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Survivors of childhood cancer lost to follow-up can be re-engaged into active long-term follow-up by a postal health questionnaire intervention

A.B. Edgar [a,*], S. Borthwick [b], K. Duffin [b], P. Marciniak-Stepak [c], W.H.B. Wallace [a]

[a] Department of Oncology, Royal Hospital for Sick Children, Edinburgh, UK
[b] University of Edinburgh Medical School, Edinburgh, UK
[c] Department of Paediatric Oncology, Poznan University of Medical Sciences, Poland

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ABSTRACT

Lifelong long-term follow-up (LTFU) is recommended for all survivors of childhood cancer. National guidelines recommend risk-stratified levels of follow-up by a multidisciplinary team, in an age-appropriate environment. Many survivors do not participate in long-term follow-up.

Objective: To re-engage childhood cancer survivors lost to follow-up in late effects programmes by means of postal questionnaire.

Population and methods: Retrospective cohort study of all children (<19 years) diagnosed with cancer in a single institution in the UK between 1971 and 2003. All lost to follow-up survivors (not seen in clinic >2 years) were sent a postal health and well-being questionnaire.

Results: 831 patients were diagnosed with childhood cancer between 1971 and 2003, with 575 long-term survivors (overall survival rate 69%). Information was available on 550 survivors (males 290 (53%), median age (range) at review 18.8 (5.4–44.2) years and at diagnosis 5.0 (0.0–18.8) years, and disease free survival (range) was 10.8 (1.0–37.4) years. Of the 550 survivors, 256 (46%) were lost to follow-up. 99 (39%) of lost to follow-up survivors returned completed postal questionnaires (58% female). 45% of responders reported at least one late effect, 36% mild-moderate, and 8% severe-life threatening. 19% reported two or more late effects. 74% of all childhood cancer survivors are now in active follow-up.

Conclusions: Almost half (46%) of all long-term survivors of childhood cancer are lost to follow-up, Postal follow-up is an effective means of re-engaging more than one third of survivors of childhood cancer in active long-term follow-up, half of whom had at least one late effect.

1. Introduction

More effective treatments for childhood cancer mean that almost 80% of children will survive more than five years from diagnosis, compared with survival rates of 25% in the 1960s.[1] As a result, there is a rapidly growing population of young adult survivors of childhood cancer. In the UK, it is estimated that 30,000 young adults, or 1 in 630 of the young adult population, is a survivor of childhood cancer.[1,2] However, as many as two thirds of survivors are at increased risk of

* *Corresponding author:* Address: Department of Haematology/Oncology, Royal Hospital for Sick Children, 17 Millerfield Place, Edinburgh EH9 1LW, UK. Tel.: +44 131 536 0420; fax: +44 131 536 0430.
E-mail address: angela.edgar@luht.scot.nhs.uk (A.B. Edgar).
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morbidity and even mortality, due to adverse late effects secondary to cancer or cancer therapy.[3–5] Treatment related late complications include secondary malignancies, organ system damage, cognitive impairment and psychosocial disabilities.[6,7]

A greater awareness of late complications dictates the need for vigilant long-term follow-up of survivors, with early intervention, treatment, and appropriate counselling. There is no available evidence to define an optimum model of follow-up for long-term survivors, and there is currently wide variation in clinical practice.[8] In some centres many survivors are followed up in paediatric oncology clinics long into adulthood. It is known that many survivors are lost to follow-up, particularly as they enter adulthood and become responsible for their own health[9] Survivors are often unaware of their past medical history and do not know that they may be at risk of treatment related late complications.[10] The appropriate transition to adult services is hampered in many centres by the lack of adult physicians with specialist knowledge of the late complications of childhood cancer.[11]

With increasing time from the end of treatment, the emphasis in follow-up clinics shifts from disease surveillance to toxicity monitoring and screening, with five years from diagnosis signifying a major milestone of 'cure' and transitioning to long-term cancer survivor. Although life-long follow-up is recommended for all survivors not all survivors require the same intensity of follow-up. The Scottish Intercollegiate Guidelines Network (SIGN 76) has developed an evidence-based approach to LTFU, incorporating the risk-based levels of follow-up described by the UKCCLG Late Effects Group in 2001.[12,13] The risks of developing treatment related late effects depend upon the underlying malignancy, the site of the tumour, the type of treatment and the age at time of treatment.

