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Caring for survivors of childhood cancers: The size of the problem

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ABSTRACT

Many survivors of childhood cancer have significant health problems due to their illness or treatment. This population-based study examines the number of long-term survivors, their disabilities and consequent long-term care needs. Survival rates for children diagnosed with cancer between 1960 and 1999 in the West Midlands, United Kingdom (UK), were used to estimate future long-term survivor numbers. Treatment and late effects data on a cohort of patients surviving for more than 5 years were used to consider continuing care needs. Between the 1960s and 1990s, 5-year survival increased from 23% to 70%. There were 98 5-year survivors in 1970, and numbers may exceed 2100 by the end of 2005. Most (at least 61%) survivors in the West Midlands Region have one or more chronic medical problems and may require multidisciplinary care. We conclude that, in order to determine how to provide cost-effective care for this increasing population, protocol delivered management with audit is needed.

1. Introduction

Approximately 70% of children diagnosed with cancer now have long-term survival prospects[1] resulting from advances in chemotherapy, paediatric surgery, radiotherapy, supportive care and treatment at specialist paediatric oncology centres with inclusion in clinical trials. The proportion of children referred to the UK's 22 paediatric oncology centres rose between 1977 and 1984 from 44% to 71%.[2] This had a significant impact on survival, particularly for patients with acute lymphoblastic leukaemia, non-Hodgkin's lymphoma, Ewing's sarcoma, rhabdomyosarcoma and osteosarcoma.[2] Also, the number of patients entered into clinical trials increased. The first national trials for leukaemia began in 1969, and following the formation of the United Kingdom Children's Cancer Study Group (UKCCSG) in 1977, the number of trials for patients with other types of cancer rose sharply.

Results from the Manchester Children's Tumour Registry[3] and the Northern Region Young Persons' Malignant Disease Registry[4] have demonstrated striking improvements in survival over time, but do not describe the numbers and health status of the survivors.

A previous audit of 290 adult survivors attending our centre for follow-up revealed that chronic medical problems were present in 58% of patients.[5] Such problems may not be detected until many years after the completion of treatment.[6]

This large population-based study examines survival trends for patients diagnosed between 1960 and 1999 in the West Midlands Health Region (population in 2001 5.2 million,[7] approximately 9% of the UK population) and describes a current group of long-term survivors (defined as alive 5 years after diagnosis) with respect to their number, characteristics and likely requirement for ongoing medical care.

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2. Methods

The West Midlands Regional Children's Tumour Registry (WMRCTR) provided data on all children aged 0–14 years, resident in the West Midlands and diagnosed with malignant disease (or a benign brain/central nervous system (CNS) tumour) between 1960 and 1999. Diagnoses were considered to be generally reliable following a pathology review of solid and brain tumour cases diagnosed between 1957 and 1992.[8]

Trends in survival, for all cancers and specific tumour groups, were examined for four successive 10-year cohorts using Kaplan–Meier survival analysis. Survival rates for all tumours were then derived for eight 5-year cohorts. These rates were used to estimate the number of long-term survivors at various time points between 1980 and 2005. For example, in 1995, survivors from the 1970 to 1974 cohort would have a median follow-up time of 23 years. Multiplying the original number of patients in that cohort by the 23-year actuarial survival rate from the cohort's survival curve gives an estimate of the number of survivors in 1995. These estimates were compared with the observed number of survivors recorded by the WMRCTR.

For 2005 survival estimates (survival data were analysed in 2000), the longest available survival time from the Kaplan–Meier curves was used; this was slightly shorter than the median follow-up time at 2005 for all cohorts. Consequently, the figure for 2005 is a crude estimate that assumes no late deaths occur between 2000 and 2005 and that incidence and survival rates are stable.

Finally, details were reviewed of the treatments received and chronic health problems of those long-term survivors attending follow-up clinics at Birmingham Children's Hospital (BCH) and registered on the WMRCTR's long-term follow-up (LTFU) database on 31st December 2002. This hospital-based register is derived from information abstracted from medical notes and coded into broad categories. It incorporates information on patients treated at BCH who are at least 5 years from diagnosis, off cancer treatments for over 3 years and still attending BCH's follow-up clinics. Chronic health problems were defined as those justifying ongoing medical intervention or advice and/or were causing or were likely to cause functional difficulty or disability.[5]

Information on health problems in survivors not attending these clinics was derived from the WMRCTR's postal follow-up system. The general practitioners (GPs) of patients treated at other hospitals, living outside the Region or defaulting from follow-up clinics, are sent periodic letters requesting brief details of any health problems. Further details are sought if the GP notifies a death or second malignancy. Sensitivity analysis was used to estimate the prevalence of health problems among long-term cancer survivors in the Region.

