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Original Article

Physician Preferences and Knowledge Regarding the Care of Childhood Cancer Survivors in Japan: A Mailed Survey of the Japanese Society of Pediatric Oncology

Yasushi Ishida[1,*], Miyako Takahashi[2], Mitsue Maru[3], Michiko Mori[4], Tara O. Henderson[5], Christopher K. Daugherty[6] and Atsushi Manabe[1]

[1]Department of Pediatrics, St Luke's International Hospital, Tokyo, [2]Department of Public Health, Dokkyo Medical University, Tochigi, [3]Department of International Nursing Development, Tokyo Medical and Dental University, Tokyo, [4]The Japanese Red Cross Akita College of Nursing, Akita, Japan, [5]Department of Pediatrics, University of Chicago Pritzker School of Medicine, Chicago, IL and [6]Department of Medicine, University of Chicago Pritzker School of Medicine, Chicago, IL, USA

*For reprints and all correspondence: Yasushi Ishida, Department of Pediatrics, St Luke's International Hospital, 9-1 Akashi-cho, Chuo-ku, Tokyo 104-8560, Japan. E-mail: yaishida@luke.or.jp

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Objective: Japanese physicians' attitudes regarding the health-care needs of young adult childhood cancer survivors (CCSs) are not well described. Thus, we examined the self-reported preferences and knowledge of pediatric oncologists and surgeons.
Methods: A mailed survey was sent to 858 physician members of the Japanese Society of Pediatric Oncology. We compared the responses of pediatric oncologists and pediatric surgeons.
Results: The pediatric oncologists' response rate was 56% (300 out of 533) and that of pediatric surgeons 32% (105 out of 325). The median age of respondents was 46 and 48 years, respectively; 79 and 84% were men. When comfort levels in caring for CCSs were described (i.e. 1 = very uncomfortable; 7 = very comfortable), the mean levels were 4.4 and 3.8 with CCSs $\leq$ 21 years, 3.6 and 3.6 with 21 years $<$ CCSs $\leq$ 30 years, and 2.8 and 3.3 with CCSs $>$ 30 years, respectively. In clinical vignette questions, 62% of the pediatric oncologists and 43% of the surgeons answered three or more questions appropriately. Pediatric surgeons reported significantly lower familiarity with long-term follow-up guidelines than pediatric oncologists. Most pediatric oncologists and many surgeons conducted truth-telling of cancer diagnosis to adult CCSs now. They thought that the most important issues are an original long-term follow-up guideline suitable for the Japanese situation and collaborations with adult-based general physicians.
Conclusions: Many Japanese pediatric oncologists are uncomfortable with caring for survivors as they age and have suboptimal knowledge regarding late effects. The change in truth-telling situation and preference for collaboration with adult-based physicians was demonstrated also in Japan.

Key words: pediatric cancer – long-term survivors – transition to adult care – pediatric oncologist – pediatric surgeon

INTRODUCTION

As a result of treatment advances, almost 80% of children diagnosed with cancer become long-term survivors (1). In Japan, there are over 50 000 childhood cancer survivors (CCSs), or approximately 1 in 700 adults between the ages of 20 and 39 years has cancer experience (2). Many of these survivors face significant life-long health risks (3) and early mortality (4). Treatment-related late effects are often clinically insidious for years or decades after the completion of cancer treatment (5,6). Promotion of healthy lifestyle behaviors and provision of regular risk-based medical care and surveillance may modify the evolution of these late effects. However, many CCSs engage in risky health behaviors and do not receive adequate risk-based medical care (7).

In 2007, the members of the International Berlin-Frankfurt-Munster (I-BFM) Early and Late Toxicity Educational Committee (ELTEC) published the Erice statement to summarize what the group considers essential for the care of survivors (8). Included in the Erice statement was the following point: 'when the survivor enters adulthood, he/she should be referred to an appropriate health care provider who coordinates long-term care' (8). Despite these recommendations, many reports suggest that effective transitions from the pediatric to the adult-focused health-care system are difficult (9–11).

One well-described barrier to risk-based long-term health-care is that CCSs themselves are not well informed regarding their previous therapies or their potential risks for late effects (12,13). In the past study, CCSs in Japan did not always know the precise diagnosis of cancer itself (14). We recently reported that the previous treatment hospitals (where CCSs were treated for their cancer) were the most commonly visited medical facilities for the CCS group (74% for females and 64% for males) and more than half of CCSs preferred to continue visiting the previous treatment hospitals with full satisfaction in Japan (15). Recently, Henderson et al. (16) published a comprehensive report on physicians' attitudes and knowledge regarding the health-care needs of CCSs in the USA. On the other hand, there is no information in Japan regarding whether the pediatric oncologists in the previous treatment hospitals are comfortable with these adult-aged CCSs and have knowledge of the published guidelines or recommendations for late-effect surveillance (17,18). In addition, many CCSs have received long-term follow-up not only with pediatric oncologists but also with pediatric surgeons in Japan. To further understand physician attitudes and knowledge regarding the care of CCSs as they transition into adulthood in Japan, we conducted a comparative survey of pediatric oncologists and pediatric surgeons who belonged to the Japanese Society of Pediatric Oncology (JSPO).

PATIENTS AND METHODS

Participants

The approval of both St Luke's International Hospital review board and the director board in JSPO was obtained before initiation of this study. Candidate participants were selected from the 2010 JSPO Membership Directory. From the available directory, 1381 potential survey members with sufficient addresses for survey mailings were identified. Of those, we identified 1022 members specialized in pediatric hematology/oncology or pediatric surgical oncology.

Survey Mailings

A self-addressed survey was mailed to the 1022 eligible members. Through the initial mailing, 16 physicians were eliminated because of incorrect mailing addresses or because physicians were no longer clinically active, yielding a final sample of 1006 survey members. A second mailing was sent to all potential participants 4 weeks after the initial mailing.

Survey Method

The survey instrument was developed originally. Survey content and format was based on a previous study (16) regarding physician preferences and knowledge. The survey included 14 questions and used both quantitative (i.e. closed-ended questions) and qualitative (i.e. open-ended questions that asked for short responses) items (Supplementary data 1). The survey sought demographic information about participant's age, sex, practice environment, years since completion of formal training, estimated number of patients with cancer and cancer survivors seen per week in clinical practice, and information regarding prior learning with regard to childhood cancer survivorship. The definition of CCS was a patient who was at least 5 years from the completion of cancer therapy and was malignancy free.

Quantitative survey items queried participants regarding whether their practices were affiliated with a long-term follow-up program for cancer survivors and if it was routine practice to eventually refer their long-term survivors to other physicians. By using a seven-point Likert scale, physicians were asked about their comfort with caring for survivors at varying ages and were asked about their familiarity with the available monitoring guidelines for adolescent and young adult cancer survivors. Quantitative questions queried self-reported attitudes toward caring for long-term CCSs, referral pattern practices for their CCSs and their opinion of the best trajectory of care for CCSs.

The survey included a vignette of a 25-year-old woman treated at age 1 year for acute lymphoblastic leukemia whose treatment included prophylactic cranial radiation (24 Gy) and anthracycline and cyclophosphamide chemotherapy in Supplementary data 2. Three follow-up questions sought physicians' self-reports of the knowledge of health risks caused by pediatric cancers and the physicians' understanding of appropriate surveillance for these health risks on the basis of Japanese leukemia/lymphoma study group (JPLSG)'s recommendation (19).