Current practice in Edinburgh is to follow survivors up indefinitely within the paediatric environment; there is no standard procedure for risk-based follow-up, no established nurse-led services, no active discharge or transfer of care to primary care physicians, and no transition to adult late effects services. The aim of this study was to evaluate the impact of an intervention to re-engage patients lost to follow-up in a survivorship programme using postal questionnaires on health and wellbeing. Survivors were assigned a risk category as described in SIGN 76, and the burden of adverse health outcomes was determined for the cohort of survivors lost to follow-up.

2. Methods

2.1. Study population

All patients aged <19 years, who were treated for childhood cancer at the Royal Hospital for Sick Children in Edinburgh between 1971 and 2003, and who were 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 medical records. The last Late Effects Clinic attendance date for all patients was recorded from regional electronic hospital records system (NHS Lothian TRAK) or from medical notes. Those patients not seen in the Late Effects Clinic within the last two years were identified as not followed up (NFU). Deceased patients and patients less than five years from diagnosis were excluded from the study.

2.2. Data collection

All survivors identified as not followed up (NFU) were sent a questionnaire, designed by the authors, with an accompanying letter informing them of the benefits of long-term follow-up and invited to return the completed document using the prepaid envelope provided. Two months after the initial questionnaire, a reminder letter was sent to those non-respondents. Patient contact and primary care physicians' details were obtained from the regional electronic medical records system (NHS Lothian TRAK system). Patient characteristics including diagnosis, date of diagnosis and date of treatment completion were collected from medical records. If the questionnaire was returned by the Royal Mail undelivered, the registered primary care physician was contacted to confirm their current address. If the patient was no longer registered at their original practice, NHS Lothian Practitioner Services was contacted for the details of the patients' new primary care practice and subsequently contacted to ascertain the current postal address of the patient. The questionnaire was then re-sent to the new address.

2.3. Measures

The questionnaire sent out to survivors lost to follow-up was designed to evaluate physical health problems and to gather information on the education, social issues, family health and current follow-up status, as well as assessing the respondent's knowledge of the potential adverse effects of the cancer treatment. The patients received a tailored version of the questionnaire depending on their age. The parents of patients aged 5–12 years were invited to complete the questionnaire on their child's behalf. The parents of patients aged 13–15 years were invited to complete the questionnaire on their child's behalf or to offer the child the opportunity to complete it themselves. Patients over 16 years were invited to complete the questionnaire themselves.

2.4. Risk stratification by SIGN levels of follow-up

SIGN Guideline 76 has identified three groups of survivors who require an increasing intensity of follow-up: Level 1 (low risk): patients followed up annually or biennially by nurse-led postal or telephone contact and supported by primary care; Level 2 (intermediate risk): these patients could be followed up in a nurse-led clinic or by primary care, supported by the Late Effects Multidisciplinary Team; Level 3 (high risk): these patients require specialist-led hospital based clinics delivered by a multidisciplinary team.[12] Two independent members of the oncology team assigned risk-stratified levels of follow-up retrospectively to all survivors.

2.5. Grading of late effects

All late effects were identified from the patient information provided in the physical health problems section of the

questionnaire. 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 by in the UK by the Children's Cancer and Leukaemia Group (CCLG). The CTCAEv3.0 tool can be used for acute and chronic conditions in patients with cancer and grades conditions as mild (grade 1), moderate (grade 2), severe (grade 3), life-threatening or disabling (grade 4), or adverse event-related death (grade 5). To investigate and reduce inter-observer variability, graded adverse events were compared and inconsistencies were discussed and detailed coding rules were developed (available on request form the authors).

2.6. *Ethical approval*

Ethical approval for this study was requested from the Lothian Research Ethics Committee (LREC). On review by LREC, the committee decided that ethical approval was not required as long-term follow-up of cancer survivors was deemed to be an appropriate part of clinical practice.

