Survivors of Childhood Cancer for More than Twenty Years

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Present health status, complications, and development of long-term survivors of childhood cancer followed for more than 20 years in a single institution were reviewed. The departmental database was searched to identify patients diagnosed with childhood cancer and consequently treated between 1965 and 1978. A total of 124 (77%) long-term survivors participated on a voluntary basis in the study. A semi-standardized interview consisted of measures evaluating the present health condition, sequelae of treatment, second malignancies, intellectual development and presence of offspring of the former patients. The majority of patients were treated with chemotherapy (82%), 67% received radiotherapy and 67% underwent surgery. A relapse of the primary tumor was diagnosed in four patients as well as a second malignancy in four other patients. In 33% of the long-term survivors one or more serious therapy-related health problems were noted. Adequate mental and intellectual development was achieved in 65%. Children treated in the early years of pediatric oncology seem to have a satisfactory outcome as viewed over the long term. Consequent ongoing follow-up is still necessary to detect health problems and enhance quality of life for subsequent generations of children with cancer.

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Whereas 40 years ago, the survival rate of children with cancer was low (1, 2), expanded therapeutic options and further implementation of a multidisciplinary approach over the last decades have made it possible to achieve high cure rates in most childhood malignancies (3). Careful estimations based on 1990 data predict a steadily increasing number of young adults between 20 and 29 years of age who will be long-term survivors of childhood cancer (4). Studies in the past focused particularly on the percentage of patients surviving to 5 or 10 years from diagnosis and treatment, but increased survival has led also to concern about the quality of life of the outcome.

During the initial phase of the disease, with diagnostic procedures, treatment, and hospitalization, children and families are subject to significant stress, which may act as a lifelong trauma (5). The risks of recurrence, in combination with chronic side effects of treatment modalities (fertility problems, organ system damage, and blood-product-related infections) require lifelong follow-up. Nevertheless, attention must be paid to the well being of those patients who reached adulthood in continuous remission of neoplasia. Several well-designed observations have been published (6–8), using complex methods, and have raised questions regarding appropriate techniques to assess possible chronic injuries caused by treatment of childhood cancer (9–11).

The purpose of our retrospective study was to assess the present health condition, especially with regard to residuals of the primary disease, sequelae of treatment and secondary malignancies. In addition, the achieved level of education, occupation (if available in comparison with siblings), marital state and offspring of the former patients were evaluated.

MATERIAL AND METHODS

Between 1965 and 1978 (14 years), a total of 532 children were diagnosed with childhood cancer and subsequently treated at our institution. In 1998, 161 (30%) former patients were identified as long-term survivors of their disease for more than 20 years, utilizing the hospital charts and the database of the outpatient clinic. Of the remainder, 357 (67%) patients died, and 14 (3%) were lost to follow-up. Among the survivors, 124 (77%) participated on a voluntary basis and were included in the study population. The remaining 37 (23%) patients are alive but declined to reveal information.

A semi-standardized interview either in the hospital or by phone was carried out by one of the investigators

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Table 1

Details of patients diagnosed 1965 and 1978

Diagnosis	All patients	Patients included in the study	Gender (m/f)	Age at study (years: mean/SD)
Acute lymphoblastic leukemia	167	24	13/11	29.8 ($\pm$4.2)
Acute myeloid leukemia	9	0	0/0	0
Chronic myeloid leukemia	2	0	0/0	0
Non-Hodgkin's lymphoma	36	13	8/5	33.0 ($\pm$3.4)
Hodgkin's disease	23	6	5/1	34.0 ($\pm$2.3)
Neuroblastoma	44	7	4/3	29.1 ($\pm$5.5)
Rhabdomyosarcoma	32	7	6/1	28.1 ($\pm$4.3)
Sarcoma	25	7	2/5	31.8 ($\pm$3.9)
Wilms tumor	32	20	11/9	29.1 ($\pm$2.8)
CNS tumor	120	32	15/17	33.0 ($\pm$3.9)
Histiocytosis	4	3	1/2	28.4 ($\pm$8.4)
PNET	3	1	1/0	20.3
Germ cell tumor	12	3	2/1	27.8 ($\pm$3.5)
Retinoblastoma	4	1	1/0	33.3
Other	19	0	0/0	0
Total	532	124	69/55	30.9 ($\pm$4.4)

(M.F.). If preferred by the former patients, a questionnaire was sent for completion at home.

Data included age at diagnosis, disease and therapy (type and extent of surgery, chemotherapy, radiotherapy with field and dose); current health status (with history of remission, relapse, second malignancy, sequelae of therapy, handicap); delay of mental development, educational progress, highest level of education; marital status; offspring; and participation in routine check-ups.

The study was completed by 31 December 1998.