Finally, participants were asked to give a free description whether they had anything else to add about their

Table 1. Demographic and practice characteristics of eligible study respondents

Characteristic	Pediatric oncologists ($n = 300$)		Pediatric surgeons ($n = 105$)		χ^2 (P value)
	No.	Per cent	No.	Per cent	
Age, years					
39 years of age or younger	87	30	22	21	0.180
40–47 years of age	79	27	24	23	
48–53 years of age	69	24	29	28	
54 years of age or older	58	20	28	27	
Gender					
Male	233	79	87	84	0.279
Female	63	21	17	16	
Years in practice					
14 years or shorter	82	28	26	26	0.316
15–21 years	74	25	22	22	
21–27 years	80	28	25	25	
28 years or longer	55	19	28	28	
Childhood cancer patients in outpatient clinic per week					*t*-test
Mean ± SD (median, range)	8.3 ± 11.8 (5.0, 0–100)		1.5 ± 2.4 (0.5, 0–10)		<0.001
Position					
Professor/Head	76	26	27	26	0.441
Associate Prof./Lecturer/Chief	103	35	42	41	
Assistant Prof./Fellow	87	30	25	24	
Resident/Doctor course	10	3	1	1	
Other (Clinics etc.)	16	6	8	8	
Living place (Post stamp)					
Hokkaido	15	5	4	4	0.001
Touhoku	21	7	4	4	
Kantou-Koushinetsu	78	26	34	32	
Toukai-Hokuriku	31[a]	10	3	3	
Kinki	51[a]	17	8	8	
Chu-Shikoku	20	7	11	10	
Kyusu-Okinawa	16	5	17[a]	16	
Unknown	68	23	24	23	
Practice environment					
Children's Hospital	24	8	12	11	0.152
University Hospital	154	52	52	50	
General Hospital	93	31	38	36	
Cancer Center	12[a]	4	0	0	
Private practice/others	15	5	3	3	
LT-FU Clinic at Hospital					
Yes	63	21	14	13	0.008
No	230	77	83	79	
Not sure	7	2	8[a]	8	

Continued

Table 1. *Continued*

Characteristic	Pediatric oncologists ($n = 300$)		Pediatric surgeons ($n = 105$)		χ^2 (P value)
	No.	Per cent	No.	Per cent	
Received Education or Learned about Late effects					
Yes	168[a]	56	21	20	<0.001
No	106	36	80[a]	77	
Not sure	24	8	3	3	
Educational experiences in the evaluation and management of childhood cancer survivors					
Government-sponsored meeting	70	23	1	1	<0.001
Symposium/Workshop	113	38	15	14	<0.001
Special Lecture	64	21	3	3	<0.001
Journal article(s)	104	35	12	11	<0.001
Book(s)	82	27	6	6	<0.001
Other	3	1	0	0	0.571

[a]Adjusted standardized residual $> +1.96$.

experiences with CCSs or the survey itself. After conducting a pilot testing with five pediatric oncologists, revisions were made. The survey questions were mailed with a cover letter to explain the purpose of the study and how to return the survey and introduce the original article (16). The survey was designed to be sealed within an envelope and mailed back to the study investigator (Y.I.) anonymously.

Statistical Analyses

All survey data were coded and entered into a database by using standard SPSS statistical software, ver. 19.0 (IBM Japan Co. Ltd, Tokyo, Japan). Descriptive statistics reported included the following: proportions, means and standard deviations, or medians and ranges. For between-group comparisons of continuous or ordinal variables, t-tests or non-parametric Wilcoxon's rank-sum tests were used as appropriate. For comparisons of categorical variables, χ^2 tests were used. As for cross-table comparisons, we used adjusted standardized residuals to evaluate the difference between the observed and expected values; the columns which give more than 1.96 of the adjusted standardized residual were considered as significant.

RESULTS

The two survey mailings were completed between October 2010 and January 2011. Four hundred fifty surveys returned; we excluded 45 sheets from non-pediatricians or non-pediatric surgeons. The total final survey response rate was 47% (405 out of 858): pediatric oncologists 56% (300 out of 533) and pediatric surgeons 32% (105 out of 325).

Demographic Data

Respondent demographic characteristics are listed in Table 1. The median age of respondents was 46 years (range: 29–78) for pediatric oncologists and 48.5 years of age (range: 29–71) for pediatric surgeons. Respondents had been in clinical practice a median of 20 years for pediatric oncologists and 22.5 years for pediatric surgeons. They saw a median of 5.0 and 0.5 CCS patients per week, respectively. A total of 19% of respondents reported that their hospital had a long-term follow-up clinic for CCSs. Pediatric surgeons had significant fewer learning experiences for care about CCSs in any type than pediatric oncologists did. The most popular educational or learning experience consisted of symposiums or workshops at the annual meeting and journal article for pediatric oncologists.

Physician Preferences in Care of CCSs and Optimal (Ideal) Care of Long-term CCSs

Physicians were asked to choose one of four responses that best summarized their current attitudes toward caring for long-term CCSs. As depicted in Table 2, 38% of the pediatric oncologists and 32% of the pediatric surgeons preferred following long-term CCSs as long as possible. There was no statistically significant difference between pediatric oncologists and pediatric surgeons.

As the optimal care of long-term CCSs, 51% of the pediatric oncologists and 42% of the pediatric surgeons answered that a CCS stays in their care until age 21 and then is referred. More pediatric surgeons answered that a CCS stays in their care anywhere between 2 and 5 years after the completion of therapy and then is referred regardless of his/her age.

Table 2. Responses to survey question

Response (select only one)	Pediatric oncologists (%)	Pediatric surgeons (%)	χ^2 (*P* value)
About current attitude toward care for long-term survivors of childhood cancer			
(a) I prefer to be their doctor as long as possible	115 (38)	34 (32)	0.211
(b) Although I enjoy some of the social aspects of their clinic visits, I prefer these patients be seen by a physician other than myself	23 (8)	14 (13)	
(c) I prefer to refer them and/or discharge them from my clinic at the first opportunity	19 (6)	7 (7)	
(d) I am willing to see them and continue to care for them in the absence of a more suitable clinician	129 (43)	50 (48)	
(e) Other	14[a] (5)	0	
About the trajectory which best summarizes your opinion of the OPTIMAL care of long-term cancer survivors			
(a) The patient stays in my care forever (throughout childhood and adulthood)	60 (21)	23 (23)	0.089
(b) The patient stays in my care anywhere between 2 and 5 years after the completion of therapy and then is referred regardless of his/her age	67 (23)	34[a] (34)	
(c) The patient stays in my care until age 21 and then is referred	148 (51)	42 (42)	
(d) Other	15 (5)	2 (2)	

[a]Adjusted standardized residual $> +1.96$.

Referral Preferences

Respondents were asked to report if it was their practice to eventually refer their long-term cancer survivors to other physicians and 31% of respondents answered yes. One-third (34%) of these respondents reported referring long-term survivors to a long-term follow-up program, 23% reported referring them to a primary care physician, 29% responded that they referred them to adult oncologists and 13% reported referring them to some other physician or health-care provider.

Comfort Levels of Caring for CCSs

Three survey items queried participants' comfort levels with caring for pediatric cancer survivors within three different age groups (Fig. 1). Respondents were asked to report their comfort levels on a seven-point Likert scale. A score of 1 was associated with very uncomfortable; a score of 7 was associated with being very comfortable. Both pediatric oncologists and pediatric surgeons reported being most comfortable with caring for survivors who were 21 years of age or younger (mean $\pm$ SD, 4.4 ± 1.3 and 3.8 ± 1.4 level, respectively), being less comfortable with survivors older than 21 years and <30 years (3.6 ± 1.4 and 3.6 ± 1.4 level, respectively) and being most uncomfortable caring for survivors 30 years or older (2.8 ± 1.5 and 3.3 ± 1.6 level, respectively). While pediatric oncologists became less comfortable with survivors as they aged out of the pediatric age range, pediatric surgeons' comfort levels remained relatively consistent throughout all age groups.

Knowledge of Recommendations for Late Effects

Participants' knowledge of the current JPLSG recommendations for surveillance of late effects was examined through a vignette that described a 25-year-old woman treated at age 1 year for ALL with 24 Gy cranial radiation and anthracyclines (cumulative dose: 180 mg/m^2). Respondents were asked about the follow-up frequency and method, hepatitis C infection and late effects of cranial radiation (Supplementary data 2). On the basis of the JPLSG recommendations, 78% of the pediatric oncologists and 70% of the pediatric surgeons appropriately recommended the follow-up frequency and method (not significant); however, 53% of the pediatric oncologists and 38% of the pediatric surgeons appropriately recommended hepatitis C infection treatment; this difference was significant. Lastly, 92/49% of the pediatric oncologists and 77/36% of the pediatric surgeons appropriately answered the questions related with the late effects of cranial radiation (statistically significant, respectively). Overall, only 47% of the respondents (62% of the pediatric oncologists and 43% of the pediatric surgeons) answered three or more questions appropriately.

