

Guidelines for follow-up in survivors of childhood cancer 5 years after diagnosis.

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Guidelines for follow-up in survivors of childhood cancer 5 years after diagnosis.

Part 1

Guidelines from the Dutch Childhood Oncology Group (DCOG) / SKION

In conjunction with:

CBO

NHG

NIP

NIV

NOG

NVAB

NVK

NVMO

NVOG

NVRO

Orde

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VOKK

VRA

(for organisational full titles please refer to page 5)

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Preface

This booklet is the first part 1 of the guidelines for follow-up in childhood cancer survivors 5 years after diagnosis and is available on request from the SKION, Stichting Kinderoncologie Nederland, Leyweg 299, 2545 CJ Den Haag (ISBN 978 90 79691 03 6); email address: info@skion.nl.

Part 1 contains the introduction, the methodology and guidelines of all working parties and the formation of the working parties.

Part 2 (Diagnostics and consequences, scientific evidence) and part 3 (employment and social consequences together with organization of health care) are available online at www.skion.nl.

Initiating group

Task force LATER of the Dutch Childhood Oncology Group (DCOG / SKION)

Participating alliances

Organization for Integrated Cancer Centers (De Vereniging van Integrale Kankercentra VIKC)

Institute for Quality in Health Care (Kwaliteitsinstituut voor de Gezondheidszorg CBO)

The Dutch General Practitioner's society (Nederlands Huisartsen Genootschap NHG)

The Dutch Ophthalmological society (Nederlands Oogheelkundig Gezelschap NOG)

The Dutch Institute for Psychologists (Nederlands Instituut van Psychologen NIP)

The Dutch Society for Internal Medicine (Nederlandse Internisten Vereeniging NIV)

The Dutch Rehabilitation Physicians society (Nederlandse Vereniging van Revalidatieartsen VRA)

The Dutch society for Occupational Health Physicians (Nederlandse Vereniging voor Arbeids- en Bedrijfsgeneeskunde NVAB)

The Dutch Pediatric Society (Nederlandse Vereniging voor Kindergeneeskunde NVK)

The Dutch Society for Medical Oncology (Nederlandse Vereniging voor Medische Oncologie NVMO)

The Dutch society of Obstetrics and Gynaecology (Nederlandse Vereniging voor Obstetrie en Gynaecologie NVOG)

The Dutch society for Radiation Oncology (Nederlandse Vereniging voor Radiotherapie en Oncologie NVRO)

Medical Specialist Discipline (Orde van Medisch Specialisten)

Government Department for Unemployment and Social Security (Uitvoeringsinstituut Werknemers Verzekeringen UWV)

Parents Organization for Children with Cancer (Vereniging Ouders, Kinderen en Kanker VOKK)

The Dutch Nursing and Pediatric Nursing Society (Verpleegkundigen en Verzorgenden Nederland Kinderverpleegkunde V&VN)

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Dr. L.C.M. Kremer en Dr. A. Postma

Projectleaders

Chapter 1 Introduction

Indication for optimal care for survivors of childhood cancer more than 5 years after diagnoses

Chances of surviving pediatric cancer have considerably increased over the last thirty years. Over 70% of children who are being treated for pediatric cancer now will survive more than 5 years. However, 75% of these survivors will be confronted with several health and/or psychosocial issues, concerning their former disease and/or treatment strategy. These late effects will sometimes unexpectedly arise years after treatment and they are usually irreversible. They cause high mortality rates in pediatric cancer survivors compared to their peers (Geenen 2007, Blaauwbroek 2007, Mertens 2007, Oeffinger 2006, Cardous-Ubbink 2004).

Early detection and treatment of these late effects are of importance to prevent further health problems. This will contribute to enhanced good health and facilitates good quality of life.

Prognoses for 2010 is that 1 out of 250 young adults is a survivor of pediatric cancer and that, given the current survival analyses in the Netherlands, the total of survivors will increase with at least 300 persons per year.

The burden of disease for survivors of childhood cancer has, for a long time and still is in daily practice, been underestimated. Over the last 10 years several pediatric cancer centers have showed initiatives to optimize the care for this new group of former patients. Follow-up and treatment is available at unique survivor outpatient clinics for pediatric and adult survivors of pediatric cancer. Guidelines for follow-up for these survivors are different per cancer center. Until very recently no national guideline for survivors of pediatric cancer was available. The care is provided by pediatric oncology wards but not yet structural embedded in hospitals. Nationally and internationally, there is a consensus that combining care and knowledge is necessary.

The guideline aims for optimal care of survivors of pediatric cancer more than 5 years after diagnosis. It does not include information about follow-up time between last therapy and 5 years after diagnosis. This guideline is developed by a new national collaboration: the task group SKION LATER (long term effects after pediatric cancer). Formation of the task group SKION LATER originates from the SKION (The Dutch Childhood Oncology Group) by pediatric oncologists, radiotherapists, internal medicine specialists, general practitioners, psychologists and other disciplines embedded in care for survivors of pediatric cancer. The aim of SKION LATER is to optimize care for survivors of pediatric cancer by national and multidisciplinary collaboration in patient care, registration of data and research.

Experience has shown that patient care should be geared towards early detection of treatable diseases and suitable therapy regimens for these conditions. Furthermore, providing information and coordinating complex care involving different disciplines are also of importance. Availability of National Guidelines will lead to high standards of care for all survivors of pediatric cancer in the Netherlands. In addition, guidelines will facilitate the follow-up for all survivors and ensure that care for this high risk group is embedded in the health care system.

A project group for the guideline follow-up after pediatric cancer was assigned to monitor the process and three working parties were formed:

Working group 1. Diagnostic and therapeutic consequences

Working group 2. Employment and social consequences

Working group 3. Organization of health care

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4. Oeffinger KC, Mertens AC, Sklar CA, et al. Chronic health conditions in adult survivors of childhood cancer. *N Engl J Med*. 2006; 355:1572-1582.
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Chapter 2 Procedure

2.1 Procedure working group

The project group consisted of project leaders and representatives of pediatric oncology, internal medicine, radiotherapy, general practitioners and the patient organization group. The project group was responsible for monitoring the process and organization of this project. During the first half year the group had monthly (telephone-) meetings. To answer the various questions three working groups were formed with representatives from different disciplines. During the course of the project, meetings were conducted between members of the project group and the chairs of the three different working parties. It took just over one and a half years to complete the project.

The working group's content was multidisciplinary and included as many practitioners as possible from different disciplines, who were involved in the follow up for pediatric cancer patients. Representatives from the patient organization group and health insurances were also involved.

Different members of the working parties were asked by their professional organizations to participate in this project based upon their personal expertise and/or affinity to the subject. Members of the working group involved in formulating these guidelines had no relevant relationships with pharmaceutical industries to disclose.

2.2 Procedure working group 1 Diagnostic and therapeutic consequences

Working group 1. Diagnostic and therapeutic consequences consisted of representatives of pediatric oncology, radiotherapy, epidemiology, internal medicine, general practitioners, pediatric oncology nurses, the patient organization and a guideline advisor of the Institute for Quality in Health Care (Kwaliteitsinstituut voor de Gezondheidszorg CBO). Many other professionals of different disciplines were involved in the guideline development. Chairs of the working group were: dr. L. Kremer and dr. A. Postma. The working group continued the work previously performed by the task group SKION LATER. This task group analyzed research literature for problem definitions of eighteen different subjects as the first incentive for recommendations. Working group 1 started off with the analysis of a bottleneck issue (Part 2, attachment Analysis of a bottleneck, www.skion.nl), which was sent to a large group of professionals and representatives of the patient organizations. Eight hypotheses were formulated for which a thorough literature search was conducted. Searching strategies were performed by the Cochrane Childhood Cancer Group. The Institute for Quality in Health Care was asked to select studies, to review the selected studies and to summarize these. Results and recommendations of the working group were reported to the task group SKION LATER at two different meetings.

