original article

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Comprehensive clinical follow-up of late effects in childhood cancer survivors shows the need for early and well-timed intervention

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Background: Due to recent advances in treatment, nearly 80% of childhood cancer patients become long-term survivors. Studies on the late effects of survivors are under way worldwide. However, data on Asian survivors remain limited.

Methods: Data on 241 survivors at the Long-term Follow-up Clinic in Severance Hospital, South Korea, were collected and late effects were confirmed by oncologists.

Results: The median follow-up from diagnosis was 7.8 years. Late effects were identified in 59.8% of survivors and 23.2% had two or more late effects. Grade 3 or higher late effects were present in 10.8%. The most common late effects involved endocrine system (29.0%). Late effects were present in 95.7% of brain tumor survivors and 36.0% of Wilms' tumor survivors. Chemotherapy, hematopoietic stem-cell transplantation and radiotherapy were significant factors associated with the number and severity of late effects ($P < 0.05$). Brain tumor survivors had more severe late effects ($P < 0.001$), whereas Wilms' tumor survivors had fewer and milder late effects ($P < 0.05$).

Conclusion: The observation that over 50% of cancer survivors suffered from late effects during the short follow-up period and that a high frequency of endocrine late effects was present indicates the need for early and well-timed intervention of the survivors.

Key words: cancer, childhood cancer, late effect, survivor

introduction

Recent advances in diagnosis, treatment and supportive care have greatly increased the childhood cancer survival rate to up to 80% [1]. As more survivors reach adulthood, chronic toxic effects in the survivors, the so-called 'late effects', are increasing in frequency [2, 3]. In the United States, ~1 of every 640 adults between the ages of 20 and 39 years is a childhood cancer survivor, and two of three of the survivors have at least one late effect [4].

The range of late effects is quite broad; growth, endocrine, cardiovascular, pulmonary, kidney and neurocognitive abnormalities have been reported [5, 6]. Due to increasing concern about the chronic health conditions and health status including quality of life (QoL) of survivors, many guidelines for long-term follow-up have been developed [7]. Many health professionals, including general physicians, oncologists, nurse practitioners and social workers, are working together to improve the health and QoL of the survivors [8, 9].

There are many published reports on late effects and health status, which includes general, mental and functional status [4, 10–13]. As for chronic adverse health conditions or late effects, most of the studies are on the single late effect of childhood cancer survivors and only a few reports are on their overall status of late effects. Furthermore, most prior reports investigated late effects in Caucasian populations. The purpose of this study was to assess the overall status of late effects of Asian childhood cancer survivors.

methods

patient selection

In January 2005, the Long-term Follow-up Clinic (LTFUC) for childhood cancer survivors was established at Severance Hospital, Yonsei University Health System (YUHS), Seoul, Korea. A childhood cancer survivor was defined as a person who survived for at least 2 years off of cancer therapy. There is a society of childhood cancer survivors at Severance Hospital comprising over 700 members including 408 survivors. We invited the survivors registered in this society by mail to come to the LTFUC. All patients were diagnosed at <18 years of age and were treated from 1980 to 2007 at Severance Hospital. Three hundred and fifty members visited the LTFUC from January 2005 to October 2007. We excluded the following members: those with a time after completion of treatment of <2 years

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(48 cases) and patients with incomplete data (61 cases). Finally, data from 241 survivors were analyzed. Remaining 167 survivors in the society were regarded as the nonrespondents.

data collection

The treatment history and health risks of each survivor were reviewed through medical records. Patient-individualized follow-up schedules, based on individual risks, were prepared for each survivor. The follow-up protocol at YUHS was adopted and modified from the Long-term Follow-up Guidelines of the Children's Oncology Group, the national clinical guideline for long-term follow-up of childhood cancer survivors developed by the Scottish Intercollegiate Guidelines Network and the Practice Statement of the UK Children's Cancer Study Group, taking the cost, effectiveness and regional environments of Korea into consideration [14–16].

The LTFUC focused on three primary areas: late effects, follow-up of disease status and psychological assessment. For the follow-up of disease status, disease relapse was assessed; patients with disease relapse were referred to the hematology–oncology clinic (HOC). For assessment of late effects, a complete history and physical examination was carried out for each survivor. Laboratory and radiological tests were carried out based on the follow-up schedule. All survivors who visited the LTFUC at least once were followed regularly.

data analysis

Late effects were defined as the adverse events that the survivors had at least 2 years after completion of therapy (Table 1). Specific late effects evaluated in the LTFUC were selected referring to the late effects stated in the aforementioned protocols [14–16]. The severity of specific late effect was graded by the Common Terminology Criteria for Adverse Events version 3.0 in the same way as in previous reports [4, 11]. The late effects were scored from grades 1 to 5 with descriptions of severity for each adverse event (grade 1, mild; 2, moderate; 3, severe; 4, life threatening or disabling; 5, death-related adverse event). To compare the severity between risk groups and utilize the ordered meaning of grades, the grade was considered as a continuous variable from 1 to 5, based on other reports [17, 18].

