



**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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3 **Can Intensity of long-term follow-up for survivors of childhood and teenage**  
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5 **cancer be safely determined by therapy-based risk-stratification?**  
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51 Key words: Childhood cancer, treatment, survival, cure, late effects, models of  
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53 follow-up, long-term follow-up.  
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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.

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- 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.

### 15 **Limitations**

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- 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 1<sup>st</sup> January 1971-31<sup>st</sup> 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

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3 607 five-year survivors were identified. Risk-stratification identified 86 (14.2%),  
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5 271 (44.6%) and 250 (41.2%) level 1, 2 and 3 survivors respectively. The  
6  
7 prevalence of late effects (LE) for level 1 survivors was 11.6% with only 1 patient  
8  
9 with grade 3 or above toxicity. 35.8% of level 2 survivors had a LE, of whom  
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11 9.3%, 58.8%, 18.5%, 10.3% and 3% had grade 1, 2, 3, 4 and 5 toxicity  
12  
13 respectively. 65.2 % of level 3 survivors had LE), of whom 5.5% (n=9), 34.4%  
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15 (n=56), 36.2% (n=59), 22.1% (n=36) and 1.8% (n=3) had grade 1,2,3,4 and 5  
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17 toxicity respectively.  
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## 24 **Conclusions**

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27 Therapy-based, risk-stratification of survivors can safely predict which patients  
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29 are at significant risk of developing moderate to severe late effects and require  
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31 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.<sup>1</sup> It is estimated that 1 in 640 young adults is a survivor of childhood cancer.<sup>2</sup> 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.<sup>3-5</sup> Late effects are diverse and include secondary malignancies, organ system damage, infertility, cognitive impairment, and disorders of growth and development.<sup>6, 7</sup> Appropriate LTFU of these patients is essential to detect, treat and prevent morbidity and mortality.<sup>8</sup>

There is wide variation of long-term follow-up practices throughout the UK with a propensity for hospital dependency, often in age-inappropriate settings.<sup>9</sup> A recent study has highlighted how excess morbidity in survivors translates into increased use of health care facilities.<sup>10</sup> 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.<sup>11</sup> 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

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3 intensity of follow-up<sup>8</sup>. In the UK, we published a Practice Statement 'Therapy  
4 Based Long-term Follow-up' which is designed to inform and guide clinicians  
5 responsible for the long-term follow-up of childhood cancer survivors.<sup>12</sup> The  
6 Practice Statement recommends follow-up assessments and investigations  
7 based on the treatment that the individual has received and is informed by the  
8 evidence-based recommendations published by SIGN 76.  
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20 An integrated and systematic approach is now considered a requirement of the  
21 National Institute of Health and Clinical Excellence (NIHCE) Improving Outcomes  
22 for Children and Young People with Cancer Guidance (2005) and National  
23 Delivery Plan for Children and Young People's Specialist Services in Scotland  
24 (2008).<sup>13,14</sup> In England, the National Cancer Survivorship Initiative (NCSI) has  
25 developed as a partnership between the Department of Health, Macmillan  
26 Cancer Support, and supported by NHS Improvement, to develop models of care  
27 to ensure that those living with and beyond cancer have access to safe and  
28 effective care and receive the support they need to lead as healthy and active a  
29 life as possible. Improved awareness of cancer survivorship as a chronic health  
30 problem will facilitate the development of care pathways that will meet the needs  
31 of every patient throughout their lifetime.<sup>15</sup>  
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50 Although there is growing guidance on whom, where and how long-term  
51 survivors should be followed-up, evidence to show that adopting a model of risk-  
52 stratified follow-up is safe is lacking. A recent study has shown that assigning  
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3 patients to one of three agreed levels of follow up, as described by Wallace et al,  
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5 was relatively simple for experienced clinic staff.<sup>16</sup> The objective of this study was  
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7 to evaluate the safety and efficacy of this risk-based follow-up model by  
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9 retrospectively stratifying an unselected cohort of long-term survivors of  
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11 childhood cancer from a single centre and objectively evaluating their health  
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## 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-

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

38 To determine the severity of late effects, each reported late effect was graded  
39 independently by two of the authors using the Common Terminology Criteria for  
40 Adverse Events, Version 3.0 (CTCAEv3.0, available at  
41 <http://ctep.cancer.gov/forms/CTCAEv3.pdf>), a scoring system developed through  
42 the US National Cancer Institute by a multidisciplinary group and adopted in the  
43 UK by the Children's Cancer and Leukaemia Group (CCLG).<sup>17</sup> The CTCAEv3.0  
44 tool can be used for acute and chronic conditions in patients with cancer and  
45 grades conditions as mild (grade 1), moderate (grade 2), severe (grade 3), life-  
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3 threatening or disabling (grade 4), or adverse event-related death (grade 5). To  
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5 investigate and reduce inter-observer variability, graded adverse events were  
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7 compared and inconsistencies were discussed and detailed coding rules were  
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9 developed (available on request from the authors). Inconsistencies in grading  
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11 revolved mainly around scoring subjective psychosocial and neuropsychological  
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13 items of grade 1 or 2, grading of 3 or higher adverse events was straightforward.  
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### 20 **Ethical Approval**

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

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

### Study Population

883 patients were diagnosed with childhood and teenage cancer between 1<sup>st</sup> January 1971 to 1<sup>st</sup> 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-

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

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31 Among the 34 deaths in the five year survivors (n=607), 26 (76.5%) died from  
32 progression or relapse of the underlying primary cancer, two (5.9%) died from  
33 unrelated causes and six (17.6%) died from treatment related sequelae; five from  
34 second primary malignancy and one from end-stage renal failure. Of the five  
35 survivors who went on to die from second primary malignancy, three patients (all  
36 Level 2) had a meningioma, presumed to be secondary to low dose cranial  
37 irradiation as part of CNS directed therapy for the treatment of childhood ALL,  
38 one (Level 3) developed extensive intra-abdominal desmoid tumour having  
39 previously been treated for medulloblastoma and with a background of APC gene  
40 and Turcot's syndrome and the other patient (Level 3) developed AML presumed  
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3 to be related to previous topo-isomerase II inhibitor therapy for primary bone  
4 sarcoma (Figure 1).  
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10 Prevalence and severity of treatment related late effects were determined for  
11 each patient with an assigned level of follow up (n=607, Figures 3 and 4). Among  
12 Level 1 survivors (n=86), 11.6% (n=10) had late effects, of whom seven (8.1%)  
13 had one late effect and three (3.5%) had two late effects; 60% (n=6) of which  
14 were grade 1 toxicity, 30% (n=3) of whom were grade 2 toxicity and 10% (n=1)  
15 grade 3 toxicity. Within the Level 2 group (n=271), the prevalence of late effects  
16 was 35.8% (n=97), of whom 62 (22.9%) had 1 late effect, 23 (8.5%) had 2 late  
17 effects, 9 (3.3%) had 3 late effects and 3 (1.1%) had four late effects, of whom  
18 9.3% (n=9) had a maximum toxicity grade of 1, 58.8% (n=57) grade 2, 18.5%  
19 (n=18) grade 3, 10.3% (n=10) grade 4 and 3% (n=3) grade 5. The prevalence of  
20 late effects in the Level 3 survivors (n=250) was 65.2% (n=163) of whom 37  
21 (14.8%) had 1 late effect, 39 (15.6%) had 2 late effects, 22 (8.8%) had 3 late  
22 effects, 16 (6.4%) had 4 late effects and 46 (18.4%) had 5 or more late effects, of  
23 whom 9 (5.5%), 56 (34.4%), 59 (36.2%), 36 (22.1%) and 3 (1.8%) had grade  
24 1,2,3,4 and 5 toxicity respectively.  
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## 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.<sup>18</sup> However follow-up should be individually tailored and hospital based follow-up should not be necessary for all survivors.<sup>19</sup> The incidence of chronic conditions continues to increase with time and there is therefore no safe time after which these patients can be discharged.<sup>20</sup> 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.<sup>18,21</sup> 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



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3 mortality risk associated with treatment related complications that is present in  
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5 the 25 years after the initial cancer diagnosis.<sup>22</sup>  
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10 It is reported that up to 50% of long-term survivors do not attend Late Effects  
11 Clinics and many of these patients are considered to be at high risk of developing  
12 treatment-related late complications.<sup>23</sup> There are many reasons why survivors  
13 choose not to participate in long-term follow-up including lack of awareness of  
14 risks of late morbidity, desire to 'move on', lack of appropriate adult services and  
15 clinical discharge. In a study by Blaauwbroek et al they assessed late effects in a  
16 group of adult survivors of childhood cancer who were not involved in regular  
17 long-term follow-up and reported that almost 40% of survivors suffered from  
18 moderate to severe late effects and 33% had previously unknown late effects.<sup>24</sup>  
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20 This reiterates the need to educate survivors about their past medical history,  
21 their treatment and the importance of engaging in regular survivorship  
22 programmes.  
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41 Low rates of participation in long-term follow-up are universally reported. In 2004,  
42 a Delphi panel of 20 expert childhood cancer survivors in US identified a number  
43 of barriers contributing to this.<sup>25</sup> Understanding these barriers will lead to  
44 improved medical care for these patients. It was recognized that most childhood  
45 cancer survivors are not aware of their adverse health risks and often unaware of  
46 the details of their cancer or its treatment. Even where LTFU clinics are attended  
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3 transferred to the child. The Delphi Panel also highlighted the limitations within  
4 the health care setting including lack of LTFU service, discharge to primary care  
5 physician who lacks expertise in this field and often receive no communication  
6 about the child's past medical history. Improving communication between  
7 professionals and patients is essential and will be an integral part of development  
8 of survivorship programmes.  
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20 The traditional model of LTFU has been in paediatric oncology clinics, generally  
21 jointly with paediatric endocrinologists, neurologists and clinical oncologists, long  
22 into adulthood which brings with it the advantage of continuity of care, familiarity  
23 with treatments but there are a number of disadvantages to this system. This is  
24 not only an age appropriate environment for these patients, but also an  
25 unsustainable situation for paediatric oncologists, as the population of long-term  
26 survivors increase and age. In addition, survivors are protected in this paediatric  
27 environment and don't develop the skills necessary to navigate the health care  
28 system as they develop into adulthood. Ideally, once the long-term survivor  
29 reaches adulthood he/she should be transitioned into the appropriate adult late  
30 effects services. At present, such a service does not exist and it is difficult to  
31 identify which clinicians should take on this role, especially with increasing sub-  
32 specialisation in adult medicine. In a busy and overstretched tertiary oncology  
33 healthcare service, medical and clinical adult oncology consultants are unlikely to  
34 be in a position to take on this responsibility, and may well feel inadequately  
35 trained in caring for childhood cancer survivors. In current practice, the only adult  
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3 services supporting the long-term follow-up of those patients requiring specialist  
4 hospital follow-up are the adult endocrine and neurology clinics.  
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10 It has been highlighted that improved communication of cancer information to  
11 patients/families and between health care providers may contribute to greater  
12 engagement in follow-up programmes, raises awareness of potential late effects  
13 amongst survivors and enable clinicians to diagnose and, where possible, treat  
14 late effects earlier. Based on national guidelines, we have developed a template  
15 for the End of Treatment Summary and Individualised Care Plan, or 'Health  
16 Passport', which has been introduced nationally, and welcomed by health  
17 professionals and survivors.  
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32 Models of care for LTFU of survivors of childhood cancer must be flexible enough  
33 to accommodate the needs of the young survivor as they transition throughout  
34 their life cycle and also to accommodate the individual heterogeneity of cancer  
35 survivors, reflecting the wide range of treatment exposure and adverse long-term  
36 sequelae. Development of a service that can deliver individualized,  
37 comprehensive, therapy-based patient centred care is essential.  
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48 The UK National Cancer Survivorship Initiative is currently exploring models of  
49 aftercare services for children and young people who have been treated for  
50 cancer. National pathways that identify how follow-up can be delivered in line  
51 with current pressures and aspirations are being developed. Clinical risk  
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3 stratification will play an integral role in tailoring individualised care to meet the  
4 clinical, psychological and practical needs of each survivor. A recent study from  
5 the CCSS has reviewed how data derived from the CCSS have characterized  
6 specific groups that are deemed to be at highest risk of morbidity and subsequent  
7 cancers.<sup>26</sup> Our study has shown that those patients at highest risk of late  
8 morbidity can be identified and appropriately stratified into a high risk (level 3)  
9 follow-up programme.  
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22 Stratification of patients according to risk of late morbidity will maximise the use  
23 of health service resources and provide age appropriate care as locally as  
24 possible. With increasing time from completion of treatment, it is hoped that the  
25 majority of adult survivors will be independent and take responsibility for their  
26 own health, with health care support provided by their primary care physician. As  
27 a result, the primary care team is likely to play an increasing role in the long-term  
28 follow-up of survivors of childhood cancer. Primary care services may be already  
29 stretched but GPs are used to meeting targets and ensuring guidelines are  
30 implemented. Good communication between the hospital services and primary  
31 care will be essential. Early involvement of general practitioners in the Late  
32 Effects Services will establish collaborations between the two teams and enable  
33 primary Care Physicians to become familiar with the surveillance programme.  
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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

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3 patients would see their family doctor for long-term follow-up: the family doctors  
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5 were interested in sharing survivors' care; and family doctors would return the  
6  
7 necessary medical information needed for continued follow-up.<sup>27</sup> Appropriate  
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9 education of the family doctors, which has resource implications, was a key  
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11 finding of this study. More recently this group has shown that a web based  
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13 survivor care plan can facilitate the long-term care of survivors by family  
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15 doctors.<sup>28</sup>  
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22 In order to improve our understanding of treatment-related side effects and help  
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24 develop treatment protocols to minimise toxicity, lifelong monitoring of health and  
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26 well-being of all long-term survivors will be necessary. Our understanding of the  
27  
28 late effects of the treatment of Hodgkin's lymphoma has led to studies which are  
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30 ongoing and are designed to reduce the risk of second malignancy by avoiding  
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32 radiotherapy in selected cases and replace gonadotoxic chemotherapy with  
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34 drugs that are efficacious in Hodgkin's lymphoma but less likely to compromise  
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36 reproductive function.<sup>29</sup> Balancing safety and efficacy in the treatment of  
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38 Hodgkin's lymphoma remains an important goal in the treatment of this curable  
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40 malignancy.<sup>30</sup>  
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48 We have shown that it is possible to safely predict which survivors of childhood  
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50 cancer are at significant risk of developing moderate to severe late effects and  
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52 require moderate or high intensity long-term follow. Importantly we have also  
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54 shown that there is a group of survivors who can be reliably identified who can be  
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3 safely discharged from clinic based follow-up. Structured, risk-adapted follow-up  
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5 of childhood cancer survivors following evidence-based guidelines would reduce  
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7 cost ineffective or excessive evaluations and focus individual health care  
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9 delivery. Education of survivors and health care providers will hopefully reduce  
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11 the burden of chronic health problems and improve quality of life for the growing  
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13 population of children and young people who have been treated for cancer.  
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34  
35 deceased patients.  
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41 **Word count: 3301**  
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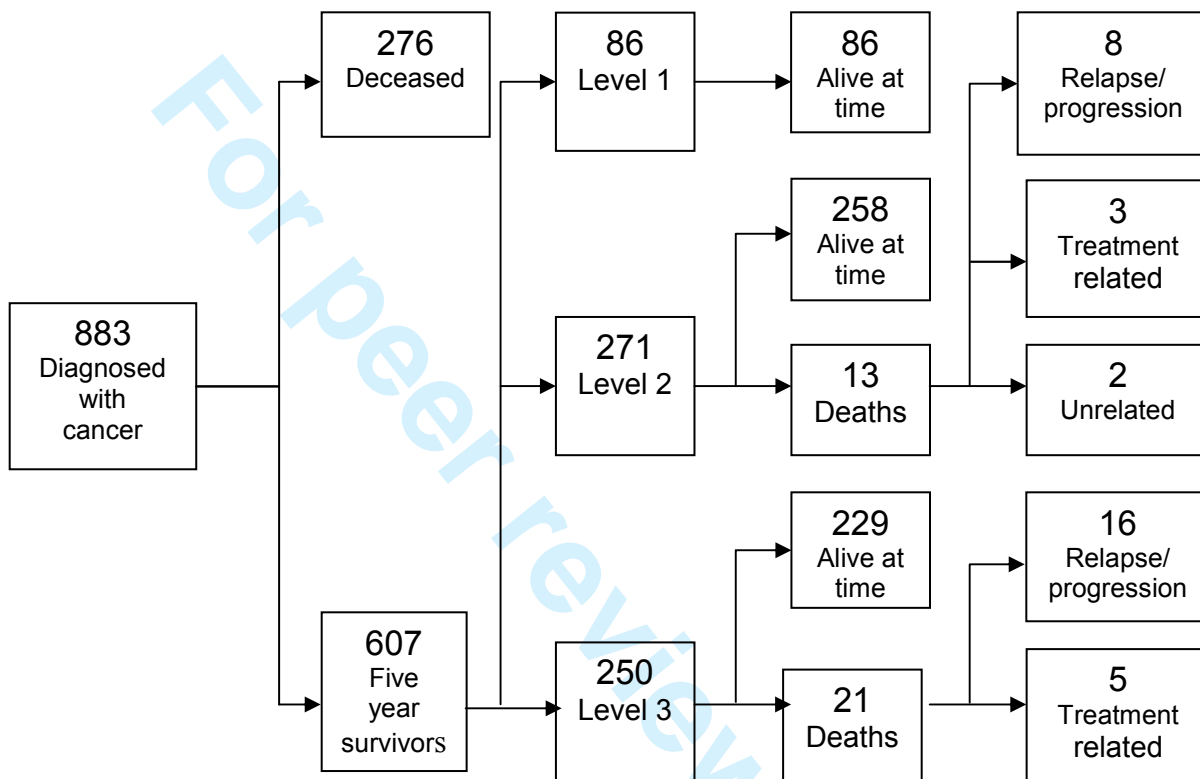
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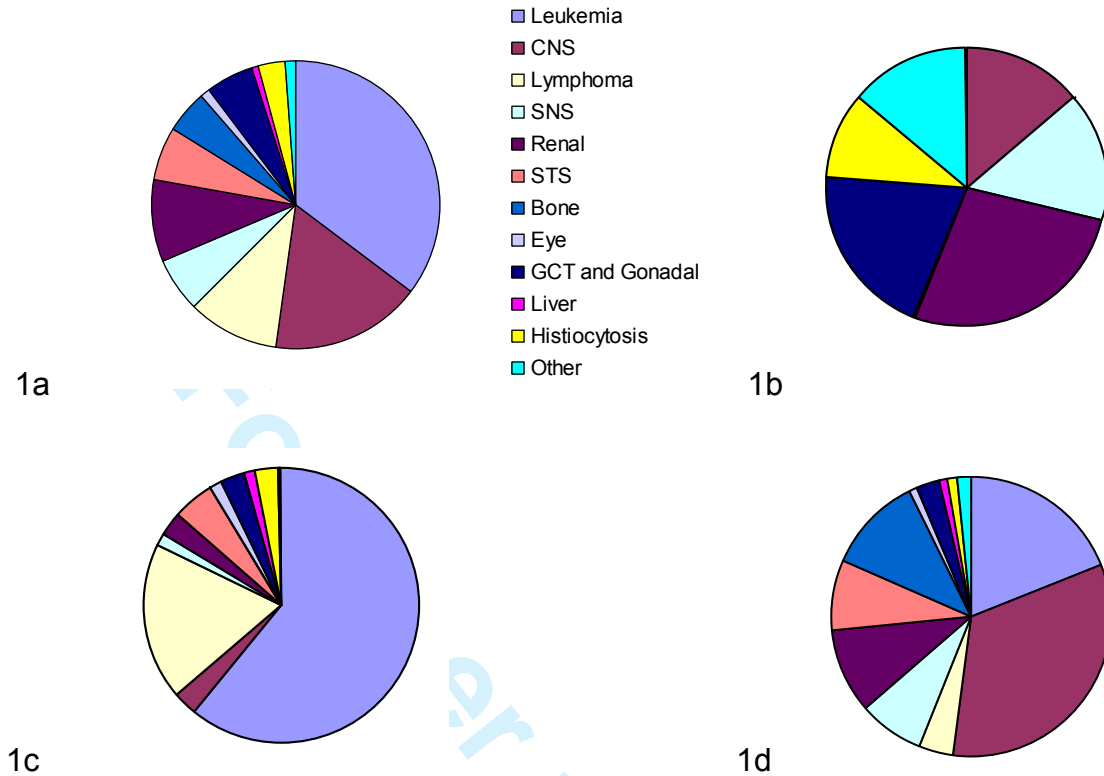
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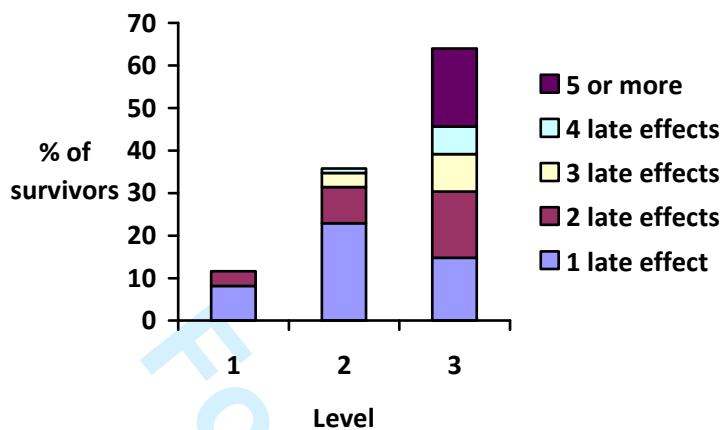
**Figure 1. Study flow of childhood and teenage cancer patients.**

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.



