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原著

Applying a Self-administered Neurocognitive Questionnaire (CCSS-NCQ) to Japanese Childhood Cancer Survivors

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本邦の小児がん経験者における主観的認知機能尺度 (CCSS-NCQ) の適用

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[Abstract]

Background: While the life expectancy of childhood cancer has improved dramatically, late complications, particularly neurocognitive dysfunction has a profound impact on the life of childhood cancer survivors (CCS) in later years. The Childhood Cancer Survivor Study-Neurocognitive Questionnaire (CCSS-NCQ) developed by St. Jude Children's Research Hospital in the United States is a self-administered scale for screening daily difficulties regarding Organization, Emotional Regulation, Memory, and Task Efficiency. In this study, we aimed to apply the "CCSS-NCQ Japanese Version" to Japanese CCS and evaluated its reliability. **Method:** All cancer types were included, aged 10 years and older were asked to complete a 33-question self-administered questionnaire via paper-based or online survey. **Results:** In total, 123 responses were collected, with male 50.4%, with the mean age of 21.6 ± 8.5 years old, the mean age at diagnosis of 8.5 ± 4.8 years old, and 42.3% diagnosed with Central Nervous System tumors, 38.2% with hematological malignancy, and 13.0% with solid tumors. Factor analysis showed Cronbach's alpha of 0.842-0.918. **Conclusion:** The reliability of the CCSS-NCQ Japanese version was observed. Further validation is needed to investigate if the Japanese CCSS-NCQ is four-factor structured as the original version. With further verification of the scale, the use of it is expected to facilitate the detection of neurocognitive dysfunction affecting the daily lives of CCS. This standardized, validated, self-reported measure is expected to lead to the referral of CCS with high scores for formal neurocognitive assessments and establishment of a system to provide appropriate evidence-based educational and vocational support.

[Key words] Childhood Cancer, Late complications, Neurocognitive dysfunction, CCSS-NCQ Japanese Version, Questionnaire

[要旨]

背景: 小児がん治療後の認知機能障害を含む晩期合併症は小児がん生存者 (CCS) の青年期以降に大きな影響を及ぼしている。CCSS-NCQは、組織化、感情統制、記憶、作業効率における日常的困難を抽出する自記式質問票である。本研究では日本版CCSS-NCQを日本人CCSに適用し、その信頼性を評価する。**方法:** 全がん種の10歳以上のCCSが、紙面またはオンラインにて33問の日本版CCSS-NCQに回答した。**結果:** 回答者123名のうち男性50.4%、平均年齢 21.6 ± 8.5 歳、平均診断時年齢 8.5 ± 4.8 歳、診断は中枢神経系腫瘍42.3%、造血器腫瘍38.2%、固形腫瘍13.0%、因子分析にてCronbach α は0.842-0.918であった。結

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語：日本版CCSS-NCQの信頼性は示された。本質問票の検証を進め、認知機能障害のスクリーニングとして確立すれば、得点に応じた支援の検討が可能になると考える。

〔キーワード〕 小児がん, 晩期合併症, 認知機能障害, 日本版CCSS-NCQ, 質問票

I. INTRODUCTION

1. Background Information

The number of new cases of childhood cancer is about 2,000 - 2,500 annually in Japan¹⁾, and the long-term survival rate has improved dramatically worldwide within half a century largely driven by improvements and development of cancer treatments. According to the latest statistic review, the 5-year overall survival rate of Childhood Cancer Survivors (CCS) has reached 80%²⁾. However, late complications, including secondary cancers, organ dysfunction, endocrine abnormalities, metabolic disorders, neurocognitive dysfunction, due to the cancer itself or treatment toxicity can significantly impair patients' health-related quality of life (QOL). Neurocognitive dysfunction in particular is reported among as high as 40% of childhood cancer survivors³⁾. It is also acknowledged that advanced physiologic aging in adult survivors of childhood cancer is accompanied by a decline in neurocognitive function and structural brain characteristics that may be suggestive of early-onset dementia⁴⁾. This places additional emphasis on the importance of screening and timely intervention of neurocognitive dysfunction given the continual risk imposed on CCS⁵⁾.