Regular follow-up clinics are held at BCH. Procedures are based on the long-term follow-up guidelines of the United Kingdom Cancer Study Group's Late Effects Group,[9] for example, for patients who have received anthracyclines, echocardiography is recommended at the completion of treatment and then 5-yearly. At these clinics clinicians are encouraged to use a standard form for recording details of the patients' health and social circumstances. Although recorded problems rely on the subjective assessment of the patient by the clinician, only problems that could have a significant impact on the patient are recorded. Heavy workloads precluded psychometric testing and the formal grading of quality of life or severity of toxicity.

3. Results

3.1. Survival

Survival for all cancers combined improved substantially over the 40-year period (Fig. 1) and 70% (95% confidence interval (CI) 67–72%) of patients diagnosed in 1990–1999 can expect to survive for 5 years or more. Table 1 shows how survival has improved over time for different tumour types.

3.2. Survivors

Fig. 2 illustrates the growing number of long-term survivors between 1980 and 2005. The derivation of the number of survivors expected in 2005 is shown in Table 2. The curve for the observed number of survivors can be almost superimposed on the curve for estimated numbers up to the year 2000, demonstrating the validity of the method for predicting survivor numbers. Thus we calculated that by the end of 2005 there would be at least 2130 long-term survivors in the Region.

3.3. Long-term survivors – tumour types

The distribution of tumour types among the survivors is shown in Fig. 3. The composition of the group of long-term survivors in terms of tumour type has altered over time. In the earlier decades, half of all survivors were those originally diagnosed with brain tumours, but by 2000, leukaemia patients comprised nearly a third of all survivors.

3.4. LTFU patients – treatment received and their health problems

Of the 5022 children in the study, 2165 survived their tumour for 5 years or more and so were *potentially* eligible for clinical

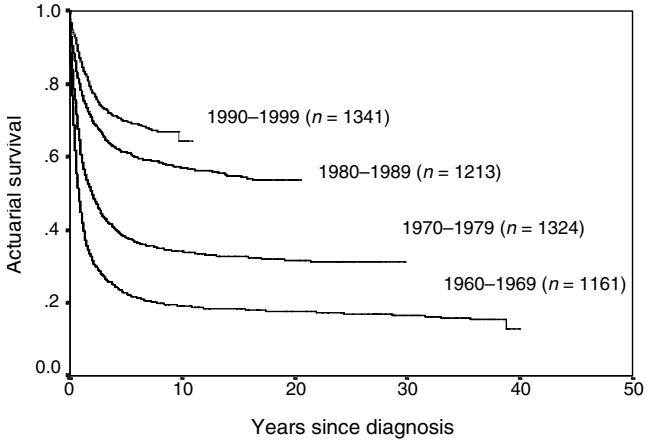

Fig. 1 – Childhood cancer survival in the West Midlands 1960–1999.

Table 1 – Childhood cancer survival in the West Midlands Region 1960–1999

Tumour type	Number of cancers in 5016 children	Five and 10-year actuarial survival rate (%)								Test for trend (P)
		1960–1969		1970—1979		1980–1989		1990–1999		
		5 year	10 year	5 year	10 year	5 year	10 year	5 year	10 year	
All cancers	5038	23	19	38	34	61	57	70	64	<0.001
Leukaemia (all cases)	1712	6	3	32	25	61	57	74	66	<0.001
ALL	1203	10	5	41	32	69	63	80	71	<0.001
AML	333	2	1	7	7	37	36	50	50	<0.001
Hodgkin's	209	55	39	79	72	97	88	98	90	<0.001
NHL	259	20	20	23	22	67	65	79	79	<0.001
CNS tumours	1251	36	30	36	34	53	48	60	55	<0.001
Soft tissue sarcoma	336	18	14	33	32	61	59	59	59	<0.001
Neuroblastoma <1 year	87	20	20	14	14	77	72	82	82	<0.001
Neuroblastoma >1 year	213	12	12	14	14	17	13	36	27	<0.001
Renal tumours	268	24	22	75	75	82	80	85	85	<0.001
Germ cell	108	21	16	56	56	82	82	93	93	<0.001
Liver tumours	58	14	14	15	15	23	23	66	66	0.002
Bone tumours	209	19	19	27	24	52	48	55	55	<0.001
Retinoblastoma	177	85	85	88	83	83	83	92	92	0.515

AML, acute myeloid leukaemia; ALL, acute lymphoblastic lymphoma; NHL, non-Hodgkin's lymphoma; CNS, central nervous system.

