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Can Intensity of long-term follow-up for survivors of childhood and teenage cancer be safely determined by therapy-based risk-stratification?

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Article summary

Article Focus

- Therapy-based, risk-stratification of survivors can safely predict which survivors of childhood and teenage cancer are at significant risk of developing moderate to severe late effects and require high intensity long-term follow-up.

Key messages

- Patients who had received the most complex cancer treatments had the largest number and most severe late effects. Those patients assigned to low risk category of follow-up had few late effects and those late effects were mild.
- Long term survivors of childhood and teenage cancer can safely be assigned to primary care, nurse-led or hospital follow-up based on the intensity of treatment they received for the original cancer.
- Stratification of patients according to risk of late morbidity will maximise the use of NHS resources and provide age appropriate care as locally as possible.

Strengths

- This study shows that it is possible to safely predict which survivors of childhood cancer are at significant risk of developing moderate to severe late effects. Life long follow-up for all childhood cancer survivors is not only cost ineffective but also difficult to organize. Until now there was no evidence available to define the optimum follow-up for long-term survivors.

- Risk stratification will enable young adult survivors to benefit from a transition process that takes them into an appropriate follow-up model and can help to identify those survivors who can be safely discharged from hospital based follow-up.

Limitations

- 30% of the cohort had not been seen in the hospital based late effects service for more than two years and health problems may be underestimated in this group.
- It would be helpful in future studies to determine the proportion of late effects detected as a direct result of clinic attendance and to determine the proportion of late effects which are treatable.

Abstract

Objective

To determine the safety of therapy-based, risk-stratified follow-up guidelines for childhood and teenage cancer survivors by evaluating adverse health outcomes in a survivor cohort retrospectively assigned a risk category.

Design

Retrospective cohort study.

Setting

Tertiary level, single centre, paediatric cancer unit in South East Scotland

Participants

All children and teenagers diagnosed with cancer (<19 years) between 1st January 1971-31st July 2004, who were alive more than five years from diagnosis formed the study cohort. Each survivor was retrospectively assigned a level of follow-up, based on their predicted risk of developing treatment related late effects (level 1, 2 and 3 for low, medium and high risk, respectively). Adverse health outcomes were determined from review of medical records and postal questionnaires. Late effects were graded using the Common Terminology Criteria for Adverse Event, Version 3 (CTCAEv3).

Results

607 five-year survivors were identified. Risk-stratification identified 86 (14.2%), 271 (44.6%) and 250 (41.2%) level 1, 2 and 3 survivors respectively. The prevalence of late effects (LE) for level 1 survivors was 11.6% with only 1 patient with grade 3 or above toxicity. 35.8% of level 2 survivors had a LE, of whom 9.3%, 58.8%, 18.5%, 10.3% and 3% had grade 1, 2, 3, 4 and 5 toxicity respectively. 65.2 % of level 3 survivors had LE), of whom 5.5% (n=9), 34.4% (n=56), 36.2% (n=59), 22.1% (n=36) and 1.8% (n=3) had grade 1,2,3,4 and 5 toxicity respectively.

Conclusions

Therapy-based, risk-stratification of survivors can safely predict which patients are at significant risk of developing moderate to severe late effects and require high intensity long-term follow-up.

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Introduction

Dramatic improvements in survival for children with cancer have highlighted the need for evidence based long-term follow-up (LTFU) for these young people. Approximately 80% of children diagnosed with cancer can now expect to survive more than 5 years, and around 70 % will survive ten years, from their diagnosis.[1] It is estimated that 1 in 640 young adults is a survivor of childhood cancer.[2] As many as two thirds of long-term survivors are reported to be at increased risk of substantial morbidity and even mortality, due to adverse late effects secondary to cancer or cancer therapy.[3-5] Late effects are diverse and include secondary malignancies, organ system damage, infertility, cognitive impairment, and disorders of growth and development.[6, 7] Appropriate LTFU of these patients is essential to detect, treat and prevent morbidity and mortality.[8]

There is wide variation of long-term follow-up practices throughout the UK with a propensity for hospital dependency, often in age-inappropriate settings.[9] A recent study has highlighted how excess morbidity in survivors translates into increased use of health care facilities.[10] An awareness of the need for an integrated and systematic approach to follow-up was recognised by the Scottish Intercollegiate Guidelines Network (SIGN) who developed an evidence-based approach to long-term follow-up.[11] The risks of developing treatment related late effects depend upon the underlying malignancy, the site of the tumour, the type of treatment and the age at time of treatment. A risk-stratified approach to health surveillance was developed which identified three groups of survivors who require an increasing

intensity of follow-up[8]. In the UK, we published a Practice Statement 'Therapy Based Long-term Follow-up' which is designed to inform and guide clinicians responsible for the long-term follow-up of childhood cancer survivors.[12] The Practice Statement recommends follow-up assessments and investigations based on the treatment that the individual has received and is informed by the evidence-based recommendations published by SIGN 76.

An integrated and systematic approach is now considered a requirement of the National Institute of Health and Clinical Excellence (NIHCE) Improving Outcomes for Children and Young People with Cancer Guidance (2005) and National Delivery Plan for Children and Young People's Specialist Services in Scotland (2008).[13,14] In England, the National Cancer Survivorship Initiative (NCSI) has developed as a partnership between the Department of Health, Macmillan Cancer Support, and supported by NHS Improvement, to develop models of care to ensure that those living with and beyond cancer have access to safe and effective care and receive the support they need to lead as healthy and active a life as possible. Improved awareness of cancer survivorship as a chronic health problem will facilitate the development of care pathways that will meet the needs of every patient throughout their lifetime.[15]

Although there is growing guidance on whom, where and how long-term survivors should be followed-up, evidence to show that adopting a model of risk-stratified follow-up is safe is lacking. A recent study has shown that assigning

patients to one of three agreed levels of follow up, as described by Wallace et al, was relatively simple for experienced clinic staff.[16] The objective of this study was to evaluate the safety and efficacy of this risk-based follow-up model by retrospectively stratifying an unselected cohort of long-term survivors of childhood cancer from a single centre and objectively evaluating their health status.

Methods

Study population

All patients, aged less than 19 years, who were diagnosed with childhood cancer in a single institution in South East Scotland, between 1971 and 2004, and who were alive at least five years from diagnosis, were included in the study. The patients were identified from the Oxford Children's Cancer Registry, established in 1992; patients diagnosed before 1992 were identified from the Scottish Cancer Registry, established in 1958, and hospital records.

Data Collection

All health problems directly attributable to cancer, or cancer therapy, were obtained from medical records, electronic hospital records systems, self-reported questionnaires. Medical data were obtained from medical records, electronic hospital records, clinical correspondence from other health professionals and self-completed health status questionnaire and is likely to be an underestimate of the health problems. Cause of death for the deceased patients as assigned by the General Register Office for Scotland, was obtained from the Scottish Cancer Registry, courtesy of Information Services Division, NHS National Services, Scotland (personal communication).

Therapy-based risk stratification

The Scottish Intercollegiate Guidelines Network (SIGN) has developed an evidence-based approach to LTFU, incorporating the risk-based levels of follow-

up described in 2001.[8] Patients are classified into one of three groups (Levels 1,2 and 3): Level 1 patients, treated with surgery alone or low risk chemotherapy treatment, who could be followed up by postal or telephone contact; Level 2 patients, treated with standard risk chemotherapy, such as survivors of ALL or lymphoma, who are considered to be at moderate risk of developing late effects, eg anthracycline-induced cardiotoxicity, could be followed up by an appropriately trained individual, such as a late effects nurse specialist; Level 3 patients, who would require medically supervised follow-up within a multi-disciplinary team – that is those patients that have had a CNS tumour (treated with chemotherapy and/or radiotherapy), bone marrow transplants, stage 4 disease, any radiotherapy except low dose cranial radiotherapy and those that have had intensive therapy. Risk-stratified levels of follow-up were independently assigned to all survivors by two researchers.

Grading of Late Effects

To determine the severity of late effects, each reported late effect was graded independently by two of the authors using the Common Terminology Criteria for Adverse Events, Version 3.0 (CTCAEv3.0, available at http://ctep.cancer.gov/forms/CTCAEv3.pdf), a scoring system developed through the US National Cancer Institute by a multidisciplinary group and adopted in the UK by the Children's Cancer and Leukaemia Group (CCLG).[17] The CTCAEv3.0 tool can be used for acute and chronic conditions in patients with cancer and grades conditions as mild (grade 1), moderate (grade 2), severe (grade 3), life-

threatening or disabling (grade 4), or adverse event-related death (grade 5). To investigate and reduce inter-observer variability, graded adverse events were compared and inconsistencies were discussed and detailed coding rules were developed (available on request form the authors). Inconsistencies in grading revolved mainly around scoring subjective psychosocial and neuropsychological items of grade 1 or 2, grading of 3 or higher adverse events was straightforward.

Ethical Approval

Ethical approval for this study was requested from the Lothian Research Ethics Committee (LREC). On review by the LREC, the committee decided that ethical approval was not required as long-term follow-up of childhood cancer survivors was deemed to be an acceptable and routine part of clinical practice and there were no experimental interventions.

Analysis

The statistical package for social sciences (SPSS) Windows version 14.0 was used for the statistical analyses. Data were analyzed by descriptive techniques using frequencies, percentages and medians as appropriate.

Results

Study Population

883 patients were diagnosed with childhood and teenage cancer between 1st January 1971 to 1st July 2004 and 607 of these patients were alive five years from diagnosis (5 year overall survival rate 69%). Medical information was collected from a retrospective case note review, regional electronic hospital systems and self-reported health outcomes from questionnaires. Of the 607 five year survivors, 34 patients were deceased (5.6%) at the time of the study (figure 1). Of the 573 long-term survivors alive at the time of this study 122 patients were not known to be under any kind of hospital review (21%). Of the 451 patients under hospital follow-up, 370 (82%) were followed up within the South East Scotland Late Effects Service, either by postal questionnaire follow-up (n=67, 17%) or clinic appointment (n=307, 83%). The remaining 81 (18%) of survivors attended other paediatric hospital-based clinics within the same paediatric setting (n=14) or in Tayside (n=26), or Adult Services in South East Scotland (n=31) and in other cities throughout the UK (n=10). Data were gathered from medical records from information based on a clinic visit of more than two years previously, without supplementation from postal questionnaires in 178 patients (31%) and is likely to represent an underestimate of late effects.

Demographics

607 long-term survivors were identified (males 321 (52.9%)) with median age (range) of 19.2 (5.1-45.1) years and median age (range) at diagnosis 5.1 (0.0-

17.5) years. Of the cohort, 34 (5.6%) were deceased, with a median overall survival (range) of 9.9 (5.0-30.9) years. Of the 573 long-term survivors alive at the time of the study, the median age (range) was 19.4 (5.1-45.1) years and disease free survival (range) 11.3 (0.8-38.3) years (Table 1). The primary cancer diagnosis is shown for all patients and within each risk level (Figure 2). Risk-stratification of all long-term survivors (n=607) identified 86 (14.1%), 271 (44.6%) and 250 (41.2%) at Level 1, 2 and 3 respectively with detailed breakdown of ages and survival interval for each level of patients alive at the time of the study only (n=573), shown in Table 1 and Figure 1. Demographic data is similar between the three populations.

Adverse health outcomes according level of risk

Among the 34 deaths in the five year survivors (n=607), 26 (76.5%) died from progression or relapse of the underlying primary cancer, two (5.9%) died from unrelated causes and six (17.6%) died from treatment related sequelae; five from second primary malignancy and one from end-stage renal failure. Of the five survivors who went on to die from second primary malignancy, three patients (all Level 2) had a meningioma, presumed to be secondary to low dose cranial irradiation as part of CNS directed therapy for the treatment of childhood ALL, one (Level 3) developed extensive intra-abdominal desmoid tumour having previously been treated for medulloblastoma and with a background of APC gene and Turcot's syndrome and the other patient (Level 3) developed AML presumed

to be related to previous topo-isomerase II inhibitor therapy for primary bone sarcoma (Figure 1).

Prevalence and severity of treatment related late effects were determined for each patient with an assigned level of follow up (n=607, Figures 3 and 4). Among Level 1 survivors (n=86), 11.6% (n=10) had late effects, of whom seven (8.1%) had one late effect and three (3.5%) had two late effects; 60% (n=6) of which were grade 1 toxicity, 30% (n=3) of whom were grade 2 toxicity and 10% (n=1) grade 3 toxicity. Within the Level 2 group (n=271), the prevalence of late effects was 35.8% (n=97), of whom 62 (22.9%) had 1 late effect, 23 (8.5%) had 2 late effects, 9 (3.3%) had 3 late effects and 3 (1.1%) had four late effects, of whom 9.3% (n=9) had a maximum toxicity grade of 1, 58.8% (n=57) grade 2, 18.5% (n=18) grade 3, 10.3% (n=10) grade 4 and 3% (n=3) grade 5. The prevalence of late effects in the Level 3 survivors (n=250) was 65.2% (n=163) of whom 37 (14.8%) had 1 late effect, 39 (15.6%) had 2 late effects, 22 (8.8%) had 3 late effects, 16 (6.4%) had 4 late effects and 46 (18.4%) had 5 or more late effects, of whom 9 (5.5%), 56 (34.4%), 59 (36.2%), 36 (22.1%) and 3 (1.8%) had grade 1,2,3,4 and 5 toxicity respectively.

Discussion

We have shown that therapy-based, risk-stratification of long-term survivors of childhood and teenage cancer can safely predict which patients are at risk of developing moderate to severe side effects and require high intensity clinic based long-term follow-up. Retrospective assignment of patients into a risk category identified almost half (45%) of patients could be considered at moderate risk of developing late effects, while 41% were deemed to be at high risk of developing late effects, with only a small proportion felt to be at low risk of late complications. The prevalence and severity of side effects increased with increasing level of follow up.

Lifelong follow-up is recommended for survivors of childhood cancer because many of the health problems may be reduced by prevention or early detection.[18] However follow-up should be individually tailored and hospital based follow-up should not be necessary for all survivors.[19] The incidence of chronic conditions continues to increase with time and there is therefore no safe time after which these patients can be discharged.[20] There is increasing evidence that with increasing time from diagnosis, medical problems associated with ageing, including second cancers, cardiovascular disease, infertility and osteoporosis, may exhibit an accelerated course following certain cancer treatments.[18,21] Mertens et al showed that while recurrent disease remains the most important contributor to late mortality in 5 year survivors there is a significant excess

mortality risk associated with treatment related complications that is present in the 25 years after the initial cancer diagnosis.[22]

It is reported that up to 50% of long-term survivors do not attend Late Effects Clinics and many of these patients are considered to be at high risk of developing treatment-related late complications.[23] There are many reasons why survivors choose not to participate in long-term follow-up including lack of awareness of risks of late morbidity, desire to 'move on', lack of appropriate adult services and clinical discharge. In a study by Blaauwbroek et al they assessed late effects in a group of adult survivors of childhood cancer who were not involved in regular long-term follow-up and reported that almost 40% of survivors suffered from moderate to severe late effects and 33% had previously unknown late effects.[24] This reiterates the need to educate survivors about their past medical history, their treatment and the importance of engaging in regular survivorship programmes.

Low rates of participation in long-term follow-up are universally reported. In 2004, a Delphi panel of 20 expert childhood cancer survivors in US identified a number of barriers contributing to this.[25] Understanding these barriers will lead to improved medical care for these patients. It was recognized that most childhood cancer survivors are not aware of their adverse health risks and often unaware of the details of their cancer or its treatment. Even where LTFU clinics are attended much of the education of late effects was directed at parents and often not

transferred to the child. The Delphi Panel also highlighted the limitations within the health care setting including lack of LTFU service, discharge to primary care physician who lacks expertise in this field and often receive no communication about the child's past medical history. Improving communication between professionals and patients is essential and will be an integral part of development of survivorship programmes.

The traditional model of LTFU has been in paediatric oncology clinics, generally jointly with paediatric endocrinologists, neurologists and clinical oncologists, long into adulthood which brings with it the advantage of continuity of care, familiarity with treatments but there are a number of disadvantages to this system. This is not only an age appropriate environment for these patients, but also an unsustainable situation for paediatric oncologists, as the population of long-term survivors increase and age. In addition, survivors are protected in this paediatric environment and don't develop the skills necessary to navigate the health care system as they develop into adulthood. Ideally, once the long-term survivor reaches adulthood he/she should be transitioned into the appropriate adult late effects services. At present, such a service does not exist and it is difficult to identify which clinicians should take on this role, especially with increasing sub-specialisation in adult medicine. In a busy and overstretched tertiary oncology healthcare service, medical and clinical adult oncology consultants are unlikely to be in a position to take on this responsibility, and may well feel inadequately trained in caring for childhood cancer survivors. In current practice, the only adult

services supporting the long-term follow-up of those patients requiring specialist hospital follow-up are the adult endocrine and neurology clinics.

It has been highlighted that improved communication of cancer information to patients/families and between health care providers may contribute to greater engagement in follow-up programmes, raises awareness of potential late effects amongst survivors and enable clinicians to diagnose and, where possible, treat late effects earlier. Based on national guidelines, we have developed a template for the End of Treatment Summary and Individualised Care Plan, or 'Health Passport', which has been introduced nationally, and welcomed by health professionals and survivors.

Models of care for LTFU of survivors of childhood cancer must be flexible enough to accommodate the needs of the young survivor as they transition throughout their life cycle and also to accommodate the individual heterogeneity of cancer survivors, reflecting the wide range of treatment exposure and adverse long-term sequelae. Development of a service that can deliver individualized, comprehensive, therapy-based patient centred care is essential.

The UK National Cancer Survivorship Initiative is currently exploring models of aftercare services for children and young people who have been treated for cancer. National pathways that identify how follow-up can be delivered in line with current pressures and aspirations are being developed. Clinical risk

stratification will play an integral role in tailoring individualised care to meet the clinical, psychological and practical needs of each survivor. A recent study from the CCSS has reviewed how data derived from the CCSS have characterized specific groups that are deemed to be at highest risk of morbidity and subsequent cancers.[26] Our study has shown that those patients at highest risk of late morbidity can be identified and appropriately stratified into a high risk (level 3) follow-up programme.

Stratification of patients according to risk of late morbidity will maximise the use of health service resources and provide age appropriate care as locally as possible. With increasing time from completion of treatment, it is hoped that the majority of adult survivors will be independent and take responsibility for their own health, with health care support provided by their primary care physician. As a result, the primary care team is likely to play an increasing role in the long-term follow-up of survivors of childhood cancer. Primary care services may be already stretched but GPs are used to meeting targets and ensuring guidelines are implemented. Good communication between the hospital services and primary care will be essential. Early involvement of general practitioners in the Late Effects Services will establish collaborations between the two teams and enable primary Care Physicians to become familiar with the surveillance programme. The feasibility of a shared-care model between cancer paediatric oncology cancer centres and primary-care doctors to deliver survivor-focused risk based health care was tested successfully by a Dutch group. The study showed that

patients would see their family doctor for long-term follow-up: the family doctors were interested in sharing survivors' care; and family doctors would return the necessary medical information needed for continued follow-up.[27] Appropriate education of the family doctors, which has resource implications, was a key finding of this study. More recently this group has shown that a web based survivor care plan can facilitate the long-term care of survivors by family doctors.[28]

In order to improve our understanding of treatment-related side effects and help develop treatment protocols to minimise toxicity, lifelong monitoring of health and well-being of all long-term survivors will be necessary. Our understanding of the late effects of the treatment of Hodgkin's lymphoma has led to studies which are ongoing and are designed to reduce the risk of second malignancy by avoiding radiotherapy in selected cases and replace gonadotoxic chemotherapy with drugs that are efficacious in Hodgkin's lymphoma but less likely to compromise reproductive function.[29] Balancing safety and efficacy in the treatment of Hodgkin's lymphoma remains an important goal in the treatment of this curable malignancy.[30]

We have shown that it is possible to safely predict which survivors of childhood cancer are at significant risk of developing moderate to severe late effects and require moderate or high intensity long-term follow. Importantly we have also shown that there is a group of survivors who can be reliably identified who can be

safely discharged from clinic based follow-up. Structured, risk-adapted follow-up of childhood cancer survivors following evidence-based guidelines would reduce cost ineffective or excessive evaluations and focus individual health care delivery. Education of survivors and health care providers will hopefully reduce the burden of chronic health problems and improve quality of life for the growing population of children and young people who have been treated for cancer.

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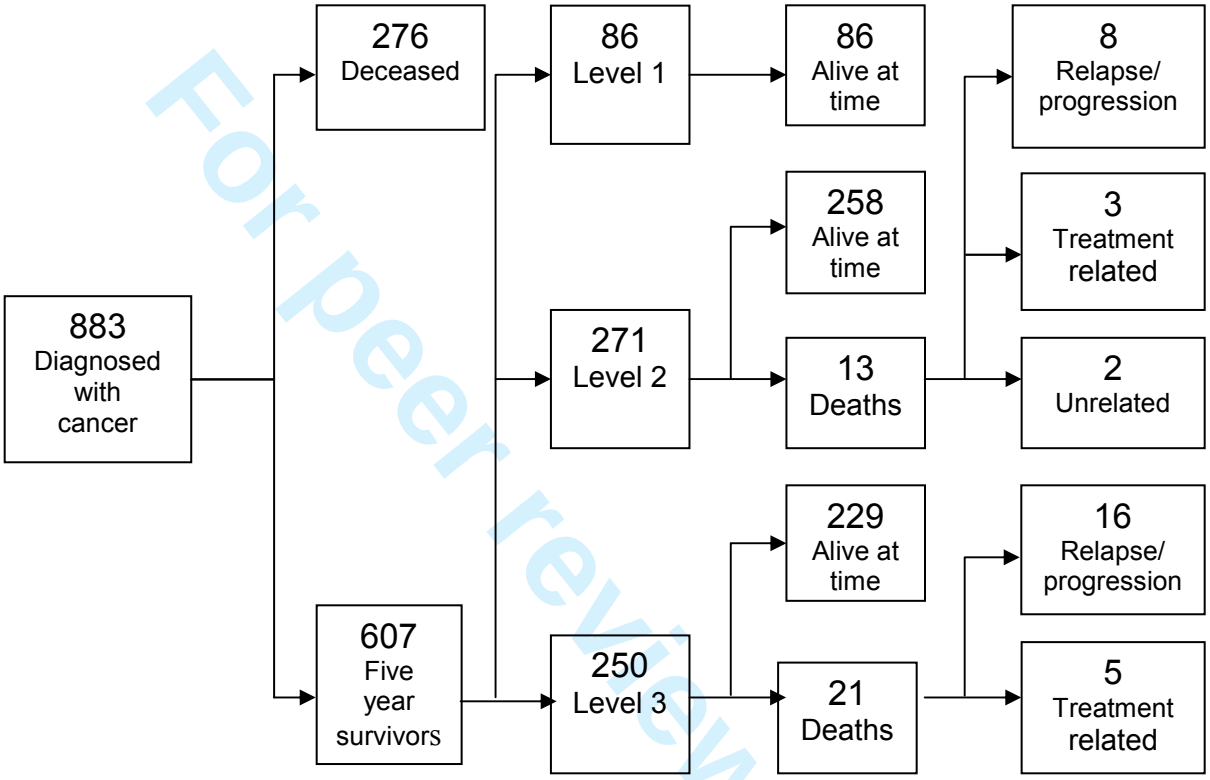

Figure 1. Study flow of childhood and teenage cancer patients.

Flow chart shows the study population and the risk stratification of patients into Levels 1,2 and 3 and the proportion of patients alive at the time of the study.

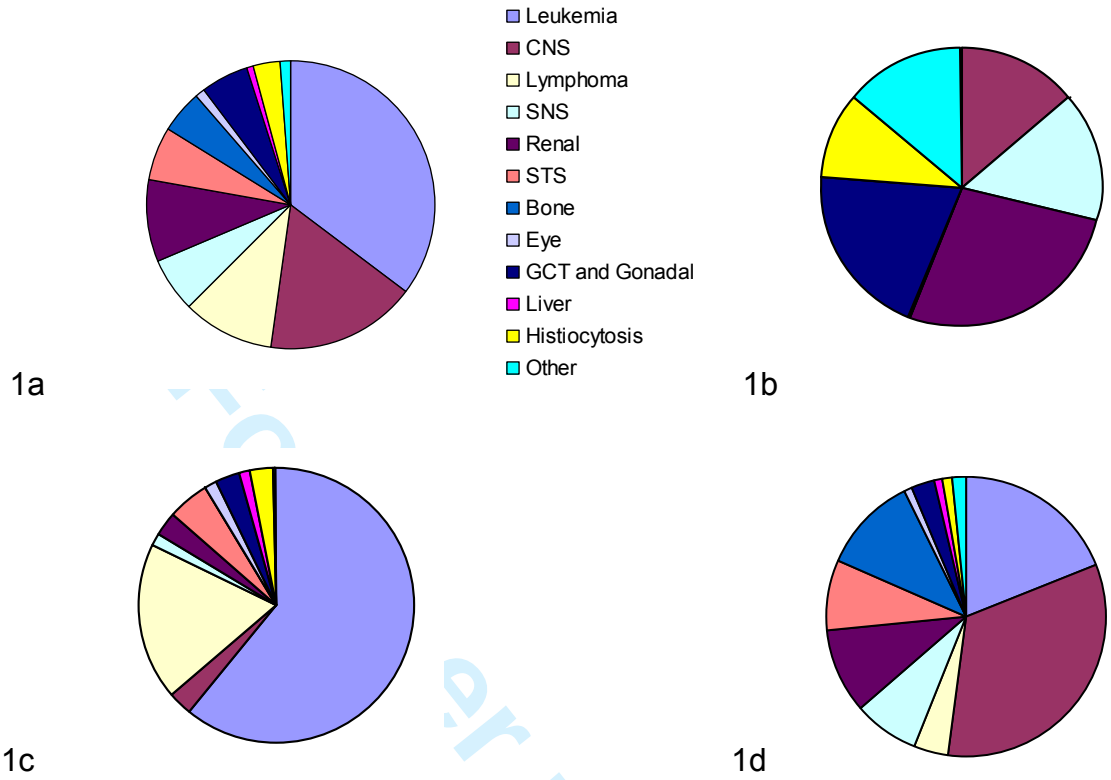

Figure 2 Diagnoses of five year survivors (n-607)

1a. All survivors (n=607), 1b. Level 1 (n= 86), 1c. Level 2 (n=271), 1d. Level 3 (n=250). Abbreviations: CNS – central nervous system tumours, SNS – sympathetic nervous system tumours, GCT – germ cell tumours, STS – soft tissue sarcomas

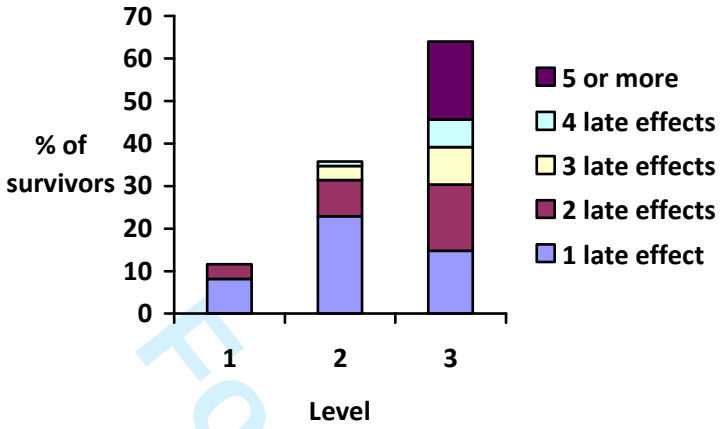

Figure 3

Prevalence of late effects by risk stratified level of follow-up for all five year survivors (n=607).

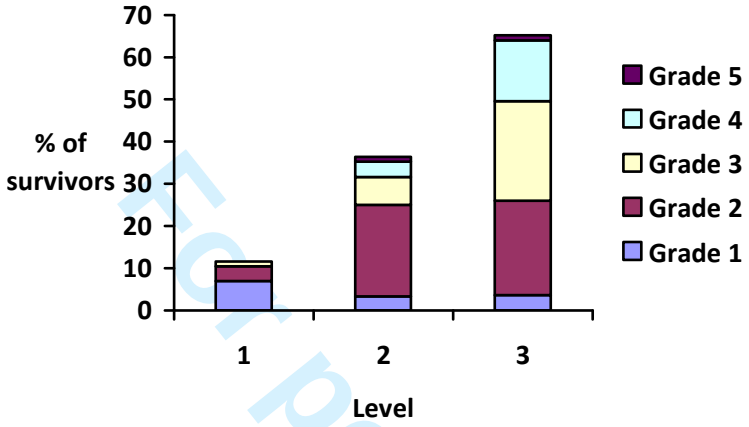

Figure 4

Severity of late effects by risk stratified level (CTCAEv3.0): grade 1- mild, grade 2-moderate, grade 3 severe, grade 4 – life threatening or disabling and grade 5 – death for all five year survivors (n=607). [17]

Table 1. Demographic characteristics of all the five year survivors alive at the time of the study (n=573) and for Level 1, Level 2 and Level 3 subgroups.

