ORIGINAL ARTICLE
Pediatrics

JKMS

http://dx.doi.org/10.3346/jkms.2013.28.5.755 • J Korean Med Sci 2013; 28: 755-762

Increasing and Worsening Late Effects in Childhood Cancer Survivors during Follow-up

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Received: 25 September 2012
Accepted: 15 February 2013

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Recent advances in childhood cancer treatment have increased survival rates to 80%. Two out of three survivors experience late effects (LEs). From a group of 241 survivors previously described, 193 were followed at the long-term follow-up clinic (LTFC) of Severance Hospital in Korea; the presence of LEs was confirmed by oncologists. We reported the change in LEs during 3 yr of follow-up. The median follow-up from diagnosis was 10.4 yr (5.1-26.2 yr). Among 193 survivors, the percentage of patients with at least one LE increased from 63.2% at the initial visit to 75.1% at the most recent visit ($P = 0.011$). The proportion of patients having multiple LEs and grade 2 or higher LEs increased from the initial visit ($P = 0.001$ respectively). Forty-eight non-responders to the LTFC were older and had less frequent and severe LEs than responders at initial visit (all $P < 0.05$). In multivariate analysis, younger age at diagnosis, older age at initial visit, a diagnosis of a brain tumor or lymphoma, and use of radiotherapy were significant risk factors for LEs (all $P < 0.05$). Adverse changes in LEs were seen among the survivors, regardless of most clinical risk factors. They need to receive comprehensive, long-term follow up.

Key Words: Complications; Health; Late Effects; Morbidity; Neoplasms; Survivors

INTRODUCTION

Recent advances in the diagnosis, treatment, and supportive care of childhood cancers have increased the survival rate up to 80% (1). As more survivors of childhood cancers reach adulthood, chronic toxic effects from treatment–the so called "late effects (LEs)"–are also increasing in frequency (2, 3). In the United States, there are about 270,000 survivors of childhood cancers, and about one of every 640 young adults (20-39 yr of age) is a childhood cancer survivor. In general, two out of three of survivors experience at least one late effect (2).

The range of LEs is quite broad and can involve endocrine (including gonadal and growth), cardiovascular, pulmonary, and renal systems, or result in neurocognitive abnormalities (4, 5). Increasing concerns about chronic health conditions and health status, including quality of life, have prompted a call for guidelines for long-term follow-up of survivors of childhood cancers in various regions of the world, and multidisciplinary approach is being performed (6, 7).

There are many published reports on LEs and health status (i.e., general and mental health status). While most of the studies were focused on a single LE or a single disease entity, some large scale studies on overall health status were recently conducted in Western countries (2, 8-10). Due to the large number of childhood cancer survivors, many studies have used public health data or questionnaires instead of confirming LEs by physicians.

We have previously published a report on the overall health conditions of childhood cancer survivors seen at a long-term follow-up clinic (LTFC), the first one to be established in Korea (11). Here we report the follow-up data for these survivors. The purpose of this study was to determine the characteristic changes in LEs in the same cohort of survivors and to present insights for development of well-coordinated, follow-up protocols for survivors.

MATERIALS AND METHODS

In January 2005, an LTFC for childhood cancer survivors was established in Severance Hospital, Yonsei University Health System (YUHS) in Seoul, Korea. A childhood cancer survivor was defined as a person who survived for at least 2 yr after completion of cancer therapy. Members of a society of childhood cancer survivors treated at Severance Hospital were invited to the LTFC. This study included 241 childhood cancer survivors who were included in our previous report on the health status of survivors. All patients were diagnosed before the age of 18 yr and were treated at Severance Hospital between 1980 and 2007. Other inclusion and exclusion criteria for survivor recruitment are described in the previous study (11). While follow-up on a

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pISSN 1011-8934
eISSN 1598-6357

regular basis was recommended for all 241 survivors, only 193 survivors were being followed at the clinic as of February 25, 2011.

Medical records were reviewed to determine treatment history and health risks for each survivor. Many published long-term follow-up guidelines for the survivors were adopted and modified by YUHS to develop a follow-up protocol, taking into consideration the expertise, effectiveness, and regional reimbursement environments of Korea (12-14). Detailed operation of our LTFC is described in the previous report (11).

Data analysis

In the previous study, late effects were defined as adverse events experienced by survivors at least 2 yr after completion of therapy. The severity of each LE was graded according to the Common Terminology Criteria for Adverse Events v3.0 (CTCAE). Based on other reports, the grades were considered as continuous variables in order to compare the severity of LEs between risk groups (15, 16).

Late effects were analyzed in three ways: the number of LEs, the mean severity of LEs, and the sum of LEs grades (sum). Since LEs were classified by both individual organs and body systems, to avoid counting an LE more than once, the number of LEs represents the number of affected body systems (online supplemental Table S1). The mean severity is the arithmetic mean of the severity grades. The sum of grades of LEs takes the sum of all LE grades in each survivor and it reflects both the number and severity of LEs that each survivor has.

Statistical analyses

Health conditions were compared between 48 survivors who were lost to follow-up (non-responders) and the 193 survivors (responders) who were followed. The significance of the number, mean severity, and sum of LEs was tested by chi-square test, Student t-test, paired t-test, and one-way analysis of variance (ANOVA). A correlation analysis (Pearson's coefficient) was also conducted. Non-parametric variables were tested using the Mann-Whitney test. A multiple linear regression analysis was performed to examine the association between clinical risk factors and the number, mean severity, or sum of LEs.

