Table 6 Factors related to calculated scores of parents' perception about child's HRQOL ($N = 134$)

	n	*r*	95% CI	*b*	95% CI
K10 score[a]	132	−0.24*	(−0.40, −0.07)	−0.21*	(−0.37, −0.04)
Treatment status (0: on treatment, 1: off treatment)	134	0.36*	(0.20, 0.50)	0.26*	(0.09, 0.43)
Gender of parents (0: Male, 1: Female)	134	0.05	(−0.12, 0.22)	–	
Age of parents at survey	133	−0.14	(−0.30, 0.03)	–	
Academic background of parents (0: high schools, 1: colleges and universities)	131	0.16	(−0.01, 0.32)	0.17*	(0.00, 0.34)
Parents' time with children per a day	132	−0.04	(−0.21, 0.13)	–	
Subjective opinion regarding parents' own economic status and life (0: not affluent, 1: affluent)	132	0.14	(−0.03, 0.30)	–	

Missing data were excluded

HRQOL health-related quality of life, *CI* confidence interval, *r* Spearman's rank correlation coefficient, *b* Standardized partial regression coefficient by multiple linear regression analysis

* $P < 0.05$

– variables not selected by step-down procedure

[a] Kessler-10. A higher score indicates that parents have higher psychological distress

Table 7 Descriptive statistics of the differences and correlation between child- and parent-reported HRQOL ($N = 134$)

	n	HRQOL[a]				Difference[b]	95% CI		Pearson's correlation coefficient
		Child-reported		Parent-reported					
		Mean	SD	Mean	SD				
Trait anxiety score of STAIC[c]									
Less than 36 (median)	48	85.8	10.2	77.1	14.9	8.7	4.3	13.2	0.30*
36 or over	49	77.3	12.9	72.2	15.7	5.2	1.9	8.5	0.69*
K10 score[d]									
Less than 6 (median)	65	83.0	12.7	79.2	12.2	3.8	0.6	6.9	0.47*
6 or over	67	75.7	15.6	65.9	15.9	9.8	6.3	13.3	0.58*
Treatment status									
On treatment	53	75.5	15.4	66.2	15.2	9.4	5.5	13.3	0.57*
Off treatment	81	81.5	13.6	76.9	14.6	4.6	1.5	7.7	0.52*
Academic background of parents									
High schools	51	79.1	13.9	70.1	14.9	9.0	2.0	13.0	0.53*
Colleges and universities	80	78.9	15.2	74.3	15.7	4.6	1.7	7.5	0.64*

Missing data were excluded

HRQOL health-related quality of life, *CI* confidence interval, *SD* standard deviation

* $P < 0.05$

[a] Mean of six subscale scores of PedsQL Brain Tumor Module

[b] "child-reported mean HRQOL score" minus "parent-reported mean HRQOL score"

[c] State Trait Anxiety Inventory for Children. A higher score indicates higher anxiety

[d] Kessler-10. A higher score indicates that parents have higher psychological distress

reported scores for the PedsQL™ Brain Tumor Module (Table 9). For all subscales, interviewer-administration scores were lower than child-reported scores. However, given that the 95% CIs included values of zero, the method of administration appears to have little effect on children's perception. This result was similar to that obtained on

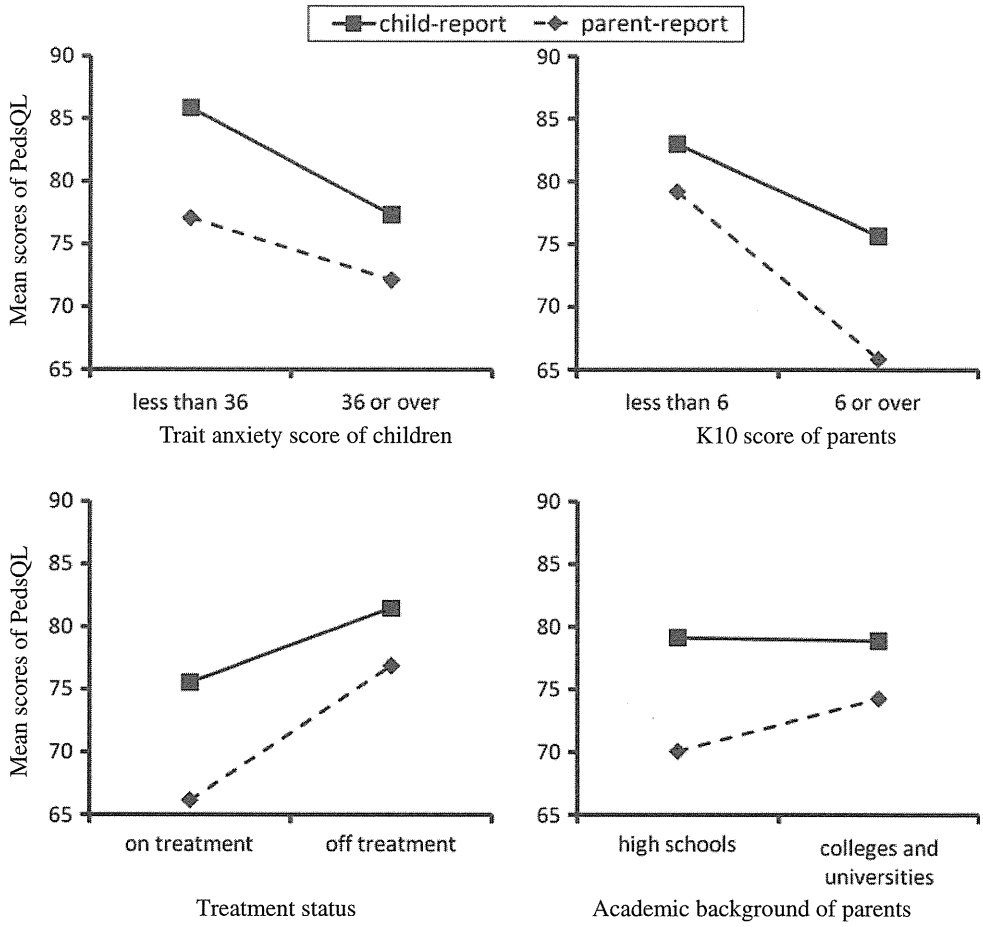

Fig. 5 Differences between child- and parent-reported mean scores of six subscales of PedsQL Brain Tumor Module by socio-demographic and health characteristics

Table 8 Regression of the differences[a] between child- and parent-reported HRQOL[b] ($N = 134$)

	n	*r*	95% CI	*b*	95% CI
Trait anxiety score of STAIC[c]	97	−0.21*	(−0.39, −0.01)	−0.27*	(−0.47, −0.07)
K10 score[d]	132	0.21*	(0.04, 0.37)	0.29*	(0.09, 0.49)
Treatment status (0: on treatment, 1: off treatment)	134	−0.15	(−0.31, 0.02)	−0.13	(−0.33, 0.06)
Academic background of parents (0: high schools, 1: colleges and universities)	131	−0.14	(−0.30, 0.03)	−0.13	(−0.33, 0.06)

Missing data were excluded

CI confidence interval, *HRQOL* health-related quality of life, *r* Spearman's rank correlation coefficient, *b* Standardized partial regression coefficient by multiple linear regression analysis ($n = 93$, $R^2 = 0.168$)

* $P < 0.05$

[a] "child-reported mean HRQOL score" minus "parent-reported mean HRQOL score"

[b] Mean of six subscale scores of PedsQL Brain Tumor Module

[c] State Trait Anxiety Inventory for Children. A higher score indicates higher anxiety

[d] Kessler-10. A higher score indicates that parents have higher psychological distress

analysis of factors related to children's perception (Table 4).

In contrast, children receiving interviewer-administered surveys had significantly lower scores for cognitive problems, pain and hurt, and movement and balance subscales than those who were self-administered (Table 9).

Discussion

We show that the response of children aged 5–18 to questions on HRQOL was altered by trait anxiety, while a parent's perception about their child's HRQOL was affected by the child's treatment status and the parent's

Table 9 Changes in child-reported HRQOL score based on method of administration ($N = 134$)

	Direct effect		Indirect effect			
	D	95% CI	*I*	95% CI	I1	I2
Cognitive problems	−6.4	(−12.0, −0.8)	−2.5	(−7.5, 2.5)	−0.14	18.1
Pain and hurt	−7.9	(−13.8, −1.9)	−1.3	(−3.8, 1.3)	−0.14	9.2
Movement and balance	−12.6	(−19.3, −6.0)	−2.5	(−7.6, 2.6)	−0.14	18.3
Procedural anxiety	−8.8	(−19.4, 1.8)	−1.1	(−3.5, 1.3)	−0.14	8.1
Nausea	−2.6	(−9.8, 4.6)	−1.1	(−3.5, 1.2)	−0.14	8.2
Worry	−0.6	(−8.0, 6.8)	−2.1	(−6.4, 2.2)	−0.14	15.3

CI confidence interval, *HRQOL* health-related quality of life, *D* path coefficients from the method of administration to child-reported HRQOL, *I* indirect effect from the method of administration to child-reported HRQOL, *I1* path coefficients from the method of administration to children's perception, *I2* path coefficients from the children's perception to child-reported HRQOL

own psychological distress and academic background. Interestingly, children's HRQOL scores from self- and interviewer-administered reports were comparable, showing that the results from bivariate and multivariate analyses were not biased by the method of administration. This important result suggests interviewer measurement of HRQOL for children who are unable to self-administer the questionnaire is valid.

The correlation coefficient between the method of administration and tendency for children to score their own HRQOL highly was −0.06 (95% CI −0.23 to 0.11). Given that correlation coefficients >0.1 are regarded as small, >0.3 as medium and >0.5 as large [37], this finding suggests that the method of questionnaire administration has only a small effect on the assessment of children's perception.

All scales of PedsQL™ were scored from 0 to 100, and the actual difference in child-reported score resulting from administration method ranged from −2.5 to −1.1 points. The US Department of Health suggests methods for inferring minimum clinically significant difference (MID) [38]. Using an empirical rule (e.g., 8% of the theoretical range of scores), the MID in a PedsQL™ score is 8 points. Using a distribution-based approach (e.g., defining the MID as 0.5 times the standard deviation), the MID in the PedsQL™ Brain Tumor Module scores reported a range from 9.2 to 17.2 points [24]. Other authors used a standard error of measurement approach to determine the MID for the PedsQL™ Generic Core Scales child-report was 4.4 [39]. Taken together, these previous findings suggest that the difference in child-reported score resulting from administration method in the present study, while not negligible, is not comparatively significant. As such, we feel confident in adopting an administration method for monitoring HRQOL in clinical settings best adapted to the environment.