Characteristic	Five year survivors (n-573)		Level 1 (n=86)		Level 2 (n=258)		Level 3 (n=229)	
	No.	%	No.	%	No.	%	No.	%
Sex								
Male	303	52.9	37	43	137	53.1	129	56.3
Female	270	47.1	49	57	121	46.9	100	43.7
Current age, years								
5-9	44	7.7	11	12.8	15	5.8	18	7.8
10-14	110	19.2	19	22.1	56	21.7	35	15.3
15-19	148	25.8	31	36.0	66	25.6	51	22.3
20-24	129	22.5	19	22.1	51	19.8	59	25.8
25-29	69	12.0	6	7.0	30	11.6	33	14.4
30-34	40	7.0	-	-	16	6.2	24	10.5
35-39	21	3.7	-	-	15	5.8	6	2.6
40-44	11	1.9	-	-	8	3.1	3	1.3

45-49	1	0.2	-	-	1	0.4	-	-
Median, Range	19.4	5.1-45.1	17.5	5.1-28.4	19.4	8.0-45.1	20.1	5.6-43.7
Age at diagnosis, years								
0-4	286	49.9	54	62.8	140	54.3	92	40.2
5-9	144	25.1	16	18.6	68	26.4	60	26.2
10-14	122	21.3	15	17.4	48	18.6	59	25.8
15-19	21	3.7	1	1.2	2	0.7	18	7.8
Median, Range	5.0	0-20.9	2.9	0-15.4	4.5	0-20.9	6.5	0-17.5
Time from diagnosis, years								
5-9	197	34.4	33	38.4	80	31.0	84	36.7
10-14	166	29.0	32	37.2	76	29.5	58	25.3
15-19	100	17.5	11	12.8	38	14.7	51	22.3
20-24	58	10.1	8	9.3	30	11.6	20	8.7
25-29	30	5.2	2	2.3	16	6.2	12	5.2
30-34	12	2.1	-	-	10	3.9	2	0.9
35-39	10	1.7	-	-	8	3.1	2	0.9
Median, Range	12.4	5.0-39.3	11.0	5.0-26.9	13.0	5.0-38.4	12.9	5.0-39.3
DFS, years								
0-4	36	6.3	1	1.2	20	7.7	15	6.5

5-9	198	34.5	34	39.5	82	31.8	82	35.8
10-14	160	27.9	31	36.0	67	26.0	62	27.1
15-19	84	14.7	10	11.6	34	13.2	40	17.5
20-24	57	9.9	8	9.3	31	12.0	18	7.9
25-29	19	3.4	2	2.4	8	3.1	9	3.9
30-34	17	3.0	-	-	15	5.8	2	0.9
35-39	2	0.3	-	-	1	0.4	1	0.4
Median, Range	11.3	0.5-38.3	10.9	4.4-26.9	11.6	1.9-36.4	11.6	0.5-38.3
Time since last seen in Hospital Based Late Effects Clinic, years								
0-2	328	57.2	31	36.0	143	55.4	154	67.2
3-4	75	13.1	16	18.6	36	13.9	23	10.1
5-7	78	13.6	20	23.3	40	15.5	18	7.9
8-10	28	5.0	6	7.0	10	3.9	12	5.2
>10	41	7.1	8	9.3	19	7.4	14	6.1
Unknown	23	4.0	5	5.8	10	3.9	8	3.5
Median, Range	2.3	0-13.1	4.5	0-12.7	2.2	0-12.7	1.8	0-13.1

Competing interest statement

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work, no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

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Contributorship statement

ABE initiated the project, designed data collection tools, monitored data collection for the study, analysed the data, and drafted and revised the paper. KD designed data collection tools, monitored data collection for the study, analysed the data

and revised the draft paper. SB designed data collection tools, monitored data collection for the study, analysed the data and revised the draft paper. PM-S analysed the data and drafted and revised the paper. WHBW designed data collection tools, monitored data collection for the study, analysed the data, and drafted and revised the paper. All authors had full access to all of the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Data sharing statement

Dataset available from the corresponding author at angela.edgar@luht.scot.nhs.uk. Consent was not obtained but the presented data are anonymised and risk of identification is low.

Ethical approval

Ethical approval for this study was requested from the Lothian Research Ethics Committee (LREC). On review by the LREC, the committee decided that ethical approval was not required as long-term follow-up of childhood cancer survivors was deemed to be an acceptable and routine part of clinical practice and there were no experimental interventions.

Funding

No specific funding was received for this research.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	4
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6-8
Objectives	3	State specific objectives, including any prespecified hypotheses	8
Methods			
Study design	4	Present key elements of study design early in the paper	9
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	9
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	9
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*10*
Bias	9	Describe any efforts to address potential sources of bias	10
Study size	10	Explain how the study size was arrived at	9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9-10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	11 N/A
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	12
		(b) Give reasons for non-participation at each stage	12
		(c) Consider use of a flow diagram	26
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	12-14
		(b) Indicate number of participants with missing data for each variable of interest	12
		(c) Summarise follow-up time (eg, average and total amount)	12-14, 27
Outcome data	15*	Report numbers of outcome events or summary measures over time	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	n/a
		(*b*) Report category boundaries when continuous variables were categorized	n/a
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	15
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15-20
Generalisability	21	Discuss the generalisability (external validity) of the study results	15-20
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	34

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Can Intensity of long-term follow-up for survivors of childhood and teenage cancer be determined by therapy-based risk-stratification?

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Can Intensity of long-term follow-up for survivors of childhood and teenage cancer be safely determined by therapy-based risk-stratification?

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Key words: Childhood cancer, treatment, survival, cure, late effects, models of follow-up, long-term follow-up.

Article summary

Article Focus

- Therapy-based, risk-stratification of survivors can safely predict which survivors of childhood and teenage cancer are at significant risk of developing moderate to severe late effects and require high intensity long-term follow-up.

Key messages

- Patients who had received the most complex cancer treatments had the largest number and most severe late effects. Those patients assigned to low risk category of follow-up had few late effects and those late effects were mild.
- Long term survivors of childhood and teenage cancer can safely be assigned to primary care, nurse-led or hospital follow-up based on the intensity of treatment they received for the original cancer.
- Stratification of patients according to risk of late morbidity will maximise the use of NHS resources and provide age appropriate care as locally as possible.

Strengths

- This study shows that it is possible to safely predict which survivors of childhood cancer are at significant risk of developing moderate to severe late effects. Life long follow-up for all childhood cancer survivors is not only cost ineffective but also difficult to organize. Until now there was no evidence available to define the optimum follow-up for long-term survivors.

- Risk stratification will enable young adult survivors to benefit from a transition process that takes them into an appropriate follow-up model and can help to identify those survivors who can be safely discharged from hospital based follow-up.

Limitations

- 30% of the cohort had not been seen in the hospital based late effects service for more than two years and health problems may be underestimated in this group.
- It would be helpful in future studies to determine the proportion of late effects detected as a direct result of clinic attendance and to determine the proportion of late effects which are treatable.

Abstract

Objective

To determine the safety of therapy-based, risk-stratified follow-up guidelines for childhood and teenage cancer survivors by evaluating adverse health outcomes in a survivor cohort retrospectively assigned a risk category.

Design

Retrospective cohort study.

Setting

Tertiary level, single centre, paediatric cancer unit in South East Scotland

Participants

All children and teenagers diagnosed with cancer (<19 years) between 1st January 1971-31st July 2004, who were alive more than five years from diagnosis formed the study cohort. Each survivor was retrospectively assigned a level of follow-up, based on their predicted risk of developing treatment related late effects (level 1, 2 and 3 for low, medium and high risk, respectively). Adverse health outcomes were determined from review of medical records and postal questionnaires. Late effects were graded using the Common Terminology Criteria for Adverse Event, Version 3 (CTCAEv3).

Results

607 five-year survivors were identified. Risk-stratification identified 86 (14.2%), 271 (44.6%) and 250 (41.2%) level 1, 2 and 3 survivors respectively. The prevalence of late effects (LE) for level 1 survivors was 11.6% with only 1 patient with grade 3 or above toxicity. 35.8% of level 2 survivors had a LE, of whom 9.3%, 58.8%, 18.5%, 10.3% and 3% had grade 1, 2, 3, 4 and 5 toxicity respectively. 65.2 % of level 3 survivors had LE), of whom 5.5% (n=9), 34.4% (n=56), 36.2% (n=59), 22.1% (n=36) and 1.8% (n=3) had grade 1,2,3,4 and 5 toxicity respectively.

Conclusions

Therapy-based, risk-stratification of survivors can safely predict which patients are at significant risk of developing moderate to severe late effects and require high intensity long-term follow-up.

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Introduction

Dramatic improvements in survival for children with cancer have highlighted the need for evidence based long-term follow-up (LTFU) for these young people. Approximately 80% of children diagnosed with cancer can now expect to survive more than 5 years, and around 70 % will survive ten years, from their diagnosis.[1] It is estimated that 1 in 640 young adults is a survivor of childhood cancer.[2] As many as two thirds of long-term survivors are reported to be at increased risk of substantial morbidity and even mortality, due to adverse late effects secondary to cancer or cancer therapy.[3-5] Late effects are diverse and include secondary malignancies, organ system damage, infertility, cognitive impairment, and disorders of growth and development.[6, 7] Appropriate LTFU of these patients is essential to detect, treat and prevent morbidity and mortality.[8]

There is wide variation of long-term follow-up practices throughout the UK with a propensity for hospital dependency, often in age-inappropriate settings.[9] A recent study has highlighted how excess morbidity in survivors translates into increased use of health care facilities.[10] An awareness of the need for an integrated and systematic approach to follow-up was recognised by the Scottish Intercollegiate Guidelines Network (SIGN) who developed an evidence-based approach to long-term follow-up.[11] The risks of developing treatment related late effects depend upon the underlying malignancy, the site of the tumour, the type of treatment and the age at time of treatment. A risk-stratified approach to health surveillance was developed which identified three groups of survivors who require an increasing

intensity of follow-up[8]. In the UK, we published a Practice Statement 'Therapy Based Long-term Follow-up' which is designed to inform and guide clinicians responsible for the long-term follow-up of childhood cancer survivors.[12] The Practice Statement recommends follow-up assessments and investigations based on the treatment that the individual has received and is informed by the evidence-based recommendations published by SIGN 76.

An integrated and systematic approach is now considered a requirement of the National Institute of Health and Clinical Excellence (NIHCE) Improving Outcomes for Children and Young People with Cancer Guidance (2005) and National Delivery Plan for Children and Young People's Specialist Services in Scotland (2008).[13,14] In England, the National Cancer Survivorship Initiative (NCSI) has developed as a partnership between the Department of Health, Macmillan Cancer Support, and supported by NHS Improvement, to develop models of care to ensure that those living with and beyond cancer have access to safe and effective care and receive the support they need to lead as healthy and active a life as possible. Improved awareness of cancer survivorship as a chronic health problem will facilitate the development of care pathways that will meet the needs of every patient throughout their lifetime.[15]

Although there is growing guidance on whom, where and how long-term survivors should be followed-up, evidence to show that adopting a model of risk-stratified follow-up is safe is lacking. A recent study has shown that assigning

patients to one of three agreed levels of follow up, as described by Wallace et al, was relatively simple for experienced clinic staff.[16] The objective of this study was to evaluate the safety and efficacy of this risk-based follow-up model by retrospectively stratifying an unselected cohort of long-term survivors of childhood cancer from a single centre and objectively evaluating their health status.

Methods

Study population

All patients, aged less than 19 years, who were diagnosed with childhood cancer in a single institution in South East Scotland, between 1971 and 2004, and who were alive at least five years from diagnosis, were included in the study. The patients were identified from the Oxford Children's Cancer Registry, established in 1992; patients diagnosed before 1992 were identified from the Scottish Cancer Registry, established in 1958, and hospital records.

Data Collection

All health problems directly attributable to cancer, or cancer therapy, were obtained from medical records, electronic hospital records systems, self-reported questionnaires. Medical data were obtained from medical records, electronic hospital records, clinical correspondence from other health professionals and self-completed health status questionnaire and is likely to be an underestimate of the health problems. Cause of death for the deceased patients as assigned by the General Register Office for Scotland, was obtained from the Scottish Cancer Registry, courtesy of Information Services Division, NHS National Services, Scotland (personal communication).

Therapy-based risk stratification

The Scottish Intercollegiate Guidelines Network (SIGN) has developed an evidence-based approach to LTFU, incorporating the risk-based levels of follow-

up described in 2001.[8] Patients are classified into one of three groups (Levels 1,2 and 3): Level 1 patients, treated with surgery alone or low risk chemotherapy treatment, who could be followed up by postal or telephone contact; Level 2 patients, treated with standard risk chemotherapy, such as survivors of ALL or lymphoma, who are considered to be at moderate risk of developing late effects, eg anthracycline-induced cardiotoxicity, could be followed up by an appropriately trained individual, such as a late effects nurse specialist; Level 3 patients, who would require medically supervised follow-up within a multi-disciplinary team – that is those patients that have had a CNS tumour (treated with chemotherapy and/or radiotherapy), bone marrow transplants, stage 4 disease, any radiotherapy except low dose cranial radiotherapy and those that have had intensive therapy. Risk-stratified levels of follow-up were independently assigned to all survivors by two researchers.

Grading of Late Effects

To determine the severity of late effects, each reported late effect was graded independently by two of the authors using the Common Terminology Criteria for Adverse Events, Version 3.0 (CTCAEv3.0, available at http://ctep.cancer.gov/forms/CTCAEv3.pdf), a scoring system developed through the US National Cancer Institute by a multidisciplinary group and adopted in the UK by the Children's Cancer and Leukaemia Group (CCLG).[17] The CTCAEv3.0 tool can be used for acute and chronic conditions in patients with cancer and grades conditions as mild (grade 1), moderate (grade 2), severe (grade 3), life-

threatening or disabling (grade 4), or adverse event-related death (grade 5). To investigate and reduce inter-observer variability, graded adverse events were compared and inconsistencies were discussed and detailed coding rules were developed (available on request form the authors). Inconsistencies in grading revolved mainly around scoring subjective psychosocial and neuropsychological items of grade 1 or 2, grading of 3 or higher adverse events was straightforward.

Ethical Approval

Ethical approval for this study was requested from the Lothian Research Ethics Committee (LREC). On review by the LREC, the committee decided that ethical approval was not required as long-term follow-up of childhood cancer survivors was deemed to be an acceptable and routine part of clinical practice and there were no experimental interventions.

Analysis

The statistical package for social sciences (SPSS) Windows version 14.0 was used for the statistical analyses. Data were analyzed by descriptive techniques using frequencies, percentages and medians as appropriate.

Results

Study Population

883 patients were diagnosed with childhood and teenage cancer between 1st January 1971 to 1st July 2004 and 607 of these patients were alive five years from diagnosis (5 year overall survival rate 69%). Medical information was collected from a retrospective case note review, regional electronic hospital systems and self-reported health outcomes from questionnaires. Of the 607 five year survivors, 34 patients were deceased (5.6%) at the time of the study (figure 1). Of the 573 long-term survivors alive at the time of this study 122 patients were not known to be under any kind of hospital review (21%). Of the 451 patients under hospital follow-up, 370 (82%) were followed up within the South East Scotland Late Effects Service, either by postal questionnaire follow-up (n=67, 17%) or clinic appointment (n=307, 83%). The remaining 81 (18%) of survivors attended other paediatric hospital-based clinics within the same paediatric setting (n=14) or in Tayside (n=26), or Adult Services in South East Scotland (n=31) and in other cities throughout the UK (n=10). Data were gathered from medical records from information based on a clinic visit of more than two years previously, without supplementation from postal questionnaires in 178 patients (31%) and is likely to represent an underestimate of late effects.

Demographics

607 long-term survivors were identified (males 321 (52.9%)) with median age (range) of 19.2 (5.1-45.1) years and median age (range) at diagnosis 5.1 (0.0-

17.5) years. Of the cohort, 34 (5.6%) were deceased, with a median overall survival (range) of 9.9 (5.0-30.9) years. Of the 573 long-term survivors alive at the time of the study, the median age (range) was 19.4 (5.1-45.1) years and disease free survival (range) 11.3 (0.8-38.3) years (Table 1). The primary cancer diagnosis is shown for all patients and within each risk level (Figure 2). Risk-stratification of all long-term survivors (n=607) identified 86 (14.1%), 271 (44.6%) and 250 (41.2%) at Level 1, 2 and 3 respectively with detailed breakdown of ages and survival interval for each level of patients alive at the time of the study only (n=573), shown in Table 1 and Figure 1. Demographic data is similar between the three populations.

Adverse health outcomes according level of risk

Among the 34 deaths in the five year survivors (n=607), 26 (76.5%) died from progression or relapse of the underlying primary cancer, two (5.9%) died from unrelated causes and six (17.6%) died from treatment related sequelae; five from second primary malignancy and one from end-stage renal failure. Of the five survivors who went on to die from second primary malignancy, three patients (all Level 2) had a meningioma, presumed to be secondary to low dose cranial irradiation as part of CNS directed therapy for the treatment of childhood ALL, one (Level 3) developed extensive intra-abdominal desmoid tumour having previously been treated for medulloblastoma and with a background of APC gene and Turcot's syndrome and the other patient (Level 3) developed AML presumed

to be related to previous topo-isomerase II inhibitor therapy for primary bone sarcoma (Figure 1).

Prevalence and severity of treatment related late effects were determined for each patient with an assigned level of follow up (n=607, Figures 3 and 4). Among Level 1 survivors (n=86), 11.6% (n=10) had late effects, of whom seven (8.1%) had one late effect and three (3.5%) had two late effects; 60% (n=6) of which were grade 1 toxicity, 30% (n=3) of whom were grade 2 toxicity and 10% (n=1) grade 3 toxicity. Within the Level 2 group (n=271), the prevalence of late effects was 35.8% (n=97), of whom 62 (22.9%) had 1 late effect, 23 (8.5%) had 2 late effects, 9 (3.3%) had 3 late effects and 3 (1.1%) had four late effects, of whom 9.3% (n=9) had a maximum toxicity grade of 1, 58.8% (n=57) grade 2, 18.5% (n=18) grade 3, 10.3% (n=10) grade 4 and 3% (n=3) grade 5. The prevalence of late effects in the Level 3 survivors (n=250) was 65.2% (n=163) of whom 37 (14.8%) had 1 late effect, 39 (15.6%) had 2 late effects, 22 (8.8%) had 3 late effects, 16 (6.4%) had 4 late effects and 46 (18.4%) had 5 or more late effects, of whom 9 (5.5%), 56 (34.4%), 59 (36.2%), 36 (22.1%) and 3 (1.8%) had grade 1,2,3,4 and 5 toxicity respectively.

Discussion

We have shown that therapy-based, risk-stratification of long-term survivors of childhood and teenage cancer can safely predict which patients are at risk of developing moderate to severe side effects and require high intensity clinic based long-term follow-up. Retrospective assignment of patients into a risk category identified almost half (45%) of patients could be considered at moderate risk of developing late effects, while 41% were deemed to be at high risk of developing late effects, with only a small proportion felt to be at low risk of late complications. The prevalence and severity of side effects increased with increasing level of follow up.

Lifelong follow-up is recommended for survivors of childhood cancer because many of the health problems may be reduced by prevention or early detection.[18] However follow-up should be individually tailored and hospital based follow-up should not be necessary for all survivors.[19] The incidence of chronic conditions continues to increase with time and there is therefore no safe time after which these patients can be discharged.[20] There is increasing evidence that with increasing time from diagnosis, medical problems associated with ageing, including second cancers, cardiovascular disease, infertility and osteoporosis, may exhibit an accelerated course following certain cancer treatments.[18,21] Mertens et al showed that while recurrent disease remains the most important contributor to late mortality in 5 year survivors there is a significant excess

mortality risk associated with treatment related complications that is present in the 25 years after the initial cancer diagnosis.[22]

It is reported that up to 50% of long-term survivors do not attend Late Effects Clinics and many of these patients are considered to be at high risk of developing treatment-related late complications.[23] There are many reasons why survivors choose not to participate in long-term follow-up including lack of awareness of risks of late morbidity, desire to 'move on', lack of appropriate adult services and clinical discharge. In a study by Blaauwbroek et al they assessed late effects in a group of adult survivors of childhood cancer who were not involved in regular long-term follow-up and reported that almost 40% of survivors suffered from moderate to severe late effects and 33% had previously unknown late effects.[24] This reiterates the need to educate survivors about their past medical history, their treatment and the importance of engaging in regular survivorship programmes.

Low rates of participation in long-term follow-up are universally reported. In 2004, a Delphi panel of 20 expert childhood cancer survivors in US identified a number of barriers contributing to this.[25] Understanding these barriers will lead to improved medical care for these patients. It was recognized that most childhood cancer survivors are not aware of their adverse health risks and often unaware of the details of their cancer or its treatment. Even where LTFU clinics are attended much of the education of late effects was directed at parents and often not

transferred to the child. The Delphi Panel also highlighted the limitations within the health care setting including lack of LTFU service, discharge to primary care physician who lacks expertise in this field and often receive no communication about the child's past medical history. Improving communication between professionals and patients is essential and will be an integral part of development of survivorship programmes.

The traditional model of LTFU has been in paediatric oncology clinics, generally jointly with paediatric endocrinologists, neurologists and clinical oncologists, long into adulthood which brings with it the advantage of continuity of care, familiarity with treatments but there are a number of disadvantages to this system. This is not only an age appropriate environment for these patients, but also an unsustainable situation for paediatric oncologists, as the population of long-term survivors increase and age. In addition, survivors are protected in this paediatric environment and don't develop the skills necessary to navigate the health care system as they develop into adulthood. Ideally, once the long-term survivor reaches adulthood he/she should be transitioned into the appropriate adult late effects services. At present, such a service does not exist and it is difficult to identify which clinicians should take on this role, especially with increasing sub-specialisation in adult medicine. In a busy and overstretched tertiary oncology healthcare service, medical and clinical adult oncology consultants are unlikely to be in a position to take on this responsibility, and may well feel inadequately trained in caring for childhood cancer survivors. In current practice, the only adult

services supporting the long-term follow-up of those patients requiring specialist hospital follow-up are the adult endocrine and neurology clinics.

It has been highlighted that improved communication of cancer information to patients/families and between health care providers may contribute to greater engagement in follow-up programmes, raises awareness of potential late effects amongst survivors and enable clinicians to diagnose and, where possible, treat late effects earlier. Based on national guidelines, we have developed a template for the End of Treatment Summary and Individualised Care Plan, or 'Health Passport', which has been introduced nationally, and welcomed by health professionals and survivors.

Models of care for LTFU of survivors of childhood cancer must be flexible enough to accommodate the needs of the young survivor as they transition throughout their life cycle and also to accommodate the individual heterogeneity of cancer survivors, reflecting the wide range of treatment exposure and adverse long-term sequelae. Development of a service that can deliver individualized, comprehensive, therapy-based patient centred care is essential.

The UK National Cancer Survivorship Initiative is currently exploring models of aftercare services for children and young people who have been treated for cancer. National pathways that identify how follow-up can be delivered in line with current pressures and aspirations are being developed. Clinical risk

stratification will play an integral role in tailoring individualised care to meet the clinical, psychological and practical needs of each survivor. A recent study from the CCSS has reviewed how data derived from the CCSS have characterized specific groups that are deemed to be at highest risk of morbidity and subsequent cancers.[26] Our study has shown that those patients at highest risk of late morbidity can be identified and appropriately stratified into a high risk (level 3) follow-up programme.

Stratification of patients according to risk of late morbidity will maximise the use of health service resources and provide age appropriate care as locally as possible. With increasing time from completion of treatment, it is hoped that the majority of adult survivors will be independent and take responsibility for their own health, with health care support provided by their primary care physician. As a result, the primary care team is likely to play an increasing role in the long-term follow-up of survivors of childhood cancer. Primary care services may be already stretched but GPs are used to meeting targets and ensuring guidelines are implemented. Good communication between the hospital services and primary care will be essential. Early involvement of general practitioners in the Late Effects Services will establish collaborations between the two teams and enable primary Care Physicians to become familiar with the surveillance programme. The feasibility of a shared-care model between cancer paediatric oncology cancer centres and primary-care doctors to deliver survivor-focused risk based health care was tested successfully by a Dutch group. The study showed that

patients would see their family doctor for long-term follow-up: the family doctors were interested in sharing survivors' care; and family doctors would return the necessary medical information needed for continued follow-up.[27] Appropriate education of the family doctors, which has resource implications, was a key finding of this study. More recently this group has shown that a web based survivor care plan can facilitate the long-term care of survivors by family doctors.[28]

In order to improve our understanding of treatment-related side effects and help develop treatment protocols to minimise toxicity, lifelong monitoring of health and well-being of all long-term survivors will be necessary. Our understanding of the late effects of the treatment of Hodgkin's lymphoma has led to studies which are ongoing and are designed to reduce the risk of second malignancy by avoiding radiotherapy in selected cases and replace gonadotoxic chemotherapy with drugs that are efficacious in Hodgkin's lymphoma but less likely to compromise reproductive function.[29] Balancing safety and efficacy in the treatment of Hodgkin's lymphoma remains an important goal in the treatment of this curable malignancy.[30]

We have shown that it is possible to safely predict which survivors of childhood cancer are at significant risk of developing moderate to severe late effects and require moderate or high intensity long-term follow. Importantly we have also shown that there is a group of survivors who can be reliably identified who can be

safely discharged from clinic based follow-up. Structured, risk-adapted follow-up of childhood cancer survivors following evidence-based guidelines would reduce cost ineffective or excessive evaluations and focus individual health care delivery. Education of survivors and health care providers will hopefully reduce the burden of chronic health problems and improve quality of life for the growing population of children and young people who have been treated for cancer.

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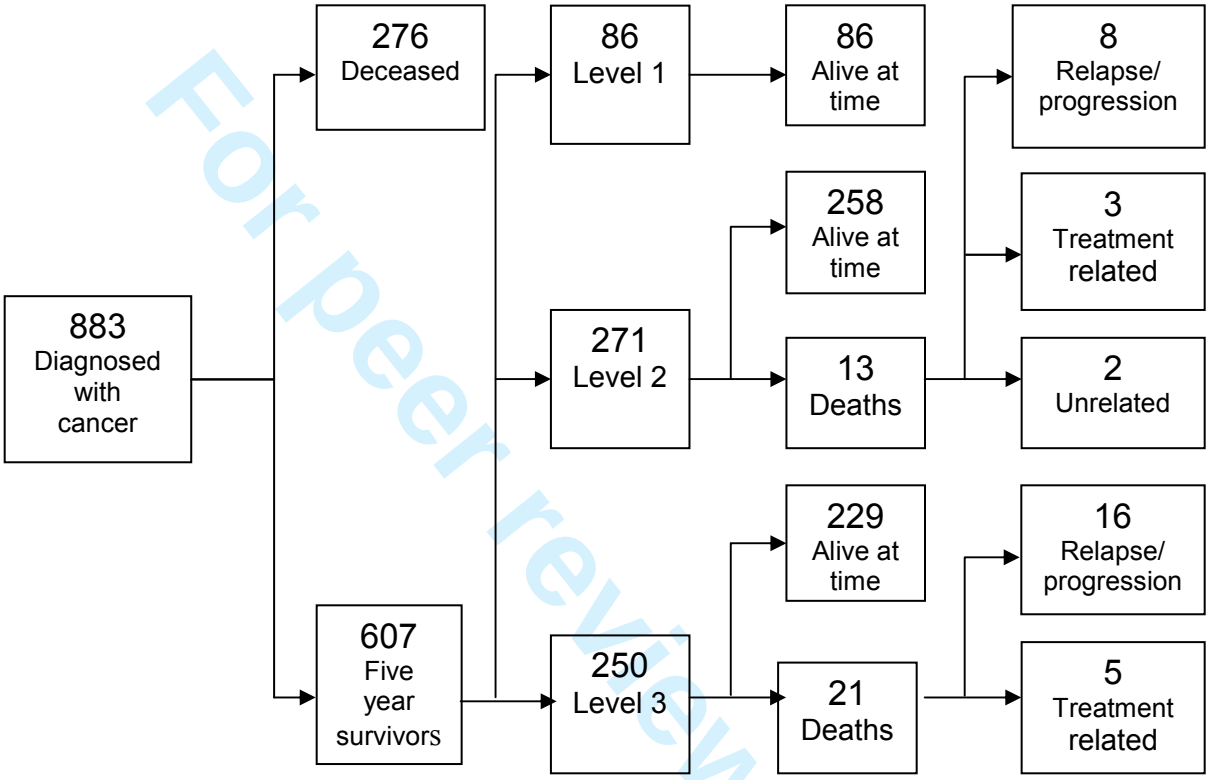

Figure 1. Study flow of childhood and teenage cancer patients.

Flow chart shows the study population and the risk stratification of patients into Levels 1,2 and 3 and the proportion of patients alive at the time of the study.