Below is an overview of the different areas in which health problems of patients can occur after treatment for pediatric cancer.

1. Secondary tumors (including secondary breast cancer)
2. Cardiology (heart)
3. Growth hormone
4. Gonadal function axis
5. Adrenal-axis
6. Thyroid function-axis
7. Osteoporosis

8. Fertility - female
9. Fertility - male
10. Pulmonology (lungs)
11. Nephrology (kidneys)
12. Hepatology (liver)
13. Spleen/Immune function
14. Neurology
15. Neuropsychology
16. Psychology
17. Weight
18. Audiology (hearing)
19. Ophthalmology (eyes)
20. Fatigue
21. Dental care (teeth)
22. Dermatology (skin)

To conceptualize recommendations for optimal care of survivors of pediatric cancer more than 5 years after diagnosis, the subsequent problem definitions were endorsed as of essential importance for health issues of above presented items:

1. Frequency side effect/incidence, prevalence.
What is the risk to reveal these health problems and is this a greater risk than in the normal population ?
2. Etiology.
What are risk predictors ?
3. Prognosis.
What is the time course ?
4. Diagnostic procedure.
Are the diagnostic procedures accurate to reveal treatable diseases at an early stage ?
5. Therapy
Is there an effective treatment ?

A summary for at least one hundred problem definitions was written by several participants. Former work conducted by the task force SKION LATER before this ZonMW-project was initiated was included. Furthermore two handbooks about late effects after pediatric cancer and international guidelines were used as fundamental concepts (H. Wallace, D. Green (eds): Late Effects of Childhood Cancer. Arnold, London 2004; C.L. Schwartz, W.L. Hobbie, L.S. Constine, K.S. Ruccione (eds): Survivors of Childhood and Adolescent Cancer. Springer Verslag Berlin-Heidelberg, 2005). Additional information from recent literature found through PubMed searching was added to the script. When there was consensus about recommendations no further systematic search or review of literature was conducted.

As previously mentioned, the working group completed a bottleneck issue analysis and eight problem definitions were selected for which an extensive search according to the evidence-based guidelines was carried out. This concerned problem definitions for heart, endocrinology (growth hormone axis), lungs, kidneys and hearing.

- What is the prognostic value of a reduced ejection or shortening fraction of the heart (asymptomatic cardiac failure) on the development of late clinical (asymptomatic) cardiac failure or death?
- What is the effect of interventions (ACE inhibitors, beta-blockers) in patients with asymptomatic cardiac failure on the development of late clinical (symptomatic) cardiac failure and mortality?
- What is the effect of growth hormone treatment in adults on quality of life, the cardiovascular system or bone mineral density?
- What is the time course to pulmonary dysfunction in survivors of childhood cancer?
- What is the prognostic value of microalbuminuria for renal dysfunction and cardiovascular disease?
- What is the effect of medication (like ACE inhibitors) for microalbuminuria on cardiovascular disease or mortality?
- Does treatment with carboplatin cause hearing toxicity? What is the time course of this occurrence?
- Which dose of scalp radiation induces hearing toxicity?

The Institute for Quality in Health Care (CBO) solved part of these problem definitions, another part was elaborated by members of the working group.

It was decided to give a brief conclusion in the body of the text regarding the level of evidence for the different questions about the frequency of an adverse effect, incidence, prevalence, aetiology, prognosis, diagnostics and therapy. This was possible for the majority of the questions. Where it has not been added, this will be addressed in the next version of the guidelines.

Classification of the methodological quality of individual studies (evidence based guideline development (EBRO) manual; www.cbo.nl)

	Intervention	diagnostic punctuality research	Damage or side effects, aetiology, prognosis
A1	Systematic review of at least two independently conducted studies of A2-level		
A2	Randomized double blinded compared clinical study of good quality and of adequate extent	Research according to a reference test (golden standard) with in advance defined cut off points and an independent review analysis of the results of the test and golden standard in an adequate volume of consecutive patients, all screened with the index- and reference test	Prospective cohort study with an adequate amount of patients and follow-up, monitored for 'confounding' and in which selective follow-up is excluded
B	Comparison study without all characteristics as mentioned in A2 (this includes patient-control studies and cohort analysis)	Research regarding a reference test but without all characteristics as mentioned in A2	Prospective cohort studies, but without all characteristics as mentioned in A2 or retrospective cohort studies or patient-control studies

C	Non-comparison studies
D	Expert opinion

Level of conclusions (evidence based guideline development (EBRO) manual; www.cbo.nl) (the description is adjusted according to the vision of the working group follow-up after childhood cancer)

	The conclusion is based on
Level 1	Research of level A1 or at least 2 independently conducted studies of level A2 It is proven that....
Level 2	1 study of level A2 or at least 2 independently conducted studies of level B It is probable that...
Level 3	1 study of level B or C There are indications that....
Lack of evidence	There is a lack of evidence that....

2.3 Procedure working group 2. Employment and social consequences

Working group 2 Employment and social consequences consisted of executives of occupational health physicians, pediatric oncology, internal medicine, nurses, health insurance physicians, rehabilitation medical specialists, patient organization group, neuropsychology, governmental department for unemployment and social security, a guideline expert and the project leaders (dr. A. Postma en dr. L. Kremer). Chair of this working group was Drs. T. Van Barneveld. The blueprint 'Employment in Guidelines' of the Dutch society for Occupational Health Physicians was used for developing this part of the guideline. The working group was assigned the task to formulate recommendations to improve employment participation and social functioning. The working group gathered for meetings in Utrecht and in addition participated in several telephone conference calls. For the selected problem definitions (questions) of this working group a search of literature was conducted by the Coronel Institute (AMC, Amsterdam). The working group discussed the summary of literature and the recommendations were formulated. These recommendations were again discussed in the task group SKION LATER.

Problem definitions (questions):

- What are the prospects for employment (defined as paid work) and the risks for (partially) unemployment or (partially) incapacitated or social payment in survivors of childhood cancer compared to a population without a history of childhood cancer?
- What are the risk factors for (partially) unemployment or (partially) incapacitated or social payment in survivors of childhood cancer?
- What are the consequences for quality of life of problematic job achievement, unemployment and/or incapacity for survivors of childhood cancer?
- Which interventions improve employment participation for survivors of childhood cancer or children/adolescents with chronic diseases such as asthma, epilepsy, congenital heart disease, rheumatism, diabetes or haemophilia (and its disabilities)?
- Is the education level of survivors of childhood cancer decreased in comparison to a population without a history of childhood cancer? And if so, what are the chances for employment (defined as paid jobs) and the risk for (partially) unemployment or (partially) incapacitated or social

payment in survivors of childhood cancer subgroups with a diminished level of education compared to a population without a history of childhood cancer but with the same level of education?