2.7. *Analysis*

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

3. Results

3.1. *Participation in long-term follow-up*

Between 1971 and 2003 at the Royal Hospital for Sick Children in Edinburgh, 831 patients, aged <19 years, were diagnosed with childhood cancer, including tumours of the central nervous system. 575 survived at least five years giving an overall survival rate of 69%. Of 575 five-year long-term survivors, information was available on 550 survivors (males 290, 53%). The remaining 25 patients were patients who had been diagnosed and registered in Edinburgh but who were not treated by the haematology/oncology team and on whom there was no other information available (Fig. 1). At the time of the study the median age (range) was 18.8 (5.4–44.2) years, at diagnosis 5.0 (0–18.8) years and disease free survival (range) 10.8 (1.0–37.4) years.

Of the 550 survivors, 256 (46%) were not followed up in the Late Effects Clinic. Of the not followed up survivors, 99 returned the postal questionnaire (58% female, overall response rate 39%) and 157 (61%) could not be traced or did not respond. 80% of the NFU group were more than 10 years from diagnosis and tracing survivors was difficult. However, there was no difference in survival interval between the responders and non-responders. The majority (87%) of replies from survivors were received within one month (median 15 days, range 3–50 days). 37 (14%) questionnaires were returned by Royal Mail undelivered, 29 (78%) of these were re-sent to updated addresses, eight (28%) of these were returned complete. Six (2%) of the NFU patients were unable to be traced to a current UK address; five of these patients are now living outside the UK. A significant number of NFU patients (23%), are involved in clinical review, either within the paediatric setting locally or in other hospital settings in the UK or overseas, but no clinical correspondence has been received for patients attending other hospital clinics. Of the 99 responders, one declined to participate, two returned incomplete questionnaires, resulting in 96 (38%) returned completed questionnaires for analysis. Thirty-four (34%) of the responders requested a follow-up appointment in the Late Effects Clinic and 93 (94%) agreed to follow-up by two-yearly postal questionnaire. Postal follow-up resulted in a 37% increase in long-term survivors of childhood cancer engaging in follow-up with almost three quarters (74%) of all survivors of childhood cancer now in an active survivorship programme.

Characteristics for the NFU survivors, including responders and non-responders are presented in Table 1.

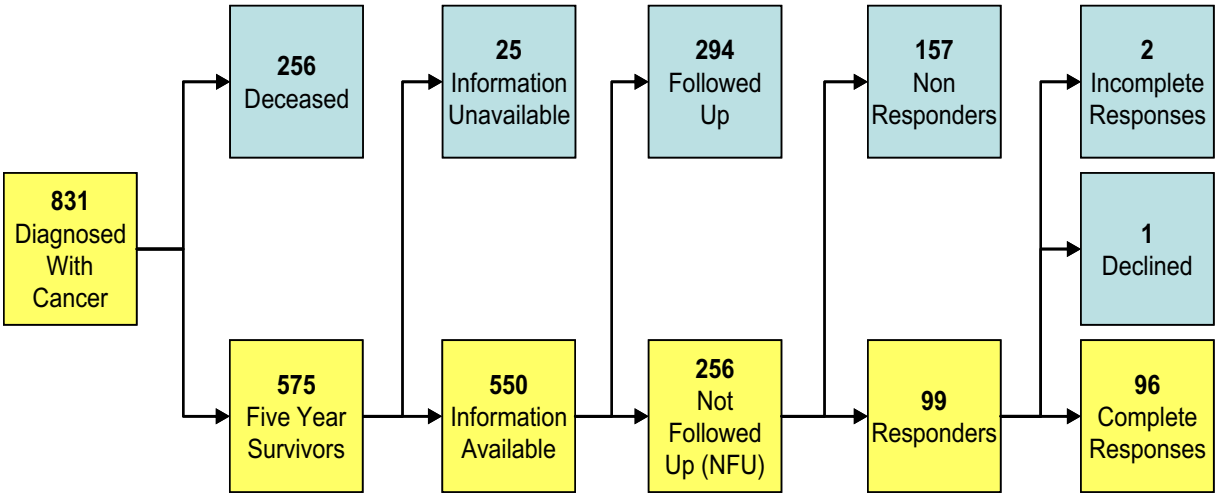

Fig. 1 – Study flow of the childhood cancer survivors showing the not followed up population and their response to the questionnaire.

