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Organisation of follow-up in paediatric oncology

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1. Introduction

To organise, at a local or national level, the follow-up of children with cancer is important since 75–80% of these children now survive in affluent countries. Interest in long-term follow-up arose in the 1970s, when both the survival rates and the number of late effects increased. In our clinic long-term survival is defined as disease-free survival of 5 or more years after diagnosis.

The main concerns of childhood cancer survivors and their families are [1]

- recurrence of the primary tumour;
- the risk of second malignancy;
- vital organ function;
- statural growth;
- intellectual and psychosocial development; and
- sexual maturation and fertility.

The main goals of follow-up in paediatric oncology are shown in Table 1. To match these goals, cost-efficient, long-term cooperation involving medical health professionals, educators and teachers, lawyers and insurance specialists is required.

2. Long-term follow-up clinics

A recent survey in the USA revealed, that around one half of all member institutions of the Children's Cancer Group (CCG) and the Pediatric Oncology Group (POG) have a long-term follow-up clinic and mechanisms for following adult survivors, but only 15% have established a data-base for adults [2]. An adult oncologist was involved in only 13% of these programmes, a primary care physician in only 8%. The conclusion of this survey was, that "few programmes focus on the long-term healthcare needs of adult survivors of childhood cancer. The majority of existing programmes are in paediatric institutions, without significant input from adult-oriented, generalist health care providers". So it appears, that, generally speaking, the healthcare needs of adult survivors of childhood cancer in the United States are not yet met by an adult-oriented clinic that can follow survivors for very long periods.

In a paediatric cancer unit (PCU), there are several reasons to keep separate long-term follow-up clinics. One is that former patients and their families often prefer not to be confronted again with the acute phases of the disease. In addition, in order to be cost-efficient, it might be worthwhile to run different long-term clinics, e.g. one each for survivors with brain tumour, ocular tumour, lymphoma, etc.

A pivotal element of the paediatric long-term clinic team, besides the paediatric oncologist and radiation oncologist, is the paediatric nurse with special training in oncology (paediatric nurse practitioner in oncology) working with long-term survivors, who can act as specialty care provider, educator, programme manager, researcher and consultant [3]. Other essential personnel include the social worker, the data manager and the psychologist.

3. Stratification of survivors

Survivors can be stratified according to whether they have or do not have tumour- or treatment-related sequelae at the end of treatment. As a rule these survivors would be enrolled in special rehabilitation and surveillance programmes or may be followed more closely for hormonal substitution, special schooling or training.

For survivors with few or no defects requiring immediate intervention, an individual screening programme for late effects—taking into account risk factors such as age at diagnosis, diagnosis, localisation of the disease and type, intensity and duration of treat-

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Table 1
Goals of long-term follow-up in paediatric oncology

Early detection and treatment of recurrent cancer and cancer- or treatment-induced sequelae
Promotion of the survivor's and his or her family's understanding of the disease
Instruction regarding health-promoting behaviour
Restoration of normalcy by providing psychosocial, educational and socioeconomic support
Reducing the likelihood of discrimination
Reduction of treatment components associated with handicapping effects

ment— should be established. Other factors to be considered are (i) the neurocognitive and educational status since they might influence the future behaviour of a survivor; and (ii) genetic data.

A subgroup of survivors not needing invasive and prolonged follow-up includes patients treated with surgery only (e.g. low stage neuroblastoma, ganglioneuroblastoma, germ cell tumour) and a majority of patients with acute lymphoblastic leukaemia (ALL) treated with antimetabolite-based chemotherapy (no or <125 mg/m^2 of anthracyclines, no cranial radiotherapy). These patients may require only the examinations specified by the treatment protocols and go off follow-up after 10 years provided that no late effects have been observed and so long as the patient has received instructions regarding health-promoting behaviours.

An important source of guidance for the establishment of an individual screening programme are data on the late mortality from childhood cancer. Two recent studies [4,5] indicate that approximately 10% of all long-term survivors die within 20 years, i.e. 25 years from diagnosis, 60–70% from a recurrence of the primary tumour, around 20% from treatment-related effects and 10% or so from other causes. Two-thirds of those who die of a recurrence, die 5–9 years, one quarter 10–14 years and only 7% 15–20 years after diagnosis. Those with the highest risk (10–15%) of death within 20 years are long-term survivors who had a central nervous system (CNS) or bone tumour, Hodgkin's disease or leukaemia and the lowest ($<5\%$) those with Wilms' tumour or neuroblastoma. In one study [4], death was attributed to a secondary or subsequent cancer in 13%, to cardiac toxicity in 5% and to pulmonary complications in 2%. Radiation, alkylating agents and epipodophyllotoxins increased the risk of dying from secondary or subsequent cancers almost 20-fold. The risk of cardiac death was increased in those who had received either anthracyclines or chest irradiation or both.