2.4 Procedure working group 3. Organization of health care

Working group 3 Organization of health care consisted of representatives of pediatric oncology, internal medicine, general practitioners, radiotherapy, health insurance companies, managers, parent organization, nurses, executives of all seven pediatric oncology departments and the project leaders dr. A. Postma en dr. L. Kremer). Chairman was Prof. Dr. W.A. Kamps, Professor of pediatric oncology, Groningen,. The working group assigned to formulate recommendations for organization of care for survivors of childhood cancer. The working group gathered for meetings in Utrecht and in addition participated in several telephone conference calls.

The Institute for Quality in Health Care (CBO) conducted a review of literature in collaboration with the Cochrane Childhood Cancer Group. By this review of the literature information was obtained for

- Systematic obtained opinions of patients and professionals about requirements for follow-up
- Already implemented models for follow-up procedures
- Effects of these implemented models
- Other proposed feasible models

In November 2008 an 'open-space' meeting was organised in Amersfoort to create an inventory of the opinions of the target group (professionals and survivors) (www.openspaceworld.org). Participants brought forward themes at this meeting which were discussed in light of the following questions:

1. Is a specific outpatient clinic for long-term effects after childhood cancer necessary? This question, raised by the chair in his introduction, was also to initiate further discussions.
2. If ever, periodical controls are needed, where and by whom should they be accomplished?

Furthermore participants from the professional and survivor group introduced several themes to be further discussed together. Most time-consuming was the discussion of topics associated with question 2. This suggests that question 1 might be seen as a rhetorical, despite the fact that the requirement for a specialized outpatient clinic was explicitly mentioned as a discussion point during the introduction. The statement of one of the participants was significant, and as such, was stated: 'Because of the patient history one has a right for specialized care by specialists in childhood cancer'. Further report of this meeting can be found in part 3 (www.skion.nl). The review of literature and the findings from the open space meeting formed the basis for the recommendations about organization of care.

2.5 Procedure task group SKION LATER & other projects

The task group SKION LATER (late effects after childhood cancer) originates from the Dutch Childhood Oncology Group (SKION). The task force SKION LATER did a great deal of work in advance of this guideline during the two years before the ZonMW-project was initiated. Furthermore a patient website for survivors of childhood cancer 5 years after diagnosis, was developed, by the task group SKION LATER (www.later.skion.nl). Since 2004 KiKa and KWF have sponsored the initiative to develop the Dutch SKION LATER registration of all survivors of childhood cancer 5 years after diagnosis (www.later.skion.nl). In addition, a steering committee of SKION LATER was established in which

representatives of all academic centers were assigned to develop and implement a national research protocol. Gaps in knowledge as observed during the development of these guidelines will also be used as starting point for this initiative.

Chapter 3

Recommendations

3.1 Recommendations working group

1. Diagnostic and therapeutic consequences

General Recommendation

For whom?

All survivors attending the LATE effect out-patients clinic

Which diagnostic test ?

Clinical history and examination

General advice

- Do not smoke
- Moderate alcohol intake
- Adequate exercise
- Maintain a healthy weight, i.e. BMI between 20 and 25 kg/m²
- Maintain a balanced healthy diet i.e. low in saturated fats, high in fiber and recommended amount of fresh fruit and vegetables
- Avoid excessive exposure to sunlight and reduce sunbathing.

In survivors who are pregnant

- Following cardio-toxic medication: be aware of the possibility of progressive (sub) clinical heart failure induced by increased circulatory load, especially in the third trimester of pregnancy. (see also part 2: Heart, www.skion.nl).
- Be mindful of subclinical hypothyroidism; consider early intervention of latent hypothyroidism during pregnancy in light of the possible damage to the fetus.
- Be aware of hypertension following previous nephrotoxic medications

Secondary tumors

Recommendation

Following treatment for childhood cancer there is an increased risk of secondary tumor development in various organs and tissues, which persists during the entire follow-up period, even after a considerably long time interval.

Second tumors occur following all modalities of treatment, but especially following radiotherapy and usually (but not always) in or around the edge of the irradiated area.

For whom?

All survivors of childhood cancer

Which diagnostic test?

Guided by the clinical signs and symptoms

General advice

- Active screening for secondary tumors is only recommended for secondary breast cancer in female survivors (see secondary breast cancer).
- For secondary tumors following treatment for retinoblastoma will be available in a separate chapter in the next version of the guidelines.
- For other possible secondary tumors no specific screening is recommended, as such specific diagnostic tests will only be undertaken if clinically indicated,
- In survivors of childhood cancer with rare genetic syndromes associated with an increased risk of developing cancer (including hereditary retinoblastoma) we recommended screening to be undertaken in collaboration with the treating physician and/or clinical geneticist according to the established national guidelines.
- All those surviving more than five years following diagnosis, especially those who have undergone thoracic radiotherapy, should be made aware of the importance of stopping/or not starting to smoke.

Secondary breast cancer

Recommendation

For whom?

- Female survivors having undergone radiation to the chest area
- For patients with a family history please check the national guidelines for breast cancer (NABON)
- For other groups see the recommendations of the National Breast Cancer Screening Program (BOB)

Which diagnostic test?

- Clinical breast examination by a specialist in this field
- Mammogram
- MRI
- In accordance with the National Breast Cancer Screening Program (BOB)

Frequency

Survivors in the **VERY HIGH** risk group (in accordance with the national NABON breast cancer guidelines)

- 25-60 years old - once a year MRI
- 30-60 years old - annual mammogram
- 25-60 years old - annual clinical breast examination
- 60-75 years old - participation in BOB
- Following preventative surgery no indication for controls

Survivors in the **HIGH** risk group (in accordance with the national NABON breast cancer guidelines)

- 35-60 years old, annual mammogram and clinical breast examination to be carried out by a specialist in the field, for instance the breast clinic or LATER outpatients clinic
- 60-75 years old participation in BOB

OTHER survivors (in accordance with the National Breast Cancer Screening Program (BOB))

Risk classification

*Survivors with an **EXTREMELY HIGH** risk*

Women with a family history, regardless of past radiation exposure:

Screening as described above for the VERY HIGH risk. To be carried out by the out-patient clinic for hereditary/familial tumors with the involvement of a multi-disciplinary team

This involves:

- Women with a proven BRCA1/2 mutation
- Women with 50% chance thereof, regardless of past radiation exposure. Women without a family history with an estimated breast dose of 20 Gy or more or TBI regardless of dose: Screening as described above for the VERY HIGH risk in the LATER out-patient clinic or by a specialist in this field, coordinated by the LATER outpatient clinic.

This involves:

- Female patients who received radiation to the chest (breast, thorax, lungs, mantle, axillary) with a tumor dose of 20 Gy or more
- Female patients who received radiation to the whole abdomen with the diaphragm in the radiation field with a tumor dose of 40 GY or more: and an estimated nipple dose of 20 GY or more

- Ipsilateral breast of female patients following hemi-abdominal or hemi-flank radiation with the diaphragm in the radiation field with a tumor dose of 40 Gy or more (see other considerations)
- All women who have received TBI irrespective of the dose of radiation

*Survivors with a **HIGH** risk*

Women without a family history with an estimated breast dose of 7-19 Gy, excluding TBI:

Screening as described above for the HIGH risk in the LATER outpatient clinic or by a specialist in this field, coordinated by the LATER outpatient clinic.

This involves:

- Female patients who received radiation to the chest (breast, thorax, lungs, mantle, axillary) with a tumor dose of 7-19 Gy
- Female patients who received radiation to the whole abdomen with the diaphragm in the radiation field with a tumor dose of 14-39 Gy or more: and an estimated nipple dose of 7-19 Gy
- Ipsilateral breast of female patients following hemi-abdominal or hemi-flank radiation with the diaphragm in the radiation field with a tumor dose of 14-39 Gy

Other survivors

Women without a family history with an estimated breast dose of 0-6 Gy, excluding TBI:

No extra screening for breast cancer other than BOB.