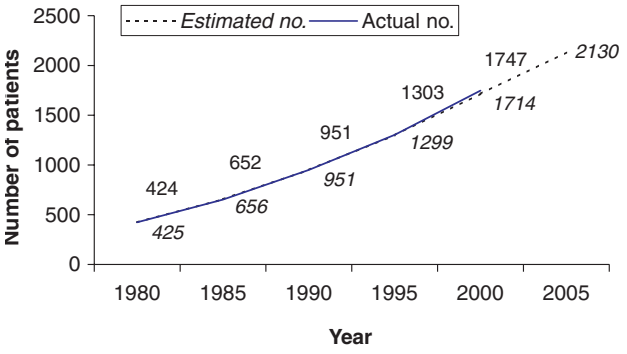

Fig. 2 – Observed and estimated numbers of long-term survivors in the West Midlands, 1980–2005.

long-term follow-up (the population-based database did not record whether they had been off-treatment for 3 years). In total, 88% (1907/2165) of 5-year survivors in the Region received some form of long-term monitoring. Of the remaining 258 cases, 181 were known to have died before 31st December 2002, so that only 3.6% (77/2165) of cases in the Region were without record of follow-up. The reasons for their omission included failure to trace the patient (emigrated or current address unknown) and GP/patient refusal to provide information.

Of the 2165 5-year survivors, 264 (12%) subsequently died (22% (165/765) of those diagnosed before 1980 and 7% (99/1400) of those diagnosed since 1980). Most of the deaths were due to a late recurrence of disease (195; 74%) or a second malignancy (36; 14%), but 8 (3%) were treatment-related, and 25 deaths (9%) were due to non-cancer related causes.

At the time of analysis (December 2002), the median duration of follow-up (date of diagnosis to date last seen) for 1901 living 5-year survivors was 14.7 years (inter-quartile range 9.6–22.5 years). The median date last seen was December 2001 (IQR September 1999 to July 2002). Median follow-up for those on clinical follow-up was shorter than for those on postal follow-up (12.2 compared with 21.8 years), indicating that the postal follow-up patients were older (63% diagnosed before 1980, compared with 11% of clinical follow-up patients). Most postal follow-up patients (77%) were treated at

Table 2 – Method for estimating the number of long-term survivors in 2005

Year of diagnosis	Number patients diagnosed	Median years of follow-up by 2005	Maximum number years of follow-up by 2000	Year 2000% survival figures (CI)	Estimated number long-term survivors in 2005
1960–1964	504	43	40	12.6 (7.4–17.9)	63.7
1965–1969	656	38	35	16.4 (13.5–19.2)	107.3
1970–1974	684	33	30	28.1 (24.8–31.5)	192.5
1975–1979	638	28	25	34.4 (30.6–38.2)	219.4
1980–1984	593	23	20	49.8 (45.7–53.9)	295.3
1985–1989	613	18	15	59.2 (54.8–63.5)	362.7
1990–1994	682	13	10	64.8 (58.6–70.9)	441.6
1995–1999	646	8	5	69.3 (64.0–74.7)	447.9
				Total	2130.4

CI, confidence interval.

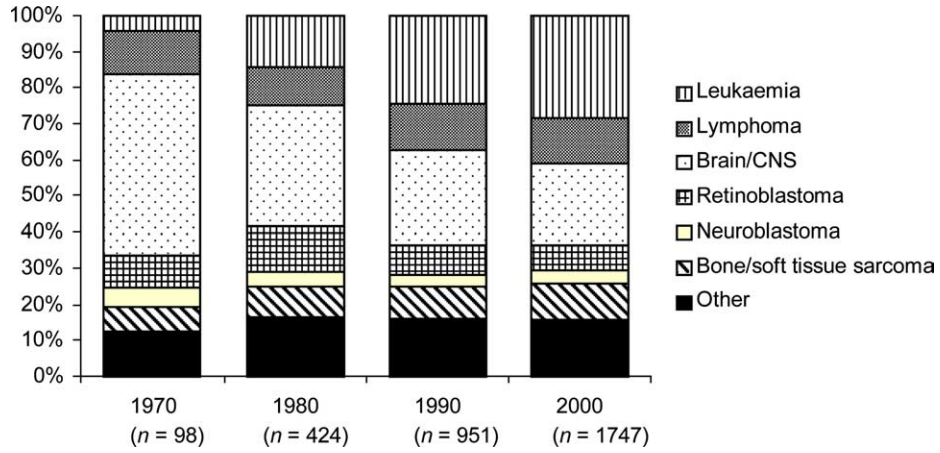

Fig. 3 – Changes over time in the distribution of tumour types in 5-year survivors (i.e., in patients alive on 31st December 1970, 1980, 1990 and 2000).

external hospitals and would have been discharged before follow-up clinics were instigated.