In addition, the late effects were classified by organs and systems to avoid overlapping counts of late effects; the number of late effects represents the number of affected body systems (Table 1). The mean number of late effects per survivor, with specific risk factors, was calculated. The existence of late effects refers to whether a late effect existed or not.

statistical analyses

The significance of various risk factors for the existence was tested by chi-square test, and the significance for number and severity of late effects was tested by Student's *t*-test, one-way analysis of variance and correlation analysis using Pearson's coefficient. The difference between two groups for nonparametric variables was tested by Mann–Whitney test.

The risk factors that were significant in the univariate analyses were considered as the variables for multivariate analysis. Multiple linear regression for the association between risk factors and the number or severity of late effects and logistic regression to assess the odds ratio (OR) for the existence of late effects were carried out. Analyses were carried out using SPSS version 11.5.0 (SPSS System Inc., Chicago, IL).

Table 1. Categorization of specific late effects

Involved system	Specific late effects[a]
Bone marrow	Anemia, polycythemia, leukopenia, marrow hypocellularity, neutropenia, thrombocytopenia, thrombocytosis, other
Skin	Alopecia, atrophy, fibrosis, nail changes, vitiligo, other
Obesity	Obesity (based on BMI), other
Ear	Hearing loss, otitis externa, otitis media, tinnitus, other
Eye	Cataract, dry eye syndrome, glaucoma, retinopathy, uveitis, vitreous hemorrhage, other
Cardiovascular	Cardiac arrhythmia, cardiomyopathy, congestive heart failure, hypertension, hypotension, ventricular dysfunction, other
Lung	Paranasal sinus infection, pneumonitis, pulmonary dysfunction, pulmonary fibrosis, other
Gastrointestinal	Bowel obstruction, colitis, dental abnormalities, chronic enterocolitis, constipation, fecal incontinence, hepatic dysfunction, ileus, malabsorption, mucositis, other
Kidney	Hematuria, hemorrhagic cystitis, incontinence, proteinuria, renal insufficiency, renal tubular disorder, other
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, other
Musculoskeletal	Fracture, limb discrepancy, musculoskeletal hypoplasia, osteonecrosis, osteopenia, osteoporosis, scoliosis, other
Thyroid	Hyperthyroidism, hypothyroidism, thyroid nodule, other
Growth	Growth deceleration, growth hormone deficiency, short stature, other
Sexual/puberty	Delayed puberty, gonadotrophin secretion abnormality, gynecomastia, primary gonadal failure, premature menopause, infertility, irregular menses, precocious puberty, other
Metabolic	Adrenal insufficiency, dyslipidemia, glucose intolerance, hypocalcemia, hypercalcemia, other

[a]Late effects were expressed using the terminology based on the Common Terminology Criteria for Adverse Events version 3.0. Adverse events confirmed 2 years after completion of cancer therapy were regarded as late effects rather than acute treatment toxic effects. Evaluation methods were selected based on risk 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. Evaluations were repeated at appropriate follow-up intervals for each late effect.
BMI, body mass index.

results

survivor characteristics

Among the members in the society, 408 were survivors and 241 had responded (Table 2, supplemental Table S1, available at *Annals of Oncology* online). One hundred and fifty survivors were male (62.2%) and 91 were female (37.8%). The median age at diagnosis was 4.4 (0–16.8) years and the median current age was 14.2 (2.6–33.7) years. The median time elapsed after completion of treatment was 6.1 (2.0–21.6) years and the median time after diagnosis was 7.8 (2.0–23.1) years.

Table 2. Demographic characteristics of childhood cancer survivors at Severance Hospital

Characteristic	No. of survivors (%)[a]
Sex	
Male	150 (62.2)
Female	91 (37.8)
Age at diagnosis (median, range)	4.4 (0–16.8) years
Current age (median, range)	14.2 (2.6–33.7) years
Time elapsed after diagnosis (median, range)	7.8 (2.0–23.1) years
Time elapsed after completion of treatment (median, range)	6.1 (2.0–21.6) years
Diagnosis	
Leukemia	95 (39.4)
Lymphoma	35 (14.5)
Wilms' tumor	25 (10.4)
Brain tumor	23 (9.5)
Neuroblastoma	13 (5.4)
Others[b]	50 (20.7)
Treatment modalities	
Chemotherapy only with/without surgery	141 (58.5)
Radiotherapy only with/without surgery	1 (0.4)
Chemotherapy and radiotherapy	92 (38.2)
Surgery only	7 (2.9)
Type of chemotherapy (n = 233, 96.7%)	
Anthracyclines	124 (51.5)
Alkylating agents	152 (63.1)
Anthracyclines and alkylating agents	103 (42.7)
Others only	60 (24.9)
Type of radiotherapy (n = 93, 38.6%)	
Head, neck and spine	65 (27.0)
Abdominopelvic	19 (7.9)
TBI	6 (2.5)
Chest	5 (2.1)
Type of surgery (n = 96, 39.8%)	
Head	23 (9.5)
Abdominopelvic—kidney	27 (11.2)
Abdominopelvic—liver/adrenal gland	13 (5.4)
Chest	7 (2.9)
Type of HSCT (n = 42, 17.4%)	
Autologous	20 (8.3)
Allogeneic	22 (9.1)