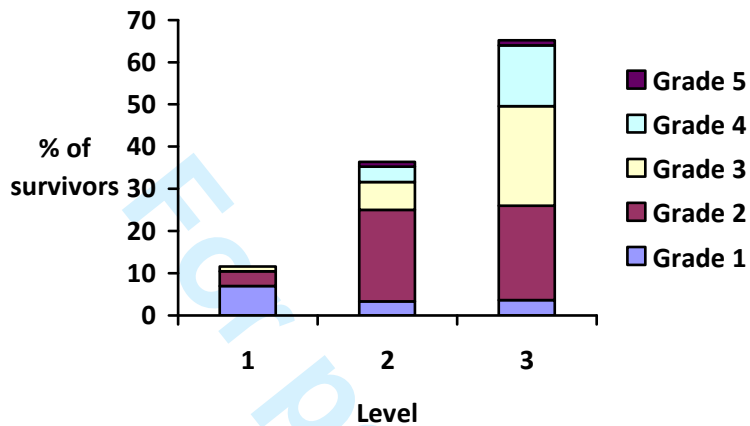
**Figure 2 Diagnoses of five year survivors (n=607)**

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).<sup>17</sup>

**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](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

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3 and revised the draft paper. SB designed data collection tools, monitored data  
4 collection for the study, analysed the data and revised the draft paper. PM-S  
5  
6 analysed the data and drafted and revised the paper. WHBW designed data  
7 collection tools, monitored data collection for the study, analysed the data, and  
8 drafted and revised the paper. All authors had full access to all of the data in the  
9 study and can take responsibility for the integrity of the data and the accuracy of  
10 the data analysis.  
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### 22 **Data sharing statement**

23  
24 Dataset available from the corresponding author at  
25 [angela.edgar@luht.scot.nhs.uk](mailto:angela.edgar@luht.scot.nhs.uk). Consent was not obtained but the presented  
26 data are anonymised and risk of identification is low.  
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### 34 **Ethical approval**

35  
36 Ethical approval for this study was requested from the Lothian Research Ethics  
37 Committee (LREC). On review by the LREC, the committee decided that ethical  
38 approval was not required as long-term follow-up of childhood cancer survivors  
39 was deemed to be an acceptable and routine part of clinical practice and there  
40 were no experimental interventions.  
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52  
53 No specific funding was received for this research.  
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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
<b>Introduction</b>			
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
<b>Methods</b>			
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	
<b>Results</b>			

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	
<b>Discussion</b>			
Key results	18	Summarise key results with reference to study objectives	15
<b>Limitations</b>			
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
<b>Other information</b>			
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](http://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?**

Journal:	<i>BMJ Open</i>
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Complete List of Authors:	Edgar, Angela; Royal Hospital for Sick Children , Paediatric Oncology Duffin, Kathleen; Royal Hospital for Sick Children, Paediatric Oncology Borthwick, Stephen; Royal Hospital for Sick Children, Paediatric Oncology Marciniak-Stępak, Patrycja; Poznan University of Medical Sciences, 2Department of Paediatric Oncology Wallace, w. Hamish; Royal Hospital for Sick Children, Paediatric Oncology
<b>Primary Subject Heading</b>:	Oncology
Secondary Subject Heading:	Paediatrics, Patient-centred medicine
Keywords:	Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Risk management < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Paediatric oncology < ONCOLOGY

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3 **Can Intensity of long-term follow-up for survivors of childhood and teenage**  
4 **cancer be safely determined by therapy-based risk-stratification?**  
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8 Edgar AB<sup>1</sup>, Duffin K<sup>1</sup>, Borthwick S<sup>1</sup>, Marciniak-Stepak P<sup>2</sup>, Wallace WH<sup>1</sup>  
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51 Key words: Childhood cancer, treatment, survival, cure, late effects, models of  
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53 follow-up, long-term follow-up.  
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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.



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- 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.

### 15 **Limitations**

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- 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 1<sup>st</sup> January 1971-31<sup>st</sup> 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

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3 607 five-year survivors were identified. Risk-stratification identified 86 (14.2%),  
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5 271 (44.6%) and 250 (41.2%) level 1, 2 and 3 survivors respectively. The  
6  
7 prevalence of late effects (LE) for level 1 survivors was 11.6% with only 1 patient  
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9 with grade 3 or above toxicity. 35.8% of level 2 survivors had a LE, of whom  
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11 9.3%, 58.8%, 18.5%, 10.3% and 3% had grade 1, 2, 3, 4 and 5 toxicity  
12  
13 respectively. 65.2 % of level 3 survivors had LE), of whom 5.5% (n=9), 34.4%  
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15 (n=56), 36.2% (n=59), 22.1% (n=36) and 1.8% (n=3) had grade 1,2,3,4 and 5  
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17 toxicity respectively.  
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## 24 **Conclusions**

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27 Therapy-based, risk-stratification of survivors can safely predict which patients  
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29 are at significant risk of developing moderate to severe late effects and require  
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31 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.<sup>1</sup> It is estimated that 1 in 640 young adults is a survivor of childhood cancer.<sup>2</sup> 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.<sup>3-5</sup> Late effects are diverse and include secondary malignancies, organ system damage, infertility, cognitive impairment, and disorders of growth and development.<sup>6, 7</sup> Appropriate LTFU of these patients is essential to detect, treat and prevent morbidity and mortality.<sup>8</sup>

There is wide variation of long-term follow-up practices throughout the UK with a propensity for hospital dependency, often in age-inappropriate settings.<sup>9</sup> A recent study has highlighted how excess morbidity in survivors translates into increased use of health care facilities.<sup>10</sup> 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.<sup>11</sup> 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

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3 intensity of follow-up<sup>8</sup>. In the UK, we published a Practice Statement 'Therapy  
4 Based Long-term Follow-up' which is designed to inform and guide clinicians  
5 responsible for the long-term follow-up of childhood cancer survivors.<sup>12</sup> The  
6 Practice Statement recommends follow-up assessments and investigations  
7 based on the treatment that the individual has received and is informed by the  
8 evidence-based recommendations published by SIGN 76.  
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20 An integrated and systematic approach is now considered a requirement of the  
21 National Institute of Health and Clinical Excellence (NIHCE) Improving Outcomes  
22 for Children and Young People with Cancer Guidance (2005) and National  
23 Delivery Plan for Children and Young People's Specialist Services in Scotland  
24 (2008).<sup>13,14</sup> In England, the National Cancer Survivorship Initiative (NCSI) has  
25 developed as a partnership between the Department of Health, Macmillan  
26 Cancer Support, and supported by NHS Improvement, to develop models of care  
27 to ensure that those living with and beyond cancer have access to safe and  
28 effective care and receive the support they need to lead as healthy and active a  
29 life as possible. Improved awareness of cancer survivorship as a chronic health  
30 problem will facilitate the development of care pathways that will meet the needs  
31 of every patient throughout their lifetime.<sup>15</sup>  
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50 Although there is growing guidance on whom, where and how long-term  
51 survivors should be followed-up, evidence to show that adopting a model of risk-  
52 stratified follow-up is safe is lacking. A recent study has shown that assigning  
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3 patients to one of three agreed levels of follow up, as described by Wallace et al,  
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5 was relatively simple for experienced clinic staff.<sup>16</sup> The objective of this study was  
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7 to evaluate the safety and efficacy of this risk-based follow-up model by  
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9 retrospectively stratifying an unselected cohort of long-term survivors of  
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11 childhood cancer from a single centre and objectively evaluating their health  
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## 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-

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

38 To determine the severity of late effects, each reported late effect was graded  
39 independently by two of the authors using the Common Terminology Criteria for  
40 Adverse Events, Version 3.0 (CTCAEv3.0, available at  
41 <http://ctep.cancer.gov/forms/CTCAEv3.pdf>), a scoring system developed through  
42 the US National Cancer Institute by a multidisciplinary group and adopted in the  
43 UK by the Children's Cancer and Leukaemia Group (CCLG).<sup>17</sup> The CTCAEv3.0  
44 tool can be used for acute and chronic conditions in patients with cancer and  
45 grades conditions as mild (grade 1), moderate (grade 2), severe (grade 3), life-  
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3 threatening or disabling (grade 4), or adverse event-related death (grade 5). To  
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5 investigate and reduce inter-observer variability, graded adverse events were  
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7 compared and inconsistencies were discussed and detailed coding rules were  
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9 developed (available on request from the authors). Inconsistencies in grading  
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11 revolved mainly around scoring subjective psychosocial and neuropsychological  
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13 items of grade 1 or 2, grading of 3 or higher adverse events was straightforward.  
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### 20 **Ethical Approval**

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

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

### Study Population

883 patients were diagnosed with childhood and teenage cancer between 1<sup>st</sup> January 1971 to 1<sup>st</sup> 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-

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

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31 Among the 34 deaths in the five year survivors (n=607), 26 (76.5%) died from  
32 progression or relapse of the underlying primary cancer, two (5.9%) died from  
33 unrelated causes and six (17.6%) died from treatment related sequelae; five from  
34 second primary malignancy and one from end-stage renal failure. Of the five  
35 survivors who went on to die from second primary malignancy, three patients (all  
36 Level 2) had a meningioma, presumed to be secondary to low dose cranial  
37 irradiation as part of CNS directed therapy for the treatment of childhood ALL,  
38 one (Level 3) developed extensive intra-abdominal desmoid tumour having  
39 previously been treated for medulloblastoma and with a background of APC gene  
40 and Turcot's syndrome and the other patient (Level 3) developed AML presumed  
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3 to be related to previous topo-isomerase II inhibitor therapy for primary bone  
4 sarcoma (Figure 1).  
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10 Prevalence and severity of treatment related late effects were determined for  
11 each patient with an assigned level of follow up (n=607, Figures 3 and 4). Among  
12 Level 1 survivors (n=86), 11.6% (n=10) had late effects, of whom seven (8.1%)  
13 had one late effect and three (3.5%) had two late effects; 60% (n=6) of which  
14 were grade 1 toxicity, 30% (n=3) of whom were grade 2 toxicity and 10% (n=1)  
15 grade 3 toxicity. Within the Level 2 group (n=271), the prevalence of late effects  
16 was 35.8% (n=97), of whom 62 (22.9%) had 1 late effect, 23 (8.5%) had 2 late  
17 effects, 9 (3.3%) had 3 late effects and 3 (1.1%) had four late effects, of whom  
18 9.3% (n=9) had a maximum toxicity grade of 1, 58.8% (n=57) grade 2, 18.5%  
19 (n=18) grade 3, 10.3% (n=10) grade 4 and 3% (n=3) grade 5. The prevalence of  
20 late effects in the Level 3 survivors (n=250) was 65.2% (n=163) of whom 37  
21 (14.8%) had 1 late effect, 39 (15.6%) had 2 late effects, 22 (8.8%) had 3 late  
22 effects, 16 (6.4%) had 4 late effects and 46 (18.4%) had 5 or more late effects, of  
23 whom 9 (5.5%), 56 (34.4%), 59 (36.2%), 36 (22.1%) and 3 (1.8%) had grade  
24 1,2,3,4 and 5 toxicity respectively.  
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## 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.<sup>18</sup> However follow-up should be individually tailored and hospital based follow-up should not be necessary for all survivors.<sup>19</sup> The incidence of chronic conditions continues to increase with time and there is therefore no safe time after which these patients can be discharged.<sup>20</sup> 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.<sup>18,21</sup> 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

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3 mortality risk associated with treatment related complications that is present in  
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5 the 25 years after the initial cancer diagnosis.<sup>22</sup>  
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10 It is reported that up to 50% of long-term survivors do not attend Late Effects  
11 Clinics and many of these patients are considered to be at high risk of developing  
12 treatment-related late complications.<sup>23</sup> There are many reasons why survivors  
13 choose not to participate in long-term follow-up including lack of awareness of  
14 risks of late morbidity, desire to 'move on', lack of appropriate adult services and  
15 clinical discharge. In a study by Blaauwbroek et al they assessed late effects in a  
16 group of adult survivors of childhood cancer who were not involved in regular  
17 long-term follow-up and reported that almost 40% of survivors suffered from  
18 moderate to severe late effects and 33% had previously unknown late effects.<sup>24</sup>  
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20 This reiterates the need to educate survivors about their past medical history,  
21 their treatment and the importance of engaging in regular survivorship  
22 programmes.  
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41 Low rates of participation in long-term follow-up are universally reported. In 2004,  
42 a Delphi panel of 20 expert childhood cancer survivors in US identified a number  
43 of barriers contributing to this.<sup>25</sup> Understanding these barriers will lead to  
44 improved medical care for these patients. It was recognized that most childhood  
45 cancer survivors are not aware of their adverse health risks and often unaware of  
46 the details of their cancer or its treatment. Even where LTFU clinics are attended  
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3 transferred to the child. The Delphi Panel also highlighted the limitations within  
4 the health care setting including lack of LTFU service, discharge to primary care  
5 physician who lacks expertise in this field and often receive no communication  
6 about the child's past medical history. Improving communication between  
7 professionals and patients is essential and will be an integral part of development  
8 of survivorship programmes.  
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20 The traditional model of LTFU has been in paediatric oncology clinics, generally  
21 jointly with paediatric endocrinologists, neurologists and clinical oncologists, long  
22 into adulthood which brings with it the advantage of continuity of care, familiarity  
23 with treatments but there are a number of disadvantages to this system. This is  
24 not only an age appropriate environment for these patients, but also an  
25 unsustainable situation for paediatric oncologists, as the population of long-term  
26 survivors increase and age. In addition, survivors are protected in this paediatric  
27 environment and don't develop the skills necessary to navigate the health care  
28 system as they develop into adulthood. Ideally, once the long-term survivor  
29 reaches adulthood he/she should be transitioned into the appropriate adult late  
30 effects services. At present, such a service does not exist and it is difficult to  
31 identify which clinicians should take on this role, especially with increasing sub-  
32 specialisation in adult medicine. In a busy and overstretched tertiary oncology  
33 healthcare service, medical and clinical adult oncology consultants are unlikely to  
34 be in a position to take on this responsibility, and may well feel inadequately  
35 trained in caring for childhood cancer survivors. In current practice, the only adult  
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3 services supporting the long-term follow-up of those patients requiring specialist  
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5 hospital follow-up are the adult endocrine and neurology clinics.  
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11 It has been highlighted that improved communication of cancer information to  
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13 patients/families and between health care providers may contribute to greater  
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15 engagement in follow-up programmes, raises awareness of potential late effects  
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17 amongst survivors and enable clinicians to diagnose and, where possible, treat  
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19 late effects earlier. Based on national guidelines, we have developed a template  
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21 for the End of Treatment Summary and Individualised Care Plan, or 'Health  
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23 Passport', which has been introduced nationally, and welcomed by health  
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25 professionals and survivors.  
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33 Models of care for LTFU of survivors of childhood cancer must be flexible enough  
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35 to accommodate the needs of the young survivor as they transition throughout  
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37 their life cycle and also to accommodate the individual heterogeneity of cancer  
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39 survivors, reflecting the wide range of treatment exposure and adverse long-term  
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41 sequelae. Development of a service that can deliver individualized,  
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43 comprehensive, therapy-based patient centred care is essential.  
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49 The UK National Cancer Survivorship Initiative is currently exploring models of  
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51 aftercare services for children and young people who have been treated for  
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53 cancer. National pathways that identify how follow-up can be delivered in line  
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55 with current pressures and aspirations are being developed. Clinical risk  
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3 stratification will play an integral role in tailoring individualised care to meet the  
4 clinical, psychological and practical needs of each survivor. A recent study from  
5 the CCSS has reviewed how data derived from the CCSS have characterized  
6 specific groups that are deemed to be at highest risk of morbidity and subsequent  
7 cancers.<sup>26</sup> Our study has shown that those patients at highest risk of late  
8 morbidity can be identified and appropriately stratified into a high risk (level 3)  
9 follow-up programme.  
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22 Stratification of patients according to risk of late morbidity will maximise the use  
23 of health service resources and provide age appropriate care as locally as  
24 possible. With increasing time from completion of treatment, it is hoped that the  
25 majority of adult survivors will be independent and take responsibility for their  
26 own health, with health care support provided by their primary care physician. As  
27 a result, the primary care team is likely to play an increasing role in the long-term  
28 follow-up of survivors of childhood cancer. Primary care services may be already  
29 stretched but GPs are used to meeting targets and ensuring guidelines are  
30 implemented. Good communication between the hospital services and primary  
31 care will be essential. Early involvement of general practitioners in the Late  
32 Effects Services will establish collaborations between the two teams and enable  
33 primary Care Physicians to become familiar with the surveillance programme.  
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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

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3 patients would see their family doctor for long-term follow-up: the family doctors  
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5 were interested in sharing survivors' care; and family doctors would return the  
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7 necessary medical information needed for continued follow-up.<sup>27</sup> Appropriate  
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9 education of the family doctors, which has resource implications, was a key  
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11 finding of this study. More recently this group has shown that a web based  
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13 survivor care plan can facilitate the long-term care of survivors by family  
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15 doctors.<sup>28</sup>  
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22 In order to improve our understanding of treatment-related side effects and help  
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24 develop treatment protocols to minimise toxicity, lifelong monitoring of health and  
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26 well-being of all long-term survivors will be necessary. Our understanding of the  
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28 late effects of the treatment of Hodgkin's lymphoma has led to studies which are  
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30 ongoing and are designed to reduce the risk of second malignancy by avoiding  
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32 radiotherapy in selected cases and replace gonadotoxic chemotherapy with  
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34 drugs that are efficacious in Hodgkin's lymphoma but less likely to compromise  
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36 reproductive function.<sup>29</sup> Balancing safety and efficacy in the treatment of  
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38 Hodgkin's lymphoma remains an important goal in the treatment of this curable  
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40 malignancy.<sup>30</sup>  
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48 We have shown that it is possible to safely predict which survivors of childhood  
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50 cancer are at significant risk of developing moderate to severe late effects and  
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52 require moderate or high intensity long-term follow. Importantly we have also  
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54 shown that there is a group of survivors who can be reliably identified who can be  
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3 safely discharged from clinic based follow-up. Structured, risk-adapted follow-up  
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5 of childhood cancer survivors following evidence-based guidelines would reduce  
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7 cost ineffective or excessive evaluations and focus individual health care  
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9 delivery. Education of survivors and health care providers will hopefully reduce  
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11 the burden of chronic health problems and improve quality of life for the growing  
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13 population of children and young people who have been treated for cancer.  
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35 deceased patients.  
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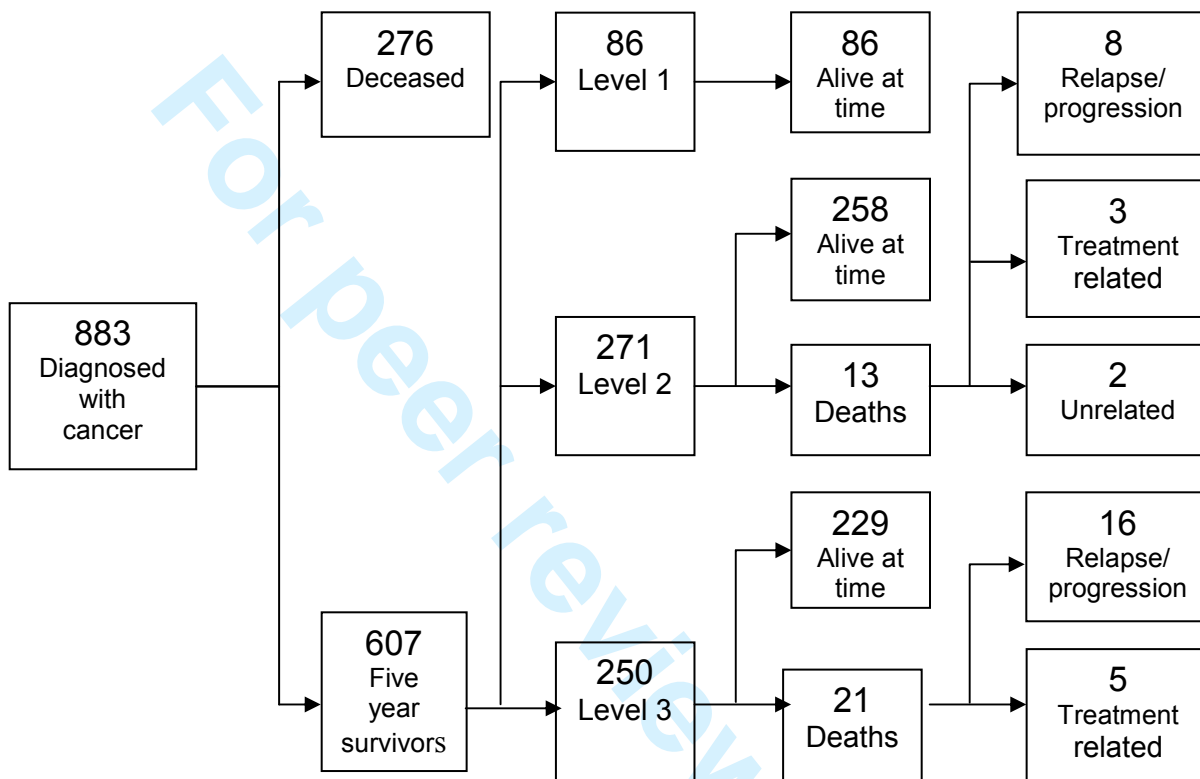
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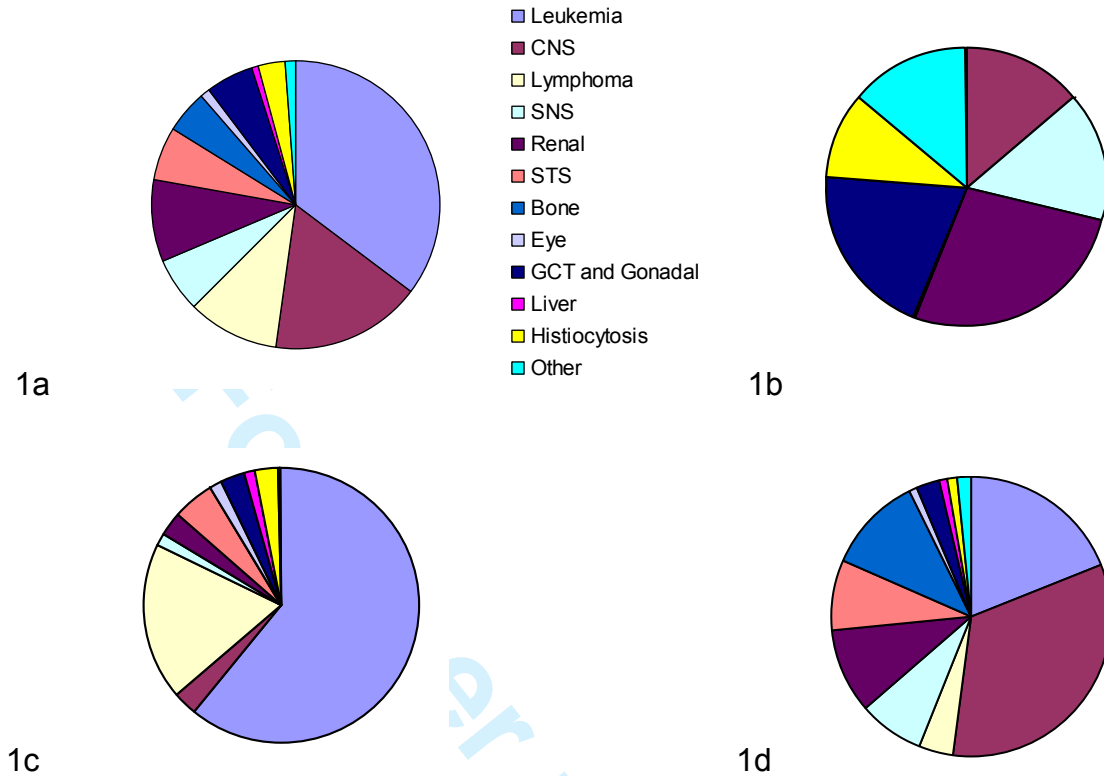
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**Figure 1. Study flow of childhood and teenage cancer patients.**

