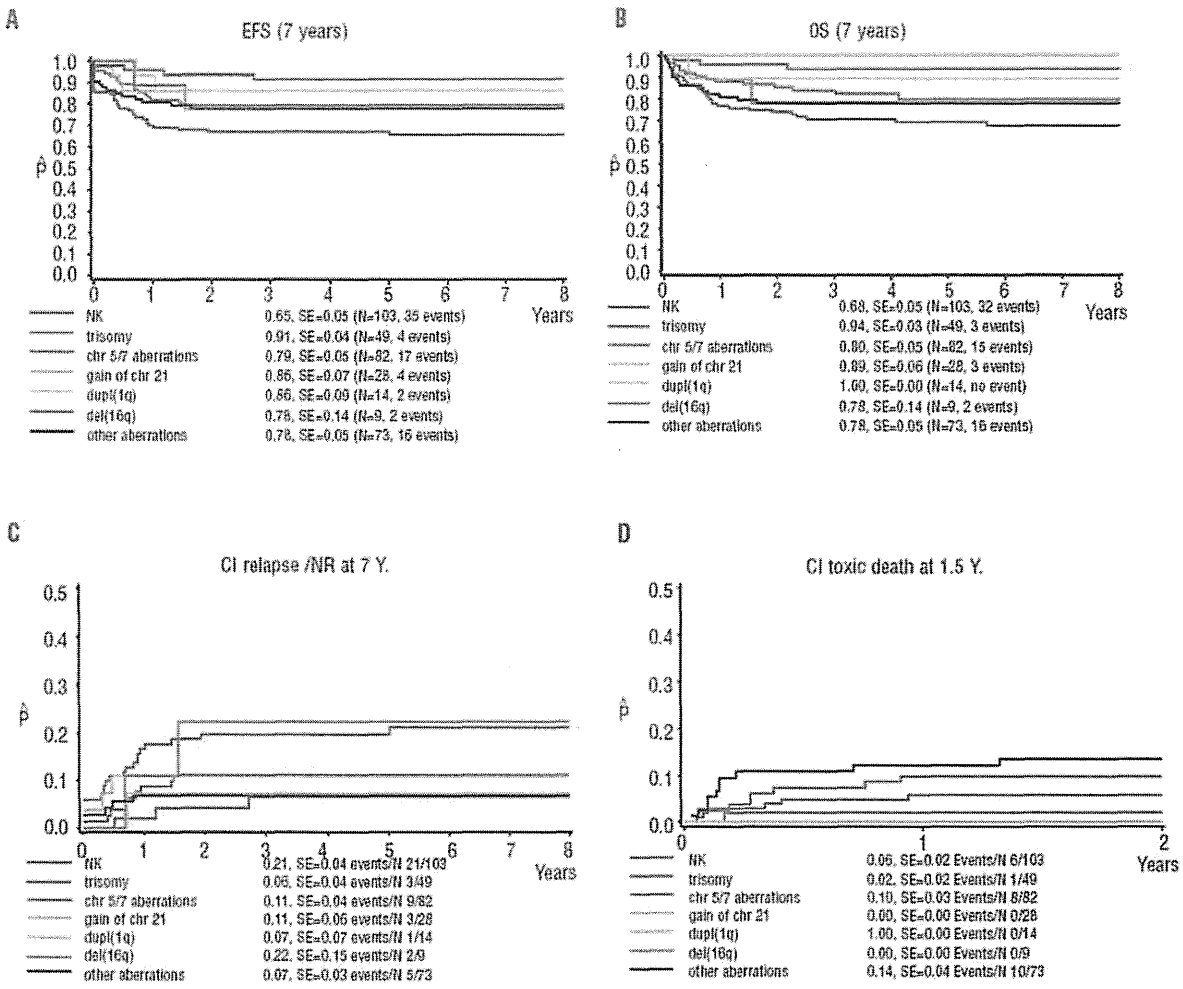

Figure 4. Survival curves for ML-DS patients (n=358) based on their cytogenetic status. (A) Event-free survival (EFS). (B) Overall survival (OS). (C) Cumulative incidence (CI) of relapse. (D) Cumulative incidence of toxic death. Assignment to groups was based on cytogenetic status, as identified after central review.

2%) *versus* 14% (± 2%); *P*=0.06]. The cumulative incidence of toxic death was significantly lower in the patients treated with higher cytarabine doses (≥ 20 g/m²) [2% (± 1%) *versus* 9% (± 2%); *P*=0.02].

Forty-three percent of all patients received therapy reduction or were treated with adjusted DS treatment protocols. Overall, no differences in outcome estimates were found between patients given reduced therapy and those who received standard therapy.

Multivariate analyses

Cox regression analysis of survival estimates from diagnosis revealed both age ≥3 years and WBC counts ≥20x10⁹/L were independent predictors for poor event-free survival (see Table 4), but not for overall survival. In addition, NK independently predicted for poor overall survival [hazard ratio (HR)= 1.58 and *P*=0.05)], event-free survival (HR= 1.65; *P*=0.03) and for relapse-free survival (HR= 2.22; *P*=0.01). Age ≥3 years was also an independent predictor for a lower relapse-free survival with a HR= 2.55 (*P*=0.01).

Discussion

In this collaborative study we analyzed a large international series of ML-DS cases with the aim of identifying differences in outcome related to cytogenetic features that could enable risk group stratification and risk-adapted therapy for ML-DS patients in the future. The results underscore the importance of international collaboration in the investigation of rare diseases or groups.

It was confirmed that overall outcome for ML-DS was superior to that of AML in non-DS children, with 7-year overall survival and event-free survival rates of 78% and 79%, respectively, in ML-DS, compared to 62% and 50% for non-DS AML patients from the same era treated on AML-BFM regimens as a reference cohort (both *P*<0.001; see *Online Supplementary Figure S9*). Of interest, the overall and event-free survival estimates were superimposed in ML-DS, suggesting that most relapsed patients could not be salvaged. However, it is unknown whether these patients were treated with curative intent at relapse.

Table 2. Survival estimates per cytogenetic subgroup.

Survival estimates per cytogenetic subgroup	7-year CIR	7-year OS	7-year EFS	7-year CI of toxic death
Normal karyotype (n=103)	21% (± 4%)	68% (± 5%)	65% (± 5%)	6% (± 2%)
del(16q) (n=9)	22% (± 15%)	78% (± 14%)	78% (± 14%)	0%
Loss of chromosome 5/7 material (n=82)	11% (± 4%)	80% (± 6%)	79% (± 5%)	10% (± 3%)
Gain of chromosome 21 (n=28)	11% (± 6%)	89% (± 6%)	86% (± 7%)	0%
Dup(1q) (n=14)	7% (± 7%)	100%	86% (± 9%)	0%
Trisomy 8 (n=49)	6% (± 4%)	94% (± 4%)	91% (± 4%)	2% (± 2%)
Other aberrations (n=73)	7% (± 3%)	78% (± 5%)	78% (± 5%)	14% (± 4%)

CIR: cumulative incidence of relapse; OS: overall survival; EFS: event-free survival; CI of toxic death: cumulative incidence of toxic death; del: deletion; dupl: duplication.

Although there is great concern about toxic mortality in ML-DS, in the present series relapse was more frequent than treatment-related mortality, with cumulative incidences of 12% and 7%, respectively. The relapse frequency of 12% is remarkably low when compared with that in non-DS AML patients from the AML-BFM study group from the same era, who had a CIR of 42% ($P<0.001$). However, the cumulative incidence of toxic death was similar between DS and non-DS children: 7% and 5%, respectively ($P=0.12$). The reasonable balance between toxic death and leukemia relapse in ML-DS may be due to the fact that treatment reduction was more frequently applied than in older studies in which higher toxic death rates in ML-DS were reported.[6,7,25]

Non-random cytogenetic aberrations that are common in non-DS pediatric AML, such as core-binding factor [CBF; t(8;21)], *MLL*-rearrangements and t(15;17), were identified in single cases only in our ML-DS cohort, which is in line with previous studies.[30]

The salient finding in the present study was that NK ML-DS patients had poorer survival parameters compared to ML-DS cases with aberrant karyotypes, and that NK independently predicted for poor clinical outcome. NK may, therefore, be used for treatment stratification in future treatment ML-DS protocols. In the NK ML-DS cases, the complete remission rate was significantly lower, and relapse (CIR 21%) determined prognosis to a greater extent than cumulative toxic death (6%). Hence, in this subgroup no further therapy reduction should be applied, whereas until now the increase in survival in ML-DS patients has mainly been achieved through the application of reduced-intensity chemotherapy protocols.[4,6,8,9] In fact, treatment intensification may even be needed. In order to reduce the number of induction failures a double induction based, for instance, on day 15 bone marrow blasts may be considered in patients with residual demonstrable leukemia. In addition, detection of *GATA1*-mutations using real-time quantitative polymerase chain reaction analysis may be feasible as a marker for minimal residual disease in the nearby future,[26] but is not routinely used yet. Alternative methods for detecting minimal residual disease include flow cytometry or reverse-transcription polymerase chain reaction for the *WT1* gene.[27] Increasing the cumulative doses of cytarabine, for example, may be of benefit during consolidation and intensification, as the CIR was lower in patients treated with higher doses. Recently, stem cell transplantation in ML-DS was reviewed but transplant-related mortality (24%) was significantly higher in this setting than in non-DS AML,[28] so its use should be limited to patients who do not attain sufficient remission or as salvage therapy at relapse.