4. Time and type of screening

Algorithms have been published permitting access to information on the more common late effects and methods of detecting them by entering the tumour type and the given treatment [6]. Tables 2 and 3 have been compiled from this information. Table 2 lists the sequelae of irradiation and Table 3 those of cytotoxic drugs. Apart from amputation, surgery contributes to scoliosis after thoraco- or laminectomy, to postsplenectomy sepsis, to hyperammonaemic encephalopathy, hyperchloraemic metabolic acidosis and benign or malignant colonic tumours after ureteral diversion, or to impotence, retrograde ejaculation and/or hydroceles after retroperitoneal lymph node dissection.

In another helpful publication [7] signs and symptoms have been related to organ systems and late effects and, in separate tables, recommendations are made for the evaluation and management of patients at risk for a specific type of late effects.

For very long-term follow-up (>20 years after diagnosis), a postal questionnaire method can be considered.

5. Baseline assessments and standardisation of screening

In order to compare observations made at different centres, tests used for the screening of survivors should be standardised. Thus "an age-standardised battery of tests should be used to measure intellectual ability, visual and somatosensory perception, visual-motor and motor skills, language, memory and learning, academic achievement, behaviour and social functioning. Ideally, these tests should first be done within 3 months of diagnosis to allow for pre-existing conditions such as learning disabilities" [8]. In a standardised assessment protocol the neuropsychological evaluation consisted of a Wechsler Intelligence Scale in Children - Revised (WISC-R) for survivors <16 years and a Wechsler Adult Intelligence Scale - Revised (WAIS-R) in older patients while the socioeconomic status (SES) of the family was a score based on the father's employment and mother's schooling (scale 1–12, with a higher score denoting poorer SES) [9]. At the national level, Paediatric Oncology Groups could define standardised assessment protocols for the screening of long-term survivors.

6. Database for adult long-term survivors

Based on a consensus on a new dataset dealing with adverse late effects of paediatric oncology treatment, a

Table 2
Screening for late effects after radiotherapy (RT) (adapted from Ref. [7])

Localisation of RT	Screening
Cranial	Educational and neurocognitive assessment yearly Dental panorex at age 5 years (root hypoplasia) Eye exam yearly (cataracts, optic nerve damage) Serum LH, FSH, oestradiol/testosterone, prolactin (age < 12 years) (pubertal delay, precocious puberty, reduced libido) Growth curve every year (every 6 months up to age 10–12 years) (bone age, growth hormone stimulation) Free T4, TSH yearly for 10 years (primary or secondary hypothyroidism)
Orbit, ear, pharynx	Eye exam yearly (cataracts) Audiogram Hypothalamic/pituitary axis: Growth, LH, FSH, oestradiol/testosterone, free T4, TSH Sinus evaluation (sinus inflammation or obstruction) Dental panorex at age 5 years (root hypoplasia)
Neck, cervical	Dental panorex at age 5 years (root hypoplasia) Free T4, TSH yearly for 10 years (primary or secondary hypothyroidism)
Spinal	Free T4, TSH yearly for 10 years (primary or secondary hypothyroidism) Growth curve, sitting/standing height Observe for scoliosis yearly (every 6 months during puberty)
Mantle, whole lung	Free T4, TSH yearly for 10 years (primary or secondary hypothyroidism) Chest X-ray, pulmonary function tests every 5 years (fibrosis) Breast self examination, monthly. Mammogram every 2 years (age > 25 years) ECG, echo every 3 years (pericarditis, valvulitis, myocardial dysfunction)
Abdomen	Urinalysis, creatinine, blood urea nitrogen yearly, creatinine clearance every 5 years (reduced glomerular filtration rate) Liver function test yearly (hepatic fibrosis) Observe for scoliosis yearly (every 6 months during puberty) LH, FSH, oestradiol/testosterone (> 12 years), semen analysis (gonadal failure)
Pelvic	LH, FSH, oestradiol/testosterone (> 12 years), semen analysis (gonadal failure)
Testicular	LH, FSH, oestradiol/testosterone (> 12 years) (gonadal failure)
Bone	Radiograph every 5 years (second malignancy) Monitor for leg length discrepancy

LH, luteinising hormone; FSH, follicular stimulating hormone; TSH, thyroid stimulating hormone.

computerised documentation system covering both standardised documentation of all relevant data for evaluating late effects, as well as review facilities on an individual patient basis or on a cohort of patients, is actually installed at all Dutch PCUs in order to develop a National Pediatric Oncology Follow-up Registry [10]. Similar programmes have been started in other countries. Each PCU has first to establish the database for follow-up [11], but close cooperation with adult oncologists and general health providers is essential.

