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Comparison of ^{11}C-Methionine, ^{11}C-Choline, and ^{18}F-Fluorodeoxyglucose-PET for Distinguishing Glioma Recurrence from Radiation Necrosis

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Abstract

The aim of this study is to assess the different metabolic activities characteristic of glioma recurrence and radiation necrosis (RN) and to explore the diagnostic accuracy for differentiation of the two conditions using ^{11}C-methionine (MET), ^{11}C-choline (CHO), and ^{18}F-fluorodeoxyglucose (FDG)-positron emission tomography (PET). Fifty patients with lesions suggestive of recurrent glioma by MRI underwent MET, CHO, and FDG-PET. All patients who had previously been treated with radiotherapy for malignant glioma were subjected to open surgery and pathological diagnosis (17 recurrent grade 3- gliomas (Gr.3s) comprising 7 anaplastic astrocytomas (AAs) and 10 anaplastic oligodendrogliomas (AOs), 17 recurrent glioblastomas (Gr.4s), and 16 RNs). We measured the PET/Gd volume ratio, the PET/Gd overlap ratio, and the lesion/normal brain uptake ratio (L/N ratio) and determined the optimal index of each PET scan. The PET/Gd volume ratio and the PET/Gd overlap ratio for RN were significantly lower than those of glioma recurrence only with MET-PET ($P < 0.05$). The L/N ratio of RN was significantly lower than that of Gr.4 with all PET imaging ($P < 0.001$) and was significantly lower than that of Gr.3, especially for AO, only with MET-PET images ($P < 0.005$). Receiver operating characteristic (ROC) analysis showed that the area under the curve of MET, CHO, and FDG was 92.5, 81.4, and 77.4, respectively. MET L/N ratio of greater than 2.51 provided the best sensitivity and specificity for establishing glioma recurrence (91.2% and 87.5%, respectively). These results demonstrated that MET-PET was superior to both CHO and FDG-PET for diagnostic accuracy in distinguishing glioma recurrence from RN.

Key words: ^{11}C-methionine, positron emission tomography, radiation necrosis, glioma

Introduction

Radiation necrosis (RN) is a serious clinical complication in the diagnosis and treatment of patients with malignant gliomas. Because the imaging features of most RN appear similar to those of malignant gliomas by computed tomography (CT) or magnetic resonance imaging (MRI), it is difficult to distinguish glioma recurrence from RN. Since therapeutic strategies for these pathological entities are fundamentally different, their differential diagnosis is crucial. Recently, several clinical studies using diffusion MRI,[1–4] perfusion MRI,[3] MR spectroscopy,[3–5] and ^{201}thallium-SPECT[6] have been undertaken in attempts to distinguish between the two conditions. These modalities have made it possible to easily diagnose some cases compared to protocols from the previous era in which only conventional CT or MRI was used. Furthermore, ^{11}C-methionine (MET) and ^{18}F-fluorodeoxyglucose (FDG)-positron emission tomography (PET) have been reported to be more useful for differential diagnosis between glioma recurrence and RN.[6–13] These PET methods were suggested to be superior to other structural neuroimaging modalities from the view-point of feasibility of quantitative evaluation of MET or FDG metabolism in lesions. ^{11}C-choline (CHO) is another tracer candidate which has been

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suggested to be useful for diagnosis of brain tumors in recent PET studies.[14,15]

It is still unclear which PET tracer is best for distinguishing glioma recurrence from RN. We hypothesized that MET-PET is superior to CHO and FDG-PET in this regard, since previous reports have shown the prominent high uptake of CHO may not differentiate non-neoplastic brain lesions with Gd-enhancement from malignant glioma on PET and the high background uptake of FDG in the brain may make it difficult to visually distinguish lesions from normal brain tissue. In this study, the three PET tracers, MET, CHO, and FDG, were compared to determine which PET method was superior for differentially diagnosing glioma recurrence from RN.

Materials and Methods

In this retrospective study from 2002 to 2008, we examined PET scans from 50 consecutive patients with supratentorial space-occupying lesions following radiotherapy for malignant gliomas at the Chubu Medical Center for Prolonged Traumatic Brain Dysfunction, Kizawa Memorial Hospital. All supratentorial space-occupying lesions were Gd-enhanced, and interpretation of the lesions as glioma recurrence or RN was unclear. Presurgical radiologic evaluation was performed with MET, CHO, FDG-PET, and MR imaging in all patients. PET scans and MR imaging were performed in a single day, and the PET images were evaluated using the co-registered MR images. All patients underwent open surgical procedures within 4 weeks after PET scanning, and tumors were classified upon histological examination using the World Health Organisation (WHO) classification system.[16] Of the 50 patients, 17 had recurrent grade 3- glioma (Gr.3), 17 had recurrent glioblastoma (Gr.4), and 16 had RN. The 17 Gr.3s were further classified as 7 anaplastic astrocytomas (AAs) and 10 anaplastic oligodendrogliomas (AOs). RN was pathologically diagnosed in the limited cases in which the surgical specimen showed typical necrotic tissues including thickness and fibrinoid necrosis of the vascular walls, multiple microcysts, coagulation necrosis, endothelial proliferation, and inflammatory cells interspersed with or without scattered tumor cells. The clinical features of the patients are summarized in Table 1. All patients gave written informed consent, and the study protocol was approved by the research committee of the Kizawa Memorial Hospital Foundation.

The PET study was carried out according to standardized procedures recommended by the Japan Radioisotope Association.[17,18] The PET scanner was an ADVANCE NXi Imaging System (General Electric Yokokawa Medical System, Hino-shi, Tokyo), which provided 35 transaxial images at 4.25 mm intervals covering a 25.6 cm in-plane field of view. The in-plane spatial resolution (full width at half maximum) was 4.8 mm, and the scan mode was the standard 2D mode. Before the emission scan was performed, a 3 minute transmission scan was performed to correct photon attenuation with a ring source containing ^{68}Ge. Patients had fasted for at least 4 hours before PET studies. A venous cannula was inserted into the forearm for injection of radiopharmaceuticals. From this cannula, blood samples could also be collected if necessary. A dose of 7.0 MBq/kg of MET, 7.0 MBq/kg of CHO, or 5.0 MBq/kg of FDG was injected intravenously, depending on the particular examination.[17,18] Emission scans were acquired as follows: (1) for 30 minutes, beginning 5 minutes after MET injection, (2) for 7 minutes, beginning 2 minutes after CHO injection, and (3) for 7 minutes, beginning 35 minutes after FDG injection. During PET data acquisition, head motion was continuously monitored using laser beams projected onto ink marks drawn on the forehead and was corrected manually, as necessary. Scan images were reconstructed using the ordered-subsets expectation maximization algorithm (2 iterations, 14 subsets).[19] Images were reconstructed into a 128 × 128 matrix with a pixel size of 2 × 2 mm.

MR imaging was performed with a 1.5 T system (Signa; GE Medical Systems, Milwaukee, Wisconsin, USA). Axial T_1-weighted images (TR/TE/NEX = 350/9/2), T_2-weighted images (2300/100/2), and FLAIR images (800/110/1, inversion time = 2400 ms) (FOV 24 × 24 cm, matrix size 512 × 256) were acquired. The slice thickness was 6 mm, with a 3-mm slice gap. For co-registration of metabolic and anatomic data, 3D spoiled gradient-echo images were also acquired after administration of 0.2 ml/kg of gadopentate dimeglumine (Gd-DTPA) (Magnevist; Nihon Shering, Osaka) using the following parameters: no gap, 1.0 mm thickness, TR/TE = 20.0/1.6 ms, flip angle = 15°, NEX = 1, and axial views.

Tracer accumulation in the regions of interest (ROIs) was analyzed as the standardized uptake value (SUV), which is the activity concentration in the ROI at a fixed time point divided by the injected dose normalized to the patient's measured weight. MET, CHO, and FDG lesion/normal brain uptake ratios (L/N ratios) were calculated by dividing the maximum SUV for the enhanced lesion on the MR image by the mean SUV of the contralateral normal frontal cortex. The lesion SUVs were selected at the highest accumulation, and reference ROIs on each of the three axial planes were drawn with a diameter of 10 mm. Co-registration

Table 1 Summary of clinical features of patients

Pathology	Number of patients	Sex (male: female)	Age (Mean ± SD, y.o.)	Primary tumor pathology (no. of patients)	Primary radiation therapy (no. of patients)	RT dose (Mean ±SD, Gy)	Primary chemotherapy (no. of patients)	Time between RT and this study (Mean ± SD, months)
RN	16	7 : 9	49.1 ± 15.7	AA: 9 AO: 2 GBM: 5	Ex-RT: 8 SRT: 5 Proton therapy + RT: 3	56.1 ± 9.3	TMZ: 8 ACNU + VCR: 2 PCV: 1 CBDCA+VP-16:1 None: 4	28.2 ± 34.4
Gr.3	17	12 : 5	45.7 ± 18.0			53.2 ± 4.4		39.8 ± 41.8
AA	7	6 : 1	45.9 ± 19.2	AA: 7	Ex-RT: 5 SRT: 2	54.6 ± 4.6	TMZ: 1 MCNU: 1 CBDCA+VP-16: 1 None: 4	34.0 ± 49.0
AO	10	6 : 4	45.6 ± 18.1	AO: 10	Ex-RT: 10	52.2 ± 4.2	PCV: 3 MCNU+INF-β: 1 TMZ: 1 None: 5	43.9 ± 38.2
Gr.4	17	7 : 10	42.1 ± 15.6	AA: 7 GBM: 10	Ex-RT: 14 SRT: 2 Proton therapy + RT: 1	60.1 ± 10.2	TMZ: 5 ACNU+VCR: 4 CBDCA+VP-16: 2 None: 6	31.6 ± 42.0

