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Original Paper

The Health Status of Adult Survivors of Cancer in Childhood

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The success of treatment for children with cancer has resulted in a growing population of adult survivors, yet these individuals may be at risk of serious long-term health problems as a result of the treatment they have received. This study explores the pattern of morbidity within a population of 290 adult survivors of cancer in childhood assessed at a median of over 15 years from diagnosis. Acute lymphoblastic leukaemia (33%) and Hodgkin's disease (15%) were the most common primary diagnoses represented. 85% of the whole group had received treatment with chemotherapy, 81% with radiotherapy, 48% with significant surgery and 28% with all three modalities. Overall, 58% of the survivors had at least one 'chronic medical problem' and 32%, two or more. Infertility (14%), nephrectomy (11%), thyroid hormone deficiency (9%), visual handicap (9%), sex hormone (7%) and growth hormone (7%) replacement therapy were the most common problems. Compliance with long term follow-up was good and an audit of an unselected sub group of all the survivors in the study showed that 84% had attended for surveillance over a period of 1 year, accounting for 222 visits to follow up clinics: 15% were also attending other specialist follow-up including psychiatry, orthopaedic, endocrine, dental and cardiac clinics. In conclusion, survivors of cancer in childhood experience actual or potential threats to future health. More than half have at least one chronic medical problem and demonstrate a significant use of medical resources. These data support the need for the continuing follow-up of survivors of cancer in childhood into adult life and the provision of the resources to do so. Optimal patterns of care and future approaches to the reduction of sequelae in future generations of survivors are discussed. © **1998 Elsevier Science Ltd. All rights reserved.**

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INTRODUCTION

SURVIVAL IN childhood cancer has increased to an extraordinary degree over the past 20 years and now over two thirds of these children are likely to be cured [1]. It is well recognised that treatment can be associated with significant adverse late effects including increased mortality [2], a second malignancy [3], serious organ toxicities [4–6], growth and endocrine dysfunction [7] and infertility [8]. Furthermore, the total impact of the experience on the child and family may result in social, psychological and educational difficulties [9].

By the year 2000, 1 in 900 adults aged between 16 and 34 years will be survivors of cancer in childhood [10] and estimates from the Childhood Cancer Research Group, University of Oxford suggest that there are now over 10 000 known adult survivors of childhood cancer in the U.K. (C. Stiller, Childhood Cancer Research Group, Oxford, U.K.). Most of these individuals will have been treated before modern therapy and the late effects of treatment documented in this group will not necessarily reflect the sequelae encountered by more recently treated patients [11]. As some consequences of treatment are not encountered for many years, follow-up should include surveillance into adult life [12]. Although risk factors for some late effects are well known, there is relatively little information about the overall experience of the whole population of adult survivors or what resources are likely to be required for their care.

The purpose of this study was to document the pattern of late effects of treatment encountered by a population of adult survivors who were under routine surveillance in a structured

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follow-up programme. An assessment was also made of the use of hospital resources by this group of patients.

PATIENTS AND METHODS

Since approximately 1968, Birmingham Children's Hospital (BCH) has offered facilities for the systematic care of children with cancer. Indefinite surveillance of survivors has been a long-standing policy.

From 1989 details of initial diagnosis and all treatment received were abstracted from the hospital records of all patients who survived 5 years from first diagnosis and who were at least 3 years off therapy and attending the long-term follow-up clinic in the oncology department. These data were entered into a specially constructed data base. Treatment details included: cumulative doses of chemotherapy exposure; dose, field and fractionation of radiotherapy; and type of surgery. Follow-up information was collected using a semi-structured questionnaire applied to all patients at routine annual or biennial review. This included data about growth and pubertal development; medication and major medical events; contacts with other hospitals or clinics; educational progress and employment; and family/social events including marriage/partnership and offspring. These details were briefly coded into the data base at the time of entry into the long-term follow-up programme and the records routinely reviewed and updated.

Between January 1968 and December 1990 (23 years) 1954 patients with registrable tumours were diagnosed at Birmingham Children's Hospital; 1,124 (57%) were boys. 1,160 patients had been born before February 1979 and would have been $\geq$ 18 years of age on 1 February 1997. 600 patients (52%) had survived 5 years from first diagnosis but 67 (6%) died later. Of the 533 patients known to be alive, 88 had had benign tumours; 101 had been transferred for follow-up elsewhere (56 before and 45 after survival of 5 years from first diagnosis) but were known to be alive from contact via the West Midlands Regional Children's Tumour Research Group; 28 patients were being followed by other clinical services at BCH, but were not seen in the oncology department long-term follow-up clinic (20 of these patients had been treated for CNS tumours); 13 were lost to follow-up; and 13 had inadequate data available for analysis. Detailed information on the other 290 patients treated for malignant disease and on continuing follow-up in the oncology department long-term follow-up clinic, who formed the study group, was the focus for this investigation.