The definition of neurocognitive function includes concepts such as memory, organization/planning, cognitive flexibility, and inhibitory control. Cognitive domains in a neuropsychological examination typically assessed include language, concentration, visuospatial perception and constructional abilities, executive functions, verbal and nonverbal learning, and memory. Findings from a neuropsychological examination can help to highlight areas of functional strengths and weaknesses that may have focal or lateralizing significance. A neuropsychological evaluation is therefore considered an essential component in the diagnosis, treatment planning, and care of patients with suspected congenital or acquired brain dysfunction. Neurocognitive function can be impaired by multiple causes such as drugs, aging, neurodegenerative

disorders, serious infections, and head trauma. For CCS in particular, the effects of radiation therapy to the brain, intracranial surgery, intravenous administration of anticancer drugs affecting the central nervous system, and direct intrathecal administration of anticancer drugs have been associated with risk of neurocognitive dysfunction⁶⁾.

It is also known that many of childhood cancers occur before the age of five¹⁾, which means that the favorable timing for the onset of childhood cancer overlaps with the timing of neurocognitive development. In other words, having childhood cancer during this period raises concerns about the impact on neurocognitive functions during development^{6, 7)}. Humans acquire higher brain functions as a result of normal development of neurocognitive functions to be able to lead a social life independently.

QOL has increased in priority. The definition of "health", a keyword in the WHO concept of health, is "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity"⁸⁾. From this perspective, it is not difficult to appreciate that having neurocognitive dysfunction as a result of childhood cancer can be a significant barrier in the pursuit of "health" in life due to its adverse impact on achievement of expected societal milestones during adulthood⁹⁾.

It is concerning that there is no validated measure to evaluate the impact of the adverse effects of cancer treatment on Japanese CCS's neurocognitive function at present. This may be because it has not been long since the concept of late complications was introduced to Japan, and the concept of neurocognitive dysfunction has not yet widely been accepted. In clinical practice, some patients exhibit neurocognitive decline after brain tumor treatment, compared with before diagnosis¹⁰⁾. Referrals to psychologists for neurocognitive testing, education of school staff about the condition of CCS, and referrals to resources by social workers are becoming needed. However, the absence of a measurement tool makes it difficult to assess neurocognitive function appropriately, and thus to

provide evidence-based support. The establishment of measures to assess neurocognitive function will lead to provisions for the support of functional weaknesses for CCS with difficulties due to neurocognitive dysfunction.

For example, it has been reported that memory and other areas of cognitive function are commonly impaired among CCS⁶⁾. It is not difficult to imagine that the adverse effects of impaired memory may deeply affect later life. The Wide Range Assessment of Memory and Learning (WRAML) by Sheslow & Adams in 1990 was rated as a well-established measure of testing memory in a previous report. However, this measure of the WRAML is limited in its ability to document meaningful change in test performance over time. Furthermore, memory deficits would not be the only and main reason why CCS may have difficulties later in life. Considering the actual difficulties in life, the memory scale alone is considered insufficient. In order to live as a member of society, in addition to IQ and memory, factors such as emotional regulation and executive function are important as well.

In a previous report of the Childhood Cancer Survivor Study (CCSS), the largest cohort study of childhood cancer patients in the world assembled by St. Jude Children’s Research Hospital, four major areas of neurocognitive dysfunction were observed among CCS including memory, Task Efficiency, Organization, and Emotional Regulation (Figure1).

The Childhood Cancer Survivor Study- Neurocognitive Questionnaire (CCSS-NCQ) was developed and validated by Dr. Kevin R. Krull in 2008, to evaluate self-administered neurocognitive dysfunction by adding items to a select subset of questions from an investigational version of the Brief Rating Inventory of Executive Function-Adult (BRIEF-A)³⁾. Exploratory

factor analysis in 382 siblings of cancer survivors revealed four factors that demonstrated good internal consistency: Task Efficiency, Emotional Regulation, Organization, and Memory. Construct and concurrent validities of the four CCSS-NCQ factors were demonstrated through correlation with factors from other established measures, including the Behavior Problem Index (BPI) and the BSI, within the CCSS cohort as a neurocognitive measure specifically designed for cancer survivors. It was shown that patients with self-reported difficulties based on the CCSS-NCQ were more likely to regard their cancer treatment as a future health risk¹¹⁾. Also, it was observed that cranial radiation therapy and female gender were associated with lower self-reported neurocognitive function⁷⁾. In order to verify whether the CCSS-NCQ Japanese version can be applied to Japanese CCS, we tested its reliability. This study describes the process of conducting a pilot study, the results of the analysis, and the future prospects for the CCSS-NCQ Japanese version.