Table 1 – Demographic characteristics of the total NFU, responder and non-responder populations.

Characteristic	All NFU (*n* = 256)		Responders (*n* = 99)		Non-responders (*n* = 157)	
	No.	%	No.	%	No.	%
Sex						
Male	125	48.8	42	42.4	83	52.9
Female	131	51.2	57	57.6	74	47.1
Current age, years						
5–9	17	6.6	4	4.0	13	8.3
10–14	33	12.9	11	11.1	22	14.0
15–19	57	22.3	25	25.3	32	20.4
20–24	63	24.6	22	22.2	41	26.1
25–29	36	14.0	12	12.1	24	15.3
30–34	26	10.2	15	15.2	11	7.0
35–39	15	5.9	4	4.0	11	7.0
40–44	9	3.5	6	6.1	3	1.9
Median, range	21.8	6.8–44.2	22.4	7.6–44.2	21.4	6.8–42.3
Age at diagnosis, years						
0–4	135	52.7	54	54.5	81	51.6
5–9	63	24.6	25	25.5	38	24.2
10–14	52	20.3	19	19.2	33	21.0
15–19	6	2.4	1	1.0	5	3.2
Median, range	4.6	0.0–18.8	4.4	0.1–15.8	4.8	0.0–18.8
Time from diagnosis, years						
5–9	51	20.0	15	15.2	36	22.9
10–14	71	27.7	25	25.3	46	29.3
15–19	55	21.5	25	25.3	30	19.1
20–24	40	15.6	15	15.2	25	15.9
25–29	22	8.6	11	11.1	11	7.0
30–37	17	6.6	8	8.1	9	5.7
Median, range	16	5–38	16.5	5.7–37.7	14.7	5.3–35.5
Disease free survival, years						
0–4	9	3.5	2	2.0	7	4.5
5–9	63	24.6	21	21.2	42	26.8
10–14	65	25.4	24	24.2	41	26.1
15–19	53	20.7	23	23.2	30	19.1
20–24	37	14.5	15	15.2	22	14.0
25–29	18	7.0	8	8.1	10	6.4
30–35	11	4.3	6	6.1	5	3.2
Median, range	14.2	2.4–35.5	15.6	2.9–35.5	13.1	2.4–32.5
Time since last seen, years						
2–4	101	39.5	46	46.5	55	35.0
5–7	69	27.0	22	22.2	47	29.9
8–10	47	18.4	16	16.2	31	19.7
11–12	14	5.5	5	5.1	9	5.7
Unknown	25	9.8	10	10.1	15	9.6
Median, range	5.5	2.0–12.2	4.9	2.0–12.2	5.7	2–12.2

The distribution of primary diagnostic categories for the 256 lost to follow-up survivors is shown in Fig. 2a. In the NFU survivors, the most frequent primary diagnoses were leukaemia in 96 (38%), representing 49% of our total leukaemia population (*n* = 197); and CNS tumours in 32 (12%) representing 34% of our long-term survivors of CNS tumours (*n* = 34). In the 96 responders, the most frequent primary diagnoses were leukaemia in 43 (43%); and soft tissue sarcoma in 13 (13%). In the 157 non-responders, the most frequent primary diagnoses were leukaemia in 53 (34%); and CNS tumours in 25 (16%).

3.2. *Therapy-based risk stratification and burden of adverse health outcomes in survivors not followed up*

Retrospective assignment of follow-up level 5 years from diagnosis, for all survivors, identified 85 (16%) survivors level 1, 255 (46%) level 2, and 210 (38%) level 3. Of the followed-up survivors, 29 (10%) were level 1, 127 (43%) level 2, and 138 (47%) level 3. Of the survivors lost to follow-up 56 (22%) were level 1, 128 (50%) level 2, and 72 (28%) level 3 (Fig. 3). From our childhood cancer survivorship registry almost half of patients are lost to follow-up, 78% of whom are considered to be at