AA: anaplastic astrocytoma, ACNU: nimustine, AO: anaplastic oligodendroglioma, CBDCA: carboplatin, Ex-RT: conventional external radiation therapy, GBM: glioblastoma, Gr.3: recurrent grade 3- glioma, Gr.4: recurrent glioblastoma, INF-β: interferon-β, MCNU: ranimustine, PCV: procarbazine-lomustine-vincristine sulfate therapy, RN: radiation necrosis, RT: radiation therapy, SD: standard deviation, SRT: stereotactic radiotherapy, TMZ: temozoromide, VCR: vincristine sulfate, VP-16: etoposide, y.o.: years old.

of PET and MR imaging was accomplished with an analysis software package (AJS, Tokyo), using the method described by Kapouleas et al.[20] We used the L/N ratio instead of the absolute SUV because of the high, unexplained intersubject variability of the SUV.[21] We used the lesion maximum SUV instead of lesion mean SUV to minimize the effect of lesion heterogeneity. For each PET tracer, we defined regions with L/N ratios greater than 1.5 as PET abnormal high uptake regions and measured the volumes of these regions in each PET image and also the volumes of the Gd-enhanced area in the MRI using an analysis software package (AJS, Tokyo). The volume of the PET abnormal high uptake region overlap with the Gd-enhanced area was measured by the same method for each case. The volume ratio of the PET abnormal high uptake area to Gd enhanced MR area (PET/Gd volume ratio) was calculated as follows: PET/Gd volume ratio (%) = [PET abnormal high uptake area (volume) ÷ Gd-enhanced area (volume)] × 100.

The ratio of the PET abnormal high uptake area overlapping the Gd-enhanced MR area (PET/Gd overlap ratio) was calculated as follows: PET/Gd overlap ratio (%) = [PET abnormal high uptake area overlapping Gd-enhanced area (volume) ÷ Gd-enhanced area (volume)] × 100.

Data are presented as means ± standard deviations (SDs). To compare the L/N ratios of the three PET modalities at the best distinction between glioma recurrence and RN, statistical analysis was performed using analysis of variance and Tukey's test for multiple comparisons. Receiver operating characteristic (ROC) curves were calculated to determine the cut off values for differential diagnosis of glioma recurrence and RN. P values less than 0.05 were considered statistically significant.

Results

I. Volume comparison between MRI and PET studies

The MET-PET/Gd volume ratios of RN, AA, AO, and Gr.4 were 21.7% ± 20.9%, 164.3% ± 158.5%, 185.5% ± 162.6%, and 123.6% ± 66.4%, respectively (Fig. 1A). The MET-PET/Gd overlap ratios of RN, AA, AO, and Gr.4 were 20.7% ± 21.4%, 63.5% ± 40.3%, 74.8% ± 34.0%, and 64.6% ± 29.4%, respectively (Fig. 1D). Both the MET-PET/Gd volume ratio and the MET-PET/Gd overlap ratio of RN were significantly lower than those of AA, AO, and Gr.4, respectively ($P < 0.05$).

The CHO-PET/Gd volume ratios of RN, AA, AO, and Gr.4 were 100.5% ± 20.5%, 110.2% ± 17.3%, 99.9% ± 15.9%, and 104.1% ± 13.7%, respectively (Fig. 1B). The CHO-PET/Gd overlap ratios of RN, AA, AO, and Gr.4 were 83.6% ± 15.1%, 97.4% ± 3.9%, 92.5% ± 10.3%, and 96.1% ± 7.1%, respectively (Fig. 1E). There were no significant differences of the CHO-PET/Gd volume ratios and the CHO-PET/Gd overlap ratios among RN, AA, AO, and Gr.4.

The FDG-PET/Gd volume ratios of RN, AA, AO, and Gr.4 were 0.4% ± 1.5%, 0.5% ± 1.3%, 0.0% ± 0.0%, and 12.1% ± 20.6%, respectively (Fig. 1C). The FDG-PET/Gd overlap ratios of RN, AA, AO, and Gr.4 were 0.4% ± 1.5%, 0.5% ± 1.3%, 0.0% ± 0.0%, and 11.7% ± 19.4%, respectively (Fig. 1F). Both the FDG-PET/Gd volume ratio and the FDG-PET/Gd overlap ratio of Gr.4 were significantly higher than those of RN ($P < 0.05$).

II. Semiquantitative analysis of PET studies

The mean SUVs of MET, CHO, and FDG from the contralateral normal frontal cortex were 1.30 ± 0.25, 0.26 ± 0.94, and 6.31 ± 1.71, respectively. MET L/N ratios of RN, Gr.3, and Gr.4 were 1.95 ± 0.60, 3.40 ± 1.04, and 4.29 ± 1.45, respectively. There was a significant difference between the MET L/N ratios of RN and Gr.3 ($P < 0.005$) and of RN and Gr.4 ($P < 0.001$). However, there was no significant difference between the MET L/N ratios of Gr.3 and Gr.4 (Fig. 2A). MET L/N ratios of AA and AO were 2.79 ± 0.68, and 3.83 ± 1.06, respectively. There was a significant difference between the MET L/N ratios of RN and AO ($P < 0.001$) and AA and AO ($P < 0.05$), but not of RN and AA (Fig. 2D).

CHO L/N ratios of RN, Gr.3, and Gr.4 were 6.90 ± 4.30, 11.18 ± 6.75, and 18.09 ± 10.82, respectively. There was a significant difference only between the CHO L/N ratios of RN and Gr.4 ($P < 0.001$) and of Gr.3 and Gr.4 ($P < 0.05$) (Fig. 2B). CHO L/N ratios of AA and AO were 9.21 ± 4.19, and 12.56 ± 8.01. There was no significant difference between CHO L/N ratios of RN and any of the Gr.3 histological types (Fig. 2E).

FDG L/N ratios of RN, Gr.3, and Gr.4 were 1.15 ± 0.50, 1.26 ± 0.23, and 1.97 ± 0.64, respectively. There was a significant difference only between the FDG L/N ratios of RN and Gr.4 ($P < 0.001$) and of Gr.3 and Gr.4 ($P < 0.001$) (Fig. 2C). FDG L/N ratios of AA and AO were 1.24 ± 0.33, and 1.27 ± 0.16, respectively. There was no significant difference between FDG L/N ratios of RN and any of the Gr.3 histological types (Fig. 2F).

Representative PET and MRI images from RN, AA, AO, and Gr.4 cases are shown in Fig. 3.

III. ROC analysis of PET studies

Fig. 2G shows the ROC curves of the 3 PET modalities. The area under the curve of MET, CHO, and FDG-PETs were 0.925, 0.814, and 0.774,