[a]Percentage is based on total survivors (n = 241).

[b]Others include 17 Langerhans cell histiocytosis (systemic type), 10 abdominopelvic germ-cell tumor, eight hepatoblastoma, five rhabdomyosarcoma, two leiomyosarcoma, two eosinophilic granuloma, two adrenocortical carcinoma, one Ewing sarcoma, one rhabdoid tumor of the neck, one mediastinal teratoma, one malignant myofibroblastic tumor.
TBI, total body irradiation; HSCT, hematopoietic stem-cell transplantation.

Ninety-five survivors (39.4%) had leukemia and 35 (14.5%) had lymphoma. Other diagnoses included Wilms' tumor (25, 10.4%), brain tumors (23, 9.5%), neuroblastoma (13, 5.4%) and others (50, 20.7%). Chemotherapy was given to 233 survivors (96.7%), radiotherapy to 93 (38.6%), surgery to 96 (39.8%) and hematopoietic stem-cell transplantation (HSCT) to 42 (17.4%). Chemotherapy and radiotherapy were given to 92 (38.2%) survivors simultaneously. Median dosage of anthracyclines in the group treated with anthracyclines was 167.9 (30.2–1160.0) mg/m^2.

Among 167 nonrespondents, 99 (59.3%) were male and 68 (40.7%) were female. The median age at diagnosis was 4.7 (0–17.1) years and it was not different from that of the respondents (P = 0.751). However, the median current age, age after completion of treatment and time after diagnosis in nonrespondents were significantly higher than those in the respondents (all $P \leq 0.001$). As for the diagnosis, the proportion of brain tumor was significantly higher in nonrespondents than in respondents [n = 35 (21.0%) versus n = 23 (9.5%), $P < 0.001$; supplemental Table S1, available at *Annals of Oncology* online].

overall late effects

Among the 241 survivors, 144 (59.8%) had at least one late effect and 97 (40.2%) had no late effects (Table 3). Two or more late effects were present in 60 survivors (24.9%). Sixty-one survivors (25.3%) had grade 1 (mild) late effects and 83 (34.4%) had grade 2 (moderate) or more severe late effects. Grade 3 or more late effects were found in 10.8% of survivors. There was no death (grade 5) in the LTFUC.

The most common late effects were endocrine related (Table 4). Among the survivors, 70 (29.0% of 241 survivors) had endocrine late effects including thyroid (n = 35), growth (n = 28), sexual (n = 28), metabolic (n = 5) and other abnormalities (n = 6). For grade 2 or higher, endocrine abnormalities were the most common late effects that required treatment (30, 12.4%). Among these cases, 16 had growth abnormalities and 10 had sexual/pubertal abnormalities. For grade 3 or higher, neurologic (n = 7) and endocrine (n = 7) abnormalities were the most common.

Three relapses occurred: a neuroblastoma patient relapsed 2.2 years after completion of therapy, a patient with medulloblastoma relapsed at 2.3 years and a patient with acute lymphoblastic leukemia relapsed at 3.8 years.

Three patients who were enrolled in the LTFUC at first are now in the HOC due to secondary malignancy: a patient diagnosed with glioblastoma multiforme at 8.5 years of age and then developed undifferentiated sarcoma in the bladder at 15.1 years of age, a patient with medulloblastoma at 14.2 years of age, and then developed acute myeloid leukemia at 19.9 years and a patient with neuroblastoma at 1.0 year of age and then developed brain germinoma at 5.5 years of age. Patients with second malignancies are treated and followed in the HOC and were not included in the analysis of late effects in the 241 survivors.

late effects and treatment

number of late effects. There was no gender difference in the number of late effects among the survivors (Table 5). Brain

Table 3. Late effects in childhood cancer survivors at Severance Hospital

Late effects	No. of survivors (%)[a]
Existence of late effects	
No	97 (40.2)
Yes	144 (59.8)
No. of late effects per survivor	
1	84 (34.9)
2	37 (15.4)
3	14 (5.8)
4	8 (3.3)
5	1 (0.4)
Severity of late effects per survivor[b]	
Mild	61 (25.3)
Moderate	57 (23.7)
Severe	25 (10.4)
Life threatening	1 (0.4)

[a]Percentage is based on total survivors ($n = 241$).
[b]Severity is graded based on the Common Terminology Criteria of Adverse Events version 3.0.