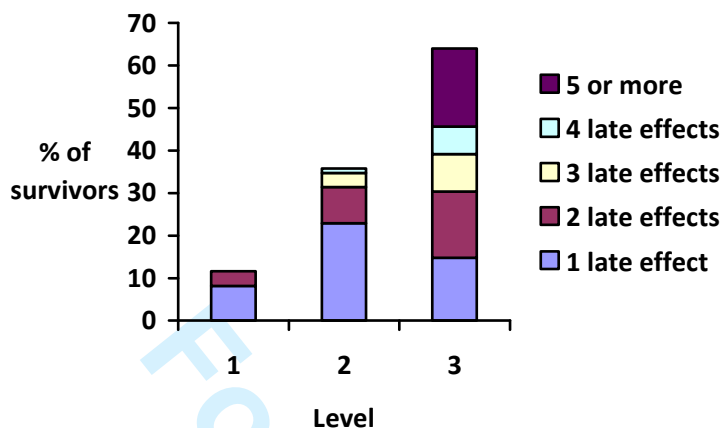
Flow chart shows the study population and the risk stratification of patients into Levels 1,2 and 3 and the proportion of patients alive at the time of the study.





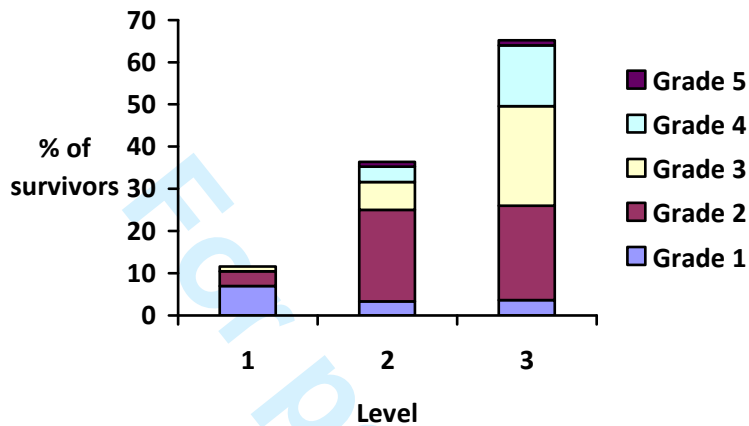
**Figure 2 Diagnoses of five year survivors (n=607)**

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).<sup>17</sup>

**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](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

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3 and revised the draft paper. SB designed data collection tools, monitored data  
4 collection for the study, analysed the data and revised the draft paper. PM-S  
5  
6 analysed the data and drafted and revised the paper. WHBW designed data  
7 collection tools, monitored data collection for the study, analysed the data, and  
8 drafted and revised the paper. All authors had full access to all of the data in the  
9 study and can take responsibility for the integrity of the data and the accuracy of  
10 the data analysis.  
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### 22 **Data sharing statement**

23  
24 Dataset available from the corresponding author at  
25 [angela.edgar@luht.scot.nhs.uk](mailto:angela.edgar@luht.scot.nhs.uk). Consent was not obtained but the presented  
26 data are anonymised and risk of identification is low.  
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### 34 **Ethical approval**

35  
36 Ethical approval for this study was requested from the Lothian Research Ethics  
37 Committee (LREC). On review by the LREC, the committee decided that ethical  
38 approval was not required as long-term follow-up of childhood cancer survivors  
39 was deemed to be an acceptable and routine part of clinical practice and there  
40 were no experimental interventions.  
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53 No specific funding was received for this research.  
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8 **Can Intensity of long-term follow-up for survivors of childhood and teenage**  
9 **cancer be ~~safely~~ determined by therapy-based risk-stratification?**

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11 Edgar AB<sup>1</sup>, Duffin K<sup>1</sup>, Borthwick S<sup>1</sup>, Marciniak-Stepak P<sup>2</sup>, Wallace WH<sup>1</sup>  
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46  
47 Key words: Childhood cancer, treatment, survival, cure, late effects, models of  
48 follow-up, long-term follow-up.  
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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.

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- 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.

### 18 **Limitations**

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- 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 1<sup>st</sup> January 1971-31<sup>st</sup> 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.<sup>1</sup> It is estimated that 1 in 640 young adults is a survivor of childhood cancer.<sup>2</sup> 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.<sup>3-5</sup> Late effects are diverse and include secondary malignancies, organ system damage, infertility, cognitive impairment, and disorders of growth and development.<sup>6, 7</sup> Appropriate LTFU of these patients is essential to detect, treat and prevent morbidity and mortality.<sup>8</sup>

There is wide variation of long-term follow-up practices throughout the UK with a propensity for hospital dependency, often in age-inappropriate settings.<sup>9</sup> A recent study has highlighted how excess morbidity in survivors translates into increased use of health care facilities.<sup>10</sup> 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.<sup>11</sup> 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

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8 intensity of follow-up<sup>8</sup>. In the UK, we published a Practice Statement 'Therapy  
9 Based Long-term Follow-up' which is designed to inform and guide clinicians  
10 responsible for the long-term follow-up of childhood cancer survivors.<sup>12</sup> The  
11 Practice Statement recommends follow-up assessments and investigations  
12 based on the treatment that the individual has received and is informed by the  
13 evidence-based recommendations published by SIGN 76.  
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22 An integrated and systematic approach is now considered a requirement of the  
23 National Institute of Health and Clinical Excellence (NIHCE) Improving Outcomes  
24 for Children and Young People with Cancer Guidance (2005) and National  
25 Delivery Plan for Children and Young People's Specialist Services in Scotland  
26 (2008).<sup>13,14</sup> In England, the National Cancer Survivorship Initiative (NCSI) has  
27 developed as a partnership between the Department of Health, Macmillan  
28 Cancer Support, and supported by NHS Improvement, to develop models of care  
29 to ensure that those living with and beyond cancer have access to safe and  
30 effective care and receive the support they need to lead as healthy and active a  
31 life as possible. Improved awareness of cancer survivorship as a chronic health  
32 problem will facilitate the development of care pathways that will meet the needs  
33 of every patient throughout their lifetime.<sup>15</sup>  
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46 Although there is growing guidance on whom, where and how long-term  
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48 stratified follow-up is safe is lacking. A recent study has shown that assigning  
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8 patients to one of three agreed levels of follow up, as described by Wallace et al,  
9 was relatively simple for experienced clinic staff.<sup>16</sup> The objective of this study was  
10 to evaluate the safety-feasibility and efficacy of this risk-based follow-up model by  
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12 | retrospectively stratifying an unselected cohort of long-term survivors of  
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14 childhood cancer from a single centre and objectively evaluating their health  
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## 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.<sup>8</sup> 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).<sup>17</sup> The CTCAEv3.0

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

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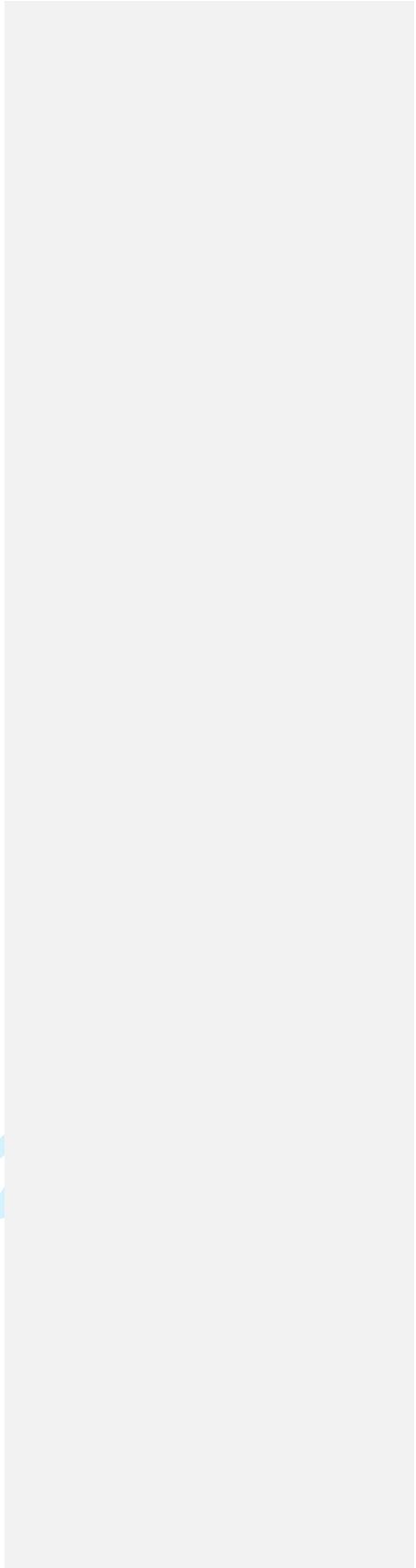
### 39 **Analysis**

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

### Study Population

883 patients were diagnosed with childhood and teenage cancer between 1<sup>st</sup> January 1971 to 1<sup>st</sup> 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

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8 (range) at diagnosis 5.1 (0.0-17.5) years. Of the cohort, 34 (5.6%) were  
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10 deceased, with a median overall survival (range) of 9.9 (5.0-30.9) years. Of the  
11  
12 573 long-term survivors alive at the time of the study, the median age (range)  
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14 was 19.4 (5.1-45.1) years and disease free survival (range) 11.3 (0.8-38.3) years  
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16 (Table 1). The primary cancer diagnosis is shown for all patients and within each  
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18 risk level (Figure 2). Risk-stratification of all long-term survivors (n=607) identified  
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20 86 (14.1%), 271 (44.6%) and 250 (41.2%) at Level 1, 2 and 3 respectively with  
21  
22 detailed breakdown of ages and survival interval for each level of patients alive at  
23  
24 the time of the study only (n=573), shown in Table 1 and Figure 1. Demographic  
25  
26 data is similar between the three populations.  
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### 29 **Adverse health outcomes according level of risk**

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31 Among the 34 deaths in the five year survivors (n=607), 26 (76.5%) died from  
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33 progression or relapse of the underlying primary cancer, two (5.9%) died from  
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35 unrelated causes and six (17.6%) died from treatment related sequelae; five from  
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37 second primary malignancy and one from end-stage renal failure. Of the five  
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39 survivors who went on to die from second primary malignancy, three patients (all  
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41 Level 2) had a meningioma, presumed to be secondary to low dose cranial  
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43 irradiation as part of CNS directed therapy for the treatment of childhood ALL,  
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45 one (Level 3) developed extensive intra-abdominal desmoid tumour having  
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47 previously been treated for medulloblastoma and with a background of APC gene  
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49 and Turcot's syndrome and the other patient (Level 3) developed AML presumed  
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8 to be related to previous topo-isomerase II inhibitor therapy for primary bone  
9 sarcoma (Figure 1).

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14 Prevalence and severity of treatment related late effects were determined for  
15 each patient with an assigned level of follow up (n=607, Figures 3 and 4). Among  
16 Level 1 survivors (n=86), 11.6% (n=10) had late effects, of whom seven (8.1%)  
17 had one late effect and three (3.5%) had two late effects; 60% (n=6) of which  
18 were grade 1 toxicity, 30% (n=3) of whom were grade 2 toxicity and 10% (n=1)  
19 grade 3 toxicity. Within the Level 2 group (n=271), the prevalence of late effects  
20 was 35.8% (n=97), of whom 62 (22.9%) had 1 late effect, 23 (8.5%) had 2 late  
21 effects, 9 (3.3%) had 3 late effects and 3 (1.1%) had four late effects, of whom  
22 9.3% (n=9) had a maximum toxicity grade of 1, 58.8% (n=57) grade 2, 18.5%  
23 (n=18) grade 3, 10.3% (n=10) grade 4 and 3% (n=3) grade 5. The prevalence of  
24 late effects in the Level 3 survivors (n=250) was 65.2% (n=163) of whom 37  
25 (14.8%) had 1 late effect, 39 (15.6%) had 2 late effects, 22 (8.8%) had 3 late  
26 effects, 16 (6.4%) had 4 late effects and 46 (18.4%) had 5 or more late effects, of  
27 whom 9 (5.5%), 56 (34.4%), 59 (36.2%), 36 (22.1%) and 3 (1.8%) had grade  
28 1,2,3,4 and 5 toxicity respectively.  
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## 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.<sup>18</sup> However follow-up should be individually tailored and hospital based follow-up should not be necessary for all survivors.<sup>19</sup> The incidence of chronic conditions continues to increase with time and there is therefore no safe time after which these patients can be discharged.<sup>20</sup> 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.<sup>18,21</sup> 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



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8 mortality risk associated with treatment related complications that is present in  
9 the 25 years after the initial cancer diagnosis.<sup>22</sup>  
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14 It is reported that up to 50% of long-term survivors do not attend Late Effects  
15 Clinics and many of these patients are considered to be at high risk of developing  
16 treatment-related late complications.<sup>23</sup> There are many reasons why survivors  
17 choose not to participate in long-term follow-up including lack of awareness of  
18 risks of late morbidity, desire to 'move on', lack of appropriate adult services and  
19 clinical discharge. In a study by Blaauwbroek et al they assessed late effects in a  
20 group of adult survivors of childhood cancer who were not involved in regular  
21 long-term follow-up and reported that almost 40% of survivors suffered from  
22 moderate to severe late effects and 33% had previously unknown late effects.<sup>24</sup>  
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24 This reiterates the need to educate survivors about their past medical history,  
25 their treatment and the importance of engaging in regular survivorship  
26 programmes.  
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39 Low rates of participation in long-term follow-up are universally reported. In 2004,  
40 a Delphi panel of 20 expert childhood cancer survivors in US identified a number  
41 of barriers contributing to this.<sup>25</sup> Understanding these barriers will lead to  
42 improved medical care for these patients. It was recognized that most childhood  
43 cancer survivors are not aware of their adverse health risks and often unaware of  
44 the details of their cancer or its treatment. Even where LTFU clinics are attended  
45 much of the education of late effects was directed at parents and often not  
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8 transferred to the child. The Delphi Panel also highlighted the limitations within  
9 the health care setting including lack of LTFU service, discharge to primary care  
10 physician who lacks expertise in this field and often receive no communication  
11 about the child's past medical history. Improving communication between  
12 professionals and patients is essential and will be an integral part of development  
13 of survivorship programmes.  
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21 The traditional model of LTFU has been in paediatric oncology clinics, generally  
22 jointly with paediatric endocrinologists, neurologists and clinical oncologists, long  
23 into adulthood which brings with it the advantage of continuity of care, familiarity  
24 with treatments but there are a number of disadvantages to this system. This is  
25 not only an age appropriate environment for these patients, but also an  
26 unsustainable situation for paediatric oncologists, as the population of long-term  
27 survivors increase and age. In addition, survivors are protected in this paediatric  
28 environment and don't develop the skills necessary to navigate the health care  
29 system as they develop into adulthood. Ideally, once the long-term survivor  
30 reaches adulthood he/she should be transitioned into the appropriate adult late  
31 effects services. At present, such a service does not exist and it is difficult to  
32 identify which clinicians should take on this role, especially with increasing sub-  
33 specialisation in adult medicine. In a busy and overstretched tertiary oncology  
34 healthcare service, medical and clinical adult oncology consultants are unlikely to  
35 be in a position to take on this responsibility, and may well feel inadequately  
36 trained in caring for childhood cancer survivors. In current practice, the only adult  
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8 services supporting the long-term follow-up of those patients requiring specialist  
9 hospital follow-up are the adult endocrine and neurology clinics.