Consequences (possible therapy or referral)

Treatment for breast cancer should preferably be undertaken in an academic center (University Medical Center) or a specialized cancer center because of the important aspect of previous treatments for childhood cancer

General advice

Survivors in the risk groups for developing breast cancer should be given information about self breast examination in accordance with the leaflet produced by the Dutch Cancer Society (KWF) namely "Self examination of the breast".

Cardiology (Heart)

Recommendation

For whom?

- Following anthracyclines
- Following radiotherapy in the region of the heart
- Following mitoxantrone

Which abnormalities can occur?

- Heart failure
- Arrhythmias
- Valvular abnormalities
- Myocardial infarction

Which diagnostic test?

- Echocardiography:- left ventricular function (shortening fraction or ejection fraction), examination of the valves. If echo examination is not possible e.g. because of adiposity, a nuclear ejection fraction may be carried out
- ECG/Blood pressure/BMI

Frequency

Echocardiography

- Anthracyclines (doxorubicine, epirubicine, daunorubicine):
 - $< 300 \text{ mg/m}^2$: Once every 5 years
 - $\geq 300 \text{ mg/m}^2$: Twice every 5 years or dependent on other concerns once every three years
- Anthracyclines and radiotherapy in the region of the heart:
 - Twice every 5 years
- Radiotherapy in the region of the heart without anthracyclines:
 - $< 30 \text{ G}$: Once every 5 years
 - $\geq 30 \text{ G}$: Twice every 5 years or dependent on other concerns once every three years
- Mitoxantrone:
 - $> 40 \text{ mg/m}^2$: Once every 5 years

ECG

As a baseline one time evaluation 5 years following diagnosis, and thereafter not a standard investigation. Later if there are clinical concerns a new ECG can be made and compared to the baseline. In the event of detected abnormalities refer to a cardiologist.

Consequences (possible therapy or referral)

Actions based on abnormal echocardiographic results:

- SF $\geq 30\%$, EF $\geq 50\%$, + no other abnormalities:
controls continue unchanged

- SF \geq 30%, EF \geq 50%, but with other echocardiographic abnormalities such as:
Dilated left ventricular diameter, abnormal valve, abnormal E/A-ratio, left ventricular hypertrophy, wall movement disorders or relevant chance findings (e.g. ASD): refer to cardiologist
- SF 25%-29%, EF 45%-49% consult with/refer to cardiologist (consider treatment with ACE-inhibitors)
- SF < 25%, EF < 45% refer to cardiologist

Treatment with ACE-inhibitors or β blockers in survivors of childhood cancer with asymptomatic left ventricular dysfunctions (following radiotherapy or anthracyclines) should preferably be undertaken in a research setting.

General advice

- Consider total cholesterol/HDL/LDL in (a)symptomatic left ventricular dysfunction.
- Advice on life style: no smoking, adequate exercise and healthy diet

Endocrinology growth hormone

Recommendation

For whom?

- Following radiation to the head and neck region
- Following TBI
- Brain tumor in the hypothalamus or hypophyseal region

Which abnormalities can occur?

Growth hormone deficiency (GHD)

Which diagnostic test?

- ≤ 18 years: growth chart & IGF-1
- > 18 years: IGF-1

Note: A IGF-1-concentration within the (age specific) reference values does not exclude GHD. So with a "normal" IGF-1-concentration and a (clinical) suspected GHD, or when there are other abnormalities of the pituitary axis, additional tests (GH stimulation tests) are required.

Frequency

- ≤ 18 years: annually
- > 18 years: Once per 3 years

Consequences (possible therapy or referral)

- ≤ 18 years:

○ In case of falling off the growth curve, or delayed growth spurt at puberty, or growth outside the target range: refer to pediatric endocrinologist.

○ In case of a low IGF-1-concentration (see age specific references) with normal growth: repeat the IGF-1-concentration measurement after 6 months and if once again abnormal: discuss with pediatric endocrinologist.

○ In case of non-increasing IGF-1-concentration in puberty: repeat the IGF-1- concentration measurement after 6 months and if once again abnormal: discuss with pediatric endocrinologist.

- > 18 years:

In case of a low IGF-1-concentration: refer to an endocrinologist (indicate whether oral contraceptives are used).

Endocrinology gonadal axis

Recommendation

For whom?

All survivors

Which abnormalities can occur?

- Hypogonadotrophic hypogonadism or hypergonadotrophic hypogonadism
- Pubertas praecox

Which diagnostic test?

- Before and during puberty:

Physical examination: Tanner-stadia (boys: also testicular volume)

- After completion of puberty:

Clinical history and physical examination: inspection (and optional palpation) of external genitalia (men: also testicular volume)

Frequency

At the LATER-out-patient visit (all survivors)

Consequences (possible therapy or referral)

- When evidence of pubertas praecox: refer to pediatric endocrinologist.

Criteria pubertas praecox:

○ Girls: Breasts development + pubic-/axillary hair < 8 years, menses < 10 years

○ Boys: testicular volume growth ≥ 4 ml + enlargement of the penis < 9 years

- When evidence of pubertas tarda: refer to pediatric endocrinologist.

Criteria pubertas tarda:

○ Girls: Absence of secondary sexual characteristics (Tanner stadium M2) when > 13 years

○ Boys: Absence of secondary sexual characteristics (Tanner stadia G2 and/or P2) when > 14 years

- When evidence of hypogonadism: Additional tests LH/FSH/oestradiol/testosterone (check testosterone levels in the morning after fasting for 10 hours) and/or refer to a pediatric endocrinologist (≤ 18 years) or endocrinologist (> 18 years)

Endocrinology Adrenal axis

Recommendation

For whom?

Following high dose cranial irradiation (≥ 50 Gy), or lower dose cranial irradiation and failure of other pituitary axes; these survivors are probably already being seen by an endocrinologist

Which abnormalities can occur?

Adrenal insufficiency due to ACTH-deficiency

Which diagnostic test?

Plasma cortisol concentration, as early as possible in the morning (08:00 to 09:00 am)

Note: in case of suspicion of hypocortisolism (cortisol < 550 nmol/l) this should be confirmed by an adrenal-axis functional test via a pediatric endocrinologist.

Frequency

- In case of clinical suspicion of hypocortisolism or failure of other pituitary axes
- In any case once 5 year after diagnosis

Consequences (possible therapy or referral)

Provide information about the importance of taking extra cortisol in situations of illness, stress, etc. Hypocortisolism is a reason to wear an SOS armband or necklace.

Endocrinology thyroid axis

Recommendation

For whom?

- Following radiotherapy to the neck region
- Following TBI
- Following 131-I-MIBG-therapy

Which abnormalities can occur?

- Hypothyroidism en hyperthyroidism
- Benign nodule
- Thyroid cancer (carcinoma)

Which diagnostic test ?

- Plasma FT4 and TSH
- Palpation of the thyroid during out-patient visit

Note: Following irradiation of the head central hypothyroidism can occur, in which the TSH concentration is not very informative. A FT4 concentration below the (age specific) reference values is a reason for referral, especially for those planning a pregnancy

Frequency

- ≤ 18 years: annually
- > 18 years: once per 2 to 3 years

Consequences (possible therapy or referral)

- When abnormal FT4- or TSH-concentration: refer to (pediatric-)endocrinologist
- In the case of a palpable nodule discuss with/refer to (pediatric) endocrinologist for analysis, echography and/or scintigraphy, and optional cytological puncture
- Subclinical or (developing) central hypothyroidism in pregnancy or in those wishing to become pregnant: early treatment to prevent possible embryonal damage

Osteoporosis

Recommendation

For whom?