An audit of medical records was undertaken on a consecutive series of 200 patients who represented an otherwise unselected subset of the study group to identify their attendance at hospital over a period of 12 months. Contact with primary or occupational health care providers was not assessed.

Chronic medical problems were recorded in all patients. These were defined as those issues which were thought to justify ongoing medical intervention or advice and/or were causing, or were likely to cause, functional difficulty or disability.

RESULTS

Age, diagnosis and treatment modalities

Table 1 gives details of age at presentation and the most common diagnoses for patients in the study group and, for comparison, for patients who had died beyond 5 years from first diagnosis and for those who were known to be alive but who had been transferred for follow-up elsewhere and were no longer attending the oncology department long-term follow-up clinic. The study group had been followed up for a median 15 years 4 months (range, 6 years 2 months to 24 years 10 months) from diagnosis and 13 years 6 months (4 years 2 months to 26 years 8 months) from the completion of therapy. Median age at the time of this analysis was 22 years 10 months (18 years 1 month to 35 years 2 months).

Table 2 gives details of the combinations of modalities used for the treatment of patients in the study group only. The information is presented in three roughly equal time periods illustrating differences in treatment strategy that may have emerged over time.

34 (12%) of the study group had survived treatment for relapse (5 during primary treatment and 29 after completion of initial therapy) and 3 (1%) had survived treatment for a second malignancy—one each with acute myeloid leukaemia, adrenocortical carcinoma and adenocarcinoma of the bowel.

Table 1. *Details of patients diagnosed* 1968–1990, *born before February* 1979 *and surviving at least* 5 *years from diagnosis*

	Study Group (%)	Died > 5 years from first diagnosis (%)	Follow up transferred elsewhere > 5 years from first diagnosis (%)
No.	290	67	45
M:F	1.25	1.79	1.5
Median age at diagnosis	7 yr 8 m	8 yr 2 m	8 yr 2 m
Range	Birth–16 yr 6 m	10 m–16 yr 0 m	2 m–14 yr 1 m
Diagnoses			
Leukaemia	105 (36)	31 (46)	17 (38)
Acute lymphoblastic	96 (33)	27 (40)	17 (38)
Hodgkin's disease	43 (15)	8 (12)	5 (11)
CNS tumours	31 (11)	13 (19)	3 (7)
Wilms' tumour	31 (11)	4 (6)	4 (9)
Other	80 (28)	11 (16)	16 (36)
Treatment			
Chemotherapy	247 (85)	58 (87)	40 (89)
Radiotherapy	235 (81)	62 (93)	28 (62)
Surgery	140 (48)	30 (45)	24 (53)

Table 2. Treatment modalities received by patients in the study group by era of diagnosis

Treatment	Era of diagnosis			
	1968–1975 $n = 40$ (%)	1976–1983 $n = 155$ (%)	1984–1990 $n = 95$ (%)	Total $n = 290$ (%)
Chemotherapy	38 (95)	132 (85)	77 (81)	247 (85)
Radiotherapy	32 (80)	130 (84)	73 (77)	235 (81)
Cranial RT	17 (43)	95 (61)	52 (55)	164 (57)
Surgery*	18 (45)	78 (50)	44 (46)	140 (48)

*Excluding diagnostic biopsy.

Chronic medical problems

Analysis of chronic medical problems was undertaken within seven functional clinical areas—endocrine, fertility, sensory, neuropsychological, organ toxicity, mobility and cosmetic. Details of this analysis are given in Table 3 together with footnotes characterising some of the definitions used. Overall 169 (58%) of the study group were recorded to have at least one problem and 93 (32%) two or more.

Social issues

86 patients (30%) had entered further or higher education courses and 21 (7%) had been in special education programmes (75% of these individuals had received cranial radiation). 200 survivors had completed education and were known to be eligible for employment of whom 75% were employed. 28 (10%) of the survivors had children of their own.

Hosptial resource utilisation

A review of the hospital records of an unselected subset of the patients identified that 168 of 200 (84%) of those audited had been seen in the follow-up clinic over a period of 12 months. In total this accounted for 222 clinic visits: 129 patients attended once only, 27 were seen twice, 9 three times and 3 patients attended four times each. 52 (31%) of those who attended had had investigations performed of which the most frequent were chest X-ray (25), full blood count (23) and thyroid function tests (20). No patients were referred for inpatient care but 1 patient was transferred to an adult oncology service for management of a second malignancy (adenocarcinoma of the stomach) from which he subsequently died. 26 patients (15%) also attended other outpatient clinics during the same period, either at the BCH or elsewhere. These included psychiatry (5); orthopaedic (4); endocrine (4); dental (3); ENT (3); cardiac (2); and genetics, urodynamics, eye, fertility and dietetic clinics (1 each).