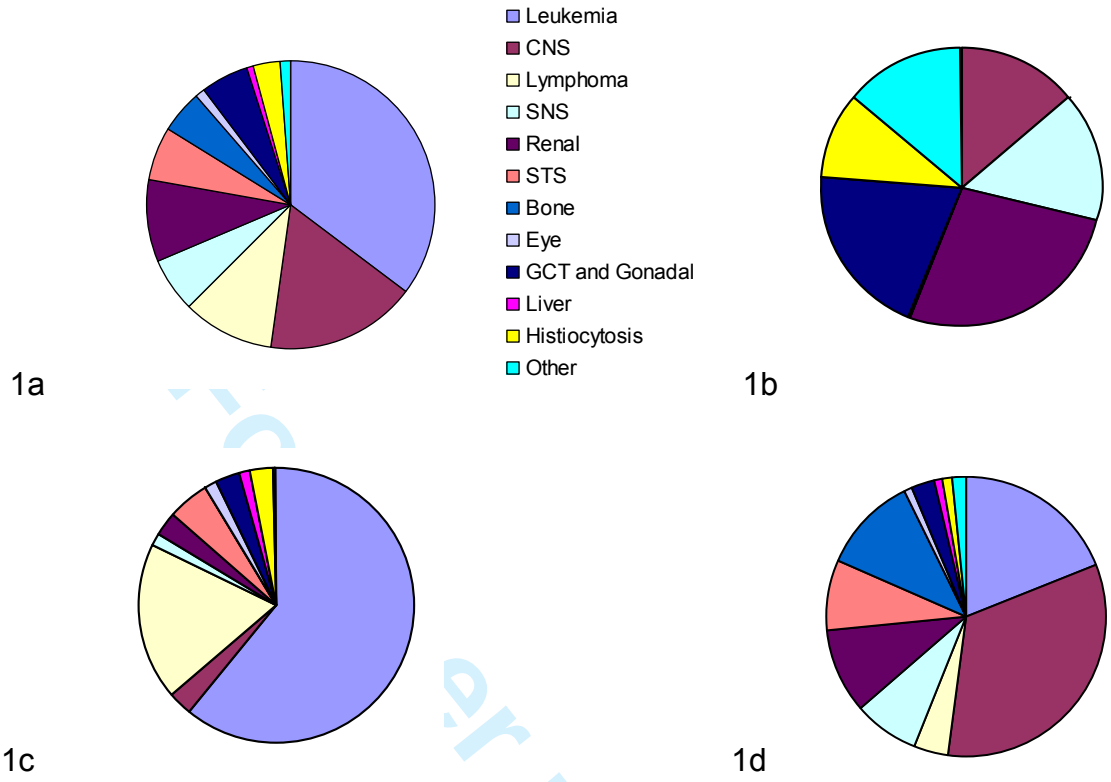

Figure 2 Diagnoses of five year survivors (n-607)

1a. All survivors (n=607), 1b. Level 1 (n= 86), 1c. Level 2 (n=271), 1d. Level 3 (n=250). Abbreviations: CNS – central nervous system tumours, SNS – sympathetic nervous system tumours, GCT – germ cell tumours, STS – soft tissue sarcomas

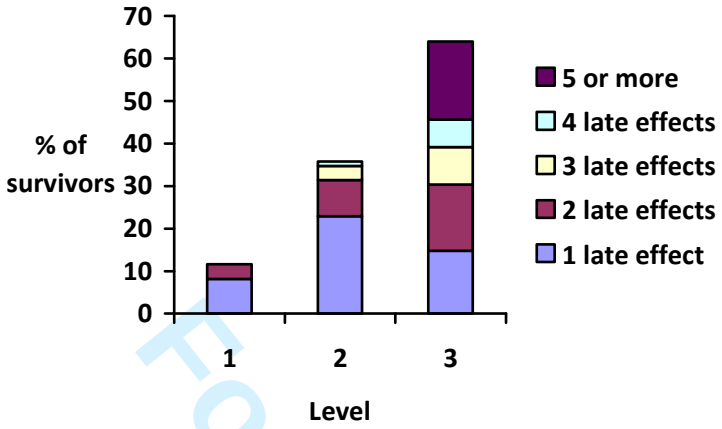

Figure 3

Prevalence of late effects by risk stratified level of follow-up for all five year survivors (n=607).

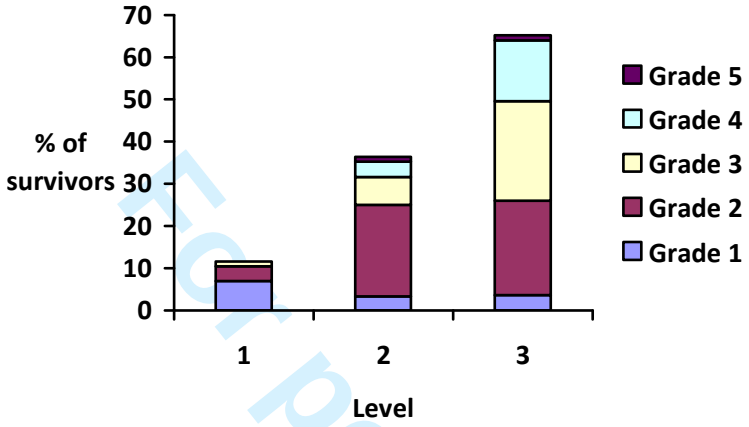

Figure 4

Severity of late effects by risk stratified level (CTCAEv3.0): grade 1- mild, grade 2-moderate, grade 3 severe, grade 4 – life threatening or disabling and grade 5 – death for all five year survivors (n=607). [17]

Table 1. Demographic characteristics of all the five year survivors alive at the time of the study (n=573) and for Level 1, Level 2 and Level 3 subgroups.

Characteristic	Five year survivors (n-573)		Level 1 (n=86)		Level 2 (n=258)		Level 3 (n=229)	
	No.	%	No.	%	No.	%	No.	%
Sex								
Male	303	52.9	37	43	137	53.1	129	56.3
Female	270	47.1	49	57	121	46.9	100	43.7
Current age, years								
5-9	44	7.7	11	12.8	15	5.8	18	7.8
10-14	110	19.2	19	22.1	56	21.7	35	15.3
15-19	148	25.8	31	36.0	66	25.6	51	22.3
20-24	129	22.5	19	22.1	51	19.8	59	25.8
25-29	69	12.0	6	7.0	30	11.6	33	14.4
30-34	40	7.0	-	-	16	6.2	24	10.5
35-39	21	3.7	-	-	15	5.8	6	2.6
40-44	11	1.9	-	-	8	3.1	3	1.3

45-49	1	0.2	-	-	1	0.4	-	-
Median, Range	19.4	5.1-45.1	17.5	5.1-28.4	19.4	8.0-45.1	20.1	5.6-43.7
Age at diagnosis, years								
0-4	286	49.9	54	62.8	140	54.3	92	40.2
5-9	144	25.1	16	18.6	68	26.4	60	26.2
10-14	122	21.3	15	17.4	48	18.6	59	25.8
15-19	21	3.7	1	1.2	2	0.7	18	7.8
Median, Range	5.0	0-20.9	2.9	0-15.4	4.5	0-20.9	6.5	0-17.5
Time from diagnosis, years								
5-9	197	34.4	33	38.4	80	31.0	84	36.7
10-14	166	29.0	32	37.2	76	29.5	58	25.3
15-19	100	17.5	11	12.8	38	14.7	51	22.3
20-24	58	10.1	8	9.3	30	11.6	20	8.7
25-29	30	5.2	2	2.3	16	6.2	12	5.2
30-34	12	2.1	-	-	10	3.9	2	0.9
35-39	10	1.7	-	-	8	3.1	2	0.9
Median, Range	12.4	5.0-39.3	11.0	5.0-26.9	13.0	5.0-38.4	12.9	5.0-39.3
DFS, years								
0-4	36	6.3	1	1.2	20	7.7	15	6.5

5-9	198	34.5	34	39.5	82	31.8	82	35.8
10-14	160	27.9	31	36.0	67	26.0	62	27.1
15-19	84	14.7	10	11.6	34	13.2	40	17.5
20-24	57	9.9	8	9.3	31	12.0	18	7.9
25-29	19	3.4	2	2.4	8	3.1	9	3.9
30-34	17	3.0	-	-	15	5.8	2	0.9
35-39	2	0.3	-	-	1	0.4	1	0.4
Median, Range	11.3	0.5-38.3	10.9	4.4-26.9	11.6	1.9-36.4	11.6	0.5-38.3
Time since last seen in Hospital Based Late Effects Clinic, years								
0-2	328	57.2	31	36.0	143	55.4	154	67.2
3-4	75	13.1	16	18.6	36	13.9	23	10.1
5-7	78	13.6	20	23.3	40	15.5	18	7.9
8-10	28	5.0	6	7.0	10	3.9	12	5.2
>10	41	7.1	8	9.3	19	7.4	14	6.1
Unknown	23	4.0	5	5.8	10	3.9	8	3.5
Median, Range	2.3	0-13.1	4.5	0-12.7	2.2	0-12.7	1.8	0-13.1

Competing interest statement

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work, no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

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Contributorship statement

ABE initiated the project, designed data collection tools, monitored data collection for the study, analysed the data, and drafted and revised the paper. KD designed data collection tools, monitored data collection for the study, analysed the data

and revised the draft paper. SB designed data collection tools, monitored data collection for the study, analysed the data and revised the draft paper. PM-S analysed the data and drafted and revised the paper. WHBW designed data collection tools, monitored data collection for the study, analysed the data, and drafted and revised the paper. All authors had full access to all of the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Data sharing statement

Dataset available from the corresponding author at angela.edgar@luht.scot.nhs.uk. Consent was not obtained but the presented data are anonymised and risk of identification is low.

Ethical approval

Ethical approval for this study was requested from the Lothian Research Ethics Committee (LREC). On review by the LREC, the committee decided that ethical approval was not required as long-term follow-up of childhood cancer survivors was deemed to be an acceptable and routine part of clinical practice and there were no experimental interventions.

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Can Intensity of long-term follow-up for survivors of childhood and teenage cancer be ~~safely~~ determined by therapy-based risk-stratification?

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Key words: Childhood cancer, treatment, survival, cure, late effects, models of follow-up, long-term follow-up.

Article summary

Article Focus

- Therapy-based, risk-stratification of survivors can ~~safely~~ predict which survivors of childhood and teenage cancer are at significant risk of developing moderate to severe late effects and require high intensity long-term follow-up.

Key messages

- Patients who had received the most complex cancer treatments had the largest number and most severe late effects. Those patients assigned to low risk category of follow-up had few late effects and those late effects were mild.
- Long term survivors of childhood and teenage cancer can ~~safely~~ be assigned to primary care, nurse-led or hospital follow-up based on the intensity of treatment they received for the original cancer.
- Stratification of patients according to risk of late morbidity will maximise the use of NHS resources and provide age appropriate care as locally as possible.

Strengths

- This study shows that it is possible to ~~safely~~ predict which survivors of childhood cancer are at significant risk of developing moderate to severe late effects. Life long follow-up for all childhood cancer survivors is not only cost ineffective but also difficult to organize. Until now there was no evidence available to define the optimum follow-up for long-term survivors.

- Risk stratification will enable young adult survivors to benefit from a transition process that takes them into an appropriate follow-up model and can help to identify those survivors who can be ~~safely~~ discharged from hospital based follow-up.

Limitations

- 30% of the cohort had not been seen in the hospital based late effects service for more than two years and health problems may be underestimated in this group.
- It would be helpful in future studies to determine the proportion of late effects detected as a direct result of clinic attendance and to determine the proportion of late effects which are treatable.

Abstract

Objective

To determine the ~~safety~~ feasibility of therapy-based, risk-stratified follow-up guidelines for childhood and teenage cancer survivors by evaluating adverse health outcomes in a survivor cohort retrospectively assigned a risk category.

Design

Retrospective cohort study.

Setting

Tertiary level, single centre, paediatric cancer unit in South East Scotland

Participants

All children and teenagers diagnosed with cancer (<19 years) between 1st January 1971-31st July 2004, who were alive more than five years from diagnosis formed the study cohort. Each survivor was retrospectively assigned a level of follow-up, based on their predicted risk of developing treatment related late effects (level 1, 2 and 3 for low, medium and high risk, respectively). Adverse health outcomes were determined from review of medical records and postal questionnaires. Late effects were graded using the Common Terminology Criteria for Adverse Event, Version 3 (CTCAEv3).

Results

607 five-year survivors were identified. Risk-stratification identified 86 (14.2%), 271 (44.6%) and 250 (41.2%) level 1, 2 and 3 survivors respectively. The prevalence of late effects (LE) for level 1 survivors was 11.6% with only 1 patient with grade 3 or above toxicity. 35.8% of level 2 survivors had a LE, of whom 9.3%, 58.8%, 18.5%, 10.3% and 3% had grade 1, 2, 3, 4 and 5 toxicity respectively. 65.2 % of level 3 survivors had LE), of whom 5.5% (n=9), 34.4% (n=56), 36.2% (n=59), 22.1% (n=36) and 1.8% (n=3) had grade 1,2,3,4 and 5 toxicity respectively.

Conclusions

Therapy-based, risk-stratification of survivors can ~~safely~~ predict which patients are at significant risk of developing moderate to severe late effects and require high intensity long-term follow-up.

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Introduction

Dramatic improvements in survival for children with cancer have highlighted the need for evidence based long-term follow-up (LTFU) for these young people. Approximately 80% of children diagnosed with cancer can now expect to survive more than 5 years, and around 70 % will survive ten years, from their diagnosis.[1] It is estimated that 1 in 640 young adults is a survivor of childhood cancer.[2] As many as two thirds of long-term survivors are reported to be at increased risk of substantial morbidity and even mortality, due to adverse late effects secondary to cancer or cancer therapy.[3-5] Late effects are diverse and include secondary malignancies, organ system damage, infertility, cognitive impairment, and disorders of growth and development.[6, 7] Appropriate LTFU of these patients is essential to detect, treat and prevent morbidity and mortality.[8]

There is wide variation of long-term follow-up practices throughout the UK with a propensity for hospital dependency, often in age-inappropriate settings.[9] A recent study has highlighted how excess morbidity in survivors translates into increased use of health care facilities.[10] An awareness of the need for an integrated and systematic approach to follow-up was recognised by the Scottish Intercollegiate Guidelines Network (SIGN) who developed an evidence-based approach to long-term follow-up.[11] The risks of developing treatment related late effects depend upon the underlying malignancy, the site of the tumour, the type of treatment and the age at time of treatment. A risk-stratified approach to health surveillance was developed which identified three groups of survivors who require an increasing

intensity of follow-up[8]. In the UK, we published a Practice Statement 'Therapy Based Long-term Follow-up' which is designed to inform and guide clinicians responsible for the long-term follow-up of childhood cancer survivors.[12] The Practice Statement recommends follow-up assessments and investigations based on the treatment that the individual has received and is informed by the evidence-based recommendations published by SIGN 76.

An integrated and systematic approach is now considered a requirement of the National Institute of Health and Clinical Excellence (NIHCE) Improving Outcomes for Children and Young People with Cancer Guidance (2005) and National Delivery Plan for Children and Young People's Specialist Services in Scotland (2008).[13,14] In England, the National Cancer Survivorship Initiative (NCSI) has developed as a partnership between the Department of Health, Macmillan Cancer Support, and supported by NHS Improvement, to develop models of care to ensure that those living with and beyond cancer have access to safe and effective care and receive the support they need to lead as healthy and active a life as possible. Improved awareness of cancer survivorship as a chronic health problem will facilitate the development of care pathways that will meet the needs of every patient throughout their lifetime.[15]

Although there is growing guidance on whom, where and how long-term survivors should be followed-up, evidence to show that adopting a model of risk-stratified follow-up is safe is lacking. A recent study has shown that assigning

patients to one of three agreed levels of follow up, as described by Wallace et al, was relatively simple for experienced clinic staff.[16] The objective of this study was to evaluate the ~~safety~~ feasibility and efficacy of this risk-based follow-up model by retrospectively stratifying an unselected cohort of long-term survivors of childhood cancer from a single centre and objectively evaluating their health status.

Methods

Study population

All patients, aged less than 19 years, who were diagnosed with childhood cancer in a single institution in South East Scotland, between 1971 and 2004, and who were alive at least five years from diagnosis, were included in the study. The patients were identified from the Oxford Children's Cancer Registry, established in 1992; patients diagnosed before 1992 were identified from the Scottish Cancer Registry, established in 1958, and hospital records.

Data Collection

All health problems directly attributable to cancer, or cancer therapy, were obtained from medical records, electronic hospital records systems, self-reported questionnaires. Medical data were obtained from medical records, electronic hospital records, clinical correspondence from other health professionals and self-completed health status questionnaire and is likely to be an underestimate of the health problems. Cause of death for the deceased patients as assigned by the General Register Office for Scotland, was obtained from the Scottish Cancer Registry, courtesy of Information Services Division, NHS National Services, Scotland (personal communication).

Therapy-based risk stratification

The Scottish Intercollegiate Guidelines Network (SIGN) has developed an evidence-based approach to LTFU, incorporating the risk-based levels of follow-

up described in 2001.[8] Patients are classified into one of three groups (Levels 1,2 and 3): Level 1 patients, treated with surgery alone or low risk chemotherapy treatment, who could be followed up by postal or telephone contact; Level 2 patients, treated with standard risk chemotherapy, such as survivors of ALL or lymphoma, who are considered to be at moderate risk of developing late effects, eg anthracycline-induced cardiotoxicity, could be followed up by an appropriately trained individual, such as a late effects nurse specialist; Level 3 patients, who would require medically supervised follow-up within a multi-disciplinary team – that is those patients that have had a CNS tumour (treated with chemotherapy and/or radiotherapy), bone marrow transplants, stage 4 disease, any radiotherapy except low dose cranial radiotherapy and those that have had intensive therapy. Risk-stratified levels of follow-up were independently assigned to all survivors by two researchers. Level of follow-up was retrospectively assigned to each patient, as if they were five years from diagnosis and before any medical review of late effects was undertaken.

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Grading of Late Effects

To determine the severity of late effects, each reported late effect was graded independently by two of the authors using the Common Terminology Criteria for Adverse Events, Version 3.0 (CTCAEv3.0, available at http://ctep.cancer.gov/forms/CTCAEv3.pdf), a scoring system developed through the US National Cancer Institute by a multidisciplinary group and adopted in the UK by the Children's Cancer and Leukaemia Group (CCLG).[17] The CTCAEv3.0

tool can be used for acute and chronic conditions in patients with cancer and grades conditions as mild (grade 1), moderate (grade 2), severe (grade 3), life-threatening or disabling (grade 4), or adverse event-related death (grade 5). To investigate and reduce inter-observer variability, graded adverse events were compared and inconsistencies were discussed and detailed coding rules were developed (available on request form the authors). Inconsistencies in grading revolved mainly around scoring subjective psychosocial and neuropsychological items of grade 1 or 2, grading of 3 or higher adverse events was straightforward.

Ethical Approval

Ethical approval for this study was requested from the Lothian Research Ethics Committee (LREC). On review by the LREC, the committee decided that ethical approval was not required as long-term follow-up of childhood cancer survivors was deemed to be an acceptable and routine part of clinical practice and there were no experimental interventions.

Analysis

The statistical package for social sciences (SPSS) Windows version 14.0 was used for the statistical analyses. Data were analyzed by descriptive techniques using frequencies, percentages and medians as appropriate.

Results

Study Population

883 patients were diagnosed with childhood and teenage cancer between 1st January 1971 to 1st July 2004 and 607 of these patients were alive five years from diagnosis (5 year overall survival rate 69%). Medical information was collected from a retrospective case note review, regional electronic hospital systems and self-reported health outcomes from questionnaires. Of the 607 five year survivors, 34 patients were deceased (5.6%) at the time of the study (figure 1). Of the 573 long-term survivors alive at the time of this study 122 patients were not known to be under any kind of hospital review (21%). Of the 451 patients under hospital follow-up, 370 (82%) were followed up within the South East Scotland Late Effects Service, either by postal questionnaire follow-up (n=67, 17%) or clinic appointment (n=307, 83%). The remaining 81 (18%) of survivors attended other paediatric hospital-based clinics within the same paediatric setting (n=14) or in Tayside (n=26), or Adult Services in South East Scotland (n=31) and in other cities throughout the UK (n=10). Data were gathered from medical records from information based on a clinic visit of more than two years previously, without supplementation from postal questionnaires in 178 patients (31%) and is likely to represent an underestimate of late effects.

Demographics

In this population-based study, 607 long-term survivors were identified (males 321 (52.9%)) with median age (range) of 19.2 (5.1-45.1) years and median age

(range) at diagnosis 5.1 (0.0-17.5) years. Of the cohort, 34 (5.6%) were deceased, with a median overall survival (range) of 9.9 (5.0-30.9) years. Of the 573 long-term survivors alive at the time of the study, the median age (range) was 19.4 (5.1-45.1) years and disease free survival (range) 11.3 (0.8-38.3) years (Table 1). The primary cancer diagnosis is shown for all patients and within each risk level (Figure 2). Risk-stratification of all long-term survivors (n=607) identified 86 (14.1%), 271 (44.6%) and 250 (41.2%) at Level 1, 2 and 3 respectively with detailed breakdown of ages and survival interval for each level of patients alive at the time of the study only (n=573), shown in Table 1 and Figure 1. Demographic data is similar between the three populations.

Adverse health outcomes according level of risk

Among the 34 deaths in the five year survivors (n=607), 26 (76.5%) died from progression or relapse of the underlying primary cancer, two (5.9%) died from unrelated causes and six (17.6%) died from treatment related sequelae; five from second primary malignancy and one from end-stage renal failure. Of the five survivors who went on to die from second primary malignancy, three patients (all Level 2) had a meningioma, presumed to be secondary to low dose cranial irradiation as part of CNS directed therapy for the treatment of childhood ALL, one (Level 3) developed extensive intra-abdominal desmoid tumour having previously been treated for medulloblastoma and with a background of APC gene and Turcot's syndrome and the other patient (Level 3) developed AML presumed

to be related to previous topo-isomerase II inhibitor therapy for primary bone sarcoma (Figure 1).

Prevalence and severity of treatment related late effects were determined for each patient with an assigned level of follow up (n=607, Figures 3 and 4). Among Level 1 survivors (n=86), 11.6% (n=10) had late effects, of whom seven (8.1%) had one late effect and three (3.5%) had two late effects; 60% (n=6) of which were grade 1 toxicity, 30% (n=3) of whom were grade 2 toxicity and 10% (n=1) grade 3 toxicity. Within the Level 2 group (n=271), the prevalence of late effects was 35.8% (n=97), of whom 62 (22.9%) had 1 late effect, 23 (8.5%) had 2 late effects, 9 (3.3%) had 3 late effects and 3 (1.1%) had four late effects, of whom 9.3% (n=9) had a maximum toxicity grade of 1, 58.8% (n=57) grade 2, 18.5% (n=18) grade 3, 10.3% (n=10) grade 4 and 3% (n=3) grade 5. The prevalence of late effects in the Level 3 survivors (n=250) was 65.2% (n=163) of whom 37 (14.8%) had 1 late effect, 39 (15.6%) had 2 late effects, 22 (8.8%) had 3 late effects, 16 (6.4%) had 4 late effects and 46 (18.4%) had 5 or more late effects, of whom 9 (5.5%), 56 (34.4%), 59 (36.2%), 36 (22.1%) and 3 (1.8%) had grade 1,2,3,4 and 5 toxicity respectively.

Discussion

We have shown that therapy-based, risk-stratification of long-term survivors of childhood and teenage cancer can ~~safely~~ predict which patients are at risk of developing moderate to severe side effects and require high intensity clinic based long-term follow-up. Retrospective assignment of patients into a risk category identified almost half (45%) of patients could be considered at moderate risk of developing late effects, while 41% were deemed to be at high risk of developing late effects, with only a small proportion felt to be at low risk of late complications. The prevalence and severity of side effects increased with increasing level of follow up.

Lifelong follow-up is recommended for survivors of childhood cancer because many of the health problems may be reduced by prevention or early detection.[18] However follow-up should be individually tailored and hospital based follow-up should not be necessary for all survivors.[19] The incidence of chronic conditions continues to increase with time and there is therefore no safe time after which these patients can be discharged.[20] There is increasing evidence that with increasing time from diagnosis, medical problems associated with ageing, including second cancers, cardiovascular disease, infertility and osteoporosis, may exhibit an accelerated course following certain cancer treatments.[18,21] Mertens et al showed that while recurrent disease remains the most important contributor to late mortality in 5 year survivors there is a significant excess

mortality risk associated with treatment related complications that is present in the 25 years after the initial cancer diagnosis.[22]

It is reported that up to 50% of long-term survivors do not attend Late Effects Clinics and many of these patients are considered to be at high risk of developing treatment-related late complications.[23] There are many reasons why survivors choose not to participate in long-term follow-up including lack of awareness of risks of late morbidity, desire to 'move on', lack of appropriate adult services and clinical discharge. In a study by Blaauwbroek et al they assessed late effects in a group of adult survivors of childhood cancer who were not involved in regular long-term follow-up and reported that almost 40% of survivors suffered from moderate to severe late effects and 33% had previously unknown late effects.[24] This reiterates the need to educate survivors about their past medical history, their treatment and the importance of engaging in regular survivorship programmes.

Low rates of participation in long-term follow-up are universally reported. In 2004, a Delphi panel of 20 expert childhood cancer survivors in US identified a number of barriers contributing to this.[25] Understanding these barriers will lead to improved medical care for these patients. It was recognized that most childhood cancer survivors are not aware of their adverse health risks and often unaware of the details of their cancer or its treatment. Even where LTFU clinics are attended much of the education of late effects was directed at parents and often not

transferred to the child. The Delphi Panel also highlighted the limitations within the health care setting including lack of LTFU service, discharge to primary care physician who lacks expertise in this field and often receive no communication about the child's past medical history. Improving communication between professionals and patients is essential and will be an integral part of development of survivorship programmes.

The traditional model of LTFU has been in paediatric oncology clinics, generally jointly with paediatric endocrinologists, neurologists and clinical oncologists, long into adulthood which brings with it the advantage of continuity of care, familiarity with treatments but there are a number of disadvantages to this system. This is not only an age appropriate environment for these patients, but also an unsustainable situation for paediatric oncologists, as the population of long-term survivors increase and age. In addition, survivors are protected in this paediatric environment and don't develop the skills necessary to navigate the health care system as they develop into adulthood. Ideally, once the long-term survivor reaches adulthood he/she should be transitioned into the appropriate adult late effects services. At present, such a service does not exist and it is difficult to identify which clinicians should take on this role, especially with increasing sub-specialisation in adult medicine. In a busy and overstretched tertiary oncology healthcare service, medical and clinical adult oncology consultants are unlikely to be in a position to take on this responsibility, and may well feel inadequately trained in caring for childhood cancer survivors. In current practice, the only adult

services supporting the long-term follow-up of those patients requiring specialist hospital follow-up are the adult endocrine and neurology clinics.

It has been highlighted that improved communication of cancer information to patients/families and between health care providers may contribute to greater engagement in follow-up programmes, raises awareness of potential late effects amongst survivors and enable clinicians to diagnose and, where possible, treat late effects earlier. Based on national guidelines, we have developed a template for the End of Treatment Summary and Individualised Care Plan, or 'Health Passport', which has been introduced nationally, and welcomed by health professionals and survivors.

Models of care for LTFU of survivors of childhood cancer must be flexible enough to accommodate the needs of the young survivor as they transition throughout their life cycle and also to accommodate the individual heterogeneity of cancer survivors, reflecting the wide range of treatment exposure and adverse long-term sequelae. Development of a service that can deliver individualized, comprehensive, therapy-based patient centred care is essential.

The UK National Cancer Survivorship Initiative is currently exploring models of aftercare services for children and young people who have been treated for cancer. National pathways that identify how follow-up can be delivered in line with current pressures and aspirations are being developed. Clinical risk

stratification will play an integral role in tailoring individualised care to meet the clinical, psychological and practical needs of each survivor. A recent study from the CCSS has reviewed how data derived from the CCSS have characterized specific groups that are deemed to be at highest risk of morbidity and subsequent cancers.[26] Our study has shown that those patients at highest risk of late morbidity can be identified and appropriately stratified into a high risk (level 3) follow-up programme.

Stratification of patients according to risk of late morbidity will maximise the use of health service resources and provide age appropriate care as locally as possible. With increasing time from completion of treatment, it is hoped that the majority of adult survivors will be independent and take responsibility for their own health, with health care support provided by their primary care physician. As a result, the primary care team is likely to play an increasing role in the long-term follow-up of survivors of childhood cancer. Primary care services may be already stretched but GPs are used to meeting targets and ensuring guidelines are implemented. Good communication between the hospital services and primary care will be essential. Early involvement of general practitioners in the Late Effects Services will establish collaborations between the two teams and enable primary Care Physicians to become familiar with the surveillance programme. The feasibility of a shared-care model between cancer paediatric oncology cancer centres and primary-care doctors to deliver survivor-focused risk based health care was tested successfully by a Dutch group. The study showed that

patients would see their family doctor for long-term follow-up: the family doctors were interested in sharing survivors' care; and family doctors would return the necessary medical information needed for continued follow-up.[27] Appropriate education of the family doctors, which has resource implications, was a key finding of this study. More recently this group has shown that a web based survivor care plan can facilitate the long-term care of survivors by family doctors.[28]

In order to improve our understanding of treatment-related side effects and help develop treatment protocols to minimise toxicity, lifelong monitoring of health and well-being of all long-term survivors will be necessary. Our understanding of the late effects of the treatment of Hodgkin's lymphoma has led to studies which are ongoing and are designed to reduce the risk of second malignancy by avoiding radiotherapy in selected cases and replace gonadotoxic chemotherapy with drugs that are efficacious in Hodgkin's lymphoma but less likely to compromise reproductive function.[29] Balancing safety and efficacy in the treatment of Hodgkin's lymphoma remains an important goal in the treatment of this curable malignancy.[30]

We have shown that it is possible to ~~safely~~ predict which survivors of childhood cancer are at significant risk of developing moderate to severe late effects and require moderate or high intensity long-term follow. Importantly we have also shown that there is a group of survivors who can be reliably identified who can be ~~safely~~ discharged from clinic based follow-up *and followed up by annual questionnaire or telephone contact.* ~~—~~Structured, risk-adapted follow-up of

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childhood cancer survivors following evidence-based guidelines would reduce cost ineffective or excessive evaluations and focus individual health care delivery. Education of survivors and health care providers will hopefully reduce the burden of chronic health problems and improve quality of life for the growing population of children and young people who have been treated for cancer.