Familiarity with Long-term Follow-up Guidelines

Participants were queried about their familiarity with the available monitoring guidelines for adolescent and young adult cancer survivors by using a seven-point Likert scale. The definition of familiarity was left to the discretion of the individual respondent. A score of 1 meant a respondent was very unfamiliar, a score of 4 meant they were somewhat familiar and a score of 7 reflected that a respondent was very

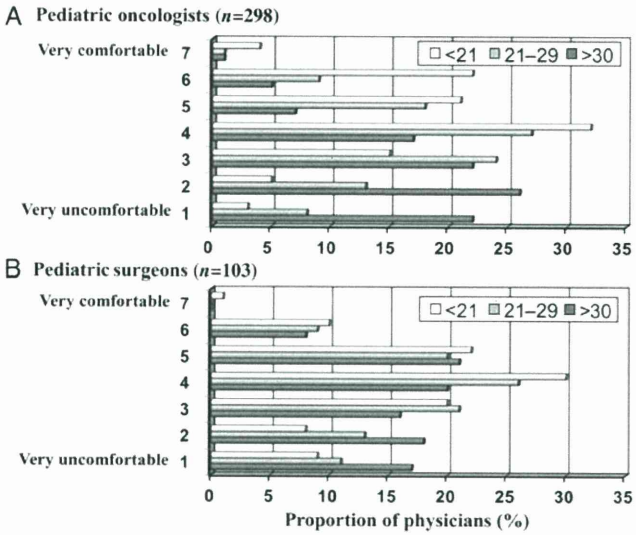

Figure 1. How comfortable are you in managing and caring for adolescent and young adult survivors of childhood cancer depending age? Respondents were asked to report their comfort levels on a seven-point Likert scale. A score of 1 was associated with very uncomfortable; a score of 7 was associated with being very comfortable. (A) Pediatric oncologists and (B) pediatric surgeons.

familiar. Overall, surveyed pediatric oncologists were significantly more familiar with the available guidelines than pediatric surgeons; the mean score ($\pm$SD) was 2.8 ($\pm$1.4) for pediatric oncologists and 1.5 ($\pm$1.4) for pediatric surgeons ($P < 0.001$).

The Proportion of Truth-telling of Cancer Diagnosis in Adult CCSs

Seventy percent of the pediatric oncologists and 62% of the pediatric surgeons in this study reported that the proportion of truth-telling of cancer was 80–100% (Fig. 2). There was a statistical significant difference in distribution between pediatric oncologists and pediatric surgeons ($P < 0.001$).

Level of Interest in Collaborations with Adult-based Clinicians to Care for CCS

Participants were queried about their interest in collaborations with adult-based clinicians to care for CCSs by using a seven-point Likert scale. Overall, both pediatric oncologists and pediatric surgeons were much interested in collaborations with adult physicians, as the mean score ($\pm$SD) was 3.1 ($\pm$1.6) for pediatric oncologists and 3.0 ($\pm$1.5) for pediatric surgeons.

Important Issues for a Long-term Follow-up of Adult CCSs

The most important issues for long-term follow-up for adult CCSs cited by both pediatric oncologists and pediatric surgeons were an original long-term follow-up guideline

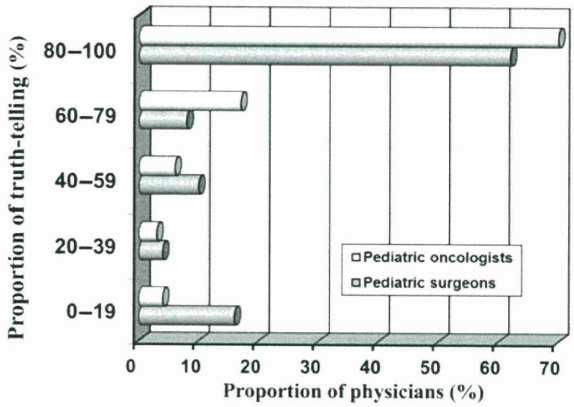

Figure 2. The proportion of truth-telling of cancer diagnosis in adult survivors with childhood cancer. The percentage of adult survivors with childhood cancer giving truth-telling of cancer diagnosis was categorized into five groups: 0–19, 20–39, 40–59, 60–79 or 80–100%.

suitable for the Japanese situation and a passport (individualized clinical records) to share information (Table 3). There was no significant difference in distribution between pediatric oncologists and pediatric surgeons with regard to the most important issues. However, as for important issues for collaboration with adult-based general physicians, both pediatric oncologists and surgeons think that it is of prime importance to have enough knowledge about late effects. More pediatric oncologists than pediatric surgeons demanded sympathy with CCSs and/or their parents, and the ability to introduce organ-specific specialists.

DISCUSSION

We found that pediatric oncologists in Japan were increasingly uncomfortable with caring for adult survivors as they age, and the preference and knowledge with regard to long-term follow-up care of young-adult CCSs were different between pediatric oncologists and surgeons in Japan. To our knowledge, our survey is the first large study in Japan that examines physician attitudes toward and knowledge of risk-based healthcare, including surveillance of late effects of CCSs.

The results of our study are consistent with Henderson et al.'s study of US pediatric oncologists (16). First, as the age of CCSs increases, pediatric oncologist-reported comfort levels in caring for them decrease. However, in contrast to the Henderson study, more physicians report that they prefer to observe their CCSs for as long as possible when compared with US physicians (16). Japanese physicians have had profound attachment with their patients, which is observed in doctor–patient relationships in chronically or severely ill children as reported also in western countries (20–22). In this study, many Japanese physicians had felt uncomfortable to follow adult CCSs by themselves. Systematic efforts should be made after cancer treatment not only to empower the CCSs/families by making available age-appropriate

Table 3. Important issue when you conduct a long-term follow-up for adult childhood cancer survivors and collaboration with adult-based general physicians

Issues	Pediatric oncologists (%)	Pediatric surgeons (%)	*P* value
Long-term follow-up of adult CCSs (select only one)			
(a) An original long-term follow-up guideline suitable to Japan situation	110 (39)	50 (50)	0.494
(b) A passport (individualized clinical records) to share with information	100 (38)	30 (30)	
(c) Provide information to adult-based physician	24 (9)	7 (7)	
(d) Education and empowerment for CCSs	41 (15)	13 (13)	
(e) Other	1 (0.4)	0	
Collaboration with adult-based general physicians (select all that apply)?			
(a) Enough knowledge about late effects of CCSs	270 (90)	82 (98)	0.495
(b) Sympathy with CCSs and/or their parents	238 (79)	73 (70)	0.040
(c) Ability to introduce organ-specific specialists if needed	184 (61)	46 (44)	0.002
(d) Equipment of enough machines for further examination	35 (12)	15 (14)	0.483
(e) Experience as a pediatrician	18 (6)	12 (11)	0.068
(f) Other	3 (0.1)	0	—

information but also to provide adult-based physicians the necessary information (8). These efforts will be especially important in dealing with the sustainable transition from the pediatric to the adult-focused health-care system. A specific program will be needed to facilitate these transitions (10,23,24).

Secondly, the survey results suggest that many pediatric oncologists in Japan are not familiar with available long-term follow-up guidelines compared with US pediatric oncologists (16), mainly because there is no available long-term follow-up guideline for CCSs in Japanese today. Recently, we formulated the Japanese translated version of COG long-term follow-up guidelines in JPLSG homepage (http://www.jplsg.jp/) (19). Only 62% of the pediatric oncologists and 43% of the pediatric surgeons answered three or more of our four vignette-based questions regarding late effects on the basis of available JPLSG recommendations (19).

To achieve effective follow-up for CCSs, truth-telling is an indispensable process for CCSs (12,13). In 2007, Parsons et al. (14) reported that US physicians had a consistent pattern of telling children (65% always told the child; $<1\%$ rarely or never told), while Japanese physicians had greater variability in their patterns of telling (with only 9.5% always telling and 34.5% rarely or never telling). During these 10 years, the situation around truth-telling to children with cancer has been dramatically changed in Japan. Our study demonstrated that most pediatric oncologists conduct truth-telling of cancer diagnosis at least to adult CCSs now, and there are no barriers to facilitating effective follow-up.

The most important issues for long-term follow-up for adult CCSs cited by both pediatric oncologists and pediatric surgeons in this survey were an original long-term follow-up guideline suitable for the Japanese situation and a follow-up passport to share information. The long-term follow-up committee of JPLSG has been developing new original guidelines and a long-term follow-up diary now.

It is very interesting that most pediatric oncologists and pediatric surgeons demand not only enough knowledge about late effects of CCSs but also 'sympathy' with CCSs and/or their parents from adult-based general physicians for the purpose of collaboration. There were a lot of opinions to list 'sympathetic ability' as an indispensable nature to succeed transition though semi-structured interviews of the pediatricians in long-term follow-up (25). To our knowledge, many CCSs who were once introduced to an adult department returned to the pediatric department again because of the reasons: 'an adult-based physician is cold' or 'he/she doesn't listen to my story enough', and many CCSs had a sense of hesitation in consulting the adult-based physician.

This study has important strengths. First, this study is based on a national study including not only pediatric oncologists but also pediatric surgeons involved in pediatric oncology practice in JSPO. We can compare between pediatric oncologists and pediatric surgeons with regard to their preference and knowledge about adult CCSs. Secondly, this study revealed for the first time the change in the truth-telling situation in Japan and the preference for collaboration with adult-based physicians to care for adult CCSs.