Table 4. Late effects by body system

System	Severity of late effects[a]				Grade 2 or higher severity (% in total number of late effects)	Total
	1	2	3	4		
Bone marrow	5	1	0	1	2 (28.6)	7
Skin	2	3	0	0	3 (60.0)	5
Obesity	1	23	1	0	24 (96.0)	25
Ear	4	6	5	0	11 (73.3)	15
Eye	3	3	2	0	5 (62.5)	8
Cardiovascular	21	4	0	0	4 (16.0)	25
Lung	2	1	0	0	1 (33.3)	3
Gastrointestinal	8	2	1	0	3 (27.3)	11
Kidney	10	4	3	0	7 (41.2)	17
Neurologic	4	8	7	0	15 (78.9)	19
Musculoskeletal	23	3	1	0	4 (14.8)	27
Endocrine[c]	40	23	7	0	30 (42.9)	70
Thyroid	26	9	0	0	9 (25.7)	35
Growth	12	15	1	0	16 (57.1)	28
Sexual/puberty	18	4	6	0	10 (35.7)	28
Metabolic	5	0	0	0	0 (0)	5
Others[b]	0	6	0	0	6 (100)	6

[a]Severity is graded based on the Common Terminology Criteria of Adverse Events version 3.0.
[b]Others include three diabetes insipidus and three corticosteroid deficiency.
[c]Endocrine system includes thyroid, growth, sexual/puberty, metabolic and other endocrine abnormalities.

tumor survivors had the highest probability of having late effects (95.7%, 22 of 23). Wilms' tumor survivors had the lowest risk for late effects (36.0%, 9 of 25). In terms of multiple late effects, 52.2% of brain tumor survivors (12 of 23) had two or more late effects. Only one Wilms' tumor (4.0%, 1 of 25) and two neuroblastoma survivors (15.3%, 2 of 13) had multiple late effects. A history of a brain tumor was a significant risk factor for an increased number of late effects (1.83 ± 0.22; $P < 0.001$) compared with a history of other childhood cancers. Wilms' tumor survivors were at lower risk for late effects compared with other cancer survivors (0.44 ± 0.14; $P < 0.001$).

Chemotherapy, HSCT and radiotherapy were significant risk factors for a high number of late effects (all $P < 0.001$) when compared with survivors not treated with each of these modalities. The age at diagnosis and the current age correlated positively to the number of late effects ($r = 0.25$, $P < 0.001$; $r = 0.13$, $P = 0.049$). Multivariate analysis showed that all treatment modalities were related to an increased mean number of late effects. Wilms' tumor survivors had a decreased number of late effects (Table 6).

overall grade of severity of late effects. Survivors treated with radiotherapy had a much higher grade of late effects than did survivors who did not receive radiotherapy (1.5 ± 0.1 versus 0.8 ± 0.1, $P < 0.001$) (Figure 1). A history of chemotherapy or HSCT was associated with more severe late effects when compared with the grade of late effects in survivors who did not receive chemotherapy or HSCT (1.1 ± 0.1 versus 0.1 ± 0.1, $P < 0.001$; 1.4 ± 0.1 versus 1.0 ± 0.1, $P = 0.025$). These findings were confirmed by the multivariate analysis controlling for other factors such as gender, age at diagnosis and current age (all $P < 0.05$, Table 6).

Regarding diagnosis, 52.2% of all brain tumor survivors (12 of 23) had grade 3 or higher late effects, compared with only 4.2% of leukemia survivors (4 of 95). The mean grade of late effects in brain tumor survivors was much higher than that for survivors who did not have a brain tumor (2.3 ± 0.2 versus 0.9 ± 0.1, $P < 0.001$) (Figure 1). The severity of late effects in Wilms' tumor survivors was milder than in the survivors who did not have Wilms' tumor (0.6 ± 0.2 versus 1.1 ± 0.1, $P < 0.012$). The effects associated with a history of brain tumors and Wilms' tumors were confirmed by the multivariate analysis (Table 6). The mean age at diagnosis correlated positively with the severity grade of late effects ($r = 0.180$, $P = 0.001$); however, the current age and the time elapsed after treatment did not.