Similarly, results for previous comparisons of administration methods show small differences albeit in opposing directions. Huguet and Miro, using a Catalan version of PedsQL™, reported that interviewer-administered scores were 2 points higher than self-administered scores [40]. In their assessment of very low birth weight children aged 14 years by the TACQOL, Verrips et al. [41] found that the interviewer-administered scores were 2 points lower than the self-administered score, whereas Tsakos et al. [42] found no significant difference between self- and interviewer-administered scores for oral HRQOL. Taken together, the findings from the present and previous studies suggest little difference between self- and interviewer-administered scores for child-reporting. Differences between findings for these present and previous studies may be due to differing criteria for HRQOL measured or differences in the children's diseases. To our knowledge, our present study is the first to report that the scores of self- and interviewer-administered questionnaires for HRQOL in children with brain tumors using PedsQL™ are comparable.

Consistent with results for other children with cancer [14], we also found that trait anxiety alters children's own perception about HRQOL. As trait anxiety has a greater effect than the other factors, it should be considered in the interpretation of child-reported scores. Given that trait anxiety is one personality characteristic that does not vary substantially over time [28], if self-reported scores from repeated measurements of a child with a brain tumor are consistently lower than parent-reported scores, the measured result may be attributed to high trait anxiety of the child.

The effect of treatment status on a parent's perception about their child's HRQOL has not been previously investigated. Parents of children on treatment tended to have a lower perception about their child's HRQOL than those of children off treatment, whereas treatment status had no influence on children's perception. As a result, clinical practice or research should use both child- and parent-reports whenever possible, particularly when

HRQOL questionnaires are needed to assess HRQOL variations during the course of treatment, changes in environment, or psychosocial intervention. For example, HRQOL reports from parents and children changed at 1, 6, and 12 months after diagnosis of brain tumor [19]. The pattern of child-reported HRQOL was different from parent-reported HRQOL over time indicating the importance of using use both child- and parent-reports.

Parents may feel a stronger impact of their child's illness than the child himself or herself [43]. In previous studies, parent-reported HRQOL scores were higher than child-reported scores for children without health problems and lower than child-reported scores for children with health problems. Our study also suggests that parents are more aware of their child's treatment through knowledge of tumor symptoms and treatment pain. In other words, the parents may feel a stronger impact of their child's treatment than the child himself or herself and accordingly tend to score the HRQOL of these children lower than the parents of children off treatment.

Vance et al. [44] suggested that parent-reported HRQOL was not influenced by parent's depression. The present study, however, which had a larger sample size than previous studies, found that the parent-reported HRQOL was affected by the parent's own psychological distress. This suggests that the parent's own prospects and cognitive tendency influence their perception about their child's HRQOL.

The present study is the first to use an MTMM model to identify factors that influence child or parent perception about HRQOL. This knowledge will be useful in interpreting the discordance between child- and parent-reports of HRQOL in children with brain tumors. In clinical settings, this finding will allow clinicians to take high trait anxiety in the child or high psychological distress in the parent into account. For example, when the child is off treatment, it will be less surprising that child-reported HRQOL score is low and parent-reported HRQOL score is high if the child has low trait anxiety. Routine measurements in clinical settings thus have the potential to allow the monitoring of both the child's personality and the mental state of his/her parents. This finding will also improve the selection of children for comparison of HRQOL among multiple groups. For example, in non-randomized controlled trials, children may be allocated among groups with consideration to equality of anxiety in children and mental health in parents. Our findings also suggest that single group studies should collect information on parents' academic background as well as other demographic characteristics, such as gender, age, race, etc., that influence selection bias.

Several limitations to our study warrant mention. First, as a cross-sectional study, changes in perception over time were not tested. Accordingly, we cannot conclude that the perception of a parent or child with a brain tumor will change at the end of treatment. Clarification of intrapersonal change in perception or response shift of children with brain tumors and their parents will require a longitudinal study.

Second, we did not conduct an a priori sample size calculation because this study is a part of another study [24] that has a predetermined sample size. The effect of sample size was calculated by G*Power software [45]. If a characteristic that has a medium effect ($f^2 \geq 0.15$ [37]) on either children's or parents' perception is added to a multiple linear regression model with 3 variables, a sample of 55 would enable detection of the characteristic as the 4th independent variable with 80% power and a 5% alpha error. Similarly, a sample of 395 would be required to detect a characteristic that has a small effect ($f^2 \geq 0.02$ [37]) as the 4th independent variable. It follows that the sample size of the present study was sufficient to detect factors having a medium effect. A larger sample might discriminate additional characteristics that were not found to be statistically significant in the present study, such as children's age and economic status.

A larger sample size would also enable simultaneous modeling of responses (MTMM model, Fig. 3) and predictors (predictor model, Tables 4, 6, and Fig. 1), which might then detect any correlation between the predictors and the latent variables of rater-independent assessments of the child's condition. Further, a larger sample size should enable researchers to detect the effect of interviewer type (e.g., parent or researcher interviewer) on a child's perception. Among children aged five-to-seven and eight or more years, those interviewed by a parent tended to have a lower perception about HRQOL than those interviewed by a researcher, although this result was not statistically significant.

Third, we were unable to measure all possible factors that might influence child-parent agreement. We limited the length of our questionnaires to avoid placing further stress on the children, and therefore, measurements of the child's psychological background were limited to anxiety. Other aspects of a child's personality, such as defensiveness [14], might also influence the results, and future research should therefore investigate different personality traits. We also omitted measurements of the child's physical background, such as tumor location, tumor malignancy, relapse history, or treatment intensity [18–22]. All data in the present study were collected not from medical experts but from the children and their parents; as such, obtaining accurate, detailed answers about medical information was somewhat difficult. Additional information derived from patients with specific tumors or under specific treatment regimens will be required to identify residual confounders.

An additional constraint arises from the sample type. The present study collected data from a broad spectrum of children who had experienced brain tumors and included, for example, children diagnosed from 1 month to 17 years before the study. We could cover the broad spectrum to make up the study sample of the two subsamples. The hospitals subsample included more children with short time since diagnosis, young at survey, and on treatment than the CCAJ subsample did. To provide further insight into self- or parent-perceptions about HRQOL, further studies should focus on children at different phases of treatment or follow-up.

Families were excluded if the doctors or social workers determined that the family found the subject of the child's condition too uncomfortable to discuss. Although the number of such excluded families was not recorded, this exclusion may have limited data collection to more well-adjusted families and thereby limited the generalizability of the conclusions as well.

Finally, independent variables identified in this study accounted for 26.4% of the children's perception and 17.3% of the parents' perception. Other independent factors were not identified.

Conclusion

The method of administration—self- or interviewer-administered—had little influence on child-reporting of HRQOL. Children's perception of their own HRQOL was influenced by their trait anxiety, while parents' perception was influenced by their psychological distress, academic background, and their child's treatment status. These factors underlie the difference between child- and parent-reported HRQOL scores.

Acknowledgments This work was supported by a Grant-in-Aid for Pediatric Cancer Treatment and Research from the CCAJ 2008 and a Grant-in-Aid for Cancer Research from the Ministry of Health, Labour and Welfare of Japan (No. 18-14) 2008.

References

1. Collins, J. J., Byrnes, M. E., Dunkel, I. J., Lapin, J., Nadel, T., Thaler, H. T., et al. (2000). The measurement of symptoms in children with cancer. *Journal of Pain and Symptom Management, 19*(5), 363–377.
2. Sugiyama, K., Yamasaki, F., Kurisu, K., & Kenjo, M. (2009). Quality of life of extremely long-time germinoma survivors mainly treated with radiotherapy. *Progress in Neurological Surgery, 23*, 130–139.
3. Ribi, K., Relly, C., Landolt, M. A., Alber, F. D., Boltshauser, E., & Grotzer, M. A. (2005). Outcome of medulloblastoma in children: Long-term complications and quality of life. *Neuropediatrics, 36*(6), 357–365.
4. Poretti, A., Grotzer, M. A., Ribi, K., Schonle, E., & Boltshauser, E. (2004). Outcome of craniopharyngioma in children: Long-term complications and quality of life. *Developmental Medicine and Child Neurology, 46*(4), 220–229.
5. Sønderkær, S., Schmiegelow, M., Carstensen, H., Nielsen, L. B., Muller, J., & Schmiegelow, K. (2003). Long-term neurological outcome of childhood brain tumors treated by surgery only. *Journal of Clinical Oncology, 21*(7), 1347–1351.
6. Fuemmeler, B. F., Elkin, T. D., & Mullins, L. L. (2002). Survivors of childhood brain tumors: Behavioral, emotional, and social adjustment. *Clinical Psychology Review, 22*(4), 547–585.
7. Testa, M. A., & Simonson, D. C. (1996). Assessment of quality-of-life outcomes. *New England Journal of Medicine, 334*(13), 835–840.
8. Sherifali, D., & Pinelli, J. (2007). Parent as proxy reporting: Implications and recommendations for quality of life research. *Journal of Family Nursing, 13*(1), 83–98.
9. Pickard, A. S., & Knight, S. J. (2005). Proxy evaluation of health-related quality of life: A conceptual framework for understanding multiple proxy perspectives. *Medical Care, 43*(5), 493–499.
10. Erhart, M., Ellert, U., Kurth, B. M., & Ravens-Sieberer, U. (2009). Measuring adolescents' HRQoL via self reports and parent proxy reports: An evaluation of the psychometric properties of both versions of the KINDL-R instrument. *Health and Quality of Life Outcomes, 7*, 77.
11. Varni, J. W., Seid, M., & Kurtin, P. S. (2001). PedsQL 4.0: Reliability and validity of the Pediatric Quality of Life Inventory version 4.0 generic core scales in healthy and patient populations. *Medical Care, 39*(8), 800–812.
12. Verrips, E. G. H., Vogels, T. G. C., Koopman, H. M., & Theunissen, N. C. M. (1999). Measuring health-related quality of life in a child population. *The European Journal of Public Health, 9*, 188–193.
13. Landgraf, I., Abetz, L., & Ware, I. (1997). *Child Health Questionnaire (CHQ): A user's manual*. Boston: The Health Institute Press.
14. Jurbergs, N., Russell, K. M. W., Long, A., & Phipps, S. (2008). Adaptive style and differences in parent and child report of health-related quality of life in children with cancer. *Psychooncology, 17*(1), 83–90.
15. Davis, E., Davies, B., Waters, E., & Priest, N. (2008). The relationship between proxy reported health-related quality of life and parental distress: Gender differences. *Child: Care, Health and Development, 34*(6), 830–837.
16. Tamim, H., McCusker, J., & Dendukuri, N. (2002). Proxy reporting of quality of life using the EQ-5D. *Medical Care, 40*, 1186–1195.
17. Hays, R. D., Vickrey, B. G., Hermann, B. P., Perrine, K., Cramer, J., Meador, K., et al. (1995). Agreement between self reports and proxy reports of quality of life in epilepsy patients. *Quality of Life Research, 4*, 159–168.
18. Aarsen, F. K., Paquier, P. F., Reddingius, R. E., Streng, I. C., Arts, W. F. M., Evera-Preesman, M., et al. (2006). Functional outcome after low-grade astrocytoma treatment in childhood. *Cancer, 106*(2), 396–402.
19. Penn, A., Lowis, S. P., Hunt, L. P., Shortman, R. I., Stevens, M. C. G., McCarter, R. L., et al. (2008). Health related quality of life in the first year after diagnosis in children with brain tumours compared with matched healthy controls; a prospective longitudinal study. *European Journal of Cancer, 44*(9), 1243–1252.
20. Meeske, K. Katz., Katz, E. R., Palmer, S. N., Burwinkle, T., & Varni, J. W. (2004). Parent proxy-reported health-related quality of life and fatigue in pediatric patients diagnosed with brain tumors and acute lymphoblastic leukemia. *Cancer, 101*, 2116–2125.
21. Bhat, S. R., Goodwin, T. L., Burwinkle, T. M., Landsdale, M. F., Dahl, G. V., Huhn, S. L., et al. (2005). Profile of daily life in