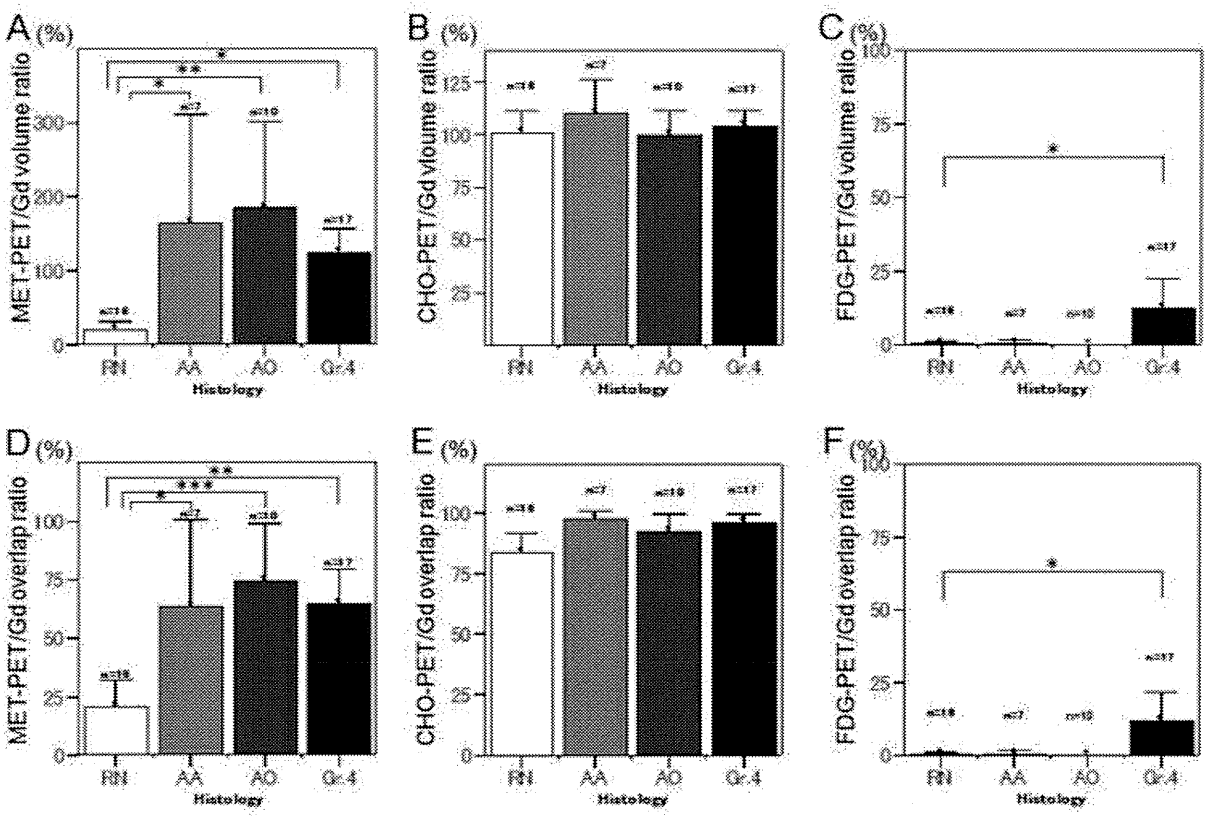

Fig. 1 Graphs showing ^{11}C-methionine (MET)-PET/Gd (A), ^{11}C-choline (CHO)-PET/Gd (B), and ^{18}F-fluorodeoxyglucose (FDG)-PET/Gd (C) volume ratios, and MET-PET/Gd (D), CHO-PET/Gd (E), and FDG-PET/Gd (F) overlap ratios of radiation necrosis (RN), anaplastic astrocytoma (AA), anaplastic oligodendroglioma (AO), and recurrent glioblastoma (Gr.4). The significant low values ($P < 0.05$) of both the PET/Gd volume ratio and the PET/Gd overlap ratio of RN compared with glioma recurrence were shown to be characteristic only for MET-PET. *$P < 0.05$, **$P < 0.005$, ***$P < 0.001$.

respectively. Table 2 shows the best cutoff values, diagnostic sensitivities, and specificities of the 3 PET modalities for recurrent gliomas. The best MET L/N ratio cutoff value was 2.51, which provided a sensitivity of 91.2% and a specificity of 87.5% for diagnosis of glioma recurrence. These results indicate that MET-PET is the most informative method for differentiating tumor recurrence from RN.

Discussion

Radiotherapy has been used for the past four decades as a standard treatment following surgical mass reduction in malignant gliomas. More recently, conventional external radiotherapy has been expanded to include stereotactic radiotherapy, intensity modulated radiotherapy, boron neutron captured therapy, and radiotherapy using heavy ions.[22–25] The usefulness of radiotherapy for malignant gliomas is not in doubt as it has been verified by improved patient survival and local control. However, identifying RN, which deteriorates the clinical condition of patients, is still a critical problem.[26] Normally, 60 Gy of whole brain external irradiation induces necrosis in about 50% of patients up to 5 years after irradiation. Although the therapeutic strategy for RN is different from that for glioma recurrence in most cases of malignant gliomas, it has been difficult to distinguish these pathological entities from each other even using conventional neuroradiological modalities.

With advancements in metabolic neuroimaging, ^{201}thallium-SPECT and FDG-PET have been anticipated to be useful for differential diagnosis between glioma recurrence and Gómez-Río et al. prospectively evaluated ^{201}thallium-SPECT and FDG-PET in 76 patients with suspicion of glioma recurrence after

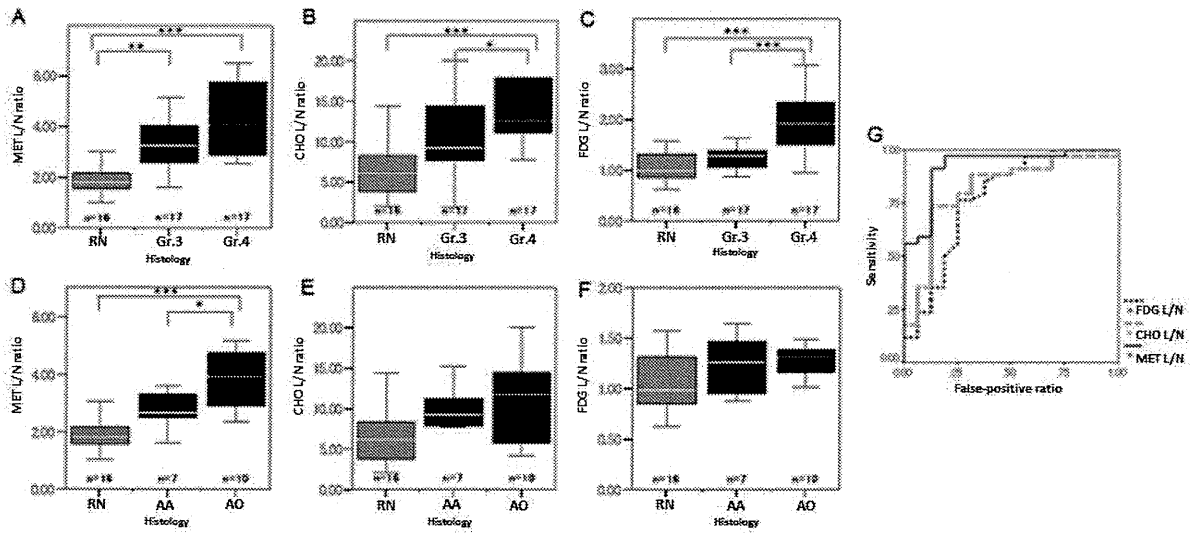

Fig. 2 Graphs showing ^{11}C-methionine (MET) (A), ^{11}C-choline (CHO) (B), and ^{18}F-fluorodeoxyglucose (FDG) (C) lesion/normal brain uptake ratios (L/N ratios) of radiation necrosis (RN), recurrent grade 3- glioma (Gr.3), and recurrent glioblastoma (Gr.4), and MET (D), CHO (E), and FDG (F) L/N ratios of RN, anaplastic astrocytoma (AA), and anaplastic oligodendroglioma (AO). The significant differences of tracer uptake intensity between Gr.4 glioma recurrence and RN were shown in MET ($P < 0.001$), CHO ($P < 0.001$), and FDG ($P < 0.001$) -PETs. Gr. 3 glioma recurrence, especially for AO, could be distinguished from RN only in MET-PET ($P < 0.005$). Graph (G) shows receiver operating characteristic (ROC) curves for the three PET tracers for distinguishing glioma recurrence from RN. The areas under the curve of MET, CHO, and FDG are 0.926, 0.822, and 0.755, respectively. $*P < 0.05$, $**P < 0.005$, $***P < 0.001$.

surgical excision and radiotherapy.[27] Their results showed that although FDG-PET yielded a slightly higher specificity for diagnosis of glioma recurrence, the sensitivity was considerably lower than that of ^{201}thallium-SPECT. This means that FDG-PET does not clearly improve upon the diagnostic accuracy of ^{201}thallium-SPECT in glioma recurrence.

CHO is another PET tracer recently used for neuroradiological evaluation of gliomas, and it was reported to be a diagnostic agent which was able to differentiate between low-grade gliomas and high-grade gliomas in PET studies, but had not been used for studies of RN.[14] Apart from RN, a high uptake of CHO is also reported in non-neoplastic lesions including brain abscess, inflammatory granulomas, tuberculomas, and some demyelinating diseases which present Gd-enhancement by MRI.[28] A study by Ohtani et al. showed that CHO-PET did not differentiate, in particular, between low-grade gliomas and non-neoplastic lesions.[14] Utriainen et al. described that an association between CHO uptake measured with PET and the concentration of choline containing components measured by 1H-MR spectroscopy was not statistically significant.[29] This data suggests that CHO uptake is scarcely related to intracellular metabolite pools of phosphocholine and glycerophosphocholine.[28] In this study, both the CHO-PET/Gd volume ratio and the CHO-PET/Gd overlap ratio of RN, AA, AO, and Gr.4 were all at levels near 100%. This suggests that there is a regional correspondence between areas of high CHO uptake on PET images and areas with Gd-enhancement on the MRI. These results imply that CHO uptake is mostly dependent on the enhancement effect, which is related to the passive diffusion of materials in regions with BBB disruption, rather than tissue biological activity, which is related to the active transport of materials.

One of the most promising modern neuroimaging protocols in this regard is MET-PET, a popular amino acid imaging modality in oncology indications. MET-PET has been a useful and reliable neuroimaging modality for diagnosis of gliomas because of the correlation of MET-uptake with malignancy and proliferative activity in gliomas and its accumulation during glioma cell invasion.[30,31] Normally, MET uptake is reported to be lower in RN than in glioma recurrence. Tsuyuguchi et al. reported that the mean L/N ratios for RN and glioma recurrence were 1.31 and 1.87.[11] In