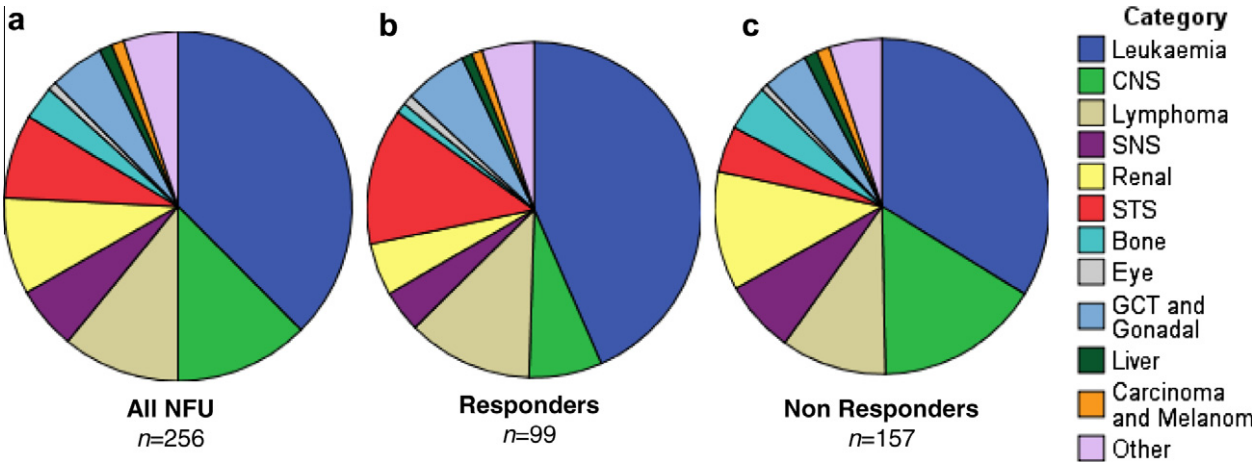

Fig. 2 – Primary diagnostic categories for the total NFU (a), responder (b) and non-responder (c) populations Abbreviations: CNS, central nervous system tumours; SNS, sympathetic nervous system tumours; STS, soft tissue sarcoma; GCT, germ cell tumour.

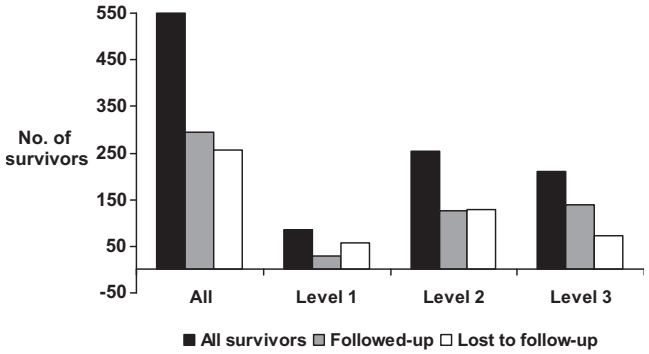

Fig. 3 – Risk-stratified level of survivors according to follow-up status.

moderate to high risk of developing late adverse health outcomes.

3.3. *Socio-demographic characteristics of responders*

Of the 96 responders that returned completed questionnaires, 76 (79%) were aged 16 and over (median age (range): 24.7 (16.2–44.2) years). Of these survivors, 33 (43%) lived with their parents; 27 (36%) lived with a partner; and 46 (60%) were single. Nineteen (25%) had smoked or were ex-smokers; 14 (18%) currently smoke; and 61 (80%) drank alcohol. 51 (67%) were employed; and 24 (32%) had life insurance. Ten (13%) had given birth or fathered children; 23 (30%) had discussed fertility issues with a doctor; and eight (10%) had been told they were unlikely to have children. Twenty (21%) of the responders were less than 16 years (12.6 (7.6–15.8) years), all of whom lived with their parents and were in full time education.