2. Objectives/Aims and Hypothesis

The objective of this study was to evaluate the reliability of the CCSS-NCQ Japanese version. Screening and identification of CCS with difficulties with the CCSS-NCQ Japanese version could facilitate referral for objective neurocognitive testing. In this way, it will be possible to obtain guidance for educational support based on data from comprehensive testing. We hypothesized that the Japanese translated and cross-cultural adapted version of the CCSS-NCQ will show a four-factor structure as in the original version.

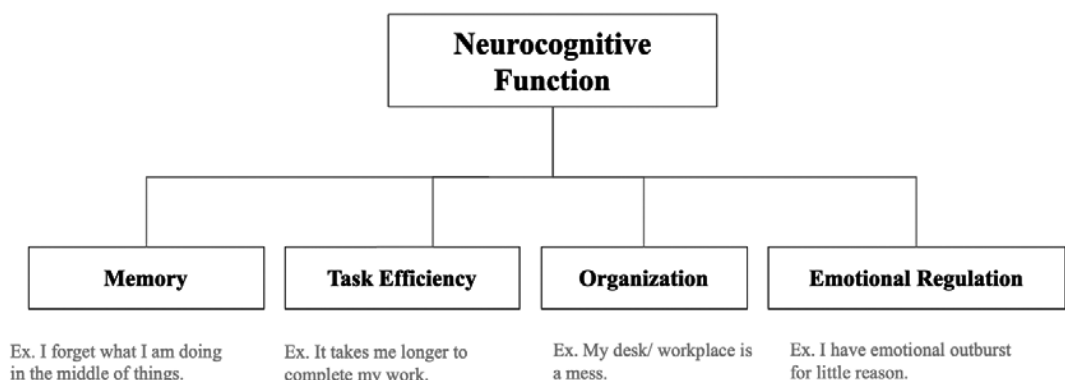


Figure 1 . Four-factor structure, showing four domains that are likely to be impaired among CCS after cancer treatment

II. METHODS

1. Participants

Participants of this study were cancer survivors in Japan who were at least age 10 years or older. All cancer types were included in the study. Those who had a head injury, unrelated neurologic condition, and genetic disorders were excluded from this study. We recruited the participants from 2019 to 2021.

2. Procedures

To assess self-administered neurocognitive dysfunction among CCS in Japan, the CCSS-NCQ was translated into the Japanese language through linguistic validation, with a permission of an original author¹²⁾. Linguistic validation is a process in which an instrument is translated into the targeted language while maintaining conceptual equivalence. The translation and cross-cultural adaptation of the CCSS-NCQ was based on guidelines¹³⁾. To maintain consistency with the English version of the CCSS-NCQ, the following steps were taken in the translation process: forward translation, reconciliation, back-translation, and back translation review. In a questionnaire survey, it is said that it takes 3–20 times as many items to validate the content¹⁴⁾. In this study, we set the minimum sample size of 99 as there are 33 items.

At the beginning of this study, the CCSS-NCQ Japanese version was distributed mainly to the CCS attending the long-term follow-up outpatient clinic of the National Center for Child Health and Development by hand or postal mail. It was also distributed at a meeting of a childhood cancer patient association. However, after collecting 90 participants, due to the COVID-19 pandemic which started in late 2019, direct contact with patients became difficult and the enrollment stalled. Thus, we conducted a web-based survey with Google Forms (Google, Inc., California, U.S.) among four other different childhood cancer patient associations from different regions of Japan, with no particular restrictions regarding age or diagnoses, from August 2021 until October 2021. There was no direct contact between the investigator and the participants since the representatives of the patient associations recruited participants via e-mail.

In conducting the online survey, the readability, clarity and wording of the questionnaire were reviewed again based on suggestions from respondents and

feedback by members of the patient associations.

Initially, the study was conducted with a small number of patients, and then the online survey was conducted with the input of patient representatives. Since the respondents' faces were not visible, it was not possible to directly confirm that the participants themselves were answering the questionnaires but to minimize the risk, only the patient group members was authorized to access the questionnaire.

3. Survey instrument

Participants were asked to complete a 33-item questionnaire, containing 8 items each for "Memory", "Task Efficiency", "Organization", and "Emotional Regulation" backed by theory to capture each ability, and one preliminary question which asked them to report the frequency with which they experienced the problem described by each item over the past 6 months. Items were measured on a 3-point Likert scale (1= Never a problem, 2= Sometimes a problem, 3= Often a problem). The questionnaire also inquired about the participant's age, gender, education, employment, as well as the diagnosis and the type of treatment they had received.