children with brain tumors: An assessment of health-related quality of life. *Journal of Clinical Oncology, 23*, 5493–5500.
22. Gerber, N. U., Zehnder, D., Zuzak, T. J., Poretti, A., Boltshauser, E., & Grotzer, M. A. (2008). Outcome in children with brain tumours diagnosed in the first year of life: Long-term complications and quality of life. *Archives of Disease in Childhood, 93*, 582–589.
23. Palmer, S. N., Meeske, K. A., Katz, E. R., Burwinkle, T. M., & Varni, J. W. (2007). The PedsQL brain tumor module: Initial reliability and validity. *Pediatric Blood & Cancer, 49*(3), 287–293.
24. Sato, I., Higuchi, A., Yanagisawa, T., Mukasa, A., Ida, K., Sawamura, Y., et al. (2010). Development of the Japanese version of the Pediatric Quality of Life Inventory Brain Tumor Module. *Health and Quality of Life Outcomes, 8*(1), 38.
25. Cronbach, L. J. (1951). Coefficient alpha and the internal structure of tests. *Psychometrika, 16*(3), 297–334.
26. Kobayashi, K., & Kamibeppu, K. (2010). Measuring quality of life in Japanese children: Development of the Japanese version of PedsQL™. *Pediatrics International, 52*(1), 80–88.
27. Soga, S. (1983). A study on standardization of Japanese version of the STAIC [Japanese]. *The Japanese Journal of Psychology, 54*(4), 215–221.
28. Spielberger, C. D., Edward, C. D., Lushene, R. E., Montouri, J., & Platzek, D. (1973). *STAIC preliminary manual for the State-Trait Anxiety Inventory for Children ("How I feel questionnaire")*. California: Consulting Psychological Press Inc.
29. Furukawa, T. A., Kawakami, N., Saitoh, M., Ono, Y., Nakane, Y., Nakamura, Y., et al. (2008). The performance of the Japanese version of the K6 and K10 in the World Mental Health Survey Japan. *International Journal of Methods in Psychiatric Research, 17*(3), 152–158.
30. Furukawa, T. A., Kessler, R. C., Slade, T., & Andrews, G. (2003). The performance of the K6 and K10 screening scales for psychological distress in the Australian National Survey of Mental Health and Well-Being. *Psychological Medicine, 33*(2), 357–362.
31. Campbell, D. T., & Fiske, D. W. (1959). Convergent and discriminant validation by the multitrait-multimethod matrix. *Psychological Bulletin, 56*(2), 81–105.
32. Theunissen, N. C., Vogels, T. G., Koopman, H. M., Verrips, G. H., Zwinderman, K. A., Verloove-Vanhorick, S. P., et al. (1998). The proxy problem: Child report versus parent report in health-related quality of life research. *Quality of Life Research, 7*(5), 387–397.
33. Hadorn, D. C. M. D., & Hays, R. D. P. (1991). Multitrait-multimethod analysis of health-related quality-of-life measures. *Medical Care, 29*(9), 829–840.
34. Hu, L., & Bentler, P. M. (1999). Cutoff criteria for fit indices in covariance structure analysis: Conventional criteria versus new alternatives. *Structural Equation Modeling: A Multidisciplinary Journal, 6*, 1–55.
35. Duncan, O. D. (1966). Path analysis: Sociological examples. *American Journal of Sociology, 72*, 1–16.
36. Sobel, M. E. (1982). Asymptotic confidence intervals for indirect effects in structural equation models. *Sociological Methodology, 13*, 290–312.
37. Cohen, J. (1988). *Statistical power analysis for the behavioral sciences* (2nd ed.). New Jersey: Lawrence Erlbaum Associates.
38. U.S. Department of Health and Human Services FDA Center for Drug Evaluation and Research, U.S. Department of Health and Human Services FDA Center for Biologics Evaluation and Research, & U.S. Department of Health and Human Services FDA Center for Devices and Radiological Health. (2006). Guidance for industry: Patient-reported outcome measures: Use in medical product development to support labeling claims: Draft guidance. *Health and Quality of Life Outcomes, 4*, 79.
39. Varni, J. W., Burwinkle, T. M., Seid, M., & Skarr, D. (2003). The PedsQL 4.0 as a pediatric population health measure: Feasibility, reliability, and validity. *Ambulatory Pediatrics, 3*, 329–341.
40. Huguet, A., & Miro, J. (2008). Development and psychometric evaluation of a Catalan self- and interviewer-administered version of the Pediatric Quality of Life Inventory version 4.0. *Journal of Pediatric Psychology, 33*(1), 63–79.
41. Verrips, G. H., Vogels, A. G., den Ouden, A. L., Paneth, N., & Verloove-Vanhorick, S. P. (2000). Measuring health-related quality of life in adolescents: Agreement between raters and between methods of administration. *Child: Care, Health and Development, 26*(6), 457–469.
42. Tsakos, G., Bernabe, E., O'Brien, K., Sheiham, A., & de Oliveira, C. (2008). Comparison of the self-administered and interviewer-administered modes of the child-OIDP. *Health & Quality of Life Outcomes, 6*, 40.
43. Eiser, C., & Morse, R. (2001). Can parents rate their child's health-related quality of life? Results of a systematic review. *Quality of Life Research, 10*(4), 347–357.
44. Vance, Y. H., Morse, R. C., Jenney, M. E., & Eiser, C. (2001). Issues in measuring quality of life in childhood cancer: Measures, proxies, and parental mental health. *Journal of Child Psychology and Psychiatry and Allied Disciplines, 42*, 661–667.
45. Faul, F., Erdfelder, E., Lang, A. G., & Buchner, A. (2007). G*Power 3: A flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Behavior Research Methods, 39*, 175–191.

小児がん経験者の晩期合併症の予測は可能か
—聖路加国際病院小児科の経験—

石田也寸志*，渡辺　静，小澤　美和，米川　聡子，小川千登世，長谷川大輔，細谷　要介，
吉原　宏樹，真部　淳，森本　克，西村　昴三，細谷　亮太

聖路加国際病院小児科

Can we predict the late effects of childhood cancer survivors?—St. Luke's experience

Yasushi Ishida, Shizuka Watanabe, Miwa Ozawa, Satoko Yonekawa, Chitose Ogawa, Daisuke Hasegawa, Yosuke Hosoya, Hiroki Yoshihara, Atsushi Manabe, Tsuyoshi Morimoto, Kozo Nishimura, Ryota Hosoya

St. Luke's International Hospital, Department of Pediatrics

Abstract

We evaluated whether the five-level follow-up (FU) classification proposed by the Japanese Pediatric Leukemia and Lymphoma Study Group (JPLSG) long-term FU committee can predict the incidence of late effects in the childhood cancer survivors. <Methods> Using a retrospective cohort design, all childhood cancer survivors in the pediatric department of St. Luke's International Hospital between 1972 and 2011 were retrospectively assigned an FU level intensity at the end of treatment. We evaluated the odds ratios (ORs) for late effects at the last observation using uni-variate and logistic regression analyses. <Results> We analyzed 300 cases from 388 survival cases up unitl March 31, 2011, excluding 88 cases because an FU level judgment was impossible. As for hematological cancers: level 3=41%, 4=37%, brain tumors: level 4=100%, solid tumors: level 2=25%, level 3=44%, LCH: level 1=62%, bone and soft tissue tumors were level 3=36%, 4=25%, 5=40%. The cumulated incidence of late effects: level 1 survivors were 0%, level 2 was 15%, level 3 was 37%, level 4 was 72%, level 5 was 100%, respectively. The logistic regression analysis showed that a brain tumor (OR: 65.4), a solid tumor (OR: 3.45), a bone or soft tissue tumor (OR: 10.4), age 26 years or older at the last observation (OR: 6.75), CPM>5 g/m^2 (OR: 5.64), and an allogeneic hematopoietic stem cell transplantation (OR: 10.9) were independent risk factors for late effects. <Conclusion> The JPLSG 5-FU level classification at the end of treatment are useful in the prediction for late effects, and FU plan can be made on a risk by utilizing this classification.

Key words: ???

要　旨

JPLSG長期フォローアップ（FU）委員会の5段階のFUレベルが，晩期合併症発症の予想に役立つかどうか検証した．【対象と方法】研究デザインはレトロスペクティブコホート研究で，対象は1972年から2011年に当院小児科で診療した小児がん症例で治療を終了しているものである．治療終了時FUレベルと最終観察日の晩期合併症について単変量とロジステック解析を行いオッズ比（OR）を求めた．【結果】2011年3月31日の時生存388例で，FUレベル判定不能88例を除き，残り300例を解析した．血液がんではレベル3=41%，4=37%，脳腫瘍はレベル4=100%，固形腫瘍はレベル2=25%，レベル3=44%，LCHはレベル1=62%，骨軟部腫瘍はレベル3=36%，4=25%，5=40%であった．晩期合併症は，レベル1：0%，レベル2：15%，レベル3：37%，レベル4：72%，レベル5：100%で，ロジスティク解析では，脳腫瘍（OR: 65.4），固形腫瘍（OR: 3.45），骨軟部腫瘍（OR: 10.4），最終観察年齢26歳以上（OR: 6.75），CPM>5 g/m^2（OR: 5.64），同種造血細胞移植（OR: 10.9）が晩期合併症の独立したリスク因子であった．【結語】治療終了時の5段階のFUレベル評価は晩期合併症の予測に有用であり，この分類を活用することによりリスクに基づいたFU計画が可能である．

キーワード：小児がん経験者，晩期合併症，予測，フォローアップレベル，リスク

I　はじめに

小児がんの治療成績の進歩は顕著であり，現在では小児がん患児の70%以上が治癒するようになったが，成人がんとは違い身体的・精神的に成長途上に発病するため，疾患のみの影響だけではなく治療の影響を強く受けると考えら

2011年7月15日受付，2011年9月1日受理
* 別刷請求先：〒104-8560 東京都中央区明石町9-1
聖路加国際病院小児科　石田也寸志
E-mail: yaishida@luke.or.jp

