53% and 44% during the concomitant and adjuvant courses, respectively. Although the reasons for the high hematologic toxicity rates in the nonelderly and the elderly patients in the present study were not evident, most of these toxicity seemed not to have affected the schedule of TMZ administration because much of Grade 3 and 4 hematologic toxicity that we recorded was lymphocytopenia without severe infectious disease. On the other hand, the incidence of Grade 4 toxicity that caused discontinuation or delay of TMZ administration was significantly higher in the elderly than in the nonelderly patients, and such Grade 4 toxicity was mostly observed during concomitant course; these findings indicated that there was a potential risk in treating elderly patients with TMZ in this fashion.

Besides hematologic toxicity, it is noteworthy that cognitive dysfunction was found only in elderly patients; this adverse event occurred in 11% of elderly patients during the concomitant course and in 5% during the adjuvant course. Cognitive dysfunctions were observed ahead of disease progression, and median time to onset of cognitive dysfunction was 1 month, while median time to progression of these patients was 11.7 months. So we think these cognitive dysfunctions were not caused by disease progression. As Brandes et al. reported mental status deterioration during adjuvant TMZ chemotherapy after concomitant chemoradiotherapy in 56% of elderly patients,[6] neurotoxicity is a common finding in elderly patients. In contrast to the report from Brandes et al.,[6] we observed a higher frequency of cognitive dysfunction during concomitant course of TMZ in the elderly. Thus, the cognitive function of elderly patients should be monitored carefully. However, the causal association between cognitive dysfunction and TMZ was unclear because there were many causes for cognitive dysfunction other than TMZ, such as aging and radiotherapy itself; a controlled study is required to evaluate the causes of cognitive dysfunction in elderly patients with GBM.

In contrast to during the concomitant course, the incidence of Grade 3 and 4 adverse events during the adjuvant course did not differ significantly between the elderly group and the nonelderly group. The mean interval of each adjuvant cycle was also similar between the two groups (32.4 versus 31.8; $p = 0.69$). Therefore, the elderly patients seemed to tolerate the adjuvant course as well as the younger patients did. The reason why severe adverse events happen more frequently during concomitant course is unclear; however, one hypothesis is that a higher accumulated dose of TMZ within a course of chemotherapy tends to cause severe toxicity in elderly patients who have relatively poor tolerance potential to chemotherapy including bone marrow function than the younger. Indeed, in this treatment regimen, patients were scheduled to receive 6 weeks of continuous administration of TMZ in concordance with 60 Gy radiation, which amounts to over 3,000 mg/m^2 of TMZ. On the other hand, during a cycle of adjuvant course, patients were administered with only 750–1,000 mg/m^2 of TMZ with 23 days cessation period. If this explanation is true, a reduction of the TMZ dose or a shortening of administration period of TMZ during the concomitant course might decrease the rates of complications, although these changes may also cause a reduction in therapeutic effect because concomitant course is theoretically the most active portion of the TMZ-based chemoradiotherapy regimen.

The median OS and the median PFS in the elderly group were 15.2 and 8.4 months, respectively, in this study. Brandes et al. recently reported median OS of 13.7 months and PFS of 9.5 months in 58 patients with GBM who were 65 years of age or older and were treated with concomitant and adjuvant TMZ added to standard radiotherapy.[6] Minniti et al. also reported a median OS of 12.8 months and a median PFS of 7.5 months in a study of 83 patients 70 years of age or older who received standard radiotherapy plus concomitant and adjuvant TMZ.[15] The present results compare favorably with these reports. Notably, patients aged 75 years and older (7/27 patients; 26%) had no worse outcomes than did those of 65–74 years; the median OS and median PFS were 15.3 and 8.9 months in patients aged 75 years and older, 18.5 and 9.8 months in the 70–74 year group, and 15.1 and 5.3 in the 65–70 year group. Baseline KPS ranged from 50 to 90 with median KPS of 80 in patients aged 75 years or older and from 60 to 90 with median KPS of 80 in the 65–74 year group. These facts make it difficult to set an age-based cut-off line for determining who should be treated as the elderly patient. In this analysis, we categorized the patients older than 65 years as the elderly as have other research groups[6,9,16,17] and does the ongoing randomized clinical trial (NCIC/EORTC 26062).

Several important findings on the optimal treatment of the elderly patients with GBM have been reported recently. Findings from randomized controlled trials demonstrated (1) that radiotherapy alone (60 Gy/30 fractions) could prolong survival more than the best supportive care could and radiotherapy did not compromise quality of life or cognition[18] and (2) that an abbreviated course of radiotherapy (40 Gy/15 fractions) was equivalent to standard radiotherapy of 60 Gy over 30 fractions in the elderly GBM patients.[19] Thus, considering the

generally poor prognosis of elderly patients with GBM, short-course radiotherapy may be a reasonable treatment option. Furthermore, the Nordic Brain Tumor Group compared three separate treatment modalities: standard fractionated radiotherapy (60 Gy in 30 fractions), hypofractionated radiotherapy (34 Gy in 10 fractions), and six cycles of TMZ (5 of 28 days) in their recent phase III study[20]; the findings indicated that the elderly patient treated with standard radiotherapy had worse prognosis than did the elderly patients treated with 34 Gy hypofractionated irradiation or with TMZ alone. In the elderly patients, they found no significant difference in survival between hypofractionated radiotherapy arm and TMZ alone arm. However, both this study and another phase III study (NOA-08 trial), which showed that dose-dense TMZ chemotherapy is noninferior to standard radiotherapy for elderly patients with malignant astrocytoma,[17] demonstrated retrospectively that TMZ treatment seems more effective than radiotherapy alone for the elderly patients with methylated *MGMT* promoter, whereas no significant effect of TMZ was observed for patients with an unmethylated *MGMT* promoter. Methylation of the *MGMT* promoter is reportedly a prognostic and predictive factor for GBM treated with TMZ in elderly cases.[6,15,17,20,21] However, in the present study, *MGMT* methylation was not shown to be a prognostic factor for OS or PFS in elderly patients treated with TMZ and radiotherapy; one reason for this contradictory finding might be the small number of cases in this study; only 19 of 27 elderly patients were evaluated for *MGMT* promoter methylation. The significance of *MGMT* promoter methylation for the treatment of elderly patients with GBM by TMZ and radiotherapy would need to be ascertained in large, prospective clinical trial.

Another remaining question is whether TMZ is effective for elderly patients when concomitantly administered during radiotherapy. Considering recent findings and the frequent Grade 4 adverse events during concomitant TMZ administration with standard radiotherapy in the elderly group, a combined TMZ-based chemotherapy with short-course radiotherapy may be a reasonable treatment option, especially for those elderly patients with a methylated *MGMT* promoter. A currently ongoing randomized controlled trial comparing short-course radiotherapy plus concurrent followed by adjuvant TMZ and short-course radiotherapy alone (NCIC/EORTC 26062) is expected to provide some answer for this question.

The present study has several limitations, including those limitations that are associated with any retrospective study. There was selection bias because patients treated with short-course radiotherapy, radiotherapy alone, or supportive care were excluded. Besides, as age itself is a prognostic factor for GBM, it is difficult to interpret the results of survival comparison between elderly and nonelderly group.

Conclusion

In the elderly patients, especially during the period of concomitant chemoradiotherapy, there was an increased risk of Grade 4 adverse events, which have disrupted the schedule of TMZ administration and in turn may cause the shortening of the survival time. Since probability of severe toxicity seems currently difficult to predict by patient characteristics, such as sex, KPS, or RPA score, the elderly patients who undergo a concomitant course of TMZ must be closely monitored for toxic events. A reduced dose of TMZ might worth considering for elderly patients, and predictive factors for toxicity are expected to be clarified in the future. In addition, the impact of concomitant use of TMZ during short-course radiotherapy, in combination with the *MGMT* promoter methylation status, on the survival of elderly GBM patients needs to be clarified in prospective randomized controlled studies.