3.4. *Health problems and late effects*

Of the total 96 responders, 29 (30%) self-reported attendance at regular hospital based follow-up clinics and 79 (82%) had visited their primary care physician in the last year: there was no correspondence available in the medical records and no further details available. Fifty-six (58%) had taken prescription medication in the last year and 17 (18%) had used complementary or alternative therapies. Twenty-three (24%) described their health as excellent; 47 (49%) as good; 20 (21%) as fair; and 4 (4%) as poor. Fifty-four (56%) said they were concerned about their health considering their history of cancer and 49 (51%) felt they were not educated about the possible side-effects of treatment for cancer.

Twenty-three (24%) reported no health problems, 45 (47%) reported one-to-two health problems, 20 (21%) reported three-to-four health problems, five (5%) reported five-to-six health problems and three (3%) reported seven-to-ten health problems (Table 2).

Fifty-three (55%) of the 96 responders reported no treatment related late effects. 43 (45%) reported at least one late effect, of these 35 (36%) had one mild to moderate late effect (grade 1 or 2), and eight (8%) had one severe to life-threatening late effect (grade 3 or 4) (3). Twenty-five (26%) reported only one late effect and 18 (19%) reported two or more late effects (Table 3).

The 96 responders self-reported 188 individual health problems in total. The most commonly reported health problems were: visual (30, 16%); migraines and headaches (21, 11%); breathing or lung (20, 11%); stomach, liver, bowel (19, 10%); and weakness (18, 10%) (Fig. 4a). It was possible to relate self-reported health problems to cancer treatment in 85 incidences, although this is likely to be an underestimate

Table 2 – Self-reported health problems of the NFU responder population ($n = 96$).

Health problems	No.	%
None	23	24.0
1–2	45	46.9
3–4	20	20.8
5–6	5	5.2
7–10	3	3.1

Table 3 – Late effects graded with Common Terminology Criteria for Adverse Events (CTCAE) version 3 in the NFU responder population (*n* = 96).

Late effects	No.	%
No	53	55.2
Yes	43	44.8
One	25	26.0
Two or more	18	18.8
Grade		
1 or 2	35	36.5
3 or 4	8	8.3

(Fig. 4b). These 85 treatments related late effects were then graded according to the Common Terminology Criteria for Adverse Event, Version 3 (CTCAEv3) (Fig. 4c). In total, 85 graded late effects were reported from 43 (45%) of the 96 responders. The most frequently occurring late effects were; weakness (14, 16%); stomach, bowel, liver (13, 15%); hormonal (8, 9%); and hearing (8, 9%). Hearing adverse events were accountable for three (33%) of the severe to life-threatening late effects; weakness for 10 (24%) of the moderate late effects; and migraines and headaches for nine (26%) of the mild late effects.

4. Discussion

At a single institution with a longstanding commitment to long-term follow-up of survivors, almost half (46%) of long-term survivors of childhood cancer are lost to follow-up after a median follow-up of 16 years (range 5–38 years), with 78% considered to be at moderate to high risk of developing late complications of cancer treatment. The introduction of a postal follow-up questionnaire led to re-engagement of more than one third of survivors in active follow-up and a total of 74% of all long-term survivors of childhood cancer participating in a survivorship programme.

In our self-reported health assessment of survivors lost to follow-up, 45% had at least one treatment related late effect. Over a third had one mild to moderate late effect, and almost 10% had one severe or life threatening late effect. Approximately one fifth reported two or more late effects. Almost half of survivors reported one-to-two health problems and one fifth, three-to-four health problems. This is a high burden of disease considering the young age of the study population (median age 22.4 years, range 7.6–44.2 years). Reassuringly, a quarter of survivors described their health as excellent, and almost half described it as good. The results of our study are consistent with other studies that have also assessed the burden of adverse effects, all reporting at least one late ef-