表1　JPLSG提案のフォローアップレベル

レベル	分類	対象者	ケアプロバイダー	コンタクト頻度
1	一般的健康管理群	外科手術のみ（頭頚部，胸腹部，四肢）	健康診断医	1/年*
2	経過観察群	低リスクの化学療法を受けた患者 DOX 250 mg/m^{2}未満，かつ CPM 5 g/m^{2}未満，かつ CDDP 300 mg/m^{2}未満，かつ IFO 45 g/m^{2}未満，かつ DEX使用歴なし	家庭医，または長期フォローアップ外来	1/年*
3	標準的FU群	高リスクの化学療法を受けた患者 250 mg/m^{2}以上，あるいは CPM 5 g/m^{2}以上，あるいは CDDP 300 mg/m^{2}以上，あるいは IFO 45 g/m^{2}以上，あるいは DEX使用歴ありを受けた患者 20 Gy未満頭蓋照射患者 自家移植併用大量化学療法（放射線放射線含まない） 頭蓋以外の放射線照射患者	長期フォローアップ外来	1/年*
4	強化FU群	20 Gy以上頭蓋放射線照射患者 同種造血細胞移植を受けた患者 再発治療を受けた患者 遺伝性腫瘍症候群のある患者 脳腫瘍患者 自家血液細胞移植併用大量化学療法（放射線照射を含む）を受けた患者	長期フォローアップ外来	1/年*
5A	要介入群（重篤な病態・全身的問題）	臓器機能障害による社会参加不能患者 臓器機能低下に伴う要生活制限患者 晩期合併症の症状のある患者 晩期合併症に対して治療が必要な患者	長期フォローアップ外来	1/3–6ヶ月
5B	要介入群（疾患特異的な問題）	臓器特異的な外科的治療後のフォローが必要な患者 （例；骨肉腫後の人工関節，網膜芽細胞腫後の義眼）	専門診療科外来	必要時

DOX: Doxorubicin, CPM: Cyclophosphamide, CDDP: Cisplatin, IFO: Ifosfamidem, DEX: Dexamethasone
*；年1回の受診では，受診日を誕生月にするなどの工夫が望まれる．
**；乳児期にanthracyclineの投与を受けた経験者については，強い心機能低下を合併することが知られており，特に注意を要する．

れている[1]．北米CCSS（Childhood Cancer Survivor Study）研究では，経時的な身体的な晩期合併症の累積割合が分析された[2]．それによると身体的な晩期合併症のうち，少なくとも1つの軽度以上の障害は62.3%，医療行為を必要とする重症な障害は27.5%の小児がん経験者でみられ，2つ以上複数の晩期合併症は37.6%でみられた．身体的晩期合併症の30年の累積発症率は軽度以上の障害で73.4%，重症な障害では42.4%にも達し観察期間でプラトーになることはなかった．このことから治療終了後5年経過した時点で晩期合併症がない場合であっても長期フォローアップ（FU）は必須であることが裏付けられた[2]．

著者らは，これまでに青年期から成人期を迎えた本邦の小児がん経験者の晩期合併症とQOLの実態を調査した[3,4]．診断時年齢は経験者では約8歳で，調査時年齢は約23歳であった．原疾患では，造血器腫瘍が129例を占め，固形腫瘍では，神経芽腫11例，脳腫瘍と骨腫瘍が10例ずつであった．治療としては，化学療法98%，放射線60%，手術38%，造血幹細胞移植25%であった[3]．医師記載情報による何らかの晩期合併症は女性50%，男性64%で認められ，内分泌障害，低身長，骨筋肉系，肝機能障害，皮膚・脱毛などが多く認められた[4]．

以上のように，本邦でも欧米の報告[2,5]同様に晩期合併症はまれではないことが知られるようになってきた[6]が，晩期合併症は小児がん経験者すべてに均一なリスクがあるわけではない[7]．リスクに応じてFUの強度を工夫することが，小児がん経験者や家族の心身の負担を減らし，医療経済的にも重要と考えられる．JPLSG長期フォローアップ委員会では，晩期合併症発症のリスクを評価するために表1のような5段階のフォローアップレベルを提案している[8]．

本研究では，この提案されたFUレベルが，過去のコホート症例において晩期合併症をアウトカムとして評価したリスク予想に妥当性を持つかどうか検証するために，FUレベルとアウトカム頻度の相関，個人特性（診断時年齢や性別）とアウトカムとの関連，アウトカムに影響が強い治療因子を検討した．

II　対象と方法

研究デザインは，1病院のレトロスペクティブコホート研究である．

1. 研究対象

発症時年齢が20歳未満で，1972年から2011年に当院小児科に診療録のある小児がん患者のうち，以下の基準を満たすものとした．

1）当院で診断・治療を行ったものまたは長期フォロー

アップ目的で当科に紹介されたもの，2）2011年3月31日までに治療を終了しているもの，除外基準としては，1）セカンドオピニオンのみで受診した症例，

2）2011年3月31日までに死亡が確認されたもの，3）日常生活・合併症に影響する原病と関係のない基礎疾患を有するもの，とした．

2. 検討した項目

1）個人特性：診断時年齢，性別，基礎疾患，2）診断名，病期，再発（有無），3）治療：プロトコール名，手術（有無），放射線（頭蓋照射，それ以外，線量），化学療法（Doxorubicine: DOX, Cyclophospamide: CPM, Cis-platin: CDDP, Ifospamide: IFO, Dexamethasone: DEX—3分割カテゴリカルデータ），造血細胞移植（有無，種類），4）転帰（無病生存，有病生存，死亡），5）カルテで確認された最終観察日．

各項目について，表1に示したJPLSG長期FU委員会提案のFUレベル分類に従い，治療終了時のFUレベルを判定した．

3. アウトカム

FUレベルを調査した担当者とは別に外来担当主治医がアウトカムを判断し分類した．治療終了の時点でのアウトカムとしては，1）晩期合併症は，①特になし，②何らかの症状あり（軽度の臨床症状があるか臨床検査所見の異常のみで治療を要さないもの），③治療の必要あり（何らかの治療・薬物補充を必要とするもの），④不明の4分類で，前記②と③を晩期合併症ありと判定した．2）日常生活については，①特に問題なし，②社会参加困難（日常生活に支障はないが社会生活上何らかの問題を有するもの），③要生活制限（身の回りの日常生活に支障があるもの），④不明の4分類である．また晩期合併症があったものについては，その種類を調査した．

4. 統計学的な方法

性別，現在の年齢，初発時年齢，原疾患（診断病名），化学療法の内容・放射線療法の種類と線量・造血細胞移植の種類（自家・同種）・再発について，晩期合併症をアウトカムとしてオッズ比を算出した．それらのうち，$p<0.2$ のものを説明変数としたロジスティク回帰分析を行い，ステップワイズ変数減少法を用いて独立したリスク因子を解析した．すべての統計解析は，SPSS Statistics Ver. 19 日本語版（日本IBM社，東京）を用いた．

III 結　果

図1に対象症例から解析症例を選択した過程を示した．

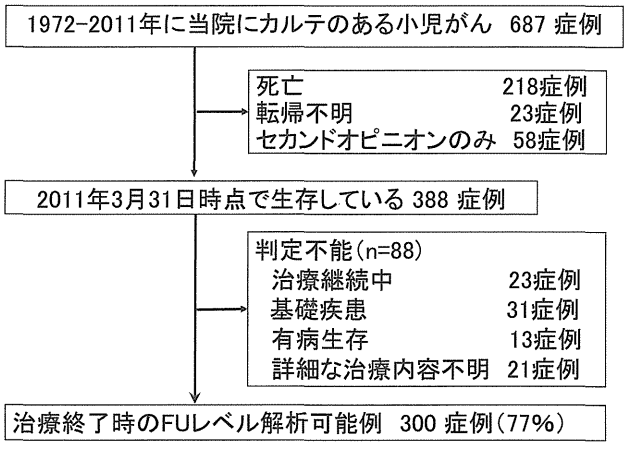

図1　解析症例の選択プロセス

1972–2011年に当院にカルテのある小児がんは687症例であり，死亡例・転帰不明例，セカンドオピニオンのみで受診した症例を除き，2011年3月31日の時点で生存が確認された症例は388例であった．FUレベルが判定不能とした症例は88例であった．その中で判定不能とした基礎疾患としてはダウン症候群12症例，診断時から内分泌障害が存在した3症例，診断時に認められた広汎性発達障害11症例，診断時に認められた内部障害4症例（内訳は心室中隔欠損，QT延長，てんかん，WAGR症候群），その他低出生体重児のため発達遅延を認めた1症例であった．最終的に今回は，300症例（生存例の77%）を対象として以下の解析を行った．

表2に男女別に解析対象疾患の背景を示した．診断時平均年齢は，男女とも約6歳で，解析時の平均年齢は約18歳であった．原疾患の診断名は，急性リンパ芽球性白血病（ALL）が153例で約半数を占め，血液がんが合計で215例（72%）を占めた．脳腫瘍は15例（5%），固形腫瘍は合計48例（16%），ランゲルハンス細胞組織球症（LCH）が13例（4%），骨軟部組織肉腫が20例（7%）であった．病期はIII期あるいは高危険群が約40%を占め，31例（10%）に再発を認めた．治療としては，94例（32%）で手術が行われ，頭蓋照射は59例（23%），頭蓋以外への照射は39例（15%）で施行されていた．化学療法としては，DOXは184/252（73%），CPMは173/248（70%），CDDPは32/253（13%），IFOは23/255（9%），DEXは71/230（31%）で使用されていた．造血細胞移植としては，自家移植が14例（5%），同種移植が34例（11%）施行されていた．疾患や治療の背景に大きな性差はなかった．

表3に原疾患別の治療終了時のFUレベル分類を示した．血液がんでは，レベル3=41%，4=37%，脳腫瘍はレベル4=100%，固形腫瘍はレベル2=25%，レベル3=44%，LCHはレベル1=62%，骨軟部腫瘍はレベル3=36%，4=25%，5=40%であった．図2に治療終了時のFUレベル別に晩期

表2　解析対象症例の背景

	男性（n=164）	女性（n=137）	合計（n=300）
診断時の年齢（平均±標準偏差（中央値））	5.9±4.8（5.0）	6.2±5.1（4.5）	6.0±5.0（5.0）
解析時の年齢#（平均±標準偏差（中央値））	17.5±8.7（17.0）	18.2±9.3（18.0）	17.8±9.0（18.0）
診断名			
急性リンパ芽球性白血病（ALL）	87	66	153
急性骨髄性白血病（AML）	14	10	24
骨髄異形成症候群（MDS）	3	2	5
慢性骨髄性白血病（CML）	2	2	5
非ホジキンリンパ腫（NHL）	10	8	18
脳腫瘍	10	5	15
神経芽腫	10	12	22
網膜芽細胞腫	1	1	2
肝芽腫	0	2	2
Wilms腫瘍	4	6	10
胚細胞腫瘍	4	2	6
その他固形腫瘍	0	6	6
ランゲルハンス細胞組織球症（LCH）	5	8	13
骨肉腫	7	1	8
Ewing肉腫	3	3	5
横紋筋肉腫	4	3	7
病期			
I期あるいは標準危険群	42	40	82
II期あるいは中間危険群	15	23	38
III期あるいは高危険群	67	50	117
IV期あるいは超危険群（HEX）	40	23	63
再発あり *	39	2	31
手術あり *	49/160	45/134	94/294
頭蓋照射なし *	106/140	96/122	202/262
照射線量<20 Gy	16	17	33
照射線量≧20 Gy	18	9	27
頭蓋以外への照射なし *	118/140	108/125	226/265
照射あり	22	17	39
化学療法 *			
Doxorubicin < 250 mg/m^2	74/129	64/123	138/252
≧250 mg/m^2	24/129	22/123	46/252
Cyclophosphamide < 5 g/m^2	57/125	53/123	110/248
≧5 g/m^2	37/125	26/123	63/248
Cisplatin < 300 mg/m^2	3/131	5/122	8/253
≧300 mg/m^2	15/131	9/122	24/253
Ifosfamide < 45 g/m^2	012/131	6/255	18/255
≧45 g/m^2	5/131	0/124	5/255
Dexamethasone使用あり	36/121	35/109	71/230
造血細胞移植なし *	130	119	249/297
自家移植	10	4	14
同種移植	23	11	34