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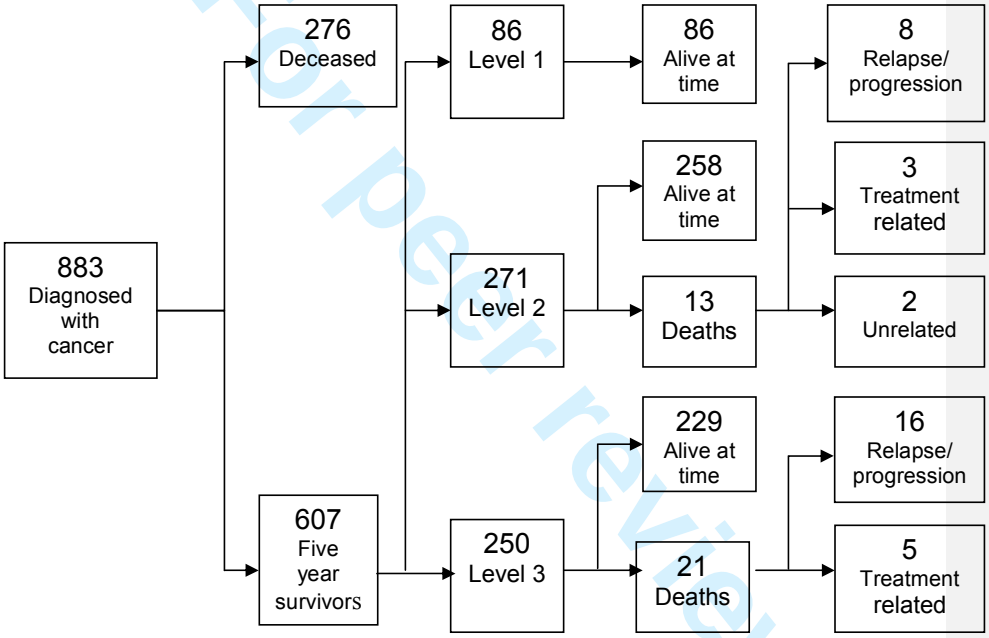

Figure 1. Study flow of childhood and teenage cancer patients.

Flow chart shows the study population and the risk stratification of patients into Levels 1,2 and 3 and the proportion of patients alive at the time of the study.

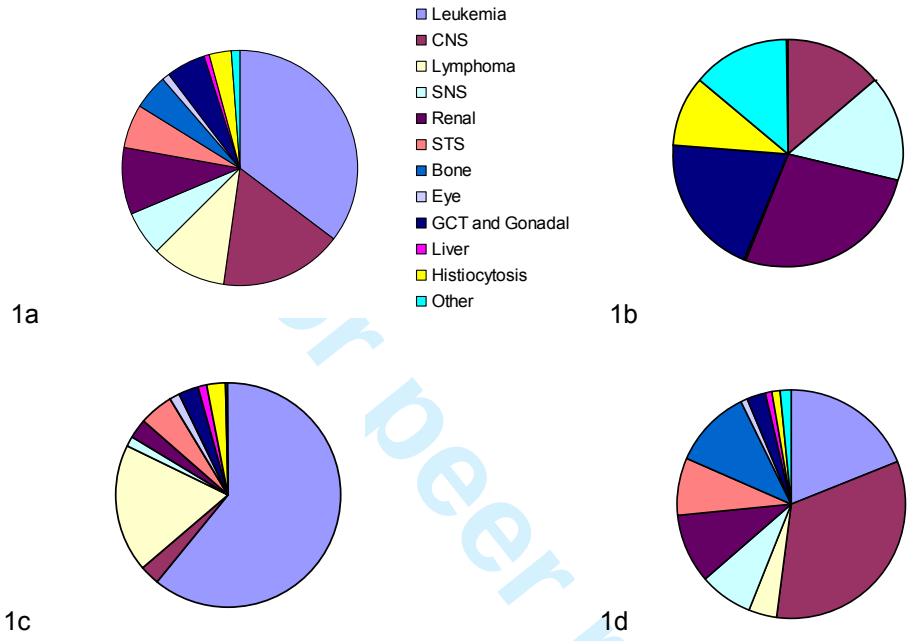

Figure 2 Diagnoses of five year survivors (n-607)

1a. All survivors (n=607), 1b. Level 1 (n= 86), 1c. Level 2 (n=271), 1d. Level 3 (n=250). Abbreviations: CNS – central nervous system tumours, SNS – sympathetic nervous system tumours, GCT – germ cell tumours, STS – soft tissue sarcomas

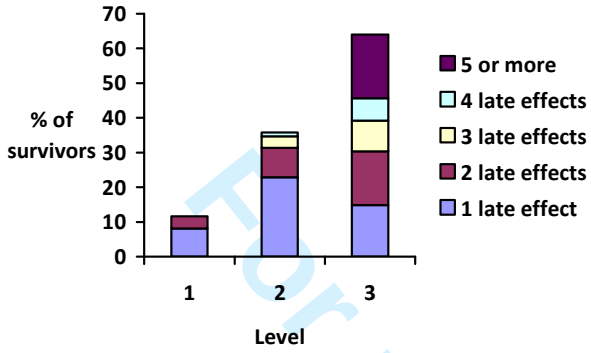

Figure 3

Prevalence of late effects by risk stratified level of follow-up for all five year survivors (n=607).

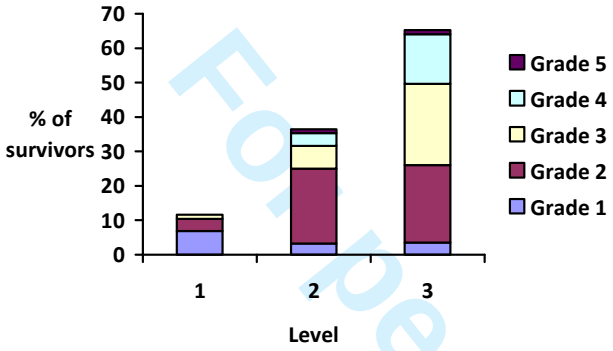

Figure 4

Severity of late effects by risk stratified level (CTCAEv3.0): grade 1- mild, grade 2-moderate, grade 3 severe, grade 4 – life threatening or disabling and grade 5 – death for all five year survivors (n=607). [17]

Table 1. Demographic characteristics of all the five year survivors alive at the time of the study (n=573) and for Level 1, Level 2 and Level 3 subgroups.

Characteristic	Five year survivors (n-573)		Level 1 (n=86)		Level 2 (n=258)		Level 3 (n=229)	
	No.	%	No.	%	No.	%	No.	%
Sex								
Male	303	52.9	37	43	137	53.1	129	56.3
Female	270	47.1	49	57	121	46.9	100	43.7
Current age, years								
5-9	44	7.7	11	12.8	15	5.8	18	7.8
10-14	110	19.2	19	22.1	56	21.7	35	15.3
15-19	148	25.8	31	36.0	66	25.6	51	22.3
20-24	129	22.5	19	22.1	51	19.8	59	25.8
25-29	69	12.0	6	7.0	30	11.6	33	14.4
30-34	40	7.0	-	-	16	6.2	24	10.5
35-39	21	3.7	-	-	15	5.8	6	2.6
40-44	11	1.9	-	-	8	3.1	3	1.3

45-49	1	0.2	-	-	1	0.4	-	-
Median, Range	19.4	5.1-45.1	17.5	5.1-28.4	19.4	8.0-45.1	20.1	5.6-43.7
Age at diagnosis, years								
0-4	286	49.9	54	62.8	140	54.3	92	40.2
5-9	144	25.1	16	18.6	68	26.4	60	26.2
10-14	122	21.3	15	17.4	48	18.6	59	25.8
15-19	21	3.7	1	1.2	2	0.7	18	7.8
Median, Range	5.0	0-20.9	2.9	0-15.4	4.5	0-20.9	6.5	0-17.5
Time from diagnosis, years								
5-9	197	34.4	33	38.4	80	31.0	84	36.7
10-14	166	29.0	32	37.2	76	29.5	58	25.3
15-19	100	17.5	11	12.8	38	14.7	51	22.3
20-24	58	10.1	8	9.3	30	11.6	20	8.7
25-29	30	5.2	2	2.3	16	6.2	12	5.2
30-34	12	2.1	-	-	10	3.9	2	0.9
35-39	10	1.7	-	-	8	3.1	2	0.9
Median, Range	12.4	5.0-39.3	11.0	5.0-26.9	13.0	5.0-38.4	12.9	5.0-39.3
DFS, years								
0-4	36	6.3	1	1.2	20	7.7	15	6.5

5-9	198	34.5	34	39.5	82	31.8	82	35.8
10-14	160	27.9	31	36.0	67	26.0	62	27.1
15-19	84	14.7	10	11.6	34	13.2	40	17.5
20-24	57	9.9	8	9.3	31	12.0	18	7.9
25-29	19	3.4	2	2.4	8	3.1	9	3.9
30-34	17	3.0	-	-	15	5.8	2	0.9
35-39	2	0.3	-	-	1	0.4	1	0.4
Median, Range	11.3	0.5-38.3	10.9	4.4-26.9	11.6	1.9-36.4	11.6	0.5-38.3
Time since last seen in Hospital Based Late Effects Clinic, years								
0-2	328	57.2	31	36.0	143	55.4	154	67.2
3-4	75	13.1	16	18.6	36	13.9	23	10.1
5-7	78	13.6	20	23.3	40	15.5	18	7.9
8-10	28	5.0	6	7.0	10	3.9	12	5.2
>10	41	7.1	8	9.3	19	7.4	14	6.1
Unknown	23	4.0	5	5.8	10	3.9	8	3.5
Median, Range	2.3	0-13.1	4.5	0-12.7	2.2	0-12.7	1.8	0-13.1

Competing interest statement

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work, no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

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Contributorship statement

ABE initiated the project, designed data collection tools, monitored data collection for the study, analysed the data, and drafted and revised the paper. KD designed data collection tools, monitored data collection for the study, analysed the data

and revised the draft paper. SB designed data collection tools, monitored data collection for the study, analysed the data and revised the draft paper. PM-S analysed the data and drafted and revised the paper. WHBW designed data collection tools, monitored data collection for the study, analysed the data, and drafted and revised the paper. All authors had full access to all of the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Data sharing statement

Dataset available from the corresponding author at angela.edgar@luht.scot.nhs.uk. Consent was not obtained but the presented data are anonymised and risk of identification is low.

Ethical approval

Ethical approval for this study was requested from the Lothian Research Ethics Committee (LREC). On review by the LREC, the committee decided that ethical approval was not required as long-term follow-up of childhood cancer survivors was deemed to be an acceptable and routine part of clinical practice and there were no experimental interventions.

Funding

No specific funding was received for this research.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	4
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6-8
Objectives	3	State specific objectives, including any prespecified hypotheses	8
Methods			
Study design	4	Present key elements of study design early in the paper	9
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	9
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	9
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*10*
Bias	9	Describe any efforts to address potential sources of bias	10
Study size	10	Explain how the study size was arrived at	9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9-10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	11 N/A
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	12
		(b) Give reasons for non-participation at each stage	12
		(c) Consider use of a flow diagram	26
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	12-14
		(b) Indicate number of participants with missing data for each variable of interest	12
		(c) Summarise follow-up time (eg, average and total amount)	12-14, 27
Outcome data	15*	Report numbers of outcome events or summary measures over time	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	n/a
		(*b*) Report category boundaries when continuous variables were categorized	n/a
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	15
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15-20
Generalisability	21	Discuss the generalisability (external validity) of the study results	15-20
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	34

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Can Intensity of long-term follow-up for survivors of childhood and teenage cancer be determined by therapy-based risk-stratification?

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Can Intensity of long-term follow-up for survivors of childhood and teenage cancer be safely determined by therapy-based risk-stratification?

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Article summary

Article Focus

- Therapy-based, risk-stratification of survivors can safely predict which survivors of childhood and teenage cancer are at significant risk of developing moderate to severe late effects and require high intensity long-term follow-up.

Key messages

- Patients who had received the most complex cancer treatments had the largest number and most severe late effects. Those patients assigned to low risk category of follow-up had few late effects and those late effects were mild.
- Long term survivors of childhood and teenage cancer can safely be assigned to primary care, nurse-led or hospital follow-up based on the intensity of treatment they received for the original cancer.
- Stratification of patients according to risk of late morbidity will maximise the use of NHS resources and provide age appropriate care as locally as possible.

Strengths

- This study shows that it is possible to safely predict which survivors of childhood cancer are at significant risk of developing moderate to severe late effects. Life long follow-up for all childhood cancer survivors is not only cost ineffective but also difficult to organize. Until now there was no evidence available to define the optimum follow-up for long-term survivors.

- Risk stratification will enable young adult survivors to benefit from a transition process that takes them into an appropriate follow-up model and can help to identify those survivors who can be safely discharged from hospital based follow-up.

Limitations

- 30% of the cohort had not been seen in the hospital based late effects service for more than two years and health problems may be underestimated in this group.
- It would be helpful in future studies to determine the proportion of late effects detected as a direct result of clinic attendance and to determine the proportion of late effects which are treatable.

Abstract

Objective

To determine the safety of therapy-based, risk-stratified follow-up guidelines for childhood and teenage cancer survivors by evaluating adverse health outcomes in a survivor cohort retrospectively assigned a risk category.

Design

Retrospective cohort study.

Setting

Tertiary level, single centre, paediatric cancer unit in South East Scotland

Participants

All children and teenagers diagnosed with cancer (<19 years) between 1st January 1971-31st July 2004, who were alive more than five years from diagnosis formed the study cohort. Each survivor was retrospectively assigned a level of follow-up, based on their predicted risk of developing treatment related late effects (level 1, 2 and 3 for low, medium and high risk, respectively). Adverse health outcomes were determined from review of medical records and postal questionnaires. Late effects were graded using the Common Terminology Criteria for Adverse Event, Version 3 (CTCAEv3).

Results

607 five-year survivors were identified. Risk-stratification identified 86 (14.2%), 271 (44.6%) and 250 (41.2%) level 1, 2 and 3 survivors respectively. The prevalence of late effects (LE) for level 1 survivors was 11.6% with only 1 patient with grade 3 or above toxicity. 35.8% of level 2 survivors had a LE, of whom 9.3%, 58.8%, 18.5%, 10.3% and 3% had grade 1, 2, 3, 4 and 5 toxicity respectively. 65.2 % of level 3 survivors had LE), of whom 5.5% (n=9), 34.4% (n=56), 36.2% (n=59), 22.1% (n=36) and 1.8% (n=3) had grade 1,2,3,4 and 5 toxicity respectively.

Conclusions

Therapy-based, risk-stratification of survivors can safely predict which patients are at significant risk of developing moderate to severe late effects and require high intensity long-term follow-up.

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Introduction

Dramatic improvements in survival for children with cancer have highlighted the need for evidence based long-term follow-up (LTFU) for these young people. Approximately 80% of children diagnosed with cancer can now expect to survive more than 5 years, and around 70 % will survive ten years, from their diagnosis.[1] It is estimated that 1 in 640 young adults is a survivor of childhood cancer.[2] As many as two thirds of long-term survivors are reported to be at increased risk of substantial morbidity and even mortality, due to adverse late effects secondary to cancer or cancer therapy.[3-5] Late effects are diverse and include secondary malignancies, organ system damage, infertility, cognitive impairment, and disorders of growth and development.[6, 7] Appropriate LTFU of these patients is essential to detect, treat and prevent morbidity and mortality.[8]

There is wide variation of long-term follow-up practices throughout the UK with a propensity for hospital dependency, often in age-inappropriate settings.[9] A recent study has highlighted how excess morbidity in survivors translates into increased use of health care facilities.[10] An awareness of the need for an integrated and systematic approach to follow-up was recognised by the Scottish Intercollegiate Guidelines Network (SIGN) who developed an evidence-based approach to long-term follow-up.[11] The risks of developing treatment related late effects depend upon the underlying malignancy, the site of the tumour, the type of treatment and the age at time of treatment. A risk-stratified approach to health surveillance was developed which identified three groups of survivors who require an increasing

intensity of follow-up[8]. In the UK, we published a Practice Statement 'Therapy Based Long-term Follow-up' which is designed to inform and guide clinicians responsible for the long-term follow-up of childhood cancer survivors.[12] The Practice Statement recommends follow-up assessments and investigations based on the treatment that the individual has received and is informed by the evidence-based recommendations published by SIGN 76.

An integrated and systematic approach is now considered a requirement of the National Institute of Health and Clinical Excellence (NIHCE) Improving Outcomes for Children and Young People with Cancer Guidance (2005) and National Delivery Plan for Children and Young People's Specialist Services in Scotland (2008).[13,14] In England, the National Cancer Survivorship Initiative (NCSI) has developed as a partnership between the Department of Health, Macmillan Cancer Support, and supported by NHS Improvement, to develop models of care to ensure that those living with and beyond cancer have access to safe and effective care and receive the support they need to lead as healthy and active a life as possible. Improved awareness of cancer survivorship as a chronic health problem will facilitate the development of care pathways that will meet the needs of every patient throughout their lifetime.[15]

Although there is growing guidance on whom, where and how long-term survivors should be followed-up, evidence to show that adopting a model of risk-stratified follow-up is safe is lacking. A recent study has shown that assigning

patients to one of three agreed levels of follow up, as described by Wallace et al, was relatively simple for experienced clinic staff.[16] The objective of this study was to evaluate the safety and efficacy of this risk-based follow-up model by retrospectively stratifying an unselected cohort of long-term survivors of childhood cancer from a single centre and objectively evaluating their health status.

Methods

Study population

All patients, aged less than 19 years, who were diagnosed with childhood cancer in a single institution in South East Scotland, between 1971 and 2004, and who were alive at least five years from diagnosis, were included in the study. The patients were identified from the Oxford Children's Cancer Registry, established in 1992; patients diagnosed before 1992 were identified from the Scottish Cancer Registry, established in 1958, and hospital records.

Data Collection

All health problems directly attributable to cancer, or cancer therapy, were obtained from medical records, electronic hospital records systems, self-reported questionnaires. Medical data were obtained from medical records, electronic hospital records, clinical correspondence from other health professionals and self-completed health status questionnaire and is likely to be an underestimate of the health problems. Cause of death for the deceased patients as assigned by the General Register Office for Scotland, was obtained from the Scottish Cancer Registry, courtesy of Information Services Division, NHS National Services, Scotland (personal communication).

Therapy-based risk stratification

The Scottish Intercollegiate Guidelines Network (SIGN) has developed an evidence-based approach to LTFU, incorporating the risk-based levels of follow-

up described in 2001.[8] Patients are classified into one of three groups (Levels 1,2 and 3): Level 1 patients, treated with surgery alone or low risk chemotherapy treatment, who could be followed up by postal or telephone contact; Level 2 patients, treated with standard risk chemotherapy, such as survivors of ALL or lymphoma, who are considered to be at moderate risk of developing late effects, eg anthracycline-induced cardiotoxicity, could be followed up by an appropriately trained individual, such as a late effects nurse specialist; Level 3 patients, who would require medically supervised follow-up within a multi-disciplinary team – that is those patients that have had a CNS tumour (treated with chemotherapy and/or radiotherapy), bone marrow transplants, stage 4 disease, any radiotherapy except low dose cranial radiotherapy and those that have had intensive therapy. Risk-stratified levels of follow-up were independently assigned to all survivors by two researchers.

Grading of Late Effects

To determine the severity of late effects, each reported late effect was graded independently by two of the authors using the Common Terminology Criteria for Adverse Events, Version 3.0 (CTCAEv3.0, available at http://ctep.cancer.gov/forms/CTCAEv3.pdf), a scoring system developed through the US National Cancer Institute by a multidisciplinary group and adopted in the UK by the Children's Cancer and Leukaemia Group (CCLG).[17] The CTCAEv3.0 tool can be used for acute and chronic conditions in patients with cancer and grades conditions as mild (grade 1), moderate (grade 2), severe (grade 3), life-

threatening or disabling (grade 4), or adverse event-related death (grade 5). To investigate and reduce inter-observer variability, graded adverse events were compared and inconsistencies were discussed and detailed coding rules were developed (available on request form the authors). Inconsistencies in grading revolved mainly around scoring subjective psychosocial and neuropsychological items of grade 1 or 2, grading of 3 or higher adverse events was straightforward.

Ethical Approval

Ethical approval for this study was requested from the Lothian Research Ethics Committee (LREC). On review by the LREC, the committee decided that ethical approval was not required as long-term follow-up of childhood cancer survivors was deemed to be an acceptable and routine part of clinical practice and there were no experimental interventions.

Analysis

The statistical package for social sciences (SPSS) Windows version 14.0 was used for the statistical analyses. Data were analyzed by descriptive techniques using frequencies, percentages and medians as appropriate.

Results

Study Population

883 patients were diagnosed with childhood and teenage cancer between 1st January 1971 to 1st July 2004 and 607 of these patients were alive five years from diagnosis (5 year overall survival rate 69%). Medical information was collected from a retrospective case note review, regional electronic hospital systems and self-reported health outcomes from questionnaires. Of the 607 five year survivors, 34 patients were deceased (5.6%) at the time of the study (figure 1). Of the 573 long-term survivors alive at the time of this study 122 patients were not known to be under any kind of hospital review (21%). Of the 451 patients under hospital follow-up, 370 (82%) were followed up within the South East Scotland Late Effects Service, either by postal questionnaire follow-up (n=67, 17%) or clinic appointment (n=307, 83%). The remaining 81 (18%) of survivors attended other paediatric hospital-based clinics within the same paediatric setting (n=14) or in Tayside (n=26), or Adult Services in South East Scotland (n=31) and in other cities throughout the UK (n=10). Data were gathered from medical records from information based on a clinic visit of more than two years previously, without supplementation from postal questionnaires in 178 patients (31%) and is likely to represent an underestimate of late effects.

Demographics

607 long-term survivors were identified (males 321 (52.9%)) with median age (range) of 19.2 (5.1-45.1) years and median age (range) at diagnosis 5.1 (0.0-

17.5) years. Of the cohort, 34 (5.6%) were deceased, with a median overall survival (range) of 9.9 (5.0-30.9) years. Of the 573 long-term survivors alive at the time of the study, the median age (range) was 19.4 (5.1-45.1) years and disease free survival (range) 11.3 (0.8-38.3) years (Table 1). The primary cancer diagnosis is shown for all patients and within each risk level (Figure 2). Risk-stratification of all long-term survivors (n=607) identified 86 (14.1%), 271 (44.6%) and 250 (41.2%) at Level 1, 2 and 3 respectively with detailed breakdown of ages and survival interval for each level of patients alive at the time of the study only (n=573), shown in Table 1 and Figure 1. Demographic data is similar between the three populations.

Adverse health outcomes according level of risk

Among the 34 deaths in the five year survivors (n=607), 26 (76.5%) died from progression or relapse of the underlying primary cancer, two (5.9%) died from unrelated causes and six (17.6%) died from treatment related sequelae; five from second primary malignancy and one from end-stage renal failure. Of the five survivors who went on to die from second primary malignancy, three patients (all Level 2) had a meningioma, presumed to be secondary to low dose cranial irradiation as part of CNS directed therapy for the treatment of childhood ALL, one (Level 3) developed extensive intra-abdominal desmoid tumour having previously been treated for medulloblastoma and with a background of APC gene and Turcot's syndrome and the other patient (Level 3) developed AML presumed

to be related to previous topo-isomerase II inhibitor therapy for primary bone sarcoma (Figure 1).

Prevalence and severity of treatment related late effects were determined for each patient with an assigned level of follow up (n=607, Figures 3 and 4). Among Level 1 survivors (n=86), 11.6% (n=10) had late effects, of whom seven (8.1%) had one late effect and three (3.5%) had two late effects; 60% (n=6) of which were grade 1 toxicity, 30% (n=3) of whom were grade 2 toxicity and 10% (n=1) grade 3 toxicity. Within the Level 2 group (n=271), the prevalence of late effects was 35.8% (n=97), of whom 62 (22.9%) had 1 late effect, 23 (8.5%) had 2 late effects, 9 (3.3%) had 3 late effects and 3 (1.1%) had four late effects, of whom 9.3% (n=9) had a maximum toxicity grade of 1, 58.8% (n=57) grade 2, 18.5% (n=18) grade 3, 10.3% (n=10) grade 4 and 3% (n=3) grade 5. The prevalence of late effects in the Level 3 survivors (n=250) was 65.2% (n=163) of whom 37 (14.8%) had 1 late effect, 39 (15.6%) had 2 late effects, 22 (8.8%) had 3 late effects, 16 (6.4%) had 4 late effects and 46 (18.4%) had 5 or more late effects, of whom 9 (5.5%), 56 (34.4%), 59 (36.2%), 36 (22.1%) and 3 (1.8%) had grade 1,2,3,4 and 5 toxicity respectively.

Discussion

We have shown that therapy-based, risk-stratification of long-term survivors of childhood and teenage cancer can safely predict which patients are at risk of developing moderate to severe side effects and require high intensity clinic based long-term follow-up. Retrospective assignment of patients into a risk category identified almost half (45%) of patients could be considered at moderate risk of developing late effects, while 41% were deemed to be at high risk of developing late effects, with only a small proportion felt to be at low risk of late complications. The prevalence and severity of side effects increased with increasing level of follow up.

Lifelong follow-up is recommended for survivors of childhood cancer because many of the health problems may be reduced by prevention or early detection.[18] However follow-up should be individually tailored and hospital based follow-up should not be necessary for all survivors.[19] The incidence of chronic conditions continues to increase with time and there is therefore no safe time after which these patients can be discharged.[20] There is increasing evidence that with increasing time from diagnosis, medical problems associated with ageing, including second cancers, cardiovascular disease, infertility and osteoporosis, may exhibit an accelerated course following certain cancer treatments.[18,21] Mertens et al showed that while recurrent disease remains the most important contributor to late mortality in 5 year survivors there is a significant excess

mortality risk associated with treatment related complications that is present in the 25 years after the initial cancer diagnosis.[22]

It is reported that up to 50% of long-term survivors do not attend Late Effects Clinics and many of these patients are considered to be at high risk of developing treatment-related late complications.[23] There are many reasons why survivors choose not to participate in long-term follow-up including lack of awareness of risks of late morbidity, desire to 'move on', lack of appropriate adult services and clinical discharge. In a study by Blaauwbroek et al they assessed late effects in a group of adult survivors of childhood cancer who were not involved in regular long-term follow-up and reported that almost 40% of survivors suffered from moderate to severe late effects and 33% had previously unknown late effects.[24] This reiterates the need to educate survivors about their past medical history, their treatment and the importance of engaging in regular survivorship programmes.

Low rates of participation in long-term follow-up are universally reported. In 2004, a Delphi panel of 20 expert childhood cancer survivors in US identified a number of barriers contributing to this.[25] Understanding these barriers will lead to improved medical care for these patients. It was recognized that most childhood cancer survivors are not aware of their adverse health risks and often unaware of the details of their cancer or its treatment. Even where LTFU clinics are attended much of the education of late effects was directed at parents and often not

transferred to the child. The Delphi Panel also highlighted the limitations within the health care setting including lack of LTFU service, discharge to primary care physician who lacks expertise in this field and often receive no communication about the child's past medical history. Improving communication between professionals and patients is essential and will be an integral part of development of survivorship programmes.

The traditional model of LTFU has been in paediatric oncology clinics, generally jointly with paediatric endocrinologists, neurologists and clinical oncologists, long into adulthood which brings with it the advantage of continuity of care, familiarity with treatments but there are a number of disadvantages to this system. This is not only an age appropriate environment for these patients, but also an unsustainable situation for paediatric oncologists, as the population of long-term survivors increase and age. In addition, survivors are protected in this paediatric environment and don't develop the skills necessary to navigate the health care system as they develop into adulthood. Ideally, once the long-term survivor reaches adulthood he/she should be transitioned into the appropriate adult late effects services. At present, such a service does not exist and it is difficult to identify which clinicians should take on this role, especially with increasing sub-specialisation in adult medicine. In a busy and overstretched tertiary oncology healthcare service, medical and clinical adult oncology consultants are unlikely to be in a position to take on this responsibility, and may well feel inadequately trained in caring for childhood cancer survivors. In current practice, the only adult

services supporting the long-term follow-up of those patients requiring specialist hospital follow-up are the adult endocrine and neurology clinics.

It has been highlighted that improved communication of cancer information to patients/families and between health care providers may contribute to greater engagement in follow-up programmes, raises awareness of potential late effects amongst survivors and enable clinicians to diagnose and, where possible, treat late effects earlier. Based on national guidelines, we have developed a template for the End of Treatment Summary and Individualised Care Plan, or 'Health Passport', which has been introduced nationally, and welcomed by health professionals and survivors.

Models of care for LTFU of survivors of childhood cancer must be flexible enough to accommodate the needs of the young survivor as they transition throughout their life cycle and also to accommodate the individual heterogeneity of cancer survivors, reflecting the wide range of treatment exposure and adverse long-term sequelae. Development of a service that can deliver individualized, comprehensive, therapy-based patient centred care is essential.

The UK National Cancer Survivorship Initiative is currently exploring models of aftercare services for children and young people who have been treated for cancer. National pathways that identify how follow-up can be delivered in line with current pressures and aspirations are being developed. Clinical risk

stratification will play an integral role in tailoring individualised care to meet the clinical, psychological and practical needs of each survivor. A recent study from the CCSS has reviewed how data derived from the CCSS have characterized specific groups that are deemed to be at highest risk of morbidity and subsequent cancers.[26] Our study has shown that those patients at highest risk of late morbidity can be identified and appropriately stratified into a high risk (level 3) follow-up programme.