relationship between severity grade of specific late effects and treatment. Among the treatment modalities, chemotherapy was associated with an increased growth and obesity severity grade compared with the survivors who did not receive chemotherapy (0.22 ± 0.04 versus 0, $P < 0.001$; 0.27 ± 0.05 versus 0, $P < 0.001$) (Figure 1). Radiotherapy increased the severity of growth, thyroid and sexual late effects (0.36 ± 0.08 versus 0.11 ± 0.04, $P = 0.006$; 0.50 ± 0.08 versus 0.15 ± 0.05, $P = 0.001$; 0.51 ± 0.11 versus 0.14 ± 0.06, $P = 0.003$). However, all the effects associated with a history of radiotherapy were not confirmed by the multivariate analysis after controlling for age, gender, diagnosis and other treatment modalities. A history of surgery increased the severity of growth, thyroid and kidney late effects compared with the survivors who did not have surgery by the univariate analysis (0.42 ± 0.08 versus 0.08 ± 0.03, $P < 0.001$; 0.56 ± 0.11 versus 0.24 ± 0.05, $P = 0.013$; 0.22 ± 0.07 versus 0.05 ± 0.02, $P = 0.023$). The effects of surgery on growth and kidney abnormalities were confirmed by the multivariate analysis ($P < 0.05$).

Table 5. Number of late effects

Risk factor	No. of late effects per survivor (*n*, %)						Survivors with late effects (*n*, %)	Total survivors (*n*, %)	No. of late effects (mean, SEM)[a]	*P* value
	0	1	2	3	4	5				
Sex										
Male	58 (38.7)	50 (33.3)	29 (19.3)	8 (5.3)	4 (2.7)	1 (0.7)	92 (61.3)	150 (100)	1.02 ± 0.09	0.499
Female	39 (42.9)	34 (37.4)	8 (8.8)	6 (6.6)	4 (4.4)	0 (0)	52 (57.1)	91 (100)	0.92 ± 0.11	
Diagnosis										
Leukemia	36 (37.9)	39 (41.1)	12 (12.6)	5 (5.3)	3 (3.2)	0 (0)	59 (62.1)	95 (100)	0.95 ± 0.10	<0.001
Lymphoma	18 (51.4)	9 (25.7)	5 (14.3)	2 (5.7)	0 (0)	1 (2.9)	17 (48.6)	35 (100)	0.86 ± 0.20	
Brain tumor	1 (4.3)	10 (43.5)	6 (26.1)	4 (17.4)	2 (8.7)	0 (0)	22 (95.7)	23 (100)	1.83 ± 0.22	
Wilms' tumor	16 (64.0)	8 (32.0)	0 (0)	1 (4.0)	0 (0)	0 (0)	9 (36.0)	25 (100)	0.44 ± 0.14	
NB	6 (46.2)	5 (38.5)	1 (7.7)	0 (0)	1 (7.7)	0 (0)	7 (53.8)	13 (100)	0.85 ± 0.32	
Others[b]	20 (40.0)	13 (26.0)	13 (26.0)	2 (4.0)	2 (4.0)	0 (0)	30 (60.0)	50 (100)	1.06 ± 0.15	
Chemotherapy										
No	7 (87.5)	1 (12.5)	0 (0)	0 (0)	0 (0)	0 (0)	1 (12.5)	8 (100)	0.13 ± 0.13	<0.001
Yes	90 (38.6)	83 (35.6)	37 (15.9)	14 (6.0)	8 (3.4)	1 (0.4)	143 (61.4)	233 (100)	1.01 ± 0.07	
HSCT										
No	90 (45.2)	68 (34.2)	26 (13.1)	9 (4.5)	5 (2.5)	1 (0.5)	109 (54.8)	199 (100)	0.86 ± 0.07	<0.001
Yes	7 (16.7)	16 (38.1)	11 (26.2)	5 (11.9)	3 (7.1)	0 (0)	35 (83.3)	42 (100)	1.55 ± 0.17	
Radiotherapy										
No	75 (50.7)	54 (36.5)	16 (10.8)	2 (1.4)	0 (0)	1 (0.7)	73 (49.3)	148 (100)	0.66 ± 0.07	<0.001
Yes	22 (23.7)	30 (32.3)	21 (22.6)	12 (12.9)	8 (8.6)	0 (0)	71 (76.3)	93 (100)	1.50 ± 0.13	
Surgery										
No	57 (39.3)	57 (39.3)	21 (14.5)	7 (4.8)	3 (2.1)	0 (0)	88 (60.7)	145 (100)	0.91 ± 0.08	0.219
Yes	40 (41.7)	27 (28.1)	16 (16.7)	7 (7.3)	5 (5.2)	1 (1.0)	56 (58.3)	96 (100)	1.09 ± 0.13	

[a]Stands for the mean number of late effects for each survivor with a specific risk factor.
[b]Others are shown in Table 1.
SEM, standard error of mean; NB, neuroblastoma; HSCT, hematopoietic stem-cell transplantation.