2011年3月31日現在　*に関しては全例調査ができていない項目である（分母に調査症例数を示した）

合併症の有無（症状ありと治療が必要）と社会生活上の問題の有無（生活制限ありと社会参加困難）の割合を示した．レベル1では，晩期合併症は0%であり，レベル2では晩期合併症15%（症状あり13%，治療必要2%），レベル3では晩期合併症37%（症状あり22%，治療必要16%），レベル4では晩期合併症72%（症状あり31%，治療必要41%），レベル5では晩期合併症100%（症状あり55%，治療必要45%）であった．社会生活上の問題に関しては，レベル1と2では0%，レベル3では問題11%（生活制限あり5%，社会生活困難6%），レベル4では問題36%（生活制限あり

表3　原疾患別のフォローアップレベル

	フォローアップレベル				
	1	2	3	4	5
血液がん合計	2（1%）	39（19%）	85（41%）	76（37%）	3（1%）
急性リンパ芽球性白血病（ALL）	0	34（22%）	67（44%）	49（32%）	3（2%）
急性骨髄性白血病（AML）	0	3（12%）	10（42%）	11（46%）	0
骨髄異形成症候群（MDS）	1	1（20%）	0	4（80%）	0
慢性骨髄性白血病（CML）	0	0	0	4（100%）	0
非ホジキンリンパ腫（NHL）	1（6%）	1（6%）	8（44%）	8（44%）	0
脳腫瘍	0	0	0	15（100）	0
固形腫瘍合計	9（19%）	12（25%）	21（44%）	6（13%）	0
神経芽腫	4（18%）	7（32%）	8（36%）	3（14%）	0
網膜芽細胞腫	0	1（50%）	0	1（50%）	0
肝芽腫	0	1（50%）	1（50%）	0	0
Wilms 腫瘍	0	3（30%）	6（60%）	1（10%）	0
胚細胞腫瘍	2（33%）	0	3（50%）	1（17%）	0
その他固形腫瘍	3（50%）	0	3（50%）	0	0
ランゲルハンス細胞組織球症（LCH）	8（62%）	3（23%）	2（15%）	0	0
骨軟部組織腫瘍計	0	1（5%）	6（30%）	5（25%）	8（40%）
骨肉腫	0	0	2（25%）	2（25%）	4（50%）
Ewing 肉腫	0	1（20%）	1（20%）	1（20%）	2（40%）
横紋筋肉腫	0	0	3（43%）	2（29%）	2（29%）
合　計	18（6%）	55（18%）	114（38%）	102（34%）	11（4%）

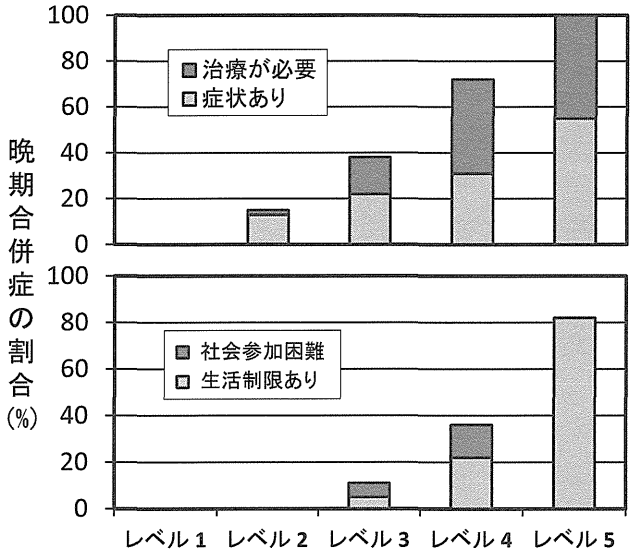

図2　治療終了時FUレベルと晩期合併症

22%，社会生活困難14%），レベル5では問題82%（生活制限あり82%）であった．

表4に晩期合併症（症状ありまたは治療必要）に対する各々のリスク因子について単変量解析でオッズ比（OR）を示した．有意のリスク因子は，診断時12歳以上（OR: 2.95），最終観察年齢26歳以上（OR: 3.46），治療した年が最近のもの（OR: 0.36と0.43），原発疾患としては脳腫瘍（OR: 20.2），骨軟部腫瘍（OR: 7.79），病期II期（OR: 2.50），III期（OR: 7.78），IV期（OR: 7.40），CPM 5 g/m^{2}以上（OR: 3.80），CDDP 300 mg/m^{2}以上（OR: 5.66），IFO使用（OR: 5.75），頭蓋照射20 Gy以上（OR: 3.23），頭蓋以外の照射あり（OR: 9.12），造血細胞移植：自家（OR: 5.09）同種（OR: 3.71），外科手術（OR: 2.34），再発あり（OR: 3.44）であった．

晩期合併症に影響の強い独立したリスク因子を探索するため，ロジッスティク回帰分析を行った結果を表5に示した．最終的なモデルで有意のリスク因子と考えられたのは，脳腫瘍（OR: 65.4），固形腫瘍（OR: 3.45），骨軟部腫瘍（OR: 10.4），最終観察年齢26歳以上（OR: 6.75），CPM>5 g/m^2（OR: 5.64），同種造血細胞移植（OR: 10.9）であった．

IV　考　察

今回のレトロスペクティブな聖路加国際病院小児科症例の解析において，JPLSGの提唱したFUレベルに従って対象症例を5段階に分類した．FUレベル分類別の全体症例分布は，表3に見られたようにレベル1: 6%，レベル2: 18%，レベル3: 38%，レベル4: 34%，レベル5: 4%と正規分布に近い分布を示し，理想的と考えられた．また最も重要な知見は，図2に示したように晩期合併症や社会生活の問題点を有する割合と極めて良い相関が認められ，この治療終了時FUレベル分類が，治療終了後の晩期合併症や社会生活

表4　晩期合併症のリスクに関する単変量解析

リスク候補因子	カテゴリー	症例数	晩期合併症割合	オッズ比（95%CI）	p値
診断時年齢	＜1歳	36	50%	1.71（0.80–3.65）	0.162
	1–5歳	114	37%	1	
	6–11歳	69	39%	1.10（0.60–2.04）	0.757
	12歳以降	49	63%	2.95（1.47–5.91）	0.002
性別	男性	144	47%	1	
	女性	124	41%	0.80（0.49–1.30）	0.375
最終観察年齢	15歳以下	111	34%	1	
	16–25歳	100	44%	1.51（0.87–2.63）	0.147
	26歳以上	56	64%	3.46（1.77–6.78）	＜0.001
治療年	1990年以前	53	62%	1	
	1990–99年	94	37%	0.36（0.18–0.72）	0.004
	2000年以降	121	41%	0.43（0.22–0.83）	0.012
原発腫瘍	血液がん	179	39%	1	
	脳腫瘍	14	93%	20.2（12.59–158）	0.004
	固形腫瘍	44	43%	1.18（0.61–2.31）	0.621
	LCH	13	8%	0.13（0.02–1.02）	0.052
	骨軟部腫瘍	18	83%	7.79（2.20–27.9）	0.002
病期・リスク	I期・標準危険	75	16%	1	0.065
	II期・中間危険	31	32%	2.50（0.94–6.62）	＜0.001
	III期・高危険	109	60%	7.76（3.75–16.0）	＜0.001
	IV期・超危険	53	59%	7.40（3.24–16.9）	＜0.001
Cyclophospamide	なし	68	32%	1	
	＜5 g/m^2	101	31%	0.93（0.48–1.79）	0.820
	≧5 g/m^2	62	65%	3.80（1.84–7.87）	＜0.001
Doxorubicin	なし	66	42%	1	
	＜250 mg/m^2	125	43%	0.81（0.44–1.50）	0.506
	≧250 mg/m^2	45	56%	1.51（0.70–3.24）	0.290
Cisplatin	なし	205	35%	1	
	＜300 mg/m^2	7	71%	4.72（0.89–24.9）	0.068
	≧300 mg/m^2	24	75%	5.66（2.15–14.9）	＜0.001
Ifosphamide	なし	216	36%	1	
	＜45 g/m^2	17	77%	5.75（1.81–18.2）	0.003
	≧45 g/m^2	5	100%	N/A	
Dexamethason	なし	175	41%	1	
	あり	73	42%	1.03（0.57–1.85）	0.924
頭蓋照射	なし	183	38%	1	
	＜20 Gy	31	42%	1.17（0.54–2.53）	0.697
	≧20 Gy	24	67%	3.23（1.31–7.94）	0.011
他部位照射	なし	209	35%	1	
	あり	36	83%	9.12（3.63–22.9）	＜0.001
	不明	19	58%	2.51（0.97–6.51）	0.059
造血細胞移植	なし	230	40%	1	
	自家移植	13	77%	5.09（1.36–19.0）	0.015
	同種移植	24	71%	3.71（1.48–9.30）	0.005
外科手術	なし	177	37%	1	
	あり	86	58%	2.34（1.38–3.95）	0.002
再発	なし	244	41%	1	
	あり	24	71%	3.44（1.38–8.60）	0.008

N/A: not available

表5　晩期合併症のリスクに関する多変量解析（ロジスティック回帰）

リスク因子	カテゴリー	n	多変量オッズ比（95%CI）	p値
原発腫瘍	血液がん	153	Reference	
	脳腫瘍	12	65.4（6.78–631）	<0.001
	固形腫瘍	40	3.45（1.22–9.74）	0.019
	LCH	12	0.70（0.07–6.86）	0.757
	骨軟部腫瘍	14	10.4（2.34–46.5）	0.002
最終観察年齢	15歳以下	99	Reference	
	16–25歳	87	2.18（0.99–4.83）	0.054
	26歳以上	45	6.75（2.70–17.1）	<0.001
CPM	なし	68	Reference	
	<5 g/m	101	1.77（0.69–4.54）	0.234
	≧5 g/m	62	5.64（2.00–15.9）	0.001
造血細胞移植	なし	207	Reference	
	自家移植	9	1.92（0.31–12.0）	0.438
	同種移植	15	10.9（2.44–48.9）	0.002
再発	なし	221	Reference	
	あり	10	4.63（0.83–25.8）	0.080