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Conflicts of Interest Disclosure

All authors have no conflict of interest to disclose.

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Short Communication Open Access

Controversies in Clinical Trials of Cancer Vaccines for Glioblastoma

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Keywords: Glioblastoma; Clinical trial; Tumour progression; Best recommended treatment

Glioblastoma multiforme (GBM), the most common primary brain tumour, continues to have a dismal prognosis. The standard initial treatment for GBM is surgical resection along with postoperative adjuvant therapy, including temozolomide, concomitant with 60 Gy of radiation therapy (RT) [1]. However, most patients eventually relapse and long-term survival remains elusive [2,3]. Thus, novel therapeutic modalities for GBM are being explored, and different types of immune-mediated approaches have been preclinically and clinically evaluated in phase I and II trials [4]. However, these GBM clinical trials face significant limitations in terms of their assessment of tumour progression and protocol setting. A critical and comprehensive review of how GBM trials should be conducted is required with a focus on how progression can be defined and clinical benefits can be evaluated following the administration of cancer vaccines.

Limitations of the Conventional Tumour Progression Criteria

In current clinical trials of therapies for solid Tumours, cessation of treatment is recommended once "progressive disease" (PD) is detected according to the WHO or response evaluation criteria in solid Tumours (RECIST) criteria. In the WHO criteria, PD is defined as at least a 25% increase in the sum of the products of the two largest perpendicular diameters (SPD) compared with nadir and/or unequivocal progression of non-index lesions and/or the appearance of new lesions [5]. In the RECIST criteria, a 20% increase is defined as PD [6]. Criteria developed by Macdonald and colleagues in 1990 have also been used for assessing the anti-Tumour responses of gliomas [7]. These criteria are based on the two-dimensional WHO response criteria and mark the transition from a subjective interpretation of clinical and radiologic changes to a more objective evaluation. Other factors, such as the use of steroids and changes in neurologic status, are also included in the response assessment. Although they are widely accepted, a number of groups have reported a few limitations of these criteria [8-10]. Clinical evidences indicate that the traditional Macdonald's criteria may not be sufficient for completely characterizing responses in the new era of targeted therapies. Thus, ideal progression criteria that can comprehensively describe all patterns of anti-Tumour responses to cancer vaccines for gliomas remain to be developed.

New systematic criteria designated "immune-related response criteria" for describing additional response patterns observed with immunotherapies that cannot be assessed by the traditional RECIST or WHO criteria have recently been defined [11]. In these new criteria, progression is defined as ≥ 25% increase in Tumour burden compared with nadir at two consecutive time points at least 4 weeks apart in the absence of rapid clinical deterioration. However, these novel criteria may also be of limited value for assessing the anti-Tumour responses of gliomas, as explained below.

Tumour Size Threshold for Defining PD

Tumours with enhancement are defined as PD when the changes in the enhancing areas reach 25% according to Macdonald's criteria. However, whether it is appropriate to define a ≥ 25% increase in Tumour size as "PD" remains unknown. In fact, this issue was raised by our retrospective analysis of the personalized peptide ITK-1 vaccine trial for recurrent GBM, where a 54% increase according to the WHO criteria or a 43% increase according to the RECIST criteria was predictive of a high mortality with a sensitivity of 69% (95% confidence interval: 42%-87%) and 85% (58%-96%), respectively (Figures 1A and 1B). Our experience suggests that the Tumour size threshold for defining PD when evaluating the efficacy of cancer vaccines remains to be carefully determined.

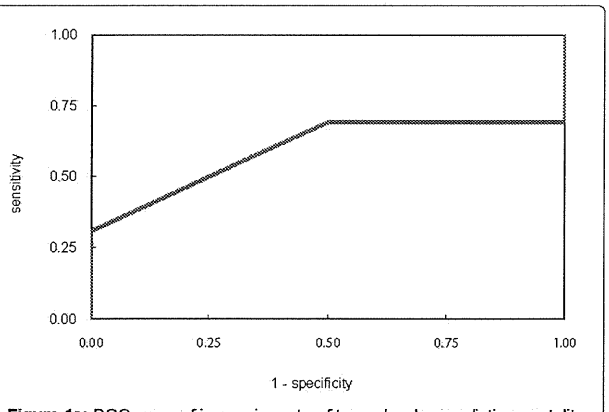

Figure 1a: ROC curve of increasing rate of tumor burden predicting mortality at progression according to the WHO criteria. The area under the ROC curve was 0.69 (95% CI: 0.43, 0.95). Increase in the SPD of at least 54% is predictive of mortality at progression with a sensitivity of 67% (42%, 87%) and a specificity of 50% (9%, 91%).

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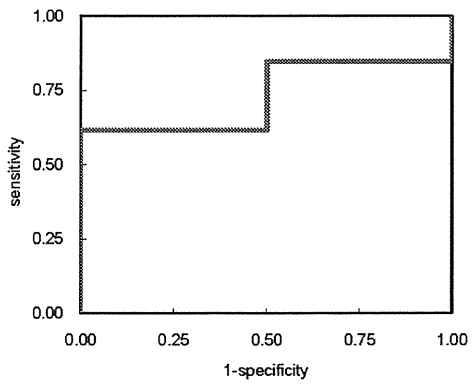

Figure 1b: ROC curve of increasing rate of tumor burden predicting mortality at progression according to the RECIST criteria. The area under the ROC curve was 0.73 (95% CI: 0.42, 1.00). Increases in the largest perpendicular diameters of at least 43% are predictive of mortality at progression with a sensitivity of 85% (58%, 96%) and a specificity of 50% (9%, 91%).

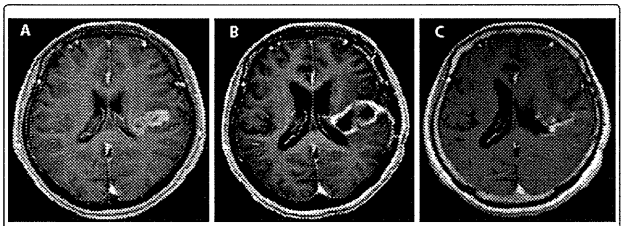

Figure 2: Example of pseudoprogression after vaccination.

(A) T1-weighted contrast-enhanced magnetic resonance image (MRI) from a 59-year-old patient with biopsy-proven glioblastoma before vaccination.

(B) Eight weeks after vaccination, a significant increase in contrast enhancement was shown.

(C) On a follow-up MRI 24 weeks later, a significant reduction was observed in the enhancing lesions.

Controversy Evaluating Enhancing Lesions

Tumour enhancement has been assessed based on the extent of Tumour-occupying lesions when evaluating Tumour size. However, considering that clinical trials of cancer vaccines for gliomas have been attempted in patients at various stages and with various conditions of disease, tumour enhancement may be influenced by not only cancer cell occupation but also by several other factors, including postsurgical changes, disruption of the blood-brain barrier, inflammation, radiation necrosis, and use of corticosteroids [12-17]. These changes in enhancing areas are not always directly correlated with those of Tumour-occupying lesions. Stable disease (SD) in the enhancing areas might be considered an indicator of significant therapeutic effects in cancer vaccine trials [18]. For example, it is possible that enhancement within Tumours may be, at least in part, attributed to autoimmune responses and/or brain inflammation caused by systemic immunization [4].