Table 3 lists the main chronic conditions coded in the long-term follow-up database (i.e., conditions mentioned in the follow-up clinic records), grouped into broad categories. It shows for each category the three most commonly recorded conditions.

Table 4 shows the distribution of these 5-year survivors according to tumour type, along with the number of health problems recorded. At least one recorded problem was experienced by 80% of patients on clinical and 55% of those on postal follow-up. Overall, 70% of survivors with follow-up data had some record of problems. CNS tumour survivors were most commonly affected: of those attending the follow-up clinics, only 6% were problem-free and over 70% had three or more different conditions recorded.

If all patients without follow-up data are assumed to be problem-free, then at least 61% of all survivors have experienced one or more health problems. Within the diagnostic groups the proportions are 57% for CNS tumours, 47% for leukaemias and 73% for solid tumours.

Table 5 shows the treatment received by the 1104 patients attending clinics. At the time of analysis, the treatment details of postal follow-up patients were not available. Chemotherapy agents given included anthracyclines which were given to only one patient with a CNS tumour, but to 78% with leukaemia and 43% with lymphoma/other solid tumours. Alkylating agents were given to 45% of patients with lymphomas/other solid tumours, 31% with CNS tumours and 35% with leukaemia. Exposure to epipodophyllotoxins in the CNS group was rare, as was platinum therapy in leukaemia. Cranial irradiation was received by 76% of cases of CNS tumour, usually in doses of >24 Gy, by 67% of those with leukaemia (some of these also had total body irradiation), but by only 6% of patients in the lymphoma/other solid tumours group. No treatment was given to an infant with acute myeloid leukaemia and Down's syndrome, another with stage 4S neuroblastoma and a child with optic glioma.

Table 6 shows details of the most common problems encountered (the ones affecting at least 10% of patients). Endocrine, growth and fertility problems, mostly due to pituitary or thyroid irradiation or gonadal damage from alkylating

Table 3 – Major categories of chronic medical conditions recorded at follow-up (among 1104 patients) (comprising over 95% of all conditions recorded)

Category	Chronic medical problems
Growth/endocrine	Thyroxine deficiency,[a] growth hormone deficiency,[b] infertility,[c] sex hormone deficiency, diabetes, short stature, abnormal sexual development
Neurological	Epilepsy[a]; cerebral palsy; ataxia/dyspraxia[b]; migraine[c]
Organ/system	Respiratory problems[a] (including asthma); organ removal (kidney[b], spleen, gonad); cardiovascular problems[c] (including hypertension); bladder problems; renal, hepatic and gastro-intestinal problems
Special sense/dental	Visual handicap (excluding refractive disorders)[a], deafness[b], dental problems[c], cataract, speech defects
Intellectual/psychological	Learning difficulties[a], behaviour problems[b], psychiatric referral, anxiety/depression[c], pre-existing conditions, e.g., Down's syndrome
Cosmetic effects	Obesity and overweight[a] (clinician's assessment – BMI not recorded); tissue atrophy and hypoplasia[b]; skin problems[c]; growth asymmetry; alopecia; scarring; cosmetic implants
Orthopaedic	Scoliosis[a], paraplegia/hemiplegia[b], amputation/endoprosthesis[c], arthritis, osteopaenia, loss of limb function

BMI, body mass index.
a Most commonly recorded condition in that category.
b Second most common condition.
c Third most common condition.

Table 4 – Type of follow-up and health problems recorded in 2165 survivors

Number (*n*) and percentage of survivors by diagnostic group

	CNS		Leukaemia		Solid tumours[a]		All tumours	
	n	%	*n*	%	*n*	%	*n*	%
5-Year survivors with no follow-up	83	16.1	115	17.5	60	6.0	258	11.9
5-Year survivors with clinical follow-up	147	28.6	408	62.6	549	55.2	1104	51.0
No problems recorded	9	6.1	147	36.0	65	11.8	221	20.0
1–2 problems recorded	33	22.4	178	43.6	291	53.0	502	45.5
3+ problems recorded	105	71.4	83	20.3	193	35.2	381	34.5
5-Year survivors with postal follow-up	284	55.3	133	20.3	386	38.8	803	37.1
No problems recorded	127	44.7	85	63.9	146	37.8	358	44.6
1–2 problems recorded	136	47.9	46	34.6	229	59.3	411	51.2
3+ problems recorded	21	7.4	2	1.5	11	2.8	34	4.2
5-Year survivors with any type of follow-up	431	83.9	541	82.5	935	94.0	1907	88.1
No problems recorded	136	31.6	232	42.9	211	22.6	579	30.4
1–2 problems recorded	169	39.2	224	41.4	520	55.6	913	47.9
3+ problems recorded	126	29.2	85	15.7	204	21.8	415	21.8
Total	514	100	656	100	995	100	2165	100

a Including lymphoma.

