Original Article

A Report from the Singapore Childhood Cancer Survivor Study (SG-CCSS): A Multi-institutional Collaborative Study on Long-term Survivors of Childhood Cancer, Initial Analysis Reporting for the SG-CCSS

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Abstract

Introduction: Worldwide, the survival rates among childhood cancer patients are increasing. As such, assessing the risk of late effects and complications are increasingly becoming more important. The degree of risk of late effects may be influenced by various treatment-related factors. Materials and Methods: The Singapore Childhood Cancer Survivor Study (SG-CCSS) consists of all individuals who survived at least 2 or more years after treatment for cancer diagnosed during childhood or adolescence. Phase I of SG-CCSS is the identification of all eligible patients between 1981 and 2005. Results: There were a total of 1440 patients registered in the Singapore Childhood Cancer Registry. Among these, 704 (48.9%) patients were from the KK Women's and Children's Hospital (KKH) and 626 (43.5%) were from the National University Hospital (NUH). Of all the registered patients, the most common cancer in childhood was leukaemia [42.6% (n = 613)] and the second most common was brain tumour [14.9% (n = 215)]. A total of 1043 (72.4%) patients were surviving, of whom 839 (80.4%) were long-term survivors. Haematological malignancies were found in 492 (58.6%) survivors whilst 347 (41.4%) were diagnosed with various solid tumours. Among leukaemic patients (n = 613), 65.6% (n = 402) were long-term survivors. Acute lymphoblastic leukaemia (ALL) (n = 484) had the highest percentage of [80.9% (n = 392)] of surviving patients, of whom 73.4% were long term-survivors. For brain tumour (n = 215), there were 95 (44.2%) long-term survivors. Conclusion: Preliminary analysis revealed that 58.3% of patients were long-term survivors. Our hope is to tailor all future therapy for childhood cancers, optimising cure rates whilst minimising long-term side-effects.

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Introduction

Worldwide, the survival rates among childhood cancer patients are increasing. Thus, assessing the risk of late effects and complications are increasingly becoming more important.

The Singapore media recently reported cancer to be the number one killer in the country. Approximately 1 in every 250 individuals living in Singapore develops a type of cancer. The crude mortality rate from all cancers in Singapore was 27.1%, as reported in the recent Singapore Cancer Registry Report.[1,2] Between the 1940s and 1970s, few children survived cancer. In the 1960s, researchers discovered ways to design treatment therapies to include combination chemotherapy drugs together with various treatment modalities such as surgery and radiation therapy. As a result of these approaches, an increasing number of children are experiencing sustained survival and cure rates.

With the use of current therapies, more than 80% to 90% of children diagnosed with cancer can be expected to be long-term survivors. Unfortunately, as a consequence of their disease and the treatments they received, these survivors now face significant risks to their health for the rest of their lives.

It has been shown that, to varying degrees, long-term survivors of childhood cancer are at risk of developing second cancers and of experiencing organ dysfunction such as heart failure, renal insufficiency, endocrine dysfunction, reduced growth and development, decreased fertility,

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neuro-cognitive dysfunction, and even early death.[3-13] The degree of risk of late effects may be influenced by various treatment-related factors such as the intensity, duration and timing of therapy, as well as by individual characteristics such as the type of cancer diagnosis, the person's sex, and age at time of treatment, and genetic factors as indicated by, for example, a family history of cancer.[14,15]

In 2007, we set up a multi-institutional collaborative study called the Singapore Childhood Cancer Survivor Study (SG-CCSS), funded by the Singapore Cancer Syndicate, to investigate and follow this subset of long-term survivors of childhood cancer diagnosed and treated in Singapore. They present researchers with both an obligation and unique opportunity to: (1) Gain new knowledge about long-term effects of cancer and therapy that will help design treatment protocols and intervention strategies which will increase survival and minimise harmful health effects; (2) Educate survivors about the potential impact of cancer diagnosis and treatment, provide follow-up care, and implement programmes for the prevention and early detection of late effects; and (3) To provide a data resource for the entire scientific research community of Singapore.