* Hosmer-Lemeshow（χ^2 乗値 =2.701，p=0.952）

の問題の予測に役立つことが示されたことである．

多変量解析で最終モデルに独立したリスク因子として残ったのは，ORの高い順に，脳腫瘍（65.4），同種造血細胞移植（10.9），骨軟部腫瘍（10.4），最終観察年齢26歳以上（6.75），CPM>5 g/m^2（5.64），固形腫瘍（3.45）であった．興味深かったのは，単変量解析では自家移植の方が同種移植よりもオッズ比が高かったものの，多変量解析では自家移植は有意のリスク因子ではなくなり，同種移植のみがリスク因子として残ったこと，CDDPやIFOなどの抗がん剤，放射線照射や手術，病期・リスク分類，再発などが，最終モデルでは有意なリスク因子としては残らなかったことである．今後はこの結果を参考にして，レベル分けの基準を見直し，もう少しレベル分けをシンプルにすることも可能になるかもしれない．

これまで報告されている小児がん経験者のFUレベル評価としては，表6に示したイギリスのもの[9,10]が最も有名である．Eiserらは，198人の小児がん経験者を分類し，レベル1が8人，レベル2が97人，レベル3は93人であり，7人で分類の不一致症例が認められたと報告している[10]．またEdgarらは2009年のEuropean Symposium on Late Complications after Childhood Cancer（ESLCCC）で575人の分類を試み，レベル1が94人（16%），レベル2が257人（45%），レベル3は224人（39%）であり，平均11.5年後の晩期合併症の累積割合は，レベル1で3%，レベル2で51%，レベル3で93%と報告した[11]．この割合は本研究のJPLSGのレベル分けの結果と類似した結果ではあるが，イギリスの3-レベル分類は内容がシンプルすぎて（しかし逆に評価者の一致率が高いというメリットもある），ほとんどがレベル2か3であり晩期合併症の推定に関してきめ細やかな対応が困難であることが問題と考えられる．またフィラデルフィア小児病院が提唱しているthe intensity of treatment rating scale 2.0（ITR-2）[12]は，原疾患と病期で主に分類しており，分類方法の評価者による一致率などを検討しているが，著者らの調べた限りでまだその晩期合併症予測の有用性を検討した報告は見られず，アウトカムとの関連に関しては妥当性に問題が残る．また本研究の結果では前述したように，多変量解析の結果で病期・リスク分類の有意性が消失し，原疾患の種類と実際に受けた治療内容の方が重要なリスク因子になる可能性が示唆され，原疾患と病期の組み合わせによるITR-2分類よりもJPLSGのレベル分けの方が予測に役立つ可能性が高いと考えられた．

本研究の一番の限界は，解析対象が1施設の現在無病生存している比較的少数例の研究であり，ALLが50%を占め固形腫瘍が少なかったことなど選択バイアスがありえるため結果の一般化が可能かどうか不明な点である．次にレトロスペクティブなコホート研究であり，23例の転帰不明例，21例の詳細な治療内容が不明の症例が存在したことである．またプロスペクティブに計画された研究ではなかったため，Common Terminology Criteria for Adverse Events（CTCAE）を用いて詳細な晩期合併症のgrade分類ができなかった．最後に，解析対象年齢の中央値が17.8歳（診断後約12年）と観察期間が比較的短かったため，今回のJPLSGレベル分けで診断後20年30年経過後の長期の晩期合併症の予測が可能かどうかが不明な点である．

本研究には以上の様な限界はあるものの，長期フォローアップ委員会提案の治療終了時5段階FUレベル評価の妥

表6　既報告のフォローアップレベル分け

	3-Level（英国）	ITR-2（フィラデルフィア）	JPLSG
レベル1	外科手術のみ 低リスク化学療法 例）Wilms 腫瘍の Stage 1/2 LCH（SS 型） 胚細胞腫（手術のみ）	外科手術のみ（脳腫瘍除く） 例）Wilms 腫瘍の Stage 1/2 LCH（SS 型） 胚細胞腫（手術のみ） 神経芽腫（手術のみ） 網膜芽細胞腫（眼球摘出）	外科手術のみ（頭頚部，胸腹部，四肢）
レベル2	通常の化学療法 24 Gy 以下の頭蓋照射 例）多くの小児がん 第一寛解期の ALL	ALL（標準危険群） CML（非移植例） 脳腫瘍（単独治療法） 胚細胞腫（化学療法 / 放射線） 肝芽腫（非転移症例） HL（Stage 1 ～ 3，非 bulk 腫瘍） 神経芽腫（Stage 1/2/4S） NHL（Stage 1 ～ 3） 網膜芽細胞腫（化学療法併用） 横紋筋肉腫（Stage 1/2）	低リスク化学療法を受けた患者 DOX 250 mg/m^2 未満，かつ CPM 5 g/m^2 未満，かつ CDDP 300 mg/m^2 未満，かつ IFO 45 g/m^2 未満，かつ DEX 使用歴なし
レベル3	放射線照射（24 Gy 以下の頭蓋照射以外） 大量療法 例）脳腫瘍 造血細胞移植後 Stage IV の小児がん	再発プロトコール（HL と Wilms の初回再発のみ） ALL（高危険・超危険群） APL 脳腫瘍 Ewing 肉腫 肝芽腫（転移症例） HL（Stage 3B/4B/ 高危険群） JMML（非移植例） 神経芽腫（Stage 3/4，非移植例） NHL（Group C/Stage 4） 骨肉腫 横紋筋肉腫（Stage 3/4） Wilms 腫瘍（Stage 3/4）	高リスク化学療法 250 mg/m^2 以上，あるいは CPM 5 g/m^2 以上，あるいは CDDP 300 mg/m^2 以上，あるいは IFO 45 g/m^2 以上，あるいは DEX 使用歴あり 20 Gy 未満頭蓋照射 自家移植併用大量化学療法（放射線放射線照射患者 頭蓋以外の放射線照射患者
レベル4	—	再発プロトコール（HL と Wilms の初回再発を除く） 造血細胞移植 AML JMML—移植症例	20 Gy 以上頭蓋放射線照射患者 同種造血細胞移植を受けた患者 再発治療を受けた患者 遺伝性腫瘍症候群のある患者 脳腫瘍患者 自家血液細胞移植併用大量化学療法（放射線照射を含む）を受けた患者
レベル5A	—	—	社会参加不能患者 要生活制限患者 晩期合併症の症状のある患者 晩期合併症に対して治療が必要
レベル5B	—	—	臓器特異的な外科的治療後のフォローが必要な患者（例；骨肉腫後の人工関節，網膜芽細胞腫後の義眼）
設定根拠	使われた治療法	原疾患と病期	詳細な治療内容 一部原疾患を活用

LCH: Langerhans cell histiocytosis, ALL: acute lymphoblastic leukemia, CML: chronic myeloid leukemia, HL: Hodgkin lymphoma, NHL: non-Hodgkin lymphoma, APL: acute promyelocytic leukemia, JMML: juvenile myelomonocytic leukemia, DOX: Doxorubicin, CPM: Cyclophosphamide, CDDP: Cisplatin, IFO: Ifosfamide, DEX: Dexamethasone

当性を初めて検証し，この分類が晩期合併症発症の予測に有用であり，これを活用することによりリスクに基づいたFU計画が可能なことが示唆された意義は大きいと考えている．今後多施設共同研究を行い，結果の妥当性と一般化可能性を検証していく予定である．

本研究は，平成23・24年度厚生労働科学研究費補助金（がん臨床研究事業）「小児がんの罹患数把握および晩期合併症・二次がんの実態把握のための長期フォローアップセンター構築に関する研究」（研究代表者：黒田達夫）および平成24年度厚生労働科学研究費補助金（がん臨床研究事業）「小児造血器腫瘍に対する標準治療・診断確立のための研究」（研究代表者：堀部敬三）の補助を受けた．

謝　辞

本研究のデータ収集に際して協力をいただいた聖路加国際病院小児医療センターの下平友紀恵さんと井上真紀子さんに深謝します．英文抄録の校閲に関しては，聖ルカ・ライフサイエンス研究所臨床疫学センター客員研究員のDeshpande GA先生に深謝します．

文　献

1）JPLSG 長期フォローアップ委員会監訳：小児がん経験者の長期フォローアップ．日本医学館，東京，2008.
2）Oeffinger KC, Mertens AC, Sklar CA, et al: Chronic health conditions in adult survivors of childhood cancer. N Engl J Med, 355: 1572–1582, 2006.
3）石田也寸志，本田美里，上別府圭子，他：小児がん経験者の晩期合併症およびQOLの実態に関する横断的調査研究　第1報．日本小児科学会雑誌，114: 665–675, 2010.
4）石田也寸志，大園秀一，本田美里，他：小児がん経験者の晩期合併症およびQOLの実態に関する横断的調査研究　第2報．日本小児科学会雑誌，114: 676–686, 2010.
5）Geenen MM, Cardous-Ubbink MC, Kremer LC, et al: Medical assessment of adverse health outcomes in long-term survivors of childhood cancer. JAMA, 297: 2705–2715, 2007.
6）Miyoshi Y, Ohta H, Hashii Y, et al: Endocrinological analysis of 122 Japanese childhood cancer survivors in a single hospital. Endocr J, 55: 1055–1063, 2008.
7）Hudson MM, Mulrooney DA, Bowers DC, et al: High-risk populations identified in Childhood Cancer Survivor Study investigations: implications for risk-based surveillance. J Clin Oncol, 27: 2405–2414, 2009.
8）石田也寸志：小児がん経験者の長期フォローアップ，堀部敬三（編）：小児がん診療ハンドブック　医薬ジャーナル社．大阪，2011, 46–56.
9）Wallace WH, Blacklay A, Eiser C, et al: Developing strategies for long term follow up of survivors of childhood cancer. BMJ, 323: 271–274, 2001.
10）Eiser C, Absolom K, Greenfield D, et al: Follow-up after childhood cancer: evaluation of a three-level model. Eur J Cancer, 42: 3186–3190, 2006.
11）Edgar AB, Harrison S, Kelly S-L, et al: Intensity of Long Term Follow Up for Survivors of Childhood Cancer can be Safely Determined by Therapy-based Risk-stratification, ESLCCC09. Edinburgh 2009, pp. 65.
12）Werba BE, Hobbie W, Kazak AE, et al: Classifying the intensity of pediatric cancer treatment protocols: the intensity of treatment rating scale 2.0 (ITR-2). Pediatr Blood Cancer, 48: 673–677, 2007.

PEDIATRICS INTERNATIONAL Official Journal of the Japan Pediatric Society

Pediatrics International (2012) **54**, 663–668 doi: 10.1111/j.1442-200X.2012.03633.x

Original Article

Job discrimination against childhood cancer survivors in Japan: A cross-sectional survey

Keiko Asami,[1] Yasushi Ishida[2] and Naoko Sakamoto[3]

[1]*Department of Pediatrics, Niigata Cancer Center Hospital, Niigata,* [2]*Department of Pediatrics, St. Luke's International Hospital and* [3]*Department of Epidemiology, National Research Institute for Child Health and Development, Tokyo, Japan*

Abstract ***Background***: The aim of this study was to investigate the policies to identify job discrimination by company recruiters against childhood cancer survivors in Japan.