Table 5 – Treatment received by 1104 clinical follow-up patients (many received several treatment modalities and drugs)

	CNS tumours *n* = 147	Leukaemias *n* = 408	Solid tumours/lymphomas *n* = 549	Total *n* = 1104
Treatment type	Number (%)	Number (%)	Number (%)	Number (%)
No treatment	1 (1)	1 (<1)	1 (< 1)	3 (<1)
Surgery alone	29 (20)	0 (0)	60 (11)	89 (8)
Chemotherapy alone	0 (0)	128 (31)	82 (15)	210 (19)
Radiotherapy alone	11 (7)	0 (0)	20 (4)	31 (3)
Total receiving chemotherapy	56 (38)	407 (100)	441 (80)	904 (82)
Anthracyclines	1 (1)	320 (78)	234 (43)	555 (50)
Alkylating agents	46 (31)	144 (35)	248 (45)	438 (40)
Epipodophyllotoxins	9 (6)	238 (58)	112 (20)	359 (33)
Platinums	35 (24)	3 (1)	93 (17)	131 (12)
Total receiving radiotherapy	115 (78)	278 (68)	240 (44)	633 (57)
Cranial irradiation	112 (76)	274 (67)	32 (6)	418 (38)
<24 Gy	1 (1)	173 (42)	7 (1)	181 (16)
⩾24 Gy	111 (76)	97 (24)	25 (5)	233 (21)
Record missing	1 (1)	4 (1)	0 (0)	5 (< 1)
Total body irradiation	0 (0)	44 (11)	0 (0)	44 (4)

CNS, central nervous system.

agents, were common, especially in survivors of CNS tumours. These figures may be underestimated as some survivors, particularly of leukaemia, were still awaiting pituitary function tests. Moreover, the obesity present in some may also have had an endocrine basis. Although the aetiology of obesity is likely to be multi-factorial, of 175 cases marked as overweight/obese, 79 (45%) also had a growth/endocrine problem recorded. The marked differences between the disease subsets also strongly indicates an endocrine basis for the obesity. For example, 96% of overweight/obese brain tumour survivors also had a growth/endocrine problem recorded, compared with 40% of overweight/obese leukaemia patients and 32% of solid tumour/lymphoma patients. In only 15% of all overweight/obese patients was this the only problem recorded. Unsurprisingly, survivors of CNS tumours had more neurological, intellectual and visual/auditory problems than the other groups. Organ damage and toxicity (renal, cardiovascular and pulmonary) were most common in the solid tumour group, who also had more cosmetic problems (tissue atrophy and hypoplasia).

4. Discussion

During 1960–1999 5022 children resident in the West Midlands were diagnosed with cancer and by 2000 1747 of them were long-term (>5 years) survivors. The actuarial 5-year survival rates rose from 23% (95% CI 20–25%) for those diagnosed in the 1960s to 70% (95% CI 67–72%) for those diagnosed in the 1990s. Consequently, both the proportion of children surviving and their cumulative numbers increased steadily over time.

Based on current incidence and survival data the estimated number of long-term survivors will be 2130 by the end of 2005. The method used for this estimate appears to

Table 6 – Health problems affecting 10% or more of clinical follow-up patients: by tumour type (many patients had more than one problem)

Health problems by tumour type	%
All tumours (n = 1104)	
Obesity, overweight	15.9
Thyroxine treatment	11.9
Visual handicap	11.4
Growth hormone treatment	11.2
Respiratory problems (including asthma)	11.1
Nephrectomy	10.8
Tissue atrophy, hypoplasia	10.5
Learning difficulties	10.3
CNS tumours (n = 147)	
Growth hormone treatment	50.3
Thyroxine treatment	40.8
Visual handicap	38.1
Learning difficulties	29.3
Ataxia, dyspraxia	23.1
Obesity, overweight	18.4
Epilepsy	16.3
Precocious puberty	12.9
Deaf and hearing problems	11.6
Leukaemias (n = 408)	
Obesity, overweight	17.2
Learning difficulties	11.0
Respiratory problems (including asthma)	10.3
Growth hormone treatment	10.8
Solid tumours/lymphomas (n = 549)	
Nephrectomy	21.7
Tissue atrophy, hypoplasia	19.5
Obesity, overweight	14.2
Respiratory problems (including asthma)	13.5
Visual handicap	10.6
Infertility	10.4
Cardiovascular problems (including hypertension)	10.2