The aims of our SG-CCSS are to be met in 4 phases:

Phase I: Identification of the patient population and the formation of the multi-institutional study group. This data will be integrated with the National Medical Research Council (NMRC) and Singapore Cancer Syndicate (SCS) funded Singapore Childhood Cancer registry (SCCR) for completeness of information gathered. This in turn will provide unparalleled resource for the scientific research community in Singapore. The development of a multi-disciplinary Long-term Survivors/Late Effects Clinic is to occur simultaneously.

Phase II: Aetiology research – investigations into molecular aetiology with a focus on genetics and environmental factors, which could either be laboratory or non-laboratory based, as well as investigations into the aetiology of second malignancies.

A prospective collection of tumour tissue and family DNA genome for study on future risk of development of cancer, secondary cancers and toxicity will also be performed.

Phase III: Outcomes Research – to perform clinical and analytical research into the mechanisms of and risk factors for adverse late events.

Phase IV: Survivor Education – the debt owed to survivors of childhood cancer is great and thus providing education plays an integral role.

We report here, our results of the initial Phase I, the identification of the patients for the study.

Materials and Methods

Patients

This is a multi-institutional and multi-disciplinary collaborative study consisting of a cohort of all individuals who survived at least 2 or more years after treatment for cancer, leukaemia, tumour, or similar illness diagnosed during childhood or adolescence, under the age of 21 years. Our study is limited to survival for a minimum of 2 years rather than the accepted 5 years, due to the fairly recent establishment of the first formal SCCR and the rather short duration of follow-up time available at the time of initiation of the study. Each participant is recruited through the participating clinical research centres, National University Hospital (NUH) and KK Women's and Children's Hospital (KKH), where he or she was diagnosed and/or treated. In 1997, the SCCR was initiated to study the epidemiology of childhood cancer in Singapore. The study group of patients was selected from the first monograph of the SCCR from 1981 to 2005.

The detailed medical record of each patient was thoroughly reviewed by the study research coordinator. Inclusion was restricted to patients first seen at the Department of Paediatrics, NUH and KKH between January 1981 and December 2005. Every attempt was made to include all the patients seen during the study period. The former date was chosen arbitrarily as a date by which the earliest NUH and KKH census recorded the first patient diagnosed with childhood cancer. The latter date was chosen to allow adequate time for follow-up at the time of the analysis.

Statistical Analysis

All analyses were performed using SPSS15.0. Descriptive statistics was used for quantitative variables and were presented as median (range) and n (%) for qualitative variables.

Results

There were a total of 1440 patients registered in the SCCR. Of the cohort, 57.9% were male and 42.1% were female. Seven hundred and four (48.9%) patients were from KKH, 626 (43.5%) were from NUH, and 110 (7.6%) were from private institutions. Further analysis revealed that 494 (70.2%) patients from KKH were surviving, 186 (26.4%) were dead and 24 (3.4%) were of unknown status at the time of last follow-up. From NUH, 464 (74.1%) patients were surviving, 143 (22.8%) were dead and 19 (3.0%) were of unknown status at the time of last follow-up. From the private institutions, 85 (77.2%) patients were surviving, whilst 24 (21.8%) were dead at the time of last follow-up (Fig. 1).

Of the 1043 (72.4%) patients who were surviving, 839

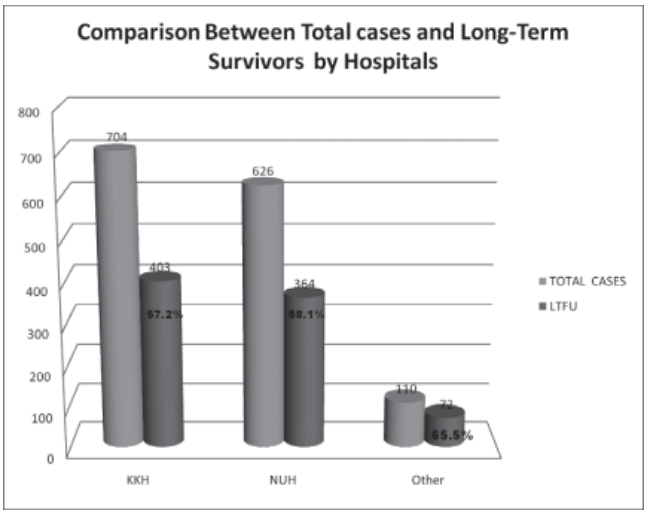

Fig. 1. Comparison between total number of patients and long-term survivors by hospital.