Methods: We conducted a cross-sectional study using a mailed questionnaire for the Japanese companies that were divided into three groups: companies listed on the stock market, companies not listed on the stock market, and public offices. We randomly selected 2000 of the 4000 listed companies and 2500 of the 4300 unlisted companies. We selected 47 public offices from prefectures and 17 from government ordinance-designated cities. Outcomes were health certificate requirements, how to treat past medical history and present illness, childhood cancer survivors' employment experience, and company's policy for evaluating applicants based on past medical history and present illness.

Results: Response rates were 17.7% for listed companies, 28.9% for unlisted companies, and 56.3% for public offices. A health certificate was required by 86% of listed companies, 77% of unlisted companies, and 75% of public offices. However, 33% of listed companies and 36% of unlisted companies, and none of the public offices demanded it at the time of application. Small numbers of private companies (0.7% of listed companies and 1.0% of unlisted companies) and public offices (4%) reject applicants outright if they have a disease in their past medical history. Using multivariate analysis, we found that large companies and company policies were significantly associated with the demand for a health certificate at the time of job applications.

Conclusions: In Japan, employment-related discrimination still occurs in a small number of companies and public offices.

Key words childhood cancer, health certificate, long-term survivors, job application, social discrimination.

Introduction

Because of advances in treatment, between 70% and 80% of children diagnosed with cancer become long-term survivors. In Japan, the estimated number of pediatric cancer survivors is over 50 000: approximately one out of every 700 adults between the ages of 20 and 39 years. Although an increased number of children have been cured of cancer, many survivors experience various health problems later in life because of their treatments.[1,2] In addition to various physical problems in childhood cancer survivors (CCS),[3] future social outcomes, including marriage, education, and employment, are apparently affected by these late effects, both directly and indirectly. In addition, the CCS have made many efforts to attain educational/ vocational goals; however, a significant proportion of CCS remains at increased risk of developing poor social outcomes and quality of life.[4]

Many articles have noted discrimination against adult cancer survivors in obtaining employment appropriate to their abilities and training or returning to their previous jobs.[5–8] Among CCS, these problems are more complicated, as nearly all CCS have no employment experience before the onset of cancer. These CCS generally have more easily recognizable work-related limitations at the time of their employment examinations than adult cancer survivors do.[9] Many CCS have problems even filling out job applications, and their reactions to employment examinations are far more variable than the reactions of adult cancer survivors are (Asami and Ishida, unpublished data). However, the extent to which CCS in Japan have suffered from job discrimination remains to be determined. In this article, we investigate the policies of private companies and public offices to identify the extent of job discrimination against CCS in Japan by company recruiters.

Correspondence: Yasushi Ishida, MD, St. Luke's International Hospital, Department of Pediatrics, 9-1 Akashi-cho, Chuo-ku, Tokyo 104-8460, Japan. Email: yaishida@luke.or.jp

Received 25 January 2012; accepted 15 March 2012.

Methods

Study design and companies selection

In 2009, we performed a cross-sectional survey using a questionnaire (see Supplemental Appendix 1). The companies were divided into three groups: companies listed on the stock market, companies not listed on the stock market, and public offices. We randomly selected 2000 of the 4000 listed companies and 2500 of

the 4300 unlisted companies in the Japan company handbook *Kaisyasikihou*. We selected 47 public offices from prefectures and 17 from government ordinance-designated cities. Public servants were classified into four groups: general desk workers, schoolteachers, police officers, and medical service providers. We sent a questionnaire to the personnel department of each company or public office under the auspices of the Japanese Ministry of Health, Labour and Welfare with a request that it be filled out and returned anonymously. If the company wanted our report on the survey, we asked them to enclose their company's name and address separately.

Measurement of variables

The questionnaire consisted of 13 items, with four items (question [Q] 4–6, Q12) that included free writing. We evaluated health certificate requirements (Q1 and Q2), how past medical history and present illness are treated (Q3–Q6), employment experience of CCS (Q7), company's policy for evaluating applicants based on past medical history and present illness (Q8), and company's background (Q9–Q11). For Q4 through Q6, free writing sentences were classified using content analysis by two independent researchers and classified into seven answer types: (answer [A] 1) past medical history does not matter (hiring is based on job performance); (A2) if the disease has been cured, it does not matter; (A3) hiring will depend on a physician's determination; (A4) it depends on the applicants (case by case); (A5) hiring will depend on the state of the disease; (A6) hiring will depend on the applicant's performance during the trial period; and (A7) we are concerned that the disease will recur.

Each company was categorized as belonging to a primary, secondary, or tertiary sector of industry. Further, the company's size was classified on the basis of the number of regular workers, with each classified as either a large company (500 workers or more) or a small or intermediate company (fewer than 500 workers). Companies were also classified by location based on whether or not they were located in Kanto District.

Ethics

The study was performed following approval from the ethics committee of the principal investigator's institution (K. Asami, Niigata Cancer Center Hospital).

Statistical analysis

We performed χ^2-tests (or Fisher's exact tests for cells with expected counts of <5) within categorical predictors. We explored the association features of the companies that require a health certificate at the time of the job application limited to private companies. The adjusted odds ratios for the interesting outcome were estimated with logistic regression analysis. As predictors we assessed various typical features of companies; type of stocks, type of business, company sizes, location of the head office, and companies' experience of CCS employment and their policy. Data were analyzed with SPSS software, v. 19.0 (IBM Japan, Tokyo, Japan).

Results

The demographic data of the companies are shown in Supplemental Appendix 2. Completed questionnaire sheets were returned by 354 listed companies (a 17.7% response rate), 720 unlisted companies (28.9%) and 36 public offices (56.3%). Most companies belonged to the secondary or tertiary sector of industry (140:162 in listed companies and 296:343 in unlisted companies, respectively). The number of regular workers in a company depended largely on whether the company was listed or unlisted ($P < 0.001$). The proportion of large companies (500 workers or more) was 48% in listed and 24% in unlisted companies ($P < 0.001$). Many head offices of listed and unlisted companies were located in Kanto (around Tokyo). The distribution of locations of head offices was significantly different between private companies and public offices ($P < 0.001$).

Table 1 shows the main results of this survey (Q0 through Q8). Fifty-seven (16.2%) of the 352 listed companies and 72 (10.1%) of the 716 unlisted companies indicated that they were unable to answer our questions because of confidentiality issues; this difference was significant ($P = 0.004$). Health certificates were required by 86% of listed companies, 77% of unlisted companies, and 75% of public offices. Health certificates were required at the time of application by 33% of listed companies, 36% of unlisted companies, and none of the public offices. This difference between private companies and public offices was significant ($P < 0.001$). Small numbers of private companies (0.7% of listed companies and 1.0% of unlisted companies) and public offices (4%) reject applicants after reviewing their application or because of their internal rules if the applicant listed a disease in his or her past medical history (Q3). Only three private companies had policies in the relevant rule for applicants who listed childhood cancer or other diseases in their past medical history; in contrast, 43% of public offices had pertinent policies (Q4 and Q5). Surprisingly none of the public offices answered definitely that they have ever employed a former childhood cancer patient (Q7). About 40% of private companies (both listed and unlisted) answered that the present illness of applicants is more important than the past history (Q8).

We explored the typical associated characteristics of the companies that require a health certificate at the time of the job application (Table 2). A univariate analysis showed that company size, the importance of past medical history, and company policy for dealing with present illness and past medical history were strongly associated with the demand for a health certificate at the time of the job application. Logistic regression analysis revealed that large companies (500 or more workers) and companies with policies in effect (companies that answered that both present illness and past medical history are important) were significantly more likely to require a health certificate at the time of the job application.

We compared the answers among four kinds of jobs in public offices in Table 3. There were no differences in many questions. However, health certificates were required at the time of application in medical service providers alone ($P = 0.004$).

Table 1 Comparison between listed companies and unlisted companies and between private companies and public offices

	Listed companies (n = 354)	Unlisted companies (n = 720)	Listed vs unlisted (P-value)	Public offices (n = 36)	Private companies vs public offices (P-value)
Q0 Can you publicly answer the following questions?					
1. No	57 (16%)	72 (10%)	0.004		
Q1 Do you require a health certificate at the time of employment testing?					
1. Yes	259 (86%)	493 (77%)	0.002	27 (75%)	0.522
Q2 If so, when do you require it?	(n = 258)	(n = 489)		(n = 27)	
1. At the time of application	85 (33%)	178 (36%)	0.496	0	<0.001*
2. After hiring	128 (50%)	225 (45%)		5 (19%)	
3. It depends (case by case)	45 (17%)	96 (19%)		22 (81%)	
Q3 What are your thoughts when an applicant lists a disease in his or her past medical history?					
1. Past medical history does not matter	108 (39%)	276 (40%)	0.098	4 (15%)	<0.001
2. It depends (case by case)	107 (38%)	172 (25%)		16 (62%)	
3. It depends on desired sections	36 (13%)	68 (10%)		0	
4. It depends on the disease	61 (22%)	123 (18%)		1 (4%)	
5. The decision is entrusted to the interviewers	8 (3%)	28 (4%)		1 (4%)	
6. The applicant will be rejected after being reviewed	0	2 (0.3%)		0	
7. The applicant will be rejected because of the company's internal rules	2 (0.7%)	5 (0.7%)		1 (4%)	
8. Others	8 (3%)	16 (2%)		5 (19%)	
Q4 How would you respond if an applicant has listed childhood cancer in his or her past medical history?					
1. Yes, we have a rule	0	3 (0.4%)	0.061*	15 (43%)	<0.001*
2. No, we don't have a rule	172 (49%)	300 (42%)		10 (29%)	
3. No comment	180 (51%)	413 (58%)		10 (29%)	
Q5 How would you respond if an applicant has listed a disease other than childhood cancer in his or her past medical history?					
1. Yes, we have a rule	0	3 (0.4%)	0.042*	15 (43%)	<0.001*
2. No, we don't have a rule	173 (49%)	299 (42%)		10 (29%)	
3. No comment	179 (51%)	414 (58%)		10 (29%)	
Q6 How would you respond if an applicant were a childhood cancer patient?					
1. Yes, we have a rule	0	3 (0.4%)	0.499*	12 (34%)	<0.001*
2. No, we don't have a rule	253 (72%)	528 (74%)		18 (49%)	
3. No comment	99 (28%)	185 (26%)		5 (17%)	
Q7 Have you ever employed a former childhood cancer patient?					
1. Yes	2 (0.7%)	3 (0.5%)	0.001*	0	0.002*
2. No	45 (15%)	158 (25%)		0	
3. Not sure	253 (84%)	479 (75%)		32 (100%)	
Q8 What is your policy on the past medical history and present illness of applicants?					
1. Present illness is important	126 (42%)	264 (41%)	0.982*	0	<0.001*
2. Past history is important	0	1 (0.2%)		0	
3. Both are important,	51 (17%)	112 (18%)		5 (17%)	
4. It depends (case by case)	121 (41%)	260 (41%)		25 (83%)	

*Fisher's exact test.