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14 It has been highlighted that improved communication of cancer information to  
15 patients/families and between health care providers may contribute to greater  
16 engagement in follow-up programmes, raises awareness of potential late effects  
17 amongst survivors and enable clinicians to diagnose and, where possible, treat  
18 late effects earlier. Based on national guidelines, we have developed a template  
19 for the End of Treatment Summary and Individualised Care Plan, or 'Health  
20 Passport', which has been introduced nationally, and welcomed by health  
21 professionals and survivors.  
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31 Models of care for LTFU of survivors of childhood cancer must be flexible enough  
32 to accommodate the needs of the young survivor as they transition throughout  
33 their life cycle and also to accommodate the individual heterogeneity of cancer  
34 survivors, reflecting the wide range of treatment exposure and adverse long-term  
35 sequelae. Development of a service that can deliver individualized,  
36 comprehensive, therapy-based patient centred care is essential.  
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45 The UK National Cancer Survivorship Initiative is currently exploring models of  
46 aftercare services for children and young people who have been treated for  
47 cancer. National pathways that identify how follow-up can be delivered in line  
48 with current pressures and aspirations are being developed. Clinical risk  
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8 stratification will play an integral role in tailoring individualised care to meet the  
9 clinical, psychological and practical needs of each survivor. A recent study from  
10 the CCSS has reviewed how data derived from the CCSS have characterized  
11 specific groups that are deemed to be at highest risk of morbidity and subsequent  
12 cancers.<sup>26</sup> Our study has shown that those patients at highest risk of late  
13 morbidity can be identified and appropriately stratified into a high risk (level 3)  
14 follow-up programme.  
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23 Stratification of patients according to risk of late morbidity will maximise the use  
24 of health service resources and provide age appropriate care as locally as  
25 possible. With increasing time from completion of treatment, it is hoped that the  
26 majority of adult survivors will be independent and take responsibility for their  
27 own health, with health care support provided by their primary care physician. As  
28 a result, the primary care team is likely to play an increasing role in the long-term  
29 follow-up of survivors of childhood cancer. Primary care services may be already  
30 stretched but GPs are used to meeting targets and ensuring guidelines are  
31 implemented. Good communication between the hospital services and primary  
32 care will be essential. Early involvement of general practitioners in the Late  
33 Effects Services will establish collaborations between the two teams and enable  
34 primary Care Physicians to become familiar with the surveillance programme.  
35 The feasibility of a shared-care model between cancer paediatric oncology  
36 cancer centres and primary-care doctors to deliver survivor-focused risk based  
37 health care was tested successfully by a Dutch group. The study showed that  
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8 patients would see their family doctor for long-term follow-up: the family doctors  
9 were interested in sharing survivors' care; and family doctors would return the  
10 necessary medical information needed for continued follow-up.<sup>27</sup> Appropriate  
11 education of the family doctors, which has resource implications, was a key  
12 finding of this study. More recently this group has shown that a web based  
13 survivor care plan can facilitate the long-term care of survivors by family  
14 doctors.<sup>28</sup>

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

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

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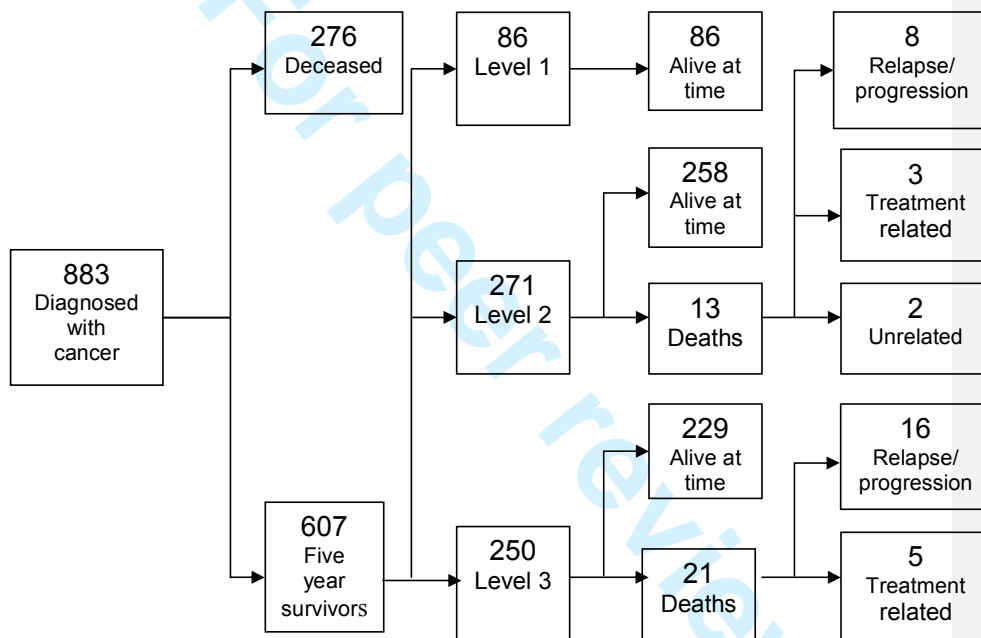


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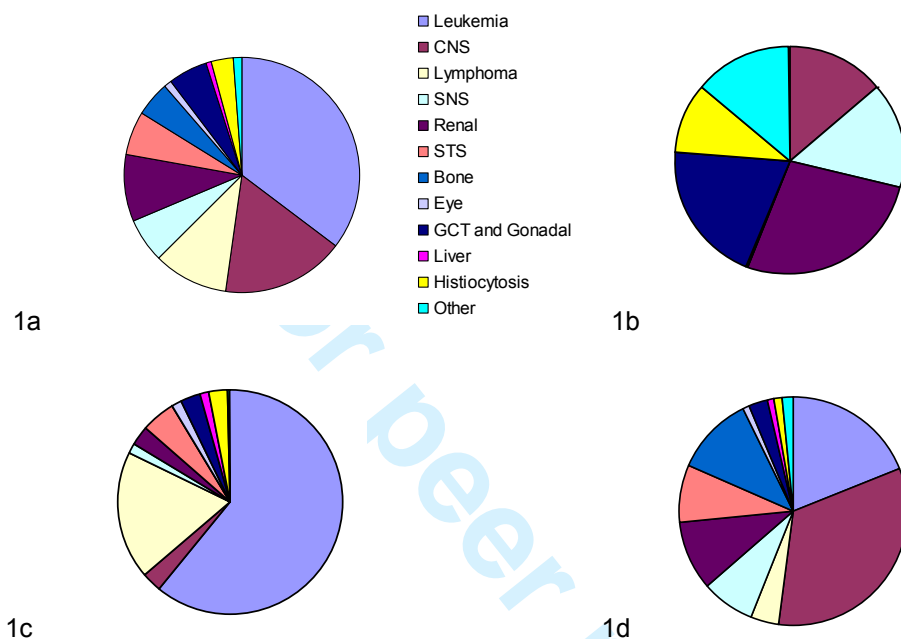
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**Figure 1. Study flow of childhood and teenage cancer patients.**

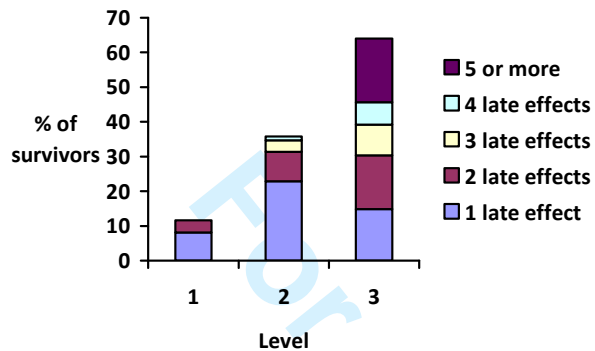
Flow chart shows the study population and the risk stratification of patients into Levels 1,2 and 3 and the proportion of patients alive at the time of the study.



**Figure 2 Diagnoses of five year survivors (n=607)**

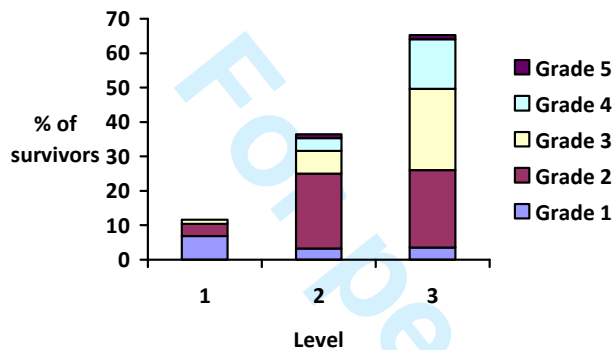
1a. All survivors (n=607), 1b. Level 1 (n= 86), 1c. Level 2 (n=271), 1d. Level 3 (n=250). Abbreviations: CNS – central nervous system tumours, SNS – sympathetic nervous system tumours, GCT – germ cell tumours, STS – soft tissue sarcomas

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**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).<sup>17</sup>

**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](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

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8 and revised the draft paper. SB designed data collection tools, monitored data  
9 collection for the study, analysed the data and revised the draft paper. PM-S  
10 analysed the data and drafted and revised the paper. WHBW designed data  
11 collection tools, monitored data collection for the study, analysed the data, and  
12 drafted and revised the paper. All authors had full access to all of the data in the  
13 study and can take responsibility for the integrity of the data and the accuracy of  
14 the data analysis.  
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#### 24 **Data sharing statement**

25 Dataset available from the corresponding author at  
26 [angela.edgar@luht.scot.nhs.uk](mailto:angela.edgar@luht.scot.nhs.uk). Consent was not obtained but the presented  
27 data are anonymised and risk of identification is low.  
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#### 33 **Ethical approval**

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

47 No specific funding was received for this research.  
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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
<b>Introduction</b>			
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
<b>Methods</b>			
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	
<b>Results</b>			

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	
<b>Discussion</b>			
Key results	18	Summarise key results with reference to study objectives	15
<b>Limitations</b>			
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
<b>Other information</b>			
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](http://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?**

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2012-002451.R2
Article Type:	Research
Date Submitted by the Author:	04-May-2013
Complete List of Authors:	Edgar, Angela; Royal Hospital for Sick Children , Paediatric Oncology Duffin, Kathleen; Royal Hospital for Sick Children, Paediatric Oncology Borthwick, Stephen; Royal Hospital for Sick Children, Paediatric Oncology Marciniak-Stępak, Patrycja; Poznan University of Medical Sciences, 2Department of Paediatric Oncology Wallace, w. Hamish; Royal Hospital for Sick Children, Paediatric Oncology
<b>Primary Subject Heading</b>:	Oncology
Secondary Subject Heading:	Paediatrics, Patient-centred medicine
Keywords:	Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Risk management < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Paediatric oncology < ONCOLOGY

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3 **Can Intensity of long-term follow-up for survivors of childhood and teenage**  
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5 **cancer be safely determined by therapy-based risk-stratification?**  
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8 Edgar AB<sup>1</sup>, Duffin K<sup>1</sup>, Borthwick S<sup>1</sup>, Marciniak-Stepak P<sup>2</sup>, Wallace WH<sup>1</sup>  
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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.



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- 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.

### 15 **Limitations**

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- 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 1<sup>st</sup> January 1971-31<sup>st</sup> 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

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3 607 five-year survivors were identified. Risk-stratification identified 86 (14.2%),  
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5 271 (44.6%) and 250 (41.2%) level 1, 2 and 3 survivors respectively. The  
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7 prevalence of late effects (LE) for level 1 survivors was 11.6% with only 1 patient  
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9 with grade 3 or above toxicity. 35.8% of level 2 survivors had a LE, of whom  
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11 9.3%, 58.8%, 18.5%, 10.3% and 3% had grade 1, 2, 3, 4 and 5 toxicity  
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13 respectively. 65.2 % of level 3 survivors had LE), of whom 5.5% (n=9), 34.4%  
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15 (n=56), 36.2% (n=59), 22.1% (n=36) and 1.8% (n=3) had grade 1,2,3,4 and 5  
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17 toxicity respectively.  
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## 24 **Conclusions**

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27 Therapy-based, risk-stratification of survivors can safely predict which patients  
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29 are at significant risk of developing moderate to severe late effects and require  
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31 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.<sup>1</sup> It is estimated that 1 in 640 young adults is a survivor of childhood cancer.<sup>2</sup> 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.<sup>3-5</sup> Late effects are diverse and include secondary malignancies, organ system damage, infertility, cognitive impairment, and disorders of growth and development.<sup>6, 7</sup> Appropriate LTFU of these patients is essential to detect, treat and prevent morbidity and mortality.<sup>8</sup>

There is wide variation of long-term follow-up practices throughout the UK with a propensity for hospital dependency, often in age-inappropriate settings.<sup>9</sup> A recent study has highlighted how excess morbidity in survivors translates into increased use of health care facilities.<sup>10</sup> 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.<sup>11</sup> 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

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3 intensity of follow-up<sup>8</sup>. In the UK, we published a Practice Statement 'Therapy  
4 Based Long-term Follow-up' which is designed to inform and guide clinicians  
5 responsible for the long-term follow-up of childhood cancer survivors.<sup>12</sup> The  
6 Practice Statement recommends follow-up assessments and investigations  
7 based on the treatment that the individual has received and is informed by the  
8 evidence-based recommendations published by SIGN 76.  
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20 An integrated and systematic approach is now considered a requirement of the  
21 National Institute of Health and Clinical Excellence (NIHCE) Improving Outcomes  
22 for Children and Young People with Cancer Guidance (2005) and National  
23 Delivery Plan for Children and Young People's Specialist Services in Scotland  
24 (2008).<sup>13,14</sup> In England, the National Cancer Survivorship Initiative (NCSI) has  
25 developed as a partnership between the Department of Health, Macmillan  
26 Cancer Support, and supported by NHS Improvement, to develop models of care  
27 to ensure that those living with and beyond cancer have access to safe and  
28 effective care and receive the support they need to lead as healthy and active a  
29 life as possible. Improved awareness of cancer survivorship as a chronic health  
30 problem will facilitate the development of care pathways that will meet the needs  
31 of every patient throughout their lifetime.<sup>15</sup>  
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50 Although there is growing guidance on whom, where and how long-term  
51 survivors should be followed-up, evidence to show that adopting a model of risk-  
52 stratified follow-up is safe is lacking. A recent study has shown that assigning  
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3 patients to one of three agreed levels of follow up, as described by Wallace et al,  
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5 was relatively simple for experienced clinic staff.<sup>16</sup> The objective of this study was  
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7 to evaluate the safety and efficacy of this risk-based follow-up model by  
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9 retrospectively stratifying an unselected cohort of long-term survivors of  
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11 childhood cancer from a single centre and objectively evaluating their health  
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## 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-

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

38 To determine the severity of late effects, each reported late effect was graded  
39 independently by two of the authors using the Common Terminology Criteria for  
40 Adverse Events, Version 3.0 (CTCAEv3.0, available at  
41 <http://ctep.cancer.gov/forms/CTCAEv3.pdf>), a scoring system developed through  
42 the US National Cancer Institute by a multidisciplinary group and adopted in the  
43 UK by the Children's Cancer and Leukaemia Group (CCLG).<sup>17</sup> The CTCAEv3.0  
44 tool can be used for acute and chronic conditions in patients with cancer and  
45 grades conditions as mild (grade 1), moderate (grade 2), severe (grade 3), life-  
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3 threatening or disabling (grade 4), or adverse event-related death (grade 5). To  
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5 investigate and reduce inter-observer variability, graded adverse events were  
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7 compared and inconsistencies were discussed and detailed coding rules were  
8  
9 developed (available on request from the authors). Inconsistencies in grading  
10  
11 revolved mainly around scoring subjective psychosocial and neuropsychological  
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13 items of grade 1 or 2, grading of 3 or higher adverse events was straightforward.  
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### 20 **Ethical Approval**

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22 Ethical approval for this study was requested from the Lothian Research Ethics  
23  
24 Committee (LREC). On review by the LREC, the committee decided that ethical  
25  
26 approval was not required as long-term follow-up of childhood cancer survivors  
27  
28 was deemed to be an acceptable and routine part of clinical practice and there  
29  
30 were no experimental interventions.  
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### 37 **Analysis**

38  
39 The statistical package for social sciences (SPSS) Windows version 14.0 was  
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41 used for the statistical analyses. Data were analyzed by descriptive techniques  
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43 using frequencies, percentages and medians as appropriate.  
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## Results

### Study Population

883 patients were diagnosed with childhood and teenage cancer between 1<sup>st</sup> January 1971 to 1<sup>st</sup> 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-

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

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31 Among the 34 deaths in the five year survivors (n=607), 26 (76.5%) died from  
32 progression or relapse of the underlying primary cancer, two (5.9%) died from  
33 unrelated causes and six (17.6%) died from treatment related sequelae; five from  
34 second primary malignancy and one from end-stage renal failure. Of the five  
35 survivors who went on to die from second primary malignancy, three patients (all  
36 Level 2) had a meningioma, presumed to be secondary to low dose cranial  
37 irradiation as part of CNS directed therapy for the treatment of childhood ALL,  
38 one (Level 3) developed extensive intra-abdominal desmoid tumour having  
39 previously been treated for medulloblastoma and with a background of APC gene  
40 and Turcot's syndrome and the other patient (Level 3) developed AML presumed  
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3 to be related to previous topo-isomerase II inhibitor therapy for primary bone  
4 sarcoma (Figure 1).  
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10 Prevalence and severity of treatment related late effects were determined for  
11 each patient with an assigned level of follow up (n=607, Figures 3 and 4). Among  
12 Level 1 survivors (n=86), 11.6% (n=10) had late effects, of whom seven (8.1%)  
13 had one late effect and three (3.5%) had two late effects; 60% (n=6) of which  
14 were grade 1 toxicity, 30% (n=3) of whom were grade 2 toxicity and 10% (n=1)  
15 grade 3 toxicity. Within the Level 2 group (n=271), the prevalence of late effects  
16 was 35.8% (n=97), of whom 62 (22.9%) had 1 late effect, 23 (8.5%) had 2 late  
17 effects, 9 (3.3%) had 3 late effects and 3 (1.1%) had four late effects, of whom  
18 9.3% (n=9) had a maximum toxicity grade of 1, 58.8% (n=57) grade 2, 18.5%  
19 (n=18) grade 3, 10.3% (n=10) grade 4 and 3% (n=3) grade 5. The prevalence of  
20 late effects in the Level 3 survivors (n=250) was 65.2% (n=163) of whom 37  
21 (14.8%) had 1 late effect, 39 (15.6%) had 2 late effects, 22 (8.8%) had 3 late  
22 effects, 16 (6.4%) had 4 late effects and 46 (18.4%) had 5 or more late effects, of  
23 whom 9 (5.5%), 56 (34.4%), 59 (36.2%), 36 (22.1%) and 3 (1.8%) had grade  
24 1,2,3,4 and 5 toxicity respectively.  
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## 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.<sup>18</sup> However follow-up should be individually tailored and hospital based follow-up should not be necessary for all survivors.<sup>19</sup> The incidence of chronic conditions continues to increase with time and there is therefore no safe time after which these patients can be discharged.<sup>20</sup> 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.<sup>18,21</sup> 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

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3 mortality risk associated with treatment related complications that is present in  
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5 the 25 years after the initial cancer diagnosis.<sup>22</sup>  
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10 It is reported that up to 50% of long-term survivors do not attend Late Effects  
11 Clinics and many of these patients are considered to be at high risk of developing  
12 treatment-related late complications.<sup>23</sup> There are many reasons why survivors  
13 choose not to participate in long-term follow-up including lack of awareness of  
14 risks of late morbidity, desire to 'move on', lack of appropriate adult services and  
15 clinical discharge. In a study by Blaauwbroek et al they assessed late effects in a  
16 group of adult survivors of childhood cancer who were not involved in regular  
17 long-term follow-up and reported that almost 40% of survivors suffered from  
18 moderate to severe late effects and 33% had previously unknown late effects.<sup>24</sup>  
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20 This reiterates the need to educate survivors about their past medical history,  
21 their treatment and the importance of engaging in regular survivorship  
22 programmes.  
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41 Low rates of participation in long-term follow-up are universally reported. In 2004,  
42 a Delphi panel of 20 expert childhood cancer survivors in US identified a number  
43 of barriers contributing to this.<sup>25</sup> Understanding these barriers will lead to  
44 improved medical care for these patients. It was recognized that most childhood  
45 cancer survivors are not aware of their adverse health risks and often unaware of  
46 the details of their cancer or its treatment. Even where LTFU clinics are attended  
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3 transferred to the child. The Delphi Panel also highlighted the limitations within  
4 the health care setting including lack of LTFU service, discharge to primary care  
5 physician who lacks expertise in this field and often receive no communication  
6 about the child's past medical history. Improving communication between  
7 professionals and patients is essential and will be an integral part of development  
8 of survivorship programmes.  
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20 The traditional model of LTFU has been in paediatric oncology clinics, generally  
21 jointly with paediatric endocrinologists, neurologists and clinical oncologists, long  
22 into adulthood which brings with it the advantage of continuity of care, familiarity  
23 with treatments but there are a number of disadvantages to this system. This is  
24 not only an age appropriate environment for these patients, but also an  
25 unsustainable situation for paediatric oncologists, as the population of long-term  
26 survivors increase and age. In addition, survivors are protected in this paediatric  
27 environment and don't develop the skills necessary to navigate the health care  
28 system as they develop into adulthood. Ideally, once the long-term survivor  
29 reaches adulthood he/she should be transitioned into the appropriate adult late  
30 effects services. At present, such a service does not exist and it is difficult to  
31 identify which clinicians should take on this role, especially with increasing sub-  
32 specialisation in adult medicine. In a busy and overstretched tertiary oncology  
33 healthcare service, medical and clinical adult oncology consultants are unlikely to  
34 be in a position to take on this responsibility, and may well feel inadequately  
35 trained in caring for childhood cancer survivors. In current practice, the only adult  
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3 services supporting the long-term follow-up of those patients requiring specialist  
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5 hospital follow-up are the adult endocrine and neurology clinics.  
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10 It has been highlighted that improved communication of cancer information to  
11 patients/families and between health care providers may contribute to greater  
12 engagement in follow-up programmes, raises awareness of potential late effects  
13 amongst survivors and enable clinicians to diagnose and, where possible, treat  
14 late effects earlier. Based on national guidelines, we have developed a template  
15 for the End of Treatment Summary and Individualised Care Plan, or 'Health  
16 Passport', which has been introduced nationally, and welcomed by health  
17 professionals and survivors.  
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32 Models of care for LTFU of survivors of childhood cancer must be flexible enough  
33 to accommodate the needs of the young survivor as they transition throughout  
34 their life cycle and also to accommodate the individual heterogeneity of cancer  
35 survivors, reflecting the wide range of treatment exposure and adverse long-term  
36 sequelae. Development of a service that can deliver individualized,  
37 comprehensive, therapy-based patient centred care is essential.  
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48 The UK National Cancer Survivorship Initiative is currently exploring models of  
49 aftercare services for children and young people who have been treated for  
50 cancer. National pathways that identify how follow-up can be delivered in line  
51 with current pressures and aspirations are being developed. Clinical risk  
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3 stratification will play an integral role in tailoring individualised care to meet the  
4 clinical, psychological and practical needs of each survivor. A recent study from  
5 the CCSS has reviewed how data derived from the CCSS have characterized  
6 specific groups that are deemed to be at highest risk of morbidity and subsequent  
7 cancers.<sup>26</sup> Our study has shown that those patients at highest risk of late  
8 morbidity can be identified and appropriately stratified into a high risk (level 3)  
9 follow-up programme.  
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22 Stratification of patients according to risk of late morbidity will maximise the use  
23 of health service resources and provide age appropriate care as locally as  
24 possible. With increasing time from completion of treatment, it is hoped that the  
25 majority of adult survivors will be independent and take responsibility for their  
26 own health, with health care support provided by their primary care physician. As  
27 a result, the primary care team is likely to play an increasing role in the long-term  
28 follow-up of survivors of childhood cancer. Primary care services may be already  
29 stretched but GPs are used to meeting targets and ensuring guidelines are  
30 implemented. Good communication between the hospital services and primary  
31 care will be essential. Early involvement of general practitioners in the Late  
32 Effects Services will establish collaborations between the two teams and enable  
33 primary Care Physicians to become familiar with the surveillance programme.  
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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