Table 3. Clinical characteristics of the NK ML-DS *vs.* all other cases (with aberrant karyotypes).

Clinical characteristics of the ML-DS patients	NK	Other	P
N.	103	255	
Male sex, n.(%)	53 (51.4)	125 (50.8)	0.86
Median age (years)	1.7 (0.5-5.0)	1.8 (0.5-5.0)	0.9
< 3 years (%)	96 (93.2)	228 (91.2)	
≥ 3 years (%)	7 (6.8)	22 (8.8)	
Median WBC (x10⁹/L)	7.5 (0.8-160)	6.9 (1.5-290)	0.7
< 20x10⁹/L (%)	81 (79.4)	205 (82.7)	
≥ 20x10⁹/L (%)	21 (20.6)	43 (17.3)	
CNS involvement, n. (%)	1 (0.01)	1 (0.01)	0.35
Hepatomegaly, n. (%)	56 (54.9)	132 (55.0)	0.97
Splenomegaly, n. (%)	47 (46.1)	95 (39.6)	0.23

WBC white blood cell count; CNS central nervous system.

Understanding the underlying biology of NK ML-DS may reveal potential new treatment targets. Non-DS pediatric NK AML cases are characterized by various abnormalities, including overexpression of specific genes (*MN1*, *BAALC*, and *ERG*),[29] but also single gene mutations such as *FLT3*-ITD, *WT1*, *NPM1*, and *CEBPA*,[30-32] as well as cryptic translocations.[33] We recently showed that the abnormalities mentioned above are absent or rare in (NK-) ML-DS.[34] Hence, the underlying biology of NK ML-DS needs to be studied in more detail, for example by using novel techniques such as whole genome sequencing.

Non-DS pediatric AML with a trisomy 8 is classified in an intermediate-risk group.[35] In the present study, we showed, in a direct comparison, that the outcome estimate of ML-DS patients with trisomy 8 is significantly better that those of non-DS AML patients with trisomy 8 (CIR of 6% *versus* 62%; $P<0.0001$) (*Online Supplementary Figure S10*). Apparently, an additional copy of chromosome 8 has biologically different consequences in ML-DS compared to non-DS AML.

Monosomy 7 is known to be a poor prognostic factor in non-DS pediatric AML, as shown in another international-BFM collaborative study.[35] Outcome was significantly worse in patients with a loss of the whole chromosome (monosomy 7) than in patients with a del(7q).[24,35] In our ML-DS series, such differences were not observed, but numbers were small. Comparing ML-DS and non-DS AML patients revealed that ML-DS patients with mono-

somy 7 and/or del(7q) had a remarkably lower CIR (14% *versus* 52%; *P*=0.003) (*Online Supplementary Figure S1*). Thus chromosome 7 aberrations do not seem to have the same implications in ML-DS as in non-DS pediatric AML.

Interestingly, most chromosome 5/7 losses in ML-DS involved the p-arms rather than the q-arms. This is in contrast to non-DS AML, in which 5q and 7q losses are much more common and also prognostically relevant.[25]

Regarding the treatment of ML-DS patients, we have no clear explanation for the fact that the cumulative incidence of toxic death was significantly lower in the patients treated with higher doses of cytarabine. A hypothesis could be that due to concern for toxicity these patients received different and more intensive supportive care. We did not find any differences in outcome estimates between ML-DS patients treated with therapy reduction and those who received standard therapy, although it should to be mentioned that exact details of treatment reduction, individual treatment protocols, protocol adherence or individual adaptations of therapy were not available given the retrospective nature of this study.

In terms of prognostic factors other than cytogenetics, Klusmann *et al.* reported that ML-DS patients with a history of transient myeloproliferative disease had a significantly better outcome than children with ML-DS without documented transient myeloproliferative disease,[19] but

Table 4. Multivariate analysis of survival parameters of survival of ML-DS patients.

Outcome	Variable	Hazard ratio (HR)	95% confidence interval (CI)	P
OS	age ≥ 3 years	1.71	0.95 - 3.08	0.07
	WBC ≥ 20,000	1.56	0.96 - 2.52	0.07
	NK	1.53	0.99 - 2.52	0.05
EFS	age ≥ 3 years	1.92	1.10 - 3.33	0.02
	WBC ≥ 20,000	1.61	1.01 - 2.56	0.04
	NK	1.65	1.05 - 2.59	0.03
RFS	age ≥ 3 years	2.55	1.23 - 5.26	0.01
	WBC ≥ 20,000	1.83	0.97 - 3.46	0.06
	NK	2.22	1.19 - 4.13	0.01

OS: overall survival; EFS: event-free survival; RFS: relapse-free survival; NK: normal karyotype; WBC: white blood cell event.

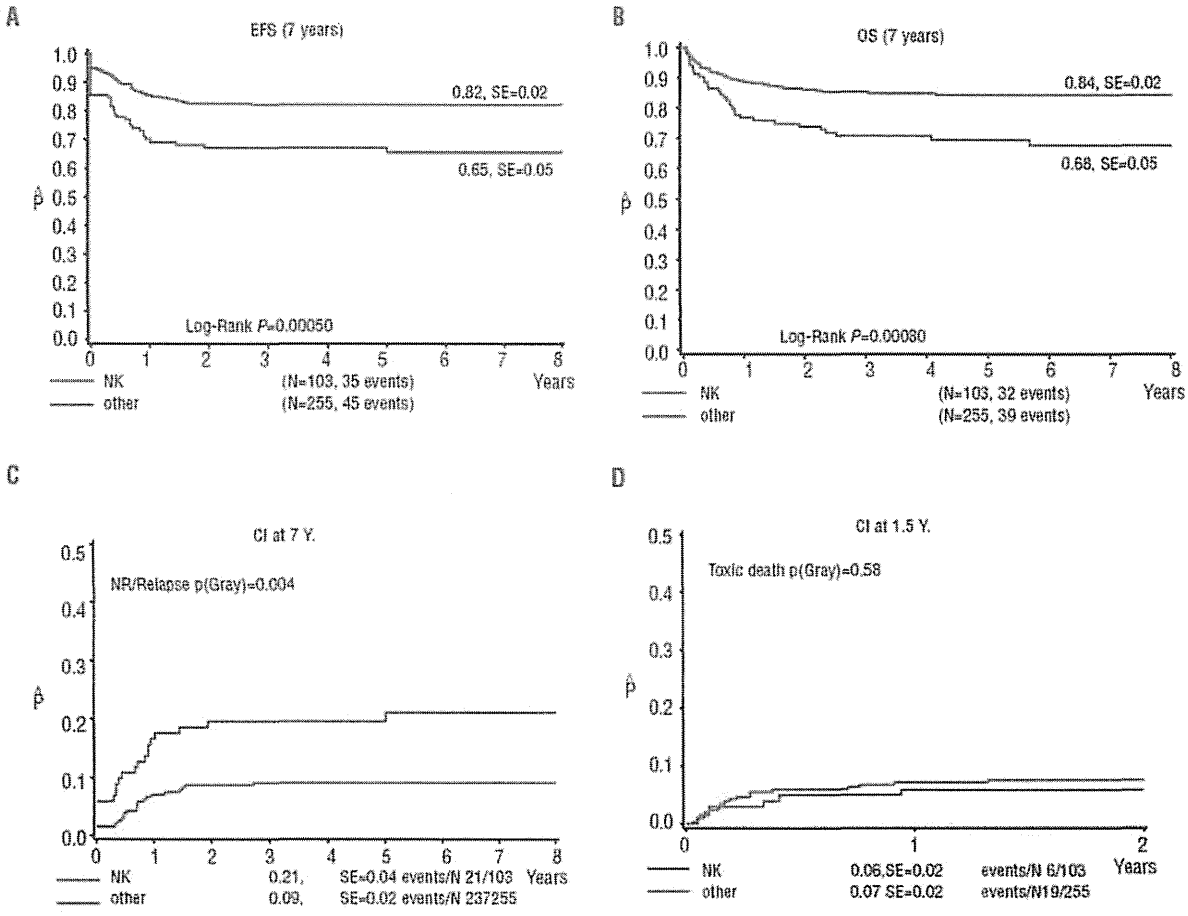

Figure 5. Survival curves for ML-DS patients (n=358) based on their cytogenetic status, divided into NK ML-DS patients (n=103) *versus* patients with aberrant karyotypes (n=255). (A) Event-free survival (EFS). (B) Overall survival (OS). (C) Cumulative incidence (CI) of relapse. (D) Cumulative incidence of toxic death. Assignment to groups was based on cytogenetic status, as identified after central review.

unfortunately we were not able to collect data on whether ML-DS was preceded by transient myeloproliferative disease.

Age ≥3 years and high WBC count (>20x10^9) were identified in the present study as independent predictors of poor outcome (event-free survival) in ML-DS, which is in concordance with the findings of previous studies.[9] This is mainly explained by the fact that there is a low(er) complete remission rate in these groups. These variables are also known from non-DS pediatric AML studies, in which older age and high WBC predict for poor outcome.[14] Regarding age in ML-DS, it has been proposed that DS children who present over 4 years of age do in fact suffer from sporadic AML occurring in a child with DS, rather than from a 'true' ML-DS.[15] For this reason we used the age cut-off in our inclusion criteria, to avoid 'contamination' with non-*GATA1* mutated AML cases in DS children. In addition, AML in children with DS older than 4 years of age is exceedingly rare.[15]

A limitation of this collaborative study is that there was a wide variation in treatment intensity. Although all included patients were treated on collaborative treatment protocols, almost half of the patients received therapy according to protocols or risk arms specifically designed for DS patients and/or treatment reductions were made in standard protocols. These factors may have biased the study results.