Tumour Regression after Apparent PD

Clinical studies of cancer vaccines have in certain cases shown that initial induction of SD or PD is followed by subsequent Tumour regression, raising concerns about evaluation of anti-Tumour responses using the WHO or RECIST criteria [11,19]. Such radiological increases in Tumour volumes that precede beneficial clinical responses in patients administered cancer vaccines may be attributed to either continued Tumour growth until sufficient anti-Tumour activity develops, or to transient infiltration of immune cells. In addition, transient increases in enhancement without actual Tumour progression, known as "pseudo progression", have been reported in multiple studies of immunotherapeutic agents [20,21]. For example, in our previous cancer vaccine trial, significant clinical effects after 12 weeks, and in certain cases even after 24 weeks, were observed in a subset of patients with apparent PD according to the classical progression criteria (Figures 2A, 2B and 2C) [22]. Considering the fact that follow-up observations cannot be mandated in patients with PD in most clinical trial protocols, the actual number of patients with beneficial clinical responses after PD may be underestimated. This could limit the value of progression-free survival as a primary end point in cancer vaccine trials.

Collectively, clinical development of cancer vaccines has been hampered by the absence of ideal progression criteria that can comprehensively describe all patterns of anti-Tumour response. Establishment of specific guidelines for classifying Tumour progression to evaluate anti-Tumour activities remains an urgent issue in relation to cancer vaccine trials for gliomas.

Overall Survival as a Primary Endpoint in Cancer Vaccine Trials for Gliomas

Since the numbers of patients with high-grade glioma, particularly GBM, are limited, it would be quite difficult to conduct large-scale immunotherapy trials for this disease [4,12]. The number of patients receiving treatments is relatively small in cancer vaccine trials, and the evaluation criteria vary depending on the trial [22-42]. Such large variations in immune-based therapeutic approaches for GBM make direct comparison difficult. Given this situation, the immunotherapy field needs to urgently address what clinical benefits can be detected in such small-scale, limited clinical trials, and how these can be evaluated. One possibility would be to concentrate on evaluating overall survival (OS). Because of a lack of effective treatments for refractory GBM, the effect of a particular treatment on OS may not be influenced by subsequent salvage treatments.

Combination with the Best Recommended Treatment

A novel hypothetical consideration may be combination therapy with additional agents in GBM vaccine trials, which may enhance the clinical effects of cancer vaccines. Recently, concomitant treatments including RT, chemotherapies, and targeted therapies, have been reported to enhance the therapeutic effects of cancer vaccines through multiple immune-related mechanisms (i.e., activation of antigen-presenting cells or cytotoxic T cells and removal of suppressor cells) [43,44]. Several clinical studies have shown that chemotherapies combined with cancer vaccines can have a synergistic effect [44]. Synergistic effects of salvage chemotherapies after therapeutic cancer vaccination were also reported to improve patient survival in two clinical studies of GBM and small cell lung cancer [45,46]. Sampson et al. [47] reported that cancer vaccination after concomitant RT and temozolomide provided a survival advantage of 9 months compared with control patients in a phase II multicenter trial in patients with newly diagnosed GBM. These clinical studies illustrate that cancer vaccines combined with other treatment modalities may provide a valid therapeutic option for GBM. Therefore, the best recommended treatment (BRT) could be combined with chemotherapies and/or radiotherapies but not with best supportive care (BSC) in clinical trials of cancer vaccines for GBM. This will facilitate the occurrence

of synergistic effects, although the appropriate doses and schedules for optimal synergy between chemotherapies and cancer vaccines remain to be determined.

Considering the disease rarity and the limited survival benefit derived from cancer vaccines for GBM, the employment of BRT (but not of BSC), which could synergistically enhance the clinical effects of the cancer vaccines, would be a breakthrough for accelerated development of cancer vaccines. The FDA also supports this type of combination therapy in their guidelines for the development of therapeutic cancer vaccines [48].

Disclosure Statement

No part of this report has been previously presented elsewhere.

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Conflict of Interest

The authors report no potential conflict of interest except for Itoh.

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Factors influencing self- and parent-reporting health-related quality of life in children with brain tumors

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Abstract
Purpose Health-related quality of life (HRQOL) is not only a degree of health but also reflects patient perceptions and expectations of health. For children with brain tumors, better understanding of HRQOL requires the use of complementary reports from parents and interviewer-administered reports for children. Here, we aimed to test whether or not the trait anxiety of children and the psychological distress of their parents influence children's and parents' responses to HRQOL questionnaires, and whether or not the report-administration method for children influences children's responses to HRQOL questionnaires.
Methods One hundred and thirty-four children aged 5–18 with brain tumors and one of their parents completed the Pediatric Quality of Life Inventory™ (PedsQL™) Brain Tumor Module questionnaires. In addition, the children also completed the State-Trait Anxiety Inventory for Children (STAIC), and the parents also completed the

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Kessler-10 (K10) and health and sociodemographic characteristics questionnaires. The child questionnaires were administered either by the child (self-administered) or an interviewer. Rater-dependent perceptions about HRQOL were derived from the subscales scores of the PedsQL™ Brain Tumor Module using structural equation modeling based on a multitrait-multimethod model. The STAIC trait-anxiety score, K10 score, report-administration method, and other health and sociodemographic factors related to each child's or parent's perceptions were identified through multiple linear regression analyses of the questionnaire responses. We used a path analysis to estimate the change in a PedsQL™ child-reported score that occurs when interviewer-administration changes the child's perception about HRQOL.

Results Surveys for 89 children were self-administered while those for 45 were interviewer-administered. The perceptions of the children and parents were calculated by fitting data to the model (chi-squared $P = 0.087$, normed fit index = 0.932, comparative fit index = 0.978, standardized root mean squared residual = 0.053, and root mean square error of approximation = 0.054). The children's perception of HRQOL was affected by their STAIC trait-anxiety score ($b = -0.43$, 95% CI [−0.60, −0.25]). The parent's perception was affected by their child's treatment status ($b = 0.26$, 95% CI [0.09, 0.43]), the parent's K10 score ($b = -0.21$, 95% CI [−0.37, −0.04]), and by education level ($b = 0.17$, 95% CI [0.00, 0.34]). The change in the child-reported PedsQL™ score in relation to the method of administration ranged from −1.1 (95% CI: −3.5, 1.3) on the procedural anxiety subscale to −2.5 (95% CI: −7.6, 2.6) on the movement and balance subscale.

Conclusion Child-reporting of HRQOL is little influenced by the method of administration. Children's perception about HRQOL tended to be influenced by their trait anxiety, while parents' perception was influenced by their psychological distress, academic background, and their child's treatment status.

Keywords Brain neoplasms · Child · Observer variation · Parents · Quality of life · Questionnaires

Abbreviations

AMOS	Analysis of moment structures
CCAJ	The Children's Cancer Association of Japan
CFI	Comparative fit index
CHQ	Child Health Questionnaire
CI	Confidence interval
HRQOL	Health-related quality of life
K10	Kessler-10
MID	Minimum clinically significant difference
MTMM	Multitrait-multimethod
NFI	Normed fit index
PedsQL™	Pediatric Quality of Life Inventory™
RMSEA	Root mean square error of approximation
SD	Standard deviation
SEM	Structural equation modeling
SPSS	Statistical package for social sciences
SRMR	Standardized root mean squared residual
STAIC	State-Trait Anxiety Inventory for Children
TACQOL	TNO/AZL Child Quality of Life

Introduction

Children with brain tumors often show symptoms, such as pain, nausea, and lack of energy [1]. Even after treatment has ended, they may experience neurological, endocrinological, and cognitive problems and difficulties with psychosocial adjustment [2–6]. Appropriate care of children with brain tumors can be enhanced by assessing the child's health-related quality of life (HRQOL).

HRQOL is a patient-based outcome measured as a continuum of the quality of health experienced by a patient in a variety of aspects, including physical, emotional, social, and cognitive domains. Each of these domains can be measured in two dimensions: by an objective assessment of function or health status and by a subjective perception of health [7]. As such, HRQOL is not only a degree of health but also reflects a patient's personal perception and expectations.