Table 6. Multivariate analysis of the effect of risk factors on the number and severity

Risk factor	No. of late effects		Severity of late effects	
	Beta	*P* value	Beta	*P* value
Sex	−0.01	0.828	0.01	0.832
Age				
Age at diagnosis	0.08	0.324	0.00	0.978
Current age	0.01	0.854	0.01	0.905
Treatment				
Chemotherapy	0.16	0.008	0.16	0.008
HSCT	0.23	<0.001	0.12	0.043
Radiotherapy	0.28	<0.001	0.25	<0.001
Surgery	0.20	0.003	0.07	0.285
Diagnosis				
Brain tumor	0.09	0.197	0.27	<0.001
Wilms' tumor	−0.21	0.001	−0.16	0.013

All factors used in the model are presented in the table.
HSCT, hematopoietic stem-cell transplantation.

Among the diagnoses evaluated, brain tumors were associated with more severe endocrine late effects including growth (1.05 ± 0.23 versus 0.12 ± 0.03, $P = 0.001$) and thyroid abnormalities (0.95 ± 0.18 versus 0.22 ± 0.05, $P = 0.001$) as well as severe neurological abnormalities (2.20 ± 0.39 versus 0.90 ± 0.22, $P = 0.004$) compared with other tumor survivors. The effects associated with a history of brain tumors were confirmed by the multivariate analysis ($P < 0.05$).

risk factors for the existence of late effects. With regards to treatment, chemotherapy, HSCT and radiotherapy all increased the odds for having late effects [OR 22.8, 95% confidence interval (CI) 1.5–358.3; OR 3.9, 95% CI 1.5–9.9; OR 2.2, 95% CI 1.1–4.5] compared with the survivors who did not undergo each of the treatment modalities (Table 7). The diagnosis of a brain tumor was associated with higher odds for the existence of late effects (OR 16.6; 95% CI 1.4–192.8) compared with the leukemia survivors. Wilms' tumor survivors had a tendency for lower risk of late effects than leukemia survivors (OR 0.3; 95% CI 0.1–1.2; $P = 0.097$).

discussion

To recognize the prevalence and severity of late effects and to provide timely intervention are the mainstay of health care for the childhood cancer survivors. Our findings showed that 59.8% of survivors had late effects and 34.4% had grade 2 or more severe late effects that required treatment. Although the overall findings for the late effects were similar to those previously reported, there were some differences.

According to the studies in the United States [4] and The Netherlands [11], 62.3% and 74.5%, respectively, of childhood cancer survivors had adverse health conditions. In the UK [19], 58% of survivors had chronic medical problems. The prevalence of late effects in our report was slightly lower than