In conclusion, this study showed that NK predicts a poor clinical outcome in ML-DS. As the incidence of relapse is higher than that of treatment-related mortality in these cases, further therapy reduction is not indicated in this group; in fact, treatment intensification may be needed. On the other hand, treatment reduction may be feasible in ML-DS cases with aberrant karyotypes. Such treatment stratification needs to be confirmed in prospective clinical studies. As the prognosis of high-risk NK ML-DS patients cannot be explained by the presence of known mutations in non-DS NK AML, the biological background must be elucidated to identify potential novel targets for therapy.

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Authorship and Disclosures

Information on authorship, contributions, and financial & other disclosures was provided by the authors and is available with the online version of this article at www.haematologica.org.

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ORIGINAL ARTICLE

Recent employment trend of childhood cancer survivors in Japan: a cross-sectional survey

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Abstract
Background Previous research has shown that some adult childhood cancer survivors (CCSs) have experienced employment difficulties. However, the actual employment status of CCSs in Japan has not been studied.
Participants and methods The participants were selected from the membership directory of Heart Link mutual-aid health insurance and recruited by the Childhood Cancer Patients' Network. We conducted a cross-sectional survey (a self-rated questionnaire on employment) via postal mail or an email communication with a link to an Internet website. We explored the association between the characteristics of CCSs who require disability qualification and having experienced unemployment. The adjusted odds ratios (ORs) for the factors with an outcome of interest were estimated with logistic regression analysis.
Results In total, 44 CCSs indicated that they had a disability qualification. The significant independent factors related to needing a disability qualification were late effects [OR 12.3; 95 % confidence interval (CI) 3.37–45.2], brain tumors (OR 9.55; 95 % CI 1.90–48.0), and being a high school graduate (OR 9.86; CI 2.67–36.4). The unemployment rate was 15.9 % among CCSs, excluding homemakers and students. Approximately 70 % of unemployed CCSs had some late effects; independent factors related to unemployment were late effects (OR 6.22; 95 % CI 1.80–21.40), dropping out of school (OR 8.46; 95 % CI 1.66–43.10), and brain tumors (OR 2.73; 95 % CI 0.83–8.96). Most unemployed CCSs were likely to seek work, despite their health problems.
Conclusions The unemployment rate is not high in Japan, but some CCSs need extended disability qualification. The independent factors related to unemployment were late effects and dropping out of school.

Keywords Childhood cancer survivors · Employment · Unemployment · Occupation · Social outcome · Disability

Abbreviations

CCS	Childhood cancer survivors
CCSS	The Childhood Cancer Survivor Study
OR	Odds ratio
CI	Confidence interval

Introduction

Because of advances in treatment, 70–80 % of children diagnosed with cancer become long-term survivors. In Japan, the estimated number of childhood cancer survivors (CCSs) is greater than 50,000, and we expect that at least 30,000 survivors have already reached adulthood (20 years of age or older). Although there is an increased number of CCSs, many survivors experience various health problems

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later in life because of the cancer and its treatment [1, 2]. In addition, these various physical problems (termed "late effects") also seem to affect CCSs' social outcomes (e.g., marriage, education, and employment, etc.), both directly and indirectly [3].

Previous research has suggested that adult CCSs experience employment difficulties [4–7]. In the previous Childhood Cancer Survivor Study (CCSS), a greater percentage of survivors reported a lack of any employment in the past 12 months (9.3 %) than their siblings did (6.7 %) [8]. Elevated risk for never having been employed was associated with failing to complete high school, young age (<4 years) at diagnosis, cranial radiation therapy of 30 Gy, and being female [9]. CCSs from all diagnostic categories were less likely to have been employed during the past 12 months than members of the sibling group; the age- and sex-adjusted likelihood of being employed was lowest among brain and bone tumor survivors [9].

Despite these findings, the actual employment status of CCSs in Japan has not been studied. In the current study, we conducted a cross-sectional survey of CCSs in Japan in order to identify their employment outcomes.

Participants and methods

Study design

We performed a cross-sectional survey (a self-rated employment questionnaire) via postal mail or email with a link to an Internet website (see Supplemental Appendix 1). The study was conducted from July until September 2012.

Participants

The first sample group was selected from 631 applications to or the membership directory of Heart Link mutual-aid health insurance in Niigata [10]. The second sample group was recruited from the Childhood Cancer Patients' Network, including the Pediatric Brain Tumor Association in Japan [11].

Survey method

The first group was sent a brochure explaining the purpose and methods of the study, and asking them to return the questionnaire directly to the Heart Link mutual-aid health insurance office by postal mail anonymously within 1 month. The second group was sent an email explaining the purpose and methods of the study, and asking them to respond to the questionnaire via an Internet website link. Informed consent was assumed if the participant returned the questionnaire.

The questionnaire consisted of 32 items, with 9 items (questions Q1–8 and Q15) that asked about the participant's basic characteristics. Through the questionnaire, we evaluated regular, routine checkups (Q9), health status and the presence of late effects (Q10–Q11), disability qualification (Q12 and 14), employment (Q13), marriage (Q16–17), and present issues found worrisome (Q18). Through Q21–Q23, we assessed job satisfaction, influence of childhood cancer experience, and sharing about the cancer diagnosis with one's employer. Q24 through Q30 assessed unemployment-related issues: reasons for unemployment, employment difficulties, worries about unemployment, major living costs, and whether participants' and/or their parents want them to work. Q31 assessed worries of student CCSs about future employment.

Ethical issues

The study was performed in accordance with the Declaration of Helsinki and approved by the ethics committee of St. Luke's International Hospital, no. 12-R046.

Statistical analyses

We performed χ^2 tests (or Fisher's exact tests for cells with expected counts of more than five) within categorical predictors. A trend test was used to rank trends of health and economic status over CCSs with late effects. We explored the association between characteristics of the CCSs who required a disability qualification (limited to the CCSs who were 18 years or older to evaluate educational achievement) and those who had experienced unemployment (excluding housewives and students). The adjusted odds ratios (ORs) for factors with an outcome of interest were estimated with logistic regression analysis. Data were analyzed with SPSS software, v. 20.0 (IBM Japan, Tokyo, Japan).

Results

A total of 240 questionnaires (217 from the first sample group and 23 from the second sample group) were collected by November 2012. The response rate was 34.4 % (217 out of 631) for the first sample group. The response rate for the second sample group could not be calculated because we only informed the web-site homepage of this research to the Childhood Cancer Patients' Network and we couldn't know the number of the CCSs who have watched the homepage. One questionnaire was excluded because the CCS did not answer the questionnaire him/herself. There were 123 male and 116 female respondents.

Demographic data

The participants' demographic characteristics are listed in Table 1. The mean age was 24.3 years (median 24; range

Table 1 Background of the participating childhood cancer survivors

	Male ($n = 123$)	Female ($n = 116$)	χ^2 (p value)
Age at survey (years)			
20 years or younger	39 (32 %)	33 (28 %)	0.226
21–24 years	26 (21 %)	30 (26 %)	
25–29 years	35 (29 %)	23 (20 %)	
30 years or older	22 (18 %)	30 (26 %)	
Diagnosis of cancer			
Leukemia	60 (50%)	66 (57 %)	0.681
Lymphoma	15 (13 %)	8 (7 %)	
Other solid cancers	18 (15 %)	19 (16 %)	
Bone/soft tissue sarcoma	7 (6 %)	6 (5 %)	
Brain tumor	20 (17 %)	17 (15 %)	
Age at diagnosis (years)			
3 years or younger	36 (29 %)	33 (28 %)	0.341
4–7 years	32 (26 %)	25 (22 %)	
8–12 years	27 (22 %)	37 (32 %)	
13 years or older	28 (23 %)	21 (18 %)	
Treatment			
Chemotherapy	108 (88 %)	106 (91 %)	0.367
Radiation	63 (51 %)	59 (51 %)	0.956
Surgery	47 (38 %)	42 (36 %)	0.749
Stem cell transplantation	29 (24 %)	19 (16 %)	0.165
Immunotherapy	6 (4 %)	3 (3 %)	0.501[a]
Others	11 (9 %)	6 (5 %)	0.257
Regular checkup (per year)			
None	37 (30 %)	30 (26 %)	0.327
Once per several years	2 (2 %)	7 (6 %)	
Once	40 (33 %)	43 (37 %)	
Twice	20 (16 %)	12 (10 %)	
Three times	7 (6 %)	9 (8 %)	
More than four times	17 (14 %)	15 (13 %)	
Living district			
Hokkaido/Tohoku	5 (4 %)	9 (8 %)	0.516
Kanto (excepting Niigata)	48 (39 %)	38 (33 %)	
Niigata	31 (25 %)	25 (22 %)	
Tokai/Hokuriku	13 (11 %)	10 (9 %)	
Kinki	13 (11 %)	14 (12 %)	
Chu-shikoku/Kyusyu	13 (11 %)	19 (17 %)	
Education			
Junior high school	10 (8 %)	8 (7 %)	0.263[a]
High school	35 (29 %)	26 (22 %)	
College or vocational school	16 (13 %)	25 (22 %)	
University or graduate school	53 (43 %)	53 (46 %)	
Dropout	9 (7 %)	4 (3 %)	

[a] Fisher's exact test

16–42 years). While female CCSs tended to be somewhat older, this difference was not significant. More than half of the CCSs (both male and female) had suffered from hematological cancers, and approximately 15 % had suffered from brain tumors and solid cancers, respectively. The mean age at cancer diagnosis was 7.5 years (median 7; range 0–19 years). The mean age at treatment completion was 10.4 years (median 10; range 0–27 years), and this survey was conducted approximately 14 years after treatment completion. Regarding primary cancer treatment, 90 % of CCSs received multiagent chemotherapy, 51 % received radiation, 37 % underwent surgery, and 20 % received hematopoietic stem cell transplantation. There were no statistical differences between males and females for all basic characteristics. Approximately 28 % of CCSs had not had a regular checkup at the time of this survey, but 33 % had regular checkups once per year, and another 33 % had two or more regular checkups per year. There was no statistical difference between the geographic locations of males and females; a majority of the participants lived in the Kanto area, including the Niigata prefecture.