Table 1. SG-CCSS: Summary of Patient Characteristics, Long-term Survivors

Age diagnosis, Median (Range)	4.8 years (range, birth-17.0 years)
Follow-up, Median (Range)	5.5 years (range, 2.0-25.7 years)
Gender	
Male	495 (58.9%)
Female	344 (41.0%)
Ethnicity	
Chinese	603 (71.8%)
Malay	132 (15.7%)
Indian	45 (5.4%)
Other	59 (7.1%)
Hospital	
KKH	403 (48.0%)
NUH	364 (43.4%)
Private	72 (8.6%)
Malignancy Type	
Hematolgic	492 (58.6%)
Solid	347 (41.4%)

KKH: KK Women's and Children's Hospital; NUH: National University Hospital

(58.2%) were alive for at least 2 years or more following from the diagnosis of a childhood cancer and were eligible for the SG-CCSS. There were 495 (58.9%) males and 344 (41.1%) females. The median age of diagnosis of childhood cancer was 4.8 years (range, birth-17.0). The median follow-up was 5.5 years (range, 2.0-25. 7). Of the long-term survivors, a majority of the patients [71.8% (n = 603)] were of Chinese ethnicity, 15.7% (n = 132) were Malay, 5.4% (n = 45) were Indian and 7.1% (n = 59) were others. This ethnic diversity is representative of the multi-cultural and multi-ethnic population in Singapore. Four hundred and ninety-two (58.6%) had haematological malignancies (HM) while 347 (41.4%) were diagnosed with solid tumours (ST). Detailed patient characteristics are shown in Table 1.

The most common cancer was leukaemia 42.6% (n = 613), second was brain tumour at 14.9% (n = 215), and the third was lymphoma 10.3%. (n = 148). The least common cancer was hepatic tumour at 2.4 % (n = 34). The second least common cancers were renal tumours, retinoblastoma and soft tissue tumours representing 3.1%, 3.3%, and 4.2%, respectively. Among a total of 613 patients with a diagnosis of leukaemia, 65.6 % (n = 402) were eligible for the long-term survivors study. Of these, acute lymphoblastic leukaemia (ALL) had the highest percentage of survival [80.9 % (n = 392)] and 73.4% (n = 354) were long-term survivors. Fifty-two (52.5%) patients with acute myeloid leukaemia (AML) were surviving and 37.9 % (n = 37) were eligible for this study. Of the 14 (73.4%) patients with chronic myeloid leukaemia (CML) who were surviving, 10 (50.0%) were long-term survivors. For germ cell tumours, 69 (73.4%) were also eligible for this study. The number of long-term survivors for hepatic tumours was 22 (64.7%), soft tissue sarcoma was 28 (46.7%), renal tumours was 30 (66.7%), bone tumours was 31 (51.7%), lymphoma was 90 (60.8%), brain tumours was 95 (44.2%), and neuroblastoma was 32 (32.0%). Details are presented in Figure 2.

By hospital, 364 (58.1%) of 626 surviving patients from NUH were long-term survivors. A diagnosis of leukaemia had a favourable status with 78.4% surviving and with 65.2% (n = 178) being long-term survivors for all diagnoses. HMs represented the higher percentage of long-term survivors in the SG-CCSS with 61%. Solid tumours were lower at 39.0% of long-term survivors. Renal tumours represented the highest percentage of long-term survivors at 72.2% (Table 2 and Figure 3). Similarly, 403 of 704 (57.2%) surviving patients from KKH were long-term survivors. From a total of 303 patients diagnosed with leukaemia, 222 (73.3%) were surviving of whom 200 (90.1%) were long-term survivors. From KKH, haematologic malignancies also represented the higher percentage of long-term survivors in the SG-CCSS with 61%. Solid tumours were lower at 39.0% among long-term survivors. Germ cell tumours represented the highest percentage of long-term survivors at 78.0% (Table 3 and Figure 4).