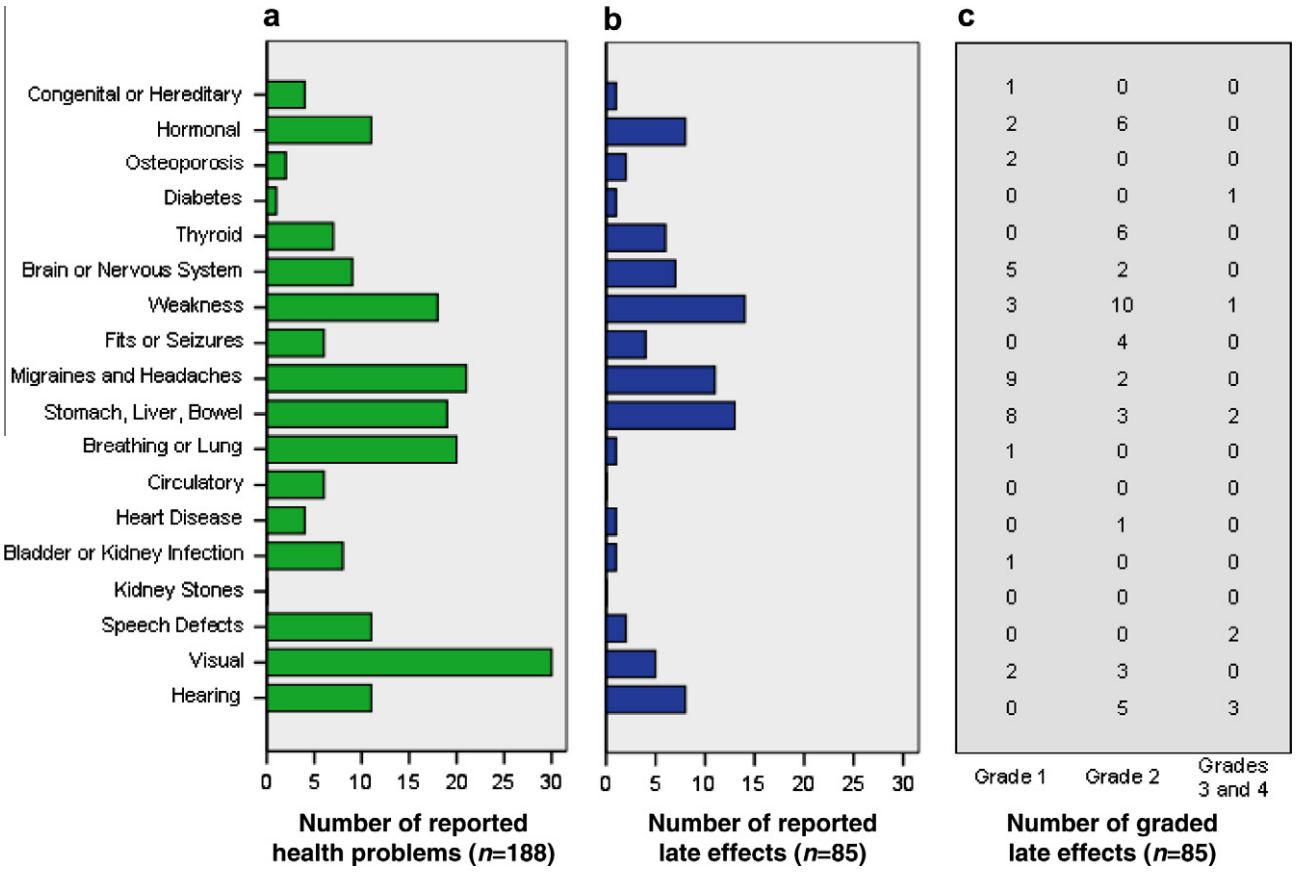

Fig. 4 – From the completed questionnaires of the NFU survivors, there were 188 self reported health problems (a). The health problems were likely to be directly related to treatment in 88 cases (b) and these treatment-related late effects were graded according to the Common Terminology Criteria for Adverse Event, Version 3 (CTCAEv3) (c).

fect in more than 40% of survivors.[5,14,15] More than half of survivors were concerned about their health considering their history of cancer. Half of them reported that they were not educated about the possible side-effects of cancer treatment, reiterating the importance of education and counselling of survivors to prepare them for the potential health problems they may encounter in adulthood.[10]