CCS characteristics

Table 2 lists the current status of different CCS characteristics according to gender. Nearly half of the CCSs reported the presence of various late effects. The most predominant late effects were endocrinological problems and short stature, which was found in both males and females. The marriage rate of females was significantly higher than that of males in the 30 years or older group. There were 17 male and 16 female unemployed CCSs; 8 of the females were housewives. The unemployment rate was 15.9 % (25 of 157), excluding homemakers and students. More than half of CCSs were in good health, and approximately 10 % were in poor or bad health. Approximately 50 % reported good or fair economic status, but male CCSs reported poor or bad economic status significantly more often than females did.

Association between CCS characteristics and late effects

The prevalence of late effects was significantly associated with multiple CCS characteristics (see Table 3). The specific cancer diagnosis was associated with different proportions of reported late effects: CCSs who had been diagnosed with a brain tumor or bone/soft tissue sarcoma reported significantly more prevalence of late effects than those with other diagnoses (76 and 67 %, respectively). With respect to cancer treatment, radiation, surgery, and stem cell transplantation were associated with a higher prevalence of late effects than other treatments (66, 61, and 77 %, respectively). Approximately 70 % of unemployed CCSs experienced some late effects compared with 44 % of employed CCSs. Finally, CCSs who had better subjective health and economic status were significantly less likely to report late effects.

Table 2 Present status of the total childhood cancer survivors

	Male (n = 123)	Female (n = 115)	χ^2 (p value)
Late effects			
Yes	60 (49 %)	52 (45 %)	0.582
Endocrinological problems	22 (18 %)	26 (22 %)	0.383
Short stature	20 (16 %)	13 (11 %)	0.258
Neurocognitive problems	10 (8 %)	7 (6 %)	0.529
Skin/hair loss	9 (7 %)	6 (5 %)	0.494
Eye problems	5 (4 %)	6 (5 %)	0.683
Hearing imparement	5 (4 %)	4 (3 %)	0.999[a]
Bone/muscle problems	4 (3 %)	2 (2 %)	0.684[a]
Psychological problems	3 (2 %)	2 (2 %)	0.999[a]
Surgery-related problems	3 (2 %)	2 (2 %)	0.999[a]
Secondary cancer	0	2 (2 %)	0.235[a]
Marriage			
20 years or younger	0/39 (0 %)	0/33 (0 %)	N/A
21–24 years	1/25 (4 %)	1/30 (3 %)	0.718[a]
25–29 years	3/35 (9 %)	5/23 (22 %)	0.259[a]
30 years or older	7/22 (32 %)	15/30 (50 %)	0.040
Employment			
Yes	66 (54 %)	66 (57 %)	0.733
No at present	16 (13 %)	16[b] (14 %)	
Never	1 (1 %)	0	
Student	40 (33 %)	34 (29 %)	
Health status at present			
Good	61 (50 %)	67 (58 %)	0.418
Fair	23 (19 %)	19 (16 %)	
Moderate	28 (23 %)	17 (15 %)	
Poor	9 (8 %)	12 (10 %)	
Bad	2 (2 %)	1 (1 %)	
Economic status			
Good	12 (10 %)	23 (20 %)	0.043
Fair	42 (35 %)	48 (42 %)	
Poor	33 (28 %)	21 (18 %)	
Bad	14 (12 %)	6 (5 %)	
Unknown	19 (16 %)	16 (14 %)	

N/A not applicable

[a] Fisher's exact test

[b] Eight out of 16 female CCSs were housewives

Table 3 Association factors or status with late effects

Late effects	Yes (n = 112)	No (n = 123)	χ^2 (p value)
Age at survey (years)			
20 years or younger	32 (44 %)	40 (56 %)	0.914
21–24 years	26 (46 %)	30 (54 %)	
25–29 years	27 (47 %)	31 (53 %)	
30 years or older	26 (51 %)	25 (49 %)	
Diagnosis of cancer			
Leukemia	52 (41 %)	74 (59 %)	0.002
Lymphoma	9 (39 %)	14 (61 %)	
Other solid cancers	15 (41 %)	22 (59 %)	
Bone/soft tissue sarcoma	8 (67 %)	4 (33 %)	
Brain tumor	28 (76 %)	9 (24 %)	
Age at diagnosis (years)			
3 years or younger	32 (46 %)	37 (54 %)	0.854
4–7 years	27 (47 %)	30 (53 %)	
8–12 years	28 (44 %)	36 (56 %)	
13 years or older	25 (52 %)	23 (48 %)	
Treatment			
Chemotherapy	104 (49 %)	109 (51 %)	0.111
Radiation	80 (66 %)	42 (34 %)	<0.001
Surgery	54 (61 %)	35 (39 %)	0.001
Stem cell transplantation	37 (77 %)	11 (23 %)	<0.001
Immunotherapy	4 (44 %)	5 (56 %)	0.999[a]
Marriage			
Yes	14 (44 %)	19 (56 %)	0.687
Employment			
Yes	57 (44 %)	74 (56 %)	0.041
No at present	22 (69 %)	10 (31 %)	
Never	1 (100 %)	0	
Student	32 (43 %)	42 (57 %)	
Health status at present			
Good	35 (27 %)	93 (73 %)	<0.001
Fair	25 (60 %)	17 (40 %)	<0.001[b]
Moderate	30 (68 %)	14 (32 %)	
Poor	20 (95 %)	1 (5 %)	
Bad	2 (67 %)	1 (33 %)	
Economic status			
Good	11 (31 %)	24 (69 %)	0.04
Fair	40 (45 %)	49 (55 %)	0.005[b]
Poor	28 (52 %)	26 (48 %)	
Bad	14 (70 %)	5 (30 %)	

[a] Fisher's exact test

[b] Trend test

Disability qualification

Among the 239 participants, 29 CCSs (12 %) already had the disability qualification, and an additional 15 reported that they needed it (Fig. 1). The total number of CCSs who need the disability qualification is 44. Table 4 shows associations between CCS characteristics and the need for the disability qualification limited to survivors 18 years or older. Univariate analysis showed that the significantly

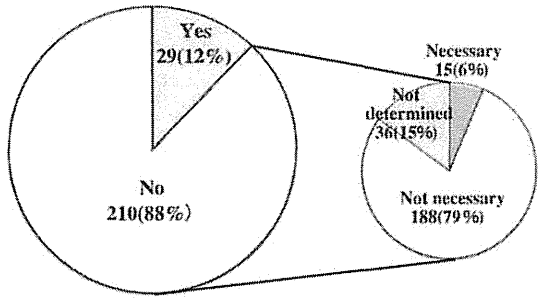

Fig. 1 Do you have or need the disability qualification?

related factors were education, primary cancer diagnosis, radiation, surgery, and late effects. Logistic regression analysis revealed that the significant independent related factors were late effects (OR 12.3; 95 % CI 3.37–45.2), brain tumors (OR 9.55; 95 % CI 1.90–48.0), lymphoma (OR 5.92; 95 % CI 1.07–32.7), and being a high school graduate (OR 9.86; CI 2.67–36.4). Gender and treatment contents were not associated with reporting a need for the disability qualification after adjustment of other factors.

Employment status

We classified the CCSs into three groups according to employment status: employed, unemployed, and students (see Table 5). More than half of the employed CCSs reported being satisfied with their current job, but approximately 40 % also reported that their work had been influenced by their childhood cancer experience. In addition, 61 % had told their employer and/or colleagues about their cancer diagnosis. There were no significant differences between males and females.