All former patients were offered continued contact with the interviewer or the attending oncologist.

RESULTS

Patients' characteristics are shown in Table 1. The mean age of the individuals at the time of initial therapy was 6 years (SD $\pm$ 4.3 years). The mean time since initial treatment was 23.9 years (SD $\pm$ 3.4 years). Treatment included chemotherapy in 101 (82%) of the patients, 83 (67%) received radiotherapy, 83 (67%) underwent surgery of differing extent (Table 2). Combination therapy, consisting of chemotherapy and radiotherapy, was used in 75 (61%) patients.

A relapse of the primary disease was diagnosed in 4 patients, all of them are in remission after additional therapy (Table 2).

Forty-one (33%) of the individuals demonstrated one or more serious therapy-related health problems, 6 (5%) of the total group had undergone psychotherapy (depression).

A total of 105 (85%) of the long-term survivors agreed with the decision for therapy, carried out by their parents, whereas 4 (3%) disagreed in retrospect. Fifteen (12%) were not able to give a definite answer (Table 2). The four patients who did not consent to the decision made for them were diagnosed and treated for acute lymphoblastic leukemia (ALL) (age at diagnosis 10 years, at time of the study 37 years), non-Hodgkin's lymphoma (NHL) (8 years, 34 years), rhabdomyosarcoma (2 years, 25 years) and ependymoma (9 years, 32 years). The reason for their statement was mainly 'bad memory of the treatment', but also significantly impaired quality of life.

Intellectual development, educational progress

Eighty (65%) of the former patients achieved an adequate intellectual and mental development (Table 3). The remaining 44 (36%) had serious learning problems or were not able to be educated (n = 9, 7%). Forty (27%) of the former patients achieved a secondary school qualification, 41 (33%) finished high school. An intermediate high-school qualification was accomplished by 34 (27%) of the long-term survivors. At the time of the study, six (5%) of the group had attained a university degree, and eight (7%) were registered at a university.

Offspring

Nineteen (15%) of the former patients have children, whereas 105 (85%) are childless. There was one neonatal death (mother former NHL) and one miscarriage in the last trimester with multiple malformations (father former Wilms' tumor patient). Major congenital malformation or childhood cancer in the surviving offspring was not noted.

Central nervous system (CNS)

Major late effects after therapy for tumors of the CNS (n = 32) were seen as severe reduction of vision including blindness in eight (25%) and seizures in seven (22%) pa-

Table 2

Therapy, sequealae of therapy in long-term survivors to childhood cancer

	n	Chemotherapy	Radiotherapy	Surgery	Sequelae of therapy, relapse health status, complications	Agree with parental decision for therapy
ALL	24	Pred, VCR, MTX, 6-MP, CP, (ARA-C) n = 24	Cranial 24 Gy: n = 19 18 Gy: n = 3 0 Gy: n = 2	None	Lens Opacity: n = 1 Menigioma (SMN): n = 1 Gastric cancer (SMN): n = 1 Male infertility: n = 6 Relapse: n = 1 (in remission)	Yes: n = 23 No: n = 1 No comment: n = 0
NHL	13	Pred, VCR, CP, 6-MP, ARA-C, ADR, (L-ASP) n = 13	Cranial 24 Gy: n = 6 0 GY: n = 2 local: 26-40 Gy: n = 9	Partial: n = 6 None	Esophageal cancer: n = 1 Odontopathy: n = 1	Yes: n = 11 No: n = 1 No comment: n = 1
Hodgkin	6	VBL, Pred, CP, PCA n = 6	Supradiaphragmatic 40 Gy: n = 5 0 Gy: n = 1	Splenectomy: n = 5	Hepatitis B: n = 2 Altered thyroid function: n = 2 Male infertility: n = 1 Death (liver disease): n = 1	Yes: n = 5 No: n = 0 No comment: n = 1
Neuroblastoma	7	VCR, CP, ADR, ACT-D n = 7	Local 40 Gy: n = 1 3 Gy: n = 1 30 Gy (post-relapse)	Radical: n = 5 Partial: n = 1	Altered thyroid function: n = 1 Relapse: n = 1 (in remission)	Yes: n = 7 No: n = 0 No comment: n = 0
RMS	7	VCR, ACT-D ADR, CP, MTX, n = 7	Local 60 Gy: n = 2 30 Gy: n = 1	Radical: n = 5 Partial: n = 1	Corneal dysfuction: n = 1 Non erection after pouch surgery: n = 1	Yes: n = 5 No: n = 1 No comment: n = 1
Sarcoma	7	VCR, ADR, CP MIX, ACT-D, n = 7	Local 70 Gy: n = 2	Radical: n = 5	Notable limb shortening: n = 2 Scoliosis: n = 1 Relapse: n = 1 (in remission)	Yes: n = 6 No: n = 0 No comment: n = 1
Wilms tumor	20	ACT-D (VCR, ADR) n = 19	Local 10-49 Gy: n = 20	Radical (tumor nephrectomy): n = 20	Scoliosis: n = 7 Hypertension; n = 2 Renal insufficiency: n = 1	Yes; n = 17 No: n = 0 No comment: n = 3
CNS tumor	32	CP, VCR, MTX n = 12	Cranial 50-60 Gy: n = 15 Cranio-spinal 30/50-40/60 Gy: n = 5 0 Gy: n = 13	Radical: n = 8 Subtotal: n = 20	Epilepsy: n = 7 Blindness: n = 8 Deafness: n = 2 No verbal ability: n = 1 Stroke: n = 1 Imbalance: n = 1 Ataxia: n = 4 Wheelchair dependent: n = 1 Altered thyroid function: n = 1 Hyposomnia: n = 1 Obesity: n = 3 Relapse: n = 1 (in remission)	Yes: n = 24 No: n = 1 No comment: n = 7
Histocytosis	3	Pred, VBL n = 3	None	Partial: n = 3	None	Yes: n = 3 No: n = 0 No comment: n = 0
PNET	1	VCR, ADR, ACT-D, CYC n = 1	None	None	None	Yes: n = 1 No: n = 0 No comment: n = 0
Germ cell tumor	3	ACT-D, MTX, CP, n = 2	None	Radical: n = 3	None	Yes: n = 3 No: n = 0 No comment: n = 0
Retinoblastoma	1	None	None	Radical: n = 1	None	Yes: n = 1 No: n = 0 No comment: n = 0