CNS, central nervous system.

be valid and suitable for service planning purposes, although it may overestimate the number, as late deaths are not accounted for. This number is likely to be balanced by an additional small group of survivors who had tumours of borderline or non-malignant type, such as histiocytosis and fibromatosis. These individuals are excluded from the data. Thus, over the 5 years 2000–2005 for our Region, resources will need to have expanded to provide appropriate follow-up care for some 77 extra patients per annum. For the whole of the UK this equates to 856 extra patients per annum, similar to the figure of 850 per annum calculated from national data.[1]

The principal purpose of follow-up is to ensure that survivors enjoy the best possible quantity and quality of life. Seven percent of the survivors diagnosed since 1980 subsequently died, and actuarial survival analysis suggests that some 6% of West Midlands patients diagnosed during 1990–1999 will die from late recurrences, second malignancies or treatment-related complications (the difference between 5 and 10 year survival rates in Table 1). Others will develop tumour- or treatment-related conditions, which, if well managed, may be compatible with longevity and a good quality of life. In our series, 74% of late deaths were due to a recurrence of the original malignancy and 3% to a secondary malignancy. These findings agree with those of Mertens and colleagues,[10] who found that a recurrence of the original cancer accounted for 67% of late deaths although second malignancies also accounted for a statistically significant number of deaths. Mertens and colleagues[10] also found a 10.8-fold excess in mortality in 5-year survivors compared with the United States of America (USA) population as a whole. A strong treatment-related association was also found for subsequent cancer mortality, cardiac mortality and other deaths.

The secondary objective of follow-up is to provide information on late effects for those devising current protocols, an essential component of the audit 'loop'. This allows changes in treatments, sparing the next generation of patients as many adverse effects as possible.

How ongoing surveillance and care should be organised is unclear. Most paediatric oncologists and haematologists believe that follow-up should be lifelong and involve a transition to adult-orientated healthcare by adult 'providers', who, while maintaining links with the paediatric services will encourage the patient to develop independence.[1,11–14] The range of late effects demands access to a multidisciplinary team including specialists in endocrinology, cardiology, neuro-psychology, cognitive problems and rehabilitation.[15–20]

Among patients attending our follow-up clinics, 80% had at least 1 health problem recorded, as did 55% of those on postal follow-up. Assuming that those without any follow-up were problem-free, at least 61% of all survivors had experienced at least one health problem. If this figure is extrapolated to the UK population, by the end of 2005 there may be some 23,700 long-term survivors of cases diagnosed since 1960, of whom some 19,000 have chronic problems justifying ongoing medical care. While the lower prevalence of problems in the postal follow-up group might suggest under-diagnosis by GPs, postal follow-up patients are probably at lower risk of chronic problems since most were diagnosed before chemotherapy use became widespread in the 1980s. They may also represent more favourable tumours; for instance astrocytoma (a good prognosis tumour with few long-term sequelae) comprised 36% of the CNS cases on postal follow-up, compared with 15% on clinical follow-up (data not shown).

For survivors of brain tumours on clinical follow-up, our data demonstrate the multiplicity of problems that affect many patients and that the majority (76%) had received radiotherapy to the brain. Growth hormone deficiency had been diagnosed in 50% of our patients and the overweight present in 18% may also have had an endocrine basis. Many also had neurological, neuropsychological and visual/auditory problems. Our findings, therefore, support the view that the majority of brain tumour survivors are likely to benefit from follow-up in a specialised late effects clinic.[11]

Until 1990s most children in the UK with acute leukaemia received cranial radiotherapy. Doses were generally larger in the 1970s than in more recent years, but growth hormone deficiency has been demonstrated following doses as low as 18 Gy.[21] Ten percent of leukaemia survivors attending follow-up clinics had been diagnosed as having growth hormone deficiency. Furthermore, 17% were overweight, which may indicate a growth hormone-related metabolic syndrome.

Several studies have described such a syndrome and suggested that there is a case for instituting growth hormone therapy, even in adult life.[21–24] We therefore suggest that all patients who have had cranial radiotherapy (67% of our leukaemia survivors) should receive endocrine surveillance.