There are, however, some limitations to our study. First, the response rates were not satisfactory especially for pediatric surgeons. These results may be subject to a response bias (i.e. those with a stronger interest in the topic may have been more likely to have responded to our survey). Conversely, there was no statistically significant difference in the gender or geographic location of responders compared with non-responders, age and time in practice of non-responders by the available JSPO member's information. Secondly, the

results were entirely based on pediatric oncologists' self-report of comfort levels with caring for and transitioning care for CCSs. Thus, these results cannot necessarily be relied on to represent what occurs in actual pediatric oncologist clinical practice. In addition, these results cannot be relied on to represent the experiences of other physicians who may be involved in caring for long-term CCSs (e.g. primary care physicians). Given the limitations, it is important that additional studies be undertaken to explore physician attitudes and knowledge outside the cancer center-based pediatric oncology specialty to include physicians in adult oncology as well as in primary care, including pediatrics, internal medicine and family medicine. Lastly, it must be highlighted that the current JPLSG recommendations, on which our clinical vignette questions were created, are based on limited data and, in many cases, expert opinion.

In conclusion, our study suggests that pediatric oncologists are increasingly uncomfortable with caring for survivors as they age and have suboptimal knowledge regarding the current recommendations for late effects. Preference and knowledge with regard to long-term follow-up care of young-adult CCSs are different between pediatric oncologists and pediatric surgeons in Japan. Findings from this study should provide a foundation for additional research and possible targeted interventions that hope to improve physician knowledge.

Authors' contributions

Conception and design: Y.I., M.T. and M.Ma.; financial support: Y.I., M.Mo. and A.M.; administrative support: Y.I.; provision of study materials or patients: Y.I. and A.M.; collection and assembly of data: Y.I.; data analysis and interpretation: Y.I., M.T., M.Ma., T.O.H. and C.K.D.; manuscript writing: Y.I., M.T., T.O.H. and A.M.; final approval of manuscript: Y.I., M.T., M.Ma., M.Mo., T.O.H., C.K.D. and A.M.

Supplementary data

Supplementary data are available at http://www.jjco.oxfordjournals.org.

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Conflict of interest statement

None declared.

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ORIGINAL ARTICLE

Social outcomes and quality of life of childhood cancer survivors in Japan: a cross-sectional study on marriage, education, employment and health-related QOL (SF-36)

Yasushi Ishida · Misato Honda · Kiyoko Kamibeppu · Shuichi Ozono · Jun Okamura · Keiko Asami · Naoko Maeda · Naoko Sakamoto · Hiroko Inada · Tsuyako Iwai · Naoko Kakee · Keizo Horibe

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Abstract Social outcomes and quality of life (QOL) of childhood cancer survivors (CCSs) remain unknown in Japan. We investigated these outcomes in young adult CCSs compared to those of their siblings in Japan, and analyzed the association between social outcome and SF-36 health survey subscale scores. Between 2007 and 2009, we performed a cross-sectional survey using self-rating questionnaires. We estimated social outcomes and health-related QOL by performing the SF-36 in each group: CCSs with or without stem cell transplantation (SCT)/radiotherapy (RT) and their siblings. Adjusted odds ratios for outcomes of interest were estimated using logistic regression analysis. Questionnaires from 185 CCSs and 72 CCS's siblings were analyzed. There were no differences in educational attainment or annual income. The SF-36 subscale scores of CCSs with SCT and RT were significantly lower than those of siblings in physical functioning (PF) ($p < 0.001$ and 0.003, respectively) and general health (GH) (both $p = 0.001$). Lower PF scores correlated with recurrence ($p = 0.041$) and late effects ($p = 0.010$), and poor GH scores with late effects ($p = 0.006$). The CCSs had made efforts to attain educational/vocational goals; however, a significant proportion of CCSs who had experienced late effects remain at increased risk of experiencing diminished QOL.

Keywords Childhood cancer survivors · Marriage · Education · Employment · Health-related QOL · SF-36

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Y. Ishida (✉)
Department of Pediatrics, St. Luke's International Hospital, 10-1 Akashi-cho, Chuo-ku, Tokyo 104-0044, Japan
e-mail: yaishida@luke.or.jp

M. Honda
Department of Pediatrics, Ehime University Graduate School of Medicine, Toon, Japan

K. Kamibeppu
Department of Family Nursing, The University of Tokyo, Tokyo, Japan

S. Ozono · H. Inada
Department of Pediatrics, Kurume University School of Medicine, Fukuoka, Japan

J. Okamura
Institute for Clinical Research, National Kyushu Cancer Center, Fukuoka, Japan

K. Asami
Department of Pediatrics, Niigata Cancer Center Hospital, Niigata, Japan

N. Maeda · K. Horibe
Department of Pediatrics, Center for Clinical Research, Nagoya Medical Center, Aichi, Japan

N. Sakamoto
Department of Epidemiology, National Research Institute for Child Health and Development, Tokyo, Japan

T. Iwai
Department of Hemato-Oncology, Kagawa Children's Hospital, Kagawa, Japan

N. Kakee
Department of Health Policy, National Research Institute for Child Health and Development, Tokyo, Japan

1 Introduction

As a result of advances in treatment, 70–80% of children diagnosed with cancer become long-term survivors. In Japan, the estimated number of pediatric cancer survivors is upward of 50,000, or approximately one in 700 adults between the ages of 20 and 39 years. Although an increased number of children with cancer have been cured, many survivors experience various health problems or late effects as a result of their treatments [1, 2]. In addition to various physical problems in childhood cancer survivors (CCSs) [3], social outcomes vis-à-vis marriage, education and employment are apparently affected by these late effects, either directly or indirectly. An increasing number of studies have focused on the social outcomes of CCSs [4–12].

A Swedish population-based study [4] revealed that central nervous system (CNS) tumor survivors had poorer social outcomes compared to the general population, whereas outcomes for non-CNS cancer survivors were similar to those of the general population. On the other hand, the results of the Childhood Cancer Survivor Study (CCSS) suggest that CCSs generally have high school graduation rates similar to those in the general population, but they are slightly less likely to attend college; they are also more likely to be unemployed and not married as young adults [5]. Johannsdottir et al. [6] also outline important differences in social outcomes (i.e., employment and parenthood) between CCS and controls early in adult life.

The health-related quality of life (QOL) of CCSs has been studied extensively using the 36-item Short Form Health Survey (SF-36). Reulen et al. [13] demonstrated the validity and reliability of the SF-36 when used with CCSs, but they point out that ceiling effects should be recognized for researchers in using the SF-36 with CCSs. Maunsell et al. [14] show that QOL differences between CCSs and controls are small, and for the most part are probably not clinically important. In their study, survivors' scores on most subscales of the SF-36 were similar to those of controls, despite experiencing some difficulties in their daily activities [15].

Many reports including meta-analyses or systematic reviews of social outcomes [16] and QOL [17, 18] among CCSs have been published; however, the association between social outcomes and SF-36 scores remains to be elucidated [12, 19]. We have already reported that both stem cell transplantation (SCT) and radiotherapy (RT) are closely associated with the late effects of CCSs [20, 21] and that no significant differences are found between CCSs and siblings in terms of depression and anxiety, but CCSs have significantly more posttraumatic stress symptoms and greater posttraumatic growth [22]. In this article, we investigated the social outcomes and QOL of young adult CCSs with or without SCT/RT compared to those of their siblings in the same population, and analyzed the association between social outcomes and SF-36 subscale scores.

2 Patients and methods

2.1 Study design and participants

We performed a cross-sectional survey involving self-rating questionnaires vis-à-vis the social outcomes and QOL of CCSs, compared to those of the siblings [20, 23]. The study was conducted between 1 August 2007, and 31 March 2009. The subjects were divided into three groups: the CCS with or without SCT/RT, and siblings. The last group was considered as a control that matched with the CCSs with regard to genetic capabilities and environmental similarity. The CCS and their siblings were recruited from the participating hospitals listed in the supplemental appendix 1.

The eligibility criteria for CCSs and their siblings were as follows: (1) the subjects were 16 years old or older at the time of the survey, (2) CCSs had been diagnosed with cancer at 18 years of age or younger, (3) CCSs had been in continuous remission for more than 5 years since cancer diagnosis without any additional need for anticancer therapy, (4) they had been informed about their diagnoses, and (5) informed consent was provided by both CCSs/siblings and their guardians. If CCSs had two or more siblings, we selected the subject with the nearest age to the CCSs among the siblings. The exclusion criteria were as follows: (1) the attending physicians believed that the survey would cause an undesirable effect on CCSs, (2) the subjects had some underlying disease besides cancer that affected their social outcome or QOL, or (3) the subjects were unable to answer the questionnaires by themselves.