Ethics statement

This is an observational cohort study which is approved by the Yonsei University Health System's institutional review roard (IRB, 4-2008-0268). Informed consent was waived by the board.

RESULTS

Late effects–initial versus recent visit

For the 193 survivors (responders), the mean sum of grades at the most recent visit was increased compared with the initial visit (2.6 ± 0.2 vs 1.7 ± 0.1, respectively, $P < 0.001$; Table 1). Late effects were observed in 75.1% of responders at the recent visit, which was higher than at the initial visit (63.2%, $P = 0.011$). Five LEs were observed in 3.6% of responders at a recent visit, compared with only one (0.5%) of all survivors at initial visit. Among responders, 53.3% had grade 2 or higher LEs, compared with 26.4% at initial visit ($P = 0.001$). There was one death (grade 5) among responders, due to dilated cardiomyopathy related with anthracyclines.

Table 1. Late effects (LEs) in childhood cancer survivors at the initial and recent visits

Late effects	Initial visit	Recent visit	*P* value
	No. of survivors (%)*	No. of survivors (%)†	
Sum of grades	1.7 ± 0.1	2.6 ± 0.2	< 0.001
Presence of LEs			0.011
No	71 (36.8)	48 (24.9)	
Yes	122 (63.2)	145 (75.1)	
No. of LEs per survivor			< 0.001
1	71 (36.8)	48 (24.9)	
2	30 (15.5)	56 (29.0)	
3	13 (6.7)	25 (13.0)	
4	7 (3.6)	9 (4.7)	
5	1 (0.5)	7 (3.6)	
Severity of LEs per survivor‡			0.001
Mild	49 (25.4)	42 (21.8)	
Moderate	50 (25.9)	62 (32.1)	
Severe	22 (11.4)	39 (20.2)	
Life-threatening	1 (0.5)	1 (0.5)	
Death	0 (0)	1 (0.5)	

*Percentage is based on all survivors at initial visit (n = 241); †Percentage is based on all followed survivors at recent visit (n = 193); ‡Severity was graded based on the Common Terminology Criteria of Adverse Events version 3.0 (CTCAE v3.0).

Demographic findings of responders and non-responders

In the responder group, 62.2% were male, and 37.8% were female (online supplemental Table S2). The median age at diagnosis was 4.4 yr (range, 0.0-16.8 yr) for responders and 5.0 yr (range, 0.2-16.8 yr) for non-responders ($P = 0.628$). Age at initial visit and current age were all higher in the non-responder group compared with the responder group (all $P = 0.001$). The median time elapsed since completion of treatment was also higher in non-responders than in responders ($P < 0.001$).

In the responder group (n = 193), 36.8% (n = 71) had leukemia and 15.5% (n = 30) had lymphoma. The distribution of malignancies and treatment modalities were not significantly different between the two groups ($P = 0.655$ and $P = 0.088$, respectively). The proportion of survivors who had undergone a hematopoietic stem cell transplant (HSCT) was significantly higher in the responder group compared with the non-responder group (20.7% [40/193] vs 4.2% [2/48], $P = 0.007$).

Overall late effects for responder and non-responder groups at initial visit

The sum at the initial visit was significantly lower in non-re-

http://dx.doi.org/10.3346/jkms.2013.28.5.755

Table 2. Change in number, proportion and severity of late effects by system from initial to recent visit