4. Statistical analyses

All survey data were coded and entered into a database by using IBM SPSS Statistics version 27. Regarding the process of missing values, one case with an incomplete face sheet with no response to the questionnaire was excluded from the factor analysis. Additionally, for eight cases with incomplete responses, the worst value of the variable in those subjects for whom it is not missing was imputed. While mean imputation is considered for a survey of the general population, the CCSS-NCQ is intended for use in clinical screening, also results can be variable. So we adopted the worst score imputation¹⁵⁾ from the viewpoint of emphasizing the detection of abnormalities.

The purpose of this study was to evaluate the CCSS-NCQ Japanese version and to verify its reliability. Descriptive statistics included the following: demographics, means and standard deviations. Confirmatory factor analysis was performed, with the threshold of 0.4 as the factor load.

5. Ethics statement

The paper-based part of the study was conducted with written consent from patients and their primary caregivers, and the web-based part of the study was conducted with a clear online statement of intent and understanding to participate in the study was confirmed, both with the approval of the ethics committees at St. Luke's International Hospital and the National Center for Child Health and Development. The institutional review boards approved the research protocol before participants' enrollment. Participants provided informed consent before the administration of questionnaires. Parental informed consent was obtained for participants who were under 20 years old at the time of the study.

It was assumed that those involved in this study would make every effort to maintain confidentiality about patient data collected during the study. The data collected on paper was kept in the locked desk of the principal investigator and was not accessible to others. Information collected online was managed in the cloud, with access rights granted only to the principal investigator and a password set to prevent others from viewing it.

III. RESULTS

The participants were recruited at the long-term follow-up outpatient clinic at the National Center for Child Health and Development, and a local patient association, as stated above. We enrolled 90 cases before we started the web-based surveys. Subsequently, 2 participants of paper responses and 31 online responses were obtained by the way previously described, bringing the total to 123 cases, which exceeded the target sample size of 99.

The demographic characteristics of the participants are presented in Table 1. The response rate was 52.3% among paper-based and 33.7% among online-based responses. The mean age of participants was 21.6 ± 8.5 years old, 50.4% of participants were male, and 48.8% were female. The mean age at diagnosis was 8.5 ± 4.8 years old, and 42.3% of participants were diagnosed with a Central Nervous System (CNS) tumor, 38.2% with hematological malignancy, 13.0% with solid tumor,

and 1.6% with other designation.

In the original CCSS-NCQ, the four-factor structure (Memory, Task Efficiency, Organization, and Emotional

Table 1. Demographic characteristics of the participants

Characteristics		N=123
Age at registration		<i>mean (SD)</i>
		21.6 (8.5)
		<i>N (%)</i>
	10-14	8 (6.5%)
	15-19	57 (46.3%)
	20-24	26 (21.1%)
	25-29	16 (13.0%)
	30-34	3 (2.4%)
	35-40	12 (9.8%)
	N/A	1 (0.8%)
Sex		<i>N (%)</i>
	Male	62 (50.4%)
	Female	60 (48.8%)
	N/A	1 (0.8%)
Diagnosis		<i>N (%)</i>
	CNS tumor	52 (42.3%)
	Hematological malignancy	47 (38.2%)
	Solid tumor	16 (13.0%)
	Other	2 (1.6%)
	N/A	6 (4.9%)
Age at diagnosis		<i>mean (SD)</i>
		8.5 (4.8)
		<i>N (%)</i>
	0-4	24 (19.5%)
	5-9	47 (38.2%)
	10-14	37 (30.1%)
	15-19	12 (9.8%)
	N/A	3 (2.4%)
Time from diagnosis		<i>mean (SD)</i>
		13.3 (8.8)
		<i>N (%)</i>
	0-4	16 (13.0%)
	5-9	27 (22.0%)
	10-14	33 (26.8%)
	15-19	24 (19.5%)
	20-	20 (16.3%)
	N/A	3 (2.4%)
Treatment		<i>N (%)</i>
	Chemotherapy only	23 (18.7%)
	Radiation only	4 (3.3%)
	Surgery only	8 (6.5%)
	Chemotherapy, Radiation	19 (15.4%)
	Chemotherapy, Surgery	2 (1.6%)
	Radiation, Surgery	7 (5.7%)
	Chemotherapy, Radiation, Surgery	27 (22.0%)
	Hematopoietic Cell Transplantation	13 (10.6%)
	N/A	20 (16.3%)
Survey instrument		<i>N (%)</i>
	Paper-based survey	92 (74.8%)
	Web-based survey	31 (25.2%)

Regulation) was identified through exploratory factor analysis.