2.2 Methods

After obtaining appropriate informed consent, the CCSs were provided with an anonymous questionnaire by the attending pediatricians and asked to return it within post-one month. The patients' clinical records were reviewed to analyze cancer-related variables, including the diagnosis, birth year and month, age at diagnosis, age at therapy completion, time since diagnosis, treatment variables and the late effects of CCSs observed at the time of the survey. We used an encrypted numbering system for dispatching data to the principal investigator, to maintain the confidentiality of patient information. Late effects were defined as adverse events that were grade 2 (i.e., symptomatic or needing some intervention) or higher, according to the

Common Terminology Criteria for Adverse Events, v. 3 (CTCAEv3), which was originally developed by the National Cancer Institute (Japanese CTCAE v. 3.0 by JCOG and JSCO, http://www.jcog.jp/).

2.3 Measurement of variables

The questionnaire consisted of 220 items, with three items involving free writing. We evaluated seven background items (Q1), two truth-telling-related items (Q2), seven lifestyle-associated items (Q3), nine items related to medical visits to the hospital (Q4), four general health-related items (Q5), six past operation and drug usage history items (Q6), seven daily habit items (Q7), nine pregnancy and delivery history items (Q8), 72 subjective physical dysfunctions items (Q9), 36 SF-36-related items (Q10), 64 psychosocial problems-related items (Q11) and three free-writing items (Q12).

In this article, we focus on Q3 and Q10. Q3 contained seven items relating to lifestyle, marital status, educational achievements, current employment, work status, working ability (frequency of absence) and annual income in the last year. Q10, comprising 36 SF-36 items, was often used to measure health-related QOL outcomes [24]. The SF-36 is a generic self-report measure that evaluates eight subscales that represent different aspects of well-being, with respect to eight physical and mental health dimensions in Table 1: physical functioning (PF), bodily pain (BP), role limitations caused by physical health problems (RP), role limitations caused by personal or emotional health problems (RE), general mental health (MH), social functioning (SF), vitality (VT) and general health perception (GH). It also involves two summary scales: the mental component score (MCS) and the physical component score (PCS). Multi-item subscales are scored on a 0–100 percentage scale, with higher scores representing higher levels of functioning and health. Data were presented as *T* scores, with a mean score of 50 and a standard deviation (SD) of 10. *T* scores were dichotomized, in which a *T* score below the population score (i.e., the respective nation's norm, while matching for both age and gender in 2007 [25]) indicated a respondent as having reported poor health-related QOL (HR-QOL). Interpretation guidelines link SF-36 subscales and summary scores to the probability of outcomes, allowing scores to be used as predictors of morbidity (physical and mental) and health-care utilization. SF-36 and summary scores have been extensively tested for reliability and validity [26]. The Cronbach's alpha coefficient of SF-36 was found to be 0.79 (CCSs only) and 0.71 (CCSs and siblings) in this study.

In terms of marital status, subjects were categorized as married, never married and others (i.e., divorced or remarried), while educational achievement was classified as follows: lower than high school, high school graduate, college or vocational school graduate, and university or graduate school graduate. Further, employment status was classified as follows: company desk workers ("white collar"); part-time workers; those with medical jobs; industrial workers ("blue collar"); homemakers; those who were unemployed, including those on job training; and others. In terms of annual income, each subject was classified into one of five categories: less than 1 million Japanese yen (JPY), 1–2 million JPY, 2–3 million JPY, 3–5 million JPY and 5 million JPY or more.

2.4 Ethical issues

The study was performed in accordance with the Declaration of Helsinki and was approved by the ethics committee of the principal investigator's institution (Y. Ishida, Ehime University Graduate School of Medicine and St. Luke's International Hospital). The study was also approved by the local ethics committees of all the participating hospitals, prior to initiation.

2.5 Statistical analysis

We estimated the prevalence of outcomes among CCSs with or without SCT/RT and the siblings group. Three primary outcomes were assessed: (1) social outcomes and (2) general QOL according to SF-36 scores between each pair groups (i.e., CCSs and siblings, CCSs with SCT and CCSs without SCT, CCSs with RT and CCSs without RT), and (3) the association between social outcomes and SF-36 scores (for the CCS group only). We performed χ^2 tests or a Fisher exact test (for any cells with expected counts <5) within categorical predictors, and the *t* test or Kruskal–Wallis methods for continuous variables. As for cross-table comparisons, we used adjusted standardized residuals to evaluate the difference between the observed and expected values; the columns which gave more than 1.96 of adjusted standardized residual were considered as significant [27]. The adjusted odds ratios (ORs) for adverse outcomes were estimated by employing logistic regression analysis. As adjusted variables, we selected independent, significant risk factors such as SCT, solid tumors, recurrence and duration after therapy completion, as shown in our previous article. To avoid multi-collinearity, we assessed associations between predictors in a pairwise fashion. Data were analyzed through the use of SPSS software, v. 18.0 (SPSS IBM Japan Inc., Tokyo, Japan).

We planned a study of independent CCSs and siblings, with five CCSs per sibling. The results of a previous study [3] indicate that the probability of chronic health conditions among siblings is 0.35. If the true probability of chronic health conditions among CCSs is 0.60, we would need to

Table 1 Information of the SF-36 subscales and summary scores [25]

Name of subscale	No. of items	Summary of contents
Physical component score (PCS)		
Physical functioning (PF)	10	Extent to which health limits physical activities such as self-care, walking, climbing stairs, bending, lifting, and moderate and vigourous exercises
Role limitations caused by physical health problems (RP)	4	Extent to which physical health interferes with work of other daily activities, including accomplishing less than that required, limitations in the kind of activities or difficulty in performing activities
Bodily pain (BP)	2	Intensity or pain and effect of pain on normal work, both inside and outside the home
General health perception (GH)	5	Personal evaluation of health, including current health, health outlook and resistance to illness
Mental component score (MCS)		
Vitality (VT)	4	Feeling energetic and full of pep versus feeling tired and worn out
Social functioning (SF)	2	Extent to which physical health or emotional problems interfere with normal social activities
Role limitations caused by personal or emotional health problems (RE)	3	Extent to which emotional problems interfere with work or other daily activities, including decreased time spent on activities, accomplishing less and not working as carefully as usual
General mental health (MH)	5	General mental health, including depression, anxiety, behavioral–emotional control, general positive affect

study 180 case patients and 36 control patients to be able to reject the null hypothesis that the outcome rates for CCSs and siblings are equal with a power of 0.8 ($\beta = 0.2$) and a type I error probability (α) of 0.05. We therefore used an uncorrected χ^2 statistic to evaluate this null hypothesis. In addition, the number needed to analyze nine determinants via multivariate logistic regression methods—to determine the risk factors for late effects—was estimated as 180 for CCSs.

3 Results

The demographic data of the participants are shown in Table 2. Among the CCSs, 189 returned the questionnaires (response rate 72%). Of these, four subjects were excluded because two of the four had an underlying disease besides cancer that affected their QOL, one questionnaire had been completed by the patient's mother and one CCS was 20 years old at diagnosis. We also excluded two questionnaires from siblings, because they were 14 and 15 years of age at the time of survey. The mean age at diagnosis was 8.3 years (SD 4.8) for female CCSs and 8.5 years (SD 5.0) for male CCSs. The proportion of those aged 16–19 years was a little smaller in the siblings group than in the CCSs group. With regard to the primary cancers involved, acute lymphoblastic leukemia comprised 43.9% of the CCSs, followed by acute myeloid leukemia/myelodysplastic syndrome (13.3%) and lymphoma (12.3%). A total of 128 cases of primary cancers were hematological, followed by brain tumors (10 cases), bone/soft tissue sarcoma (18 cases) and other solid tumors (29 cases). As for treatment of the primary cancer, 98% of the CCSs received chemotherapy, 61%, RT, 38% surgery; and 25% hematopoietic SCT. Among the CCSs, one or more late effects were found in 56%, two or more late effects in 17% and three or more in 6%.