Involved organ/Function		Severity of late effects					Sum of cases	Proportion	*P* value	Mean grade	*P* value
		1	2	3	4	5					
Bone marrow	1st*	5	1	0	1	0	7	3.6%	1.000	0.06 ± 0.03	1.000
	2nd†	5	1	0	1	0	7	3.6%		0.06 ± 0.03	
Cardiovascular	1st	19	3	0	0	0	22	11.4%	0.305	0.20 ± 0.04	0.877
	2nd	11	2	2	0	1	16	8.3%		0.20 ± 0.06	
Ear	1st	4	6	5	0	0	15	7.8%	0.375	0.78 ± 0.18	0.060
	2nd	6	8	6	0	0	20	10.4%		1.00 ± 0.18	
Eye	1st	3	3	1	0	0	7	3.6%	0.792	0.39 ± 0.14	0.374
	2nd	2	5	1	0	0	8	4.1%		0.48 ± 0.16	
Gastrointestinal‡	1st	7	2	1	0	0	10	5.2%	0.057	0.07 ± 0.02	0.022
	2nd	12	7	1	0	0	20	10.4%		0.15 ± 0.03	
Growth‡	1st	11	14	1	0	0	26	13.5%	0.322	0.23 ± 0.05	0.006
	2nd	8	22	3	0	0	33	17.1%		0.34 ± 0.06	
Metabolic	1st	5	0	0	0	0	5	2.6%	0.082	0.03 ± 0.01	0.052
	2nd	12	0	0	0	0	12	6.2%		0.07 ± 0.02	
Musculoskeletal‡	1st	15	3	1	0	0	19	9.8%	< 0.001	0.30 ± 0.07	< 0.001
	2nd	36	14	3	0	0	53	27.5%		0.92 ± 0.09	
Kidney	1st	6	3	3	0	0	12	6.2%	0.661	0.11 ± 0.03	0.158
	2nd	7	3	0	0	0	10	5.2%		0.07 ± 0.02	
Neurologic‡	1st	4	7	5	0	0	16	8.3%	0.028	0.32 ± 0.08	< 0.001
	2nd	7	14	9	0	0	30	15.5%		0.60 ± 0.10	
Obesity	1st	1	19	1	0	0	21	10.9%	0.749	0.26 ± 0.05	0.158
	2nd	1	21	1	0	0	23	11.9%		0.28 ± 0.06	
Other endo§	1st	2	6	0	0	0	8	4.1%	0.629	0.29 ± 0.11	0.058
	2nd	3	7	0	0	0	10	5.2%		0.40 ± 0.12	
Lung	1st	2	1	0	0	0	3	1.6%	0.703	0.03 ± 0.02	0.416
	2nd	2	2	0	0	0	4	2.1%		0.04 ± 0.02	
Sexual/Puberty‡	1st	14	3	6	0	0	23	11.9%	0.010	0.25 ± 0.05	< 0.001
	2nd	17	8	17	0	0	42	21.8%		0.54 ± 0.08	
Skin‡	1st	2	3	0	0	0	5	2.6%	0.082	0.14 ± 0.06	0.008
	2nd	3	9	0	0	0	12	6.2%		0.36 ± 0.10	
Thyroid‡	1st	22	9	0	0	0	31	16.1%	0.153	0.25 ± 0.04	0.003
	2nd	26	16	0	0	0	42	21.8%		0.36 ± 0.05	
Endocrine‡	1st	33	21	7	0	0	61	31.6%	0.021	0.54 ± 0.06	0.002
	2nd	31	32	20	0	0	83	43.0%		0.74 ± 0.08	

*Means initial visit; †Means recent visit; ‡Statistically significant in proportion of having late effects or severity; §"Other endo" includes diabetes insipidus and adrenal disorders.

sponders than in responders (1.0 ± 0.2 vs 1.7 ± 0.1, respectively, $P = 0.01$, online supplemental Table S3). The percentage of survivors who presented with LEs was lower in non-responders compared with responders (45.8% vs 63.2%, respectively, $P = 0.028$). Twenty-one (10.9%) survivors in the responder group had three or more LEs compared with only two (5.2%) survivors in the non-responder group ($P = 0.048$). A lower proportion of survivors (20.9%) in non-responder group had grade 2 or higher LEs in comparison with the responder group (37.8%, $P = 0.016$).

Change in late effects by body systems in responder group

The most common LEs observed at recent visit were related to the endocrine system (Table 2). Of all responders, 43% (83/193) had endocrine LEs, including thyroid (n = 42), growth (n = 33), sexual (n = 42), and metabolic (n = 12) effects. For grade 3 or higher LEs, endocrine (n = 20, 10.4%), and neurologic (n = 9) abnormalities were the most common at recent visit.

In the paired analysis for findings from initial and follow-up visits, increases in both the percentage and the mean severity of specific LEs were seen for many of the body systems. Endocrine-associated LEs increased from 31.6% to 43.0% ($P = 0.021$) with an increase in mean severity from 0.54 ± 0.06 to 0.74 ± 0.08 ($P = 0.002$). Musculoskeletal-associated and neurologic LEs increased in number and severity during the follow-up. No significant changes in percentage or severity of LEs were observed in bone marrow or in cardiovascular, auditory, ocular, pulmonary, or renal systems.

Among responders, two patients relapsed. One patient diagnosed with acute lymphoblastic leukemia at the age of 4.8 yr; relapsed at 10 yr. The other patient had non-Hodgkin's lymphoma at 5.7 yr, and developed leukemic transformation at 10.4 yr.

Three patients developed secondary malignancies. One patient with non-Hodgkin's lymphoma was diagnosed with pancreatic neuroendocrine tumor 20.3 yr after the first cancer diagnosis. A patient with acute lymphoblastic leukemia developed glioblastoma multiforme 8.9 yr later. The last patient, with a malignant fibrous histiocytoma, was found to have glioblastoma multiforme 8.6 yr later.

Table 3. Change in number of late effects from initial to recent visit by clinical factors