Learning difficulties, often associated with cranial radiotherapy, were present in 10% of leukaemia survivors and a further 9% had other neuropsychological problems (data not shown). Also, 78% had received anthracyclines, for whom the current UKCCSG guidelines[9] recommend echocardiography every 5 years, or more frequently should the patient be at extra risk, for example because of pregnancy, puberty or taking strenuous exercise. In one study, 5% of children given anthracyclines for malignancies developed clinical heart failure within 15 years,[19] but whether early diagnosis and treatment would benefit such patients is unknown. The Scottish Intercollegiate Guidelines Network (SIGN) recommend echocardiograms to be performed every 3 years following treatment, with more frequent assessment should evidence of cardiac dysfunction develop.[25] At present there are few publications on the treatment of cardiac dysfunction caused by exposure to anthracyclines,[25] meaning that many guidelines are not evidence based. In one retrospective study by Lipshulz and colleagues,[26] of 18 children who were given enalapril for doxorubicin-induced left ventricular dysfunction, a transient improvement in cardiac function and structure was found. Progressive improvements in left ventricular dimension, afterload, fractional shortening and mass were found after a period of 0–6 years of treatment, although between 6 and 10 years these improvements disappeared with a deterioration in all of these parameters. Research is currently in progress to assess whether long-term improvements can be gained from early treatment for cardiac dysfunction.[25] Until further studies have been completed it seems sensible for all leukaemia survivors to be followed up in late effects clinics.

Similar considerations apply to the follow-up of survivors of lymphomas and other solid tumours, as 43% had received anthracyclines, although only 6% had cranial irradiation. Many had received alkylating agents, epipodophyllotoxins, platinums and other agents that may cause infertility, renal dysfunction, second malignancies or other problems. Radiotherapy (usually not to the brain) had been given to 44% of these patients, for whom long-term medically supervised care in a late effects clinic is recommended.[1,25] Many also require follow-up because of surgical effects, such as amputation, prostheses or nephrectomy. Thus it seems that the majority might also benefit from care in late effects clinics.

At present there are large variations in the long-term follow-up of survivors. Taylor and colleagues[27] conducted a postal survey of clinicians at the UK's 22 paediatric oncology (UKCCSG) centres. Seventy-one replies were received (a response rate of 77%). They found that most (96%) followed-up all of their patients in hospital-based clinics for 5 years after the completion of treatment (and 52% intended to do so for life). Once 5 years had passed, however, many clinicians (45%) began to discharge their patients (almost exclusively (97%) to the patient's GP). Although many of the patients who were discharged were originally diagnosed with benign or stage 1 tumours treated with surgery alone, 16% of clinicians reported discharging all or most of their patients. A cross-sectional postal survey of the GPs of most adult survivors revealed that 65% of GPs reported that their patient was not on regular hospital follow-up.[27]

One criticism of our study is that the chronic problems were abstracted from clinical notes, and thus may be clinicians' subjective opinions rather than rigorously defined conditions (e.g., 'obesity' was not confirmed through body mass index (BMI)). Some of the conditions recorded were pre-existing, and others, such as nephrectomy, though requiring monitoring, may not justify the term 'health problem'; still others, such as obesity, depression and asthma are common in the general population. Reanalysing the data after excluding these debatable codes reduced the proportion of survivors with one or more problems by only 8%(to 53%) and thus our study still indicates the presence of considerable morbidity in this population-based series.

In conclusion, remarkable improvements in survival rates of children with cancer diagnosed in the last 40 years of the 20th century were achieved through centralisation of care undertaken by multidisciplinary teams following multicentre national or international protocols. These now need to be matched by equally rigorous protocol-driven follow-up,[13,14,20,27] mostly in age-appropriate specialised late effects clinics for which adequate financial provision is necessary. This will allow audit of the optimal and most cost-effective methods of follow-up, while also ensuring that survivors enjoy the best possible quality and quantity of survival.

Conflict of interest statement

None declared.

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REFERENCES

1. Wallace WHB, Blacklay A, Eiser C, et al. Developing strategies for long-term follow-up of survivors of childhood cancer. *BMJ* 2001;**323**:271–4.
2. Stiller CA. Centralisation of treatment and survival rates for cancer. *Arch Dis Child* 1988;**63**:23–30.
3. Birch JM, Marsden HB, Morris Jones PH, et al. Improvements in survival from childhood cancer: results of a population based survey over 30 years. *BMJ* 1988;**296**:1372–6.
4. Cotterill SJ, Parker L, Malcolm AJ, et al. Incidence and survival for cancer in children and young adults in the North of England, 1968–1995: a report from the Northern Region Young