The current social outcomes between each pair groups are shown in Table 3. The proportion of subjects living with a partner was higher and that living with parents was lower significantly in the sibling group, because the marriage rate within the female sibling group was high (36%). The marriage rate was especially high in the younger than 24 years of age group for siblings; however, the marriage rate was quite similar in the 25 years or more age group. There were also no large differences in educational attainment; the CCSs revealed a higher proportion of high school level and the CCS with SCT showed a higher proportion of university/graduate school level. The unemployment rate tended to be a little high in the CCSs, especially CCSs with SCT or RT compared to the siblings. The proportion of company desk workers ("white collar") was significantly higher in the sibling group compared to the CCSs. Of particular importance was the high proportion of CCSs holding medical jobs: 15% for females and 7% for males. Finally, there were no large differences in working

Table 2 The demographical data of participants

	Total CCS ($n = 184$)	Siblings ($n = 72$)	t test or χ^2 (p value) CCS versus siblings	CCS with SCT ($n = 46$)	CCS without SCT ($n = 138$)	t test or χ^2 (p value) SCT versus no SCT	CCS with RT ($n = 113$)	CCS without RT ($n = 72$)	t test or χ^2 (p value) RT versus no RT
Gender (female)	108 (58%)	42 (58%)	0.995	27 (59%)	81 (58%)	0.960	68 (60%)	40 (56%)	0.534
Age at diagnosis (median)	8.3 ± 4.8 (8)			10.1 ± 4.4 (10)	7.7 ± 4.8 (7)	0.003	8.6 ± 4.8 (8)	7.9 ± 4.9 (7)	0.350
0–5 years of age	60 (32%)	–		10 (22%)	50 (36%)[a]	0.036	37 (33%)	23 (32%)	0.256
6–10 years of age	50 (27%)	–		10 (22%)	40 (29%)		26 (23%)	24 (33%)	
≥11 years of age	75 (41%)	–		26 (57%)[a]	49 (35%)		50 (44%)	25 (35%)	
Age at survey (median)	23.1 ± 4.9 (22)	24.9 ± 5.1 (24)	0.001	22.9 ± 4.8 (22)	23.2 ± 5.0 (22)	0.659	24.1 ± 5.0 (23.5)	21.6 ± 4.5 (21)	0.001
16–19 years of age	47 (25%)[a]	7 (10%)	0.040	11 (24%)	36 (26%)	0.566	21 (19%)	26 (36%)[a]	0.026
20–24 years of age	75 (40%)	19 (41%)		19 (41%)	56 (40%)		46 (41%)	29 (40%)	
25–29 years of age	38 (21%)	12 (26%)		12 (26%)	26 (19%)		27 (24%)	11 (15%)	
≥30 years of age	25 (14%)	4 (9%)		4 (9%)	21 (15%)		19 (17%)	6 (8%)	
Duration after therapy cessation									
0–4 years	5 (3%)	–		3 (7%)	2 (1%)	0.003	4 (4%)	1 (1%)	0.255
5–9 years	50 (27%)	–		19 (41%)[a]	31 (22%)		28 (25%)	22 (31%)	
10–14 years	57 (31%)	–		15 (33%)	42 (30%)		31 (27%)	26 (36%)	
≥15 years	73 (40%)	–		9 (20%)	64 (46%)[a]		50 (44%)	23 (32%)	
Primary cancer									
Solid tumors	57 (31%)	–		46 (33%)	11 (24%)	0.242	80 (71%)	48 (67%)	0.553
Hematological	128 (69%)	–		93 (67%)	35 (76%)		33 (29%)	24 (33%)	
Treatment									
Operation	70 (38%)	–		14 (30%)	56 (40%)	0.232	40 (35%)	30 (42%)	0.391
Anthracyclines	152 (82%)	–		41 (89%)	111 (80%)	0.154	93 (82%)	59 (82%)	0.951
Alkylating agents	155 (84%)	–		45 (98%)	110 (79%)	0.003	101 (89%)	54 (75%)	0.010
Etoposide	76 (41%)	–		32 (70%)	44 (32%)	<0.001	50 (44%)	26 (36%)	0.273
Radiation	113 (61%)	–		39 (85%)	74 (53%)	<0.001	100%	0%	–
SCT	46 (25%)	–		100%	0%	–	39 (35%)	7 (10%)	<0.001
Recurrence	33 (18%)	–		18 (39%)	15 (11%)	<0.001	28 (25%)	5 (7%)	0.002
Late effects	103 (56%)	–		36 (78%)	67 (48%)	<0.001	77 (68%)	26 (36%)	<0.001
Only 1 late effects	61 (33%)	–		13 (28%)	48 (35%)	0.416	40 (35%)	21 (29%)	0.379
2 or more late effects	42 (23%)	–		23 (50%)	19 (14%)	<0.001	37 (33%)	5 (7%)	<0.001

Age was expressed as mean value ± standard deviation (median value)

CCS childhood cancer survivors, *SCT* stem cell transplantation, *RT* radiation

[a] Adjusted standardized residual ≥+1.96

Table 3 Current social outcome status between each pair groups (i.e., CCS and siblings, CCS with SCT and without SCT, CCS with RT[4] and without RT[4])

	Total CCS ($n = 184$)	Siblings ($n = 72$)	χ^2 (p value) CCS versus siblings	CCS with SCT ($n = 46$)	CCS without SCT ($n = 138$)	χ^2 (p value) SCT versus no SCT	CCS with RT[4] ($n = 112$)	CCS without RT[4] ($n = 72$)	χ^2 (p value) RT versus no RT
Living style									
Living alone	37 (20%)	18 (25%)	0.031	7 (15%)	30 (22%)	0.819	22 (20%)	15 (21%)	0.456
Living with parents	116 (63%)[a]	32 (44%)		31 (67%)	85 (62%)		70 (63%)	46 (64%)	
Living with partner	23 (13%)	18 (25%)[a]		6 (13%)	17 (12%)		13 (12%)	10 (14%)	
Others	8 (4%)	4 (6%)		2 (4%)	6 (4%)		7 (6%)	1 (1%)	
Marital status									
Never married	158 (86%)[a]	54 (75%)	0.090	40 (87%)	118 (86%)	0.844	98 (87%)	60 (86%)	0.444
Married	24 (13%)	17 (24%)[a]		6 (13%)	18 (13%)		15 (13%)	9 (13%)	
Divorced or re-married	1 (0.5%)	1 (1%)		0	1 (1%)		0	1 (1%)	
Marriage rate									
≤24 years of age	2 (2%)	4 (10%)	0.014	0	2 (4%)	0.413	0	2 (4%)	0.112
25–29 years of age	8 (23%)	7 (33%)	0.328	2 (17%)	6 (26%)	0.612	3 (12%)	5 (56%)	0.011
≥30 years of age	14 (56%)	6 (55%)	0.732	4 (100%)	10 (48%)	0.053	12 (63%)	2 (33%)	0.199
Educational achievement									
Lower than high school	7 (4%)	2 (3%)	0.169	0	7 (5%)	0.126	3 (3%)	4 (6%)	0.033
High school	61 (33%)[a]	14 (19%)		14 (30%)	47 (34%)		31 (27%)	30 (42%)[a]	
College/vocational School	51 (28%)	24 (39%)		10 (22%)	41 (30%)		39 (35%)[a]	12 (17%)	
University/graduate school	66 (36%)	32 (45%)		22 (48%)[a]	44 (32%)		40 (35%)	26 (36%)	
Current job									
Student	72 (39%)	24 (33%)	0.011	22 (48%)	50 (36%)	0.694	35 (31%)	37 (51%)[a]	0.099
Company (white collar)	27 (15%)	18 (25%)[a]		5 (11%)	22 (16%)		17 (15%)	10 (14%)	
Part-time job	14 (8%)	8 (11%)		3 (6%)	11 (8%)		12 (11%)[a]	2 (3%)	
Medical job	20 (11%)[a]	0		5 (11%)	15 (11%)		13 (12%)	7 (10%)	
Industry (blue collar)	14 (8%)	3 (4%)		3 (6%)	11 (8%)		11 (10%)	3 (4%)	
Homemaker	15 (8%)	9 (13%)		3 (6)	12 (9%)		9 (8%)	6 (8%)	
Unemployed	7 (4%)	0		3 (6%)	4 (3%)		6 (5%)	1 (1%)	
Others	16 (9%)	10 (14%)		2 (4%)	14 (10%)		10 (9%)	6 (8%)	
Working ability									
No. of days/month	156 (89%)	62 (94%)	0.446	37 (86%)	19 (90%)	0.822	97 (89%)	59 (88%)	0.964
1–2 days/month	13 (7%)	3 (5%)		4 (9%)	9 (7%)		8 (7%)	5 (8%)	
More than 1–2 days/week	7 (4%)	1 (1%)		2 (5%)	5 (4%)		4 (4%)	3 (5%)	