DISCUSSION

Many survivors of childhood cancer pay a price for cure and, although much has been written about individual toxicities and late mortality [1, 2, 11, 13], little is known of the

Table 3. Chromic medical problems recorded amongst the study group

Functional group	*n* (%)	Problem	No. affected*	All patients %
1. Endocrine	120 (41)	Thyroid hormone replacement therapy	27	9
		Sex hormone replacement therapy	21	7
		Growth hormone deficiency	19	7
2. Organ toxicity	74 (26)	Nephrectomy	32	11
		Splenectomy	16	6
		Cardiac dysfunction†	8	3
		Pulmonary dysfunction†	6	2
3. Mobility	50 (17)	Ataxia	13	4
		Scoliosis‡	15	5
		Limb function (amputation/endoprosthesis)	8	3
		Paraplegia/hemiplegia	5	2
4. Neuropsychological	44 (15)	Learning difficulties§	11	4
		Psychiatric therapy	10	3
		Epilepsy	7	2
5. Infertility	40 (14)	(Predicted or proven)	40	14
6. Sensory‖	38 (13)	Visual handicap	25	9
		Deafness	13	4
7. Cosmetic	28 (10)	Dental problems	6	2
		Soft tissue hypoplasia¶	4	1
		Alopecia**	4	1
		Obesity	4	1
		Small/abnormal genitalia or breasts	4	1
		Skin changes	6	2

*Some patients had more than one problem. Overall 169 (58%) patients had at least one problem and 93 (32%) had two or more. †Current or predicted abnormalities of functional importance. ‡Scoliosis requiring orthopaedic assessment but not always surgical correction. §Requiring special educational support. ‖No specific definition of visual or hearing loss but effect considered functionally important. ¶Obvious soft tissue asymmetry, potentially of cosmetic importance although not necessarily of functional relevance. **Permanent, complete or significant partial hair loss.

overall morbidity within this population. High survival rates for many diagnoses have been achieved only recently and very long-term consequences of some treatments are still uncertain. Some effects are well known and are encountered during or soon after treatment, for example growth and endocrine damage, nephrotoxicity or amputation. Other effects may not be apparent or significant before adult years, for example cardiotoxicity, second malignancy and infertility. Although the concept of follow-up for cancer patients has been questioned in an adult setting [14], the policy in most paediatric oncology centres has been to undertake indefinite surveillance of survivors [12]. Information acquired during such surveillance has importance in directing the design of future treatment strategies and in advising subsequent patients of future risks. Long-term consequences of treatment will continue to evolve as survival patterns improve but the profile of late effects experienced by an individual is determined by the treatment received and cannot necessarily be defined by diagnosis.

Patients treated for leukaemia, (91% of whom had acute lymphoblastic leukaemia), Hodgkin's disease and Wilms' tumour represented the most frequent diagnoses amongst survivors but the number of patients with central nervous system (CNS) tumours was strikingly low, reflecting historically low referral rates of such patients to BCH and to the oncology department, as well as their poorer outcome [15]. Eligible patients excluded from the study group included 67 who had died despite achieving 5 year survival and 45 who had been transferred for follow-up elsewhere after survival to 5 years (but known to be alive). A further 56 patients had been transferred before 5 years from diagnosis, reflecting their age, place of residence, choice of treatment centre or other social reasons. The 13 patients lost to follow-up included 8 who had moved abroad. 20 children treated for brain tumours and 8 additional children treated for leukaemia had been treated by neurosurgery and haematology colleagues but did not attend the oncology long-term follow-up clinic. Detailed follow-up information had not been collected in the same manner, but all were known to be alive. Case notes were missing for data abstraction for 13 patients otherwise eligible for the study. There were few differences between the study group and those excluded from the analysis, but patients treated for leukaemia and brain tumours were the most important contributors to the group who had died after 5-year survival from diagnosis. Overall, 65% of the patients who died beyond 5 years from diagnosis died from recurrence of their primary disease, a finding which remains the most important cause of late mortality in patients with all diagnoses [2].