In contrast to employed CCSs, 60–80 % of unemployed CCSs reported having experienced some job

Table 4 Related factors of childhood cancer survivors who need the disability qualification (limited to survivors 18 years or older)

	Necessary ($n = 37$)	Not necessary ($n = 164$)	χ^2 (p value)	Logistic regression analysis	
				Odds ratio (95 % CI)	p value
Age at survey (years)					
20 years or younger	10 (25 %)	30 (75 %)	0.582	N/A	
21–24 years	8 (15 %)	45 (85 %)		N/A	
25–29 years	9 (15 %)	49 (85 %)		N/A	
30 years or older	10 (20 %)	40 (80 %)		N/A	
Gender					
Male	23 (22 %)	81 (78 %)	0.16	1.58 (0.57–4.36)	0.376
Education					
Dropout	2 (15 %)	11 (85 %)	0.005	0.79 (0.10–6.38)	0.826
Junior high school	4 (22 %)	14 (78 %)		2.28 (0.04–141)	0.695
High school	21 (35 %)	39 (65 %)		9.86 (2.67–36.4)	0.001
College or vocational school	5 (13 %)	34 (87 %)		1.26 (0.28–5.79)	0.766
University	2 (12 %)	90 (88 %)		Ref.	
Diagnosis of cancer					
Leukemia	8 (8 %)	97 (92 %)	<0.001	Ref.	
Lymphoma	7 (32 %)	15 (68 %)		5.92 (1.07–32.7)	0.002
Other solid cancers	2 (7 %)	28 (93 %)		0.67 (0.07–6.09)	0.720
Bone/soft tissue sarcoma	3 (25 %)	9 (75 %)		4.11 (0.52–32.3)	0.179
Brain tumor	17 (57 %)	13 (43 %)		9.55 (1.90–48.0)	0.006
Treatment					
Chemotherapy	33 (18 %)	148 (82 %)	0.846	1.11 (0.16–7.66)	0.917
Radiation	27 (25 %)	80 (75 %)	0.008	1.81 (0.52–6.32)	0.353
Surgery	25 (32 %)	53 (68 %)	<0.001	1.91 (0.52–6.99)	0.326
Stem cell transplantation	7 (17 %)	34 (83 %)	0.805	0.37 (0.10–1.39)	0.141
Late effects					
Yes	40 (37 %)	67 (63 %)	<0.001	12.3 (3.37–45.2)	<0.001

Hosmer–Lemeshow: $\chi^2 = 3.37$ ($p = 0.909$)

N/A not applicable

Table 5 Employed, unemployed and student childhood cancer survivors

Employed childhood cancer survivors ($n = 131$)	Male ($n = 65$)	Female ($n = 66$)	χ^2 (p value)
Job satisfaction			
Good	11 (18 %)	12 (18 %)	0.690
Fair	19 (31 %)	26 (39 %)	
Moderate	21 (34 %)	16 (24 %)	
Poor	8 (13 %)	7 (11 %)	
Bad (want to quit)	3 (5 %)	5 (8 %)	
Influence by childhood cancer experience			
Much	12 (19 %)	13 (20 %)	0.626
Fair	15 (23 %)	14 (21 %)	
Moderate	9 (14 %)	10 (15 %)	
Little	17 (26 %)	11 (17 %)	
Not at all	12 (26 %)	18 (27 %)	
Telling the cancer diagnosis to the company and/or colleagues			
Yes	40 (61 %)	34 (52 %)	0.288
No	25 (39 %)	31 (48 %)	
Un-employed childhood cancer survivors ($n = 31$)	$n = 16$	$n = 15$	χ^2 (p value)
Some difficulties in employment by childhood cancer experience			
Yes	13 (81 %)	9 (60 %)	0.193
No	3 (19 %)	6 (40 %)	
Please specify the reasons of unemployment			
Failure despite of job seeking	5 (31 %)	4 (27 %)	0.921
No job seeking	2 (12 %)	1 (7 %)	
Unable to get a job because of late effects	3 (19 %)	3 (20 %)	
Others	6 (38 %)	7 (47 %)	
Worry about un-employment			
Not at all	0	1 (6 %)	0.020
Little	2 (13 %)	1 (6 %)	
Moderate	0	3 (19 %)	
Some	0	5 (31 %)	
Much	12 (75 %)	4 (25 %)	
Others	2 (13 %)	1 (6 %)	
Your parent's wish			
Prefer you to work	13 (81 %)	8 (53 %)	0.271
Either will do	0	3 (20 %)	
Prefer not you to work	1 (6 %)	1 (7 %)	
Unknown	2 (12 %)	3 (20 %)	
Major living costs covered by			
Yourself	3 (19 %)	0	0.012
Parents	11 (69 %)	7 (44 %)	
Spouse	0	8 (50 %)	
Public help	1 (6 %)	1 (6 %)	
Do you want to work if they understand CCSs?			
Yes, much to work	7 (41 %)	7 (47 %)	0.755
Yes, if possible	5 (27 %)	4 (27 %)	
It depend on the job	2 (12 %)	3 (20 %)	
Others	2 (12 %)	1 (7 %)	

Table 5 continued

Un-employed childhood cancer survivors ($n = 31$)	$n = 16$	$n = 15$	χ^2 (p value)
Do you want the job-training place like the heart link working project?			
Yes	15 (94 %)	15 (100 %)	0.999[a]
No	1 (6 %)	0	
Students ($n = 69$)	$n = 39$	$n = 30$	χ^2 (p value)
Do you have some worries about your future employment?			
Yes	19 (49 %)	18 (60 %)	0.352
No	20 (51 %)	12 (40 %)	

[a] Fisher's exact test

Table 6 Related unemployment factors (excluding housewives and students)

	Unemployed ($n = 25$)	Employed ($n = 131$)	χ^2 (p value)	Logistic regression analysis	
				Odds ratio (95 % CI)	p value
Age at survey (years)					
20 years or younger	4 (29 %)	10 (71 %)	0.608	N/A	
21–24 years	6 (14 %)	37 (86 %)		N/A	
25–29 years	8 (15 %)	45 (85 %)		N/A	
30 years or older	7 (15 %)	39 (85 %)		N/A	
Gender					
Male	17 (21 %)		0.098	2.05 (0.71–5.90)	0.183
Education					
Dropout	5 (39 %)	8 (62 %)	0.110	8.46 (1.66–43.1)	0.010
Junior high school	1 (17 %)	5 (83 %)		1.66 (0.11–24.8)	0.713
High school	8 (21 %)	30 (79 %)		1.78 (0.52–6.12)	0.359
College or vocational school	4 (12%)	29 (88 %)		1.26 (0.29–5.54)	0.757
University	7 (10 %)	60 (90 %)		Ref.	
Diagnosis of cancer					
Leukemia	10 (12 %)	74 (88 %)	0.016	Ref.	
Lymphoma	4 (25 %)	12 (75 %)		1.55 (0.34–7.19)	0.575
Other solid cancers	1 (4 %)	23 (96 %)		0.22 (0.02–2.32)	0.210
Bone/soft tissue sarcoma	2 (18 %)	9 (82 %)		1.05 (0.14–7.92)	0.964
Brain tumor	8 (38 %)	13 (62 %)		2.73 (0.83–8.96)	0.098
Treatment					
Chemotherapy	24 (17 %)	118 (83 %)	0.303	N/A	
Radiation	16 (19 %)	70 (81 %)	0.312	N/A	
Surgery	12 (19 %)	50 (81 %)	0.426	N/A	
Stem cell transplantation	8 (23 %)	26 (77 %)	0.564	N/A	
Late effects					
Yes	21 (27 %)	57 (73 %)	<0.001	6.22 (1.80–21.4)	0.004

Hosmer–Lemeshow: $\chi^2 = 4.99$ ($p = 0.759$)

N/A not applicable

difficulties because of the childhood cancer experience. While only 10 % reported not having tried to find work, 30 % reported failure in job seeking, and 20 % reported the inability to obtain employment because of their late effects. A majority of the CCSs reported worry concerning their unemployment status, especially the males

(75 %). Both males (81 %) and females (51 %) reported that their parents preferred they find employment. For the majority of the sample, living costs were being covered by parents or spouses (females only). Most unemployed CCSs reported wanting to work if their employers understood CCSs better.

Table 6 shows associations between CCS characteristics and employment status. Univariate analysis revealed significant associations between primary cancer diagnosis and late effects. Logistic regression analysis revealed the independent related factors for unemployment were late effects (OR 6.22; 95 % CI 1.80–21.40) and dropping out (OR 8.46; 95 % CI 1.66–43.1). Finally, brain tumors tended to be associated with a high unemployment rate (OR 2.73; 95 % CI 0.83–8.96).

Discussion

We found that the unemployment rate was 15.9 % among the CCSs, excluding homemakers and students, and that 40 % of all employed CCSs reported that their work had been influenced by their childhood cancer experience. Approximately 70 % of unemployed CCSs reported having some late effects. The independent related factors for unemployment were late effects (OR 6.22), dropping out of school (OR 8.46), and brain tumors (OR 2.73). Most unemployed CCSs were likely to seek work despite their health problems and the presence of late effects.

The prevalence of late effects in this study was similar to that in previous studies [12], including other Japanese populations [2]. Frequently reported late effects included endocrine dysfunction, short stature, and neurocognitive problems (that latter is frequently observed in brain tumor survivors). The high prevalence of neurocognitive problems can be explained by the high percentage of brain tumor survivors (15 %) in this study. The finding that the presence of late effects is inversely associated with employment, health, and economic status (see Table 3) is consistent with previous research [13].

A total of 44 CCSs reported that the disability qualification is necessary. The most significant related independent factors were late effects (OR 20.1), brain tumors (OR 9.29), and lower academic achievement (OR 6.3 for junior high school). The Japanese government proposed the new Cancer Control Act in 2012, which explores the employment needs and work-related problems of cancer survivors, promotes employer understanding and an employer-sponsored consultation system, and establishes a society in which cancer survivors can work and live in trust. In the US, the Americans with Disabilities Act of 1990 states that a covered entity shall not discriminate against a qualified individual with a disability, including cancer patients. This applies to job application procedures, hiring, advancement and discharge of employees, workers' compensation, job training, and other terms, conditions, and privileges of employment. In Japan, cancer survivors are not included in the disability qualification. They discussed which types of cancer survivors could be included in the current disability qualification.