Discussion

Recent reports in the Singapore media cite cancer as the number one killer in the country. Worldwide and in

Singapore, the survival rates among childhood cancer patients are increasing. A preliminary analysis from the SG-CCSS revealed that approximately 58% of patients diagnosed with a childhood cancer are long-term survivors. Thus assessing the risk of late effects and complications are increasingly important. The degree of risk of late effects may be influenced by various treatment-related factors. Thus, this subset of long-term survivors of childhood cancer presents researchers both an obligation and a unique opportunity. To our knowledge, this initial summary report from the SG-CCSS is the first to report on the outcome of childhood cancer survivors in Singapore and the surrounding Southeast Asia region.

The male-to-female ratio of survivors in our study was somewhat equivalent. The median age of the diagnosis of childhood cancer was 4.8 years. This may be lower than the actual age, due to the fact that the accepted upper age limit of children and young adults seen and treated at a paediatric hospital in the country is 15 years of age and that the study resulted from the 2 main paediatric centres in the country. However, we hope that this is representative of the population at risk (children aged <15 years). A majority of our patients were of Chinese origin, which is representative of the make-up of the country's multi-ethnic background. However, our study is limited by the definition of long-term survivors to those who are alive for a minimum of 2 years or more from the time of initial diagnosis rather than the widely accepted 5 years. This was a result of our relatively

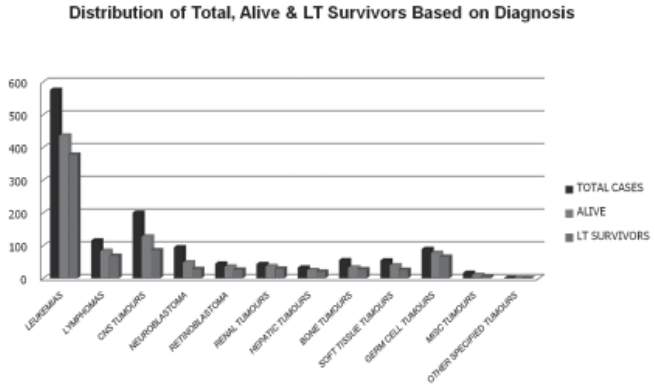

Fig. 2. SG-CCSS: Distribution of survivors by diseases, SCCR total (n = 1440) and long-term survivors.

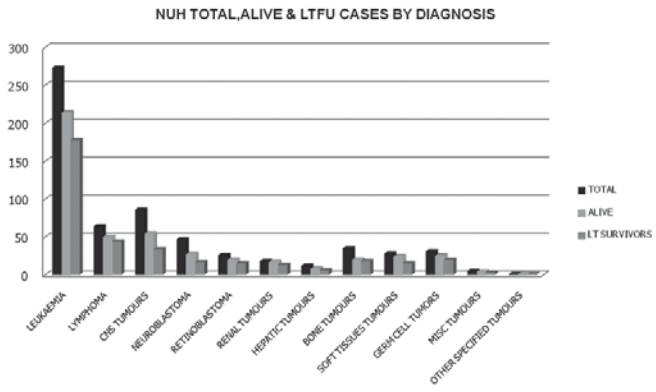

Fig. 3. SG–CCSS: Final analysis of eligible patients by diagnosis from NUH.

Table 2. SG-CCSS: Final Analysis of Eligible Patients from National University Hospital (NUH)

	NUH				
Diagnostic group	**Total**	**Alive**	**LT Survivors**	**% of alive**	**% of LTFU**
Leukaemia	273	214	178	78.4	65.2
Lymphoma	64	50	44	78.1	68.8
CNS tumours	86	54	34	62.8	39.5
Neuroblastoma	47	27	17	57.4	36.2
Retinoblastoma	26	20	15	76.9	57.7
Renal tumours	18	17	13	94.4	72.2
Hepatic tumours	12	8	6	66.7	50.0
Bone tumours	35	20	18	57.1	51.4
Soft tissue tumours	28	24	15	85.7	53.6
Germ cell tumours	31	25	20	80.6	64.5
Miscellaneous tumours	5	4	3	80.0	60.0
Other specified tumours	1	1	1	100.0	100.0
	626	**464**	**364**	**74.1**	**58.1**