Patterns of treatment are determined by diagnosis and vary over time although the data shown in Table 2 do not identify any obvious trends. The otherwise unexpected reduction in the number of children receiving chemotherapy diagnosed in the most recent era (81% in 1984–1990 compared with 95% in 1969–1975 and 85% in 1976–1983) may reflect the increasing number of survivors of brain tumour included in the more recent cohort (CNS tumours accounted for 3% of survivors in 1968–1975, 9% in 1976–1983 and 17% in 1984–1990). This study was too small to relate outcomes to specific modalities of therapy but the patterns of treatment recorded in Table 2 are likely to change with time. In particular, a reduction would be expected in the number of children with leukaemia receiving cranial radiotherapy, but a proportional increase in referral of children with CNS tumours may account for the relative stability seen in the overall number of patients who had received cranial irradiation (Table 2). In general, a national trend in increasing central referral of children with brain tumours [15], a group with particularly complex long-term problems [16], is likely to contribute a larger cohort of patients receiving radiotherapy to the brain. In contrast, current U.K. national treatment protocols for Hodgkin's disease, Wilms' tumour and soft tissue sarcoma all limit the place of radiotherapy. Such trends underline the importance of planning follow-up for survivors in relation to treatment actually received rather than by reference to underlying diagnosis. Furthermore, larger, population-based epidemiological studies will be important to provide more precise insight into the correlation between sequelae and treatment and to exclude the possibility of bias which may arise from studies from individual institutions.

Table 3 identifies the incidence of 'chronic medical problems' experienced by survivors. Infertility (14%), nephrectomy (11%), thyroid hormone deficiency (9%), visual handicap (9%), sex hormone (7%) and growth hormone replacement therapy (7%) were the most common problems. The definition of the term 'chronic medical problem' can be challenged but in this study it denotes anything causing, or likely to cause, physical, psychological or social difficulty and/or which might justify ongoing medical intervention or advice. The definition is necessarily broad but incorporates two major perspectives. First, that an individual may experience premature or unexpected ill health (for example, from late cardiotoxicity). Second, that an individual may be socially disadvantaged (for example, from infertility or from a non-progressive mobility problem). The first perspective requires clinical strategies which are directed towards surveillance and to the development of interventions designed to prevent or minimise the late consequences of therapy. The second perspective requires an assessment of the way in which survivors perceive such problems and the design of strategies to help individuals compensate for any disadvantage encountered and to maximise their abilities. In both cases these matters reflect the need for a measure of quality of life and it is towards this goal that long-term evaluations of childhood cancer must evolve [17]. Furthermore, some survivors may require counselling about the genetic risks implied by their primary disease or an associated family history [18].

The results of this study confirm that the implications of cure are not trivial: 58% of survivors had at least one long term medical 'problem', but information about the use of hospital resources by such patients has not been previously assessed. Our data show that the majority of adult survivors complied with long-term surveillance strategy and that a significant minority require the attention of other specialist services. The recent development of guidelines for long-term follow-up by the United Kingdom Children's Cancer Study Group (UKCCSG) [19] should serve to rationalise follow-up strategies and provide a basis for future audit.

The continuing provision of care for adult survivors within a paediatric setting has been challenged [20]. In contrast to young people who have conditions requiring continuing active medical management (for example, diabetes and haemophilia) for whom transfer arrangements can be made to an appropriate adult clinic, there is no pattern of care available within adult cancer services which meets the needs of adult

survivors of childhood cancer. There are however important arguments to suggest that survivors should leave the child centred environment offered by paediatric services [21] and the development of late effects programmes for survivors of cancer treated in adolescence and early adult life could provide an appropriate setting into which survivors of childhood cancer could be referred for ongoing surveillance. Nevertheless, the continuing involvement of paediatric oncologists in this process is justified as the effect of damage during growth and early development needs to be clearly understood and there is a need for paediatric oncologists to retain a perspective on the very late effects of their therapy—to guide future treatment strategies and to inform families of risks at the outset of treatment.

The extent to which some survivors of childhood cancer are disadvantaged by their disease and its treatment poses a challenge for the future. First, it is possible that a clearer understanding of the pathogenesis of treatment-related damage might offer a better prospect for its successful prevention. A biological approach to understanding the risk of specific late sequelae merits wider investigation. For example it is possible that biological or genetic markers of individual susceptibility could be sought, identifying those at special risk at the outset of treatment. Second, whilst it is important to acknowledge the increasing success of treatment, the memories of the experience and, perhaps, the need to cope with long-term sequelae, will inevitably influence the attitude of the survivor in adult life. This need not necessarily be an entirely negative experience: positive aspects of survival are well documented and there is also a need to recognise the generally well adjusted status of many survivors [22]. Empowering survivors to cope with real or potential problems involves their education about the treatment they received and its implications. The UKCCSG has recently launched an information pack which provides information generally applicable to all survivors, with more specific details according to treatment received [23].

Finally, long-term, important and potentially life threatening consequences of treatment used for cancer in childhood will continue to evolve as survival patterns change, particularly if this is achieved in association with more aggressive therapies. These issues will become an increasing focus for attention within society and clinicians themselves may face medico-legal challenges as a result of their efforts to cure. Reduction in the incidence of serious late effects may require a trade-off between alternative toxicities in the design of treatment schedules or even acceptance of a limit on possible survival. Such a debate can only be informed by continuing surveillance of all survivors, by careful documentation of the sequelae of their treatment and by the development and application of methods to assess the quality of survival achieved.

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