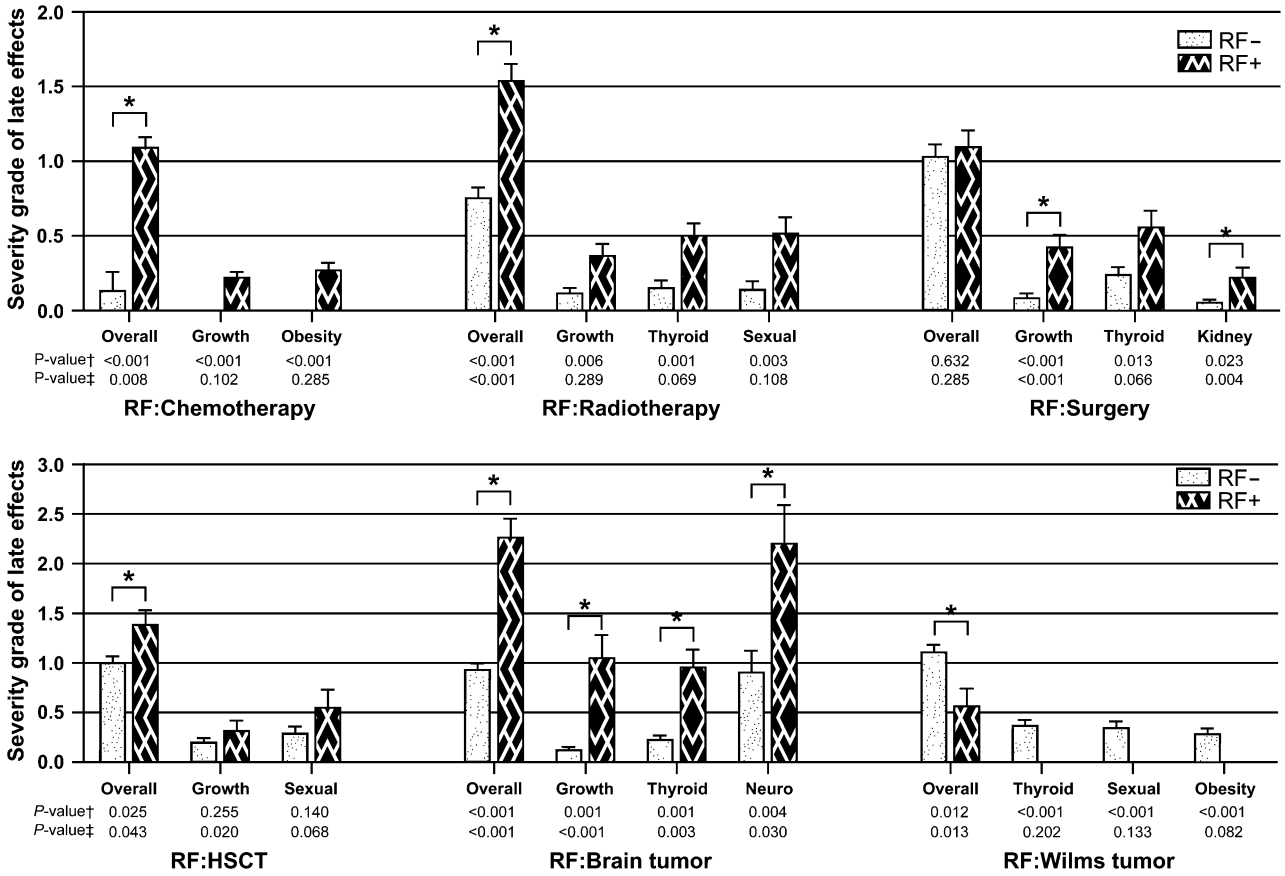

Figure 1. Severity of overall and specific late effects according to risk factors. HSCT, hematopoietic stem-cell transplantation; overall, overall severity of late effects per survivor; RF, risk factor; neuro, neurologic. *Significant both in univariate and multivariate analyses. †*P* value in univariate analysis. ‡*P* value in multivariate analysis.

the values reported in recent studies in the United States and The Netherlands. The main difference in the studies is likely due to the length of follow-up. In our study, the median time elapsed after completion of treatment was 6.1 years, and the median time after diagnosis was 7.8. However, all three prior studies had a follow-up period of over 15 years from diagnosis. The difference might also be due to the treatment intensity. The study population in this study is one of the most recent cohorts. Recent treatments are now focusing on reducing toxicity while achieving comparable survival rates in order to minimize adverse health conditions [20]. Nevertheless, the fact that nearly 60% of survivors had late effects, even within our short study period and even with less toxic treatments, raises concern that the survivors require regular follow-up and early intervention for late effects.

As for the severity of late effects, 27.5% of survivors in the United States and 40.0% in The Netherlands suffered from grade 3 or higher late effects. Only 10.8% of survivors had grade 3 or higher late effects in our study. The differences are likely due to the diagnoses included and the relatively short follow-up interval. According to other studies, brain and bone tumors, in addition to radiotherapy, are higher risk factors for late effects [11, 13]. In the USA study, 10.9% of patients had bone tumors and 12.7% of cases were central nervous system (CNS) tumor survivors. In The Netherlands study, 8.5% had bone tumors and 7.9% had CNS tumors. In our study, the proportion of brain tumor survivors was similar (9.5%), but there were no bone tumor survivors. Furthermore, survivors treated with radiotherapy (38.6%) were fewer than in other studies (62.2% [4], 44.6% [11]).

The number of late effects in this study represents the extent of affected body systems. The brain tumor survivors had the highest number of late effects among the diagnoses evaluated. Survivors with radiotherapy or HSCT had an increased number of late effects per survivor compared with survivors who did not undergo radiotherapy or HSCT. These findings suggest that these factors are associated with a greater effect on body systems compared with other factors and are consistent with other reports [4, 11, 21, 22]. The risk factors associated with brain tumors lost their significant association with the number of late effects in the multivariate analysis, which controlled for the treatment modalities (Table 6). This implies that radiotherapy and surgery were more important risk factors than the brain tumor itself for the extent of late effects.

Radiotherapy was a significant risk factor for the overall prevalence and severity of late effects, consistent with the findings of many other reports [6, 23–26]. When we evaluated the effects of radiotherapy on individual late effects such as growth, sexual and thyroid abnormalities, radiotherapy showed a clear tendency of more severe late effects; however, this tendency was not confirmed by the multivariate analysis, perhaps due to the limited number of cases.