All survivors of childhood cancer

Which diagnostic test ?

- Clinical history focused on symptoms of osteoporosis (pain or fracture) and risk factors (lack of physical activity, poor nutrition and underlying disease)
- When osteoporosis is clinically suspected: X ray of the spine and bone density measurement (BDM) or quantitative CT scans

Frequency

At the LATER-out-patient visit and/or on indication

Consequences (possible therapy or referral)

- When evident osteoporosis and osteonecrosis refer to or discuss with a specialist, (pediatric) endocrinologist or internist. In the case of BMD $<-2SD$, consider drug treatment following consultation with an appropriately qualified specialist.

Consider blood and urine tests: calcium, phosphate, alkaline phosphatase, 2-OH vitamin D, PTH, urine calcium, creatinine en phosphate

- In the case of osteonecrosis: refer to an orthopedic surgeon

General advice

For the prevention of osteoporosis weight bearing exercise is recommended

Fertility -female

Recommendation

For whom?

All female survivors

Which abnormalities can occur?

- Cycle abnormalities, and as a consequence infertility or sub-fertility.
 - Hypergonadotrophic hypogonadism in which amenorrhoea may or may not occur (primary/premature ovarian failure, primary ovarian insufficiency)
 - Acute failure of ovarian function, and as a consequence depletion of oestrogen and infertility (acute climacteric praecox)
 - Later: premature menopause, and as a consequence sub-fertility, a shorter reproductive period (climacteric praecox) and increased risk of menopausal related complaints such as osteoporosis (see recommendations [Osteoporosis](#))
 - Hypogonadotrophic hypogonadism (often associated with amenorrhoea)
 - Hypophyseal/hypothalamic damage
 - Stress/malnutrition and poor general condition
- Abnormal course of pregnancy and abnormal pregnancy outcomes

Which diagnostic test ?

- Cycle history in all survivors; in those using hormonal ant conception (oral or by Mirena coil), document periodicity before their use
- In the absence of cycle for more than 3-6 months or a highly irregular cycle (intervals of more than 35 days) without the use of hormonal contraception: consider determination of FSH and oestradiol before referring to gynaecologist.
- No standard screening; on indication only

Frequency

At the LATER-out-patient visit and/or on indication

Consequenties

- Consider hormonal replacement in premature ovarian failure (see guideline [Endocrinology gonadal axis](#))
- Refer to a specialist to/for:
 - Unfulfilled wish for pregnancy
 - Questions over fertility
 - Specific antenatal care in those with previous abdominal/ uterine/pelvic radiotherapy.
 - Previous abnormal pregnancy outcome
 - Information on fertility treatments

General advice

- Information on the possibility of sub-fertility and early menopause
- Information on abnormal course of pregnancy in certain risk group categories

Fertility -male

Recommendation

For whom?

All male survivors

Which abnormalities can occur?

- Infertility
- Subfertility

Which diagnostic test?

On indication only

Consequences (possible therapy or referral)

- On request of the survivor: semen analysis
- When azoöspemia/hypospermia and desire for children: refer to a fertility center

NB Consider freezing semen at diagnosis!

Pulmonology (lungs)

Recommendation

For whom?

Survivors who have received treatment with

- Bleomycine, busulfan, nitrosurea derivatives
- Radiotherapy to (a part of) the lungs, mediastinum, spine, TAI/TBI
- Surgery to the lungs or thoracic skeleton

Which abnormalities can occur?

- Recurrent respiratory infections and chronic cough
- Lung function (LF)-abnormalities: obstructive and/or restrictive and/or diffusion abnormalities
- Lung fibrosis
- Thoracic deformities and growth abnormalities

Which diagnostic test ?

Long function test: flow-volume curve, diffusion capacity and determination of lung volume (FVC and/or TLC by means of FV-curve and/or body plethysmography)

Frequency

5 and 10 years after diagnosis; If no abnormalities (> 75% predicted), then stop

Consequences (possible therapy or referral)

- Preventative measures* if
 - o FEV1%VC, TLC and/or TLCOc/VA < 75% predicted, or if these parameters have at least a 20% reduction from the baseline values.
 - o Recurrent respiratory infections/ chronic cough occur

* *Influenza vaccination, advice of career choice (avoid toxic substances), if symptomatic consider referral to a pulmonologist.*

- No exposure to FiO₂>30% following bleomycine > 400 mg/m² or demonstrated damage after bleomycine and/or radiotherapy to the thorax.

NB This also applies to O₂-inhalation in sports such as scuba-diving

General advice

Do not smoke

Nephrology (Kidneys)

Recommendation

For whom?

Survivors who have received treatment with

- Carboplatin, cisplatin, ifosfamide
- Radiation to the renal area
- Nephrectomy
- BMT with or without TBI

Which abnormalities can occur?

- Reduced glomerular filtration
- Tubular function abnormalities

Which diagnostic test ?

- History: Use of anti-hypertensives/supplements
- Physical examination: Blood pressure, length
- Glomerular function

In case of survivors treated with carboplatin, unilateral renal radiation, or unilateral nephrectomy

o Blood: creatinine

o Urine: albumin, creatinine

- Glomerular function en Tubular function

In case of survivors treated with ifosfamide, cisplatin, bilateral renal radiation, partial bilateral nephrectomy, BMT with or without TBI

o Blood: creatinine, K, Mg, P, bicarbonate

o Urine: albumine, creatinine, α 1-microglobuline, K, Mg, P

Frequency

Once every 5 years

Consequences (possible therapy or referral)

An abnormal value is an indication for an earlier control e.g. after 1 year in the LATER- outpatient clinic

- Referral to a nephrologist: if on repeat testing an abnormal finding is confirmed, by:
 - hypertension: Dynamap-measurement following a rest period to avoid 'white coat hypertension'
 - MDRD-GFR or Schwartz-GFR < 90 ml/min/1.73 m²
 - microalbuminuria > 2.3 mg/mmol creatinine
 - metabolic acidosis, in which the bicarbonate is below 19 (meaning that referral is needed at a bicarbonate concentration under 19)
 - significant abnormalities of serum electrolyte concentrations: K $< 3,3$ mmol/l; Mg $< 0,6$ mmol/l; phosphate below the age corrected reference values in combination with increased fractional excretion and/of TmP/GFR $< 0,90$ in post-pubertal patients or $< 1,2$ in pre-pubertal patients

Note: For the management of microalbuminuria in diabetic patients follow the advice NHG-Standard Diabetes Mellitus. In the case of non-diabetics it is still unclear whether ACE inhibitors have an effect. In the absence of evidence to the effectivity of ACE inhibitors for microalbuminuria (other than in diabetes mellitus) the indication for the use of ACE inhibitors is determined by the blood pressure and not the microalbuminuria.

The above advice is in accordance with the CBO guidelines/ NHG-Standard Cardiovascular Risk Management guidelines.

Hepatology (Liver)

Recommendation

For whom?