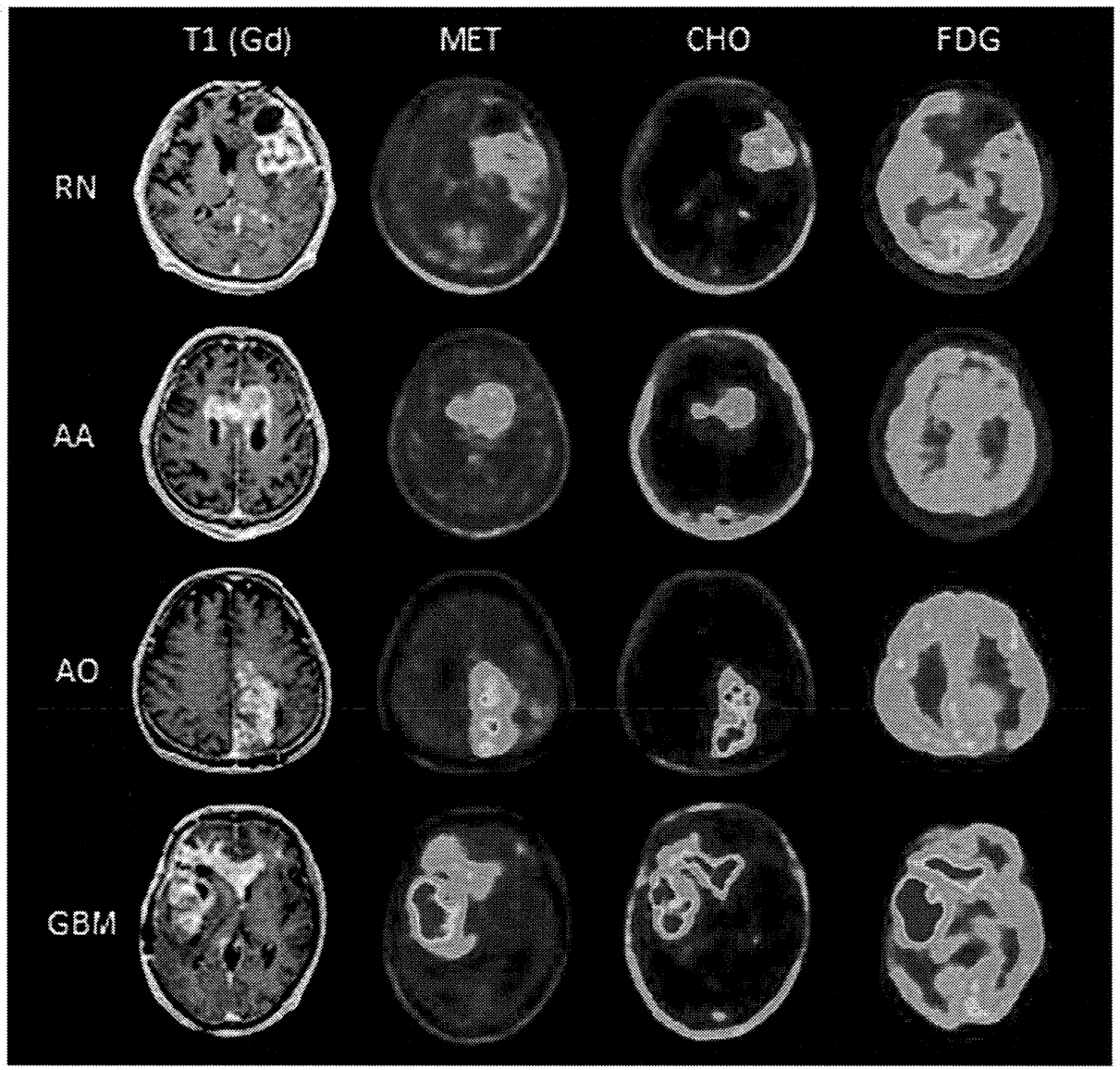

Fig. 3 Representative PET and MRI images of radiation necrosis (RN), anaplastic astrocytoma (AA), anaplastic oligodendroglioma (AO), and glioblastoma (GBM) are shown. RN: A 45-year-old man. ^{11}C-methionine (MET)-PET/Gd volume ratio = 57.0%, MET-PET/Gd overlap ratio = 57.0%, ^{11}C-choline (CHO)-PET/Gd volume ratio = 81.5%, CHO-PET/Gd overlap ratio = 81.5%, ^{18}F-fluorodeoxyglucose (FDG)-PET/Gd volume ratio = 0%, FDG-PET/Gd overlap ratio = 0%, MET lesion/normal brain uptake ratio (L/N ratio) = 3.34, CHO L/N ratio = 2.03, and FDG L/N ratio = 1.57. AA: A 67-year-old man. MET-PET/Gd volume ratio = 189.4%, MET-PET/Gd overlap ratio = 100%, CHO-PET/Gd volume ratio = 121.3%, CHO-PET/Gd overlap ratio = 100%, FDG-PET/Gd volume ratio = 0%, FDG-PET/Gd overlap ratio = 0%, MET L/N ratio = 3.39, CHO L/N ratio = 7.7, and FDG L/N ratio = 1.65. AO: A 51-year-old man. MET-PET/Gd volume ratio = 172.7%, MET-PET/Gd overlap ratio = 100%, CHO-PET/Gd volume ratio = 107.8%, CHO-PET/Gd overlap ratio = 95.3%, FDG-PET/Gd volume ratio = 0%, FDG-PET/Gd overlap ratio = 0%, MET L/N ratio = 5.03, CHO L/N ratio = 14.41, and FDG L/N ratio = 1.31. GBM: A 35-year-old man. MET-PET/Gd volume ratio = 164.9%, MET-PET/Gd overlap ratio = 100%, CHO-PET/Gd volume ratio = 109.2%, CHO-PET/Gd overlap ratio = 98.7%, FDG-PET/Gd volume ratio = 74.3%, FDG-PET/Gd overlap ratio = 67.5%, MET L/N ratio = 5.21, CHO L/N ratio = 17.94, and FDG L/N ratio = 2.33.

Table 2 The best cutoff values and diagnostic accuracy for distinguishing glioma recurrence from RN

Index	Cutoff value	Sensitivity (%)	Specificity (%)
MET L/N	> 2.51	91.2	87.5
CHO L/N	> 8.92	73.5	87.5
FDG L/N	> 1.26	76.5	75.0

CHO: ^{11}C-choline, FDG: ^{18}F-fluorodeoxyglucose, MET: ^{11}C-methionine, L/N: lesion/normal brain uptake, RN: radiation necrosis.

a comparative study, Sonoda et al. showed that MET-PET was superior to ^{201}tallium-SPECT for the differentiation of tumor recurrence from RN.[6] In a comparative study of FDG and MET-PET, van Laere et al. reported that MET was superior to FDG as a diagnostic agent for the evaluation of glioma recurrence because of its higher sensitivity for differentiation from RN.[31]

This is the first study directly comparing the three PET tracers, MET, CHO, and FDG evaluating the diagnostic accuracy in distinguishing glioma recurrence from RN in the same clinical setting. From the ROC analysis of this study, MET-PET was found to be the best of the three tracers in differentiating glioma recurrence from RN with a sensitivity of 91.2% and a specificity of 87.5% with a MET max L/N ratio cutoff value of 2.51. Additionally, only MET-PET could significantly differentiate Gr.3, especially AO, as well as Gr.4 from RN, while FDG and CHO-PET could differentiate only Gr.4 from RN. The L/N ratio cutoff values in this study were relatively higher than that of the previous studies, because L/N ratios were calculated by dividing the maximum SUV for the enhanced lesion on MR imaging by the mean SUV of the contralateral noemal frontal cortex. We used the maximum SUV instead of lesion mean SUV to minimize the effect of lesion heterogeneity.

This study showed the superiority of MET-PET for distinguishing glioma recurrence from RN based on evaluation of intensity of tracer uptake in agreement with previous reports. The significant low values of both the PET/Gd volume ratio and the PET/Gd overlap ratio of RN compared with glioma recurrence were characteristic only with the MET-PET and provide additional evidence for distinguishing glioma recurrence from RN.

The main mechanism for MET accumulation in RN; BBB disruption-related passive diffusion, is presumed to differ from that in tumor recurrence which is active transport affected by cell proliferation. The different mechanisms of MET accumulation for the two pathological processes are the means of potentially distinguishing glioma recurrence from RN by MET-PET. However, because of the substantial tissue biological activity in RN due to cells related to immunological and inflammation reactions and reactive glia cells with a high proliferation potential, some degree of active transport for MET may increase the MET uptake in RN. Additionally, there should be mixed tissues with both RN and residual/recurrent tumor cells around the irradiated region, because it is not feasible to completely kill the malignant glioma cells by clinical irradiation doses. These factors contribute to the continuing difficulty of distinguishing glioma recurrence from RN even using MET-PET in some cases, and further studies for a resolution of this problem are needed.

Recently, 3,4-dihydroxy-6-^{18}F-fluoro-L-phenylalanine (FDOPA) has been utilized as another promising amino acid PET tracer for distinguishing tumor recurrence from RN. Chen et al. reported 98% sensitivity and 86% specificity for the detection of glioma recurrence using FDOPA-PET.[32] 3'-Deoxy-3'-^{18}F-fluorothymicine (FLT) is another recently developed PET tracer for imaging tumor cell proliferation that correlated with Ki-67 values.[33] These tracers appear to be powerful predictors of tumor progression and survival, and comparative studies to evaluate which of the tracers, MET, FDOPA, and FLT, is the most accurate for distinguishing glioma recurrence from RN is needed.

In this study, three PET scans were taken on a single day. This introduced an increase of radiation exposure to patients compared with a single PET scan. "Cross-talk" between PET tracers during subsequent imaging was considered to be minimal, because ^{11}C-labeled tracers such as MET and CHO have short half-lives and sufficient time was allowed between PET scans. However, from this minimal "cross-talk", the order of PET scans (MET, CHO, FDG) could have slightly contributed to our observed result.

MET-PET appears to be superior to both CHO and FDG-PET in diagnostic accuracy for distinguishing glioma recurrence from RN on the basis of intensity as well as extent of tracer uptake volume, and it could play an important role in monitoring newly appearing Gd-enhanced lesions on MRI following radiotherapy in patients with malignant gliomas.