HRQOL questionnaires for children often use both child- and parent-reports, respectively, reflecting the child's and parent's perception of the child's HRQOL; as a result, scores on these reports may differ. Child- and parent-reports provide complementary interpretations of HRQOL [8, 9], and neither is clearly superior to the other [10].

Several standard HRQOL questionnaires have been established for use with children, including the Pediatric Quality of Life Inventory™ (PedsQL™) [11], the TNO/AZL Child Quality of Life (TACQOL) [12], and the Child Health Questionnaire (CHQ) [13]. Several factors need to be considered when choosing a questionnaire, but clinical practice requires that the HRQOL instrument chosen for children with brain tumors reflects the impact of the disease and treatment.

We chose the PedsQL™ because this questionnaire includes generic core and disease-specific modules suitable for use in assessing pediatric chronic health conditions. Further, the PedsQL™ can be administered by an interviewer, a particularly essential factor, as child-reporting by children with brain tumors may occasionally be constrained by complications, such as visual impairment, motor dysfunction, or cognitive deficit. In addition, the

PedsQL™ is the only questionnaire presently available in Japanese and has been used before for children with brain tumors.

Having selected an HRQOL instrument, we then addressed two further questions affecting the feasibility and interpretation of the HRQOL scores: First, what are the causes of any differences between child- and parent-reported scores derived from standard questionnaires? Second, are there any significant differences between self- and interviewer-administered child-reports?

Previous studies have found that questionnaire responses may vary with the personality of the child [14] or their parent's mental health [15]. Jurbergs et al. [14] indicated that children with lowered trait anxiety and elevated defensiveness reported a higher CHQ score for themselves than did their parents. In effect, the personality of the child influences his/her perception about HRQOL, such that the score for the child differs from that perceived by the parent. With regard to parents' reports, Davis et al. indicated that increased maternal psychological distress, as measured by the Kessler-6 questionnaire, lowered the mother-proxy reported PedsQL™ score. These authors further indicated that reduced income of the caregiver resulted in a lowered mother-proxy reported, but not father-proxy reported score [15]. Although these reports suggest that the gender and income of parents may also influence parent-reports on the child-HRQOL, these authors did not compare the parent and child self-reports, and no studies have been conducted on differences between child- and parent-reports for children with brain tumors.

Studies in other medical fields have also confirmed that perceptions of HRQOL are dependent on the reporter. For example, Tamim et al. [16] used a visual analog scale to compare agreement between the HRQOL reported by older people discharging from emergency departments with that reported by their caregivers. The agreement between reported HRQOL was significantly lower for caregivers who had less contact with their patients than for those who lived with or were in daily contact with older people. Similarly, Hays et al. [17] found that the degree of agreement between HRQOL self-assessed by adult epilepsy patients and proxy-reports (by a relative, friend, or other significant person) was related to educational attainment of the patients and the reporters.

HRQOL is also influenced by several factors. Predictors of HRQOL in children with brain tumors include the child's age, age at diagnosis, gender, tumor location, tumor malignancy, relapse, treatment intensity, treatment status, and time since diagnosis [18–22]. Several demographic characteristics (child's age, age at diagnosis, gender) may affect the child's personal perception and expectation about HRQOL but not their HRQOL directly. Similarly, current life status (treatment status, time since diagnosis) may affect the child's or parents' personal perception and expectation about HRQOL but not the child's HRQOL directly.

These studies indicate that reported HRQOL can be influenced by physical, psychological, and sociodemographic characteristics, which may be unrelated to the condition. Further, rater-dependent (of each child's and parent's) perceptions of HRQOL can be influenced by health and sociodemographic characteristics.

We define "children's or parents' perception about the child's HRQOL" as each child's or parent's reporting bias, which is measured as a rater-dependent variance of reported HRQOL scores. Children's or parents' perception is their personal tendency to score an HRQOL questionnaire higher or lower than their parents or child, irrespective of objective measures of the child health. As a result, a child or a parent may score the child's HRQOL differently, even though the child's health condition is the same.

However, which predictors influence the child's or the parent's perception about HRQOL in children with brain tumors remains unclear. A better understanding of the influence of perception would enable more relevant interpretation of the HRQOL score reported by children and parents.

At present, little data are available on the differences between self- or interviewer-administered child-reports for children with brain tumors. Ideally, a person surveying children should be able to choose freely between either method of administration: while self-administered child-reporting may be less expensive, interviewer-administered child-reporting may be useful for children with complications from brain tumors. If these methods can be shown not to differ, then either can be selected for use in measuring HRQOL.

In a previous study using the PedsQL™ Brain Tumor Module, Palmer et al. [23] found no statistically significant difference between self- and interviewer-administered PedsQL™ scores or between parent scores of self-administered children and interviewer-administered children. However, whether or not this finding was clinically significant remains unclear, as Palmer's study was not primarily aimed to compare self- and interviewer-administered scores. It is important to describe the difference between the PedsQL™ self- and interviewer-administered reports.

Here, we investigated the influence of child and parent health, parent socio-demographic characteristics, and report-administration method on the child and parent perceptions about HRQOL (Fig. 1). We hypothesized that a child's perception about their own HRQOL was related to trait anxiety, a parent's perception about their child's HRQOL was related to psychological distress, and a child's perception was not related to the report-administration method (child self- or interviewer administered-reporting).

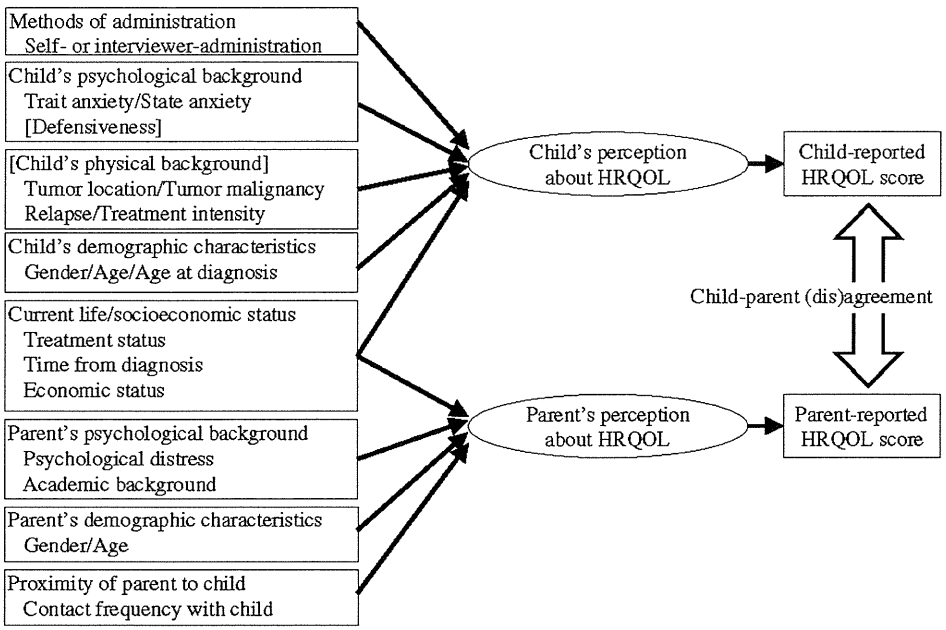

Fig. 1 Conceptual framework for organizing the factors that influence child and parent agreement. [Bracketed factors] were not measured in this study. *HRQOL* health-related quality of life

The following variables were considered as covariate to the above relationships: child's interviewer, state anxiety, age, gender, age at diagnosis, time from diagnosis, treatment status, and parent's age, gender, academic background, time with child per day, and subjective opinion regarding their economic status.