ACT-D: Actinomycin D; ADR: Adriamycin; ARA-C: Cytarabine; CP: Cyclophosphamide; L-ASP: l-asparaginase; 6-MP: 6-mercaptopurine; MTX: methotrexate; PCA: procarbazine; Pred: prednisone; VBL: vinblastine; VCR: vincristine; SMN: Second malignant neoplasm.

Table 3

Intellectual development and level of education of long-term survivors of childhood cancer

	n	Appropriate intellectual development	Delayed intellectual development	No education	Secondary school	Intermediate high school	High school diploma	University degree
ALL	24	16	8	0	8	6	10	0
NHL	13	6	7	0	6	2	5	0
Hodgkin	6	3	3	0	1	3	2	0
Neuroblastoma	7	7	0	0	2	1	4	2
RMS	7	7	0	0	4	2	1	1
Sarcoma	7	5	2	0	1	5	1	0
Wilms tumor	20	15	5	2	3	4	11	2
CNS tumor	32	13	19	7	14	8	3	1
Histocytosis	3	3	0	0	0	2	1	0
PNET	1	1	0	0	0	0	1	0
Germcell tumor	3	3	0	0	1	1	1	0
Retinoblastoma	1	1	0	0	0	0	1	0
All	124	80	44	9	40	34	41	7

tients, 60% of the patients have deficient intellectual development (Table 2). Obesity was noted in three of the six patients (50%) with craniopharyngioma.

Secondary malignancies (SMN)

Four of the analyzed patient cohort developed and survived therapy for a secondary malignancy.

There was one meningioma and one gastric cancer after ALL, one osteosarcoma after Hodgkin's disease and one esophageal cancer after NHL diagnosed 6 to 25 years after the first malignancy.

One patient with the primary diagnosis of Hodgkin's disease died shortly after completing the interview because of acute liver failure caused by chronic hepatitis B.

In this study, 106 (86%) patients participated in regular check-ups, whereas the remaining 18 (15%) patients were not involved in specific follow-ups. Out of these 106, 83 (67%) continue to be seen at our institution in the pediatric clinic, whereas 18 (15%) patients are connected to other facilities (general practitioners, adult oncology clinics).

DISCUSSION

With the increasing number of children surviving malignant diseases, the consequences of cure, especially the care of these children or young adults, in combination with the management of late effects are becoming increasingly significant issues. In a recent investigation, treatment-related death in 5-year survivors of childhood cancer was reported as 15% (12), whereas late mortality from recurrence after treatment for childhood cancer decreases with more effective initial therapy (13). Both chemotherapy and radiotherapy may cause organ dysfunction, growth defects and second malignant neoplasms (14). In addition, extensive surgery, with extirpation of an organ or amputation of a limb requires, in most cases, lifelong medical observation. The necessary transition of the former pediatric patients to an adult setting is not yet optimized. Most of our patients still take advantage of the familiar surroundings in the pediatric hospital for the follow-up outpatient clinic. In a recent report, Oeffinger et al. (15) described the current practice of long-term follow-up of former pediatric patients in pediatric institutions because of a lack of efficient adult programs.