Survivors who have received treatment with

- Surgery of the liver
- Radiotherapy of (or part of) the liver (>20 Gy of the whole liver or > 40Gy of > 1/3 of the liver or TBI)
- Chemotherapy with busulphan, methotrexate, dactinomycin, 6-mercaptopurine or 6-thioguanine
- Or those who have in the past experienced VOD or GVHD of the liver

Which abnormalities can occur?

- Liver fibrosis/liver cirrhosis
- Focal nodular hyperplasia and steatosis

Which diagnostic test?

- ALAT, ASAT, gGT
- HBV and HCV serology (In all survivors of childhood cancer this should be tested once if the results are unknown)

Frequency

First LATER-out-patient visit: All patients who fulfill the above criteria

For patients who have undergone surgery, radiotherapy (as above), or those who have experienced GVHD or VOD, this should be repeated every 5 years,

Consequences (possible therapy or referral)

In case of increased liver enzyme values (>2x normal) at at least two time points taken after a window of 6 weeks, additional investigations should be undertaken to ascertain a possible underlying cause in discussion with or after referral to a hepatologist. Examples of diagnostic tests that should be considered are functionality of the liver (albumin, bilirubin, clotting (INR)), virus serology (CMV, EBV, HBV), ferritin, auto-antibodies (IgG total, ANA, ANCA, anti-SMA, anti-LKM, anti-microsomal AL), ultrasound of the liver, test to diagnose Wilson's disease (copper, ceruloplasmin, 24 hours urine sample for copper, identify Kayser-Kleischer rings by an ophthalmologist) and diagnostic test for celiac disease (IgA total and IgA-anti tissue transglutaminase).

General advice

In the case of increased liver enzyme values: avoid alcohol and medication that is metabolized via the liver (or use of altered dose)

Spleen/immune function

Recommendation

For whom?

- In case of survivors who have undergone splenectomy
- In case of survivors who have undergone radiation therapy to the splenic area

Which abnormalities can occur?

Life threatening infections (sepsis) with encapsulated bacteria most commonly, pneumococci

Which diagnostic test?

- Following radiation to the spleen: screen for Howell-Jolly bodies
- Following splenectomy: see general advice

Frequency

Once after the end of treatment

Consequences (possible therapy or referral)

In the case of detectable Howell-Jolly bodies, treatment should be in line with the guidelines for survivors following splenectomy.

General advice

For survivors following splenectomy, the recommendations are:

- Vaccination according to the national guidelines (concept consensus Vaccination for persons without a (functional) spleen RIVM/CIE Veiligheidsbewaking en Consultatie RVP)
- Antibiotic prophylaxis according to local guidelines, following consultation with patient
- Give information repeatedly

Neurology

Recommendation

For whom?

High-risk patients

- With (remaining) brain tumor residue in situ
- Following radiation of a central nervous system tumor
- With severe neurological abnormalities following treatment of childhood cancer

Low-risk patients

- With very mild neurological problems
- Following brain tumor without other neurological abnormalities

Which abnormalities can occur?

- Neurological deficits
- Epilepsy
- Vascular abnormalities
- Behavioral disorders
- Speech disorders

Which diagnostic test?

Neurological history and neurological investigation by a (pediatric)neurologist

Frequency

High-risk patients

Every 3 years. In the case where no abnormalities are detected the interval can be extended to every 5 years.

Low-risk patients

Once, 5 years after diagnosis; In the case where no abnormalities are detected, no further long term follow up is required.

Consequences (possible therapy or referral)

Following discussion with the neurologist

General advise

Preventative advice

All patients

- In case of delayed motor development in childhood discuss (physiotherapeutic) support
- In case of neurological abnormalities and functional disabilities refer to a revalidation team specialized in acquired brain injury.

High-risk patients:

These patients mostly have a care program with an acquired brain injury team. NB proper co-ordination with the LATER outpatient clinic!

Neuropsychology

Recommendation

For whom?

- All survivors: Specific medical history
- K-SNAP*
- Following treatment for a brain tumor
- Following radiation therapy to the brain
- Following (neurological) complication where during treatment there are obvious signs of mental changes (e.g. methotrexate induced encephalopathy, immediate postoperative complication or a cerebellar syndrome)
- Following additional medical problems that affect brain functions such as e.g. epilepsy

NB If the survivor already participates in a neuropsychological counseling program no specific history or K-SNAP is required.

Which abnormalities can occur?

- Cognitive problems
- Delayed social-emotional development

Which diagnostic test?

- Specific medical history; checklist school/stages, work, living situation, social functioning (social contacts, hobbies), mobility (driving license)
- K-SNAP (from 13 years of age)

Frequency

K-SNAP at the first LATER-out-patient visit en thereafter every 3 years until 3 consecutive results are normal

Consequences (possible therapy or referral)

In case of abnormalities > cut-off-score refer to a neuropsychologist for further diagnostic testing and treatment

* *Kaufman Short Neuropsychological Assessment Procedure*

Psychology

Recommendation

For whom?

All survivors

Which abnormalities can occur?

- Behavioural disorders
- Emotional disorders
- PTSS (Post Traumatic Stress Syndrome)

Which diagnostic test ?

- Children from 7 to 10 years inclusive: SDQ-questionnaire, completed by the parent (s) (SDQ-Parent Form)
- Children from 11 to 16 years inclusive: SDQ (SDQ-Child Form)
- (Young) adults from the age of 17 years: GHQ-28 questionnaire

Frequency

Children until the age of 16 years

- 5 years after diagnosis
- At transition moments
 - o at 10-12 years of age (preferably at group 7 elementary school)
 - o at 14-16 years of age (preferably around the third year of secondary education)

Children and (young) adults older than 16 years of age

- after 5 years and after 10 years; thereafter on indication

Consequences (possible therapy or referral)

Referral to a psychologist for further evaluation is indicated by

- Score ≥ 14 on the SDQ-Parent Form
- Score ≥ 17 on the SDQ-Child Form
- Score > 5 on the GHQ

Referral of (parents of) patients with an abnormal score will depend on the capacities and procedures within each center. Possibilities include referral to community based mental health care or first line psychologist by the general practitioner or involved with the children's oncology cancer center

If the patient cannot be fully helped by this, then further referral to outpatient ambulatory psychological care.

Weight

Recommendation

(In accordance with the CBO-guidelines 2008)

For whom?

All survivors

Which abnormalities can occur?

- Overweight
- Underweight

Which diagnostic test ?

Body Mass Index (BMI). This is calculated from the weight (in kg) divided by the square of the length (in m). An additional diagnostic criteria is the waist measurement.

Frequency

At every LATER out-patient visit

Consequences (possible therapy or referral)

In case of a BMI > 30 kg/m² (adult) of BMI > +2SD (children)

- Combined life style interventions
- Diet
- Physical activities
- Psychological interventions
- Pharmacological interventions

In case of a BMI < 18 kg/m² (adult) of BMI < - 2SD (children)

Detection of the possible underlying causes and consider referral to a dietician.

Audiology (hearing)

Recommendation

For whom?

Survivors who have received treatment with

- Cisplatin
- Carboplatin
- Cranial irradiation with a dose from 30 Gy or more, in which the auditory system was located in the radiation field

Which abnormalities can occur?

- Conductive deafness
- Perception deafness
- Tinnitus

Which diagnostic test?