Methods

This study was conducted as part of the development of the Japanese version of the PedsQL™ Brain Tumor Module [24].

Study population

Children with brain tumors and their parents were recruited from six hospitals across Japan and from the Children's Cancer Association of Japan (CCAJ), a non-profit organization established in 1968, which supports children with cancer and their families, between September and December 2008. A child and one parent were included if the child was aged 5–18 years (age range covered by PedsQL™). Families were included if at least 1 month had passed since the child's brain tumor diagnosis and excluded if hospital doctors or social workers of the CCAJ determined that the family found the subject of the child's condition too uncomfortable to discuss.

Procedure

Researchers presented information about the study to 101 families in participating hospitals orally and in writing. Of these, 98 families elected to participate. At the CCAJ, a written description of the study was given to all families invited to a meeting regarding brain tumors, to which 45 families responded. In total, questionnaires were accordingly distributed to 143 families.

Parents were asked to determine, when providing informed consent, whether their child was able to self-administer the questionnaire. In accordance with the PedsQL™ administration guidelines [11], children aged 5–7 years and those determined to be incapable of self-administration were given the questionnaire by an interviewer, who was either a researcher or, if the child wanted the questionnaire to be administered at home, one of their parents. The parent-report questionnaires were self-administered by one of the parents, but we asked parents and children not to report in concert. If a child was administered the questionnaire by the parent, we asked the parent to complete the parent-report and then administer the child-report.

After distribution, 138 of the 143 families returned questionnaires. The background of the five families who did not respond is unknown. We excluded questionnaires from four families (four children and one parent) who answered less than 50% of items in one or more subscales.

The missing subscales were as follows: cognitive problems subscale for one child, pain and hurt for two children, movement and balance for two children, procedural anxiety for two children, nausea for two children and one parent, and worry for two children and one parent. Therefore, answers from a total of 134 families were analyzed. The children from the four excluded families were 3 boys and 1 girl aged 6–8 years who had been off treatment for 12-53 months.

Ethical considerations

This study was approved by the review boards of all seven participating institutions. For children aged 13 or over, informed consent from both the child and the parent was required prior to participation. For children aged 12 or under, informed verbal assent from the child and informed written consent from the parent was required.

Measurements

Child HRQOL was measured by the PedsQL™ Brain Tumor Module. The PedsQL™ Brain Tumor Module [23, 24] measures disease-specific HRQOL and comprises 24 items in six subscales: cognitive problems, pain and hurt, movement and balance, procedural anxiety, nausea, and worry. Children and parents were asked, on separate questionnaires, to describe the extent to which each item had troubled the child over the previous 7 days. For example: Item 1 of the child questionnaire stated "It is hard for me to figure out what to do when something bothers me," with the possible responses of 0 = never, 1 = almost never, 2 = sometimes, 3 = often, 4 = almost always. All subscale scores were calculated in reverse and linearly transformed so that the minimum score was 0 and maximum score was 100, with higher scores indicating a higher HRQOL. Cronbach's alpha coefficients [25] for the subscales for child- and parent-reports in the current study were 0.83 and 0.92 (cognitive problems), 0.52 and 0.78 (pain and hurt), 0.77 and 0.91 (movement and balance), 0.82 and 0.95 (procedural anxiety), 0.84 and 0.94 (nausea), and 0.75 and 0.86 (worry), respectively. Internal consistency in most subscales was considered sufficient, as Cronbach's coefficient alpha values exceeded 0.70 [25].

Global HRQOL was measured by the PedsQL™ Generic Core Scales [11, 26]. The instructions and scoring method are identical to the PedsQL™ Brain Tumor Module. Cronbach's alpha coefficients for the child- and parent-reports were 0.91 and 0.93, respectively.

State- and trait-anxiety of children were measured using the State-Trait Anxiety Inventory for Children (STAIC) [27, 28]. Children aged 8 years or over were asked to complete the questionnaire, with a higher score indicating increased anxiety. Cronbach's alpha coefficients for state- and trait-anxiety scales were 0.89 and 0.89, respectively.

Psychological distress of a parent was measured by the Kessler-10 (K10) questionnaire [29, 30]. The parent was asked to describe the frequency with which they experienced mood or anxiety symptoms over the past 30 days, with higher scores indicating higher psychological distress in relation to depression and anxiety. Cronbach's alpha coefficient for this questionnaire was 0.92.

The parent was also asked to describe their child's age, gender, tumor pathology, age at diagnosis, experience with treatment, their economic status, age, relationship to the child, academic background, and time spent with the child per day.

Statistical analyses: model for analysis

In the first step of the analysis, each child's perception, and each parent's perception about the child's HRQOL, was calculated by a multitrait-multimethod (MTMM) model [31].

MTMM models are used for quality of life research [32, 33] to test the validity of measures of multiple traits assessed by multiple raters. Here, we used a MTMM model to identify how child- and parent-reported scores of all six PedsQL™ Brain Tumor Module subscales differed. The MTMM model is known to be capable of separating variation in child- and parent-reported HRQOL scores into variation derived from the method and that derived from a trait [32]. The MTMM model also enables the division of HRQOL scores into rater-dependent perception and rater-independent condition. For example, a previous study of HRQOL using the TACQOL questionnaire with seven subscales found that children and parent scores were determined by rater-independent (38–73%) and rater-dependent (0–30%) latent factors [32].

In the present study, the HRQOL of each child was assessed by two raters: the child and one parent. The score for each HRQOL subscale was determined by two elements (Fig. 2) based on the perception of the child or the parent as well as the child's condition. Given that perceptions can differ between the child and parent, the child's perception is one element determining the child-reported scores of the six HRQOL subscales, while the parent's perception is one determining the parent-reported scores for the HRQOL subscales. The other element that determines both child-reported and parent-reported scores is the rater-independent condition, that is, a part of the child's function or health status that is recognized by both the child and the parent. These two elements—each rater's perception about HRQOL and the rater-independent condition of each aspect of HRQOL (for example, pain and hurt)—determine the rater reported score for each of the six subscales (Fig. 2).

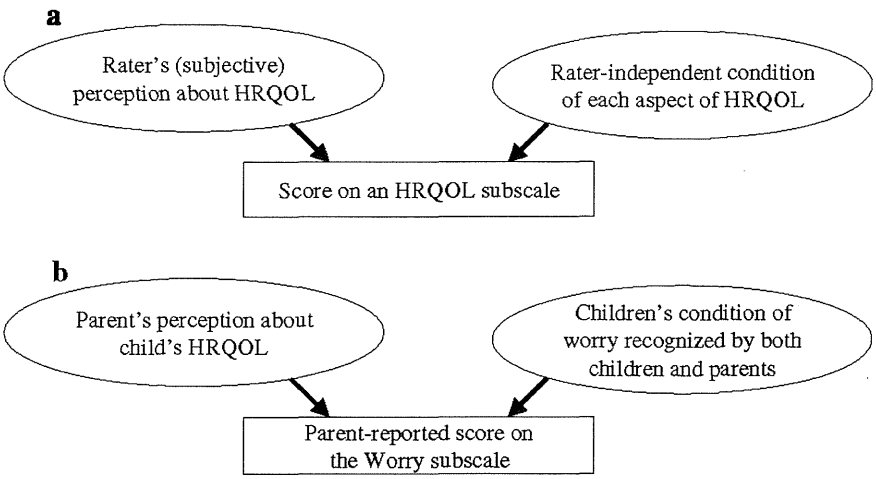

Fig. 2 **a** Two latent variables that determine the score on a health-related quality of life (HRQOL) subscale. **b** Example of two latent variables that determine parent-reported score on the Worry subscale in the Pediatric Quality of Life Inventory Brain Tumor Module