We fixed the number of factors as 4 as in the original version, and confirmatory factor analysis was conducted using the same settings (Table 2). Three items did not belong to any factor when the cutoff for the factor loadings was set to 0.4. For factors with factor loadings of less than 0.4, Q10 had the highest factor loading in Memory, which was consistent with the results. On the other hand, Q6 and Q15, which were originally expected to belong to Memory, showed the highest factor loadings in Task Efficiency. Means

and standard deviations of factor scores are also shown in the table. Cronbach's Alpha (ranging from 0.842 - 0.918) demonstrated good to excellent internal consistency of the factors. Also, correlation between Task Efficiency and Memory was observed (the inter-factor correlation coefficient=0.636), while no correlation was observed between other factors. Further validation is needed after increasing the number of cases to investigate if the Japanese CCSS-NCQ is four-factor structured as the original version.

Table 2. Factor loadings of factor analysis.

Items	1. Task Efficiency	2. Emotional Regulation	3. Organization	4. Memory
Q2 It takes me longer to complete my work	1.018	-0.060	0.081	-0.394
Q18 I am slower than others when completing my work	0.958	-0.112	0.006	-0.073
Q13 I have trouble doing more than one thing at a time	0.788	0.033	0.136	-0.021
Q19 I have trouble solving math problems in my head	0.729	0.034	0.042	-0.195
Q16 I have trouble prioritizing my activities	0.676	-0.219	0.106	0.221
Q20 I don't work well under pressure	0.666	0.050	-0.127	0.069
Q5 I have problems completing my work	0.653	0.151	0.031	-0.055
Q29 I have problems organizing activities	0.460	0.147	0.196	0.220
Q12 I am easily overwhelmed	0.446	0.266	-0.279	0.216
Q4 I forget instructions easily	0.424	0.082	0.290	0.186
Q6 I have difficulty recalling things I had previously learned (e.g., names, places, events, activities)	0.320	0.003	0.094	0.280
Q15 I have trouble remembering things, even for a few minutes (such as directions, phone numbers, etc.)	0.285	0.268	0.068	0.235
Q24 I have angry outbursts	-0.114	0.892	0.079	-0.021
Q30 I have emotional outbursts for little reason	0.014	0.892	-0.007	-0.073
Q26 I overreact emotionally	-0.028	0.890	-0.052	-0.015
Q7 I get frustrated easily	-0.059	0.857	0.091	-0.027
Q32 I react more emotionally to situations than my friends	0.035	0.790	0.189	-0.245
Q28 I overreact to small problems	0.085	0.778	-0.096	0.062
Q8 My mood changes frequently	-0.117	0.725	0.121	0.175
Q1 I get upset easily	0.342	0.571	-0.338	0.030
Q33 I leave my room or home a mess	-0.141	0.049	0.947	0.033
Q14 My desk/workspace is a mess	0.032	-0.057	0.911	-0.028
Q9 I have trouble finding things in my bedroom, closet or desk	0.286	-0.044	0.736	-0.059
Q22 I have a messy closet	0.045	0.071	0.732	0.042
Q3 I am disorganized	0.055	0.110	0.717	0.068
Q27 I have trouble organizing work	0.358	-0.136	0.452	0.219
Q31 I leave the bathroom a mess	-0.499	0.041	0.197	0.798
Q23 People say I am easily distracted	-0.085	-0.016	0.106	0.766
Q21 I have trouble staying on the same topic when talking	0.209	-0.207	-0.155	0.759
Q11 I have problems getting started on my own	0.305	0.055	-0.085	0.551
Q25 I have a short attention span	0.438	0.039	-0.063	0.501
Q10 I forget what I am doing in the middle of things	0.155	0.023	0.075	0.355
Mean factor score	1.703	1.440	1.752	1.519
Standard deviation of factor score	0.590	0.544	0.603	0.496
Cronbach's alpha	0.890	0.918	0.905	0.842

Note: Values greater than 0.40, and questions that contribute to a factor are indicated by bold font
Principal component analysis, Promax rotation, Convergence of rotation after 6 iterations