- Clinical history
- Tone audiometry from 0.5 up to, and inclusive of 12.5 kHz en tympanometry

Frequency

- Following cisplatin: every 5 years
- Following carboplatin: initial screen 5 years after treatment, if no abnormalities detected, no repeat testing required
- Following cranial irradiation with a dose from 30 Gy or more: initial screen 5 years afterwards, if no abnormalities detected, no repeat testing required

Consequences (possible therapy or referral)

- Symptomatic poor hearing, severe symptomatic tinnitus, symptomatic middle ear pathology, refractory otitis externa, radiation necrosis and /or a 'pure tone average' (PTA) 1-2-4 kHz > 35 dB (air conduction) are reason to refer to an ear, nose and throat (ENT) specialist.
- Sub-clinical poor hearing or hearing loss < 35 dB HL op 1-2-4 kHz discuss with the pediatric oncologist/ LATE effects specialist for further advice regarding counseling of the patient. Referral to an audiology center is indicated.

General advice

- Information regarding the prevention of noise pollution should be provided (noise limiting equipment, avoid careers with excess noise, noise protectors, avoid ototoxic medication).
- In case of speech/language impediment referral to a logopedist is necessary.

Ophthalmology (eyes)

Recommendation

This part of the guideline does NOT apply to survivors of retinoblastoma. This will require a separate guideline that will be developed in the future.

For whom?

Survivors younger than 10 years of age who have been treated with

- Radiotherapy whereby the lens has been included in the radiotherapy field
- Radiotherapy whereby the dose at the retina was 50 Gy or more

Which abnormalities can occur?

- Cataract
- Retinopathy

Which diagnostic test ?

Ophthalmologist to control for cataract and retinopathy

Frequency

Once per 2 years until 10 years old

Consequences (possible therapy or referral)

Via Ophthalmologist

General advice

- Survivors of childhood and young adult cancer treated with corticosteroids do not require specific screening for cataracts. However, children who have received long-term corticosteroids (>1-2 years continuous use) should be informed of the risk however small.
- Survivors in whom the lens has been included in the radiotherapy field should be warned about the development of cataract formations. After the age of 10 years they can, in accordance with the advice of the national platform for eye care, be seen by the optician for further controls. Control by an ophthalmologist is not considered necessary.

Fatigue

Recommendation

For whom?

All survivors

Which diagnostic test?

At the Later outpatient clinic complete the VVV questionnaire

Frequency

Once every 5 years

Consequences (possible therapy or referral)

With a score > 18 on the VVV there should additionally be a CIS20R- questionnaire for tiredness completed and further diagnostic tests to determine an organic cause for tiredness should be carried out.

A total score of 35 or higher on the CIS20R indicates severe fatigue.

If abnormal: refer to individual cognitive therapy, to revalidation program (Recovery and Balance) or individual physiotherapist.

General advice

Further information about chronic fatigue following cancer is available from:

- Nijmeegs Kenniscentrum Chronische Vermoeidheid: www.umcn.nl/patient (click on 'type of illness and treatment (ziektebeelden en behandelingen)' and then on ('Expert center Chronic Fatigue "Kenniscentrum Chronische Vermoeidheid"')
- Platform Fatigue of the Dutch Federation for Cancer Patients Organisations (Platform Vermoeidheid van Nederlandse Federatie van Kankerpatiëntenorganisaties)(NFK): www.kankerpatient.nl
- Recovery and Balance (Herstel en Balans): www.herstellenbalans.nl
- www.kwfkankerbestrijding.nl

Dental care (teeth)

Recommendation

For whom?

Following radiotherapy in the oral cavity region and/or age at time of chemotherapy of < 13 years

Which abnormalities can occur?

- Delayed/ abnormal tooth development
- Cariës
- Xerostomia
- Trismus
- Occlusion abnormalities

Which diagnostic test?

Targeted dental control of development abnormalities, mouth hygiene and saliva production

Frequency

- Standard dental controls; regular visits to the dentist every six months for life
- Once 5 years after diagnosis and round 10th -12th year of age specific control focusing on development abnormalities

Specific attention to

- Prevention of cariës/plaque
- Patient information on dental care, dental hygiene and nutrition
- Timely fluoride applications because of immature tooth enamel
- Sealing by occlusion cariës
- Pilocarpine and advise about fluids for problems with saliva production
- Timely referral to a specialist physiotherapist for trismus
- Timely referral to an orthodontist for developmental abnormalities of the teeth or jaw

General advice

- Adequate health insurance cover for dental health care
- Informing professional dentists and orthodontist via the patient about the late effects of treatment for childhood cancer and the above advise.

Dermatology (skin)

Recommendation

For whom?

All survivors

Which abnormalities can occur?

- Scars
- Naevi naevocellulares
- Secondary tumors (melanoma, basal cell carcinoma, squamous cell carcinoma)

Which diagnostic test?

No specific diagnostic test during LATER outpatient clinic

General advice

- Education about the risks of sun exposure
- Educate, promote and inform about self-examination of moles
- Alertness to changes of pigmentation to skin lesions, a large number of naevi (≥ 100 naevi at an age of between 20 to 50, or ≥ 50 naevi at an age younger than 20, or older than 50 years), or atypical naevi in special places such as foot sole, palm of the hands, buttocks, side of the head or in the iris of the eye.
- Patients at risk: at least once a year control of the number of (abnormal) moles by an experienced physician or dermatologist. Children controls from 12 years of age

3.2 Recommendation working group 2. Employment and social consequences

Introduction

From the literature review (see Part 3: Working Group 2 Employment and social consequences at www.skion.nl.) it is clear that young persons who have had treatment as a child for cancer are, as a group, more likely to be unemployed or unfit for work (disabled) compared to their peers who have not had cancer. This applies specifically for survivors of a central nervous system tumor and for those who have undergone cranial irradiation, but is not detectable for those with other diagnoses e.g. bone tumors. Risk factors include cognitive and emotional problems, physical limitations and female gender. Also survivors with a lower level of education have a greater chance of being unemployed or unfit for work. In light of the toxicity of treatment a lower education level will be more commonly seen in survivors of brain tumors who have undergone cranial irradiation. Lack of employment has a negative influence on the quality of life of the survivor. There are no data on effective interventions to promote employment participation.

Recommendations

The working group on the basis of the above, believes that

1. Every LATER expert center must have/ or be affiliated with a network of insurance physicians, labor experts, educationists / educators and rehabilitation specialists with specific knowledge in this area. It seems obvious to link such a network to the expert center as formulated by the working group Organization of Health Care (see chapter 3.3) and to establish cooperation with the knowledge basis concerning employment and adult cancer.
2. Survivors in the non-risk group should be asked in their questionnaires about school performance and/ or employment and social functioning: up to 17 years of age preferably at transition periods; older than 17 years at the time of contact. If necessary they should be referred to a psychologist or neuro-psychologist and if further necessary to Government Department for Unemployment and Social Security (UUV).
3. In survivors from a risk group, defined as those who have had a brain tumor or cranial irradiation, school performance should be actively followed and recorded at transition periods. If necessary expert advice/guidance should be sought (psychologist, rehabilitation physician, neuro-psychologist, school support services). At the age of 17 years plus is an expert employment appraisal indicated and where necessary referral to Government Department for Unemployment and Social Security (UUV) for further guidance.

Recommendations for further research/further development

1. The working group feels that a valid, practical and manageable questionnaire should be developed to efficiently enquire as to the difficulties that hamper employment in survivors of childhood cancer.
2. In addition the working group calls for funding into further research and development of targeted programs for those survivors of childhood cancer who have difficulties being employed.