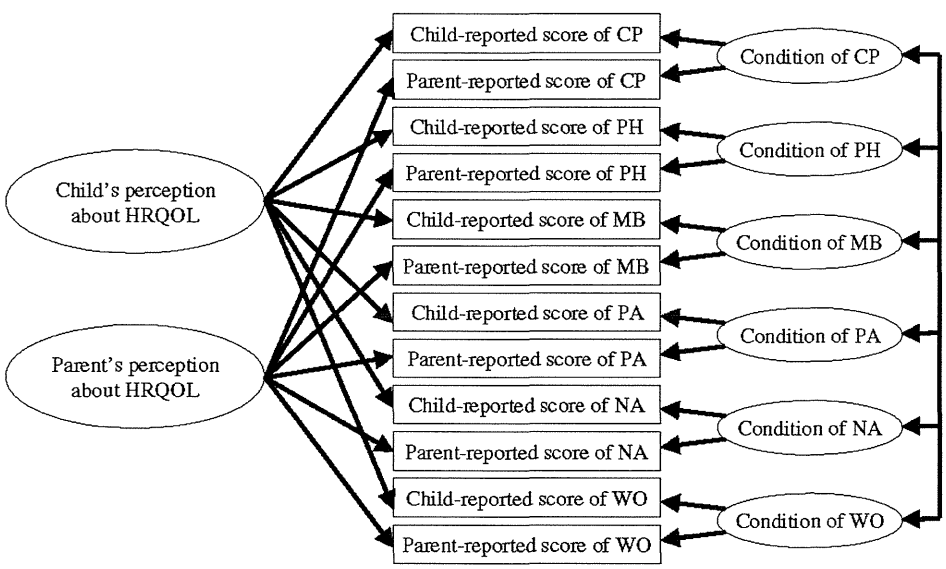

Fig. 3 Multitrait-multimethod model for Pediatric Quality of Life Inventory (PedsQL) Brain Tumor Module. Unique factors are not displayed. Pediatric Quality of Life Inventory (PedsQL) Brain Tumor Module has six subscales: *CP* cognitive problems, *PH* pain and hurt, *MB* movement and balance, *PA* procedural anxiety, *NA* nausea, *WO* worry

The MTMM model combines each subscale score (Fig. 3) into an independent element as either child's or parent's perception, thereby enabling calculation of perception from either child- or parent-reported scores. The MTMM model was tested via structural equation modeling (SEM) using a maximum-likelihood approach to derive parent and child perceptions from all six subscales in PedsQL™ Brain Tumor Module.

In previous research using an HRQOL measurement with seven subscales (the TACQOL), SEM confirmed that the MTMM model adequately explained child- and parent-reported scores [32]. We believe that SEM can also be used to validate the MTMM model for child- and parent-reported HRQOL scores and to calculate child- and parent-perception scores derived from the PedsQL™ Brain Tumor Module. Here, we tested the validity of the MTMM model via goodness-of-fit indices: model chi-squared $P > 0.05$, normed fit index (NFI) > 0.90, comparative fit index (CFI) > 0.90, standardized root mean squared residual (SRMR) < 0.06, and root mean square error of approximation (RMSEA) < 0.06 [34].

The latent scores of the child's and parent's perception about HRQOL were then estimated from the reported scores of each subscale and the factor score weight derived from the SEM. We decided to calculate the perception scores using PedsQL™ Brain Tumor Module. An exploratory factor analysis found that HRQOL derived from the PedsQL™ Brain Tumor Module may be separated into six

factors corresponding to the six subscales [24], and the total score of the brain-tumor subscales cannot be calculated. It follows then that the calculated perception scores indicate whether parents or children tend to score HRQOL high or low rather than the absolute value of children's HRQOL resulting from brain-tumor symptoms. In other words, the calculated perception scores are measuring perception, not HRQOL.

To confirm that the model effectively discriminates perception and condition, we assessed convergent and discriminant validity using the global HRQOL score of the PedsQL™ Generic Core Scales. Both the child- and parent-reported global HRQOL will be correlated with the children's HRQOL resulting from brain-tumor symptoms. The child-reported global HRQOL will also be correlated with child's reporting tendency, but uncorrelated with parent's tendency. Parent-reported global HRQOL will be correlated with parent's reporting tendency about their child's HRQOL, although uncorrelated with their child's tendency.

In the present study, the correlation of the calculated perception scores with the PedsQL™ Generic Core Scales (child's perception and self-reported global HRQOL; parent's perception and the parent-reported global HRQOL) was assessed using Spearman's rank correlation coefficient. We expected a correlation between the child's perception and the child-reported global HRQOL and a correlation between the parent's perception and the parent-reported global HRQOL, but did not expect a correlation between the parent's perception and the child-reported global HRQOL, or between the child's perception and the parent-reported global HRQOL. If there is a correlation between either reporter's (child or parent) calculated perception and the other reporter's (child or parent) reported HRQOL, we should conclude that the calculation cannot be estimating perception because the calculated scores may depend on the absolute value of the HRQOL.

Statistical analyses: regressions of perceptions about HRQOL

In the second step of the analysis, the factors that influence each child's or parent's perceptions were analyzed by multiple linear regression. Factors related to each child's perception about HRQOL and the parent's perception about their child's HRQOL were then identified by bivariate and multivariate correlation. The bivariate correlations were tested by Spearman's rank correlation coefficient, and the multivariate correlations were tested by the standardized partial regression coefficient from multiple linear regression analysis. A child's perception was treated as a dependent variable, and the following variables were treated as independent: method of administration, interviewer; child's trait anxiety, state anxiety, age, gender, age at diagnosis, time from diagnosis, and treatment status; and parent's subjective opinion regarding economic status and life. Given that we did not measure trait- or state-anxiety of children under 8 years of age, these data were not included in the multiple regression analysis, and regression for perception about children aged 5–7 years was recalculated excluding method of administration, child's trait anxiety, and state anxiety from independent variables.

In a second regression analysis, parents' perception was treated as a dependent variable, and the following variables as independent: parent's psychological distress, age, gender, academic background, time with child per day, subjective opinion regarding economic status and life, and child's treatment status. Missing values in the regression analyses were considered by list-wise case deletion, and independent variables were selected by a step-down procedure, mounted in SPSS software. This procedure was considered necessary, as when all independent variables were selected, the variables were multi-collinear and therefore regression could not be feasibly interpreted. Multi-collinearity was eliminated by removing causative variables one at a time. Regression analysis was then iterated, and after each successive calculation, the variable with the largest probability-of-F value was removed, until the probability-of-F value of all remaining variables was ≤ 0.1.

As a complementary step, we conducted a sensitivity analysis for the selected variables (related to child's or parent's perception) to assess the difference between child- and parent-reported HRQOL scores. Descriptive statistics (mean and standard deviation [SD]) of the differences between and Pearson's correlation coefficient for child- and parent-reported HRQOL were calculated for mean score of the six subscales of PedsQL™ Brain Tumor Module. We also conducted a multiple linear regression to confirm that the selected variables were related to the difference between child- and parent-reported HRQOL.

Statistical analyses: differences between self- and interviewer-administered child-reports

In the third step of the analysis, we used path analysis [35] to estimate the points difference between self- and interviewer-administered PedsQL™ child-reported scores. While ideally both types of administrations would be compared via a randomized sequence of administration, we considered this an excessive burden on the children with brain tumors. However, a simple comparison of self- and interviewer-administered HRQOL scores is likely to be biased; in that, interviewer-administered scores tend to be lower than self-administered scores because parents ask for interviewer-administration when their child presents with difficulties, such as visual impairment, motor dysfunction, or cognitive deficit.