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3 patients would see their family doctor for long-term follow-up: the family doctors  
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5 were interested in sharing survivors' care; and family doctors would return the  
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7 necessary medical information needed for continued follow-up.<sup>27</sup> Appropriate  
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9 education of the family doctors, which has resource implications, was a key  
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11 finding of this study. More recently this group has shown that a web based  
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13 survivor care plan can facilitate the long-term care of survivors by family  
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15 doctors.<sup>28</sup>  
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22 In order to improve our understanding of treatment-related side effects and help  
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24 develop treatment protocols to minimise toxicity, lifelong monitoring of health and  
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26 well-being of all long-term survivors will be necessary. Our understanding of the  
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28 late effects of the treatment of Hodgkin's lymphoma has led to studies which are  
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30 ongoing and are designed to reduce the risk of second malignancy by avoiding  
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32 radiotherapy in selected cases and replace gonadotoxic chemotherapy with  
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34 drugs that are efficacious in Hodgkin's lymphoma but less likely to compromise  
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36 reproductive function.<sup>29</sup> Balancing safety and efficacy in the treatment of  
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38 Hodgkin's lymphoma remains an important goal in the treatment of this curable  
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40 malignancy.<sup>30</sup>  
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48 We have shown that it is possible to safely predict which survivors of childhood  
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50 cancer are at significant risk of developing moderate to severe late effects and  
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52 require moderate or high intensity long-term follow. Importantly we have also  
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54 shown that there is a group of survivors who can be reliably identified who can be  
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3 safely discharged from clinic based follow-up. Structured, risk-adapted follow-up  
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5 of childhood cancer survivors following evidence-based guidelines would reduce  
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7 cost ineffective or excessive evaluations and focus individual health care  
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9 delivery. Education of survivors and health care providers will hopefully reduce  
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11 the burden of chronic health problems and improve quality of life for the growing  
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13 population of children and young people who have been treated for cancer.  
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### 27 **Acknowledgements**

28  
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32  
33 NHS National Services Scotland, for providing valuable information on the  
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35 deceased patients.  
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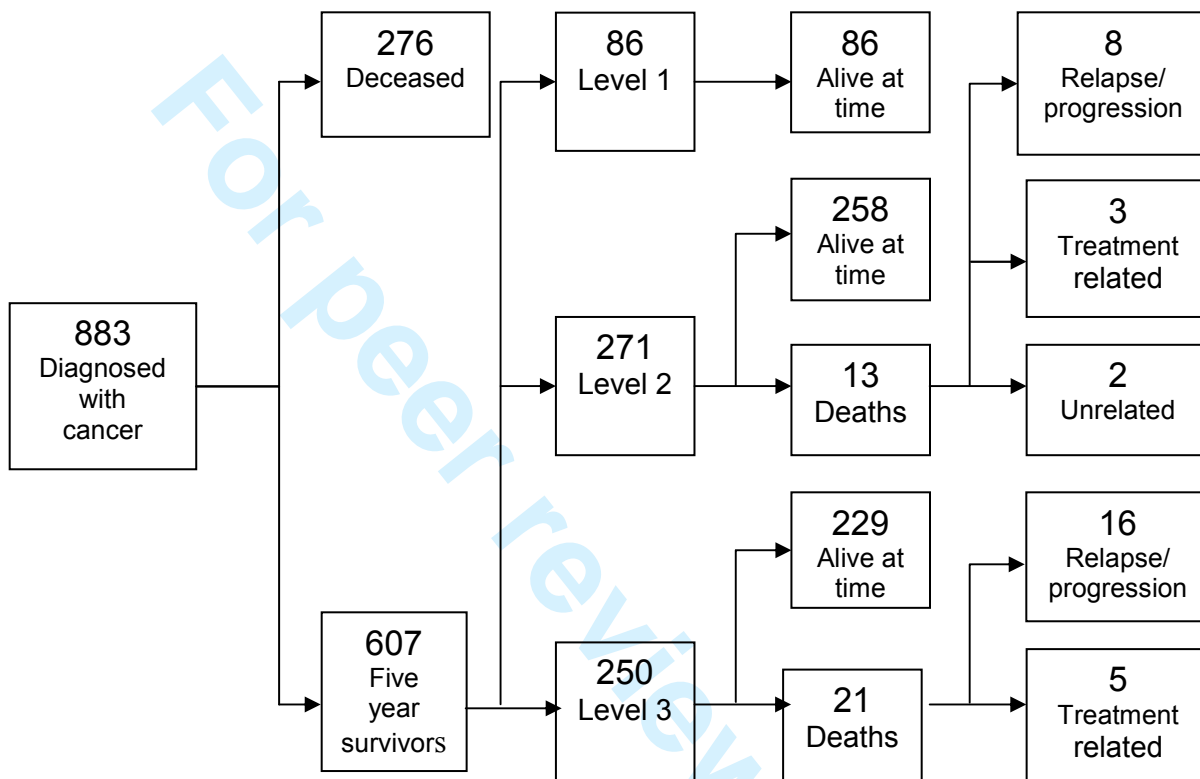
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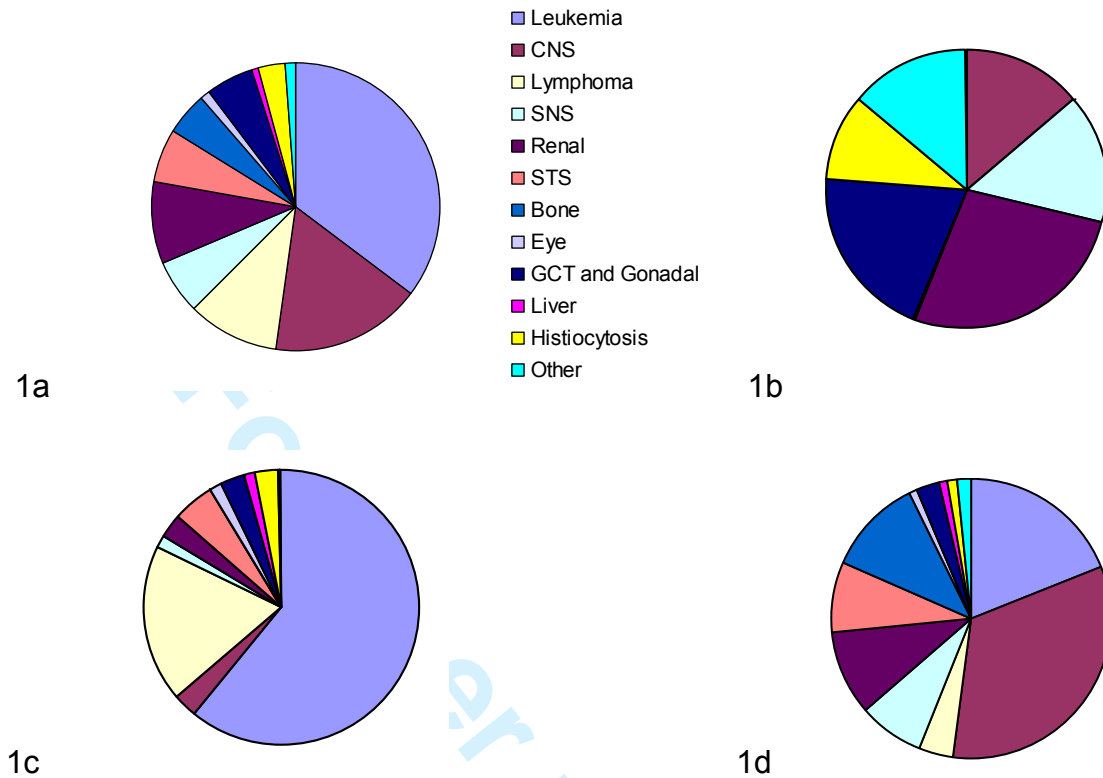
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**Figure 1. Study flow of childhood and teenage cancer patients.**

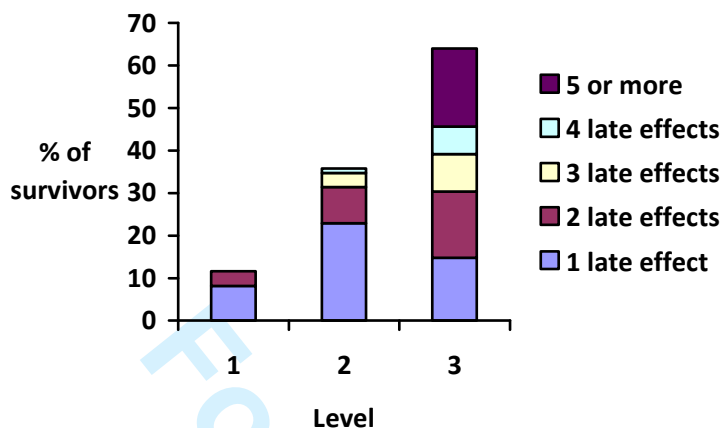
Flow chart shows the study population and the risk stratification of patients into Levels 1,2 and 3 and the proportion of patients alive at the time of the study.





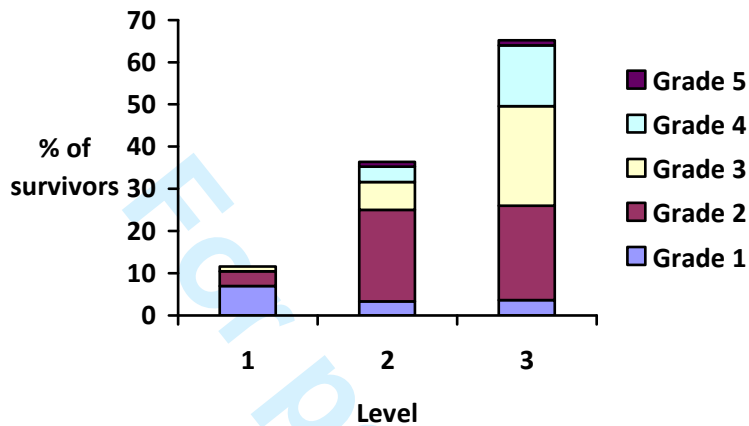
**Figure 2 Diagnoses of five year survivors (n=607)**

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).<sup>17</sup>

**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](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

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2  
3 and revised the draft paper. SB designed data collection tools, monitored data  
4 collection for the study, analysed the data and revised the draft paper. PM-S  
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6 analysed the data and drafted and revised the paper. WHBW designed data  
7 collection tools, monitored data collection for the study, analysed the data, and  
8 drafted and revised the paper. All authors had full access to all of the data in the  
9 study and can take responsibility for the integrity of the data and the accuracy of  
10 the data analysis.  
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### 22 **Data sharing statement**

23  
24 Dataset available from the corresponding author at  
25 [angela.edgar@luht.scot.nhs.uk](mailto:angela.edgar@luht.scot.nhs.uk). Consent was not obtained but the presented  
26 data are anonymised and risk of identification is low.  
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### 34 **Ethical approval**

35  
36 Ethical approval for this study was requested from the Lothian Research Ethics  
37 Committee (LREC). On review by the LREC, the committee decided that ethical  
38 approval was not required as long-term follow-up of childhood cancer survivors  
39 was deemed to be an acceptable and routine part of clinical practice and there  
40 were no experimental interventions.  
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### 51 **Funding**

52  
53 No specific funding was received for this research.  
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8 **Can Intensity of long-term follow-up for survivors of childhood and teenage**  
9 **cancer be ~~safely~~ determined by therapy-based risk-stratification?**

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11 Edgar AB<sup>1</sup>, Duffin K<sup>1</sup>, Borthwick S<sup>1</sup>, Marciniak-Stepak P<sup>2</sup>, Wallace WH<sup>1</sup>  
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46  
47 Key words: Childhood cancer, treatment, survival, cure, late effects, models of  
48 follow-up, long-term follow-up.  
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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.

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- 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.

### 18 Limitations

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- 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 1<sup>st</sup> January 1971-31<sup>st</sup> 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**

BMJ.2012.008737

## 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.<sup>1</sup> It is estimated that 1 in 640 young adults is a survivor of childhood cancer.<sup>2</sup> 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.<sup>3-5</sup> Late effects are diverse and include secondary malignancies, organ system damage, infertility, cognitive impairment, and disorders of growth and development.<sup>6, 7</sup> Appropriate LTFU of these patients is essential to detect, treat and prevent morbidity and mortality.<sup>8</sup>

There is wide variation of long-term follow-up practices throughout the UK with a propensity for hospital dependency, often in age-inappropriate settings.<sup>9</sup> A recent study has highlighted how excess morbidity in survivors translates into increased use of health care facilities.<sup>10</sup> 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.<sup>11</sup> 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

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8 intensity of follow-up<sup>8</sup>. In the UK, we published a Practice Statement 'Therapy  
9 Based Long-term Follow-up' which is designed to inform and guide clinicians  
10 responsible for the long-term follow-up of childhood cancer survivors.<sup>12</sup> The  
11 Practice Statement recommends follow-up assessments and investigations  
12 based on the treatment that the individual has received and is informed by the  
13 evidence-based recommendations published by SIGN 76.  
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21 An integrated and systematic approach is now considered a requirement of the  
22 National Institute of Health and Clinical Excellence (NIHCE) Improving Outcomes  
23 for Children and Young People with Cancer Guidance (2005) and National  
24 Delivery Plan for Children and Young People's Specialist Services in Scotland  
25 (2008).<sup>13,14</sup> In England, the National Cancer Survivorship Initiative (NCSI) has  
26 developed as a partnership between the Department of Health, Macmillan  
27 Cancer Support, and supported by NHS Improvement, to develop models of care  
28 to ensure that those living with and beyond cancer have access to safe and  
29 effective care and receive the support they need to lead as healthy and active a  
30 life as possible. Improved awareness of cancer survivorship as a chronic health  
31 problem will facilitate the development of care pathways that will meet the needs  
32 of every patient throughout their lifetime.<sup>15</sup>  
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47 Although there is growing guidance on whom, where and how long-term  
48 survivors should be followed-up, evidence to show that adopting a model of risk-  
49 stratified follow-up is safe is lacking. A recent study has shown that assigning  
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8 patients to one of three agreed levels of follow up, as described by Wallace et al,  
9 was relatively simple for experienced clinic staff.<sup>16</sup> The objective of this study was  
10 to evaluate the safety-feasibility and efficacy of this risk-based follow-up model by  
11  
12 | retrospectively stratifying an unselected cohort of long-term survivors of  
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14 childhood cancer from a single centre and objectively evaluating their health  
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## 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.<sup>8</sup> 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).<sup>17</sup> The CTCAEv3.0

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

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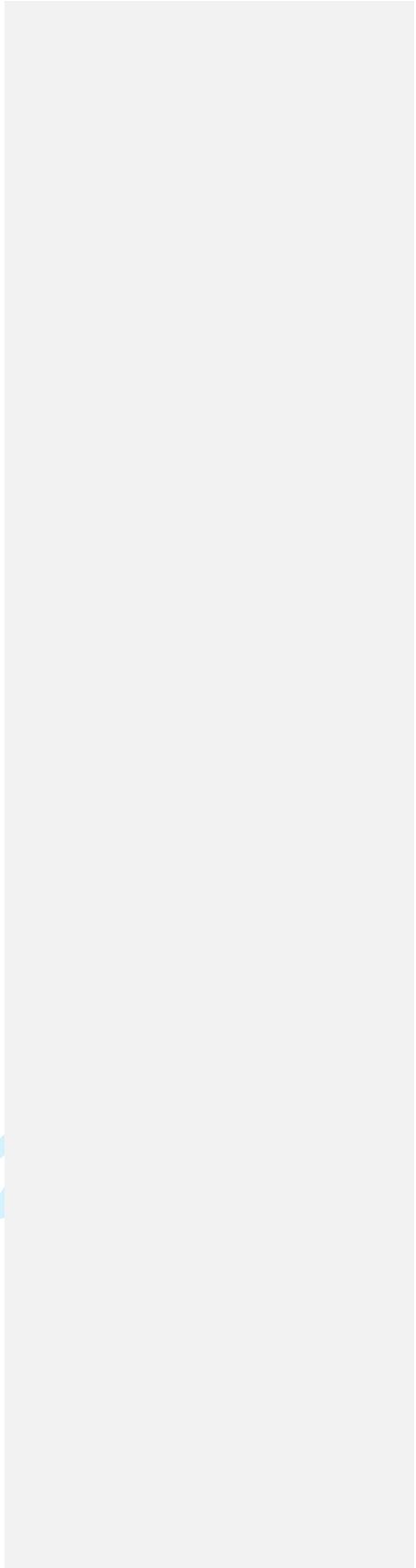
### 39 **Analysis**

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



## Results

### Study Population

883 patients were diagnosed with childhood and teenage cancer between 1<sup>st</sup> January 1971 to 1<sup>st</sup> 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

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8 (range) at diagnosis 5.1 (0.0-17.5) years. Of the cohort, 34 (5.6%) were  
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10 deceased, with a median overall survival (range) of 9.9 (5.0-30.9) years. Of the  
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12 573 long-term survivors alive at the time of the study, the median age (range)  
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14 was 19.4 (5.1-45.1) years and disease free survival (range) 11.3 (0.8-38.3) years  
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16 (Table 1). The primary cancer diagnosis is shown for all patients and within each  
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18 risk level (Figure 2). Risk-stratification of all long-term survivors (n=607) identified  
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20 86 (14.1%), 271 (44.6%) and 250 (41.2%) at Level 1, 2 and 3 respectively with  
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22 detailed breakdown of ages and survival interval for each level of patients alive at  
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24 the time of the study only (n=573), shown in Table 1 and Figure 1. Demographic  
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26 data is similar between the three populations.  
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### 29 **Adverse health outcomes according level of risk**

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31 Among the 34 deaths in the five year survivors (n=607), 26 (76.5%) died from  
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33 progression or relapse of the underlying primary cancer, two (5.9%) died from  
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35 unrelated causes and six (17.6%) died from treatment related sequelae; five from  
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37 second primary malignancy and one from end-stage renal failure. Of the five  
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39 survivors who went on to die from second primary malignancy, three patients (all  
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41 Level 2) had a meningioma, presumed to be secondary to low dose cranial  
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43 irradiation as part of CNS directed therapy for the treatment of childhood ALL,  
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45 one (Level 3) developed extensive intra-abdominal desmoid tumour having  
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47 previously been treated for medulloblastoma and with a background of APC gene  
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49 and Turcot's syndrome and the other patient (Level 3) developed AML presumed  
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8 to be related to previous topo-isomerase II inhibitor therapy for primary bone  
9 sarcoma (Figure 1).

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14 Prevalence and severity of treatment related late effects were determined for  
15 each patient with an assigned level of follow up (n=607, Figures 3 and 4). Among  
16 Level 1 survivors (n=86), 11.6% (n=10) had late effects, of whom seven (8.1%)  
17 had one late effect and three (3.5%) had two late effects; 60% (n=6) of which  
18 were grade 1 toxicity, 30% (n=3) of whom were grade 2 toxicity and 10% (n=1)  
19 grade 3 toxicity. Within the Level 2 group (n=271), the prevalence of late effects  
20 was 35.8% (n=97), of whom 62 (22.9%) had 1 late effect, 23 (8.5%) had 2 late  
21 effects, 9 (3.3%) had 3 late effects and 3 (1.1%) had four late effects, of whom  
22 9.3% (n=9) had a maximum toxicity grade of 1, 58.8% (n=57) grade 2, 18.5%  
23 (n=18) grade 3, 10.3% (n=10) grade 4 and 3% (n=3) grade 5. The prevalence of  
24 late effects in the Level 3 survivors (n=250) was 65.2% (n=163) of whom 37  
25 (14.8%) had 1 late effect, 39 (15.6%) had 2 late effects, 22 (8.8%) had 3 late  
26 effects, 16 (6.4%) had 4 late effects and 46 (18.4%) had 5 or more late effects, of  
27 whom 9 (5.5%), 56 (34.4%), 59 (36.2%), 36 (22.1%) and 3 (1.8%) had grade  
28 1,2,3,4 and 5 toxicity respectively.  
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## 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.<sup>18</sup> However follow-up should be individually tailored and hospital based follow-up should not be necessary for all survivors.<sup>19</sup> The incidence of chronic conditions continues to increase with time and there is therefore no safe time after which these patients can be discharged.<sup>20</sup> 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.<sup>18,21</sup> 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



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8 mortality risk associated with treatment related complications that is present in  
9 the 25 years after the initial cancer diagnosis.<sup>22</sup>  
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14 It is reported that up to 50% of long-term survivors do not attend Late Effects  
15 Clinics and many of these patients are considered to be at high risk of developing  
16 treatment-related late complications.<sup>23</sup> There are many reasons why survivors  
17 choose not to participate in long-term follow-up including lack of awareness of  
18 risks of late morbidity, desire to 'move on', lack of appropriate adult services and  
19 clinical discharge. In a study by Blaauwbroek et al they assessed late effects in a  
20 group of adult survivors of childhood cancer who were not involved in regular  
21 long-term follow-up and reported that almost 40% of survivors suffered from  
22 moderate to severe late effects and 33% had previously unknown late effects.<sup>24</sup>  
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24 This reiterates the need to educate survivors about their past medical history,  
25 their treatment and the importance of engaging in regular survivorship  
26 programmes.  
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39 Low rates of participation in long-term follow-up are universally reported. In 2004,  
40 a Delphi panel of 20 expert childhood cancer survivors in US identified a number  
41 of barriers contributing to this.<sup>25</sup> Understanding these barriers will lead to  
42 improved medical care for these patients. It was recognized that most childhood  
43 cancer survivors are not aware of their adverse health risks and often unaware of  
44 the details of their cancer or its treatment. Even where LTFU clinics are attended  
45 much of the education of late effects was directed at parents and often not  
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8 transferred to the child. The Delphi Panel also highlighted the limitations within  
9 the health care setting including lack of LTFU service, discharge to primary care  
10 physician who lacks expertise in this field and often receive no communication  
11 about the child's past medical history. Improving communication between  
12 professionals and patients is essential and will be an integral part of development  
13 of survivorship programmes.  
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21 The traditional model of LTFU has been in paediatric oncology clinics, generally  
22 jointly with paediatric endocrinologists, neurologists and clinical oncologists, long  
23 into adulthood which brings with it the advantage of continuity of care, familiarity  
24 with treatments but there are a number of disadvantages to this system. This is  
25 not only an age appropriate environment for these patients, but also an  
26 unsustainable situation for paediatric oncologists, as the population of long-term  
27 survivors increase and age. In addition, survivors are protected in this paediatric  
28 environment and don't develop the skills necessary to navigate the health care  
29 system as they develop into adulthood. Ideally, once the long-term survivor  
30 reaches adulthood he/she should be transitioned into the appropriate adult late  
31 effects services. At present, such a service does not exist and it is difficult to  
32 identify which clinicians should take on this role, especially with increasing sub-  
33 specialisation in adult medicine. In a busy and overstretched tertiary oncology  
34 healthcare service, medical and clinical adult oncology consultants are unlikely to  
35 be in a position to take on this responsibility, and may well feel inadequately  
36 trained in caring for childhood cancer survivors. In current practice, the only adult  
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8 services supporting the long-term follow-up of those patients requiring specialist  
9 hospital follow-up are the adult endocrine and neurology clinics.