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Conflicts of Interest Disclosure

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices in the article. All authors who are members of The Japan Neurosurgical Society (JNS) have registered online Self-reported COI Disclosure Statement Forms through the website for JNS members.

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放射線脳壊死の病態と治療法

古瀬元雅　宮武伸一

はじめに

放射線脳壊死は古くから知られる遅発性放射線障害の一つであるが，病態の詳細，診断，治療法について明らかではない．近年，放射線治療の発達と化学療法の向上により，遅発性放射線障害である放射線脳壊死に遭遇する機会が増えている．腫瘍の再発か放射線障害による変化なのか，放射線脳壊死ならどう治療してくか等，現場で悩むこともある．われわれも放射線脳壊死のメカニズムを明らかにするべく研究に取り組んでいる最中であり，本稿では現時点での知見を紹介する．

放射線脳壊死の病態

中枢神経系の放射線障害は脱髄と血管障害が主である．血管内皮細胞の損傷が血液脳関門の破綻を引きおこし，放射線脳壊死の形成に寄与していると思われる．血管内皮の損傷が減少すると，放射線脳壊死の発生頻度が減少することが実験的に示されている[1]．虚血の存在および hypoxic inducible factor-1α と vascular endothelial growth factor (VEGF)が壊死形成前より発現していることが動物実験にて報告されており，重要な役割を担っている[2,3]．われわれの臨床検体による検討では，壊死巣の周囲に炎症細胞の浸潤と新生血管の増生を認め，間質に浮腫を認めている[4,5]（図1A）．新生血管は脆弱で，微小出血を伴うことも多い．抗 VEGF 抗体によって免疫染色を行うと，新生血管周囲に VEGF 陽性の細胞を認める（図1B）．これらの細胞は主に反応性のアストロサイトであり，VEGF 産生に大きく関わっていると考える．また，炎症の関与も古くから報告されており，放射線脳壊死の組織にはリンパ球やマクロファージが浸潤しており，interleukin (IL)-1α,β, IL-6, tumor necrosis factor-α, transforming growth factor-β などがマクロファージで発現している[6]．マイクログリアの関与も示唆されている．臨床検体をみる限り，血管新生と炎症の2つの病態が主体を成しているが，放射線照射から放射線脳壊死が形成されていく間に，どの時期にどのような病態が生じ，この2病態がどのように関与し合っているのかは不明である（図2）．

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放射線脳壊死の診断

放射線脳壊死の診断は組織診断がゴールドスタンダードであることはいうまでもないが，それは病変全体を評価した場合のことであり，定位的生検術が果たして本当に正確な病態を反映する診断をもたらすかについては疑問がある．定位放射線治療後転移性脳腫瘍のうち経過中に摘出術を要した20病変を検討したところ，7例は壊死が主体であった．4例は純粋な壊死であったが，3例は腫瘍細胞の存在を認めた[7]．このような混在する病変を定位的にピンポイントで組織を採取し，診断を確定することはリスクがあると思われる．定位的生検術にて壊死の混在した腫瘍を炎症のみと診断された報告もある[8]．われわれはアミノ酸 PET による診断が低侵襲で信頼性が高いと考える．^{18}F-boronophenylalanine (BPA)-PET にて，神経膠芽腫の治療後病変が壊死が主体か腫瘍が主体かを判断できることを報告した[9]．最も頻用されるアミノ酸トレーサーは methionine であり，多くの報告がある．Terakawa らは，病変/正常脳比が転移性脳腫瘍は1.41，神経膠腫は1.58をカットオフとして高い感受性，特異性で再発と壊死が鑑別できるとしている[10]．

放射線脳壊死の治療

臨床の現場では副腎皮質ステロイドがよく使用されているが，実際にステロイドがどの程度有効であるかは不明である．進行する放射線壊死にてステロイドが単独で著効を示すことは少なく[11]，ステロイドの予防的投与も放射線脳壊死の頻度を減少させることはなかった[12]．高圧酸素療法も一部で臨床応用されている．放射線脳壊死に限定した報告はないが，遅発性放射線障害による神経症状の改善は17%のみで[13]，予防的治療により遅発性放射線障害の発生頻度を有意に減少させることはなかった[14]．少数例では抗凝固薬が放射線脳壊死を改善したという報告もある[15]．内科的治療不応性の放射線脳壊死に対しては，手術による壊死巣除去術が施行されてきた．古い review では44例の壊死巣除去術で19例が回復，16例で改善と良好な成績を呈する一方で，合併症による死亡も7例認めている[16]．最近の報告でも死亡例はないものの手術合併症は54%と高率

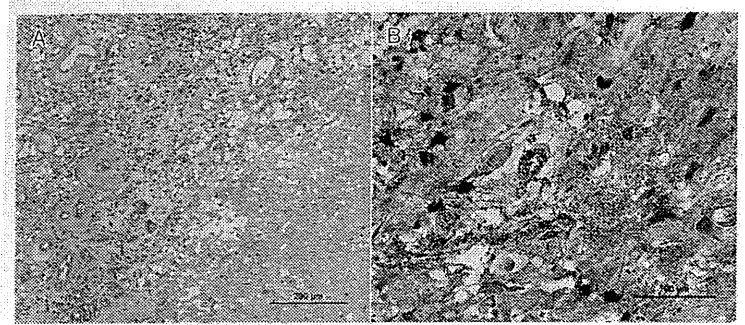

図 1　放射線脳壊死の病理学的所見

A）HE 染色（×100）．壊死巣周辺に硝子化した血管，炎症細胞の浸潤，新生血管の増生および間質浮腫を認める．B）免疫染色（抗 VEGF 抗体）（×200）．血管周囲に VEGF 陽性の細胞を認める．

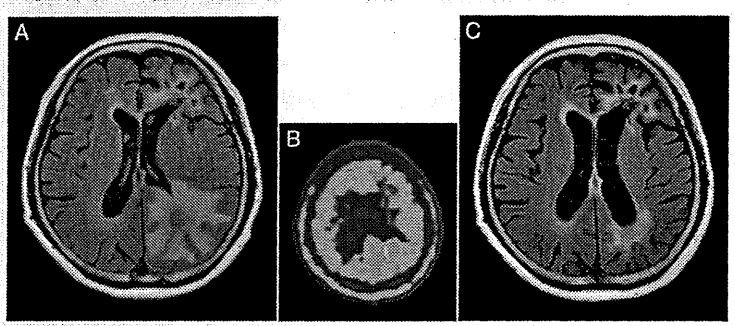

図 3　症例：53 歳，女性

子宮体癌からの多発性転移性脳腫瘍に対して複数回の定位放射線治療を行なった．経過中頭痛，言語障害を認め，MRI にて左後頭葉に広範な浮腫を認め，側脳室の圧排を認める（A）．しかし ^{18}F-BPA-PET にて病変部の取り込みは低く，病変正常組織比は 2.0 で放射線脳壊死と考えた（B）．ベバシズマブを 4 回投与後，MRI にて浮腫の改善を認め，mass effect も消失し（C），症状も軽快した．

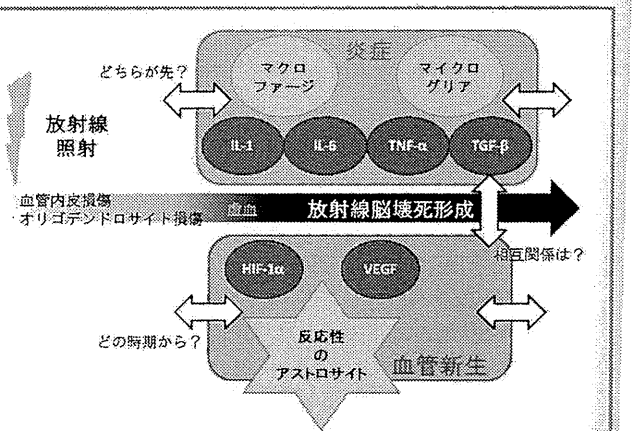

図 2　放射線脳壊死の病態

放射線照射により血管内皮損傷，オリゴデンドロサイトの損傷が生じる虚血を経て血管新生が始まる．また炎症も惹起され放射線脳壊死が形成されていくが，病態の生じる時期，この 2 病態の関連はまだまだ不明である．

であった[17]．基礎疾患に悪性新生物を有し，放射線治療や化学療法を受けた既往のある患者の手術はハイリスクであることが示唆される．

最近注目されているのは，血管新生阻害薬であるベバシズマブの放射線脳壊死に対する治療効果である．2007 年に MD Anderson Cancer Center より最初の報告が発表された．後ろ向き調査によりベバシズマブを含む抗がん剤を投与されていた 15 例のうち 8 例が画像上，放射線脳壊死であったと診断され，ベバシズマブにより造影病変および浮腫が著明に改善されたことが報告された[18]．以後，症例報告が相次いでなされ，われわれも自験例にて著明な効果を得たので報告した[19]．われわれの症例の特徴は，PET（^{18}F-BPA）にて放射線脳壊死を診断していること，基礎疾患が転移性脳腫瘍である報告は初めてで，再発する放射線脳壊死に対してもベバシズマブが再び有効であったことである．自験例のまとめでは 13 例に対してベバシズマブを投与したが，2 例は有害事象にて投与を中止した．残りの 11 例ではベバシズマブ 5 mg/kg を 2 週間毎に 3〜6 回投与し，浮腫の減少率は 65.5% と浮腫体積は投与前に比べ半分以下となり，6 例で Karnofsky Performance Status が改善した[20]．代表例を図 3 に呈示する．