Clinical factor (N)			No. of late effects per survival (N)						Survivors with late effects (%)*	Survivors with multiple late effects (%)*	No. of late effects	*P* value†
			0	1	2	3	4	5				
Sex	Male (n = 120)	1st	45	41	23	7	3	1	75 (62.5)	34 (28.3)	1.05 ± 0.10	< 0.001
		2nd	28	36	32	16	4	4	92 (76.7)	56 (46.7)	1.53 ± 0.12	
	Female (n = 73)	1st	26	30	7	6	4	0	47 (64.4)	17 (23.3)	1.07 ± 0.13	< 0.001
		2nd	20	20	16	9	5	3	53 (72.6)	33 (45.2)	1.56 ± 0.16	
Diagnosis	Leukemia (n = 71)	1st	23	31	9	5	3	0	48 (67.6)	17 (23.9)	1.07 ± 0.13	0.003
		2nd	21	22	16	8	2	2	50 (70.4)	28 (39.4)	1.35 ± 0.15	
	Lymphoma (n = 30)	1st	14	9	4	2	0	1	16 (53.3)	7 (23.3)	0.93 ± 0.22	0.002
		2nd	7	9	6	3	3	2	23 (76.7)	14 (46.7)	1.73 ± 0.28	
	Brain tumor (n = 19)	1st	1	8	5	3	2	0	18 (94.7)	10 (52.6)	1.84 ± 0.26	< 0.001
		2nd	0	3	4	6	3	3	19 (100)	16 (84.2)	2.95 ± 0.30	
	WT (n = 21)	1st	12	8	0	1	0	0	9 (42.9)	1 (4.8)	0.52 ± 0.16	0.049
		2nd	10	5	5	1	0	0	11 (52.4)	6 (28.6)	0.86 ± 0.21	
	NB (n = 10)	1st	5	4	0	1	0	0	5 (50.0)	1 (10.0)	0.80 ± 0.39	0.081
		2nd	2	4	3	1	0	0	8 (80.0)	4 (40.0)	1.40 ± 0.37	
	Others (n = 42)	1st	16	11	12	2	1	0	26 (61.9)	15 (35.7)	1.07 ± 0.16	0.005
		2nd	8	13	14	7	0	0	34 (81.0)	21 (50.0)	1.48 ± 0.15	
Chemotherapy (n = 189)		1st	67	71	30	13	7	1	122 (64.6)	51 (27.0)	1.07 ± 0.08	< 0.001
		2nd	46	54	48	25	9	7	143 (75.7)	89 (47.1)	1.57 ± 0.96	
HSCT (n = 40)		1st	6	16	10	5	3	0	34 (85.0)	18 (45.0)	1.58 ± 0.18	0.042
		2nd	5	14	8	5	5	1	33 (82.5)	19 (47.5)	1.93 ± 0.22	
Radiotherapy (n = 75)		1st	17	24	16	11	7	0	58 (77.3)	34 (45.3)	1.56 ± 0.14	< 0.001
		2nd	4	15	24	18	9	5	71 (94.7)	56 (74.7)	2.37 ± 0.15	
Surgery (n = 80)		1st	33	23	13	6	4	1	47 (58.8)	24 (30.0)	1.10 ± 0.14	< 0.001
		2nd	20	19	23	9	5	4	60 (75.0)	41 (51.3)	1.65 ± 0.16	

*Percent is based on the total number of survivors with a specific clinical risk factor; †Paired t-test. GI, gastrointestinal; HSCT, hematopoietic stem cell transplantation; NB, neuroblastoma; WT, Wilms tumor.

Change in the number of late effects

The number of LEs increased in both males and females ($P < 0.001$). The number of LEs increased regardless of the initial diagnosis, except for neuroblastoma (Table 3). All brain tumor survivors (n = 19) experienced LEs. The percentage of survivors with multiple LEs was higher among brain tumor survivors (52.6% to 84.2%, $P < 0.001$). Wilms tumor survivors experienced the lowest percentage of LEs (52.4% [11/21]) based on diagnosis.

The number of LEs increased in all treatment groups (i.e., chemotherapy, radiotherapy, and surgery). Survivors treated with radiotherapy had the highest number of LEs, and this number markedly increased during follow-up ($P < 0.001$).

Change in mean severity and total sum of grades during the follow-up

Increases were seen in the severity and the sum of LEs from initial to recent visit in both male and female survivors (Fig. 1). When assessed by diagnostic groups, all but Wilms tumor and neuroblastoma survivors showed increases in severity and sum of LEs. Brain tumor survivors scored the highest severity and sum at recent visit (2.7 ± 0.1 and 6.3 ± 0.6, respectively). In these patients, both the severity and sum increased during follow-up ($P = 0.016$ and $P < 0.001$). For Wilms tumor and neuroblastoma, neither the mean severity nor sum significantly increased from initial to recent visit. Wilms tumor survivors also had the lowest mean severity and sum among diagnostic groups at recent visit.

Mean severity and sum increased in all treatment groups. However, for HSCT survivors, the increase in mean severity from initial to recent visit did not reach statistical significance ($P = 0.086$). Survivors treated with radiotherapy presented with the highest severity and sum of LEs.

Age and change in late effects

The number, severity, and sum of LEs all increased from initial to recent visit in all age groups (Fig. 2): age at diagnosis (< 2, 2 - 6 and > 6 yr), age at initial visit (> 9, 9-16, > 16 yr), and the number of yr after completion of therapy (< 5, 5-10, > 15 yr). When groups were compared by age at diagnosis, the number, severity, and sum of LEs were all significantly higher in the older age at diagnosis group (> 6 yr).

The number of LEs at follow-up was higher in the older 'age at initial visit' group. However, there were no significant differences in severity and sum for each 'age at initial visit' group at recent LTFC visit. The number, severity, and sum of LEs at follow-up were not significantly different when 'years after completion of therapy' groups were compared.