In this study, the unemployment rate was 15.9 % among the CCSs, excluding homemakers and students. This rate was similar to the rate of 11 % in the CCSS study [6] and the rate of 16 % in Sweden [14], but relatively lower than the rate of 37 % in Turkey [15]. Independent factors related to unemployment were late effects (OR 6.22), dropping out of school (OR 8.46), and brain tumors (OR 2.73). de Boer et al. [16] reported a meta-analysis on adult CCSs and unemployment. CCSs were nearly twice as likely to be unemployed as healthy controls (OR 1.85, 95 % CI 1.27–2.69). Brain tumor survivors were nearly five times more likely to be unemployed (OR 4.74; 95 % CI 1.21–18.65), whereas the risks for blood or bone cancer survivors were elevated but not statistically significant (OR 1.42; 95 % CI 0.79–2.55; OR 1.97; 95 % CI 0.88–4.40, respectively). Apart from type of diagnosis, predictors of unemployment were a younger age, lower education, being female, late effects, and radiotherapy. Our results are primarily consistent with these findings [14, 16–18].

We have the unpublished data that most CCSs are highly motivated to become helpful to others (a survey by the Children's Cancer Association of Japan). In this study, many unemployed CCSs were likely to seek work despite their health problems and late effects [19]. They require social understanding regarding their specific difficulties including late effects, and we as a society need to make advocacy on their behalf a priority [20].

Our study has two key strengths. First, this is the first nationwide survey in Japan that has focused on CCSs' employment problems. Second, we included a large enough sample to conduct a multivariate analysis on the factors with two outcomes of interest. There are, however, some limitations to the study. First, this is a cross-sectional study, so it cannot determine causal relationships. Second, we did not include a comparison group (such as siblings of CCSs). Finally, the response rate was fairly low (34.4 %) for the first sample group and unknown for the second sample group. The results may be subject to response bias (i.e., those with a stronger interest in the topic may have been more likely to respond to the survey). These disadvantages must be considered given the logistic difficulty of obtaining information from some isolated CCSs. Our ongoing research focuses on seeking out these isolated, unemployed CCSs and individually interviewing them.

In conclusion, our study suggests that the unemployment rate of CCS in Japan is not high, but that some CCSs need

the expanded disability qualification. Approximately 70 % of unemployed CCSs had some late effects; independent factors related to unemployed CCS were late effects (OR 6.22) and dropping out of school (OR 8.46). Most unemployed CCSs were likely to seek work, despite their health problems.

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Conflict of interest The all authors declare that they have no conflict of interest.

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bjh research paper

Secondary cancers among children with acute lymphoblastic leukaemia treated by the Tokyo Children's Cancer Study Group protocols: a retrospective cohort study

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Summary

With improvement in survival, it is important to evaluate the impact of treatment on secondary cancers in acute lymphoblastic leukaemia (ALL) survivors. A retrospective cohort study comprising 2918 children diagnosed with ALL and enrolled on Tokyo Children's Cancer Study Group (TCCSG) protocols between 1984 and 2005 was conducted to evaluate the incidence of secondary cancers and associated factors including treatment protocol, cranial irradiation and other characteristics of the primary ALL. Thirty-seven patients developed secondary cancers, including acute myeloid leukaemia (n = 11), myelodysplastic syndrome (n = 5), non-Hodgkin lymphoma (n = 2), brain tumours (n = 13) and other solid carcinomas (n = 6) within a median follow-up duration of 9·5 years. The cumulative incidence of any secondary cancers was 1·0% (95% confidence interval (CI), 0·7–1·4%) at 10 years and 2·4% (95% CI, 1·5–3·7%) at 20 years, respectively. Standardized incidence rate ratio of secondary cancers was 9·3 (95% CI, 6·5–12·8). Multivariate analyses showed an increased risk of secondary cancers associated with the recent treatment protocol and cranial irradiation. There was no evidence of a reduction in secondary cancer incidence despite marked decreases in cranial irradiation use in the recent protocols.

Keywords: secondary cancers, acute lymphoblastic leukaemia, children, cumulative incidence, standardized incidence rate ratio.

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Intensive multidrug therapy has steadily improved the overall survival (OS) of children with acute lymphoblastic leukaemia (ALL) despite decreasing prophylactic cranial irradiation (Pui *et al*, 2009; Tsuchida *et al*, 2010). The immunosuppressive and cytotoxic therapy necessary to achieve this improvement increases the risk of subsequent late effects. One of the most serious late effects is the development of a secondary cancer.

Reports from previous studies including the Childhood Cancer Survivor Study (CCSS) and British CCSS (BCCSS) have contributed important evidence regarding the risk of subsequent primary neoplasms among survivors of childhood cancers, such as ALL.(Hawkins *et al*, 1992; Neglia *et al*, 2001; Mody *et al*, 2008; Meadows *et al*, 2009; Friedman *et al*, 2010; Reulen *et al*, 2011) However, the study populations comprising both of these large cohorts are childhood cancer patients who have survived at least 5 years following primary cancer diagnosis and the results do not account for the time at risk during the first 5 years.(Hawkins & Robison, 2006).

A few studies have described the overall risk of secondary cancers among children with ALL with the period of observation beginning from a time shortly following successful complete remission (CR). (Neglia *et al*, 1991; Nygaard *et al*, 1991; Kimball Dalton *et al*, 1998; Loning *et al*, 2000; Bhatia *et al*, 2002; Hijiya *et al*, 2007; Schmiegelow *et al*, 2009) Compared with the general population, the survivors with a history of childhood ALL have been estimated to have a 10- to 20-fold greater risk of developing a secondary cancer. In addition to genetic predisposition, previously administered chemotherapy and/or radiotherapy are considered the most important risk factors. (Loning *et al*, 2000) Based on the cohort of patients previously enrolled onto a Tokyo Children's Cancer Study Group (TCCSG) protocol since 1984, the current study is the first report from an Asian country to describe the incidence and types of secondary cancers observed among survivors of childhood ALL. We also aimed to evaluate potential risk factors for secondary cancers, particularly the influence of treatment protocol and cranial irradiation use.

Patients and methods

Study population

A total of 2,918 newly diagnosed children with ALL aged 1–15 years were entered into 5 consecutive TCCSG studies between 1984 and 2005 (L84-11, L89-12, L92-13, L95-14, and L99-15/L04-1502; Figure S1). The current analysis was primarily based on 2,807 patients who underwent a successful induction phase, achieved CR and survived for at least 2 months or more in the intention-to-treat group, including a total of 621 stem cell transplantations (SCT) had been performed for the primary ALL during the observation period of the study population (Fig 1). Details of the treatment regimens and main therapeutic results have been previously published. (Tsunematsu *et al*, 1974; Toyoda *et al*, 2000; Manabe *et al*, 2001; Igarashi *et al*, 2005; Hasegawa *et al*, 2012) Although the patients in our cohort were treated according to therapeutic protocols, we do not have detailed information regarding actual doses of additional therapeutic exposures given to the relapsed patients, which potentially could have influenced the development of secondary cancers. As a sensitivity analysis, we conducted the same analysis on 1716 patients (referred to as the per protocol group), limited to the patients who had completed all planned treatment leading to first CR (Fig 1).

The cumulative doses of the important treatment contents are listed in Table I. The cumulative anthracycline dose was converted to doxorubicin (DOX)-equivalent doses, which ranged from 0 to 415 mg/m^2. The cumulative cyclophosphamide (CPM) dose ranged from 0 to 6·8 g/m^2 and etoposide (up to 2·4 g/m^2) was administered in only some ALL high-risk regimens. The actual doses of oral drugs given to the patients, such as methotrexate and mercaptopurine (6-MP) were adjusted by white blood count (WBC) counts; therefore we evaluated maintenance duration in our analyses instead of oral antimetabolites doses. A major change over time across the TCCSG treatment protocols included a decrease in the executed proportion and dosage of prophylactic cranial radiation therapy (CRT) and intensified systemic and intrathecal chemotherapy. Prophylactic CRT was part of the treatment protocol for all patients in the L84-11 trial, whereas only 8·6% of the patients in the more recent L99-15/L04-1502 trial received CRT, which was limited to the high-risk group (Table I).

Follow-up and data collection

Follow-up of the patients were performed by the treating institution every 2 years, at which time any late effects including secondary cancer were documented into the TCCSG database. To obtain additional information on characteristics of the secondary cancer diagnosis, we distributed a survey to the treating institution to collect data on the date of diagnosis, cytological or histological characteristics including cytogenetic findings, cancer site, cumulative treatment exposures before secondary cancers, treatment contents given for secondary cancers and its outcomes. The time at risk for secondary cancers was computed from the date of ALL diagnosis to the date of secondary cancer diagnosis, date of death or date of last contact, whichever came first. The end of follow-up for the study was December 2011.