むすび

がん治療の進歩により放射線脳壊死をコントロールする必要性が高くなっている．最終的に放射線脳壊死をおこさない照射治療が確立することが望ましいが，それまでの間，本病態により患者の生活水準を低下させることをできるだけ回避することが医師の役目である．病態解明によってさらなる治療薬の出現も期待できるが，現時点でベバシズマブの有効性は高く，放射線脳壊死患者に対して比較的安全に使用することができている．一人でも多くの患者に本治療が供給できるように現在臨床試験を行なっており，良好な結果が得られ，薬事の効能追加に役立つことを期待している．

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A surgical loupe system for observing protoporphyrin IX fluorescence in high-grade gliomas after administering 5-aminolevulinic acid

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Available online 2 May 2013

KEYWORDS
5-Aminolevulinic acid;
Glioma;
Surgery;
Surgical loupes

Summary
Background: We recently developed a surgical loupe system for observing the fluorescence emitted by protoporphyrin IX (PpIX), a metabolite of 5-aminolevulinic acid.
Methods: This system used a semiconductor laser as the excitation light source. A compact, transparent, and ultraviolet cut-off filter was mounted on an eyepiece lens, which did not require filter on–off manipulation.
Results: Good quality protoporphyrin IX fluorescence was acquired using the surgical loupe system during glioblastoma resection, which was nearly identical to that acquired by fluorescent microscopy. In addition, surgeons can perform ordinary surgical procedures using this surgical loupe system under white light.
Conclusion: This surgical loupe system enables the detection of PpIX fluorescence during resection of high-grade glioma. Further evaluations of this system are required to determine the extent of surgical resection before its practical application.

Introduction

Surgical microscopes with integrated protoporphyrin IX (PpIX) fluorescence systems are marketed by several manufacturers. However, they involve relatively large and complicated equipment. Because surgical microscopes use xenon light that passes through a filter, the excitation light has a broad wavelength range (approximately 405 nm). Therefore, this excitation light requires attenuation, which is usually accomplished by using a band-pass or a low-cut filter that allows the passage of light with a wavelength of approximately 635 nm. Consequently, filter on–off manipulation is required and the filter is mounted on the system only during observations.

When a laser is used as the excitation light source, the light exhibits a sharp peak at approximately 405 nm. In this case, filter on–off manipulation during observation is not required if an ultraviolet (UV) cut-off filter is mounted on

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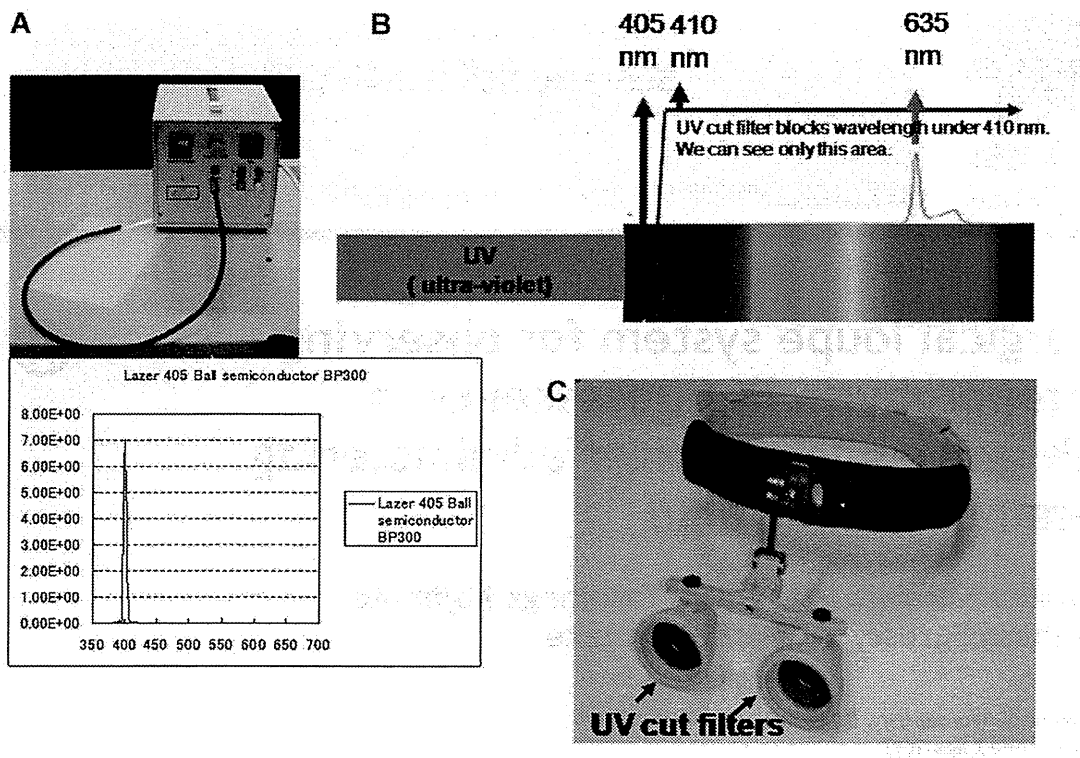

Figure 1 (A) Laser device with 405 nm irradiation and its wavelength distribution. The output at the fiber end is 300 mW. Irradiation of a 6-cm diameter area with light of 6 mW/cm^2 brightness is possible. (B) 405 nm excitation light, 635 nm fluorescence emitted by protoporphyrin IX, and their relationship to an ultraviolet cut-off filter that blocks wavelengths less than 410 nm. (C) The surgical loupes are integrated with ultraviolet cut-off filters (arrows).

the eyepiece lens. We previously reported a neuroendoscope that used this type of system [1]. We have developed a surgical loupe system using an excitation laser that does not require filter on–off manipulation during PpIX fluorescence observations.

Materials and methods

Head-mounted ×4 magnification loupes (HEINE HR® binocular loupes, Heine Optotechnik, Herrsching, Germany) and a semiconductor laser exhibiting a sharp peak at approximately 405 nm (Fig. 1A) were used as the excitation light source. A UV cut-off filter that attenuated light with wavelengths less than 410 nm was used to observe the fluorescence at 635 nm (Fig. 1B). The surgical loupe system integrated with the UV cut-off filter (Fig. 1C) did not require filter on–off manipulation because the filter was transparent.

When this system was used under an ordinary light source, surgical manipulations were possible without being affected by the UV cut-off filter. When the ordinary light source was turned off and the laser was used, PpIX fluorescence at 635 nm could be observed.

We have used this system clinically after it was approved by our institutional ethics committee. This laser was rated lower than an FDA class IIIb by The Center for Devices and Radiological Health 21 Code of Federal Regulations. Therefore, it is recommended that laser eye protection should be provided to all staff members in the operating room when using this laser.

Results

The proposed laser system was used during glioma surgery for a patient with a glioblastoma. A microscope (OPMI Pentero, Carl Zeiss Meditec, Germany) and our surgical loupe system were used during tumor resection. Silicone fence-post tubes were inserted around the tumor, and the tumor surrounded by the fence posts was resected. Fig. 2A shows an intraoperative post-resection image under white light. Fig. 2B shows the same image captured through a 410 nm-low pass filter. This image simulated the field of vision that surgeons would observe with the surgical loupes.

Fig. 2C and D show the images obtained with fluorescence microscopy (BLUE 400, Carl Zeiss Meditec, Germany) without (Fig. 2C) and with the 405 nm laser (Fig. 2D). PpIX fluorescence was more distinct when the laser was used. Similar PpIX fluorescence intensity was obtained in an image when the laser light was passed through the 410 nm-low pass filter (Fig. 2E). The residual fluorescent tumor was resected.

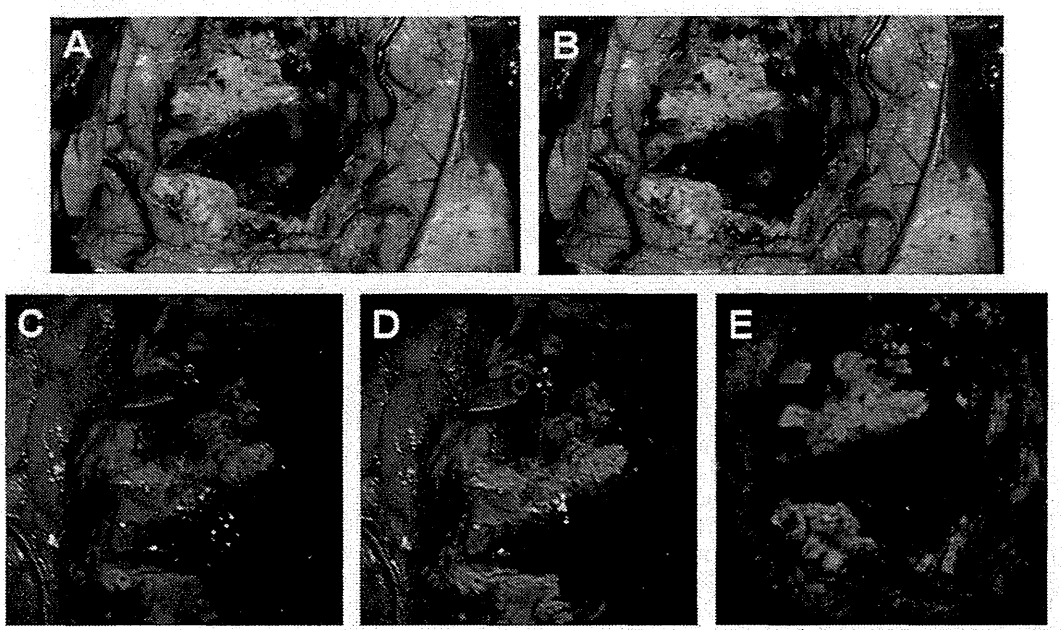

Figure 2 (A) Intraoperative image under white light during a glioblastoma resection. (B) Image obtained using a transparent ultraviolet (UV) cut-off filter, which simulates the surgeon's view using the surgical loupes. (C) Fluorescence image using a microscope. (D) Fluorescence image with a laser using a microscope. (E) Fluorescence image using a laser and a transparent UV cut-off filter.