3.3 Recommendation working group 3.

Organization of health care

Introduction

With regards to the organization of care it is not important to the survivor who delivers this care as long as he/she has the required specific knowledge. Survivors attach great importance to a permanent contact. They appreciate central co-ordination of care but prefer to decide themselves whether or not they attend for controls. In addition, there is a great willingness to participate in research on late effects. 'Out-sourcing' of (or part of) care for survivors outside the specialist center, e.g. family doctor, is for professionals and survivors under certain circumstances acceptable for those survivors with relatively uncomplicated problems. For survivors with (very) complicated problems it remains necessary to offer a multi-disciplinary outpatient clinic with expertise in the field of late effects and access to different medical and paramedical disciplines when required.

Partly on the basis of these findings the working group has decided that LATER centers of excellence should be established in all pediatric oncology centers and that care for survivors should be organized on the basis of risk stratification.

LATER-expert center

A LATER expert center must be in or be affiliated with a children's oncology unit and has the following tasks:

1. Co-ordination of care

- a) Detection of abnormalities resulting from the treatment of childhood cancer, where timely intervention provides health benefits or where advice over possible treatments or additional follow up is indicated.
- b) Consultation function for patients with (complex) problems related to previous treatment for childhood cancer.
- c) Central role / shared care in multidisciplinary care for survivors with complex health problems related to the previous treatment for childhood cancer.
- d) Contact for professionals involved in the care of all survivors of childhood cancer if the patients develop new health problems that seem to be as a result of previous treatment for childhood cancer.
- e) Contact for patients with health problems that seem to be a result of previous treatment for childhood cancer, preferably after consultation with the general practitioner.

2. Education of professionals

3. Health education for patients

4. Co-ordination of scientific research

Personnel

- Doctor/coordinator, specialized in late effects following treatment for childhood cancer
- Nurse practitioner for day to day issues, e.g. request for mortgage insurance/triage of acute problems/ telephone contact for communicating results or appointments/information
- Team of specialists with knowledge of late effects of childhood cancer: (in random

order) cardiologist, endocrinologist, medical oncologist, hematologist, rehabilitation physician, (neuro) psychologist, pulmonologist, nephrologist, neurologist, neurosurgeon, ENT specialist, ophthalmologist, radiotherapist, gynecologist, dermatologist, pediatric oncologist etc.

Risk groups

Classification of risk in survivors of childhood cancer more than 5 years after diagnosis (LATER-stratification)

Five years after diagnosis survivors of childhood cancer can be stratified into risk groups based upon previous treatment (modified model according to Wallace, subsequently referred to as LATER-stratification)

1. Level 1 low risk survivors

Survivors where no standard care is required as recommended by current guidelines: e.g. surgery only, low intensity chemotherapy (e.g. vincristine only, actinomycine only, vincristine & actinomycine, vinblastine only, low dose cyclophosphamide (< 7.5 gram) or low dose/ small field radiation therapy/ superficial radiation therapy (such as used in LCH)

2. Level 2 medium risk survivors

All survivors who do not fall into Group 1 or 3

3. Level 3 high-risk survivors

- All survivors treated with radiotherapy other than low dose or very small field radiation therapy or superficial radiation therapy (such as used in LCH) as mentioned in low risk survivors
- All survivors with chemotherapy only, where the risk of developing late effects is assumed to be high: e.g. anthracyclins dose > 300 mg/m²

NB Depending on the course and development of eventual further complications a patient can be re-classified during follow-up depending upon the required care in another (usually higher!) level

Who is taking care of health issues for childhood cancer survivors 5 years or more after diagnosis, and who is responsible for providing LATER care in the expert center?

1. Co-ordination of care

a) Detection of abnormalities resulting from the treatment of childhood cancer, where timely intervention provides health benefits or where advice over possible treatments or additional follow up is indicated.

The following classification is made on the basis of the aforementioned LATER stratification:

• Level 1 low risk survivors

In principle these patients can be seen and controls can be carried out by the general practitioner as long as they have been seen at least once 5 years after diagnosis in a LATER expert center.

A form of transition to the general practitioner should take place, preferably according to a uniform national model. In addition, these patients can, from the viewpoint of scientific research, be periodically approached e.g. once every 5 years completing a questionnaire or other form of evaluation

• Level 2 medium risk survivors and level 3 high risk survivors

The care should be coordinated from the LATER expert center, also if the care is delivered outside the center. The patients should be at a minimum seen once every 5 years in the LATER expert center by a in late effects specialist, and with consultation with other specialists as necessary

b) Consultation function for patients with (complex) problems related to previous treatment for childhood cancer.

c) Central role / shared care in multidisciplinary care for survivors with complex health problems related to the previous treatment for childhood cancer.

The LATER expert center performs the coordination of care, which can be carried out in collaboration with other professionals.

d) The coordinator of the LATER-expert center is the contact for professionals involved in the care of all survivors of childhood cancer if the patients develop new health problems that seem to be as a result of previous treatment for childhood cancer.

e) The coordinator of the LATER-expert center is the contact for patients with health problems that seem to be as a result of previous treatment for childhood cancer, preferably after consultation with the general practitioner.

2. Education of professionals

This is provided by personnel of the LATER expert center in cooperation with other involved persons.

3. Health education for patients

This is provided by personnel of the LATER expert center in cooperation with other involved persons.

Depending on how the risk of (complex) late effects based on the previous treatment is estimated and the actual state of health of the survivor, care 5 years after diagnosis, following an initial control in a LATER expert center, may take place as follows:

- By the general practitioner
- Once every 5 years in a LATER-center and in the interim by the general practitioner or peripheral specialist in the form of a 'shared care' with the center which is coordinating the care
- Completely in the center

The working group stressed that the center coordinator, who has an overview of the survivors who fall into this group and is able to liaise with and provide feedback to the caregivers in the periphery, is essential to the success of the 'shared care' option

Summary recommendations of organization of health care

1. The LATER expert center should be located in or affiliated with a pediatric cancer center.
2. The LATER expert center functions to coordinate care, educate professionals, provide health education for patients and coordinate scientific research.

3. The LATER expert center personnel should include a doctor/coordinator, nurse practitioner and a team of specialists with knowledge of late effects of treatment of childhood cancer, including a cardiologist, endocrinologist, medical oncologist, hematologist, rehabilitation physician, (neuro) psychologist, pulmonologist, nephrologist, neurologist, neurosurgeon, ENT specialist, ophthalmologist, radiotherapist, gynecologist, dermatologist, and a pediatric oncologist
4. A survivor of childhood cancer should be seen five years after diagnosis in a LATER expert center.
5. At the initial LATER expert center out-patient visit, five years after the diagnosis of childhood cancer, an individual after care plan should be formulated by the treating physician /coordinator.
6. Survivors in the low risk group level 1 according to the LATER-stratification can in principle be followed up by the general practitioner after an initial outpatient control in the LATER expert center.
7. Survivors in the medium risk group level 2 and high risk group level 3 according to the LATER-stratification should be seen at least once every 5 years in the expert center by a late effects specialist, and if necessary in consultation with other specialists.
8. Care for survivors in the medium risk group level 2 and high-risk group level 3 according to the LATER-stratification should be coordinated by the LATER expert center
9. If survivors of childhood cancers are seen in a 'shared care' model (with general practitioners or specialists in another hospital) there should be a coordinator who works in the LATER expert center, who acts as a fixed contact person for all other care providers.

Chapter 4

Composition of the working groups

4.0 Composition of the task group

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Diagnostic and therapeutic consequences

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4.1.1 Composition of groups for the development of the individual guidelines of working group 1. Diagnostics and therapeutic consequences.

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