Statistical analysis

Cumulative incidence of secondary cancers over time was calculated using competing risk methods (considering any death as a competing event).(Gooley *et al*, 1999) The incidence rates of cancer in the Japanese general population (obtained from the regional cancer registry of National Cancer Centre Hospital in Japan) (Japanese National Cancer Centre Hospital, 2013) were used to calculate the number of cancers expected to occur in the patient cohort by calculating the total person-years at risk by gender and 5-year age

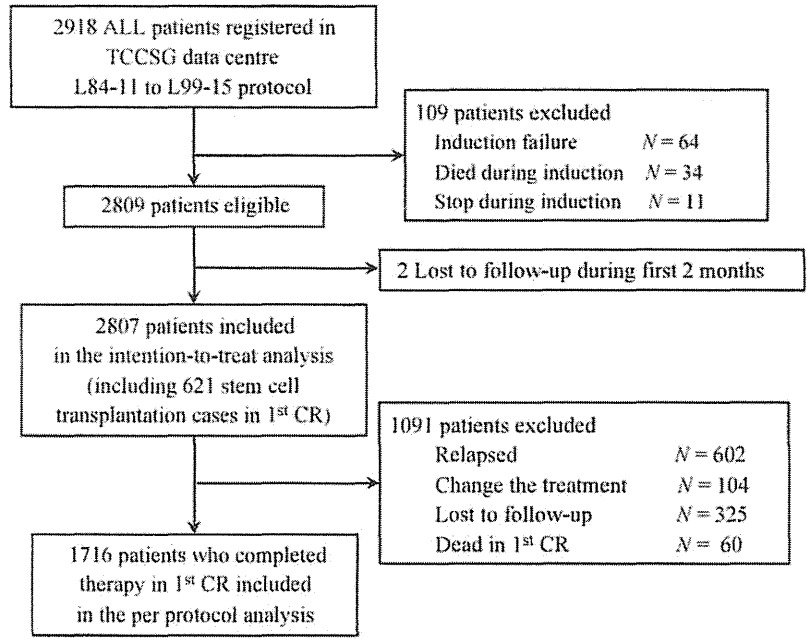

Fig 1. Flow diagram describing the criteria for patient selection. Total of 2918 newly diagnosed children with ALL aged 1–15 years entered into 5 consecutive Tokyo Children's Cancer Study Group (TCCSG) studies (L84-11, L89-12, L92-13, L95-14 and L99-15/L04-1502. The current analysis is primarily based upon 2807 patients who successfully acheived complete remission (CR) and survived at least 2 months or more as the intention-to-treat analysis. 1st CR, first complete remission.

groups and multiplying by the corresponding cancer rates observed in the general population. The standardized incidence rate ratio (SIR), defined as the ratio of the number of observed cancers divided by the number of expected cancers, was used to evaluate the difference in cancer occurrence between the ALL group and the general population. Absolute excess risk (AER) was calculated as the difference between the number of observed events and expected events divided by the number of person-years of follow-up, and was expressed as per 100 000 person-years. Survival analysis was conducted using Kaplan-Meier methods (Log-rank method for comparison) and Cox regression model for hazard ratio (HR) estimates. Variables examined in the regression model included age at ALL diagnosis, risk classification, age at last follow-up, CRT (yes or no), specific anti-cancer agents (yes or no), and duration of maintenance therapy. Treatment protocol and the anticancer agents could not be entered as co-variable factors in the same regression model due to their highly correlated nature. Thus, treatment protocol was included in the main analysis, but the same model replacing protocol with the anticancer agents was also performed to evaluate their effects. Data were analysed using the SPSS statistical software, version 20.0 (IBM Japan Ltd., Tokyo, Japan) and EZR (Saitama Medical Centre, Jichi Medical University), a graphical user interface for R. (Kanda, 2013).

Results

The OS proportions of the TCCSG ALL L84-11 to L04-1502 protocols are shown in Table I. Ninety-seven percent of the whole study population achieved CR and 602 (21·4%) of the 2,807 children among the intention-to-treat group suffered a relapse. Of the total patients, about 70% were followed until after 2008. Even with reduction in CRT use, from 100% to 8·6%, 10-year OS has increased steadily from 74% to more than 85%. The median follow-up duration after diagnosis of ALL was 9·5 years (range 0·2–27 years), with a total of 27 495 person-years of follow-up. At December 2011, a total of 37 secondary cancers had been diagnosed in our cohort, including acute myeloid leukaemia (AML, n = 11), myelodysplastic syndrome (MDS, n = 5), non-Hodgkin lymphoma (NHL, n = 2), brain tumours (n = 13) and other solid carcinomas (n = 6).

Cumulative incidence

The overall cumulative incidence of secondary cancers was 1·0% (95% confidence interval [CI], 0·7–1·4%) at 10 years, 1·4% (95%CI, 0·9–2·0%) at 15 years and 2·4% (95%CI, 1·5–3·7%) at 20 years from the diagnosis of ALL, respectively (Fig 2A). The corresponding cumulative incidence among patients remaining in first CR was 3·9% at 20 years (95% CI: 2·3%–6·1%), which was significantly higher (P < 0·001) than patients not in first CR (Fig 2B). The cumulative incidence in persons who received CRT was 2·9% at 20 years (95% CI, 1·8–4·4%), which appeared higher than the patients without CRT (P = 0·057, Fig 2C). There was no statistically significant difference in cumulative incidence by TCCSG therapeutic protocol (Fig 2D).

Clinical characteristics of secondary cancers

The clinical characteristics of the patients with secondary cancers are summarized in Table II according to type of secondary cancer. Females were predominant (75%) in secondary AML/MDS. Types of secondary cancers differed also according to the age at diagnosis of ALL; brain tumours and

Table I. Cumulative doses of selected chemotherapeutic agents and radiation of ALL trials L84-11 to L99-15 according to risk groups.

Risk Group by protocol	Patients (n)	Anthracycline (mg/m^2)						CPM (mg/m^2)	VP-16 (mg/m^2)	IV MTX (g/m^2)	Maintenance (weeks)	MTXIT	CRT (Gy)	CRT rate (%)	10-year OS (%)
		DNR	DOX	THP	ACR	MIT	Total								
L84-11	484													100	74·3 ± 2·0
SR (A/B arm)†	194	0	0	0	0	0	0	0	0	2/3·5	172	9/15	18	100	
HR (A/B arm)†	244	180	0	0	150	0	224	6800/6000	0	1/2·5	172	5/11	24	100	
HEX	48	75	100	0	0	0	162	4000	0	0	96	11	24	100	
L89-12	418													80	73·5 ± 2·2
SR (A/B arm)†	142	0	100/0	100/150	0	0	160/90	0	900	9	91	9/9	0 vs 18	44	
IR	100	0	0	210	60	0	135	3100	2400	6	91	7	18	100	
HR	146	0	0	240	60	20	210	3600	2400	6	87	6	18	100	
L92-13	347													44	77·9 ± 2·2
SR	124	0	0	150	0	20	170	0	0	6	24	8	0	0	
HR (A/B arm)†	122	0	0	100	0	20	140	1000	1200	6/0	22	10	0 vs 12/18	47	
HEX	101	0	0	100	0	40	220	1000	1200	0	16	9 (6)	18	100	
L95-14	597													44	82·0 ± 1·6
SR	231	0	0	100	0	0	60	2000	0	10·6	54	11	0	0	
HR (A/B arm)†	129	0	0	220	0	0	132	4000	0	10/1	54	8	0 vs 12/18	18	
HEX	237	100	200	220	0	0	415	4000	0	1	54	8	18	100	
L99-15/L04-1502	1007													8·6	87·6 ± 1·2‡
SR	381	100	0	0	0	0	83	2000	0	13·15	104	11	0	0	
HR (A/B arm)†	404	100	100	120	0	0	245	4000/5000	0	10	52	10/11	0	0	
HEX	242	100	0	0	0	20	163	5600	1000	6	54	17	12/18	27·4	

SR, Standard risk; IR, Intermediate risk; HR, High risk; HEX: extremely high risk; DNR, daunorubicin; DOX, doxorubicin; THP, pirarubicin; ACR, acracinomycin; MIT, mitoxantrone; Total, DOX-equivalent dose; CPM, cyclophosphamide; VP-16, etoposide; MTX, methotrexate; CRT, cranial irradiation; IT, intrathecal; OS, overall survival.

†(A/B arm): cumulative doses of A arm/B arm; Additional details of treatment regimen are provided as supplemental information.

‡4-year overall survival rate.