Multivariate analysis of change in number, severity, and total sum of grades

Age was not significantly associated with change in the number of LEs (Table 4). For diagnostic groups, both brain tumor and lymphoma had a significant effect on the change in number of LEs. Radiotherapy was the only significant treatment factor af-

http://dx.doi.org/10.3346/jkms.2013.28.5.755

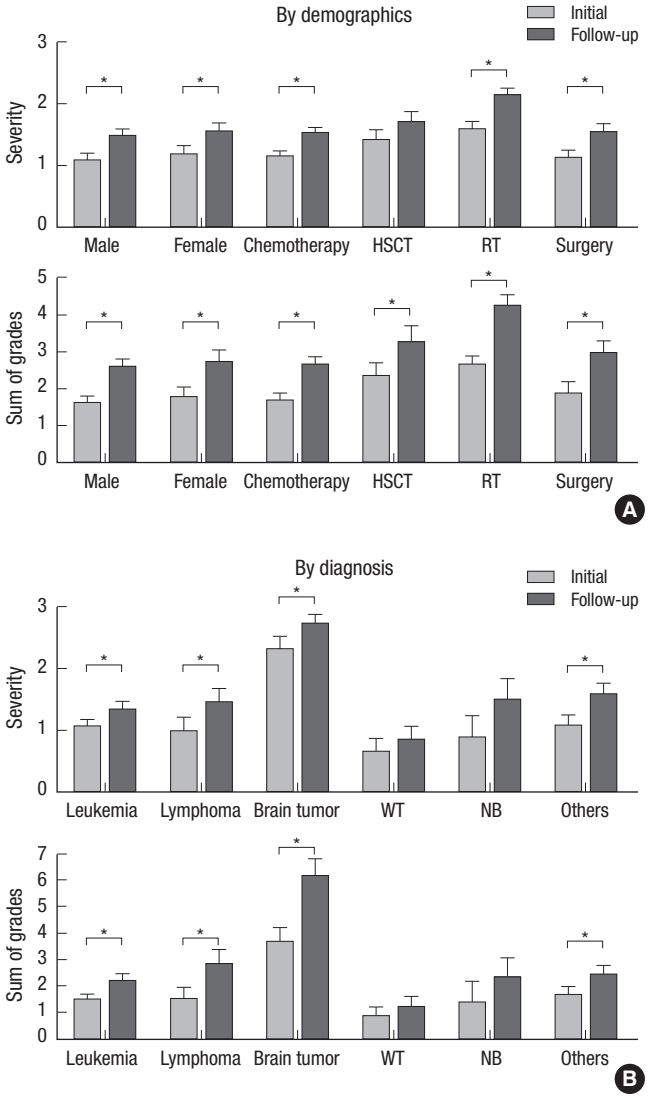

Fig. 1. Severity and sum of grades of late effects in childhood cancer survivors by demographic and clinical factors. (**A**) Demographics and treatment factors, (**B**) Diagnosis. *Significantly different between initial and recent follow-up data ($P < 0.05$). HSCT, hematopoietic stem cell transplantation; NB, neuroblastoma; RT, radiotherapy; WT, Wilms tumor.

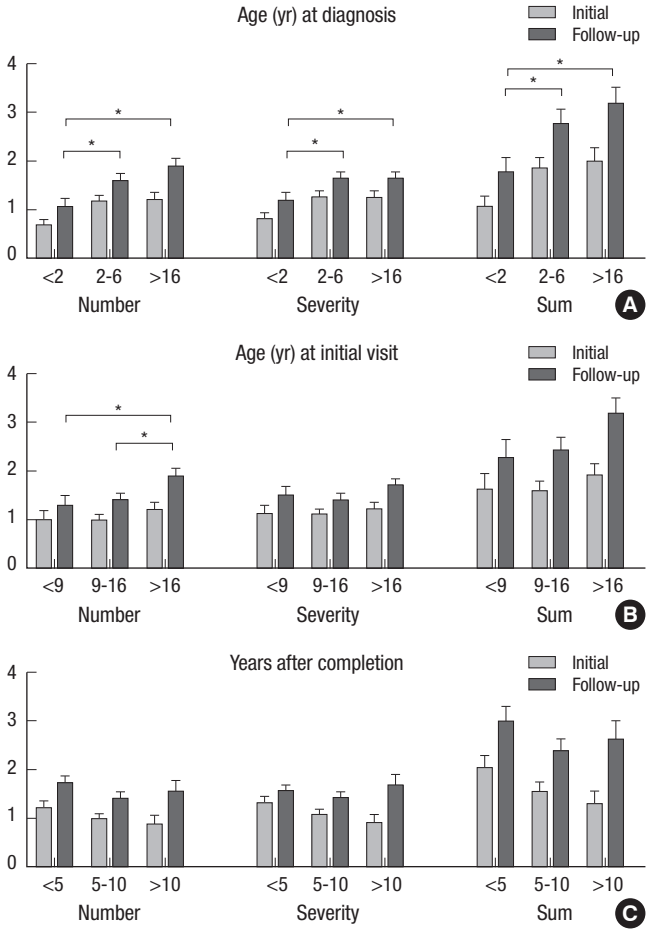

Fig. 2. Number, severity and sum of grades of late effects in childhood cancer survivors by age. (**A**) Age at diagnosis (yr), (**B**) Age at initial visit (yr), (**C**) Years after treatment completion (yr). Number, severity and sum of grades in each age group were all significantly different between initial and follow-up visits. *Data significantly different between two recent visits for each age group (using analysis of variance and post hoc testing by least significant difference [$P < 0.05$]).

fecting the change of number of LEs ($P = 0.001$) as well as the change in grade severity ($P = 0.004$).