Stratification of patients according to risk of late morbidity will maximise the use of health service resources and provide age appropriate care as locally as possible. With increasing time from completion of treatment, it is hoped that the majority of adult survivors will be independent and take responsibility for their own health, with health care support provided by their primary care physician. As a result, the primary care team is likely to play an increasing role in the long-term follow-up of survivors of childhood cancer. Primary care services may be already stretched but GPs are used to meeting targets and ensuring guidelines are implemented. Good communication between the hospital services and primary care will be essential. Early involvement of general practitioners in the Late Effects Services will establish collaborations between the two teams and enable primary Care Physicians to become familiar with the surveillance programme. The feasibility of a shared-care model between cancer paediatric oncology cancer centres and primary-care doctors to deliver survivor-focused risk based health care was tested successfully by a Dutch group. The study showed that

patients would see their family doctor for long-term follow-up: the family doctors were interested in sharing survivors' care; and family doctors would return the necessary medical information needed for continued follow-up.[27] Appropriate education of the family doctors, which has resource implications, was a key finding of this study. More recently this group has shown that a web based survivor care plan can facilitate the long-term care of survivors by family doctors.[28]

In order to improve our understanding of treatment-related side effects and help develop treatment protocols to minimise toxicity, lifelong monitoring of health and well-being of all long-term survivors will be necessary. Our understanding of the late effects of the treatment of Hodgkin's lymphoma has led to studies which are ongoing and are designed to reduce the risk of second malignancy by avoiding radiotherapy in selected cases and replace gonadotoxic chemotherapy with drugs that are efficacious in Hodgkin's lymphoma but less likely to compromise reproductive function.[29] Balancing safety and efficacy in the treatment of Hodgkin's lymphoma remains an important goal in the treatment of this curable malignancy.[30]

We have shown that it is possible to safely predict which survivors of childhood cancer are at significant risk of developing moderate to severe late effects and require moderate or high intensity long-term follow. Importantly we have also shown that there is a group of survivors who can be reliably identified who can be

safely discharged from clinic based follow-up. Structured, risk-adapted follow-up of childhood cancer survivors following evidence-based guidelines would reduce cost ineffective or excessive evaluations and focus individual health care delivery. Education of survivors and health care providers will hopefully reduce the burden of chronic health problems and improve quality of life for the growing population of children and young people who have been treated for cancer.

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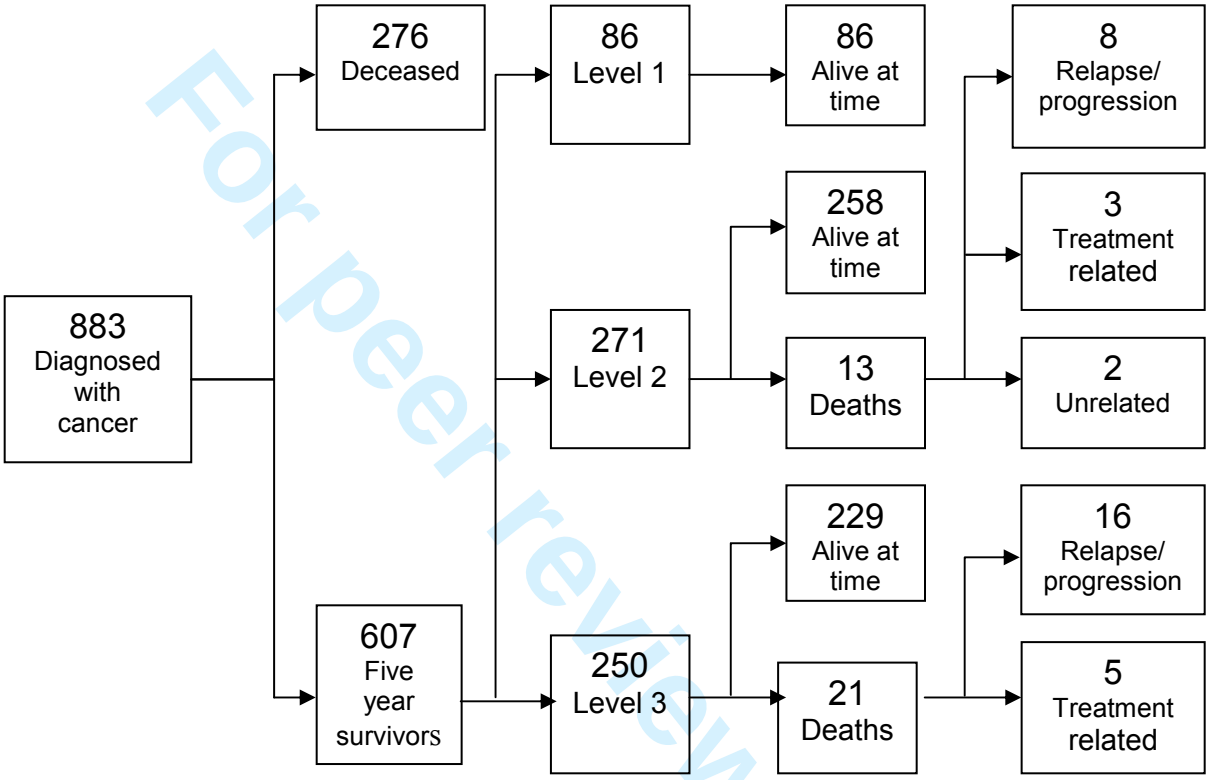

Figure 1. Study flow of childhood and teenage cancer patients.

Flow chart shows the study population and the risk stratification of patients into Levels 1,2 and 3 and the proportion of patients alive at the time of the study.

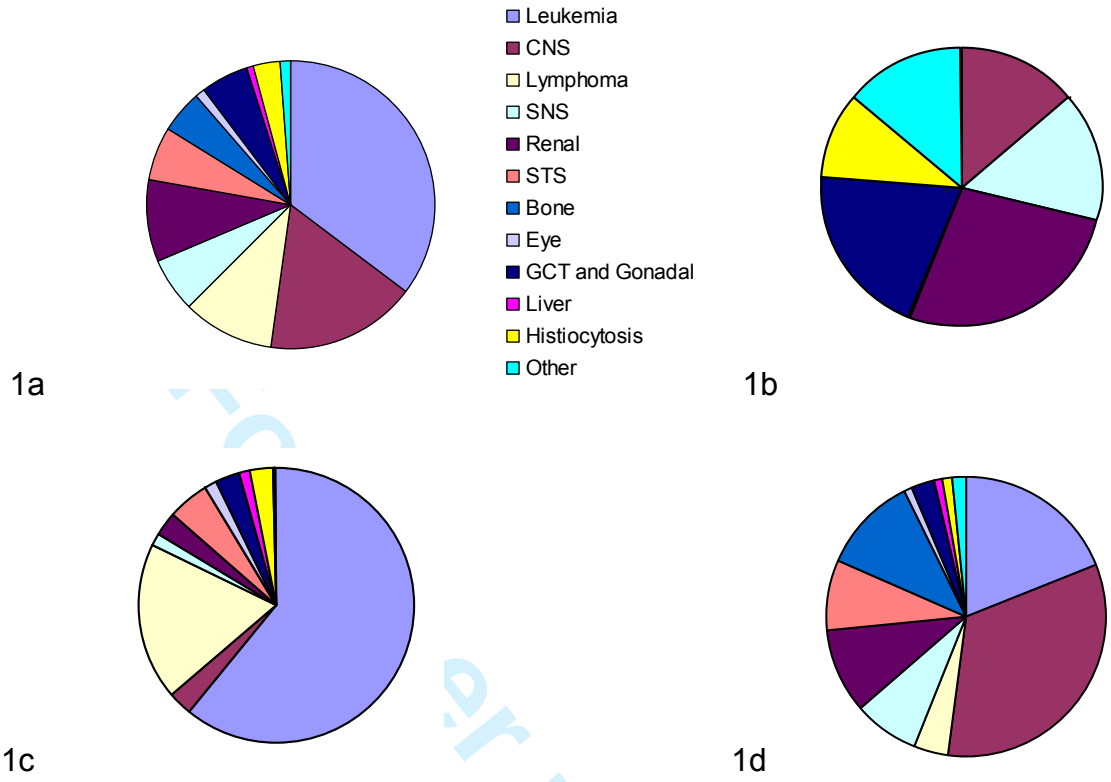

Figure 2 Diagnoses of five year survivors (n-607)

1a. All survivors (n=607), 1b. Level 1 (n= 86), 1c. Level 2 (n=271), 1d. Level 3 (n=250). Abbreviations: CNS – central nervous system tumours, SNS – sympathetic nervous system tumours, GCT – germ cell tumours, STS – soft tissue sarcomas

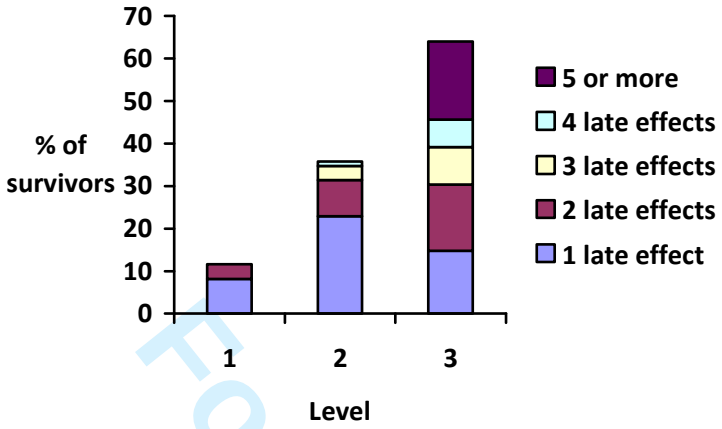

Figure 3

Prevalence of late effects by risk stratified level of follow-up for all five year survivors (n=607).

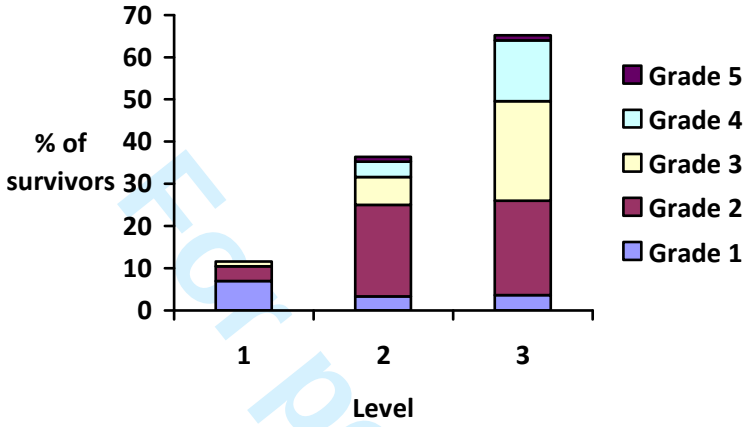

Figure 4

Severity of late effects by risk stratified level (CTCAEv3.0): grade 1- mild, grade 2-moderate, grade 3 severe, grade 4 – life threatening or disabling and grade 5 – death for all five year survivors (n=607). [17]

Table 1. Demographic characteristics of all the five year survivors alive at the time of the study (n=573) and for Level 1, Level 2 and Level 3 subgroups.

Characteristic	Five year survivors (n-573)		Level 1 (n=86)		Level 2 (n=258)		Level 3 (n=229)	
	No.	%	No.	%	No.	%	No.	%
Sex								
Male	303	52.9	37	43	137	53.1	129	56.3
Female	270	47.1	49	57	121	46.9	100	43.7
Current age, years								
5-9	44	7.7	11	12.8	15	5.8	18	7.8
10-14	110	19.2	19	22.1	56	21.7	35	15.3
15-19	148	25.8	31	36.0	66	25.6	51	22.3
20-24	129	22.5	19	22.1	51	19.8	59	25.8
25-29	69	12.0	6	7.0	30	11.6	33	14.4
30-34	40	7.0	-	-	16	6.2	24	10.5
35-39	21	3.7	-	-	15	5.8	6	2.6
40-44	11	1.9	-	-	8	3.1	3	1.3

45-49	1	0.2	-	-	1	0.4	-	-
Median, Range	19.4	5.1-45.1	17.5	5.1-28.4	19.4	8.0-45.1	20.1	5.6-43.7
Age at diagnosis, years								
0-4	286	49.9	54	62.8	140	54.3	92	40.2
5-9	144	25.1	16	18.6	68	26.4	60	26.2
10-14	122	21.3	15	17.4	48	18.6	59	25.8
15-19	21	3.7	1	1.2	2	0.7	18	7.8
Median, Range	5.0	0-20.9	2.9	0-15.4	4.5	0-20.9	6.5	0-17.5
Time from diagnosis, years								
5-9	197	34.4	33	38.4	80	31.0	84	36.7
10-14	166	29.0	32	37.2	76	29.5	58	25.3
15-19	100	17.5	11	12.8	38	14.7	51	22.3
20-24	58	10.1	8	9.3	30	11.6	20	8.7
25-29	30	5.2	2	2.3	16	6.2	12	5.2
30-34	12	2.1	-	-	10	3.9	2	0.9
35-39	10	1.7	-	-	8	3.1	2	0.9
Median, Range	12.4	5.0-39.3	11.0	5.0-26.9	13.0	5.0-38.4	12.9	5.0-39.3
DFS, years								
0-4	36	6.3	1	1.2	20	7.7	15	6.5

5-9	198	34.5	34	39.5	82	31.8	82	35.8
10-14	160	27.9	31	36.0	67	26.0	62	27.1
15-19	84	14.7	10	11.6	34	13.2	40	17.5
20-24	57	9.9	8	9.3	31	12.0	18	7.9
25-29	19	3.4	2	2.4	8	3.1	9	3.9
30-34	17	3.0	-	-	15	5.8	2	0.9
35-39	2	0.3	-	-	1	0.4	1	0.4
Median, Range	11.3	0.5-38.3	10.9	4.4-26.9	11.6	1.9-36.4	11.6	0.5-38.3
Time since last seen in Hospital Based Late Effects Clinic, years								
0-2	328	57.2	31	36.0	143	55.4	154	67.2
3-4	75	13.1	16	18.6	36	13.9	23	10.1
5-7	78	13.6	20	23.3	40	15.5	18	7.9
8-10	28	5.0	6	7.0	10	3.9	12	5.2
>10	41	7.1	8	9.3	19	7.4	14	6.1
Unknown	23	4.0	5	5.8	10	3.9	8	3.5
Median, Range	2.3	0-13.1	4.5	0-12.7	2.2	0-12.7	1.8	0-13.1

Competing interest statement

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work, no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

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Contributorship statement

ABE initiated the project, designed data collection tools, monitored data collection for the study, analysed the data, and drafted and revised the paper. KD designed data collection tools, monitored data collection for the study, analysed the data

and revised the draft paper. SB designed data collection tools, monitored data collection for the study, analysed the data and revised the draft paper. PM-S analysed the data and drafted and revised the paper. WHBW designed data collection tools, monitored data collection for the study, analysed the data, and drafted and revised the paper. All authors had full access to all of the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Data sharing statement

Dataset available from the corresponding author at angela.edgar@luht.scot.nhs.uk. Consent was not obtained but the presented data are anonymised and risk of identification is low.

Ethical approval

Ethical approval for this study was requested from the Lothian Research Ethics Committee (LREC). On review by the LREC, the committee decided that ethical approval was not required as long-term follow-up of childhood cancer survivors was deemed to be an acceptable and routine part of clinical practice and there were no experimental interventions.

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Can Intensity of long-term follow-up for survivors of childhood and teenage cancer be ~~safely~~ determined by therapy-based risk-stratification?

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Key words: Childhood cancer, treatment, survival, cure, late effects, models of follow-up, long-term follow-up.

Article summary

Article Focus

- Therapy-based, risk-stratification of survivors can ~~safely~~ predict which survivors of childhood and teenage cancer are at significant risk of developing moderate to severe late effects and require high intensity long-term follow-up.

Key messages

- Patients who had received the most complex cancer treatments had the largest number and most severe late effects. Those patients assigned to low risk category of follow-up had few late effects and those late effects were mild.
- Long term survivors of childhood and teenage cancer can ~~safely~~ be assigned to primary care, nurse-led or hospital follow-up based on the intensity of treatment they received for the original cancer.
- Stratification of patients according to risk of late morbidity will maximise the use of NHS resources and provide age appropriate care as locally as possible.

Strengths

- This study shows that it is possible to ~~safely~~ predict which survivors of childhood cancer are at significant risk of developing moderate to severe late effects. Life long follow-up for all childhood cancer survivors is not only cost ineffective but also difficult to organize. Until now there was no evidence available to define the optimum follow-up for long-term survivors.

- Risk stratification will enable young adult survivors to benefit from a transition process that takes them into an appropriate follow-up model and can help to identify those survivors who can be ~~safely~~ discharged from hospital based follow-up.

Limitations

- 30% of the cohort had not been seen in the hospital based late effects service for more than two years and health problems may be underestimated in this group.
- It would be helpful in future studies to determine the proportion of late effects detected as a direct result of clinic attendance and to determine the proportion of late effects which are treatable.

Abstract

Objective

To determine the ~~safety~~ feasibility of therapy-based, risk-stratified follow-up guidelines for childhood and teenage cancer survivors by evaluating adverse health outcomes in a survivor cohort retrospectively assigned a risk category.

Design

Retrospective cohort study.

Setting

Tertiary level, single centre, paediatric cancer unit in South East Scotland

Participants

All children and teenagers diagnosed with cancer (<19 years) between 1st January 1971-31st July 2004, who were alive more than five years from diagnosis formed the study cohort. Each survivor was retrospectively assigned a level of follow-up, based on their predicted risk of developing treatment related late effects (level 1, 2 and 3 for low, medium and high risk, respectively). Adverse health outcomes were determined from review of medical records and postal questionnaires. Late effects were graded using the Common Terminology Criteria for Adverse Event, Version 3 (CTCAEv3).

Results

607 five-year survivors were identified. Risk-stratification identified 86 (14.2%), 271 (44.6%) and 250 (41.2%) level 1, 2 and 3 survivors respectively. The prevalence of late effects (LE) for level 1 survivors was 11.6% with only 1 patient with grade 3 or above toxicity. 35.8% of level 2 survivors had a LE, of whom 9.3%, 58.8%, 18.5%, 10.3% and 3% had grade 1, 2, 3, 4 and 5 toxicity respectively. 65.2 % of level 3 survivors had LE), of whom 5.5% (n=9), 34.4% (n=56), 36.2% (n=59), 22.1% (n=36) and 1.8% (n=3) had grade 1,2,3,4 and 5 toxicity respectively.

Conclusions

Therapy-based, risk-stratification of survivors can ~~safely~~ predict which patients are at significant risk of developing moderate to severe late effects and require high intensity long-term follow-up.

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Introduction

Dramatic improvements in survival for children with cancer have highlighted the need for evidence based long-term follow-up (LTFU) for these young people. Approximately 80% of children diagnosed with cancer can now expect to survive more than 5 years, and around 70 % will survive ten years, from their diagnosis.[1] It is estimated that 1 in 640 young adults is a survivor of childhood cancer.[2] As many as two thirds of long-term survivors are reported to be at increased risk of substantial morbidity and even mortality, due to adverse late effects secondary to cancer or cancer therapy.[3-5] Late effects are diverse and include secondary malignancies, organ system damage, infertility, cognitive impairment, and disorders of growth and development.[6, 7] Appropriate LTFU of these patients is essential to detect, treat and prevent morbidity and mortality.[8]

There is wide variation of long-term follow-up practices throughout the UK with a propensity for hospital dependency, often in age-inappropriate settings.[9] A recent study has highlighted how excess morbidity in survivors translates into increased use of health care facilities.[10] An awareness of the need for an integrated and systematic approach to follow-up was recognised by the Scottish Intercollegiate Guidelines Network (SIGN) who developed an evidence-based approach to long-term follow-up.[11] The risks of developing treatment related late effects depend upon the underlying malignancy, the site of the tumour, the type of treatment and the age at time of treatment. A risk-stratified approach to health surveillance was developed which identified three groups of survivors who require an increasing

intensity of follow-up[8]. In the UK, we published a Practice Statement 'Therapy Based Long-term Follow-up' which is designed to inform and guide clinicians responsible for the long-term follow-up of childhood cancer survivors.[12] The Practice Statement recommends follow-up assessments and investigations based on the treatment that the individual has received and is informed by the evidence-based recommendations published by SIGN 76.

An integrated and systematic approach is now considered a requirement of the National Institute of Health and Clinical Excellence (NIHCE) Improving Outcomes for Children and Young People with Cancer Guidance (2005) and National Delivery Plan for Children and Young People's Specialist Services in Scotland (2008).[13,14] In England, the National Cancer Survivorship Initiative (NCSI) has developed as a partnership between the Department of Health, Macmillan Cancer Support, and supported by NHS Improvement, to develop models of care to ensure that those living with and beyond cancer have access to safe and effective care and receive the support they need to lead as healthy and active a life as possible. Improved awareness of cancer survivorship as a chronic health problem will facilitate the development of care pathways that will meet the needs of every patient throughout their lifetime.[15]

Although there is growing guidance on whom, where and how long-term survivors should be followed-up, evidence to show that adopting a model of risk-stratified follow-up is safe is lacking. A recent study has shown that assigning

patients to one of three agreed levels of follow up, as described by Wallace et al, was relatively simple for experienced clinic staff.[16] The objective of this study was to evaluate the ~~safety~~ feasibility and efficacy of this risk-based follow-up model by retrospectively stratifying an unselected cohort of long-term survivors of childhood cancer from a single centre and objectively evaluating their health status.

Methods

Study population

All patients, aged less than 19 years, who were diagnosed with childhood cancer in a single institution in South East Scotland, between 1971 and 2004, and who were alive at least five years from diagnosis, were included in the study. The patients were identified from the Oxford Children's Cancer Registry, established in 1992; patients diagnosed before 1992 were identified from the Scottish Cancer Registry, established in 1958, and hospital records.

Data Collection

All health problems directly attributable to cancer, or cancer therapy, were obtained from medical records, electronic hospital records systems, self-reported questionnaires. Medical data were obtained from medical records, electronic hospital records, clinical correspondence from other health professionals and self-completed health status questionnaire and is likely to be an underestimate of the health problems. Cause of death for the deceased patients as assigned by the General Register Office for Scotland, was obtained from the Scottish Cancer Registry, courtesy of Information Services Division, NHS National Services, Scotland (personal communication).

Therapy-based risk stratification

The Scottish Intercollegiate Guidelines Network (SIGN) has developed an evidence-based approach to LTFU, incorporating the risk-based levels of follow-

up described in 2001.[8] Patients are classified into one of three groups (Levels 1,2 and 3): Level 1 patients, treated with surgery alone or low risk chemotherapy treatment, who could be followed up by postal or telephone contact; Level 2 patients, treated with standard risk chemotherapy, such as survivors of ALL or lymphoma, who are considered to be at moderate risk of developing late effects, eg anthracycline-induced cardiotoxicity, could be followed up by an appropriately trained individual, such as a late effects nurse specialist; Level 3 patients, who would require medically supervised follow-up within a multi-disciplinary team – that is those patients that have had a CNS tumour (treated with chemotherapy and/or radiotherapy), bone marrow transplants, stage 4 disease, any radiotherapy except low dose cranial radiotherapy and those that have had intensive therapy. Risk-stratified levels of follow-up were independently assigned to all survivors by two researchers. Level of follow-up was retrospectively assigned to each patient, as if they were five years from diagnosis and before any medical review of late effects was undertaken.

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Grading of Late Effects

To determine the severity of late effects, each reported late effect was graded independently by two of the authors using the Common Terminology Criteria for Adverse Events, Version 3.0 (CTCAEv3.0, available at http://ctep.cancer.gov/forms/CTCAEv3.pdf), a scoring system developed through the US National Cancer Institute by a multidisciplinary group and adopted in the UK by the Children's Cancer and Leukaemia Group (CCLG).[17] The CTCAEv3.0

tool can be used for acute and chronic conditions in patients with cancer and grades conditions as mild (grade 1), moderate (grade 2), severe (grade 3), life-threatening or disabling (grade 4), or adverse event-related death (grade 5). To investigate and reduce inter-observer variability, graded adverse events were compared and inconsistencies were discussed and detailed coding rules were developed (available on request form the authors). Inconsistencies in grading revolved mainly around scoring subjective psychosocial and neuropsychological items of grade 1 or 2, grading of 3 or higher adverse events was straightforward.

Ethical Approval

Ethical approval for this study was requested from the Lothian Research Ethics Committee (LREC). On review by the LREC, the committee decided that ethical approval was not required as long-term follow-up of childhood cancer survivors was deemed to be an acceptable and routine part of clinical practice and there were no experimental interventions.

Analysis

The statistical package for social sciences (SPSS) Windows version 14.0 was used for the statistical analyses. Data were analyzed by descriptive techniques using frequencies, percentages and medians as appropriate.

Results

Study Population

883 patients were diagnosed with childhood and teenage cancer between 1st January 1971 to 1st July 2004 and 607 of these patients were alive five years from diagnosis (5 year overall survival rate 69%). Medical information was collected from a retrospective case note review, regional electronic hospital systems and self-reported health outcomes from questionnaires. Of the 607 five year survivors, 34 patients were deceased (5.6%) at the time of the study (figure 1). Of the 573 long-term survivors alive at the time of this study 122 patients were not known to be under any kind of hospital review (21%). Of the 451 patients under hospital follow-up, 370 (82%) were followed up within the South East Scotland Late Effects Service, either by postal questionnaire follow-up (n=67, 17%) or clinic appointment (n=307, 83%). The remaining 81 (18%) of survivors attended other paediatric hospital-based clinics within the same paediatric setting (n=14) or in Tayside (n=26), or Adult Services in South East Scotland (n=31) and in other cities throughout the UK (n=10). Data were gathered from medical records from information based on a clinic visit of more than two years previously, without supplementation from postal questionnaires in 178 patients (31%) and is likely to represent an underestimate of late effects.

Demographics

In this population-based study, 607 long-term survivors were identified (males 321 (52.9%)) with median age (range) of 19.2 (5.1-45.1) years and median age

(range) at diagnosis 5.1 (0.0-17.5) years. Of the cohort, 34 (5.6%) were deceased, with a median overall survival (range) of 9.9 (5.0-30.9) years. Of the 573 long-term survivors alive at the time of the study, the median age (range) was 19.4 (5.1-45.1) years and disease free survival (range) 11.3 (0.8-38.3) years (Table 1). The primary cancer diagnosis is shown for all patients and within each risk level (Figure 2). Risk-stratification of all long-term survivors (n=607) identified 86 (14.1%), 271 (44.6%) and 250 (41.2%) at Level 1, 2 and 3 respectively with detailed breakdown of ages and survival interval for each level of patients alive at the time of the study only (n=573), shown in Table 1 and Figure 1. Demographic data is similar between the three populations.

Adverse health outcomes according level of risk

Among the 34 deaths in the five year survivors (n=607), 26 (76.5%) died from progression or relapse of the underlying primary cancer, two (5.9%) died from unrelated causes and six (17.6%) died from treatment related sequelae; five from second primary malignancy and one from end-stage renal failure. Of the five survivors who went on to die from second primary malignancy, three patients (all Level 2) had a meningioma, presumed to be secondary to low dose cranial irradiation as part of CNS directed therapy for the treatment of childhood ALL, one (Level 3) developed extensive intra-abdominal desmoid tumour having previously been treated for medulloblastoma and with a background of APC gene and Turcot's syndrome and the other patient (Level 3) developed AML presumed

to be related to previous topo-isomerase II inhibitor therapy for primary bone sarcoma (Figure 1).

Prevalence and severity of treatment related late effects were determined for each patient with an assigned level of follow up (n=607, Figures 3 and 4). Among Level 1 survivors (n=86), 11.6% (n=10) had late effects, of whom seven (8.1%) had one late effect and three (3.5%) had two late effects; 60% (n=6) of which were grade 1 toxicity, 30% (n=3) of whom were grade 2 toxicity and 10% (n=1) grade 3 toxicity. Within the Level 2 group (n=271), the prevalence of late effects was 35.8% (n=97), of whom 62 (22.9%) had 1 late effect, 23 (8.5%) had 2 late effects, 9 (3.3%) had 3 late effects and 3 (1.1%) had four late effects, of whom 9.3% (n=9) had a maximum toxicity grade of 1, 58.8% (n=57) grade 2, 18.5% (n=18) grade 3, 10.3% (n=10) grade 4 and 3% (n=3) grade 5. The prevalence of late effects in the Level 3 survivors (n=250) was 65.2% (n=163) of whom 37 (14.8%) had 1 late effect, 39 (15.6%) had 2 late effects, 22 (8.8%) had 3 late effects, 16 (6.4%) had 4 late effects and 46 (18.4%) had 5 or more late effects, of whom 9 (5.5%), 56 (34.4%), 59 (36.2%), 36 (22.1%) and 3 (1.8%) had grade 1,2,3,4 and 5 toxicity respectively.

Discussion

We have shown that therapy-based, risk-stratification of long-term survivors of childhood and teenage cancer can ~~safely~~ predict which patients are at risk of developing moderate to severe side effects and require high intensity clinic based long-term follow-up. Retrospective assignment of patients into a risk category identified almost half (45%) of patients could be considered at moderate risk of developing late effects, while 41% were deemed to be at high risk of developing late effects, with only a small proportion felt to be at low risk of late complications. The prevalence and severity of side effects increased with increasing level of follow up.