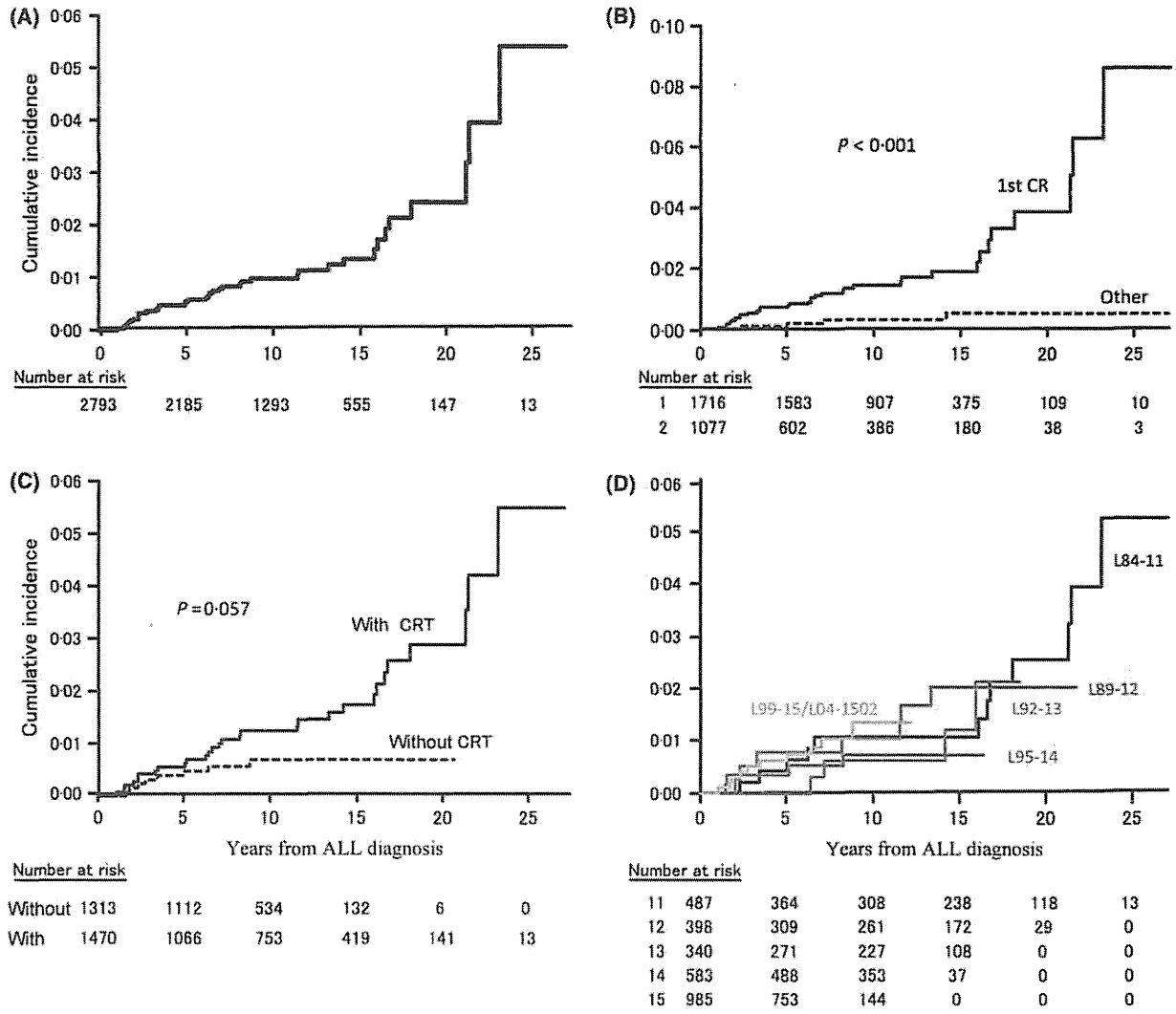

Fig 2. Cumulative incidence of secondary cancers. Shown are the cumulative incidences of secondary cancers as a function of time since primary ALL diagnosis over a maximum follow-up of 27 years. (A) Overall cumulative incidence of secondary cancer among the total patient cohort. (B) Overall cumulative incidence of patients remaining in first complete remission (1st CR) compared to others. (C) Overall cumulative incidence according to treatment with or without cranial radiation therapy (CRT). (D) Overall cumulative incidence according to treatment protocols: L84-11 (black line), L89-12 (red line), L92-13 (green line), L95-14 (purple line), and L99-15/L04-1502 (blue line). The numbers of patients at risk at a specific time point are indicated below each of the four plots.

other carcinoma tended to develop more commonly in children that were older at ALL diagnosis. There was no difference between types of secondary cancers with regard to initial WBC, immunophenotype and risk classification of the primary ALL. The median latency period from ALL diagnosis to secondary cancers was 6 years (range 1–23 years) and varied by type of secondary cancer (Fig 3). The median time to diagnosis for haematological cancers (AML, MDS and NHL) was shortest (median 3·0 years), followed by brain tumours (median 11·5 years) and other solid carcinoma (median 16·3 years). Haematological cancers developed most commonly during the first 10 years followed by brain tumours from 15 to 20 years (Fig 3A, B). The age distributions at diagnosis of secondary cancers are shown in (Fig 3C). Median age at diagnosis of secondary was earlier for haematological cancers than brain tumour (median 14 years) and other carcinomas (median 19 years). Among AML, the most common morphological type was M5 (3 had t (9;11) (p22;q23) with *MLL-MLLT3* translocation). Four MDS cases showed chromosomal abnormality. Lymphoma and solid tumours did not show any chromosomal abnormalities.

As for the characteristics related to the treatment of primary ALL, the secondary cancers with the highest proportions of patients who underwent CRT were MDS, brain tumour and other carcinoma, while the haematological cancers showed elevated cumulative anticancer drug doses. Among a total of 621 SCT that had been performed for the primary ALL during the observation period of the study population, only 3 patients

Table II. Clinical characteristics of patients with secondary cancers.

	AML	MDS	NHL	Brain tumour	Other carcinoma
Total number of secondary cancers	11	5	2	13	6
Gender (Male:Female)	3:8	1:4	2:0	8:5	3:3
Primary ALL					
Age at diagnosis of ALL (years)	5 (1–14)	5 (2–13)	4 (2–6)	8 (2–12)	11 (3–14)
Initial WBC count ($\times 10^9$/l)	20·5 (1·9–168)	11·2 (2·9–70)	8·7 (3·4–14)	12·6 (1·9–112)	4·9 (2·1–163)
Immunophenotype (B:T:Other)	7:0:4	3:0:2	2:0:0	7:1:5	6:0:0
Risk group (SR:IR:HR)	1:8:2	1:2:2	2:0:0	1:10:2	2:4:0
Secondary cancer (SC)					
Incubation time to SC (years)	3·3 (1·6–11·6)	2·3 (1·0–6·3)	3·1 (2·8–3·4)	11·5 (2·3–23·2)	16·3 (7·2–21·4)
Diagnosis on therapy	4/11 (36%)	2/5 (40%)	1/2 (50%)	0/13 (0%)	0/6 (0%)
Age at diagnosis of SC (years)	9·0 (6·4–21·3)	11·1 (4·0–14·5)	7·5 (5·3–9·7)	18·5 (10·3–27·7)	23·9 (18·8–32·6)
Sub-classification	M4: 2, M5: 7, M7: 1, Unknown: 1	RAEB: 1, CMML: 2, Unknown: 2	Diffuse large B-cell lymphoma: 1, Burkitt lymphoma: 1	Glioma: 8, Meningioma: 3, Other: 2	Oral cancer: 2, parotid cancer: 2, breast cancer: 1, thyroid cancer: 1
Treatment for primary ALL					
Protocol (11:12:13:14:15)	1:3:0:2:5	2:1:0:1:1	0:0:0:0:2	6:3:1:1:1	3:0:2:0:1
Cranial irradiation	6/11 (55%)	5/5 (100%)	0/2 (0%)	13/13 (100%)	5/6 (83%)
Dose of cranial irradiation (Gy)	18 (0–28)	18 (18–24)	24 (18–36)	0	18 (0–24)
Anthracyclines (DOX equivalent)	230 (50–330)	72 (0–190)	112 (82–142)	120 (0–190)	47 (0–230)
Cyclophosphamide ($\times 10^3$ g)	4·0 (3·1–6·0)	4·0 (0–5·6)	1·0 (0–2·0)	4·0 (0–6·8)	1·1 (0–6·0)
Etoposide ($\times 10^3$ g)	0 (0–2·4)	0 (0–2·4)	0 (0–2·4)	0	0 (0–1·2)
Duration of maintenance (weeks)	52 (28–172)	96 (62–172)	96 (22–175)	78 (52–104)	112 (0–172)
Stem cell transplantation	0	0	0	1/13 (8%)	2/6 (33%)
Treatment for secondary cancer (SC)					
Surgery	0	0	0	9	6
Radiation	0	0	0	7	3
Chemotherapy	11	4	2	6	3
Stem cell transplantation	8	1	0	0	0
Median survival duration (years)	1·7 (0·2–4·3)	4·6 (0·9–11·1)	3·6 (0·5–6·7)	2·0 (0·1–11·3)	3·0 (0·8–10·4)
4 year survival rate (%)	24%	60%	50%	50%	83%
Standardized incidence ratio (SIR) and absolute excess risk (AER)					
No. observed/expected	16/0·64	2/0·52	13/0·36	6/2·45	
SIR (95%CI)	25 (14–41)	3·8 (0·5–14)	36 (19–62)	2·5 (0·9–5·3)	
AER/100 000 person-years	118	9·4	90	26	

ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; MDS, myelodysplastic syndrome; RAEB, refractory anaemia with excess blasts; CMML, chronic myelomonocytic leukaemia NHL, Non-Hodgkin lymphoma; WBC, white blood cell; SR/IR/HR, standard/intermediate/high risk; DOX, doxorubicin; 95% CI, 95% confidence interval.
Numbers shown as median (range; minimum-maximum).

developed a secondary cancer (1 brain tumour and 2 other cancers). All 3 cases received total body irradiation-containing conditioning regimens, two of 3 developed tongue carcinoma whilst suffering from chronic graft-versus-host disease after allogeneic SCT. SCTs were common among secondary AML patients as treatment. Kaplan–Meier OS curves for the patients with secondary cancers are shown in (Fig 3D). The lowest survival probabilities were observed for patients with AML/MDS/NHL compared to patients with brain tumours and other carcinoma ($P = 0·045$ by log-rank test).

SIR and AER

We compared the incidence of secondary cancers in our cohort with that of the general population using the regional cancer registration database of the National Cancer Centre Hospital in Japan. As shown in Table II, the SIR was 25 (95% CI, 14–41) for AML/MDS, 3·8 (95% CI, 0·5–14) for lymphoma, 36 (95% CI, 19–62) for brain tumours and 2·5 (95% CI, 0·9–5·3) for other solid carcinoma. This represents a 9·3-fold (95% CI, 6·5–12·8) increase risk of all secondary cancers during a total of 27 658 person-years of observation. The total AER for secondary cancers was 256 per 100 000 person-years.

Risk factors for secondary cancers

The unadjusted analyses comparing patients with and without secondary cancers showed differences in age at ALL diagnosis, risk classification, CPM and CRT, while there were no statistically significant differences with respect to gender,