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14 It has been highlighted that improved communication of cancer information to  
15 patients/families and between health care providers may contribute to greater  
16 engagement in follow-up programmes, raises awareness of potential late effects  
17 amongst survivors and enable clinicians to diagnose and, where possible, treat  
18 late effects earlier. Based on national guidelines, we have developed a template  
19 for the End of Treatment Summary and Individualised Care Plan, or 'Health  
20 Passport', which has been introduced nationally, and welcomed by health  
21 professionals and survivors.  
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31 Models of care for LTFU of survivors of childhood cancer must be flexible enough  
32 to accommodate the needs of the young survivor as they transition throughout  
33 their life cycle and also to accommodate the individual heterogeneity of cancer  
34 survivors, reflecting the wide range of treatment exposure and adverse long-term  
35 sequelae. Development of a service that can deliver individualized,  
36 comprehensive, therapy-based patient centred care is essential.  
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45 The UK National Cancer Survivorship Initiative is currently exploring models of  
46 aftercare services for children and young people who have been treated for  
47 cancer. National pathways that identify how follow-up can be delivered in line  
48 with current pressures and aspirations are being developed. Clinical risk  
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8 stratification will play an integral role in tailoring individualised care to meet the  
9 clinical, psychological and practical needs of each survivor. A recent study from  
10 the CCSS has reviewed how data derived from the CCSS have characterized  
11 specific groups that are deemed to be at highest risk of morbidity and subsequent  
12 cancers.<sup>26</sup> Our study has shown that those patients at highest risk of late  
13 morbidity can be identified and appropriately stratified into a high risk (level 3)  
14 follow-up programme.  
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23 Stratification of patients according to risk of late morbidity will maximise the use  
24 of health service resources and provide age appropriate care as locally as  
25 possible. With increasing time from completion of treatment, it is hoped that the  
26 majority of adult survivors will be independent and take responsibility for their  
27 own health, with health care support provided by their primary care physician. As  
28 a result, the primary care team is likely to play an increasing role in the long-term  
29 follow-up of survivors of childhood cancer. Primary care services may be already  
30 stretched but GPs are used to meeting targets and ensuring guidelines are  
31 implemented. Good communication between the hospital services and primary  
32 care will be essential. Early involvement of general practitioners in the Late  
33 Effects Services will establish collaborations between the two teams and enable  
34 primary Care Physicians to become familiar with the surveillance programme.  
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36 The feasibility of a shared-care model between cancer paediatric oncology  
37 cancer centres and primary-care doctors to deliver survivor-focused risk based  
38 health care was tested successfully by a Dutch group. The study showed that  
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8 patients would see their family doctor for long-term follow-up: the family doctors  
9 were interested in sharing survivors' care; and family doctors would return the  
10 necessary medical information needed for continued follow-up.<sup>27</sup> Appropriate  
11 education of the family doctors, which has resource implications, was a key  
12 finding of this study. More recently this group has shown that a web based  
13 survivor care plan can facilitate the long-term care of survivors by family  
14 doctors.<sup>28</sup>

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

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45 We have shown that it is possible to ~~safely~~ predict which survivors of childhood  
46 cancer are at significant risk of developing moderate to severe late effects and  
47 require moderate or high intensity long-term follow. Importantly we have also  
48 shown that there is a group of survivors who can be reliably identified who can be  
49 ~~safely~~ discharged from clinic based follow-up, *and followed up by annual*  
50 *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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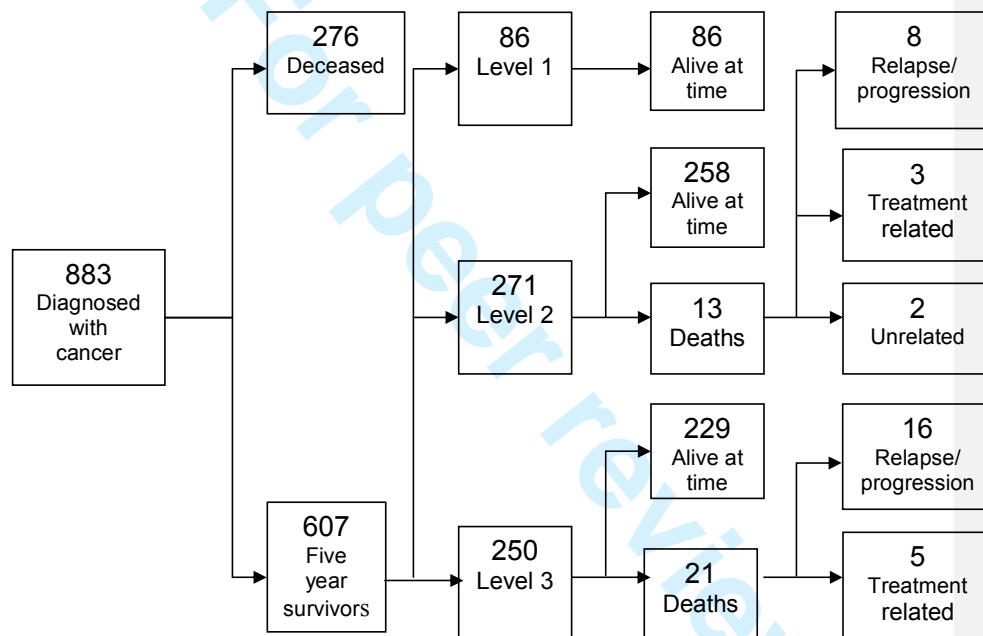


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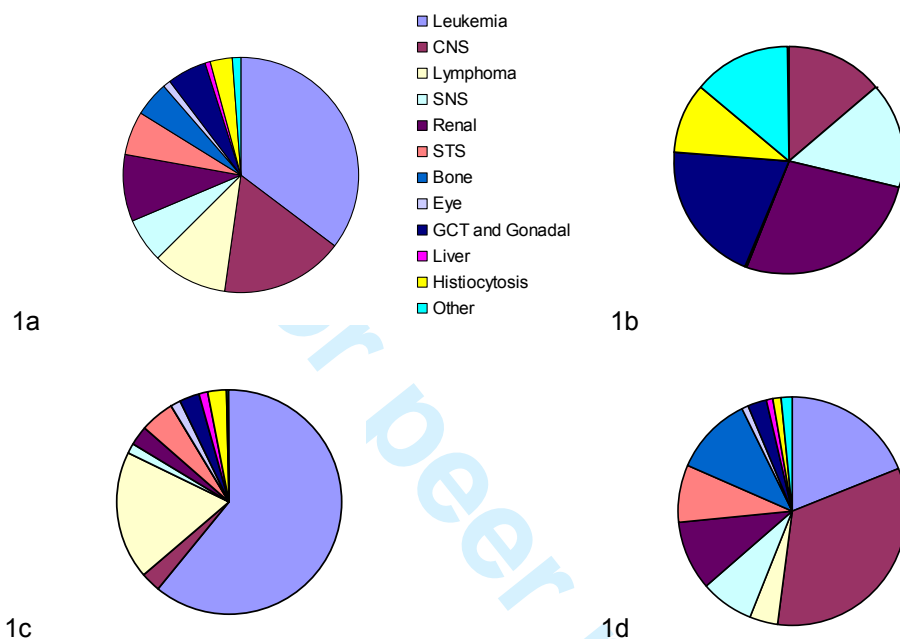
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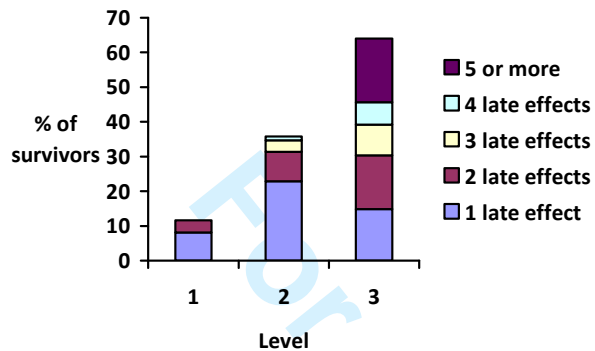
**Figure 1. Study flow of childhood and teenage cancer patients.**

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.



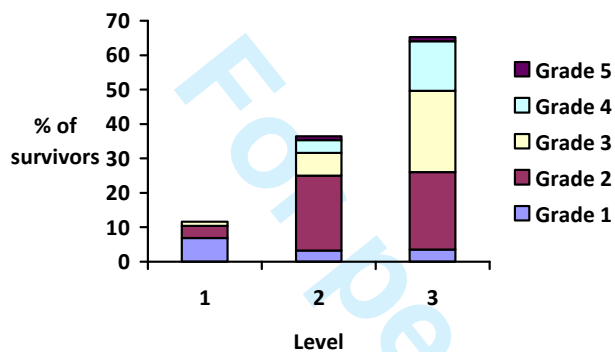
**Figure 2 Diagnoses of five year survivors (n=607)**

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).<sup>17</sup>

**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](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

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8 and revised the draft paper. SB designed data collection tools, monitored data  
9 collection for the study, analysed the data and revised the draft paper. PM-S  
10 analysed the data and drafted and revised the paper. WHBW designed data  
11 collection tools, monitored data collection for the study, analysed the data, and  
12 drafted and revised the paper. All authors had full access to all of the data in the  
13 study and can take responsibility for the integrity of the data and the accuracy of  
14 the data analysis.  
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#### 24 **Data sharing statement**

25 Dataset available from the corresponding author at  
26 [angela.edgar@luht.scot.nhs.uk](mailto:angela.edgar@luht.scot.nhs.uk). Consent was not obtained but the presented  
27 data are anonymised and risk of identification is low.  
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#### 33 **Ethical approval**

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

47 No specific funding was received for this research.  
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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
<b>Introduction</b>			
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
<b>Methods</b>			
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	
<b>Results</b>			

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	
<b>Discussion</b>			
Key results	18	Summarise key results with reference to study objectives	15
<b>Limitations</b>			
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
<b>Other information</b>			
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](http://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?**

Journal:	<i>BMJ Open</i>
Manuscript ID:	bmjopen-2012-002451.R3
Article Type:	Research
Date Submitted by the Author:	18-Jun-2013
Complete List of Authors:	Edgar, Angela; Royal Hospital for Sick Children , Paediatric Oncology Duffin, Kathleen; Royal Hospital for Sick Children, Paediatric Oncology Borthwick, Stephen; Royal Hospital for Sick Children, Paediatric Oncology Marciniak-Stępak, Patrycja; Poznan University of Medical Sciences, 2Department of Paediatric Oncology Wallace, w. Hamish; Royal Hospital for Sick Children, Paediatric Oncology
<b>Primary Subject Heading</b>:	Oncology
Secondary Subject Heading:	Paediatrics, Patient-centred medicine
Keywords:	Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Risk management < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Paediatric oncology < ONCOLOGY

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Manuscripts

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

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11 Edgar AB<sup>1</sup>, Duffin K<sup>1</sup>, Borthwick S<sup>1</sup>, Marciniak-Stepak P<sup>2</sup>, Wallace WH<sup>1</sup>  
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16 <sup>1</sup>Department of Oncology, Royal Hospital for Sick Children, Edinburgh, UK;

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



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- 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.

### 18 **Limitations**

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- 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 1<sup>st</sup> January 1971-31<sup>st</sup> 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**

BMJ.2012.008737

## 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.<sup>1</sup> It is estimated that 1 in 640 young adults is a survivor of childhood cancer.<sup>2</sup> 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.<sup>3-5</sup> Late effects are diverse and include secondary malignancies, organ system damage, infertility, cognitive impairment, and disorders of growth and development.<sup>6, 7</sup> Appropriate LTFU of these patients is essential to detect, treat and prevent morbidity and mortality.<sup>8</sup>

There is wide variation of long-term follow-up practices throughout the UK with a propensity for hospital dependency, often in age-inappropriate settings.<sup>9</sup> A recent study has highlighted how excess morbidity in survivors translates into increased use of health care facilities.<sup>10</sup> 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.<sup>11</sup> 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

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8 intensity of follow-up<sup>8</sup>. In the UK, we published a Practice Statement 'Therapy  
9 Based Long-term Follow-up' which is designed to inform and guide clinicians  
10 responsible for the long-term follow-up of childhood cancer survivors.<sup>12</sup> The  
11 Practice Statement recommends follow-up assessments and investigations  
12 based on the treatment that the individual has received and is informed by the  
13 evidence-based recommendations published by SIGN 76.  
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21 An integrated and systematic approach is now considered a requirement of the  
22 National Institute of Health and Clinical Excellence (NIHCE) Improving Outcomes  
23 for Children and Young People with Cancer Guidance (2005) and National  
24 Delivery Plan for Children and Young People's Specialist Services in Scotland  
25 (2008).<sup>13,14</sup> In England, the National Cancer Survivorship Initiative (NCSI) has  
26 developed as a partnership between the Department of Health, Macmillan  
27 Cancer Support, and supported by NHS Improvement, to develop models of care  
28 to ensure that those living with and beyond cancer have access to safe and  
29 effective care and receive the support they need to lead as healthy and active a  
30 life as possible. Improved awareness of cancer survivorship as a chronic health  
31 problem will facilitate the development of care pathways that will meet the needs  
32 of every patient throughout their lifetime.<sup>15</sup>  
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47 Although there is growing guidance on whom, where and how long-term  
48 survivors should be followed-up, evidence to show that adopting a model of risk-  
49 stratified follow-up is safe is lacking. A recent study has shown that assigning  
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8 patients to one of three agreed levels of follow up, as described by Wallace et al,  
9 was relatively simple for experienced clinic staff.<sup>16</sup> The objective of this study was  
10 to evaluate the safety-feasibility and efficacy of this risk-based follow-up model by  
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12 | retrospectively stratifying an unselected cohort of long-term survivors of  
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14 childhood cancer from a single centre and objectively evaluating their health  
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## 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.<sup>8</sup> 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).<sup>17</sup> The CTCAEv3.0



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

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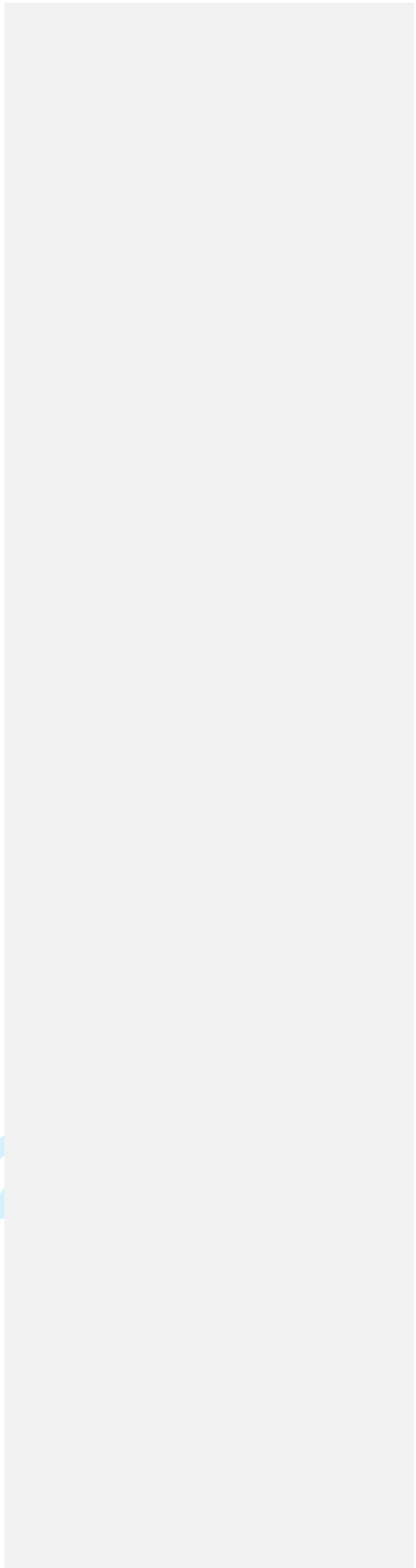
### 39 **Analysis**

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



## Results

### Study Population

883 patients were diagnosed with childhood and teenage cancer between 1<sup>st</sup> January 1971 to 1<sup>st</sup> 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

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8 (range) at diagnosis 5.1 (0.0-17.5) years. Of the cohort, 34 (5.6%) were  
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10 deceased, with a median overall survival (range) of 9.9 (5.0-30.9) years. Of the  
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12 573 long-term survivors alive at the time of the study, the median age (range)  
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14 was 19.4 (5.1-45.1) years and disease free survival (range) 11.3 (0.8-38.3) years  
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16 (Table 1). The primary cancer diagnosis is shown for all patients and within each  
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18 risk level (Figure 2). Risk-stratification of all long-term survivors (n=607) identified  
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20 86 (14.1%), 271 (44.6%) and 250 (41.2%) at Level 1, 2 and 3 respectively with  
21  
22 detailed breakdown of ages and survival interval for each level of patients alive at  
23  
24 the time of the study only (n=573), shown in Table 1 and Figure 1. Demographic  
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26 data is similar between the three populations.  
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### 29 **Adverse health outcomes according level of risk**

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31 Among the 34 deaths in the five year survivors (n=607), 26 (76.5%) died from  
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33 progression or relapse of the underlying primary cancer, two (5.9%) died from  
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35 unrelated causes and six (17.6%) died from treatment related sequelae; five from  
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37 second primary malignancy and one from end-stage renal failure. Of the five  
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39 survivors who went on to die from second primary malignancy, three patients (all  
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41 Level 2) had a meningioma, presumed to be secondary to low dose cranial  
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43 irradiation as part of CNS directed therapy for the treatment of childhood ALL,  
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45 one (Level 3) developed extensive intra-abdominal desmoid tumour having  
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47 previously been treated for medulloblastoma and with a background of APC gene  
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49 and Turcot's syndrome and the other patient (Level 3) developed AML presumed  
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8 to be related to previous topo-isomerase II inhibitor therapy for primary bone  
9 sarcoma (Figure 1).  
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14 Prevalence and severity of treatment related late effects were determined for  
15 each patient with an assigned level of follow up (n=607, Figures 3 and 4). Among  
16 Level 1 survivors (n=86), 11.6% (n=10) had late effects, of whom seven (8.1%)  
17 had one late effect and three (3.5%) had two late effects; 60% (n=6) of which  
18 were grade 1 toxicity, 30% (n=3) of whom were grade 2 toxicity and 10% (n=1)  
19 grade 3 toxicity. Within the Level 2 group (n=271), the prevalence of late effects  
20 was 35.8% (n=97), of whom 62 (22.9%) had 1 late effect, 23 (8.5%) had 2 late  
21 effects, 9 (3.3%) had 3 late effects and 3 (1.1%) had four late effects, of whom  
22 9.3% (n=9) had a maximum toxicity grade of 1, 58.8% (n=57) grade 2, 18.5%  
23 (n=18) grade 3, 10.3% (n=10) grade 4 and 3% (n=3) grade 5. The prevalence of  
24 late effects in the Level 3 survivors (n=250) was 65.2% (n=163) of whom 37  
25 (14.8%) had 1 late effect, 39 (15.6%) had 2 late effects, 22 (8.8%) had 3 late  
26 effects, 16 (6.4%) had 4 late effects and 46 (18.4%) had 5 or more late effects, of  
27 whom 9 (5.5%), 56 (34.4%), 59 (36.2%), 36 (22.1%) and 3 (1.8%) had grade  
28 1,2,3,4 and 5 toxicity respectively.  
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## 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.<sup>18</sup> However follow-up should be individually tailored and hospital based follow-up should not be necessary for all survivors.<sup>19</sup> The incidence of chronic conditions continues to increase with time and there is therefore no safe time after which these patients can be discharged.<sup>20</sup> 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.<sup>18,21</sup> 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

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8 mortality risk associated with treatment related complications that is present in  
9 the 25 years after the initial cancer diagnosis.<sup>22</sup>  
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14 It is reported that up to 50% of long-term survivors do not attend Late Effects  
15 Clinics and many of these patients are considered to be at high risk of developing  
16 treatment-related late complications.<sup>23</sup> There are many reasons why survivors  
17 choose not to participate in long-term follow-up including lack of awareness of  
18 risks of late morbidity, desire to 'move on', lack of appropriate adult services and  
19 clinical discharge. In a study by Blaauwbroek et al they assessed late effects in a  
20 group of adult survivors of childhood cancer who were not involved in regular  
21 long-term follow-up and reported that almost 40% of survivors suffered from  
22 moderate to severe late effects and 33% had previously unknown late effects.<sup>24</sup>  
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24 This reiterates the need to educate survivors about their past medical history,  
25 their treatment and the importance of engaging in regular survivorship  
26 programmes.  
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39 Low rates of participation in long-term follow-up are universally reported. In 2004,  
40 a Delphi panel of 20 expert childhood cancer survivors in US identified a number  
41 of barriers contributing to this.<sup>25</sup> Understanding these barriers will lead to  
42 improved medical care for these patients. It was recognized that most childhood  
43 cancer survivors are not aware of their adverse health risks and often unaware of  
44 the details of their cancer or its treatment. Even where LTFU clinics are attended  
45 much of the education of late effects was directed at parents and often not  
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8 transferred to the child. The Delphi Panel also highlighted the limitations within  
9 the health care setting including lack of LTFU service, discharge to primary care  
10 physician who lacks expertise in this field and often receive no communication  
11 about the child's past medical history. Improving communication between  
12 professionals and patients is essential and will be an integral part of development  
13 of survivorship programmes.  
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21 The traditional model of LTFU has been in paediatric oncology clinics, generally  
22 jointly with paediatric endocrinologists, neurologists and clinical oncologists, long  
23 into adulthood which brings with it the advantage of continuity of care, familiarity  
24 with treatments but there are a number of disadvantages to this system. This is  
25 not only an age appropriate environment for these patients, but also an  
26 unsustainable situation for paediatric oncologists, as the population of long-term  
27 survivors increase and age. In addition, survivors are protected in this paediatric  
28 environment and don't develop the skills necessary to navigate the health care  
29 system as they develop into adulthood. Ideally, once the long-term survivor  
30 reaches adulthood he/she should be transitioned into the appropriate adult late  
31 effects services. At present, such a service does not exist and it is difficult to  
32 identify which clinicians should take on this role, especially with increasing sub-  
33 specialisation in adult medicine. In a busy and overstretched tertiary oncology  
34 healthcare service, medical and clinical adult oncology consultants are unlikely to  
35 be in a position to take on this responsibility, and may well feel inadequately  
36 trained in caring for childhood cancer survivors. In current practice, the only adult  
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8 services supporting the long-term follow-up of those patients requiring specialist  
9 hospital follow-up are the adult endocrine and neurology clinics.