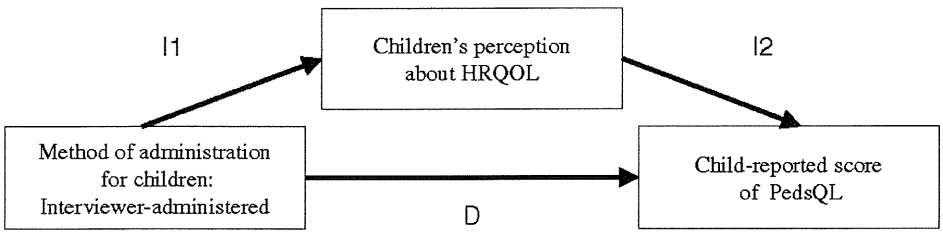

Fig. 4 Path analytic model to split the effect of the method of administration to child-reported HRQOL in two ways. Unique factors are not displayed. *D* direct effect; *I1*, *I2* subset of indirect effect

Bearing the above constraints in mind, we tested the direct and indirect effect of administration method on the children's perception about their own HRQOL (Fig. 4). An "indirect effect" was defined as a change in a child-reported HRQOL score that occurs when interviewer-administration changes the child's perception about HRQOL. A large indirect effect indicates a specific reporting bias by interviewer-administration that increases or decreases child-reported HRQOL. A "direct effect" was defined as a difference in child-reported HRQOL between self- and interviewer-administered scores, regardless of the perception. A larger direct effect indicates larger between-group differences in HRQOL condition, regardless of difference in perception.

For each PedsQL™ Brain Tumor Module subscale, we estimated three path coefficients and their standard error using path analysis [35]. The direct effect is the path from the method of administration to the child-reported scores of PedsQL™ (D in Fig. 4), and the indirect effect is the path from the method of administration to the children's perception about HRQOL (I1 in Fig. 4) times the path from the children's perception about HRQOL to the child-reported scores of PedsQL™ (I2 in Fig. 4). We also calculated 95% confidence intervals (CIs) for the direct and indirect effects [36].

All analyses were performed using SPSS software, version 12.0 J (SPSS, Inc., Chicago, Illinois, USA) and AMOS software, version 5.0 (SPSS, Inc., Chicago, Illinois, USA), and the level of significance was set at 0.05.

Results

Sample characteristics

The median age of the children was 11.0 years (Table 1). The sample was heterogeneous with respect to tumor pathology and treatment experience: the largest groups were embryonal tumors, germ cell tumors, and low-grade gliomas. Median time from diagnosis was 37 months, and 53 children (39.6%) were still under treatment. The other 81 children (61.8%) had completed treatment, and the interval from completion of treatment to the survey was 0.1–13.3 years. Of the responses from 106 children aged 8–18 years, 89 (84.0%) surveys were self-administered, and 17 (16.0%) were interviewer-administered (two with difficulty understanding the questionnaire, one with difficulty sustaining attention, two with difficulty reading, seven with optical impairment, two with difficulty writing by hand, one with both optical impairment and difficulty writing by hand, and two experiencing fatigue). All 28 children aged 5–7 years received interviewer-administered surveys.

Most parents were mothers ($n = 126$, 94.0%), with a median age of 41.0 years; 51 (38.9%) were high school graduates, and 80 (61.1%) were college or university graduates, while 84 (63.6%) considered their economic status to be affluent.

Measurement of HRQOL

The MTMM model for the PedsQL™ Brain Tumor Module was tested by the chi-squared $P = 0.087$ ($\chi^2 = 36.43$, degrees of freedom = 27), NFI = 0.932, CFI = 0.978, SRMR = 0.053, and RMSEA = 0.054, showing that the model was valid and enabling calculation of latent scores of children's and parent's perception about HRQOL. The child and parent scores were determined based on each child's or parent's perception (2–45%) and rater-independent condition (7–98%) (Table 2). A significant correlation was noted between the calculated scores of the children's perception about HRQOL and the child-reported—but not the parent-reported—global HRQOL ($r = 0.55$, $P < 0.001$ vs. $r = 0.07$, $P = 0.404$) (Table 3). Similarly, parents' perception about HRQOL was correlated with the parent-reported—but not the child-reported—global HRQOL ($r = 0.49$, $P < 0.001$ vs. $r = 0.10$, $P = 0.251$).

Factors related to children's and parent's perception

The difference in children's perception between self- and interviewer-administered reports was not significant ($P > 0.05$) (Table 4). In the multivariate analysis, the step-

Table 1 Subject characteristics ($N = 134$)

	Number of respondents (n)	% of total	Mean	SD	Median	Range
Age of children at survey (years)	134		11.1	3.7	11.0	5–18
Age at diagnosis (years)	134		7.3	4.5	7.0	0–18
Time from diagnosis (months)	134		45.8	41.6	37.0	1–202
Gender						
Male	73	54.9				
Female	60	45.1				
Tumor pathology						
Embryonal tumors	39	29.5				
Germ cell tumors	35	26.5				
Low-grade glioma	31	23.5				
High-grade glioma	15	11.4				
Other	12	9.1				
Treatment status						
On treatment	53	39.6				
Off treatment	81	60.4				
Time from treatment end (months)	79		44.7	37.1	34.0	1–160
Treatment received						
None	2	1.5				
Surgery (S)	15	11.2				
Radiation (R)	0	0.0				
Chemotherapy (C)	3	2.2				
$S + R$	13	9.7				
$S + C$	18	13.4				
$R + C$	4	3.0				
$S + R + C$	79	59.0				
Relationship of parent to child						
Mother	126	94.0				
Father	6	4.5				
Grandmother	1	0.7				
Grandfather	1	0.7				
Age of parents at survey (years)	133		41.0	5.5	41.0	26–63
Academic background of parents						
High schools						
Junior high school	1	0.8				
Senior high school	50	38.2				
Colleges and universities						
Vocational college	25	19.1				
Junior college	24	18.3				
University (undergraduate)	30	22.9				
University (graduate)	1	0.8				
Parents' time with children (hours per a day)	132		13.1	6.5	14.0	1–24
Subjective opinion regarding parents' own economic status and life						
Affluent	84	63.6				
Not affluent	48	36.4				
Method of administration for children						
Self-administered	89	66.4				
Interviewer-administered						
Interviewed by researcher	31	23.1				

Table 1 continued

	Number of respondents (*n*)	% of total	Mean	SD	Median	Range
Interviewed by parent	14	10.4				
State anxiety score of STAIC[a] (20–60)	104		29.9	7.8	29.0	20–52
Trait anxiety score of STAIC[a] (20–60)	97		34.9	8.8	36.0	20–52
K10[b] score (0–40)	132		7.7	7.0	6.0	0–31
PedsQL global HRQOL score[c] (0–100)						
Self-reported	132		77.7	17.2	80.4	11–100
Parent-reported	134		73.7	17.0	75.0	20–100

Missing data were excluded

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

[a] State Trait Anxiety Inventory for Children. A higher score indicates that children have higher anxiety

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

[c] Pediatric Quality of Life Inventory Generic Core Scales. A higher score indicates that children have higher quality of life

Table 2 Percentage-explained variance in an MTMM model of HRQOL ($N = 134$)

Subscales of PedsQL brain tumor module	Condition	Perception	Error
Cognitive problems			
Child	30	27	43
Parent	71	6	24
Pain and hurt			
Child	35	8	57
Parent	41	12	47
Movement and balance			
Child	45	23	32
Parent	96	3	1
Procedural anxiety			
Child	98	2	0
Parent	41	5	54
Nausea			
Child	95	5	0
Parent	43	19	37
Worry			
Child	48	14	38
Parent	7	45	48

HRQOL health-related quality of life, *MTMM* multitrait-multimethod, *PedsQL* Pediatric Quality of Life Inventory

down procedure excluded the method of administration as an independent variable related to the children's perception.