Age at diagnosis and age at first visit were both significant risk factors for changes in sum (Beta -0.649, $P = 0.007$, Beta 0.642, $P = 0.028$, respectively). The number of years after completion of therapy showed marginal effects on the change in sum of LEs (Beta -0.423, $P = 0.056$). When analyzed by diagnostic groups, brain tumor and lymphoma were significant factors for sum (all $P = 0.001$). Among treatment modalities, only radiotherapy was a significant factor affecting sum ($P = 0.001$). Wilms tumor was the only diagnosis to have favorable changes in the severity and sum, but the effects were not significant (Beta -0.030, $P = 0.773$; Beta -0.105, $P = 0.346$, respectively).

DISCUSSION

Although LEs in cancer survivors are a well-known health issue, comprehensive follow-up data are limited. Survivors who actively participate in an LTFC follow-up usually expect to be monitored to allow for early detection of complications and cancer recurrences (17). However, comprehensive long-term follow-up is frequently difficult to perform because of limited local resources and expertise. It has been shown that there is a discrepancy between patient self-reports, medical records, and findings on clinical examinations (8, 18).

Our present study was based on 2008 to 2011 follow-up data from an LTFC which opened in 2005. The LTFC provided survivors with continuous and detailed consulting regarding their health, and each patient was examined by an oncologist to assess LEs. As a result, the participation rate in our study was high—about 80%--from our initial report. Survivor participation rate is primarily dependent on patient satisfaction with

Table 4. Multivariate analysis on the change in sum of grades, number, and severity of late effects

Clinical factor		Change in number		Change in severity		Change in sum	
		Beta	*P* value	Beta	*P* value	Beta	*P* value
Sex		0.044	0.535	0.011	0.876	0.034	0.622
Age	Age at diagnosis*	-0.452	0.067	-0.036	0.888	-0.649	0.007
	Age at the first visit*	0.475	0.109	-0.118	0.705	0.642	0.028
	Year after completion*	-0.329	0.144	0.182	0.443	-0.423	0.056
Diagnosis	Brain tumor†	0.246	0.010	0.001	0.993	0.325	0.001
	Wilms tumor	0.059	0.578	-0.105	0.346	-0.030	0.773
	Lymphoma†	0.327	0.000	0.128	0.180	0.292	0.001
	Neuroblastoma	0.141	0.110	0.056	0.548	0.082	0.343
	Other tumors	0.137	0.175	0.077	0.468	0.101	0.309
Treatment	Chemotherapy	0.009	0.906	-0.075	0.343	0.002	0.978
	HSCT	-0.071	0.348	-0.072	0.365	0.000	1.000
	Radiotherapy‡	0.281	0.001	0.246	0.004	0.265	0.001
	Surgery	-0.034	0.735	-0.019	0.856	0.026	0.792

*Statistically significant for change in sum ($P < 0.05$); †Statistically significant for change of sum and number ($P < 0.05$); ‡Statistically significant for change of sum, number, and severity ($P < 0.01$). GI, gastrointestinal; HSCT, hematopoietic stem cell transplantation.

consulting at an LTFC, and most studies report that over 50% of survivors are lost to follow-up (19-21). High participation rate in this study, along with consulting for survivors' health issues and detailed examination of factors affecting LEs are main strengths of our study.

Most of the survivors experienced additional LEs or had an exacerbation of existing LEs during follow-up. The percentage of survivors with LEs increased from 59.8% at initial visit to 75.1% at final visit. The percentages were similar to other reports: 62.4% in the United States and 74.5% in the Netherlands (2, 8). Increase in the number of LEs can mainly be attributed to survivors' health conditions and follow-up duration. However, selection bias is also a factor. Some survivors refused to participate in the LTFC despite recommendations for LTFC. Although risk factors (e.g., diagnosis and treatment modality) in non-responders were not significantly different than responders, non-responders were older at initial visit than responders. Non-responders also had more time elapsed since the completion of treatment. The mean age at initial visit was 17.4 yr and more than 12.1 yr had passed since they completed their treatment. As these patients grew older and more time passed since completion, the concern or worry about cancer recurrence or LEs lessened (22). In addition, adult survivors can independently decide whether to participate in an LTFC follow-up unlike younger survivors for whom parents play a vital role in caring and monitoring (23).

The number and severity of LEs at initial visit were lower in non-responders than in responders. Non-responders could have been in better general health than other survivors, leading to low participation rate and selection bias (22). According to data from the Childhood Cancer Survivor Study (CCSS), survivors who were followed were significantly more likely to have a chronic health condition compared to those not participating (69.1% in LTFU clinic vs 48.7% with no follow-up) (22). Another reason survivors refuse participate may be to avoid additional emotional trauma by discussing childhood cancer experiences (24). Despite these potential biases, it is important to emphasize that most survivors who were followed at the LTFC showed an increase in the number and severity of LEs. This finding is consistent with other studies on changes of LEs during follow-up (2, 25). Thus, regular follow-up at an LTFC is recommended not only for survivors at risk but also for those who have entered adulthood and are relatively healthier than other survivors.