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14 It has been highlighted that improved communication of cancer information to  
15 patients/families and between health care providers may contribute to greater  
16 engagement in follow-up programmes, raises awareness of potential late effects  
17 amongst survivors and enable clinicians to diagnose and, where possible, treat  
18 late effects earlier. Based on national guidelines, we have developed a template  
19 for the End of Treatment Summary and Individualised Care Plan, or 'Health  
20 Passport', which has been introduced nationally, and welcomed by health  
21 professionals and survivors.  
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31 Models of care for LTFU of survivors of childhood cancer must be flexible enough  
32 to accommodate the needs of the young survivor as they transition throughout  
33 their life cycle and also to accommodate the individual heterogeneity of cancer  
34 survivors, reflecting the wide range of treatment exposure and adverse long-term  
35 sequelae. Development of a service that can deliver individualized,  
36 comprehensive, therapy-based patient centred care is essential.  
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45 The UK National Cancer Survivorship Initiative is currently exploring models of  
46 aftercare services for children and young people who have been treated for  
47 cancer. National pathways that identify how follow-up can be delivered in line  
48 with current pressures and aspirations are being developed. Clinical risk  
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8 stratification will play an integral role in tailoring individualised care to meet the  
9 clinical, psychological and practical needs of each survivor. A recent study from  
10 the CCSS has reviewed how data derived from the CCSS have characterized  
11 specific groups that are deemed to be at highest risk of morbidity and subsequent  
12 cancers.<sup>26</sup> Our study has shown that those patients at highest risk of late  
13 morbidity can be identified and appropriately stratified into a high risk (level 3)  
14 follow-up programme.  
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23 Stratification of patients according to risk of late morbidity will maximise the use  
24 of health service resources and provide age appropriate care as locally as  
25 possible. With increasing time from completion of treatment, it is hoped that the  
26 majority of adult survivors will be independent and take responsibility for their  
27 own health, with health care support provided by their primary care physician. As  
28 a result, the primary care team is likely to play an increasing role in the long-term  
29 follow-up of survivors of childhood cancer. Primary care services may be already  
30 stretched but GPs are used to meeting targets and ensuring guidelines are  
31 implemented. Good communication between the hospital services and primary  
32 care will be essential. Early involvement of general practitioners in the Late  
33 Effects Services will establish collaborations between the two teams and enable  
34 primary Care Physicians to become familiar with the surveillance programme.  
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36 The feasibility of a shared-care model between cancer paediatric oncology  
37 cancer centres and primary-care doctors to deliver survivor-focused risk based  
38 health care was tested successfully by a Dutch group. The study showed that  
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8 patients would see their family doctor for long-term follow-up: the family doctors  
9 were interested in sharing survivors' care; and family doctors would return the  
10 necessary medical information needed for continued follow-up.<sup>27</sup> Appropriate  
11 education of the family doctors, which has resource implications, was a key  
12 finding of this study. More recently this group has shown that a web based  
13 survivor care plan can facilitate the long-term care of survivors by family  
14 doctors.<sup>28</sup>

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

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45 We have shown that it is possible to ~~safely~~ predict which survivors of childhood  
46 cancer are at significant risk of developing moderate to severe late effects and  
47 require moderate or high intensity long-term follow. Importantly we have also  
48 shown that there is a group of survivors who can be reliably identified who can be  
49 ~~safely~~ discharged from clinic based follow-up, *and followed up by annual*  
50 *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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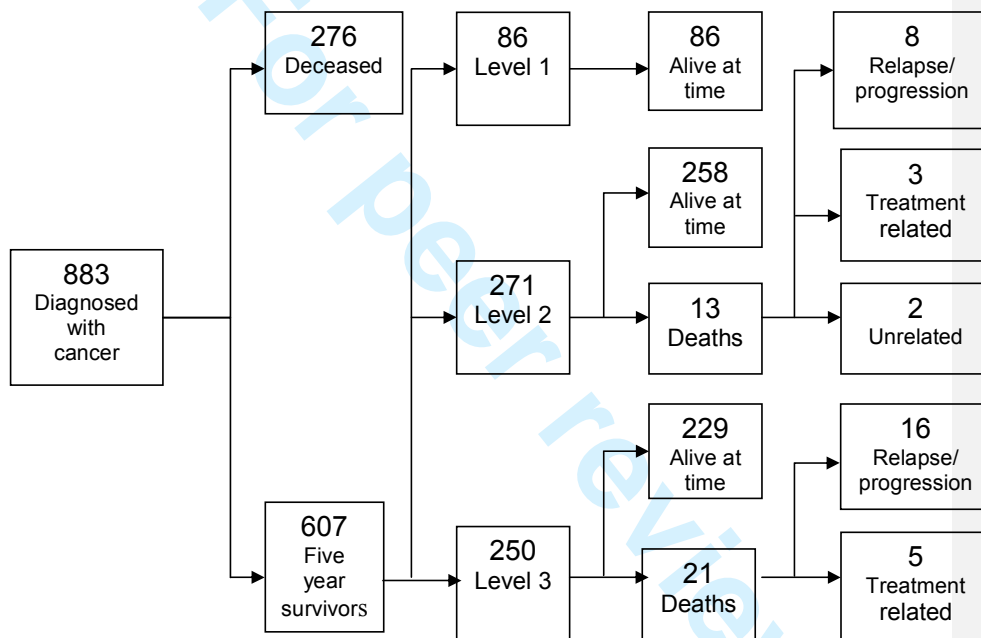
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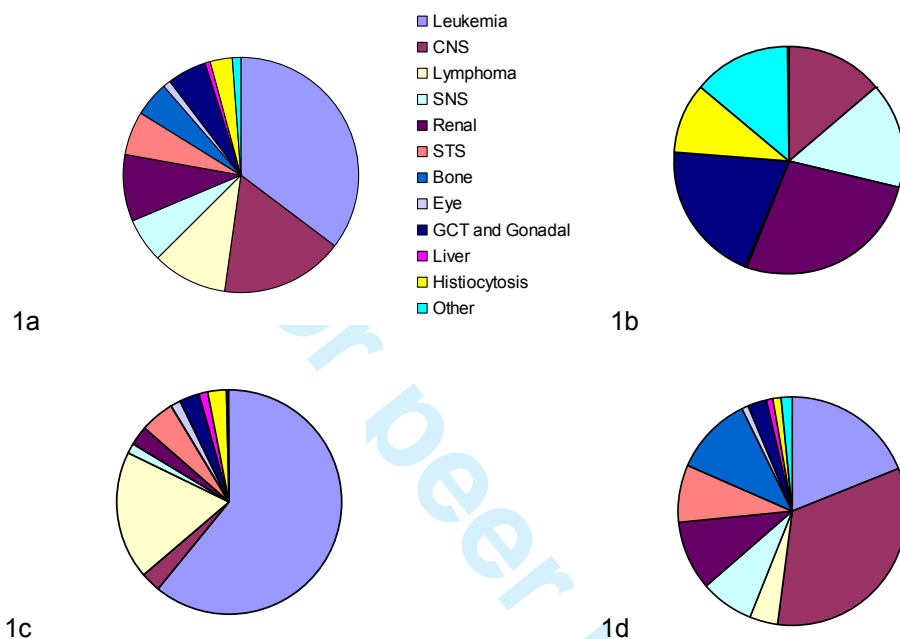
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**Figure 1. Study flow of childhood and teenage cancer patients.**

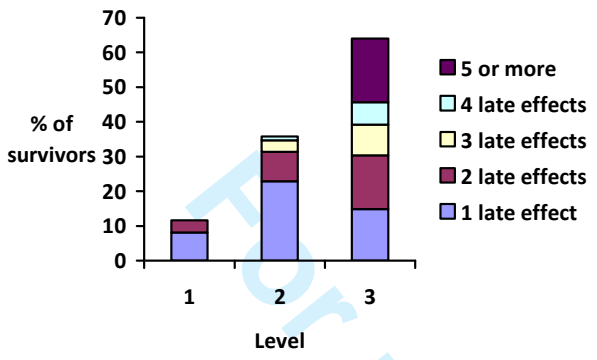
Flow chart shows the study population and the risk stratification of patients into Levels 1,2 and 3 and the proportion of patients alive at the time of the study.



**Figure 2 Diagnoses of five year survivors (n=607)**

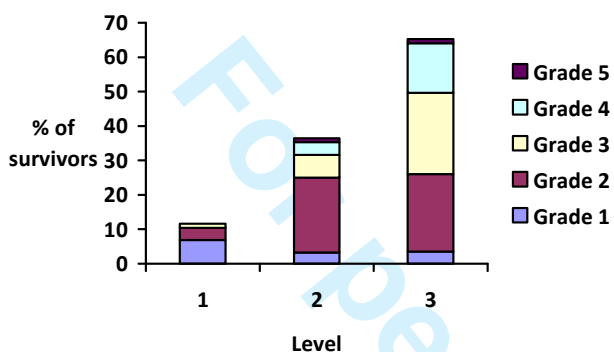
1a. All survivors (n=607), 1b. Level 1 (n= 86), 1c. Level 2 (n=271), 1d. Level 3 (n=250). Abbreviations: CNS – central nervous system tumours, SNS – sympathetic nervous system tumours, GCT – germ cell tumours, STS – soft tissue sarcomas

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**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).<sup>17</sup>

**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](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



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8 and revised the draft paper. SB designed data collection tools, monitored data  
9 collection for the study, analysed the data and revised the draft paper. PM-S  
10 analysed the data and drafted and revised the paper. WHBW designed data  
11 collection tools, monitored data collection for the study, analysed the data, and  
12 drafted and revised the paper. All authors had full access to all of the data in the  
13 study and can take responsibility for the integrity of the data and the accuracy of  
14 the data analysis.  
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#### 24 **Data sharing statement**

25 Dataset available from the corresponding author at  
26 [angela.edgar@luht.scot.nhs.uk](mailto:angela.edgar@luht.scot.nhs.uk). Consent was not obtained but the presented  
27 data are anonymised and risk of identification is low.  
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#### 33 **Ethical approval**

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

47 No specific funding was received for this research.  
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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
<b>Introduction</b>			
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
<b>Methods</b>			
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	
<b>Results</b>			

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	
<b>Discussion</b>			
Key results	18	Summarise key results with reference to study objectives	15
<b>Limitations</b>			
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
<b>Other information</b>			
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](http://www.strobe-statement.org).

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8 **Can Intensity of long-term follow-up for survivors of childhood and teenage**  
9 **cancer be determined by therapy-based risk-stratification?**  
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11 Edgar AB<sup>1</sup>, Duffin K<sup>1</sup>, Borthwick S<sup>1</sup>, Marciniak-Stepak P<sup>2</sup>, Wallace WH<sup>1</sup>  
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47 Key words: Childhood cancer, treatment, survival, cure, late effects, models of  
48 follow-up, long-term follow-up.  
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## 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.

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- 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.

### 16 Limitations

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- 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.

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- 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 1<sup>st</sup> January 1971-31<sup>st</sup> 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.

**Word count: 280**

BMJ.2012.008737



## 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.<sup>1</sup> It is estimated that 1 in 640 young adults is a survivor of childhood cancer.<sup>2</sup> 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.<sup>3-5</sup> Late effects are diverse and include secondary malignancies, organ system damage, infertility, cognitive impairment, and disorders of growth and development.<sup>6, 7</sup> Appropriate LTFU of these patients is essential to detect, treat and prevent morbidity and mortality.<sup>8</sup>

There is wide variation of long-term follow-up practices throughout the UK with a propensity for hospital dependency, often in age-inappropriate settings.<sup>9</sup> A recent study has highlighted how excess morbidity in survivors translates into increased use of health care facilities.<sup>10</sup> 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.<sup>11</sup> [This has recently been revised and superceded by SIGN132](#)<sup>12,13</sup>. 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

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8 developed which identified three groups of survivors who require an increasing  
9 intensity of follow-up<sup>8</sup>. In the UK, we published a Practice Statement 'Therapy  
10 Based Long-term Follow-up' which is designed to inform and guide clinicians  
11 responsible for the long-term follow-up of childhood cancer survivors.<sup>142</sup> The  
12 Practice Statement recommends follow-up assessments and investigations  
13 based on the treatment that the individual has received and is informed by the  
14 evidence-based recommendations published by SIGN 76.  
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24 An integrated and systematic approach is now considered a requirement of the  
25 National Institute of Health and Clinical Excellence (NIHCE) Improving Outcomes  
26 for Children and Young People with Cancer Guidance (2005) and National  
27 Delivery Plan for Children and Young People's Specialist Services in Scotland  
28 (2008).<sup>153,164</sup> In England, the National Cancer Survivorship Initiative (NCSI) has  
29 developed as a partnership between the Department of Health, Macmillan  
30 Cancer Support, and supported by NHS Improvement, to develop models of care  
31 to ensure that those living with and beyond cancer have access to safe and  
32 effective care and receive the support they need to lead as healthy and active a  
33 life as possible. Improved awareness of cancer survivorship as a chronic health  
34 problem will facilitate the development of care pathways that will meet the needs  
35 of every patient throughout their lifetime.<sup>175</sup>  
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49 Although there is growing guidance on whom, where and how long-term  
50 survivors should be followed-up, evidence to show that adopting a model of risk-  
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8 stratified follow-up is safe is lacking. A recent study has shown that assigning  
9 patients to one of three agreed levels of follow up, as described by Wallace et al,  
10 was relatively simple for experienced clinic staff.<sup>186</sup> The objective of this study  
11 was to evaluate the feasibility and efficacy of this risk-based follow-up model by  
12 retrospectively stratifying an unselected cohort of long-term survivors of  
13 childhood cancer from a single centre and objectively evaluating their health  
14 status.  
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## 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-

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

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41 To determine the severity of late effects, each reported late effect was graded  
42 independently by two of the authors using the Common Terminology Criteria for  
43 Adverse Events, Version 3.0 (CTCAEv3.0, available at  
44 <http://ctep.cancer.gov/forms/CTCAEv3.pdf>), a scoring system developed through  
45 the US National Cancer Institute by a multidisciplinary group and adopted in the  
46 UK by the Children's Cancer and Leukaemia Group (CCLG).<sup>19z</sup> The CTCAEv3.0  
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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 from 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 1<sup>st</sup> January 1971 to 1<sup>st</sup> 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

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8 (range) at diagnosis 5.1 (0.0-17.5) years. Of the cohort, 34 (5.6%) were  
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10 deceased, with a median overall survival (range) of 9.9 (5.0-30.9) years. Of the  
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12 573 long-term survivors alive at the time of the study, the median age (range)  
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14 was 19.4 (5.1-45.1) years and disease free survival (range) 11.3 (0.8-38.3) years  
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16 (Table 1). The primary cancer diagnosis is shown for all patients and within each  
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18 risk level (Figure 2). Risk-stratification of all long-term survivors (n=607) identified  
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20 86 (14.1%), 271 (44.6%) and 250 (41.2%) at Level 1, 2 and 3 respectively with  
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22 detailed breakdown of ages and survival interval for each level of patients alive at  
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24 the time of the study only (n=573), shown in Table 1 and Figure 1. Demographic  
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26 data is similar between the three populations.  
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### 29 **Adverse health outcomes according level of risk**

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31 Among the 34 deaths in the five year survivors (n=607), 26 (76.5%) died from  
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33 progression or relapse of the underlying primary cancer, two (5.9%) died from  
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35 unrelated causes and six (17.6%) died from treatment related sequelae; five from  
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37 second primary malignancy and one from end-stage renal failure. Of the five  
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39 survivors who went on to die from second primary malignancy, three patients (all  
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41 Level 2) had a meningioma, presumed to be secondary to low dose cranial  
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43 irradiation as part of CNS directed therapy for the treatment of childhood ALL,  
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45 one (Level 3) developed extensive intra-abdominal desmoid tumour having  
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47 previously been treated for medulloblastoma and with a background of APC gene  
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49 and Turcot's syndrome and the other patient (Level 3) developed AML presumed  
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8 to be related to previous topo-isomerase II inhibitor therapy for primary bone  
9 sarcoma (Figure 1).  
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14 Prevalence and severity of treatment related late effects were determined for  
15 each patient with an assigned level of follow up (n=607, Figures 3 and 4). Among  
16 Level 1 survivors (n=86), 11.6% (n=10) had late effects, of whom seven (8.1%)  
17 had one late effect and three (3.5%) had two late effects; 60% (n=6) of which  
18 were grade 1 toxicity, 30% (n=3) of whom were grade 2 toxicity and 10% (n=1)  
19 grade 3 toxicity. Within the Level 2 group (n=271), the prevalence of late effects  
20 was 35.8% (n=97), of whom 62 (22.9%) had 1 late effect, 23 (8.5%) had 2 late  
21 effects, 9 (3.3%) had 3 late effects and 3 (1.1%) had four late effects, of whom  
22 9.3% (n=9) had a maximum toxicity grade of 1, 58.8% (n=57) grade 2, 18.5%  
23 (n=18) grade 3, 10.3% (n=10) grade 4 and 3% (n=3) grade 5. The prevalence of  
24 late effects in the Level 3 survivors (n=250) was 65.2% (n=163) of whom 37  
25 (14.8%) had 1 late effect, 39 (15.6%) had 2 late effects, 22 (8.8%) had 3 late  
26 effects, 16 (6.4%) had 4 late effects and 46 (18.4%) had 5 or more late effects, of  
27 whom 9 (5.5%), 56 (34.4%), 59 (36.2%), 36 (22.1%) and 3 (1.8%) had grade  
28 1,2,3,4 and 5 toxicity respectively.  
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## 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.<sup>18</sup> However follow-up should be individually tailored and hospital based follow-up should not be necessary for all survivors.<sup>21-49</sup> The incidence of chronic conditions continues to increase with time and there is therefore no safe time after which these patients can be discharged.<sup>220</sup> 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.<sup>20-18,234</sup> 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

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8 mortality risk associated with treatment related complications that is present in  
9  
10 the 25 years after the initial cancer diagnosis.<sup>242</sup>  
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13  
14 It is reported that up to 50% of long-term survivors do not attend Late Effects  
15 Clinics and many of these patients are considered to be at high risk of developing  
16 treatment-related late complications.<sup>253</sup> There are many reasons why survivors  
17 choose not to participate in long-term follow-up including lack of awareness of  
18 risks of late morbidity, desire to 'move on', lack of appropriate adult services and  
19 clinical discharge. In a study by Blaauwbroek et al they assessed late effects in a  
20 group of adult survivors of childhood cancer who were not involved in regular  
21 long-term follow-up and reported that almost 40% of survivors suffered from  
22 moderate to severe late effects and 33% had previously unknown late effects.<sup>264</sup>  
23  
24 This reiterates the need to educate survivors about their past medical history,  
25 their treatment and the importance of engaging in regular survivorship  
26 programmes.  
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39 Low rates of participation in long-term follow-up are universally reported. In 2004,  
40 a Delphi panel of 20 expert childhood cancer survivors in US identified a number  
41 of barriers contributing to this.<sup>275</sup> Understanding these barriers will lead to  
42 improved medical care for these patients. It was recognized that most childhood  
43 cancer survivors are not aware of their adverse health risks and often unaware of  
44 the details of their cancer or its treatment. Even where LTFU clinics are attended  
45 much of the education of late effects was directed at parents and often not  
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8 transferred to the child. The Delphi Panel also highlighted the limitations within  
9 the health care setting including lack of LTFU service, discharge to primary care  
10 physician who lacks expertise in this field and often receive no communication  
11 about the child's past medical history. Improving communication between  
12 professionals and patients is essential and will be an integral part of development  
13 of survivorship programmes.  
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21 The traditional model of LTFU has been in paediatric oncology clinics, generally  
22 jointly with paediatric endocrinologists, neurologists and clinical oncologists, long  
23 into adulthood which brings with it the advantage of continuity of care, familiarity  
24 with treatments but there are a number of disadvantages to this system. This is  
25 not only an age appropriate environment for these patients, but also an  
26 unsustainable situation for paediatric oncologists, as the population of long-term  
27 survivors increase and age. In addition, survivors are protected in this paediatric  
28 environment and don't develop the skills necessary to navigate the health care  
29 system as they develop into adulthood. Ideally, once the long-term survivor  
30 reaches adulthood he/she should be transitioned into the appropriate adult late  
31 effects services. At present, such a service does not exist and it is difficult to  
32 identify which clinicians should take on this role, especially with increasing sub-  
33 specialisation in adult medicine. In a busy and overstretched tertiary oncology  
34 healthcare service, medical and clinical adult oncology consultants are unlikely to  
35 be in a position to take on this responsibility, and may well feel inadequately  
36 trained in caring for childhood cancer survivors. In current practice, the only adult  
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8 services supporting the long-term follow-up of those patients requiring specialist  
9 hospital follow-up are the adult endocrine and neurology clinics.