Table 7. Multivariate analysis of the effect of risk factors on the existence of late effects

Risk factor	Existence of late effects	
	OR (95% CI)	*P* value
Sex		
Male	1	
Female	0.9 (0.5–1.6)	0.631
Age		
Age at diagnosis	1.0 (0.9–1.1)	0.893
Current age	1.0 (0.9–1.1)	0.878
Treatment		
Chemotherapy		
No	1	
Yes	22.8 (1.5–358.3)	0.026
HSCT		
No	1	
Yes	3.9 (1.5–9.9)	0.004
Radiotherapy		
No	1	
Yes	2.2 (1.1–4.5)	0.023
Surgery		
No	1	
Yes	1.2 (0.5–3.1)	0.636
Diagnosis		
Leukemia	1	
Lymphoma	0.8 (0.3–2.0)	0.597
Brain tumor	16.6 (1.4–192.8)	0.025
Wilms' tumor	0.3 (0.1–1.2)	0.097
Neuroblastoma	1.4 (0.2–8.4)	0.716
Others	1.2 (0.5–3.0)	0.762

All factors used in the model are presented in the table.
OR, odds ratio; CI, confidence interval; HSCT, hematopoietic stem-cell transplantation.

Surgery, including brain surgery and nephrectomy, was found to be associated with an increase in the severity of endocrine and kidney abnormalities. Brain surgery is usually linked with brain tumors and radiotherapy; in such cases, the risk of having endocrine abnormalities is higher. The effect of surgery on kidney abnormalities might be due to nephrectomies for Wilms' tumor and neuroblastoma. These tumors are linked with the use of kidney-toxic agents like platinum-based drugs [27]; all these factors influence the effect of a nephrectomy on the severity of late effects.

There have been many reports documenting endocrine, especially thyroid, abnormalities in childhood cancer survivors [4, 11, 22, 23, 28, 29]. Our findings were consistent with prior reports. Endocrine late effects are common and important problems at the LTFUC. First, they adversely affect the QoL because of the interference with normal growth and development and psychological adjustment [26, 30, 31]. Secondly, endocrine abnormalities are the most common late effects. Thirdly, such problems can be appropriately managed by timely intervention during child development [30], which further emphasizes the important role of the LTFUC.

In contrast to other factors, Wilms' tumor survivors had fewer and less severe late effects than the other survivors. This finding is consistent with previous studies [4, 12]. This might be because Wilms' tumor has the best prognosis among childhood cancers; it requires less intensive therapies compared with other tumors and survivors can live without problems with only one kidney. Therefore, Wilms' tumor survivors seem to have a higher QoL to some extent compared with other tumor survivors although childhood cancer survivors generally have almost the same QoL as the general population [32, 33].

The evaluation of age points to a higher risk of late effects among adolescent survivors [23]. As the survivors grow older and enter puberty, late effects become more evident in terms of growth and pubertal development. However, the results of this study showed no consistent findings associated with the age at diagnosis or the current age with regard to the late effects. This might be due to the relatively short follow-up and the fact that many of the survivors evaluated had not entered puberty yet.

The age issue could also be related with the absence of bone tumor survivors in this study. Bone tumors are observed most frequently in adolescents [34]. Bone tumor survivors have more late effects and suffer from more severe functional impairments [35]. Moreover, second malignancies occur more frequently than other tumor survivors [36]. Musculoskeletal late effects including limb abnormalities might impair growth in adolescents, and late effects would have been more evident in the adolescent age if bone tumor survivors had been included in this study. Because of these reasons, prevalence and severity of late effects and frequency of second malignancy could have been less than in other reports.

The nonrespondents ($n = 167$) in this study might distort the results of this study. Because they have higher current age, age after completion of treatment and longer time after diagnosis, and a much higher proportion of having brain tumors than in respondents, the frequency and severity of late effects might have been higher and more severe if the nonrespondents had participated in the LTFUC.

The CIs of the OR for the existence of late effects in brain tumor survivors or survivors with chemotherapy were wide. These findings were due to the characteristics of the study subjects; almost all cancer survivors (96.7%) had chemotherapy, and almost all brain tumor survivors (95.7%) had late effects. However, it is still evident that these two factors increased the OR.

The limitations of this study included the small study population size and the short follow-up duration compared with previous studies. It is possible that the prevalence of late effects was underestimated. This could be addressed by continued follow-up of the enrolled survivors. Another limitation was the absence of bone tumor survivors.

This study has some unique points. This is the first report on late effects of childhood cancer survivors in the Asian–Pacific region. Differences in pharmacokinetics and pharmacodynamics according to the ethnicity cause differences in efficacy and side-effects [37]. Sociocultural background might influence health behaviors to seek medical care such as screening tests [38]. These factors could be related with the incidence and severity of late effects and the participation rate in the LTFUC. Secondly, we evaluated the overall health status of childhood cancer survivors, not only focusing on late effects on a single-body system. Thirdly, all survivors were examined by oncologists and assessed with laboratory and radiological tests.

In conclusion, the results of this study showed that late effects were common in survivors and were apparent during a short interval of follow-up after diagnosis. The most common late effects were associated with the endocrine system. Endocrine abnormalities can be managed by meticulous and well-timed hormone replacement therapy. These findings suggest that late effects of childhood cancer survivors must be continuously monitored after the completion of cancer treatment, so that timely and effective treatment can be initiated.

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