Both the percentage of patients with LEs and the mean severity of LEs increased during the follow-up for most of the body systems. Particularly, endocrine (including growth or sexual/pubertal effects), musculoskeletal, and neurologic abnormalities became more frequent and severe. Endocrine abnormalities are the most common LEs likely, because survivors of childhood cancers were in the stage of active growth and development of second sexual characteristics during treatment for cancers (2, 8, 11, 26).

Our study found that the number, mean severity, and sum of LEs all were increased, regardless of most clinical factors. The number of LEs, mean severity, and sum were the highest in brain tumor survivors and the lowest among Wilms tumor survivors. These findings were consistent with previous reports (2, 10, 11, 27). On the other hands, it is striking that the risk of death was still higher among these survivors than the general population when they were followed continuously (28). Therefore, survivors of Wilms tumor should also undergo comprehensive follow-up at an LTFC.

Lymphoma was also found to be a significant factor for change in the sum and the number of LEs by multivariate analysis. It has been previously reported that lymphoma is a risk factor for developing cardiovascular LEs, secondary cancers or pulmonary abnormalities (29).

In general, the number, severity and sum of LEs increased by age at diagnosis, age at initial visit, and years since completion of treatment. This means that care at an LTFC should be provided to most of survivors, regardless of age. It should also be

http://dx.doi.org/10.3346/jkms.2013.28.5.755

emphasized that LEs related to development involving endocrine, musculoskeletal, and neurologic systems are most likely to occur. Therefore, adolescents and young adult survivors should be carefully followed.

For the change in sum, all age groups were significant in multivariate analysis. Patients of younger age at the time of diagnosis were at greater risk of showing adverse changes in LEs during follow-up (Beta -0.649, $P = 0.007$). Older age at the first visit to the LTFC was found to be a risk of developing LEs in the future (Beta 0.642, $P = 0.028$). Although the significance was marginal, the risk of developing LEs decreased as survivors aged and more time passed since completing treatment (Beta -0.423, $P = 0.056$). According to these findings, survivors diagnosed at young age should be regularly and frequently followed. If survivors' first visits are at an older age, they should initially be examined more frequently. The first visit at older age implies that survivors might have lost the opportunity for early LE detection and timely treatment.

Cancer survivorship program is the emerging field in oncology. In the Western countries, the survivorship care protocols have been published and used. Many cancer centers have long-term follow-up clinics for childhood cancer survivors (30). In Asia-Pacific regions including Korea, the survivorship programs are under development. We published the first comprehensive report on the childhood cancer survivors in Korea in 2009 and the nationwide study activities for cancer survivors just have started (11, 30, 31).

Our study has some unique points. Late effects in survivors were confirmed in person by oncologists, and the cohort was comprehensively followed for 3 yr. We could also characterize non-responders to follow-up at the LTFC. Finally, this follow-up report is the first evaluating patients in Asia; similar data are still insufficient worldwide. A major limitation of this study is the small sample size. We tried to overcome this limitation by performing comprehensive follow-ups of the survivors.

In conclusion, LEs are common in childhood cancer survivors. Regardless of most clinical risk factors, the number and severity of LEs tend to increase over time. Survivors of childhood cancer need careful and comprehensive follow-up in order to identify and manage LEs.

DISCLOSURE

The authors have no conflicts of interest to disclose.

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 http://dx.doi.org/10.3346/jkms.2013.28.5.755

Table S1. Categorization of late effects by organ or system

Involved system	Specific late effects*
Bone marrow	Anemia, polycythemia, leukopenia, marrow hypocellularity, neutropenia, thrombocytopenia, thrombocytosis, others
Skin	Alopecia, atrophy, fibrosis, nail changes, vitiligo, other
Obesity	Obesity (based on body mass index), others
Ear	Hearing loss, otitis externa, otitis media, tinnitus, others
Eye	Cataract, dry eye syndrome, glaucoma, retinopathy, uveitis, vitreous hemorrhage, others
Cardio-vascular	Cardiac arrhythmia, cardiomyopathy, congestive heart failure, hypertension, hypotension, ventricular dysfunction, others
Lung	Paranasal sinus infection, pneumonitis, pulmonary dysfunction, pulmonary fibrosis, others
Gastro-intestinal	Bowel obstruction, colitis, dental abnormalities, chronic enterocolitis, constipation, fecal incontinence, hepatic dysfunction, ileus, malabsorption, mucositis, others
Kidney	Hematuria, hemorrhagic cystitis, incontinence, proteinuria, renal insufficiency, renal tubular disorder, others
Neurologic	Ataxia, cerebrovascular ischemia, cognitive disturbance, dizziness, hydrocephalus, leukoencephalopathy, memory impairment, mood alteration, neuropathy (cranial, motor, or sensory), phrenic nerve dysfunction, seizures, speech impairment, tremor, others
Musculo-skeletal	Fracture, limb discrepancy, musculoskeletal hypoplasia, osteonecrosis, osteopenia, osteoporosis, scoliosis, others
Thyroid	Hyperthyroidism, hypothyroidism, thyroid nodule, others
Growth	Growth deceleration, growth hormone deficiency, short stature, others
Sexual/Puberty	Delayed puberty, gonadotophin secretion abnormality, gynecomastia, primary gonadal failure, premature menopause, infertility, irregular menses, precocious puberty, others
Metabolic	Adrenal insufficiency, dyslipidemia, glucose intolerance, hypocalcemia, hypercalcemia, others

*Late effects were expressed using the terminology based on the Common Terminology Criteria of Adverse Events version 3.0 (CTCAE v3.0). Adverse events confirmed two years after completion of cancer therapy were regarded as late effects rather than acute treatment toxicities. Evaluation methods were selected based on the risks and individualized follow-up schedules, which were determined according to the treatment history of the survivor. For all categories, history and physical examination were included. For each late effect, evaluations were repeated with appropriate follow-up intervals.