As has been reported by other studies, the number of survivors involved in late effects follow-up programs decreases with increasing age of survivor.[16] Survivors generally become lost to follow-up as they get older, or as they reach adulthood and become more domiciliary mobile. A limitation of our study is the low response rate (39% overall: 58% female) to the questionnaire in the NFU group. Leukaemia survivors were the most frequent responders (43%) reflecting the proportionately larger population of survivors. Additionally, they have been reported in other studies to be the survivors subject to the most hospital follow-up.[16] With increasing time from diagnosis the proportion of responders engaging in active follow-up decreases. This may reflect the heightened level of anxiety around the possibility of disease recurrence within the first few years after completing treatment. As patients remain disease free and enjoy good health they are less concerned about late sequelae of treatment and often unaware of potential late effects and hence become less likely to attend for follow-up. The low response rate may reflect a sense that the treatment is over and it is now time to get on with the rest of my life.

A study by Taylor et al. (2004), which involved sending a postal questionnaire to childhood cancer survivors in the UK, observed a low response rate of 22%.[8] There may be numerous reasons for survivors failing to return the questionnaire. For many, no contact details are available. In our study only 22% of all lost to follow-up survivors with CNS tumours responded to the questionnaire. This may reflect that they have not been treated solely within the paediatric oncology setting and may have received most of their care from neurosurgeons, who were happy to discharge them from follow-up a few years after surgery. As with most other patients treated for childhood cancer from the 1960s to mid 1980s, patients in this study were discharged from care around five to ten years off treatment as little was known regarding long-term health problems.[16] These patients may remain unaware of the potential for late effects and be less inclined to return the questionnaire. It remains very important to educate survivors about the importance of long-term follow-up and the long latency of the onset of late complications.

Based on a risk-stratified intensity of follow-up, the majority of survivors lost to follow-up in our study were considered to be level 2, at moderate/intermediate risk of developing late effects. More than one quarter of survivors lost to follow-up were classified as level 3 (high risk) which recommends follow-up in a medically supervised, late effects clinic.[12,13] The concern with this sub-population is the potential for undiagnosed and untreated late effects. Reassuringly, most survivors lost to follow-up (82%) were in contact with their general practitioner at least once a year. Indeed, almost a third may already be attending hospital based clinics for chronic sequelae of childhood cancer, but no information was available in their children's hospital notes. However, it is known that many general practitioners and other hospital clinicians are not aware of the late sequelae of treatment for these survivors.[17] Improving communication, between tertiary, secondary and primary care is essential to ensure that this group of young adults receive appropriate follow-up care.

The majority of long-term survivors of childhood cancer who engage in hospital based follow-up are seen in the paediatric environment. From our own cohort of survivors, 58% were over 18 years old. More than half of level 3 survivors lost to follow-up were aged 18 years and over and may feel that follow-up in a paediatric environment is inappropriate. A more appropriate system of follow-up is required for those level 3 patients aged 16–18 years, with adequate planning for their transition into the adult late effects service.[18,19]

The overall aim of long-term follow-up is to have a positive impact on the quality of life and long-term health of adult survivors.[20,21] Long-term follow-up services often focus on the physical late effects and do not address the psychological, social, financial or education needs, lifestyle issues and information needs of the survivor that may adversely affect their quality of life. A recent population based study from Sweden has shown that CNS tumour survivors had poorer educational and social outcomes than non-CNS tumour survivors who had outcomes similar to the general population.[22]

From our study it is clear that many almost half our patients are lost to follow-up, including a substantial proportion of survivors (78%) considered to be at significant risk of developing treatment related late effects. The safety of a therapy-based, risk-stratified follow-up programme for childhood cancer survivors is currently underway. It is anticipated that the results from this study will support the introduction of postal/telephone follow-up for low risk (level 1) patients; nurse led services supported by the late effects multidisciplinary team for intermediate/moderate risk (level 2) survivors and medically supervised hospital based clinics for high risk (level 3) patients.

It is important to be aware that the objective of long-term follow-up is to provide appropriate health surveillance, together with psychosocial support and education of survivors to encourage them to develop into independent adults. Therefore, delivery of a national, comprehensive, risk-based approach to long-term follow-up, in an age-appropriate environment, supported by nurse-led services, is essential to meet the needs of a growing community of children, teenagers and young adults who have survived cancer.

Conflict of interest statement

None declared.

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