Trait anxiety was the strongest factor related to children's perception ($r = -0.46$, $b = -0.43$). Children with higher trait anxiety had lower perception about HRQOL ($P < 0.05$). Older children or children from less affluent families also had a lower perception, but these results were not statistically significant. Bivariate analysis showed that children with higher state anxiety had a lower perception about HRQOL; however, this result was not confirmed on multivariate analysis and was therefore determined to be a spurious correlation. This indicates that the relationship between state anxiety and a child's perception is superficial. This relationship was clarified by conducting a staged analysis to identify which covariates attenuated the relationship (Table 5), which found that trait anxiety attenuated the relationship.

With regard to children aged 5–7 years, none of the variables tested were found to be significantly correlated with the children's perception; the strongest relationship was "interviewer" ($r = -0.27$, $P = 0.162$, $n = 28$). Children interviewed by a parent tended to have a lower perception about HRQOL than children interviewed by researcher.

The strongest factor influencing a parent's perception was treatment status (Table 6). The parents of children on treatment had a tendency to report that their child had a

Table 3 Correlation between calculated scores of perception and reported global HRQOL ($N = 134$)

	Child-reported global HRQOL		Parent-reported global HRQOL	
	r	*P*	*r*	*P*
Calculated scores of child's perception about HRQOL	0.55	<0.001	0.07	0.404
Calculated scores of parent's perception about HRQOL	0.10	0.251	0.49	<0.001

HRQOL health-related quality of life, *r* Spearman's rank correlation coefficient

Table 4 Factors related to calculated scores of children's perception about HRQOL ($N = 134$)

	n	*r*	95% CI	*b*	95% CI
Trait anxiety score of STAIC[a]	97	−0.46*	(−0.60, −0.29)	−0.43*	(−0.60, −0.25)
State anxiety score of STAIC[a]	104	−0.27*	(−0.44, −0.08)	–	
Age at survey	133	−0.14	(−0.30, 0.03)	−0.17	(−0.35, 0.01)
Age at diagnosis	134	0.01	(−0.16, 0.18)	–	
Time from diagnosis	134	−0.09	(−0.26, 0.08)	–	
Gender (0: Male, 1: Female)	133	0.02	(−0.15, 0.19)	–	
Treatment status (0: on treatment, 1: off treatment)	134	−0.06	(−0.23, 0.11)	–	
Subjective opinion regarding parents' own economic status and life (0: not affluent, 1: affluent)	132	0.07	(−0.10, 0.24)	0.16	(−0.01, 0.34)
Method of administration for children (0: self-administered, 1: interviewer-administered)	134	−0.06	(−0.23, 0.11)	–	
Dummy-coded variable for comparison between researcher interviews and parent interviews					
Researcher interviews[b]	134	0.03	(−0.14, 0.20)	–	
Parent interviews[c]	134	−0.13	(−0.29, 0.04)	–	

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 ($n = 96$, $R^2 = 0.264$)

* $P < 0.05$

– variables not selected by step-down procedure

[a] State Trait Anxiety Inventory for Children. A higher score indicates that children have higher anxiety

[b] 0: self-administered or parent-administered, 1: researcher-administered

[c] 0: self-administered or researcher-administered, 1: parent-administered

Table 5 Factors that attenuate the relationship between children's state anxiety and lower perception about HRQOL ($N = 96$)

	b	*b*	*b*	*b*	*b*
State anxiety score of STAIC[a]	−0.29*	−0.12	−0.24*	−0.26*	−0.06
Trait anxiety score of STAIC[a]		−0.40*			−0.39*
Age at survey			−0.17		−0.17
Subjective opinion regarding parents' own economic status and life (0: not affluent, 1: affluent)				0.11	0.14

HRQOL health-related quality of life, *b* Standardized partial regression coefficient by multiple linear regression analysis

* $P < 0.05$

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

lower HRQOL than those of children who were off treatment. The parents with higher K10 scores who were high school graduates also had a lower perception about their child's HRQOL lower than those parents with lower K10 scores who were college or university graduates. Other variables (age, gender, time with the child per day, and subjective opinion regarding economic status and life) had no influence on a parent's perception about HRQOL.

The sensitivity analysis identified significant differences in the following parameters between child- and parent-reported scores: trait anxiety, parent's psychological distress, treatment status, or academic background of parents (Table 7). Children with elevated trait anxiety rated their HRQOL much lower on average, thereby reducing the difference between child- and parent-reported scores (Fig. 5). Parents with elevated K10 scores, those of children on treatment, and those who were high school graduates also scored their child's HRQOL much lower than did their children themselves, thus increasing the difference between child- and parent-reported scores. Multiple regression analysis also demonstrated that the child's trait anxiety and parent's K10 score were related to the differences between child- and parent-reported HRQOL (Table 8). The relationship between these differences and the child's treatment status and parent's academic background was not statistically significant.

Differences between self- and interviewer-administered child-reports

The method of administration induced indirect effects, which resulted in a decrease of 1.1–2.5 points in child-

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

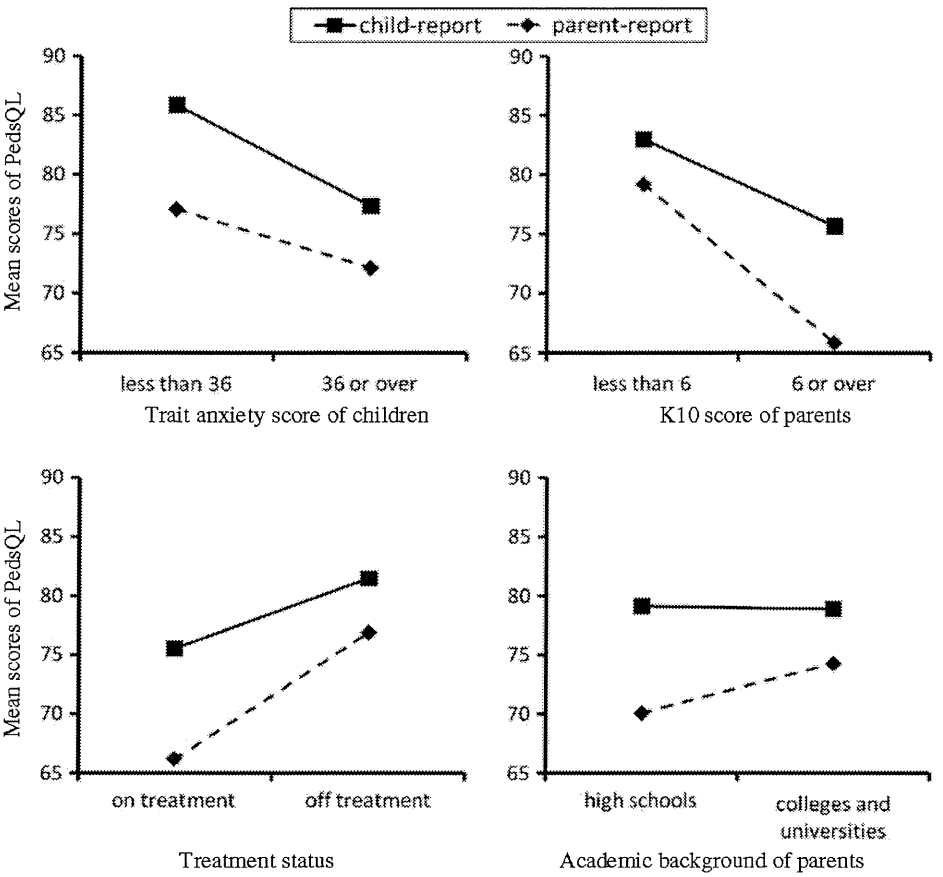

Fig. 5 Differences between child- and parent-reported mean scores of six subscales of PedsQL Brain Tumor Module by socio-demographic and health characteristics

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