalen; onderzoek naar de invloed van fysieke late effecten van jeugdkanker op het psychosociaal functioneren van volwassen overlevers.

De ontwikkeling van evidence-based interventions voor overlevers en hun ouders vormt een uitdaging voor de komende jaren. Daarnaast zijn inspanningen nodig om manieren te vinden waarmee wij overlevers kunnen stimuleren de PLEK te bezoeken zonder hen te stigmatiseren of angst aan te jagen. Hiervoor is inzicht in de risico-perceptie van overlevers vereist. Overlevers van jeugdkanker dienen zich te realiseren dat zij weliswaar genezen zijn van de oorspronkelijke kanker maar dat zij risico lopen op een tweede tumor en op nadelige gevolgen van de behandeling.

Dankwoord

Dankwoord

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Curriculum Vitae

Curriculum Vitae

Heleen Stam is op 17 december 1962 in Amsterdam geboren. Zij groeide op in Castricum, waar zij in 1981 het Gymnasium-β diploma behaalde aan het Bonhoeffer college. Aansluitend volgde zij de HBO-Jeugdwelzijnswerk (thans SPH) in Amsterdam en heeft vervolgens van 1985-1992 als groepsleidster gewerkt in Tehuis Annette (thans ondergebracht in Stichting Afra), een begeleidingscentrum voor ouders en jonge kinderen in Amsterdam.

Hierna heeft zij Gezondheidswetenschappen gestudeerd aan de Universiteit Maastricht, waar zij in 1995 cum laude afstudeerde in de richting Gezondheidsvoorlichting, met keuzevakken op het gebied van de Geestelijke Gezondheidkunde. Na ervaring te hebben opgedaan in verschillende onderzoeksinstellingen werkte zij vanaf 1996 bij het Trimbos-instituut te Utrecht. Hier heeft zij met veel plezier gewerkt aan diverse onderzoeksprojecten, aanvankelijk op het gebied van middelengebruik en gokken. Later betroffen haar onderzoekswerkzaamheden vooral effect- en procesevaluaties op het gebied van preventie van geestelijke gezondheidsproblemen.

In 2000 diende zich in het Emma Kinderziekenhuis AMC een interessant, langdurig KWF-project aan met de mogelijkheid tot promoveren. Het onderzoek 'Quality of life, course of life and coping in childhood cancer survivors' bood de unieke mogelijkheid haar ervaring met en interesse voor kinderen te combineren met onderzoek. Dit was voldoende reden om haar onderzoeksbaan bij het Trimbos-instituut te verruilen voor een baan als onderzoeker op de Psychosociale afdeling van het Emma kinderziekenhuis AMC, waar zij tot op heden werkzaam is. Naast het onderzoek dat is beschreven in dit proefschrift, is zij betrokken bij diverse onderzoeken die worden uitgevoerd op de Psychosociale afdeling.