Lifelong follow-up is recommended for survivors of childhood cancer because many of the health problems may be reduced by prevention or early detection.[18] However follow-up should be individually tailored and hospital based follow-up should not be necessary for all survivors.[19] The incidence of chronic conditions continues to increase with time and there is therefore no safe time after which these patients can be discharged.[20] There is increasing evidence that with increasing time from diagnosis, medical problems associated with ageing, including second cancers, cardiovascular disease, infertility and osteoporosis, may exhibit an accelerated course following certain cancer treatments.[18,21] Mertens et al showed that while recurrent disease remains the most important contributor to late mortality in 5 year survivors there is a significant excess

mortality risk associated with treatment related complications that is present in the 25 years after the initial cancer diagnosis.[22]

It is reported that up to 50% of long-term survivors do not attend Late Effects Clinics and many of these patients are considered to be at high risk of developing treatment-related late complications.[23] There are many reasons why survivors choose not to participate in long-term follow-up including lack of awareness of risks of late morbidity, desire to 'move on', lack of appropriate adult services and clinical discharge. In a study by Blaauwbroek et al they assessed late effects in a group of adult survivors of childhood cancer who were not involved in regular long-term follow-up and reported that almost 40% of survivors suffered from moderate to severe late effects and 33% had previously unknown late effects.[24] This reiterates the need to educate survivors about their past medical history, their treatment and the importance of engaging in regular survivorship programmes.

Low rates of participation in long-term follow-up are universally reported. In 2004, a Delphi panel of 20 expert childhood cancer survivors in US identified a number of barriers contributing to this.[25] Understanding these barriers will lead to improved medical care for these patients. It was recognized that most childhood cancer survivors are not aware of their adverse health risks and often unaware of the details of their cancer or its treatment. Even where LTFU clinics are attended much of the education of late effects was directed at parents and often not

transferred to the child. The Delphi Panel also highlighted the limitations within the health care setting including lack of LTFU service, discharge to primary care physician who lacks expertise in this field and often receive no communication about the child's past medical history. Improving communication between professionals and patients is essential and will be an integral part of development of survivorship programmes.

The traditional model of LTFU has been in paediatric oncology clinics, generally jointly with paediatric endocrinologists, neurologists and clinical oncologists, long into adulthood which brings with it the advantage of continuity of care, familiarity with treatments but there are a number of disadvantages to this system. This is not only an age appropriate environment for these patients, but also an unsustainable situation for paediatric oncologists, as the population of long-term survivors increase and age. In addition, survivors are protected in this paediatric environment and don't develop the skills necessary to navigate the health care system as they develop into adulthood. Ideally, once the long-term survivor reaches adulthood he/she should be transitioned into the appropriate adult late effects services. At present, such a service does not exist and it is difficult to identify which clinicians should take on this role, especially with increasing sub-specialisation in adult medicine. In a busy and overstretched tertiary oncology healthcare service, medical and clinical adult oncology consultants are unlikely to be in a position to take on this responsibility, and may well feel inadequately trained in caring for childhood cancer survivors. In current practice, the only adult

services supporting the long-term follow-up of those patients requiring specialist hospital follow-up are the adult endocrine and neurology clinics.

It has been highlighted that improved communication of cancer information to patients/families and between health care providers may contribute to greater engagement in follow-up programmes, raises awareness of potential late effects amongst survivors and enable clinicians to diagnose and, where possible, treat late effects earlier. Based on national guidelines, we have developed a template for the End of Treatment Summary and Individualised Care Plan, or 'Health Passport', which has been introduced nationally, and welcomed by health professionals and survivors.

Models of care for LTFU of survivors of childhood cancer must be flexible enough to accommodate the needs of the young survivor as they transition throughout their life cycle and also to accommodate the individual heterogeneity of cancer survivors, reflecting the wide range of treatment exposure and adverse long-term sequelae. Development of a service that can deliver individualized, comprehensive, therapy-based patient centred care is essential.

The UK National Cancer Survivorship Initiative is currently exploring models of aftercare services for children and young people who have been treated for cancer. National pathways that identify how follow-up can be delivered in line with current pressures and aspirations are being developed. Clinical risk

stratification will play an integral role in tailoring individualised care to meet the clinical, psychological and practical needs of each survivor. A recent study from the CCSS has reviewed how data derived from the CCSS have characterized specific groups that are deemed to be at highest risk of morbidity and subsequent cancers.[26] Our study has shown that those patients at highest risk of late morbidity can be identified and appropriately stratified into a high risk (level 3) follow-up programme.

Stratification of patients according to risk of late morbidity will maximise the use of health service resources and provide age appropriate care as locally as possible. With increasing time from completion of treatment, it is hoped that the majority of adult survivors will be independent and take responsibility for their own health, with health care support provided by their primary care physician. As a result, the primary care team is likely to play an increasing role in the long-term follow-up of survivors of childhood cancer. Primary care services may be already stretched but GPs are used to meeting targets and ensuring guidelines are implemented. Good communication between the hospital services and primary care will be essential. Early involvement of general practitioners in the Late Effects Services will establish collaborations between the two teams and enable primary Care Physicians to become familiar with the surveillance programme. The feasibility of a shared-care model between cancer paediatric oncology cancer centres and primary-care doctors to deliver survivor-focused risk based health care was tested successfully by a Dutch group. The study showed that

patients would see their family doctor for long-term follow-up: the family doctors were interested in sharing survivors' care; and family doctors would return the necessary medical information needed for continued follow-up.[27] Appropriate education of the family doctors, which has resource implications, was a key finding of this study. More recently this group has shown that a web based survivor care plan can facilitate the long-term care of survivors by family doctors.[28]

In order to improve our understanding of treatment-related side effects and help develop treatment protocols to minimise toxicity, lifelong monitoring of health and well-being of all long-term survivors will be necessary. Our understanding of the late effects of the treatment of Hodgkin's lymphoma has led to studies which are ongoing and are designed to reduce the risk of second malignancy by avoiding radiotherapy in selected cases and replace gonadotoxic chemotherapy with drugs that are efficacious in Hodgkin's lymphoma but less likely to compromise reproductive function.[29] Balancing safety and efficacy in the treatment of Hodgkin's lymphoma remains an important goal in the treatment of this curable malignancy.[30]

We have shown that it is possible to ~~safely~~ predict which survivors of childhood cancer are at significant risk of developing moderate to severe late effects and require moderate or high intensity long-term follow. Importantly we have also shown that there is a group of survivors who can be reliably identified who can be ~~safely~~ discharged from clinic based follow-up *and followed up by annual questionnaire or telephone contact.* ~~—~~Structured, risk-adapted follow-up of

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childhood cancer survivors following evidence-based guidelines would reduce cost ineffective or excessive evaluations and focus individual health care delivery. Education of survivors and health care providers will hopefully reduce the burden of chronic health problems and improve quality of life for the growing population of children and young people who have been treated for cancer.

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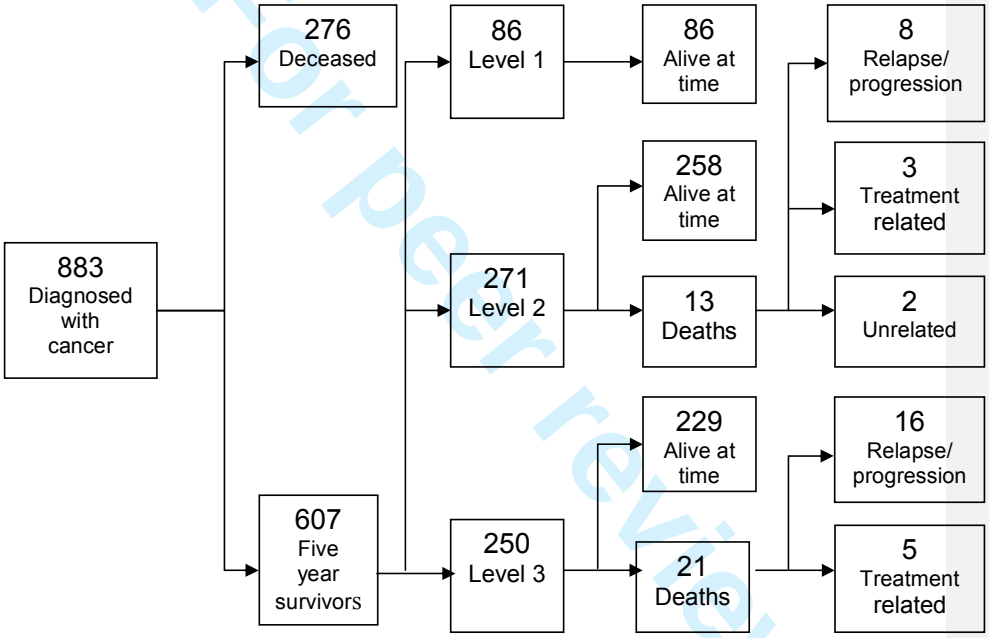

Figure 1. Study flow of childhood and teenage cancer patients.

Flow chart shows the study population and the risk stratification of patients into Levels 1,2 and 3 and the proportion of patients alive at the time of the study.

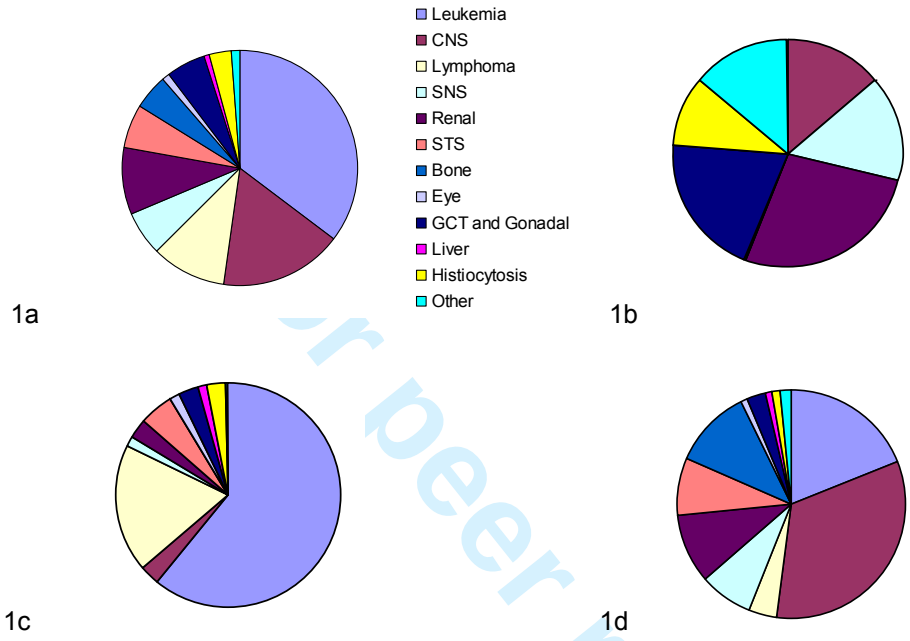

Figure 2 Diagnoses of five year survivors (n-607)

1a. All survivors (n=607), 1b. Level 1 (n= 86), 1c. Level 2 (n=271), 1d. Level 3 (n=250). Abbreviations: CNS – central nervous system tumours, SNS – sympathetic nervous system tumours, GCT – germ cell tumours, STS – soft tissue sarcomas

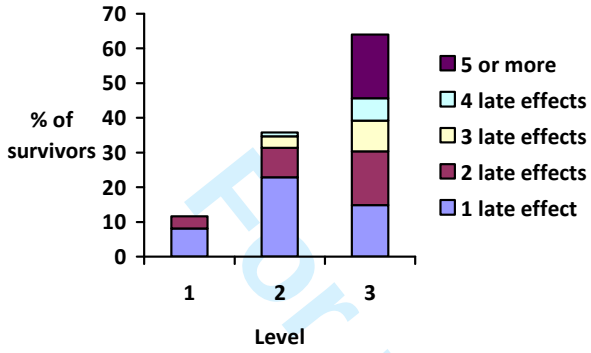

Figure 3

Prevalence of late effects by risk stratified level of follow-up for all five year survivors (n=607).

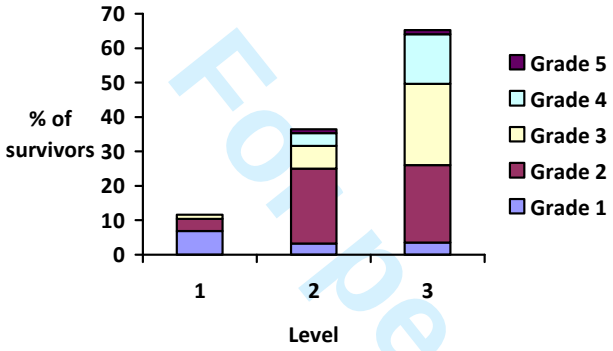

Figure 4

Severity of late effects by risk stratified level (CTCAEv3.0): grade 1- mild, grade 2-moderate, grade 3 severe, grade 4 – life threatening or disabling and grade 5 – death for all five year survivors (n=607). [17]

Table 1. Demographic characteristics of all the five year survivors alive at the time of the study (n=573) and for Level 1, Level 2 and Level 3 subgroups.

Characteristic	Five year survivors (n-573)		Level 1 (n=86)		Level 2 (n=258)		Level 3 (n=229)	
	No.	%	No.	%	No.	%	No.	%
Sex								
Male	303	52.9	37	43	137	53.1	129	56.3
Female	270	47.1	49	57	121	46.9	100	43.7
Current age, years								
5-9	44	7.7	11	12.8	15	5.8	18	7.8
10-14	110	19.2	19	22.1	56	21.7	35	15.3
15-19	148	25.8	31	36.0	66	25.6	51	22.3
20-24	129	22.5	19	22.1	51	19.8	59	25.8
25-29	69	12.0	6	7.0	30	11.6	33	14.4
30-34	40	7.0	-	-	16	6.2	24	10.5
35-39	21	3.7	-	-	15	5.8	6	2.6
40-44	11	1.9	-	-	8	3.1	3	1.3

45-49	1	0.2	-	-	1	0.4	-	-
Median, Range	19.4	5.1-45.1	17.5	5.1-28.4	19.4	8.0-45.1	20.1	5.6-43.7
Age at diagnosis, years								
0-4	286	49.9	54	62.8	140	54.3	92	40.2
5-9	144	25.1	16	18.6	68	26.4	60	26.2
10-14	122	21.3	15	17.4	48	18.6	59	25.8
15-19	21	3.7	1	1.2	2	0.7	18	7.8
Median, Range	5.0	0-20.9	2.9	0-15.4	4.5	0-20.9	6.5	0-17.5
Time from diagnosis, years								
5-9	197	34.4	33	38.4	80	31.0	84	36.7
10-14	166	29.0	32	37.2	76	29.5	58	25.3
15-19	100	17.5	11	12.8	38	14.7	51	22.3
20-24	58	10.1	8	9.3	30	11.6	20	8.7
25-29	30	5.2	2	2.3	16	6.2	12	5.2
30-34	12	2.1	-	-	10	3.9	2	0.9
35-39	10	1.7	-	-	8	3.1	2	0.9
Median, Range	12.4	5.0-39.3	11.0	5.0-26.9	13.0	5.0-38.4	12.9	5.0-39.3
DFS, years								
0-4	36	6.3	1	1.2	20	7.7	15	6.5

5-9	198	34.5	34	39.5	82	31.8	82	35.8
10-14	160	27.9	31	36.0	67	26.0	62	27.1
15-19	84	14.7	10	11.6	34	13.2	40	17.5
20-24	57	9.9	8	9.3	31	12.0	18	7.9
25-29	19	3.4	2	2.4	8	3.1	9	3.9
30-34	17	3.0	-	-	15	5.8	2	0.9
35-39	2	0.3	-	-	1	0.4	1	0.4
Median, Range	11.3	0.5-38.3	10.9	4.4-26.9	11.6	1.9-36.4	11.6	0.5-38.3
Time since last seen in Hospital Based Late Effects Clinic, years								
0-2	328	57.2	31	36.0	143	55.4	154	67.2
3-4	75	13.1	16	18.6	36	13.9	23	10.1
5-7	78	13.6	20	23.3	40	15.5	18	7.9
8-10	28	5.0	6	7.0	10	3.9	12	5.2
>10	41	7.1	8	9.3	19	7.4	14	6.1
Unknown	23	4.0	5	5.8	10	3.9	8	3.5
Median, Range	2.3	0-13.1	4.5	0-12.7	2.2	0-12.7	1.8	0-13.1

Competing interest statement

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work, no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

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Contributorship statement

ABE initiated the project, designed data collection tools, monitored data collection for the study, analysed the data, and drafted and revised the paper. KD designed data collection tools, monitored data collection for the study, analysed the data

and revised the draft paper. SB designed data collection tools, monitored data collection for the study, analysed the data and revised the draft paper. PM-S analysed the data and drafted and revised the paper. WHBW designed data collection tools, monitored data collection for the study, analysed the data, and drafted and revised the paper. All authors had full access to all of the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Data sharing statement

Dataset available from the corresponding author at angela.edgar@luht.scot.nhs.uk. Consent was not obtained but the presented data are anonymised and risk of identification is low.

Ethical approval

Ethical approval for this study was requested from the Lothian Research Ethics Committee (LREC). On review by the LREC, the committee decided that ethical approval was not required as long-term follow-up of childhood cancer survivors was deemed to be an acceptable and routine part of clinical practice and there were no experimental interventions.

Funding

No specific funding was received for this research.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	4
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6-8
Objectives	3	State specific objectives, including any prespecified hypotheses	8
Methods			
Study design	4	Present key elements of study design early in the paper	9
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	9
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	9
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*10*
Bias	9	Describe any efforts to address potential sources of bias	10
Study size	10	Explain how the study size was arrived at	9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9-10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	11 N/A
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	12
		(b) Give reasons for non-participation at each stage	12
		(c) Consider use of a flow diagram	26
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	12-14
		(b) Indicate number of participants with missing data for each variable of interest	12
		(c) Summarise follow-up time (eg, average and total amount)	12-14, 27
Outcome data	15*	Report numbers of outcome events or summary measures over time	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	n/a
		(*b*) Report category boundaries when continuous variables were categorized	n/a
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	15
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15-20
Generalisability	21	Discuss the generalisability (external validity) of the study results	15-20
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	34

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Can Intensity of long-term follow-up for survivors of childhood and teenage cancer be determined by therapy-based risk-stratification?

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Can Intensity of long-term follow-up for survivors of childhood and teenage cancer be ~~safely~~ determined by therapy-based risk-stratification?

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Key words: Childhood cancer, treatment, survival, cure, late effects, models of follow-up, long-term follow-up.

Article summary

Article Focus

- Therapy-based, risk-stratification of survivors can ~~safely~~ predict which survivors of childhood and teenage cancer are at significant risk of developing moderate to severe late effects and require high intensity long-term follow-up.

Key messages

- Patients who had received the most complex cancer treatments had the largest number and most severe late effects. Those patients assigned to low risk category of follow-up had few late effects and those late effects were mild.
- Long term survivors of childhood and teenage cancer can ~~safely~~ be assigned to primary care, nurse-led or hospital follow-up based on the intensity of treatment they received for the original cancer.
- Stratification of patients according to risk of late morbidity will maximise the use of NHS resources and provide age appropriate care as locally as possible.

Strengths

- This study shows that it is possible to ~~safely~~ predict which survivors of childhood cancer are at significant risk of developing moderate to severe late effects. Life long follow-up for all childhood cancer survivors is not only cost ineffective but also difficult to organize. Until now there was no evidence available to define the optimum follow-up for long-term survivors.

- Risk stratification will enable young adult survivors to benefit from a transition process that takes them into an appropriate follow-up model and can help to identify those survivors who can be ~~safely~~ discharged from hospital based follow-up.

Limitations

- 30% of the cohort had not been seen in the hospital based late effects service for more than two years and health problems may be underestimated in this group.
- It would be helpful in future studies to determine the proportion of late effects detected as a direct result of clinic attendance and to determine the proportion of late effects which are treatable.

Abstract

Objective

To determine the ~~safety~~ feasibility of therapy-based, risk-stratified follow-up guidelines for childhood and teenage cancer survivors by evaluating adverse health outcomes in a survivor cohort retrospectively assigned a risk category.

Design

Retrospective cohort study.

Setting

Tertiary level, single centre, paediatric cancer unit in South East Scotland

Participants

All children and teenagers diagnosed with cancer (<19 years) between 1st January 1971-31st July 2004, who were alive more than five years from diagnosis formed the study cohort. Each survivor was retrospectively assigned a level of follow-up, based on their predicted risk of developing treatment related late effects (level 1, 2 and 3 for low, medium and high risk, respectively). Adverse health outcomes were determined from review of medical records and postal questionnaires. Late effects were graded using the Common Terminology Criteria for Adverse Event, Version 3 (CTCAEv3).

Results

607 five-year survivors were identified. Risk-stratification identified 86 (14.2%), 271 (44.6%) and 250 (41.2%) level 1, 2 and 3 survivors respectively. The prevalence of late effects (LE) for level 1 survivors was 11.6% with only 1 patient with grade 3 or above toxicity. 35.8% of level 2 survivors had a LE, of whom 9.3%, 58.8%, 18.5%, 10.3% and 3% had grade 1, 2, 3, 4 and 5 toxicity respectively. 65.2 % of level 3 survivors had LE), of whom 5.5% (n=9), 34.4% (n=56), 36.2% (n=59), 22.1% (n=36) and 1.8% (n=3) had grade 1,2,3,4 and 5 toxicity respectively.

Conclusions

Therapy-based, risk-stratification of survivors can ~~safely~~ predict which patients are at significant risk of developing moderate to severe late effects and require high intensity long-term follow-up.

Word count: 254

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Introduction

Dramatic improvements in survival for children with cancer have highlighted the need for evidence based long-term follow-up (LTFU) for these young people. Approximately 80% of children diagnosed with cancer can now expect to survive more than 5 years, and around 70 % will survive ten years, from their diagnosis.[1] It is estimated that 1 in 640 young adults is a survivor of childhood cancer.[2] As many as two thirds of long-term survivors are reported to be at increased risk of substantial morbidity and even mortality, due to adverse late effects secondary to cancer or cancer therapy.[3-5] Late effects are diverse and include secondary malignancies, organ system damage, infertility, cognitive impairment, and disorders of growth and development.[6, 7] Appropriate LTFU of these patients is essential to detect, treat and prevent morbidity and mortality.[8]

There is wide variation of long-term follow-up practices throughout the UK with a propensity for hospital dependency, often in age-inappropriate settings.[9] A recent study has highlighted how excess morbidity in survivors translates into increased use of health care facilities.[10] An awareness of the need for an integrated and systematic approach to follow-up was recognised by the Scottish Intercollegiate Guidelines Network (SIGN) who developed an evidence-based approach to long-term follow-up.[11] The risks of developing treatment related late effects depend upon the underlying malignancy, the site of the tumour, the type of treatment and the age at time of treatment. A risk-stratified approach to health surveillance was developed which identified three groups of survivors who require an increasing

intensity of follow-up[8]. In the UK, we published a Practice Statement 'Therapy Based Long-term Follow-up' which is designed to inform and guide clinicians responsible for the long-term follow-up of childhood cancer survivors.[12] The Practice Statement recommends follow-up assessments and investigations based on the treatment that the individual has received and is informed by the evidence-based recommendations published by SIGN 76.

An integrated and systematic approach is now considered a requirement of the National Institute of Health and Clinical Excellence (NIHCE) Improving Outcomes for Children and Young People with Cancer Guidance (2005) and National Delivery Plan for Children and Young People's Specialist Services in Scotland (2008).[13,14] In England, the National Cancer Survivorship Initiative (NCSI) has developed as a partnership between the Department of Health, Macmillan Cancer Support, and supported by NHS Improvement, to develop models of care to ensure that those living with and beyond cancer have access to safe and effective care and receive the support they need to lead as healthy and active a life as possible. Improved awareness of cancer survivorship as a chronic health problem will facilitate the development of care pathways that will meet the needs of every patient throughout their lifetime.[15]

Although there is growing guidance on whom, where and how long-term survivors should be followed-up, evidence to show that adopting a model of risk-stratified follow-up is safe is lacking. A recent study has shown that assigning

patients to one of three agreed levels of follow up, as described by Wallace et al, was relatively simple for experienced clinic staff.[16] The objective of this study was to evaluate the ~~safety~~ feasibility and efficacy of this risk-based follow-up model by retrospectively stratifying an unselected cohort of long-term survivors of childhood cancer from a single centre and objectively evaluating their health status.

Methods

Study population

All patients, aged less than 19 years, who were diagnosed with childhood cancer in a single institution in South East Scotland, between 1971 and 2004, and who were alive at least five years from diagnosis, were included in the study. The patients were identified from the Oxford Children's Cancer Registry, established in 1992; patients diagnosed before 1992 were identified from the Scottish Cancer Registry, established in 1958, and hospital records.

Data Collection

All health problems directly attributable to cancer, or cancer therapy, were obtained from medical records, electronic hospital records systems, self-reported questionnaires. Medical data were obtained from medical records, electronic hospital records, clinical correspondence from other health professionals and self-completed health status questionnaire and is likely to be an underestimate of the health problems. Cause of death for the deceased patients as assigned by the General Register Office for Scotland, was obtained from the Scottish Cancer Registry, courtesy of Information Services Division, NHS National Services, Scotland (personal communication).

Therapy-based risk stratification

The Scottish Intercollegiate Guidelines Network (SIGN) has developed an evidence-based approach to LTFU, incorporating the risk-based levels of follow-

up described in 2001.[8] Patients are classified into one of three groups (Levels 1,2 and 3): Level 1 patients, treated with surgery alone or low risk chemotherapy treatment, who could be followed up by postal or telephone contact; Level 2 patients, treated with standard risk chemotherapy, such as survivors of ALL or lymphoma, who are considered to be at moderate risk of developing late effects, eg anthracycline-induced cardiotoxicity, could be followed up by an appropriately trained individual, such as a late effects nurse specialist; Level 3 patients, who would require medically supervised follow-up within a multi-disciplinary team – that is those patients that have had a CNS tumour (treated with chemotherapy and/or radiotherapy), bone marrow transplants, stage 4 disease, any radiotherapy except low dose cranial radiotherapy and those that have had intensive therapy. Risk-stratified levels of follow-up were independently assigned to all survivors by two researchers. Level of follow-up was retrospectively assigned to each patient, as if they were five years from diagnosis and before any medical review of late effects was undertaken.

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Grading of Late Effects

To determine the severity of late effects, each reported late effect was graded independently by two of the authors using the Common Terminology Criteria for Adverse Events, Version 3.0 (CTCAEv3.0, available at http://ctep.cancer.gov/forms/CTCAEv3.pdf), a scoring system developed through the US National Cancer Institute by a multidisciplinary group and adopted in the UK by the Children's Cancer and Leukaemia Group (CCLG).[17] The CTCAEv3.0

tool can be used for acute and chronic conditions in patients with cancer and grades conditions as mild (grade 1), moderate (grade 2), severe (grade 3), life-threatening or disabling (grade 4), or adverse event-related death (grade 5). To investigate and reduce inter-observer variability, graded adverse events were compared and inconsistencies were discussed and detailed coding rules were developed (available on request form the authors). Inconsistencies in grading revolved mainly around scoring subjective psychosocial and neuropsychological items of grade 1 or 2, grading of 3 or higher adverse events was straightforward.

Ethical Approval

Ethical approval for this study was requested from the Lothian Research Ethics Committee (LREC). On review by the LREC, the committee decided that ethical approval was not required as long-term follow-up of childhood cancer survivors was deemed to be an acceptable and routine part of clinical practice and there were no experimental interventions.

Analysis

The statistical package for social sciences (SPSS) Windows version 14.0 was used for the statistical analyses. Data were analyzed by descriptive techniques using frequencies, percentages and medians as appropriate.

Results

Study Population

883 patients were diagnosed with childhood and teenage cancer between 1st January 1971 to 1st July 2004 and 607 of these patients were alive five years from diagnosis (5 year overall survival rate 69%). Medical information was collected from a retrospective case note review, regional electronic hospital systems and self-reported health outcomes from questionnaires. Of the 607 five year survivors, 34 patients were deceased (5.6%) at the time of the study (figure 1). Of the 573 long-term survivors alive at the time of this study 122 patients were not known to be under any kind of hospital review (21%). Of the 451 patients under hospital follow-up, 370 (82%) were followed up within the South East Scotland Late Effects Service, either by postal questionnaire follow-up (n=67, 17%) or clinic appointment (n=307, 83%). The remaining 81 (18%) of survivors attended other paediatric hospital-based clinics within the same paediatric setting (n=14) or in Tayside (n=26), or Adult Services in South East Scotland (n=31) and in other cities throughout the UK (n=10). Data were gathered from medical records from information based on a clinic visit of more than two years previously, without supplementation from postal questionnaires in 178 patients (31%) and is likely to represent an underestimate of late effects.

Demographics

In this population-based study, 607 long-term survivors were identified (males 321 (52.9%)) with median age (range) of 19.2 (5.1-45.1) years and median age

(range) at diagnosis 5.1 (0.0-17.5) years. Of the cohort, 34 (5.6%) were deceased, with a median overall survival (range) of 9.9 (5.0-30.9) years. Of the 573 long-term survivors alive at the time of the study, the median age (range) was 19.4 (5.1-45.1) years and disease free survival (range) 11.3 (0.8-38.3) years (Table 1). The primary cancer diagnosis is shown for all patients and within each risk level (Figure 2). Risk-stratification of all long-term survivors (n=607) identified 86 (14.1%), 271 (44.6%) and 250 (41.2%) at Level 1, 2 and 3 respectively with detailed breakdown of ages and survival interval for each level of patients alive at the time of the study only (n=573), shown in Table 1 and Figure 1. Demographic data is similar between the three populations.