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14 It has been highlighted that improved communication of cancer information to  
15 patients/families and between health care providers may contribute to greater  
16 engagement in follow-up programmes, raises awareness of potential late effects  
17 amongst survivors and enable clinicians to diagnose and, where possible, treat  
18 late effects earlier<sup>12,13</sup>. Based on national guidelines, we have developed a  
19 template for the End of Treatment Summary and Individualised Care Plan, or  
20 'Health Passport', which has been introduced nationally, and welcomed by health  
21 professionals and survivors.  
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31 Models of care for LTFU of survivors of childhood cancer must be flexible enough  
32 to accommodate the needs of the young survivor as they transition throughout  
33 their life cycle and also to accommodate the individual heterogeneity of cancer  
34 survivors, reflecting the wide range of treatment exposure and adverse long-term  
35 sequelae. Development of a service that can deliver individualized,  
36 comprehensive, therapy-based patient centred care is essential.  
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45 The UK National Cancer Survivorship Initiative is currently exploring models of  
46 aftercare services for children and young people who have been treated for  
47 cancer. National pathways that identify how follow-up can be delivered in line  
48 with current pressures and aspirations are being developed. Clinical risk  
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8 stratification will play an integral role in tailoring individualised care to meet the  
9 clinical, psychological and practical needs of each survivor. A recent study from  
10 the CCSS has reviewed how data derived from the CCSS have characterized  
11 specific groups that are deemed to be at highest risk of morbidity and subsequent  
12 cancers.<sup>286</sup> Our study has shown that those patients at highest risk of late  
13 morbidity can be identified and appropriately stratified into a high risk (level 3)  
14 follow-up programme.  
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23 Our study has a number of important but acknowledged limitations. There are  
24 only 605 five-year survivors and the median age at follow up was only 19 years,  
25 so the study population is small but it does reflect a single centre's clinical  
26 practice and as such the findings should stimulate an interesting clinical debate  
27 about the utility of long-term follow up of childhood cancer survivors. We have not  
28 undertaken any formal statistical analysis but believe that our data is best  
29 presented as visual figures (3 and 4) showing clearly that both the prevalence  
30 and severity of late effects is related to the assigned level of follow up in our  
31 unselected cohort. We have not been able to statistically adjust our analysis to  
32 take into account of the current age of survivors for each assigned level of follow  
33 up. The percentage of five year survivors with a current age beyond 25 years is  
34 7%, 27% and 29% for levels 1,2 and 3 respectively. It is possible that as the level  
35 1 group ages more late effects will appear and although this appears unlikely, as  
36 this group has received the least intensive treatment, it should be the subject of  
37 ongoing and further study. The median follow up time for levels one, two and  
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8 three survivors is 11, 13 and 12.9 years respectively (see Table one). We believe  
9 that ascertainment of adverse health outcomes is likely to be complete or very  
10 nearly complete in our study population, although we must acknowledge that we  
11 were not able to access primary care records for our five year survivors which  
12 could result in an under-reporting of adverse events. It is however highly unlikely  
13 that missed adverse health outcomes were more likely in level 1 patients as  
14 opposed to level 2 or 3 patients.  
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24 Stratification of patients according to risk of late morbidity will maximise the use  
25 of health service resources and provide age appropriate care as locally as  
26 possible. With increasing time from completion of treatment, it is hoped that the  
27 majority of adult survivors will be independent and take responsibility for their  
28 own health, with health care support provided by their primary care physician. As  
29 a result, the primary care team is likely to play an increasing role in the long-term  
30 follow-up of survivors of childhood cancer. Primary care services may be already  
31 stretched but GPs are used to meeting targets and ensuring guidelines are  
32 implemented. Good communication between the hospital services and primary  
33 care will be essential. Early involvement of general practitioners in the Late  
34 Effects Services will establish collaborations between the two teams and enable  
35 primary Care Physicians to become familiar with the surveillance programme.  
36 The feasibility of a shared-care model between cancer paediatric oncology  
37 cancer centres and primary-care doctors to deliver survivor-focused risk based  
38 health care was tested successfully by a Dutch group. The study showed that  
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8 patients would see their family doctor for long-term follow-up: the family doctors  
9 were interested in sharing survivors' care; and family doctors would return the  
10 necessary medical information needed for continued follow-up.<sup>297</sup> Appropriate  
11 education of the family doctors, which has resource implications, was a key  
12 finding of this study. More recently this group has shown that a web based  
13 survivor care plan can facilitate the long-term care of survivors by family  
14 doctors.<sup>30<sup>28</sup></sup>

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

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37 We have shown that it is possible to predict which survivors of childhood cancer  
38 are at significant risk of developing moderate to severe late effects and require  
39 moderate or high intensity long-term follow. Importantly we have also shown in  
40 our small population based cohort of five year survivors that there is a group of  
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8 survivors who can be reliably identified who ~~may~~ be discharged from clinic  
9 based follow-up and followed up by annual questionnaire or telephone contact.  
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11 Our findings need confirmation in a prospective cohort study that has the power  
12 to adjust for all confounding variables and in particular for length of follow up.  
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15 Structured, risk-adapted follow-up of childhood cancer survivors following  
16 evidence-based guidelines would reduce cost ineffective or excessive  
17 evaluations and focus individual health care delivery. Education of survivors and  
18 health care providers will hopefully reduce the burden of chronic health problems  
19 and improve quality of life for the growing population of children and young  
20 people who have been treated for cancer.  
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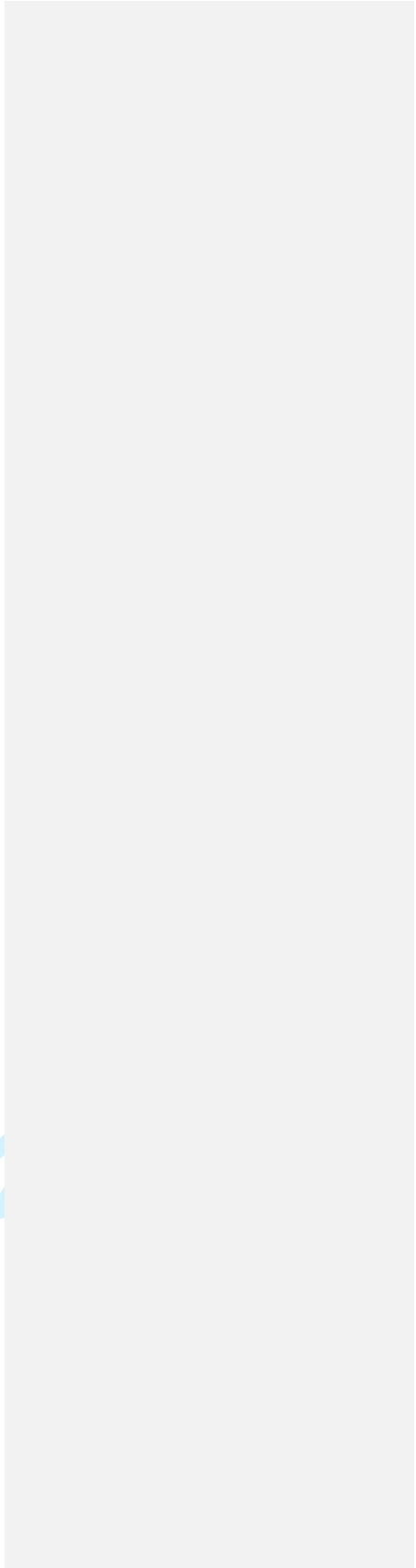
### 35 **Acknowledgements**

36  
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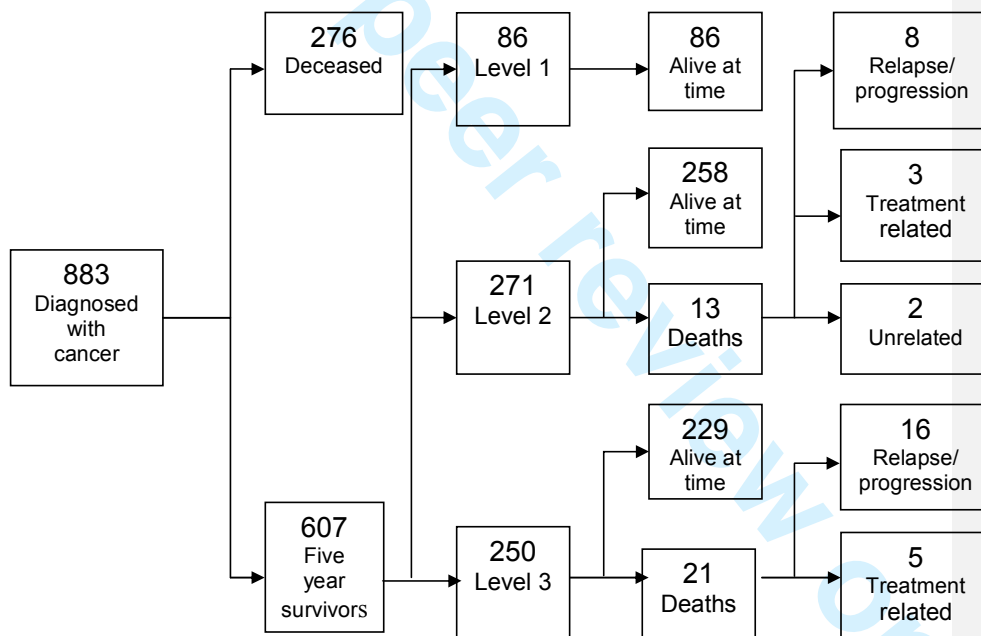
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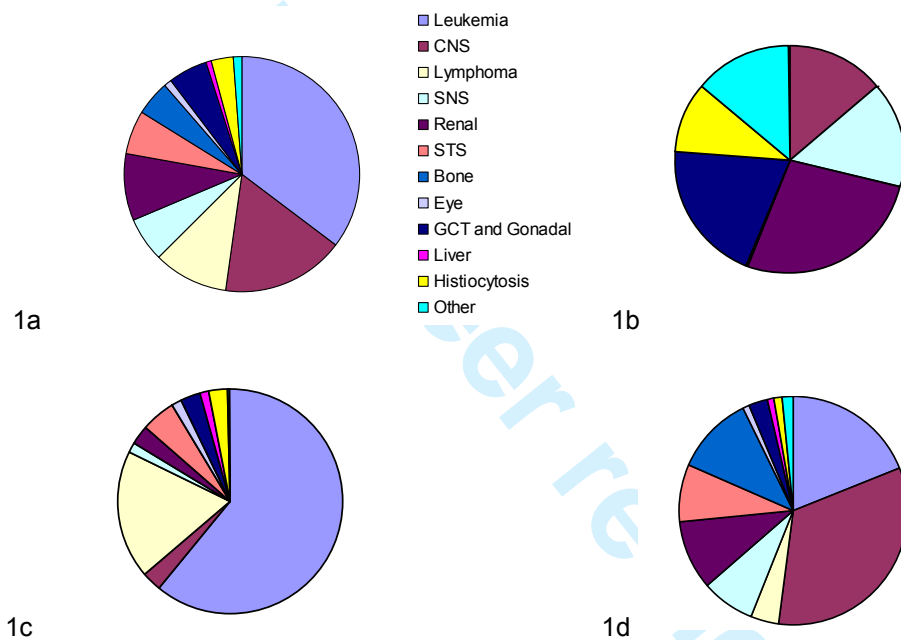
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**Figure 1. Study flow of childhood and teenage cancer patients.**

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.

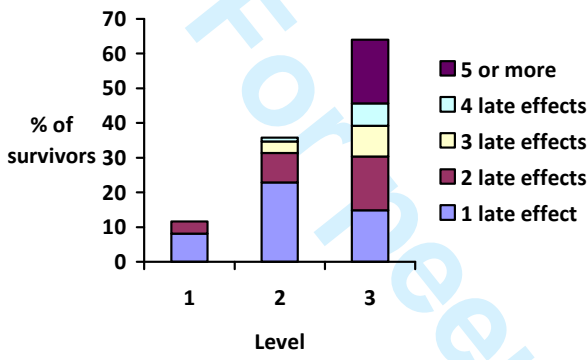


**Figure 2 Diagnoses of five year survivors (n=607)**

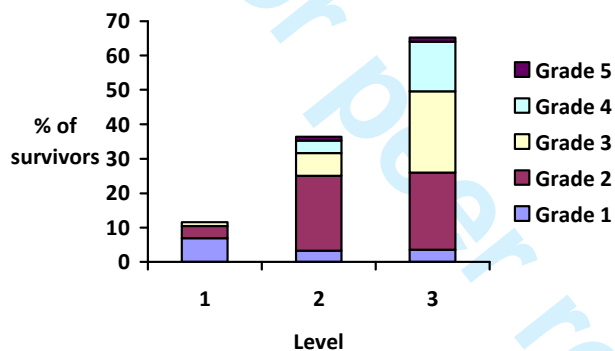
1a. All survivors (n=607), 1b. Level 1 (n= 86), 1c. Level 2 (n=271), 1d. Level 3 (n=250). Abbreviations: CNS – central nervous system tumours, SNS – sympathetic nervous system tumours, GCT – germ cell tumours, STS – soft tissue sarcomas



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**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).<sup>197</sup>

**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](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

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8 collection for the study, analysed the data and revised the draft paper. PM-S  
9 analysed the data and drafted and revised the paper. WHBW designed data  
10 collection tools, monitored data collection for the study, analysed the data, and  
11 drafted and revised the paper. All authors had full access to all of the data in the  
12 study and can take responsibility for the integrity of the data and the accuracy of  
13 the data analysis.  
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### 20 21 22 **Data sharing statement**

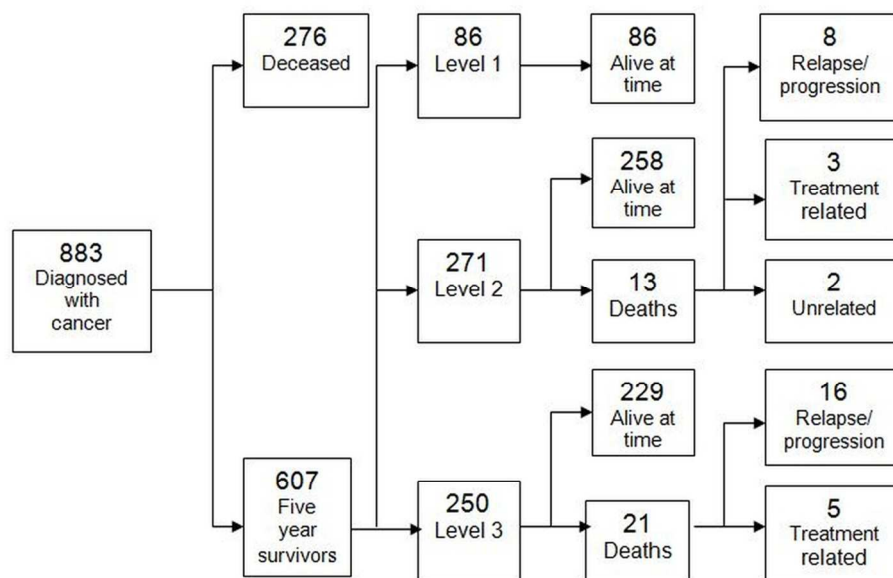
23 Dataset available from the corresponding author at  
24 [angela.edgar@luht.scot.nhs.uk](mailto:angela.edgar@luht.scot.nhs.uk). Consent was not obtained but the presented  
25 data are anonymised and risk of identification is low.  
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### 30 31 32 **Ethical approval**

33 Ethical approval for this study was requested from the Lothian Research Ethics  
34 Committee (LREC). On review by the LREC, the committee decided that ethical  
35 approval was not required as long-term follow-up of childhood cancer survivors  
36 was deemed to be an acceptable and routine part of clinical practice and there  
37 were no experimental interventions.  
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### 44 45 46 **Funding**

47 No specific funding was received for this research.  
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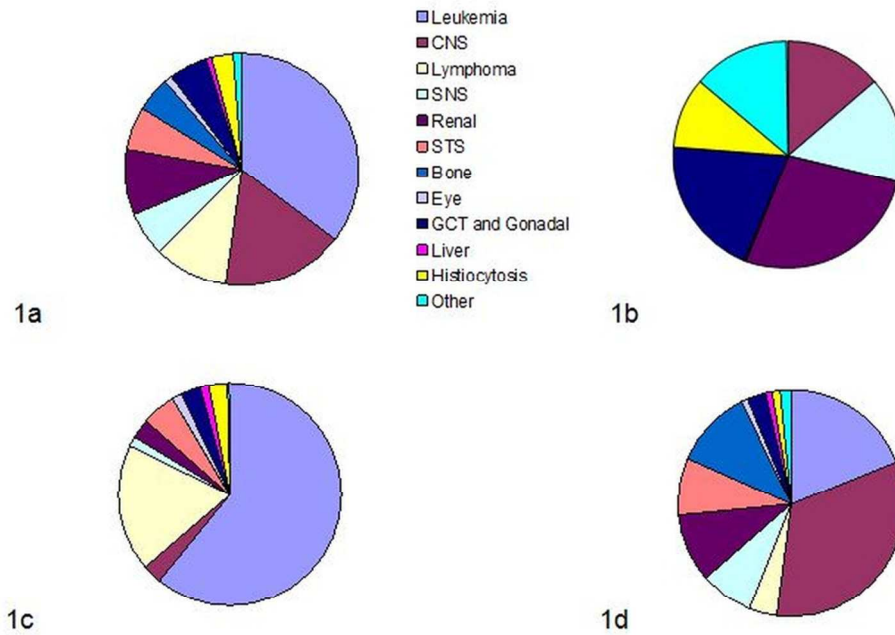


**Figure 1. Study flow of childhood and teenage cancer patients.**

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.

103x90mm (300 x 300 DPI)



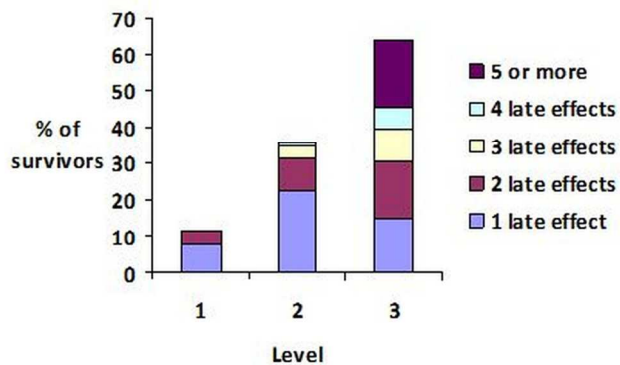


**Figure 2 Diagnoses of five year survivors (n=607)**

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

90x94mm (300 x 300 DPI)





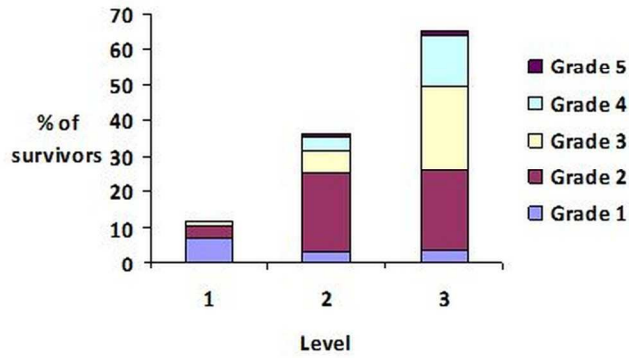
**Figure 3**

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

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**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).<sup>19</sup>

129x90mm (300 x 300 DPI)

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