Persons' Malignant Disease Registry. *Br J Cancer* 2000;**83**:397–403.
5. Stevens MC, Mahler H, Parkes S. The health status of adult survivors of cancer in childhood. *Eur J Cancer* 1988;**34**:694–8.
6. Schwartz CL. Long-term survivors of childhood cancer: the late effects of therapy. *Oncologist* 1999;**4**:45–54.
7. Office for National Statistics. Census 2001. Accessed January 2004. Available from: www.statistics.gov.uk/census2001/press_release_wm.asp.
8. Parkes SE, Muir KR, Cameron AH, et al. The need for specialist review of pathology in paediatric cancer. *Br J Cancer* 1997;**75**:1156–9.
9. Kissen GDN, Wallace WHB for the United Kingdom Childhood Cancer Study Group's Late Effects group. *Long-term follow-up therapy based guidelines*. Milton Keynes: Pharmacia; 1995.
10. Mertens AC, Yasui Y, Neglia JP, et al. Late mortality experience in five-year survivors of childhood and adolescent cancer: the childhood cancer survivor study. *J Clin Oncol* 2001;**19**:3163–72.
11. Rosen DS. Transition to adult health care for adolescents and young adults with cancer. *Cancer* 1993;**71**:3411–4.
12. Oeffinger KC, Eshelman DA, Tomlinson GE, et al. Programs for adult survivors of childhood cancer. *J Clin Oncol* 1998;**16**:2864–7.
13. Jereb B. Model for long-term follow-up of survivors of childhood cancer. *Med Pediatr Onc* 2000;**34**:256–8.
14. Callahan ST, Winitzer RF, Keenan P. Transition from pediatric to adult-oriented health care: a challenge for patients with chronic disease. *Curr Opin Pediatr* 2001;**13**:310–6.
15. Meadows AT, Gallagher JA, Bunin GR. Late effects of early childhood cancer therapy. *Br J Cancer* 1992;**18**(Suppl.):S92–5.
16. Gleeson HK, Shalet SM. Endocrine complications of neoplastic diseases in children and adults. *Curr Opin Pediatr* 2001;**13**:346–51.
17. Foreman NK, Faestel PM, Pearson J, et al. Health status in 52 long-term survivors of pediatric brain tumors. *J Neurooncol* 1999;**41**:47–53.
18. Spoudeas HA. Growth and endocrine function after chemotherapy and radiotherapy in childhood. *Eur J Cancer* 2002;**38**:1748–59.
19. Kremer LC, van Dalen EC, Offringa M, et al. Anthracycline-induced clinical heart failure in a cohort of 607 children: long-term follow-up study. *J Clin Oncol* 2001;**19**:191–6.
20. Eiser C, Levitt G, Leiper A, et al. Clinic audit for long-term survivors of childhood cancer. *Arch Dis Childh* 1996;**75**:405–9.
21. Brennan BMD, Rahim A, Mackie EM, et al. Growth hormone status in adults treated for acute lymphoblastic leukaemia in childhood. *Clin Endocrin* 1998;**48**:777–83.
22. Murray RD, Brennan BMD, Rahim A, et al. Survivors of childhood cancer: long-term endocrine and metabolic problems dwarf the growth disturbance. *Acta Paediatr Suppl* 1999;**433**:5–12.
23. Vahl N, Juul A, Jorgensen JOL, et al. Continuation of growth hormone replacement in GH-deficient patients during transition from childhood to adulthood: a two-year placebo-controlled study. *J Clin Endocrinol Metab* 2000;**85**:1874–81.
24. Sklar CA, Mertens AC, Walter A, et al. Changes in body mass index and prevalence of overweight in survivors of childhood acute lymphoblastic leukaemia: role of cranial irradiation. *Med Pediatr Oncol* 2000;**35**:91–5.
25. Scottish Intercollegiate Guidelines Network (SIGN). Long-Term Follow-Up of Survivors of Childhood Cancer. A National Clinical Guideline. Edinburgh: Scottish Intercollegiate Guidelines Network, 2004. ISBN 1 899893 83 0. (See also SIGN no. 76 on www.sign.ac.uk/guidelines/fulltext/76/index.html).
26. Lipshultz SE, Lipsitz SR, Sallan SE, et al. Long-term enalapril therapy for left ventricular dysfunction in doxorubicin-treated survivors of childhood cancer. *J Clin Oncol* 2002;**20**:4517–22.
27. Taylor A, Hawkins M, Grififths A, et al. Long-term follow-up of survivors of childhood cancer in the UK. *Paediatr Blood Cancer* 2004;**42**:161–8.