Adverse health outcomes according level of risk

Among the 34 deaths in the five year survivors (n=607), 26 (76.5%) died from progression or relapse of the underlying primary cancer, two (5.9%) died from unrelated causes and six (17.6%) died from treatment related sequelae; five from second primary malignancy and one from end-stage renal failure. Of the five survivors who went on to die from second primary malignancy, three patients (all Level 2) had a meningioma, presumed to be secondary to low dose cranial irradiation as part of CNS directed therapy for the treatment of childhood ALL, one (Level 3) developed extensive intra-abdominal desmoid tumour having previously been treated for medulloblastoma and with a background of APC gene and Turcot's syndrome and the other patient (Level 3) developed AML presumed

to be related to previous topo-isomerase II inhibitor therapy for primary bone sarcoma (Figure 1).

Prevalence and severity of treatment related late effects were determined for each patient with an assigned level of follow up (n=607, Figures 3 and 4). Among Level 1 survivors (n=86), 11.6% (n=10) had late effects, of whom seven (8.1%) had one late effect and three (3.5%) had two late effects; 60% (n=6) of which were grade 1 toxicity, 30% (n=3) of whom were grade 2 toxicity and 10% (n=1) grade 3 toxicity. Within the Level 2 group (n=271), the prevalence of late effects was 35.8% (n=97), of whom 62 (22.9%) had 1 late effect, 23 (8.5%) had 2 late effects, 9 (3.3%) had 3 late effects and 3 (1.1%) had four late effects, of whom 9.3% (n=9) had a maximum toxicity grade of 1, 58.8% (n=57) grade 2, 18.5% (n=18) grade 3, 10.3% (n=10) grade 4 and 3% (n=3) grade 5. The prevalence of late effects in the Level 3 survivors (n=250) was 65.2% (n=163) of whom 37 (14.8%) had 1 late effect, 39 (15.6%) had 2 late effects, 22 (8.8%) had 3 late effects, 16 (6.4%) had 4 late effects and 46 (18.4%) had 5 or more late effects, of whom 9 (5.5%), 56 (34.4%), 59 (36.2%), 36 (22.1%) and 3 (1.8%) had grade 1,2,3,4 and 5 toxicity respectively.

Discussion

We have shown that therapy-based, risk-stratification of long-term survivors of childhood and teenage cancer can ~~safely~~ predict which patients are at risk of developing moderate to severe side effects and require high intensity clinic based long-term follow-up. Retrospective assignment of patients into a risk category identified almost half (45%) of patients could be considered at moderate risk of developing late effects, while 41% were deemed to be at high risk of developing late effects, with only a small proportion felt to be at low risk of late complications. The prevalence and severity of side effects increased with increasing level of follow up.

Lifelong follow-up is recommended for survivors of childhood cancer because many of the health problems may be reduced by prevention or early detection.[18] However follow-up should be individually tailored and hospital based follow-up should not be necessary for all survivors.[19] The incidence of chronic conditions continues to increase with time and there is therefore no safe time after which these patients can be discharged.[20] There is increasing evidence that with increasing time from diagnosis, medical problems associated with ageing, including second cancers, cardiovascular disease, infertility and osteoporosis, may exhibit an accelerated course following certain cancer treatments.[18,21] Mertens et al showed that while recurrent disease remains the most important contributor to late mortality in 5 year survivors there is a significant excess

mortality risk associated with treatment related complications that is present in the 25 years after the initial cancer diagnosis.[22]

It is reported that up to 50% of long-term survivors do not attend Late Effects Clinics and many of these patients are considered to be at high risk of developing treatment-related late complications.[23] There are many reasons why survivors choose not to participate in long-term follow-up including lack of awareness of risks of late morbidity, desire to 'move on', lack of appropriate adult services and clinical discharge. In a study by Blaauwbroek et al they assessed late effects in a group of adult survivors of childhood cancer who were not involved in regular long-term follow-up and reported that almost 40% of survivors suffered from moderate to severe late effects and 33% had previously unknown late effects.[24] This reiterates the need to educate survivors about their past medical history, their treatment and the importance of engaging in regular survivorship programmes.

Low rates of participation in long-term follow-up are universally reported. In 2004, a Delphi panel of 20 expert childhood cancer survivors in US identified a number of barriers contributing to this.[25] Understanding these barriers will lead to improved medical care for these patients. It was recognized that most childhood cancer survivors are not aware of their adverse health risks and often unaware of the details of their cancer or its treatment. Even where LTFU clinics are attended much of the education of late effects was directed at parents and often not

transferred to the child. The Delphi Panel also highlighted the limitations within the health care setting including lack of LTFU service, discharge to primary care physician who lacks expertise in this field and often receive no communication about the child's past medical history. Improving communication between professionals and patients is essential and will be an integral part of development of survivorship programmes.

The traditional model of LTFU has been in paediatric oncology clinics, generally jointly with paediatric endocrinologists, neurologists and clinical oncologists, long into adulthood which brings with it the advantage of continuity of care, familiarity with treatments but there are a number of disadvantages to this system. This is not only an age appropriate environment for these patients, but also an unsustainable situation for paediatric oncologists, as the population of long-term survivors increase and age. In addition, survivors are protected in this paediatric environment and don't develop the skills necessary to navigate the health care system as they develop into adulthood. Ideally, once the long-term survivor reaches adulthood he/she should be transitioned into the appropriate adult late effects services. At present, such a service does not exist and it is difficult to identify which clinicians should take on this role, especially with increasing sub-specialisation in adult medicine. In a busy and overstretched tertiary oncology healthcare service, medical and clinical adult oncology consultants are unlikely to be in a position to take on this responsibility, and may well feel inadequately trained in caring for childhood cancer survivors. In current practice, the only adult

services supporting the long-term follow-up of those patients requiring specialist hospital follow-up are the adult endocrine and neurology clinics.

It has been highlighted that improved communication of cancer information to patients/families and between health care providers may contribute to greater engagement in follow-up programmes, raises awareness of potential late effects amongst survivors and enable clinicians to diagnose and, where possible, treat late effects earlier. Based on national guidelines, we have developed a template for the End of Treatment Summary and Individualised Care Plan, or 'Health Passport', which has been introduced nationally, and welcomed by health professionals and survivors.

Models of care for LTFU of survivors of childhood cancer must be flexible enough to accommodate the needs of the young survivor as they transition throughout their life cycle and also to accommodate the individual heterogeneity of cancer survivors, reflecting the wide range of treatment exposure and adverse long-term sequelae. Development of a service that can deliver individualized, comprehensive, therapy-based patient centred care is essential.

The UK National Cancer Survivorship Initiative is currently exploring models of aftercare services for children and young people who have been treated for cancer. National pathways that identify how follow-up can be delivered in line with current pressures and aspirations are being developed. Clinical risk

stratification will play an integral role in tailoring individualised care to meet the clinical, psychological and practical needs of each survivor. A recent study from the CCSS has reviewed how data derived from the CCSS have characterized specific groups that are deemed to be at highest risk of morbidity and subsequent cancers.[26] Our study has shown that those patients at highest risk of late morbidity can be identified and appropriately stratified into a high risk (level 3) follow-up programme.

Stratification of patients according to risk of late morbidity will maximise the use of health service resources and provide age appropriate care as locally as possible. With increasing time from completion of treatment, it is hoped that the majority of adult survivors will be independent and take responsibility for their own health, with health care support provided by their primary care physician. As a result, the primary care team is likely to play an increasing role in the long-term follow-up of survivors of childhood cancer. Primary care services may be already stretched but GPs are used to meeting targets and ensuring guidelines are implemented. Good communication between the hospital services and primary care will be essential. Early involvement of general practitioners in the Late Effects Services will establish collaborations between the two teams and enable primary Care Physicians to become familiar with the surveillance programme. The feasibility of a shared-care model between cancer paediatric oncology cancer centres and primary-care doctors to deliver survivor-focused risk based health care was tested successfully by a Dutch group. The study showed that

patients would see their family doctor for long-term follow-up: the family doctors were interested in sharing survivors' care; and family doctors would return the necessary medical information needed for continued follow-up.[27] Appropriate education of the family doctors, which has resource implications, was a key finding of this study. More recently this group has shown that a web based survivor care plan can facilitate the long-term care of survivors by family doctors.[28]

In order to improve our understanding of treatment-related side effects and help develop treatment protocols to minimise toxicity, lifelong monitoring of health and well-being of all long-term survivors will be necessary. Our understanding of the late effects of the treatment of Hodgkin's lymphoma has led to studies which are ongoing and are designed to reduce the risk of second malignancy by avoiding radiotherapy in selected cases and replace gonadotoxic chemotherapy with drugs that are efficacious in Hodgkin's lymphoma but less likely to compromise reproductive function.[29] Balancing safety and efficacy in the treatment of Hodgkin's lymphoma remains an important goal in the treatment of this curable malignancy.[30]

We have shown that it is possible to ~~safely~~ predict which survivors of childhood cancer are at significant risk of developing moderate to severe late effects and require moderate or high intensity long-term follow. Importantly we have also shown that there is a group of survivors who can be reliably identified who can be ~~safely~~ discharged from clinic based follow-up *and followed up by annual questionnaire or telephone contact.* ~~—~~Structured, risk-adapted follow-up of

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childhood cancer survivors following evidence-based guidelines would reduce cost ineffective or excessive evaluations and focus individual health care delivery. Education of survivors and health care providers will hopefully reduce the burden of chronic health problems and improve quality of life for the growing population of children and young people who have been treated for cancer.

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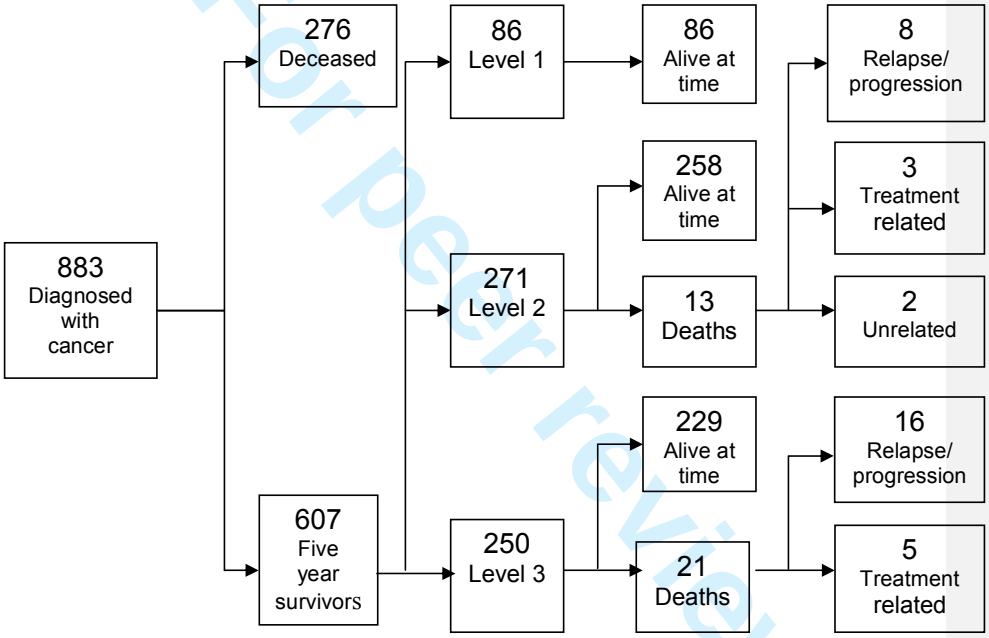

Figure 1. Study flow of childhood and teenage cancer patients.

Flow chart shows the study population and the risk stratification of patients into Levels 1,2 and 3 and the proportion of patients alive at the time of the study.

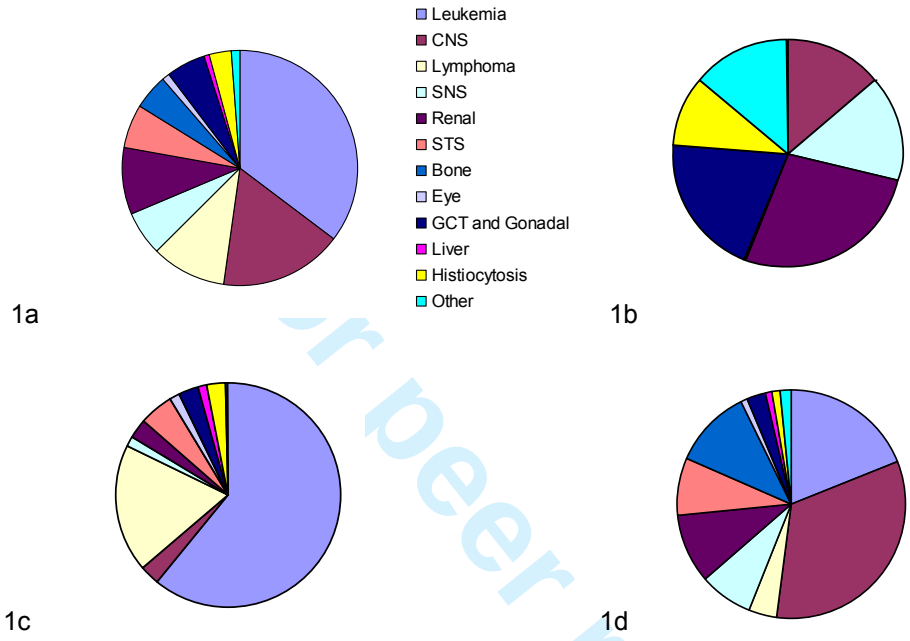

Figure 2 Diagnoses of five year survivors (n-607)

1a. All survivors (n=607), 1b. Level 1 (n= 86), 1c. Level 2 (n=271), 1d. Level 3 (n=250). Abbreviations: CNS – central nervous system tumours, SNS – sympathetic nervous system tumours, GCT – germ cell tumours, STS – soft tissue sarcomas

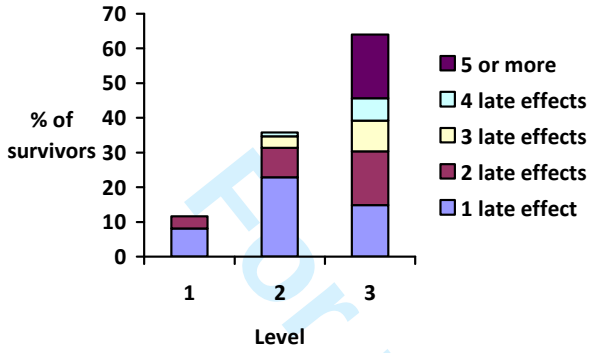

Figure 3

Prevalence of late effects by risk stratified level of follow-up for all five year survivors (n=607).

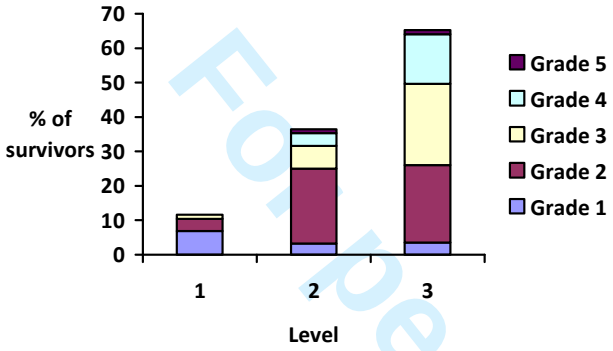

Figure 4

Severity of late effects by risk stratified level (CTCAEv3.0): grade 1- mild, grade 2-moderate, grade 3 severe, grade 4 – life threatening or disabling and grade 5 – death for all five year survivors (n=607). [17]

Table 1. Demographic characteristics of all the five year survivors alive at the time of the study (n=573) and for Level 1, Level 2 and Level 3 subgroups.

Characteristic	Five year survivors (n-573)		Level 1 (n=86)		Level 2 (n=258)		Level 3 (n=229)	
	No.	%	No.	%	No.	%	No.	%
Sex								
Male	303	52.9	37	43	137	53.1	129	56.3
Female	270	47.1	49	57	121	46.9	100	43.7
Current age, years								
5-9	44	7.7	11	12.8	15	5.8	18	7.8
10-14	110	19.2	19	22.1	56	21.7	35	15.3
15-19	148	25.8	31	36.0	66	25.6	51	22.3
20-24	129	22.5	19	22.1	51	19.8	59	25.8
25-29	69	12.0	6	7.0	30	11.6	33	14.4
30-34	40	7.0	-	-	16	6.2	24	10.5
35-39	21	3.7	-	-	15	5.8	6	2.6
40-44	11	1.9	-	-	8	3.1	3	1.3

45-49	1	0.2	-	-	1	0.4	-	-
Median, Range	19.4	5.1-45.1	17.5	5.1-28.4	19.4	8.0-45.1	20.1	5.6-43.7
Age at diagnosis, years								
0-4	286	49.9	54	62.8	140	54.3	92	40.2
5-9	144	25.1	16	18.6	68	26.4	60	26.2
10-14	122	21.3	15	17.4	48	18.6	59	25.8
15-19	21	3.7	1	1.2	2	0.7	18	7.8
Median, Range	5.0	0-20.9	2.9	0-15.4	4.5	0-20.9	6.5	0-17.5
Time from diagnosis, years								
5-9	197	34.4	33	38.4	80	31.0	84	36.7
10-14	166	29.0	32	37.2	76	29.5	58	25.3
15-19	100	17.5	11	12.8	38	14.7	51	22.3
20-24	58	10.1	8	9.3	30	11.6	20	8.7
25-29	30	5.2	2	2.3	16	6.2	12	5.2
30-34	12	2.1	-	-	10	3.9	2	0.9
35-39	10	1.7	-	-	8	3.1	2	0.9
Median, Range	12.4	5.0-39.3	11.0	5.0-26.9	13.0	5.0-38.4	12.9	5.0-39.3
DFS, years								
0-4	36	6.3	1	1.2	20	7.7	15	6.5

5-9	198	34.5	34	39.5	82	31.8	82	35.8
10-14	160	27.9	31	36.0	67	26.0	62	27.1
15-19	84	14.7	10	11.6	34	13.2	40	17.5
20-24	57	9.9	8	9.3	31	12.0	18	7.9
25-29	19	3.4	2	2.4	8	3.1	9	3.9
30-34	17	3.0	-	-	15	5.8	2	0.9
35-39	2	0.3	-	-	1	0.4	1	0.4
Median, Range	11.3	0.5-38.3	10.9	4.4-26.9	11.6	1.9-36.4	11.6	0.5-38.3
Time since last seen in Hospital Based Late Effects Clinic, years								
0-2	328	57.2	31	36.0	143	55.4	154	67.2
3-4	75	13.1	16	18.6	36	13.9	23	10.1
5-7	78	13.6	20	23.3	40	15.5	18	7.9
8-10	28	5.0	6	7.0	10	3.9	12	5.2
>10	41	7.1	8	9.3	19	7.4	14	6.1
Unknown	23	4.0	5	5.8	10	3.9	8	3.5
Median, Range	2.3	0-13.1	4.5	0-12.7	2.2	0-12.7	1.8	0-13.1

Competing interest statement

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work, no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

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Contributorship statement

ABE initiated the project, designed data collection tools, monitored data collection for the study, analysed the data, and drafted and revised the paper. KD designed data collection tools, monitored data collection for the study, analysed the data

and revised the draft paper. SB designed data collection tools, monitored data collection for the study, analysed the data and revised the draft paper. PM-S analysed the data and drafted and revised the paper. WHBW designed data collection tools, monitored data collection for the study, analysed the data, and drafted and revised the paper. All authors had full access to all of the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Data sharing statement

Dataset available from the corresponding author at angela.edgar@luht.scot.nhs.uk. Consent was not obtained but the presented data are anonymised and risk of identification is low.

Ethical approval

Ethical approval for this study was requested from the Lothian Research Ethics Committee (LREC). On review by the LREC, the committee decided that ethical approval was not required as long-term follow-up of childhood cancer survivors was deemed to be an acceptable and routine part of clinical practice and there were no experimental interventions.

Funding

No specific funding was received for this research.

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	4
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6-8
Objectives	3	State specific objectives, including any prespecified hypotheses	8
Methods			
Study design	4	Present key elements of study design early in the paper	9
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	9
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	9
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*10*
Bias	9	Describe any efforts to address potential sources of bias	10
Study size	10	Explain how the study size was arrived at	9
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	9-10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	11 N/A
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(*d*) If applicable, explain how loss to follow-up was addressed	
		(*e*) Describe any sensitivity analyses	
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	12
		(b) Give reasons for non-participation at each stage	12
		(c) Consider use of a flow diagram	26
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	12-14
		(b) Indicate number of participants with missing data for each variable of interest	12
		(c) Summarise follow-up time (eg, average and total amount)	12-14, 27
Outcome data	15*	Report numbers of outcome events or summary measures over time	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	n/a
		(*b*) Report category boundaries when continuous variables were categorized	n/a
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	n/a
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	
Discussion			
Key results	18	Summarise key results with reference to study objectives	15
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	15-20
Generalisability	21	Discuss the generalisability (external validity) of the study results	15-20
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	34

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Can Intensity of long-term follow-up for survivors of childhood and teenage cancer be determined by therapy-based risk-stratification?

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Key words: Childhood cancer, treatment, survival, cure, late effects, models of follow-up, long-term follow-up.

Article summary

Article Focus

- Therapy-based, risk-stratification of survivors can predict which survivors of childhood and teenage cancer are at significant risk of developing moderate to severe late effects and require high intensity long-term follow-up.

Key messages

- Patients who had received the most complex cancer treatments had the largest number and most severe late effects. Those patients assigned to low risk category of follow-up had few late effects and those late effects were mild.
- Long term survivors of childhood and teenage cancer can be assigned to primary care, nurse-led or hospital follow-up based on the intensity of treatment they received for the original cancer.
- Stratification of patients according to risk of late morbidity will maximise the use of NHS resources and provide age appropriate care as locally as possible.

Strengths

- This study shows that it is possible to predict which survivors of childhood cancer are at significant risk of developing moderate to severe late effects. Life long follow-up for all childhood cancer survivors is not only cost ineffective but also difficult to organize. Until now there was no evidence available to define the optimum follow-up for long-term survivors.

- Risk stratification will enable young adult survivors to benefit from a transition process that takes them into an appropriate follow-up model and can help to identify those survivors who can be discharged from hospital based follow-up.

Limitations

- 30% of the cohort had not been seen in the hospital based late effects service for more than two years and health problems may be underestimated in this group.
- It would be helpful in future studies to determine the proportion of late effects detected as a direct result of clinic attendance and to determine the proportion of late effects which are treatable.
- The study population is small (607) and the median age at follow up is only 19 years but it does reflect a single centre's clinical practice and as such the findings should stimulate an interesting clinical debate about the utility of long-term follow up of childhood cancer survivors
- Our findings will need confirmation in a prospective cohort study that has the power to adjust for all confounding variables and in particular for length of follow up.

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Abstract

Objective

To determine the feasibility of therapy-based, risk-stratified follow-up guidelines for childhood and teenage cancer survivors by evaluating adverse health outcomes in a survivor cohort retrospectively assigned a risk category.

Design

Retrospective cohort study.

Setting

Tertiary level, single centre, paediatric cancer unit in South East Scotland

Participants

All children and teenagers diagnosed with cancer (<19 years) between 1st January 1971-31st July 2004, who were alive more than five years from diagnosis formed the study cohort. Each survivor was retrospectively assigned a level of follow-up, based on their predicted risk of developing treatment related late effects (level 1, 2 and 3 for low, medium and high risk, respectively). Adverse health outcomes were determined from review of medical records and postal questionnaires. Late effects were graded using the Common Terminology Criteria for Adverse Event, Version 3 (CTCAEv3).

Results

607 five-year survivors were identified. Risk-stratification identified 86 (14.2%), 271 (44.6%) and 250 (41.2%) level 1, 2 and 3 survivors respectively. The prevalence of late effects (LE) for level 1 survivors was 11.6% with only 1 patient with grade 3 or above toxicity. 35.8% of level 2 survivors had a LE, of whom 9.3%, 58.8%, 18.5%, 10.3% and 3% had grade 1, 2, 3, 4 and 5 toxicity respectively. 65.2 % of level 3 survivors had LE), of whom 5.5% (n=9), 34.4% (n=56), 36.2% (n=59), 22.1% (n=36) and 1.8% (n=3) had grade 1,2,3,4 and 5 toxicity respectively.

Conclusions

Therapy-based, risk-stratification of survivors can predict which patients are at significant risk of developing moderate to severe late effects and require high intensity long-term follow-up. Our findings will need confirmation in a prospective cohort study that has the power to adjust for all potentially confounding variables.

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Introduction

Dramatic improvements in survival for children with cancer have highlighted the need for evidence based long-term follow-up (LTFU) for these young people. Approximately 80% of children diagnosed with cancer can now expect to survive more than 5 years, and around 70 % will survive ten years, from their diagnosis.[1] It is estimated that 1 in 640 young adults is a survivor of childhood cancer.[2] As many as two thirds of long-term survivors are reported to be at increased risk of substantial morbidity and even mortality, due to adverse late effects secondary to cancer or cancer therapy.[3-5] Late effects are diverse and include secondary malignancies, organ system damage, infertility, cognitive impairment, and disorders of growth and development.[6, 7] Appropriate LTFU of these patients is essential to detect, treat and prevent morbidity and mortality.[8]

There is wide variation of long-term follow-up practices throughout the UK with a propensity for hospital dependency, often in age-inappropriate settings.[9] A recent study has highlighted how excess morbidity in survivors translates into increased use of health care facilities.[10] An awareness of the need for an integrated and systematic approach to follow-up was recognised by the Scottish Intercollegiate Guidelines Network (SIGN) who developed an evidence-based approach to long-term follow-up.[11] This has recently been revised and superceded by SIGN132 [12,13].The risks of developing treatment related late effects depend upon the underlying malignancy, the site of the tumour, the type of treatment and the age at time of treatment. A risk-stratified approach to health surveillance was

developed which identified three groups of survivors who require an increasing intensity of follow-up[8]. In the UK, we published a Practice Statement 'Therapy Based Long-term Follow-up' which is designed to inform and guide clinicians responsible for the long-term follow-up of childhood cancer survivors.[142] The Practice Statement recommends follow-up assessments and investigations based on the treatment that the individual has received and is informed by the evidence-based recommendations published by SIGN 76.

An integrated and systematic approach is now considered a requirement of the National Institute of Health and Clinical Excellence (NIHCE) Improving Outcomes for Children and Young People with Cancer Guidance (2005) and National Delivery Plan for Children and Young People's Specialist Services in Scotland (2008).[153,164] In England, the National Cancer Survivorship Initiative (NCSI) has developed as a partnership between the Department of Health, Macmillan Cancer Support, and supported by NHS Improvement, to develop models of care to ensure that those living with and beyond cancer have access to safe and effective care and receive the support they need to lead as healthy and active a life as possible. Improved awareness of cancer survivorship as a chronic health problem will facilitate the development of care pathways that will meet the needs of every patient throughout their lifetime.[175]

Although there is growing guidance on whom, where and how long-term survivors should be followed-up, evidence to show that adopting a model of risk-

stratified follow-up is safe is lacking. A recent study has shown that assigning patients to one of three agreed levels of follow up, as described by Wallace et al, was relatively simple for experienced clinic staff.[186] The objective of this study was to evaluate the feasibility and efficacy of this risk-based follow-up model by retrospectively stratifying an unselected cohort of long-term survivors of childhood cancer from a single centre and objectively evaluating their health status.

Methods

Study population

All patients, aged less than 19 years, who were diagnosed with childhood cancer in a single institution in South East Scotland, between 1971 and 2004, and who were alive at least five years from diagnosis, were included in the study. The patients were identified from the Oxford Children's Cancer Registry, established in 1992; patients diagnosed before 1992 were identified from the Scottish Cancer Registry, established in 1958, and hospital records.

Data Collection

All health problems directly attributable to cancer, or cancer therapy, were obtained from medical records, electronic hospital records systems, self-reported questionnaires. Medical data were obtained from medical records, electronic hospital records, clinical correspondence from other health professionals and self-completed health status questionnaire and is likely to be an underestimate of the health problems. Cause of death for the deceased patients as assigned by the General Register Office for Scotland, was obtained from the Scottish Cancer Registry, courtesy of Information Services Division, NHS National Services, Scotland (personal communication).

Therapy-based risk stratification

The Scottish Intercollegiate Guidelines Network (SIGN) has developed an evidence-based approach to LTFU, incorporating the risk-based levels of follow-

up described in 2001.[8] Patients are classified into one of three groups (Levels 1,2 and 3): Level 1 patients, treated with surgery alone or low risk chemotherapy treatment, who could be followed up by postal or telephone contact; Level 2 patients, treated with standard risk chemotherapy, such as survivors of ALL or lymphoma, who are considered to be at moderate risk of developing late effects, eg anthracycline-induced cardiotoxicity, could be followed up by an appropriately trained individual, such as a late effects nurse specialist; Level 3 patients, who would require medically supervised follow-up within a multi-disciplinary team – that is those patients that have had a CNS tumour (treated with chemotherapy and/or radiotherapy), bone marrow transplants, stage 4 disease, any radiotherapy except low dose cranial radiotherapy and those that have had intensive therapy. Risk-stratified levels of follow-up were independently assigned to all survivors by two researchers. Level of follow-up was retrospectively assigned to each patient, as if they were five years from diagnosis and before any medical review of late effects was undertaken.