Intra- and interindividual differences in accepting the consequences of radical surgery, e.g. amputation of a lower limb in sarcoma patients, as a major handicap are wide-ranging. Whereas one patient is an active sportsman, a second patient with a comparable outcome is suffering serious depression with suicidal tendencies.

The estimated risk of developing a second malignant neoplasm (SMN) is 3–4% for all pediatric cancer survivors (16, 17). In a recent report, 28 of 182 former patients with Hodgkin's disease during childhood or adolescence were identified with a SMN (18). We recognized a SMN in four patients (3%) during the observation period. All the detected different cancer types may be triggered by ionizing radiation and also developed in the actual radiation field. Unlike in a recently published study (19) with a reported incidence of 1% SMN for patients treated for ALL, we found a higher rate of 8%. For the most part, ongoing health problems are related to radiation therapy. These include impaired thyroid function, odontopathy, ocular damage, stroke, and interference with normal bone growth resulting in limb shortening and scoliosis, as well as the already discussed possible induction of SMN. Two patients were diagnosed with hepatitis B as a result of blood product transfusion. Other long-term effects that were seen, especially after surgery, are failing

erection after pouch surgery for bladder rhabdomyosarcoma and deterioration of sensory perception after CNS tumors, either as a result of the primary disease or surgery.

Cognitive and mental development were considered as adequate in 65% of all the former patients, considering familial background (if available compared with the level of education in parents and siblings) and a linear progress in kindergarten, primary school, secondary school and if applicable in high school. In the general population, a high school diploma is achieved by 28 to 35%, intermediate high school diploma by 26 to 38%, a secondary school diploma by 22 to 50%. No formal education was reported in 5 to 10% (personal communication, Federal Statistical Office, Germany). Delayed development was seen mainly in patients with CNS tumors, less in ALL, non-Hodgkin and Hodgkin's disease, and least in patients with sarcoma and Wilms' tumor. Especially for tumors of the CNS, the localization, and for other cancer groups the age at diagnosis, lengths of stay in the hospital and total duration of therapy, as well as cranial irradiation, are most likely of major influence. Copeland et al. (20) concluded that children with cerebellar tumors and non-irradiation therapy in early infancy have only minimal declines in neurocognitive development compared with patients treated with cranial radiotherapy. Further, this group emphasized the possible late effects of intrathecal chemotherapy (21). Mulhern et al. observed a decline of the IQ scores in patients treated for ALL with cranial radiation and intrathecal methotrexate or with chemotherapy (22). As pointed out by Anderson et al. (23) and Schatz et al. (24), non-verbal and information-processing skills are limited in children treated with cranial irradiation and chemotherapy. Especially working memory and speed of processing are impaired in former patients who underwent radiation therapy. In contrast, patients from our series with neuroblastoma or Wilms' tumor (without cranial radiation) reached a notable higher level of education compared with the other patients. The overall prevalence of learning disabilities in the general population was reported as 4% (25) and was therefore lower than in this group.

It is important to highlight that the majority of the long-term survivors agreed in retrospect with the decision of their legal guardians with regard to the therapy, despite chemotherapy-associated side effects, pain, or remaining handicaps. This implies a positive attitude of these former cancer patients to their previous medical history.

Only 5% of the reviewed long-term survivors indicated psychological problems that required professional help, whereas there is presumably a more extensive grey area of individuals actually in need of support. Late psychological effects are not easy to define, especially as adolescent cancer survivors tend to utilize avoidance strategies to manage problems (26). Age at diagnosis and therapy, gender and certain disease inherent variables are strong predictors of psychological outcome.

Only 6 male survivors have fathered a total of 8 children, whereas 12 female survivors have given birth to 18 children. In a large cohort, pregnancy outcome, especially including perinatal complications with fetal death, neonatal deaths, low birthweight, premature delivery and congenital abnormalities seem not to be different from those of other babies (27).

Clearly, the toxic effect of therapy for ALL, NHL, and Hodgkin's disease to the male germ tissue is evident in patients treated during the early years of pediatric cancer management (28). According to Kobayashi et al., chemotherapy causes significant direct damage to the prepubertal testicular tissue, proven by biopsy of testes (29). However, the total dose of alkylating agents was significantly reduced in the more recent regimens.

CONCLUSIONS

The present study, based on a survey of medical records and interviews, shows the outcome of long-term survivors of childhood cancer from the early days of therapy in a single institution. We may not have detected all possible late effects of the previously treated patients. The findings of the present study confirm the need for lifelong follow-up of former pediatric cancer patients, and especially focus on recognizing the side effects of primary management and adjusting future therapeutic regimens to increase the quality of life for long-term survivors.

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