Table S2. Demographic characteristics of followed survivors and lost-to-follow-up survivors

Characteristic	Non-respondents (n = 48)	Respondents (n = 193)	*P* value
Sex			
Male	30 (62.5%)	120 (62.2%)	0.967
Female	18 (37.5%)	73 (37.8%)	
Age at diagnosis, yr (median, range)	5.0 (0.2-16.8)	4.4 (0.0-16.8)	0.628
Age at initial visit, yr (median, range)	17.4 (4.1-33.7)	13.1 (2.6-28.9)	0.001
Current age, yr (median, range)	20.6 (7.3-36.8)	16.2 (5.7-26.2)	0.001
Time after completion (median, range)	12.1 (5.5-21.9)	9.0 (5.1-24.7)	< 0.001
Diagnosis			
Leukemia	24 (50.0%)	71 (36.8%)	0.655
Lymphoma	5 (10.4%)	30 (15.5%)	
Wilms tumor	4 (8.3%)	19 (9.8%)	
Brain tumor	4 (8.3%)	21 (10.9%)	
Neuroblastoma	3 (6.3%)	10 (5.2%)	
Others†	8 (16.7%)	42 (21.8%)	
Treatment modalities			
Chemotherapy only ± surgery	26 (54.2%)	115 (59.6%)	0.088
Radiotherapy only ± surgery	0 (0%)	1 (0.5%)	
Chemotherapy and radiotherapy	18 (37.5%)	74 (38.3%)	
Surgery only	4 (8.3%)	3 (1.6%)	
Type of chemotherapy (n = 233, 96.7%)	44/48 (91.7%)	189/193 (97.9%)	0.030
Alkylating agents and others	7 (14.6%)	42(21.8%)	0.048
Anthracycline agents and others	2 (4.2%)	19 (9.8%)	
Anthracyclines and alkylating agents	18 (37.5%)	85 (44.0%)	
Others	21 (43.8%)	47 (24.4%)	
Type of radiotherapy (n = 93, 38.6%)	18/48 (37.5%)	75/118 (38.9%)	0.862
Head, neck and spine	15 (75%)	50 (58.8%)	0.419
Chest	0 (0%)	5 (5.9%)	
Abdominopelvic	2 (10.0%)	17 (20.0%)	
TBI	0 (0%)	6 (71%)	
Others	3 (15.0%)	7(8.3%)	
Type of surgery (n = 96, 39.8%)	16/32 (33.3%)	80/193 (41.5%)	0.304
Kidney	3 (18.8%)	13 (13.5%)	0.549
Brain	3 (18.8%)	24 (30.0%)	
Abdomen (liver, adrenal gland)	1 (6.3%)	13 (13.5%)	
Gonad	2 (12.5%)	7 (8.8%)	
GI	0 (0%)	5 (5.2%)	
Others	7 (43.8%)	19 (23.8%)	
Type of HSCT (n = 42, 17.4%)	2/46 (4.2%)	40/193 (20.7%)	0.007
Autologous	1 (50.0%)	19 (47.5%)	0.945
Allogeneic	1 (50.0%)	21 (52.5%)	

*Percentage is based on all survivors (n = 241); †Others include 17 Langerhans cell histiocytosis (systemic type), 10 abdominopelvic germ cell tumor, 8 hepatoblastoma, 5 rhabmomyosarcoma, 2 leiomyosarcoma, 2 eosinophilic granuloma, 2 adrenocortical carcinoma, 1 Ewing sarcoma, 1 rhabdoid tumor of the neck, 1 mediastinal teratoma, and 1 malignant myofibroblastic tumor. GI, gastrointestinal; HSCT, hematopoietic stem cell transplantation; TBI, total body irradiation.

Table S3. Differences in distribution of late effects at initial visit between responders and non-responders

		Initial late effects		*P* value
		Non-responders (n = 48)	Responders (n = 193)	
Total sum of grade		1.0 ± 0.2	1.7 ± 0.1	0.010
Presence	No	26 (54.2%)	71 (36.8%)	0.028
	Yes	22 (45.8%)	122 (63.2%)	
Number	1	13 (27.1%)	71 (36.8%)	0.048
	2	7 (14.6%)	30 (15.5%)	
	3	1 (2.1%)	13 (6.7%)	
	4	1 (2.1%)	7 (3.6%)	
	5	0 (0.0%)	1 (0.5%)	
Severity	Mild	12 (25.0%)	49 (25.4%)	0.016
	Moderate	7 (14.6%)	50 (25.9%)	
	Severe	3 (6.3%)	22 (11.4%)	
	Life-threatening	0 (0%)	1 (0.5%)	

http://dx.doi.org/10.3346/jkms.2013.28.5.755