Table 3 continued

	Total CCS ($n = 184$)	Siblings ($n = 72$)	χ^2 (p value) CCS versus siblings	CCS with SCT ($n = 46$)	CCS without SCT ($n = 138$)	χ^2 (p value) SCT versus no SCT	CCS with RT[4] ($n = 112$)	CCS without RT[4] ($n = 72$)	χ^2 (p value) RT versus no RT
Annual income in the last year (JPY)									
<1 million	111 (61%)	40 (58%)	0.586	32 (71%)	79 (58%)	0.276	61 (55%)	50 (70%)[a]	0.098
1–2 million	33 (18%)	9 (13%)		5 (11%)	28 (20%)		27 (24%)[a]	6 (9%)	
2–3 million	21 (12%)	11 (16%)		3 (7%)	18 (13%)		13 (12%)	8 (11%)	
3–5 million	15 (8%)	7 (10%)		5 (11%)	10 (7%)		9 (8%)	6 (9%)	
≥5 million	2 (1%)	2 (3%)		0	2 (2%)		1 (1%)	1 (1%)	

CCS childhood cancer survivors, *JPY* Japanese yen, *SCT* stem cell transplantation, *RT* radiation

[a] Adjusted standardized residual >+1.96

ability or annual income among each group; the CCSs with RT achieved a little lower annual income compared to the CCSs without RT because of a high proportion of students.

The current social outcome status of the CCSs with SCT or RT according to the number of late effects is shown in Table 4. No difference was found with respect to living style, marriage rate and annual income between CCSs lacking any late effects and CCS with only one late effect; however, CCSs with two or more late effects showed extremely low marriage rates (0 and 3%, respectively). A high unemployment rate (from 9 to 5%) was found in CCSs with any late effects in SCT and RT groups.

Figure 1 shows a box plot analysis of the SF-36 subscales and the summary scores among the CCSs with or without SCT and the siblings group. Ceiling effects were found to be high in the PF, RP, BP, SF and RE subscales, for both the CCSs and siblings (supplemental appendix 2). The distributions of each subscale score were much skewed and non-parametric methods using Kruskall–Wallis showed that there was a statistically significant difference in the PF ($p < 0.001$) and GH subscales ($p = 0.001$) between the CCSs with SCT and siblings. A statistically significant difference was also found in the J-PCS and PF subscales between the CCSs with SCT and without SCT, and in the GH subscales between the CCS without SCT and siblings. Figure 2 shows a box plot analysis of the SF-36 subscales and the summary scores among the CCSs with or without RT and the siblings group. A statistically significant difference in the PF ($p = 0.003$) and GH subscales ($p = 0.001$) between the CCSs with SCT and siblings was found. On comparison of the CCSs with the age-matched general population, a statistically significant difference was found in the J-MCS, PF, BP and RE subscales between the CCSs and the nation's standard reference values [25] (supplemental appendix 2).

We created dichotomous variables from each subscale score, to determine whether each subject showed lower SF-36 subscale scores compared to Japan's national norm standards in 2007 [25]. We explored risk factors associated with the lower PF and GH subscale scores of the CCSs, using logistic regression analysis (Table 5). Lower PF scores were associated with recurrence [OR 2.80; 95% confidence interval (CI) 1.04–8.33; $p = 0.041$] and late effects (OR 3.33; 95% CI 1.33–8.33; $p = 0.010$); also, lower GH scores were associated with late effects (OR 2.81; 95% CI 1.35–5.85; $p = 0.006$).

4 Discussion

We found that the long-term social outcome of the CCS group was almost similar to that of siblings in Japan. In line with the Erice statement [28], the majority of survivors

Table 4 Current social outcome status of cancer survivors with or without late effects in the SCT or RT groups

Gender	SCT group ($n = 46$)				RT group ($n = 77$)			
Late effects	Absent ($n = 10$)	Only 1 ($n = 13$)	2 or more ($n = 23$)	χ^2 (p value)	Absent ($n = 36$)	Only 1 ($n = 39$)	2 or more ($n = 36$)	χ^2 (p value)
Living style								
Living alone	0	2 (15%)	5 (22%)	0.126	7 (19%)	8 (21%)	7 (19%)	0.089
Living with parents	6 (60%)	8 (62%)	17 (74%)		18 (50%)	23 (59%)	28 (78%)[a]	
Living with partner	3 (30%)	3 (23%)	0		7 (19%)	6 (15%)	0	
Others	1 (10%)	0	1 (4%)		4 (11%)	2 (5%)	1 (3%)	
Marital status								
Never married	7 (70%)	10 (77%)	23 (100%)[a]	0.028	29 (81%)	33 (82%)	35 (97%)[a]	0.074
Married	3 (30%)	3 (23%)	0		7 (19%)	7 (18%)	1 (3%)	
Educational achievement								
Lower than high school	0	0	0	0.489	1 (3%)	1 (3%)	1 (3%)	0.342
High school	3 (30%)	3 (23%)	8 (35%)		5 (14%)[a]	14 (35%)	12 (33%)	
College/vocational school	1 (10%)	5 (39%)	4 (17%)		17 (47%)	13 (33%)	9 (25%)	
University/graduate school	6 (60%)	6 (39%)	11 (48%)		13 (36%)	12 (30%)	14 (39%)	
Current job								
Student	5 (50%)	3 (23%)[a]	14 (61%)	0.161	10 (28%)	8 (20%)	17 (47%)[a]	0.286
Company (white collar)	2 (20%)	1 (8%)	2 (95)		6 (17%)	7 (18%)	4 (11%)	
Part-time job	0	2 (15%)	1 (4%)		2 (6%)	8 (20%)[a]	2 (6%)	
Medical job	1 (10%)	1 (8%)	3 (13%)		3 (8%)	5 (12%)	5 (14%)	
Industry (blue collar)	0	3 (23%)	0		4 (11%)	5 (12%)	2 (6%)	
Homemaker	1 (10%)	2 (15%)	0		4 (11%)	3 (7%)	2 (6%)	
Unemployed	0	1 (8%)	2 (9%)		1 (3%)	2 (5%)	2 (6%)	
Others	1 (10%)	0	1 (4%)		6 (17%)	2 (5%)	2 (6%)	
Working ability								
No. of days/month	8 (89%)	7 (64%)[a]	22 (96%)	0.082	33 (97%)	32 (84%)	31 (86%)	0.275
1–2 days/month	1 (11%)	2 (18%)	1 (4%)		1 (3%)	3 (8%)	4 (11%)	
More than 1–2 days/week	0	2 (18%)[a]	0		0	3 (8%)	1 (3%)	
Annual income in the last year (JPY[a])								
<1 million	6 (60%)	10 (77%)	16 (73%)	0.247	17 (47%)	22 (56%)	21 (60%)	0.534
1–2 million	1 (10%)	2 (15%)	2 (9%)		11 (31%)	11 (28%)	5 (14%)	
2–3 million	0	0	3 (14%)		4 (11%)	3 (8%)	6 (17%)	
≥3 million	3 (30%)[a]	1 (8%)	1 (5%)		4 (11%)	3 (8%)	3 (9%)	

JPY Japanese yen, *SCT* stem cell transplantation, *RT* radiation

[a] Adjusted standardized residual >+1.96

become relatively well adjusted in adulthood; indeed, there is a proportion exhibiting extraordinary resilience. However, compared to siblings, a significant proportion of CCSs are at an increased risk of developing conditions that require medical, psychological or social care because SCT and RT are closely associated with various late effects reported previously [20, 21]. Our study showed that the marriage rate of the CCSs in 24 years of age or younger patients was a little lower than that of their siblings, and that little difference existed in educational achievement between the CCSs and their siblings [9, 15]. A limitation of our study was that the mean and median ages of the participants were only 23–24 years; this is too young an age to evaluate the total marriage rate, as the average marriage age has been increasing recently (i.e., in 2008, the Japanese national mean age of marriage was 30.2 years for males and 28.5 years for females). By using an analysis of stratification by age, the marriage rate became almost the same in the 25 years or more age group for both females and males.