Figure 1 shows the detailed answers for Q4, Q5, and Q6. Q4 focused on treatment of childhood cancer in the past. Q5 focused on treatment of some childhood disease other than cancer in the past. Q6 focused on treatment of workers who turned out to be childhood cancer survivors after hiring. All three groups surveyed showed the same tendency in their answers. In the listed company and public office groups, A1 (past medical history does not matter) and A4 (case by case) were the main answers, while A1 (hiring is based on job performance) was predominant in the unlisted company group. In addition, A3 (hiring will depend on a physician's determination) was also more common in the public office group. Of note was that neither A2 (if the disease has been cured, it does not matter) nor A5 (hiring will depend on the state of the disease) existed exclusively in the public office group.

Discussion

In this survey of Japanese companies, we found that a very small number of private companies or public offices would reject applicants on the basis of their history of cancer. Although large companies and the companies in effect (companies that answered that both present illness and past medical history are important) were significantly more likely to demand a health certificate at the time of the job application.

In our study there were significant varieties in company size and location of head offices among three groups. The Kanto district is located around Tokyo, in which most of the social rules are expected to be standardized, but the difference was marginal, as shown in Table 2. It is noteworthy that a substantial proportion of private companies (16% of the listed companies and 10% of

Table 2 Typical features of the companies that required health certificate at the time of application

	Required at application		χ^2/Fisher (*P*-value)	Logistic regression analysis	
	Yes	No		Odds ratio (95%CI)	*P*-value
Type of stock					
Listed companies	64 (37%)	223 (29%)	0.151	1.03 (0.69–1.52)	0.896
Unlisted companies	111 (63%)	498 (71%)		Reference	
Q9 Type of business					
Primary sector (A1–A3)	0	1 (0.1%)	0.288 (0.291*)	–	
Secondary sector (A4–A6)	88 (51%)	319 (45%)		1.12 (0.78–1.60)	0.550
Tertiary sector (A7–A20)	86 (49%)	396 (55%)		Reference	
Q10 Company size					
Less than 500 workers (A7–A8)	88 (51%)	519 (72%)	<0.001	Reference	
500 or more workers (A1–A6)	86 (49%)	201 (28%)		2.66 (1.81–3.90)	<0.001
Q11 Location					
Kanto (A3)	78 (45%)	363 (50%)	0.180	0.73 (0.51–1.05)	0.094
Non-Kanto (not A3)	96 (55%)	356 (50%)		Reference	
Q3 Importance of past history					
Past medical history does not matter (A1)	46 (26%)	331 (49%)	<0.001	0.73 (0.26–2.08)	0.554
It depends (A2–A4)	117 (67%)	315 (46%)		1.52 (0.56–4.15)	0.412
The decision is entrusted to interviewers (A5)	8 (5%)	28 (4%)		0.83 (0.32–2.15)	0.697
The applicant will be rejected (A6,A7)	4 (2%)	5 (1%)		2.39 (0.56–10.2)	0.241
Q7 Employment experience of the childhood cancer survivors					
No (A2)	48 (28%)	151 (21%)	0.063	Reference	
Not sure (A3)	125 (72%)	562 (79%)		0.78 (0.51–1.20)	0.250
Q8 Companies' policy of dealing with present illness and past history					
Present illness is very important (A1)	65 (38%)	312 (44%)	<0.001 (<0.001*)	Reference	
Past medical history is very important (A2)	1 (0.6%)	0		–	
Both are very important (A3)	58 (33%)	102 (14%)		2.06 (1.30–3.28)	0.002
It depends (case by case) (A4)	50 (29%)	299 (42%)		0.85 (0.55–1.30)	0.444

*Fisher's exact test.

the unlisted companies) indicated that they were unable to answer our questions on employment policy because of confidentiality issues.

It is a considerable problem that about one-third of private companies demand health certificates at the time of job application and small numbers of private companies as well as public offices reject applicants after reviewing their application or because of their internal rules if the applicant listed a disease in his or her past medical history in Table 1. In Japan, the Ministry of Health, Labour and Welfare prohibits companies from using an applicant's health certificate for his or her employment test and recommends using it instead for appropriate assignment after hiring.[10] Logistic regression analysis demonstrated that large companies (500 or more workers) and companies with policies in effect (companies that answered that both present illness and past medical history are important) were significantly more likely to require a health certificate at the time of the job application. The Kanto head offices made a marginal negative effect on it.

In Figure 1, it is interesting that A1 (hiring is based on job performance) was the predominant answer in the unlisted company group, which suggests that job performance by itself is crucial for the unlisted companies. On the other hand, A4 (case by case) was the main answer in the listed companies and public offices. In addition, it is also interesting that they might avoid the absolute evaluation like A2 (if the disease has been cured, it does not matter) or A5 (hiring will depend on the state of the disease) in the public office group.

Employment outcomes can be improved with improved quality of medical treatment and with clinical and supportive services designed for better management of symptoms, rehabilitation, and reasonable accommodation for disabilities.[8,11] In the USA, employment-related discrimination was, at one time, rather common.[5,8] However, four federal laws now provide some job protection to cancer patients and survivors:[8] the Americans with Disabilities Act (ADA), the Federal Rehabilitation Act, the Family and Medical Leave Act (FMLA), and the Employee Retirement and Income Security Act (ERISA).[9] If a cancer survivor needs extra time or help to do his or her job, the ADA requires the employer to provide a "reasonable accommodation," which may involve a change in working conditions, including hours or duties.

In adult cancer survivors, the inability to return to work after cancer treatment, frequent or prolonged work absenteeism, or problems with work performance may have a substantial economic impact on the survivor and his or her family.[12,13] Work changes also may have a substantial impact on self-esteem, quality of life, and social and family roles. De Boer *et al.*[14] conducted a meta-analysis and found that cancer survivorship was associated with unemployment, as cancer survivors were more likely to be unemployed than healthy control participants were (33.8% vs 15.2%; pooled relative risk [RR], 1.37; 95% confidence interval [CI], 1.21–1.55). Survivors (10.4%) reported health-related unemployment more often than their siblings did (1.8%; RR, 6.07; 95%CI, 4.32–8.53). In the same manner, the Childhood Cancer Survivors Study showed that CCS (5.7%) were more likely to

Table 3 Four kinds of jobs in public offices

	General desk workers (n = 35)	Schoolteachers (n = 35)	Police officers (n = 35)	Medical service providers (n = 35)	χ^2/Fisher (P-value)
Q1 Do you require a health certificate at the time of employment testing?					
1. Yes	27 (75%)	24 (89%)	26 (77%)	28 (85%)	0.900
Q2 If so, when do you require it?					
1. At the time of application	0	0	0	4 (14%)	0.004*
2. After hiring	5 (19%)	9 (38%)	1 (4%)	5 (18%)	
3. It depends (case by case)	22 (81%)	15 (62%)	25 (96%)	19 (68%)	
Q3 What are your thoughts when an applicant lists a disease in his or her past medical history?					
1. Past medical history does not matter	4 (15%)	10 (42%)	3 (11%)	4 (14%)	0.461
2. It depends (case by case)	16 (62%)	9 (38%)	19 (68%)	16 (55%)	
3. It depends on desired sections	0	0	0	1 (3%)	
4. It depends on the disease	1 (4%)	3 (13%)	2 (7%)	1 (3%)	
5. The decision is entrusted to the interviewers	1 (4%)	0	2 (7%)	2 (7%)	
6. The applicant will be rejected after being reviewed	0	0	0	0	
7. The applicant will be rejected because of the company's internal rules	1 (4%)	0	1 (4%)	1 (4%)	
8. Others	5 (19%)	4 (17%)	4 (14%)	6 (21%)	
Q4 How would you respond if an applicant has listed childhood cancer in his or her past medical history?					
1. Yes, we have a rule	15 (43%)	14 (40%)	15 (43%)	15 (43%)	0.999
2. No, we don't have a rule	10 (29%)	11 (31%)	10 (29%)	10 (29%)	
3. No comment	10 (29%)	10 (29%)	10 (29%)	10 (29%)	
Q5 How would you respond if an applicant has listed a disease other than childhood cancer in his or her past medical history?					
1. Yes, we have a rule	15 (43%)	14 (40%)	15 (43%)	15 (43%)	0.999
2. No, we don't have a rule	10 (29%)	11 (31%)	10 (29%)	10 (29%)	
3. No comment	10 (29%)	10 (29%)	10 (29%)	10 (29%)	
Q6 How would you respond if an applicant were a childhood cancer patient?					
1. Yes, we have a rule	12 (34%)	12 (34%)	11 (31%)	13 (37%)	0.994
2. No, we don't have a rule	18 (51%)	17 (49%)	18 (51%)	18 (51%)	
3. No comment	5 (14%)	6 (17%)	6 (17%)	4 (11%)	
Q7 Have you ever employed a former childhood cancer patient?					
1. Yes	0	0	0	0	0.045*
2. No	0	5 (19%)	2 (6%)	2 (6%)	
3. Not sure	32 (100%)	21 (81%)	30 (94%)	29 (94%)	
Q8 What is your policy on the past medical history and present illness of applicants?					
1. Present illness is very important	0	3 (13%)	2 (7%)	2 (7%)	0.177*
2. Past history is very important	0	1 (4%)	0	0	
3. Both are very important,	5 (17%)	2 (8%)	9 (31%)	5 (17%)	
4. It depends (case by case)	25 (83%)	18 (75%)	18 (62%)	23 (77%)	

*Fisher's exact test.

report that they were unemployed and seeking work than siblings were (2.7%; RR, 1.90; 95%CI, 1.43–2.54).[15]

Our previous study also showed a high unemployment rate (from 5% to 9%) among CCS, with some late effects experienced after receiving stem cell transplantation or radiotherapy.[4] This is important, as Japan's national healthcare and social support systems must address these groups of CCS. High-risk CCS may need specific vocational assistance before they can apply for jobs.[16] While the Children's Cancer Association of Japan (http://www.ccaj-found.or.jp/english/) now tries to provide assistance and job training to CCS, more effective job training systems for CCS are still needed.[17]

The limitations of our study include the potential for selection bias despite the use of random sampling because response rates were relatively low, especially from listed companies (those with a stronger interest in the topic may have been more likely to respond to our survey). In fact, it is highly possible that the data presented here are an underestimate of discrimination rates. It is possible that companies who chose not to respond were more likely to have discriminatory policies. Second, our results were reliant on companies' statements. It is important to note that this study assessed formal company policy regarding this issue, rather than what actually occurs in the real workplace (which might be quite different). Thus, these results may not represent what actually occurs. Nonetheless, our report fills a gap between Japan and Western countries, and it is valuable because it is the first survey on job discrimination against CCS in Japan.

Conclusions

A health certificate was required by 33% of listed companies, 36% of unlisted companies, and none of the public offices at the time of job application. Small numbers of private companies (0.7% of listed companies and 1.0% of unlisted companies) and public offices (4%) reject applicants outright if they have a disease in their past medical history. Our study revealed that employment-related discrimination still takes place in a small