IV. DISCUSSION

In this study, good to excellent internal consistency was observed based on the Cronbach's alpha coefficient. However, some items from Task Efficiency and Memory were mildly correlated, and three items did not converge to any of the factors. Similarity in the structure was also observed when the first version of the CCSS-NCQ Japanese version was developed and analyzed, but at that time findings were affected by insufficient sample size, an uneven distribution of cancer diagnoses, and problems with wording¹²⁾. In order to solve these problems, the number of participants were increased, the heterogeneity of cancer diagnoses was reduced, and linguistic validation was conducted again to update the scale. Even after addressing these issues, "Task Efficiency" and "Memory" were slightly correlated as in the previous analysis⁷⁾. This finding may result from the inherent similarities between "Task Efficiency" and "Memory" as concepts. Also, cultural differences might have affected the results. Further enrollment of participants may help to develop a more robust measure.

Regarding limitations of the study, there is a possibility that some CCS may not have been accustomed to web-based surveys, in which case results may have differed from the paper-based survey. However, it has been described that a web-based survey could replace a paper-based survey with minor effects on response rates¹⁶⁾. Adjusting for the impact of the change of the survey style during the study should be considered in future efforts. Another issue influencing the results may be that the participants of the study were likely to be concerned about neurocognitive dysfunction. In other words, CCS with neurocognitive dysfunction might have been likely to join the study. However, the CCSS-NCQ was not designed to detect neurocognitive dysfunction, but rather to assess the practical implications of neurocognitive deficits on a survivor's daily life. Assistance by guardians was also allowed for survivors with neurocognitive impairment to assume an accurate reflection of participants' condition. However, this information was not collected; thus, an assessment of it was not possible. Also, as nearly three-fourths of study participants were recruited from a single institution in Tokyo and the remaining from various patient associations, generalizability could be a potential

limitation. However, since there is no data in Japan measuring self-administered neurocognitive dysfunction of CCS after childhood cancer treatment, assessment within the current population may be considered of significant value. We also acknowledge the regional bias, but it may have limited influence as the CCSS-NCQ attempts to evaluate the neurocognitive dysfunction biologically, not regionally.

In the web-based survey, it was not easy to recruit participants with whom staff had not previously established relationships. Therefore, we prepared a brochure describing the purpose and significance of the study in advance to reduce anxiety. It enabled the investigator to establish a good relationship with the patient associations and facilitated research progress. Finally, the results of the study were shared to express gratitude, which created a sense of community among participants.

Interestingly, of the 123 patients, only 12 participants (9.8%) showed no sign of impairment. These data suggest that a potentially large number of CCS may benefit from screening with the CCSS-NCQ Japanese version. Neurocognitive function is deeply impactful in a survivor's attainment of expected social milestones during adulthood. For example, CNS-treated survivors performed worse than non-CNS-treated survivors on all neurocognitive tests and were more likely to have global neurocognitive impairment⁹⁾, which will lead to difficulties in later years. Neurocognitive testing is important to identify survivors with impairment that could affect educational, vocational and social goals, but universal testing is not currently feasible in the Japanese medical system. Therefore, the CCSS-NCQ Japanese version could be an efficient screening tool to identify CCS who may benefit from more detailed testing. The simplicity of the administration of the CCSS-NCQ should not pose a burden to survivors or the medical system, which may facilitate routine testing and referral for more detailed evaluations during long-term follow-up care. In addition, the results of the CCSS-NCQ can identify which aspects of neurocognitive function need intervention. Understanding such features of the CCSS-NCQ will eventually contribute to the development of a support system for CCS who present with clinical findings suggesting neurocognitive impairment.

It is anticipated that the study will lead to clinical implementation of this measure of neurocognitive

function with results that can be compared to international cohorts. If the trend between the scale and the disease or treatment becomes clear after enrollment of more cases, we aim to establish a cutoff value to guide referral for formal clinical neurocognitive examination, with the goal of identifying and providing support for observed functional weaknesses.

Identification of neurocognitive deficits may provide opportunities for remediation that improve QOL of CCS. Evidence suggests that caring for individual CCS and families contributes to positive QOL outcomes of CCS and their family members¹⁷⁾. Also it will enable health care providers to give CCS evidence-based support and utilize resources appropriately. Furthermore, it may eventually lead to the revitalization of society as a whole by supporting societal achievements related to educational and vocational goals of CCS. This will improve the awareness of people around CCS, contributing to a healthier society by providing others with opportunities to understand more about childhood cancer and neurocognitive dysfunction as a late complication. It is expected that such effects of the CCSS-NCQ Japanese version will help CCS to have more control over the life they wish to pursue.

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