Grading of Late Effects

To determine the severity of late effects, each reported late effect was graded independently by two of the authors using the Common Terminology Criteria for Adverse Events, Version 3.0 (CTCAEv3.0, available at http://ctep.cancer.gov/forms/CTCAEv3.pdf), a scoring system developed through the US National Cancer Institute by a multidisciplinary group and adopted in the UK by the Children's Cancer and Leukaemia Group (CCLG).[197] The CTCAEv3.0

tool can be used for acute and chronic conditions in patients with cancer and grades conditions as mild (grade 1), moderate (grade 2), severe (grade 3), life-threatening or disabling (grade 4), or adverse event-related death (grade 5). To investigate and reduce inter-observer variability, graded adverse events were compared and inconsistencies were discussed and detailed coding rules were developed (available on request form the authors). Inconsistencies in grading revolved mainly around scoring subjective psychosocial and neuropsychological items of grade 1 or 2, grading of 3 or higher adverse events was straightforward.

Ethical Approval

Ethical approval for this study was requested from the Lothian Research Ethics Committee (LREC). On review by the LREC, the committee decided that ethical approval was not required as long-term follow-up of childhood cancer survivors was deemed to be an acceptable and routine part of clinical practice and there were no experimental interventions.

Analysis

The statistical package for social sciences (SPSS) Windows version 14.0 was used for the statistical analyses. Data were analyzed by descriptive techniques using frequencies, percentages and medians as appropriate.

Results

Study Population

883 patients were diagnosed with childhood and teenage cancer between 1st January 1971 to 1st July 2004 and 607 of these patients were alive five years from diagnosis (5 year overall survival rate 69%). Medical information was collected from a retrospective case note review, regional electronic hospital systems and self-reported health outcomes from questionnaires. Of the 607 five year survivors, 34 patients were deceased (5.6%) at the time of the study (figure 1). Of the 573 long-term survivors alive at the time of this study 122 patients were not known to be under any kind of hospital review (21%). Of the 451 patients under hospital follow-up, 370 (82%) were followed up within the South East Scotland Late Effects Service, either by postal questionnaire follow-up (n=67, 17%) or clinic appointment (n=307, 83%). The remaining 81 (18%) of survivors attended other paediatric hospital-based clinics within the same paediatric setting (n=14) or in Tayside (n=26), or Adult Services in South East Scotland (n=31) and in other cities throughout the UK (n=10). Data were gathered from medical records from information based on a clinic visit of more than two years previously, without supplementation from postal questionnaires in 178 patients (31%) and is likely to represent an underestimate of late effects.

Demographics

In this population-based study, 607 long-term survivors were identified (males 321 (52.9%)) with median age (range) of 19.2 (5.1-45.1) years and median age

(range) at diagnosis 5.1 (0.0-17.5) years. Of the cohort, 34 (5.6%) were deceased, with a median overall survival (range) of 9.9 (5.0-30.9) years. Of the 573 long-term survivors alive at the time of the study, the median age (range) was 19.4 (5.1-45.1) years and disease free survival (range) 11.3 (0.8-38.3) years (Table 1). The primary cancer diagnosis is shown for all patients and within each risk level (Figure 2). Risk-stratification of all long-term survivors (n=607) identified 86 (14.1%), 271 (44.6%) and 250 (41.2%) at Level 1, 2 and 3 respectively with detailed breakdown of ages and survival interval for each level of patients alive at the time of the study only (n=573), shown in Table 1 and Figure 1. Demographic data is similar between the three populations.

Adverse health outcomes according level of risk

Among the 34 deaths in the five year survivors (n=607), 26 (76.5%) died from progression or relapse of the underlying primary cancer, two (5.9%) died from unrelated causes and six (17.6%) died from treatment related sequelae; five from second primary malignancy and one from end-stage renal failure. Of the five survivors who went on to die from second primary malignancy, three patients (all Level 2) had a meningioma, presumed to be secondary to low dose cranial irradiation as part of CNS directed therapy for the treatment of childhood ALL, one (Level 3) developed extensive intra-abdominal desmoid tumour having previously been treated for medulloblastoma and with a background of APC gene and Turcot's syndrome and the other patient (Level 3) developed AML presumed

to be related to previous topo-isomerase II inhibitor therapy for primary bone sarcoma (Figure 1).

Prevalence and severity of treatment related late effects were determined for each patient with an assigned level of follow up (n=607, Figures 3 and 4). Among Level 1 survivors (n=86), 11.6% (n=10) had late effects, of whom seven (8.1%) had one late effect and three (3.5%) had two late effects; 60% (n=6) of which were grade 1 toxicity, 30% (n=3) of whom were grade 2 toxicity and 10% (n=1) grade 3 toxicity. Within the Level 2 group (n=271), the prevalence of late effects was 35.8% (n=97), of whom 62 (22.9%) had 1 late effect, 23 (8.5%) had 2 late effects, 9 (3.3%) had 3 late effects and 3 (1.1%) had four late effects, of whom 9.3% (n=9) had a maximum toxicity grade of 1, 58.8% (n=57) grade 2, 18.5% (n=18) grade 3, 10.3% (n=10) grade 4 and 3% (n=3) grade 5. The prevalence of late effects in the Level 3 survivors (n=250) was 65.2% (n=163) of whom 37 (14.8%) had 1 late effect, 39 (15.6%) had 2 late effects, 22 (8.8%) had 3 late effects, 16 (6.4%) had 4 late effects and 46 (18.4%) had 5 or more late effects, of whom 9 (5.5%), 56 (34.4%), 59 (36.2%), 36 (22.1%) and 3 (1.8%) had grade 1,2,3,4 and 5 toxicity respectively.

Discussion

We have shown that therapy-based, risk-stratification of long-term survivors of childhood and teenage cancer can predict which patients are at risk of developing moderate to severe side effects and require high intensity clinic based long-term follow-up. Retrospective assignment of patients into a risk category identified almost half (45%) of patients could be considered at moderate risk of developing late effects, while 41% were deemed to be at high risk of developing late effects, with only a small proportion felt to be at low risk of late complications. The prevalence and severity of side effects increased with increasing level of follow up.

Lifelong follow-up is recommended for survivors of childhood cancer because many of the health problems may be reduced by prevention or early detection.[18] However follow-up should be individually tailored and hospital based follow-up should not be necessary for all survivors.[21,19] The incidence of chronic conditions continues to increase with time and there is therefore no safe time after which these patients can be discharged.[22,20] There is increasing evidence that with increasing time from diagnosis, medical problems associated with ageing, including second cancers, cardiovascular disease, infertility and osteoporosis, may exhibit an accelerated course following certain cancer treatments.[20,18,23,1] Mertens et al showed that while recurrent disease remains the most important contributor to late mortality in 5 year survivors there is a significant excess

mortality risk associated with treatment related complications that is present in the 25 years after the initial cancer diagnosis.[242]

It is reported that up to 50% of long-term survivors do not attend Late Effects Clinics and many of these patients are considered to be at high risk of developing treatment-related late complications.[253] There are many reasons why survivors choose not to participate in long-term follow-up including lack of awareness of risks of late morbidity, desire to 'move on', lack of appropriate adult services and clinical discharge. In a study by Blaauwbroek et al they assessed late effects in a group of adult survivors of childhood cancer who were not involved in regular long-term follow-up and reported that almost 40% of survivors suffered from moderate to severe late effects and 33% had previously unknown late effects.[264] This reiterates the need to educate survivors about their past medical history, their treatment and the importance of engaging in regular survivorship programmes.

Low rates of participation in long-term follow-up are universally reported. In 2004, a Delphi panel of 20 expert childhood cancer survivors in US identified a number of barriers contributing to this.[275] Understanding these barriers will lead to improved medical care for these patients. It was recognized that most childhood cancer survivors are not aware of their adverse health risks and often unaware of the details of their cancer or its treatment. Even where LTFU clinics are attended much of the education of late effects was directed at parents and often not

transferred to the child. The Delphi Panel also highlighted the limitations within the health care setting including lack of LTFU service, discharge to primary care physician who lacks expertise in this field and often receive no communication about the child's past medical history. Improving communication between professionals and patients is essential and will be an integral part of development of survivorship programmes.

The traditional model of LTFU has been in paediatric oncology clinics, generally jointly with paediatric endocrinologists, neurologists and clinical oncologists, long into adulthood which brings with it the advantage of continuity of care, familiarity with treatments but there are a number of disadvantages to this system. This is not only an age appropriate environment for these patients, but also an unsustainable situation for paediatric oncologists, as the population of long-term survivors increase and age. In addition, survivors are protected in this paediatric environment and don't develop the skills necessary to navigate the health care system as they develop into adulthood. Ideally, once the long-term survivor reaches adulthood he/she should be transitioned into the appropriate adult late effects services. At present, such a service does not exist and it is difficult to identify which clinicians should take on this role, especially with increasing sub-specialisation in adult medicine. In a busy and overstretched tertiary oncology healthcare service, medical and clinical adult oncology consultants are unlikely to be in a position to take on this responsibility, and may well feel inadequately trained in caring for childhood cancer survivors. In current practice, the only adult

services supporting the long-term follow-up of those patients requiring specialist hospital follow-up are the adult endocrine and neurology clinics.

It has been highlighted that improved communication of cancer information to patients/families and between health care providers may contribute to greater engagement in follow-up programmes, raises awareness of potential late effects amongst survivors and enable clinicians to diagnose and, where possible, treat late effects earlier[12,13]. Based on national guidelines, we have developed a template for the End of Treatment Summary and Individualised Care Plan, or 'Health Passport', which has been introduced nationally, and welcomed by health professionals and survivors.

Models of care for LTFU of survivors of childhood cancer must be flexible enough to accommodate the needs of the young survivor as they transition throughout their life cycle and also to accommodate the individual heterogeneity of cancer survivors, reflecting the wide range of treatment exposure and adverse long-term sequelae. Development of a service that can deliver individualized, comprehensive, therapy-based patient centred care is essential.

The UK National Cancer Survivorship Initiative is currently exploring models of aftercare services for children and young people who have been treated for cancer. National pathways that identify how follow-up can be delivered in line with current pressures and aspirations are being developed. Clinical risk

stratification will play an integral role in tailoring individualised care to meet the clinical, psychological and practical needs of each survivor. A recent study from the CCSS has reviewed how data derived from the CCSS have characterized specific groups that are deemed to be at highest risk of morbidity and subsequent cancers.[2 8 6] Our study has shown that those patients at highest risk of late morbidity can be identified and appropriately stratified into a high risk (level 3) follow-up programme.

Our study has a number of important but acknowledged limitations. There are only 605 five-year survivors and the median age at follow up was only 19 years, so the study population is small but it does reflect a single centre's clinical practice and as such the findings should stimulate an interesting clinical debate about the utility of long-term follow up of childhood cancer survivors. We have not undertaken any formal statistical analysis but believe that our data is best presented as visual figures (3 and 4) showing clearly that both the prevalence and severity of late effects is related to the assigned level of follow up in our unselected cohort. We have not been able to statistically adjust our analysis to take into account of the current age of survivors for each assigned level of follow up. The percentage of five year survivors with a current age beyond 25 years is 7%, 27% and 29% for levels 1,2 and 3 respectively. It is possible that as the level 1 group ages more late effects will appear and although this appears unlikely, as this group has received the least intensive treatment, it should be the subject of ongoing and further study. The median follow up time for levels one, two and

three survivors is 11, 13 and 12.9 years respectively (see Table one). We believe that ascertainment of adverse health outcomes is likely to be complete or very nearly complete in our study population, although we must acknowledge that we were not able to access primary care records for our five year survivors which could result in an under-reporting of adverse events. It is however highly unlikely that missed adverse health outcomes were more likely in level 1 patients as opposed to level 2 or 3 patients.

Stratification of patients according to risk of late morbidity will maximise the use of health service resources and provide age appropriate care as locally as possible. With increasing time from completion of treatment, it is hoped that the majority of adult survivors will be independent and take responsibility for their own health, with health care support provided by their primary care physician. As a result, the primary care team is likely to play an increasing role in the long-term follow-up of survivors of childhood cancer. Primary care services may be already stretched but GPs are used to meeting targets and ensuring guidelines are implemented. Good communication between the hospital services and primary care will be essential. Early involvement of general practitioners in the Late Effects Services will establish collaborations between the two teams and enable primary Care Physicians to become familiar with the surveillance programme. The feasibility of a shared-care model between cancer paediatric oncology cancer centres and primary-care doctors to deliver survivor-focused risk based health care was tested successfully by a Dutch group. The study showed that

patients would see their family doctor for long-term follow-up: the family doctors were interested in sharing survivors' care; and family doctors would return the necessary medical information needed for continued follow-up.[29~~7~~] Appropriate education of the family doctors, which has resource implications, was a key finding of this study. More recently this group has shown that a web based survivor care plan can facilitate the long-term care of survivors by family doctors.[30~~28~~]

In order to improve our understanding of treatment-related side effects and help develop treatment protocols to minimise toxicity, lifelong monitoring of health and well-being of all long-term survivors will be necessary. Our understanding of the late effects of the treatment of Hodgkin's lymphoma has led to studies which are ongoing and are designed to reduce the risk of second malignancy by avoiding radiotherapy in selected cases and replace gonadotoxic chemotherapy with drugs that are efficacious in Hodgkin's lymphoma but less likely to compromise reproductive function.[31~~29~~] Balancing safety and efficacy in the treatment of Hodgkin's lymphoma remains an important goal in the treatment of this curable malignancy.[32~~30~~]

We have shown that it is possible to predict which survivors of childhood cancer are at significant risk of developing moderate to severe late effects and require moderate or high intensity long-term follow. Importantly we have also shown in our small population based cohort of five year survivors that there is a group of

survivors who can be reliably identified who maycan be discharged from clinic based follow-up and followed up by annual questionnaire or telephone contact. Our findings need confirmation in a prospective cohort study that has the power to adjust for all confounding variables and in particular for length of follow up. Structured, risk-adapted follow-up of childhood cancer survivors following evidence-based guidelines would reduce cost ineffective or excessive evaluations and focus individual health care delivery. Education of survivors and health care providers will hopefully reduce the burden of chronic health problems and improve quality of life for the growing population of children and young people who have been treated for cancer.

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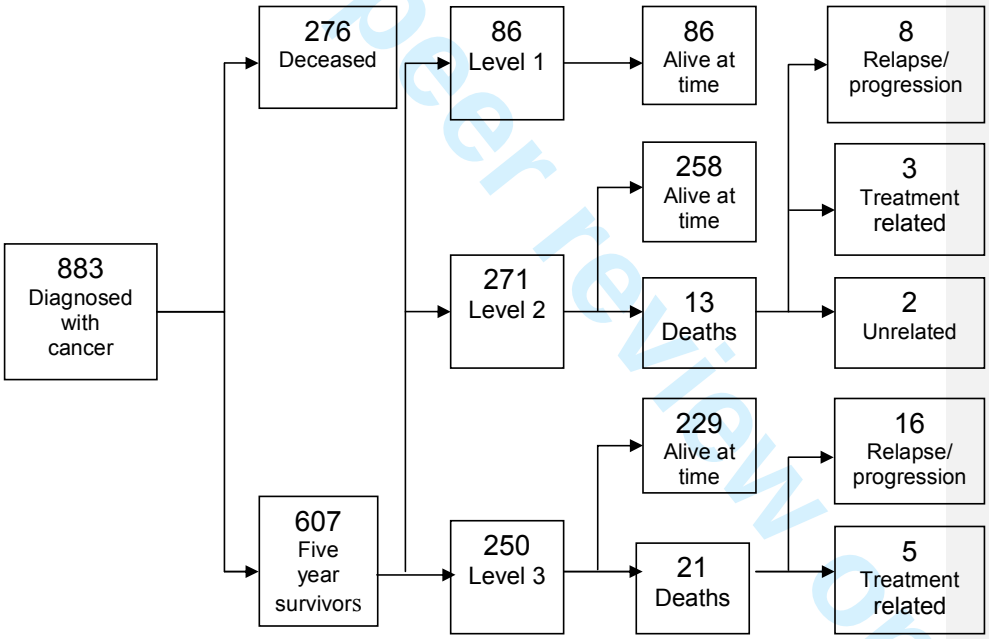

Figure 1. Study flow of childhood and teenage cancer patients.

Flow chart shows the study population and the risk stratification of patients into Levels 1,2 and 3 and the proportion of patients alive at the time of the study.

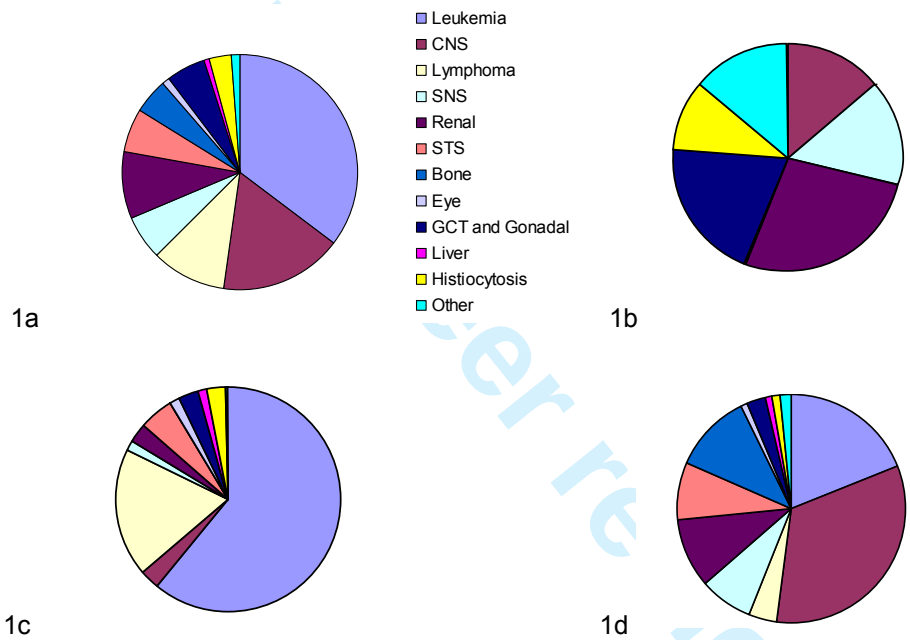

Figure 2 Diagnoses of five year survivors (n-607)

1a. All survivors (n=607), 1b. Level 1 (n= 86), 1c. Level 2 (n=271), 1d. Level 3 (n=250). Abbreviations: CNS – central nervous system tumours, SNS – sympathetic nervous system tumours, GCT – germ cell tumours, STS – soft tissue sarcomas

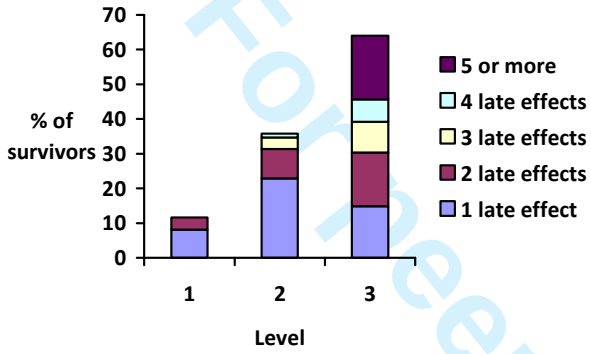

Figure 3

Prevalence of late effects by risk stratified level of follow-up for all five year survivors (n=607).

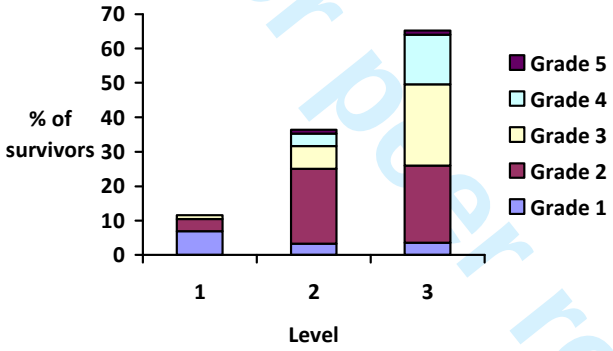

Figure 4

Severity of late effects by risk stratified level (CTCAEv3.0): grade 1- mild, grade 2-moderate, grade 3 severe, grade 4 – life threatening or disabling and grade 5 – death for all five year survivors (n=607). [197]

Table 1. Demographic characteristics of all the five year survivors alive at the time of the study (n=573) and for Level 1, Level 2 and Level 3 subgroups.

Characteristic	Five year survivors (n-573)		Level 1 (n=86)		Level 2 (n=258)		Level 3 (n=229)	
	No.	%	No.	%	No.	%	No.	%
Sex								
Male	303	52.9	37	43	137	53.1	129	56.3
Female	270	47.1	49	57	121	46.9	100	43.7
Current age, years								
5-9	44	7.7	11	12.8	15	5.8	18	7.8
10-14	110	19.2	19	22.1	56	21.7	35	15.3
15-19	148	25.8	31	36.0	66	25.6	51	22.3
20-24	129	22.5	19	22.1	51	19.8	59	25.8
25-29	69	12.0	6	7.0	30	11.6	33	14.4
30-34	40	7.0	-	-	16	6.2	24	10.5
35-39	21	3.7	-	-	15	5.8	6	2.6

40-44	11	1.9	-	-	8	3.1	3	1.3
45-49	1	0.2	-	-	1	0.4	-	-
Median, Range	19.4	5.1-45.1	17.5	5.1-28.4	19.4	8.0-45.1	20.1	5.6-43.7
Age at diagnosis, years								
0-4	286	49.9	54	62.8	140	54.3	92	40.2
5-9	144	25.1	16	18.6	68	26.4	60	26.2
10-14	122	21.3	15	17.4	48	18.6	59	25.8
15-19	21	3.7	1	1.2	2	0.7	18	7.8
Median, Range	5.0	0-20.9	2.9	0-15.4	4.5	0-20.9	6.5	0-17.5
Time from diagnosis, years								
5-9	197	34.4	33	38.4	80	31.0	84	36.7
10-14	166	29.0	32	37.2	76	29.5	58	25.3
15-19	100	17.5	11	12.8	38	14.7	51	22.3
20-24	58	10.1	8	9.3	30	11.6	20	8.7
25-29	30	5.2	2	2.3	16	6.2	12	5.2
30-34	12	2.1	-	-	10	3.9	2	0.9
35-39	10	1.7	-	-	8	3.1	2	0.9
Median, Range	12.4	5.0-39.3	11.0	5.0-26.9	13.0	5.0-38.4	12.9	5.0-39.3
DFS, years								

0-4	36	6.3	1	1.2	20	7.7	15	6.5
5-9	198	34.5	34	39.5	82	31.8	82	35.8
10-14	160	27.9	31	36.0	67	26.0	62	27.1
15-19	84	14.7	10	11.6	34	13.2	40	17.5
20-24	57	9.9	8	9.3	31	12.0	18	7.9
25-29	19	3.4	2	2.4	8	3.1	9	3.9
30-34	17	3.0	-	-	15	5.8	2	0.9
35-39	2	0.3	-	-	1	0.4	1	0.4
Median, Range	11.3	0.5-38.3	10.9	4.4-26.9	11.6	1.9-36.4	11.6	0.5-38.3
Time since last seen in Hospital Based Late Effects Clinic, years								
0-2	328	57.2	31	36.0	143	55.4	154	67.2
3-4	75	13.1	16	18.6	36	13.9	23	10.1
5-7	78	13.6	20	23.3	40	15.5	18	7.9
8-10	28	5.0	6	7.0	10	3.9	12	5.2
>10	41	7.1	8	9.3	19	7.4	14	6.1
Unknown	23	4.0	5	5.8	10	3.9	8	3.5
Median, Range	2.3	0-13.1	4.5	0-12.7	2.2	0-12.7	1.8	0-13.1

Competing interest statement

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work, no financial relationships with any organisations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

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Contributorship statement

ABE initiated the project, designed data collection tools, monitored data collection for the study, analysed the data, and drafted and revised the paper. KD designed data collection tools, monitored data collection for the study, analysed the data and revised the draft paper. SB designed data collection tools, monitored data

collection for the study, analysed the data and revised the draft paper. PM-S analysed the data and drafted and revised the paper. WHBW designed data collection tools, monitored data collection for the study, analysed the data, and drafted and revised the paper. All authors had full access to all of the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Data sharing statement

Dataset available from the corresponding author at angela.edgar@luht.scot.nhs.uk. Consent was not obtained but the presented data are anonymised and risk of identification is low.

Ethical approval

Ethical approval for this study was requested from the Lothian Research Ethics Committee (LREC). On review by the LREC, the committee decided that ethical approval was not required as long-term follow-up of childhood cancer survivors was deemed to be an acceptable and routine part of clinical practice and there were no experimental interventions.

Funding

No specific funding was received for this research.

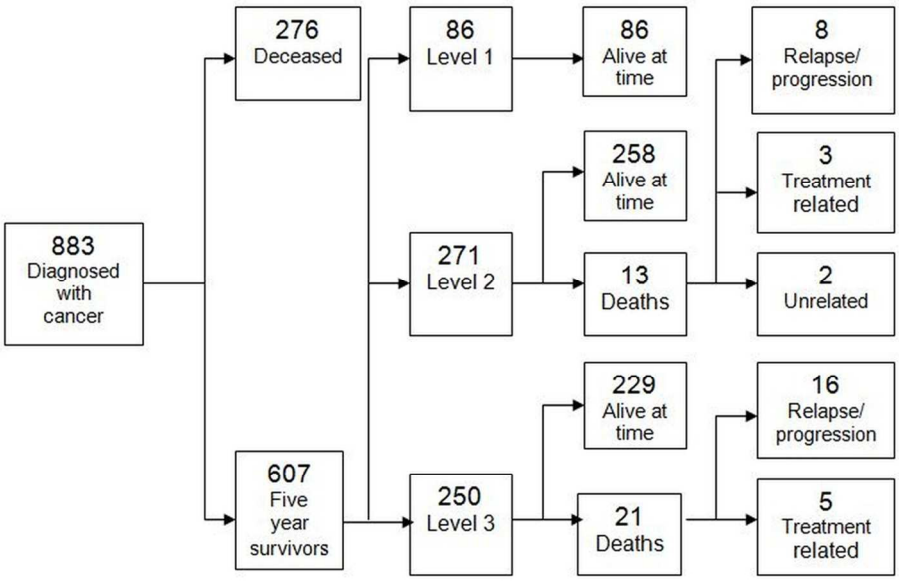

Figure 1. Study flow of childhood and teenage cancer patients.

Flow chart shows the study population and the risk stratification of patients into Levels 1,2 and 3 and the proportion of patients alive at the time of the study.

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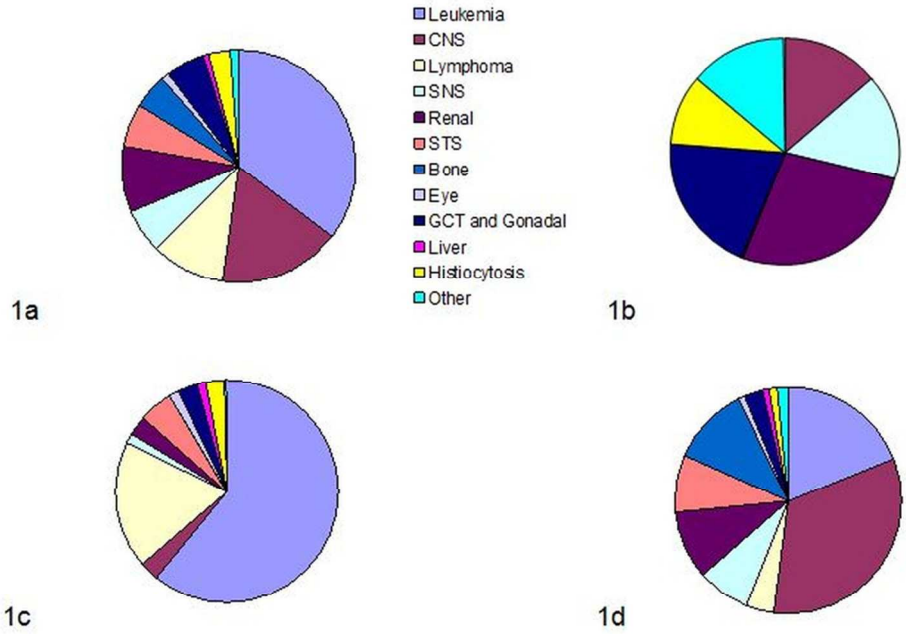

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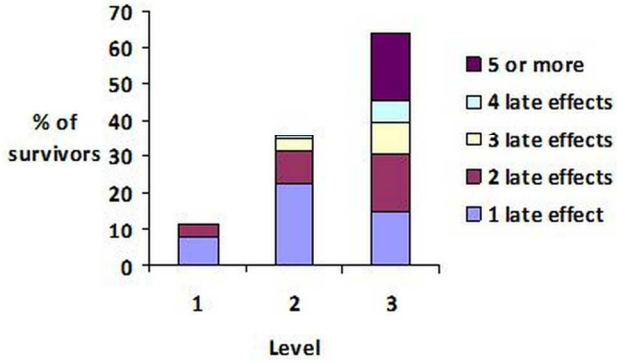

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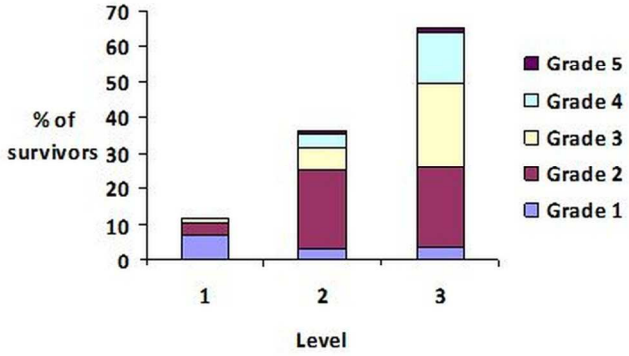

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