On the other hand, there were small differences in employment status and annual income among each group

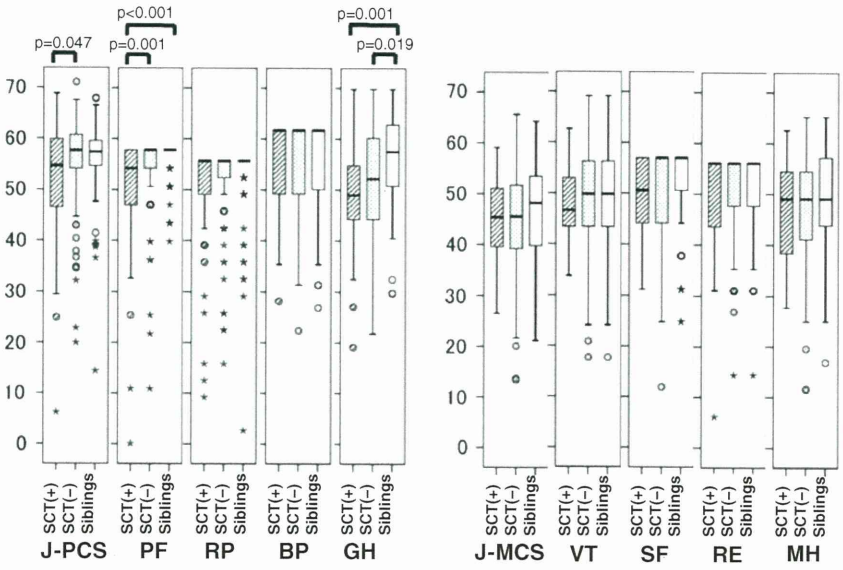

Fig. 1 Box and whisker plot of SF-36 subscale scores according to stem cell transplantation. The *bottom* and *top* of the *box* are the 25th and 75th percentile, respectively, and the thick band near the middle of the box is the 50th percentile (the median). The *ends of the whiskers* represent the lowest datum still within 1.5 interquartile range (IQR) of the lower quartile, and the highest datum still within 1.5 IQR of the upper quartile. The *open circles* are outliers between 1.5 and 3 IQR from the end of a box, and the *asterisks* are extreme values beyond 3 IQR from the end of a box. Kruskal–Wallis test reveal that SF-36 subscales scores of childhood cancer survivors (CCSs) with stem cell transplantation (SCT; *hatched bars*) are significantly lower than those of siblings (*open bars*) in PF and GH subscales, respectively. The J-PCS and PF scores in CCSs with SCT are also significantly lower than those in CCS without SCT (*dotted bars*). The GH scores of CCSs without SCT are significantly lower than those of siblings. All *p* values are adjusted by pairwise multiple comparison

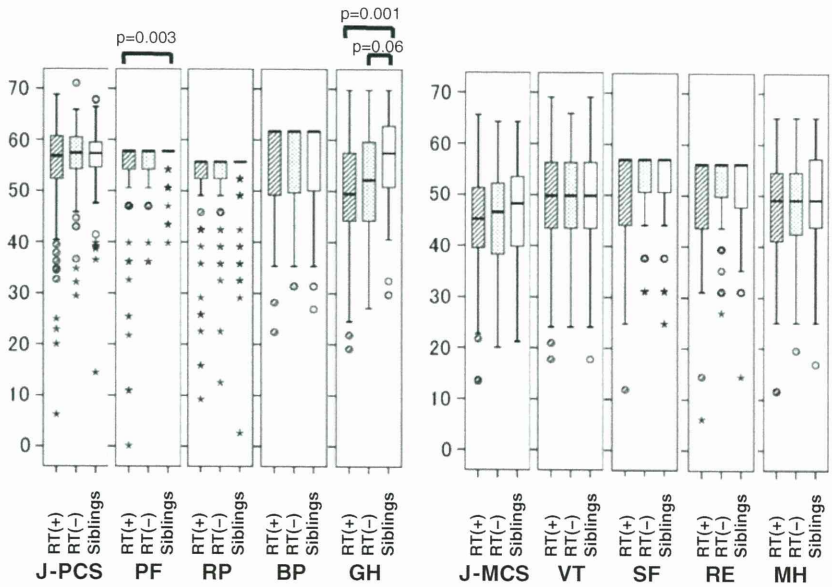

Fig. 2 Box and whisker plot of SF-36 subscale scores according to radiotherapy. Kruskal–Wallis test reveals that SF-36 subscale scores of childhood cancer survivors (CCSs) with radiotherapy (RT; *hatched bars*) are significantly lower than those of siblings (*open bars*) in PF and GH subscales, respectively. The GH scores of CCSs without RT are significantly lower than those of siblings. All *p* values are adjusted by pairwise multiple comparison

in our study despite that both SCT and RT had increased late effects for CCSs [20, 21]. The most important issue was that the proportion of CCSs with two or more late effects who were getting married was quite low. This finding accords with those of previous reports [5, 7]. In our study, the proportion of unemployment tended to be a little high (4%) in the CCSs, especially CCSs with SCT or RT compared to the siblings. A higher unemployment rate (from 9 to 5%) was found in the CCSs with any late effects. The small but significant portion of CCSs experiencing employment difficulties are of great concern [16]; in fact, meta-analysis [16] showed that CCSs were nearly twice as likely to be unemployed than healthy controls (OR 1.85; 95% CI 1.27–2.69) and that survivors in the USA had an overall threefold risk of becoming unemployed, whereas no such risk was found for European survivors. This is very

Table 5 Risk factors associated with lower subscale scores of SF-36 in cancer survivors

Factors	PF scores		χ^2 (p value)	Logistic regression analysis[a]	
	Lower[a] ($n = 51$)	Higher ($n = 132$)		Adjusted odds ratio (95% CI)	p value
Gender (female)	24	83	0.052	0.59 (0.28–1.27)	0.177
Age at Dx (years)					
0–5	13	45	**0.044**	0.40 (0.15–1.09)	0.074
6–10	10	41		0.41 (0.16–1.08)	0.070
≥11	28	46		Ref	
Tx off (years)					
≥15	16	56	0.170	0.88 (0.35–2.22)	0.787
≤14	35	76		Ref	
Solid tumors	23	33	**0.008**	1.85 (0.53–6.46)	0.334
Hematological	28	99		Ref	
Radiation	34	78	0.346	0.72 (0.30–1.73)	0.464
Stem cell transplantation	21	25	**0.002**	1.96 (0.78–4.88)	0.150
Operation	28	40	**0.001**	1.49 (0.45–4.95)	0.513
Recurrence	17	16	**0.001**	**2.80 (1.04–8.33)**	**0.041**
Late effects	41	61	**<0.0001**	**3.33 (1.33–8.33)**	**0.010**
Factors	GH scores		χ^2 (p value)	Logistic regression analysis[a]	
	Lower[a] ($n = 107$)	Higher ($n = 76$)		Adjusted odds ratio (95% CI)	p value
Gender (female)	64	43	0.662	1.48 (0.77–2.87)	0.240
Age at Dx (years)					
0–5	37	21	0.148	1.31 (0.55–3.16)	0.543
6–10	24	27		0.56 (0.26–1.24)	0.155
≥11	46	28		Ref	
Tx off (years)					
≥15	40	32	0.519	0.64 (0.29–1.38)	0.255
≤14	67	44		Ref	
Solid tumors	33	23	0.933	0.65 (0.21–1.96)	0.439
Hematological	74	53		Ref	
Radiation	71	41	0.09	1.10 (0.54–2.23)	0.792
Stem cell transplantation	32	14	0.078	1.11 (0.48–2.60)	0.809
Operation	41	27	0.700	1.26 (0.43–3.63)	0.675
Recurrence	25	8	**0.026**	1.64 (0.60–4.52)	0.335
Late effects	71	31	**0.001**	**2.81 (1.35–5.85)**	**0.006**

[a] After data were presented as T scores with a mean score of 50 and a standard deviation (SD) of 10, T scores were dichotomized, in which a T score below the population score (respective nation's norm matching both age and gender in 2007) classified a respondent as having reported poor HRQOL

important, because the national health-care and social support systems must address these groups of CCSs in Japan. The Children's Cancer Association of Japan (http://www.ccaj-found.or.jp/english/) is now providing assistance and job training to CCSs, and an effective job-training system for CCSs will continue to be warranted in the future.

In our study, the validity and reliability of applying the SF-36 to CCSs in Japan were supported by Cronbach's alpha coefficient. Reulen et al. [13] demonstrated that the occurrence of ceiling effects should be recognized. In our study, a ceiling effect was observed in PF, BP and SF in more than half of the CCSs; it was found to be highest in the RP (66.1%) and RE (61.7%) subscales. These results were quite similar to those pertaining to British CCSS and siblings. The Kruskal–Wallis test showed a statistical significant difference between CCSs with SCT/RT and siblings in the RP and GH subscales. In the CCSS study, the CCSs score was worse than that of siblings with respect to the overall physical ($p < 0.001$), but not the emotional