Table 3. SG-CCSS: Final analysis of eligible patients by diagnosis from KK Women's and Children's Hospital (KKH)

	KKH				
Diagnostic group	**Total**	**Alive**	**LT survivors**	**% of alive**	**% of LTFU**
Leukaemia	303	222	200	73.3	66.0
Lymphoma	52	34	25	65.4	48.1
CNS tumours	115	74	52	64.3	45.2
Neuroblastoma	48	22	12	45.8	25.0
Retinoblastoma	19	16	12	84.2	63.2
Renal tumours	26	20	17	76.9	65.4
Hepatic tumours	21	17	15	81.0	71.4
Bone tumours	21	13	10	61.9	47.6
Soft tissue tumours	27	16	11	59.3	40.7
Germ cell tumours	59	53	46	89.8	78.0
Miscellaneous tumours	12	7	3	58.3	25.0
Other specified tumours	1	-	-	0.0	0.0
	704	**494**	**403**	**70.2**	**57.2**

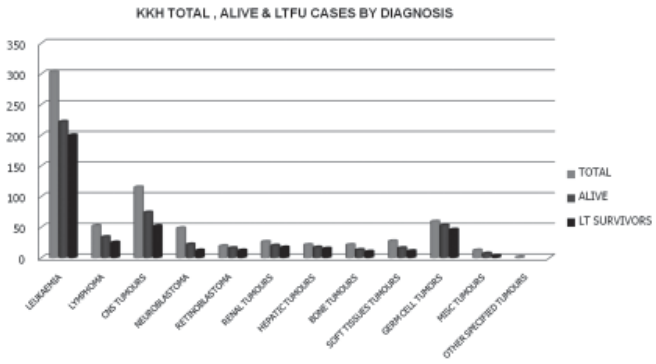

Fig. 4. SG-CCSS: Final analysis of eligible patients by diagnosis from KKH.

new set up of the first formal SCCR, the country's childhood cancer registry. Plans are underway for a close collaboration with the various cancer registries in existence, registries which are more established compared to the SCCR, in order to capture all eligible patients.

Of the long-term survivors, those with a diagnosis of HMs were more represented as expected at 58.6% (n = 492). Those with a diagnosis of STs were slightly less at 41.4% (n = 347). It is well known that leukaemia, specifically ALL is the most common diagnosis in childhood cancer cure rates reaching close to 98% at some centres worldwide. This was also representative at our local centres with children with a diagnosis of ALL occurring most frequently and contributed the most number to the survivor study with 80.9% of long-term survivors.

As previously discussed, this subset of long-term survivors of childhood cancer presents researchers an obligation and a responsibility as well as a unique opportunity for further research. In the future, we hope to focus on various disciplines of molecular and clinical research such as:

1. Outcomes research – Once the initial database of the SG-CCSS is completely established, it will provide a repository of information, and help to conduct innovative clinical and analytical research into the mechanisms of and risk factors for adverse late events.
2. Aetiology Research – molecular aetiology with a focus on genetics and environmental factors (laboratory and non-laboratory based) as well as secondary malignancies. As a prospective collection of tumour tissue and family DNA genome are obtained, studies on future risks of development of cancer, development of secondary cancers as sequelae of various therapies and toxicity will also be performed.
3. Survivor Education – As the debt owed to survivors of childhood cancer is great, education for the survivors is of utmost importance. These individuals may have already experienced significant adverse health effects as a consequence of their cancer therapy. They are almost certain to face others in the future. It is imperative that information that may improve their understanding of their disease and its consequences be shared with them. Coordination of educational activities within the cohort will be carried out. We will be using several methods for educating and informing study participants, including a website, a semi-annual newsletter and informational brochures targeted at sub-groups at risk for particular late effects. In future, participants and investigators will

also communicate via email and via the website which will be made available.

4. Future collaborations with Southeast Asian neighbouring countries will also take place.

Our hope is to tailor all future therapy for childhood cancers to optimise cure rates while minimising residual long-term side effects in order to decrease the healthcare cost burden on future generations of Singapore and the region.

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