Discussion

Fluorescence-guided glioma surgery initially used fluorescein sodium [2–5]. Recently, 5-aminolevulinic acid (5-ALA) has become widely used because PpIX has a theoretically higher selectivity than fluorescein sodium for tumor fluorescence. A randomized controlled trial using 5-ALA revealed a higher rate of complete resections and extended progression-free survival for newly diagnosed malignant gliomas [6]. Pathological examinations showed that 5-ALA fluorescence had a higher predictive value for tumor cells than white light [4].

With our system, the use of a laser as the excitation light source, which exhibits a sharp peak at 405 nm, does not require filter on–off manipulation during observations. When a laser is used with a surgical microscope, filter on–off manipulation is unnecessary as long as a UV cut-off filter is mounted on the eyepiece lens. Because the UV cut-off filter needs to be mounted only on the eyepiece lens, it can be used not only with a head-mounted loupe but also with a glasses frame-type or a lens insertion-type loupe. In addition, ordinary surgical procedures can also be performed using the surgical loupe under white light because a low pass UV cut-off filter at 410 nm does not alter the field of vision, particularly the color tone.

This system enables more accurate glioma resection than a regular surgical loupe because of the features of PpIX fluorescence technology. However, it is desirable that a video camera is mounted on the loupes to display operative images on a monitor for recording and education. Further evaluations of this system are required to determine the extent of surgical resection before its practical application for high-grade glioma.

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Cancer-specific health-related quality of life in children with brain tumors

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Abstract
Purpose To understand the influence of disease and treatment on the health-related quality of life (HRQOL) of children with brain tumors, compared to the HRQOL of children with other cancers, from the viewpoints of children and parents.
Methods A total of 133 children aged 5–18 years and 165 parents of children aged 2–18 completed questionnaires of the Pediatric Quality of Life Inventory Cancer Module (Pain and Hurt, Nausea, Procedural Anxiety, Treatment Anxiety, Worry, Cognitive Problems, Perceived Physical Appearance, and Communication scales); higher scores indicate a better HRQOL. The Cancer Module scores, weighted by age and treatment status, were compared to those obtained in a previous study of children with other cancers (mostly leukemia).
Results The weighted mean scores for Pain and Hurt (effect size $d = 0.26$) and Nausea ($d = 0.23$) from child reports and the scores for Nausea ($d = 0.28$) from parent reports were higher for children with brain tumors than scores for children with other cancers. The scores for Procedural Anxiety ($d = -0.22$) and Treatment Anxiety ($d = -0.32$) from parent reports were lower for parents of children with brain tumors than the scores for parents of children with other cancers. The child-reported Pain and Hurt score of the Cancer Module was higher ($d = 0.29$) and in less agreement (*intraclass correlation coefficient* = 0.43) with scores from the Brain Tumor Module, indicating that assessments completed with the Cancer Module misesteem pain and hurt problems in children with brain tumors.

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Conclusions The profiles of cancer-specific HRQOL in children with brain tumors differ from those of children with other cancers; we therefore suggest that these children receive specific psychological support.

Keywords Brain neoplasms · Child · Japan · Quality of life · Questionnaires

Introduction

While modern treatment methodologies have improved the outcome for pediatric cancer survival to approximately 70–80 % [1, 2], managing health-related quality of life (HRQOL) during and after treatment becomes a more important part of treatment. Brain tumors are the second most common (27 %) form of pediatric cancer after leukemia (33 %) [3]. Children with brain tumors often experience pain, nausea, lack of energy, and emotional distress [4, 5] and may also experience late effects, such as endocrinological problems, cognitive impairment, neurological (motor and sensory) disability, and posttraumatic stress symptoms [6–8]. Consequently, survivors of brain tumors who receive intensive treatment [9, 10] are at higher risk of physical, psychological, social, and developmental difficulties than survivors of other cancers [11–14]. By understanding the HRQOL profile of these children, medical practitioners can design targeted interventions to maintain and improve HRQOL in this population during and after treatment.

Global profiles of HRQOL (for example, physical, emotional, and social) in children with brain tumors are lower than those of children with other cancers or without cancer [15–18]. However, little information is available on disease-specific HRQOL profiles in children with brain tumors. Meeske et al. compared cancer-specific HRQOL between children with brain tumors and those with acute lymphoblastic leukemia (ALL) using the parent-reported Pediatric Quality of Life Inventory (PedsQL) Cancer Module [17], finding that parents of children with brain tumors and acute lymphoblastic leukemia report different experiences for their children during and after treatment. This highlights the need to understand how children with brain tumors perceive their own HRQOL.

The disease-specific HRQOL of patients with brain tumors can be measured with one of several cancer-specific tools [19–21], such as the PedsQL Cancer Module, or with a brain-tumor-specific tool [15, 22, 23], such as the PedsQL Brain Tumor Module. Different tools may provide different measures of HRQOL, as the questionnaire structure, number, and time of the questions differ among available tools. Here, we compared cancer-specific HRQOL in children with brain tumors with the HRQOL of children with other cancers, the reported views of children and their parents, and the HRQOL as measured by two PedsQL modules—the PedsQL Cancer and the PedsQL Brain Tumor Modules.

Methods

This study was conducted jointly with 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) between September and December 2008. Inclusion criteria were as follows: age 5–18 years for children (the parent was included if their child was 2–18 years) and at least 1 month had passed since diagnosis. Children and parents were excluded if physicians at the hospital 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 the study aims to 101 children and 122 parents at participating hospitals verbally and in writing, and the CCAJ sent a written notice to all families, inviting them to a meeting regarding brain tumors. Of 55 families from the CCAJ that provided informed consent or assent, 2 families were bereaved, 1 had an adult survivor, 6 children were aged 2–4 years, and 1 child old enough to provide his own consent opted out. A total of 98 children and 120 parents from the hospitals as well as 45 children and 52 parents contacted directly by the CCAJ agreed to participate. Questionnaires were distributed to 143 children and 172 parents.

Questionnaires for children were either self-administered or administered by an interviewer. When providing

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informed consent, parents determined whether or not their child was able to self-administer the questionnaire. In accordance with the PedsQL™ administration guidelines, children aged 5–7 years or who were otherwise determined incapable of self-administration were administered the questionnaire by either their parents or a researcher (children were allowed to decide). In both cases, the instructions and each item were read to the child. Parent report questionnaires were simultaneously self-administered.

The questionnaires were returned by 138 children and 167 parents. We excluded questionnaires from 5 children and 2 parents who did not answer any scales of the PedsQL Cancer Module, and we analyzed answers from 133 children and 165 parents. Next, we analyzed answers from 124 children and 143 parents after omitting questionnaires with missing data for any scale of the PedsQL Cancer Module. Given the lack of any significant differences between the results of the former and latter analyses, we report only the latter.

Ethical considerations

This study was approved by the review boards of all seven participating institutions. Children aged ≥12 years and the parents of all children provided written consent prior to participation. Children aged <12 years provided informed verbal assent.

Measurements

The cancer-specific HRQOL of the PedsQL Cancer Module [21, 25] has eight scales: Pain and Hurt (two items), Nausea (five items), Procedural Anxiety (three items), Treatment Anxiety (three items), Worry (three items), Cognitive Problems (five items), Perceived Physical Appearance (three items), and Communication (three items).

Respondents were asked to describe the extent to which each item troubled them over the past month. Although the PedsQL Cancer Module comprises the standard (covering the previous month) and acute versions (covering the previous 7 days), we used the standard version, because it served as a historical control (described in the next section). For the child reports for ages 8–18 and all parent reports, a 5-point Likert response scale was used (0 = never a problem; 1 = almost never; 2 = sometimes; 3 = often; 4 = almost always). For the child report for children ages 5–7, a 3-point face scale was used. Items were reverse scored and linearly transformed to a 0–100 scale, with higher scores indicating a better HRQOL. To account for missing data, scale scores were computed as the sum of the items divided by the number of items answered. If more than 50 % of the items were missing or incomplete, the scale score was not computed.