7. Benefits and issues of a long-term follow-up

Good neuropsychological follow-up may provide important guidelines for a well adapted educational and professional training. An adequate hormonal substitution can prevent frustrating deficits and early detection of a recurrence, a secondary neoplasm or a cardiac or pulmonary dysfunction might increase the chance of survival. In addition, regular follow-up might provide a sense of security and stability. However, not all individuals feel the same way. Some long-term survivors want to forget the past and object to regular clinic visits, even if they are on an yearly or biannual basis. They may repress all thoughts related to dealing with their past disease to such an extent that they may not even recall what their disease was and where it was treated. Under these circumstances, it might become difficult to recognise a long-term survivor and to react appropriately, particularly if the primary cancer was treated decades ago. Should one therefore establish a national database permitting physicians to check if a patient had cancer in the past and what the treatment was? If such a database existed, why should there not be others, for other diseases? Is such a registration of personal data desirable? Clearly, there are not just economic, but also ethical considerations to life-long follow-up.

Table 3
Screening for late effects after chemotherapy (adapted from Ref. [7])

Agent	Screening
Alkylating agents	Urinanalysis yearly (haematuria, bladder cancer)
	Complete blood count yearly (marrow damage, leukaemia)
	LH, FSH, oestradiol/testosterone (>12 years), semen analysis (gonadal failure)
	Chest X-ray, pulmonary function tests every 3–5 years (fibrosis)
(Ifosfamide)	Phosphate, glucose + albumin (serum + urine) (Fanconi syndrome)
Antibiotics	
Actinomycin D	Liver function annually for 5 years (hepatic fibrosis)
Bleomycin	Chest X-ray, pulmonary function tests every 3–5 years
Anthracyclines	ECG, Echo every 3 years (cardiomyopathy, pericarditis)
Antimetabolites	
Ara-C (HD)	Neurological examination (leucoencephalopathy, ataxia)
Methotrexate (HD;IT)	Educational assessment yearly
	Neurocognitive assessment every 2–3 years
	Liver function tests yearly for 5 years (hepatic fibrosis)
6-mercaptopurine	Liver function tests yearly for 5 years (hepatic fibrosis)
6-thioguanine	Liver function tests yearly for 5 years (hepatic fibrosis)
Miscellaneous	
Prednisone	–
Dexamethasone	Bone mineral densitometry every 2–3 years (osteoporosis)
Vinca alkaloids	–
Procarbazine	LH, LSH, oestradiol/testosterone (>12 years), semen analysis (gonadal failure)
Cisplatin	Serum Mg yearly (low Mg: tubular dysfunction)
	Creatinine yearly, Creatinine clearance baseline (decreased glomerular filtration rate)
	Audiogram every 5 years (high frequency hearing loss)
VP-16, Etoposide	Complete blood count yearly for 10 years (leukaemia)
	LH, testosterone

HD, high dose; IT, intrathecal.

8. Conclusions

The long-term follow-up of survivors of childhood cancer is, by and large, in the hands of paediatric teams, and only a few adult oncologists and primary care physicians are involved. In part this can be explained by the fact that both tumour- or treatment-induced sequelae mostly occur during the first or the second decades after diagnosis, at a time when the survivors might still want to be followed by the paediatric institution where they were treated. Furthermore, it seems logical that the data of children and adolescents with cancer are stored where they are generated and that they remain available as long as the survivors live. However, as more and more survivors get older, more adult oncologists and/or primary care doctors should be integrated into the paediatric programme, in order to guarantee a seamless transition from a predominantly paediatric- to a predominantly adult-oriented surveillance facility.

To set up and organise a long-term follow-up clinic is one thing, to run it another. The quality of the service provided will always depend on the staff and how they deal with the challenges with which they are confronted. To strike the 'happy medium' between a narrow and bureaucratic routine and a 'laisser aller' is an art that when it succeeds may contribute considerably to the quality of life of the survivors.

There is, of course, another scientific aspect of follow-up programmes with all their strict requirements such as standardised data collection, transmission and storage and interdisciplinary cooperation and evaluation at the national or even international level. They are essential if the experiences acquired from follow-up clinics are to be used for the design of new, less harmful, but still effective, cancer treatments, but they may, occasionally, be difficult to reconcile with the human aspects of long-term follow-up. The provision of good follow-up requires both 'know-how' and intuition. Like much of medical practice, it demands 'art' as well as an evidence-base.

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