Table 1 Characteristics of participants

	This study				Tsuji et al. [25] ($N = 245$)	
	All participants ($N = 165$)		Complete participants ($N = 143$)[a]			
	n	%	*n*	%	*n*	%
Gender						
Male	91	55.5	84	59.2	135	55.1
Female	73	44.5	58	40.8	110	44.9
Age (years)						
2–4	25	15.2	23	16.1	41	16.7
5–7	31	18.8	21	14.7	62	25.3
8–12	56	33.9	48	33.6	75	30.6
13–18	53	32.1	51	35.7	67	27.3
Tumor pathology						
Embryonal tumors	47	29.2	39	27.9	–	–
Germ cell tumors	36	22.4	34	24.3	–	–
High-grade glioma	24	14.9	19	13.6	–	–
Low-grade glioma	39	24.2	33	23.6	–	–
Other tumors	15	9.3	15	10.7	–	–
Treatment status						
On-treatment	63	39.4	56	39.2	88	35.9
Off-treatment ≤ 12 months	23	14.4	21	14.7	33	13.5
Off-treatment > 12 months	74	46.3	66	46.2	124	50.6
Age of guardian (years)						
21–28	7	4.3	4	2.8	5	2.1
29–34	23	14.0	18	12.7	40	16.9
35–39	47	28.7	41	28.9	72	30.4
40–60	86	52.4	78	54.9	120	50.6
≥61	1	0.6	1	0.7	0	0.0
Relationship to patient						
Mother	152	92.1	133	93.0	230	96.2
Father	10	6.1	8	5.6	9	3.8
Other guardian	3	1.8	2	1.4	0	0.0
Guardian's academic background						
Junior high school	3	1.9	2	1.4	4	1.7
High school	63	38.9	49	35.0	87	36.6
Vocational school	28	17.3	27	19.3	44	18.5
Junior college	29	17.9	28	20.0	48	20.2
University	36	22.2	32	22.9	52	21.8
Graduate school	3	1.9	2	1.4	1	0.4
Other	0	0.0	0	0.0	2	0.8

Missing data were excluded

[a] Sample without missing data for any scale of the PedsQL Cancer Module

The PedsQL Brain Tumor Module [15, 24] has six scales. Questions about Nausea, Procedural Anxiety, and Worry scales are identical to those in the PedsQL Cancer Module, whereas questions on the Pain and Hurt scale (three items) and Cognitive Problems scale (seven items)

differ from those in the PedsQL Cancer Module. The parent report for toddlers (ages 2–4) does not include the Cognitive Problems scale. The Movement and Balance scale is not reported here. Agreement between the parent and child reports (intraclass correlation coefficient [ICC]) was described previously as follows: 0.41 (Pain and Hurt), 0.65 (Nausea), 0.62 (Procedural Anxiety), 0.18 (Worry), and 0.49 (Cognitive Problems) [24].

Respondents were asked to describe the extent to which each item troubled them over the previous 7 days. Although the recall period of the questionnaire differed from that of the Cancer Module, no published studies using the Brain Tumor Module as the standard (1 month) version were available when the present study was planned and designed. Because the PedsQL Brain Tumor Module adopts the acute version (covering the previous 7 days) as a standard, we employed the acute version. The respondents, response scale, and scoring method were identical to the PedsQL Cancer Module. Parents were also asked to record their child's gender, date of birth, age, tumor pathology, date of diagnosis, and date of therapy completion.

Historical control

We used data reported by Tsuji et al. [25] as a control. This study reported scores from for Japanese children with cancer (67.8 % had leukemia, 9.0 % had malignant lymphoma, followed by neuroblastoma, Wilm's tumor, rhabdomyosarcoma, and hepatoblastoma) using the Japanese version of the PedsQL Cancer Module. Children with brain tumors were excluded in that study.

The average age of children with cancer was 10.5 years (standard deviation [SD] = 3.9 years), and 55.1 % of patients were boys (Table 1). Mothers answered 93.9 % of the questionnaires, and parents' ages ranged between 40 and 60 years.

Statistical analysis

Statistics were calculated using IBM SPSS software, version 19 (SPSS, Inc., Chicago, IL, USA), and the level of significance was defined as 0.05. We calculated the sample characteristics as follows: age distribution, disease, and treatment characteristics; and scale characteristics as follows: mean, SD, minimum and maximum scores. The internal consistency of each subscale was estimated using Cronbach's alpha coefficient [26] (good consistency > 0.70). The agreement between the child and parent reports was estimated using ICC in a two-way mixed effects model [27] (ICC value of 0.20 indicates fair agreement, 0.40 moderate, 0.60 good, and 0.80 high agreement).

The cancer-specific HRQOL of children with brain tumors was compared to the HRQOL of children with other cancers. We compensated for the effect of age (toddler, young child, school child, or adolescent) and treatment status (on-treatment, soon after treatment, or off-treatment) differences using the weighted means and SDs of the PedsQL Cancer Module scale scores, adjusted for age and treatment status. The age distribution of leukemia and brain-tumor onset differs [29, 30], and previous reports have found that treatment status affects the PedsQL Cancer Module score [21, 25]. We also found in this study that the treatment status affected the PedsQL Cancer Module score (see electronic Supplementary Table 1).

These values were calculated by dividing the total sample into different groups based on age and treatment status. The control study sample size (Nc_{total}) was 245, and the brain-tumor sample size (N_{total}) was 165 if all respondents completed the PedsQL Cancer Module scale. The control and study populations were divided into groups (Nc_{ij} and N_{ij}) separated by treatment status (on-treatment, off-treatment $\leq$12 months, or off-treatment >12 months; $i = 1$–3) and by age (2–4, 5–7, 8–12, or 13–18 years; $j = 1$–4). The weighted means [31] were calculated as follows:

$$\text{Weighted mean}(\bar{X}) = \sum_{k-1}^{N_{total}} W_k X_k / \sum_{k-1}^{N_{total}} W_k.$$

$$\left(\text{The common mean} = \sum_{k-1}^{N_{total}} X_k / N_{total}\right).$$

$$W_k = \left(\frac{Nc_{ij}}{Nc_{total}}\right) / \left(\frac{N_{ij}}{N_{total}}\right).$$

where X_k was the PedsQL Cancer Module scale score of each respondent that belonged to treatment status i and age j; the weights for each respondent (W_k) were calculated from the ratio of the age and treatment status of the standard population, divided by the proportion of the age and treatment status in this study.

The weighted SDs were calculated using the same weight (W_k) as follows:

$$\text{Weighted SD} = \sqrt{\sum_{k-1}^{N_{total}} W_k (X_k - \bar{X})^2 / \left(\sum_{k-1}^{N_{total}} W_k - 1\right)}.$$

$$\left(\text{The common SD} = \sqrt{\sum_{k-1}^{N_{total}} (X_k - \bar{X})^2 / (N_{total} - 1)}.\right)$$

We compared the cancer-specific HRQOL using Welch's t test and calculated the effect size d from the difference between the two means divided by the pooled SD of both samples.

Table 2 PedsQL Cancer Module scores of children with brain tumors ($N = 143$)

	Mean	SD	Min.	Max.	Alpha[a]	ICC[b]
Child report (n = 124)						
Pain and Hurt	90.4	17.6	0	100	0.62	0.20
Nausea	87.5	20.6	15.0	100	0.86	0.68
Procedural Anxiety	74.5	30.8	0	100	0.88	0.70
Treatment Anxiety	92.8	19.0	0	100	0.88	0.41
Worry	81.9	23.4	0	100	0.76	0.27
Cognitive Problems	73.6	22.4	0	100	0.78	0.44
Perceived Physical Appearance	73.8	26.3	0	100	0.71	0.28
Communication	68.5	29.9	0	100	0.77	0.45
Parent report (n = 143)						
Pain and Hurt	84.5	20.0	0	100	0.83	
Nausea	84.7	22.6	15.0	100	0.93	
Procedural Anxiety	59.8	35.4	0	100	0.96	
Treatment Anxiety	79.7	23.1	0	100	0.93	
Worry	78.3	22.3	0	100	0.86	
Cognitive Problems	66.0	23.8	0	100	0.89	
Perceived Physical Appearance	70.6	24.6	0	100	0.81	
Communication	59.5	29.6	0	100	0.89	

ICC intraclass correlation coefficient, *Max.* maximum, *Min.* minimum, *SD* standard deviation

[a] Cronbach's alpha coefficient

[b] ICC values for child and parent reports in the two-way mixed effects model ($n = 124$)

The agreement of the two modules was evaluated using paired t tests; the effect size d (the mean score difference divided by SD of the mean score difference) [28] designated as small (0.20), medium (0.50), and large (0.80) in magnitude and by the ICC calculated from a one-way random effects model [27].

Results

Sample characteristics

The median age of the children with brain tumors was 10.0 years (range: 2–18) (Table 1), and the sample was heterogeneous for tumor pathology. Most children presented with embryonal tumors, low-grade gliomas, and germ cell tumors. Median age at diagnosis was 6.0 years; 63 children (39.4 %) were still receiving treatment, while 97 (60.6 %) had completed treatment, and the interval from completion of treatment to the survey ranged from 0.1 to 13.3 years. Most children on treatment were younger than the children who had completed treatment.

With the exceptions noted below, no significant differences were observed between the characteristics of the children and their parents and those of the historical control (Table 1). The differences were as follows: The present study enrolled fewer children between the ages of 5 and 7 years and more between the ages of 13 and 18 years ($P = 0.069$, Chi-square test).

Scale descriptions

The child-reported scores were higher than parent-reported scores on all scales of the PedsQL Cancer Module and were internally consistent for all scales except for the Pain and Hurt scale (Cronbach's alpha coefficient = 0.62); parent-reported scores were internally consistent for all scales (Table 2). Agreement between the child and parent reports was good for the Nausea and Procedural Anxiety scales, moderate for the Treatment Anxiety, Cognitive Problems, and Communication scales, and fair for the Pain and Hurt, and Perceived Physical Appearance scales.

Cancer-specific HRQOL in children with brain tumors compared with the HRQOL of children with other cancers

We noted small but significant differences between the children's reports for Pain and Hurt ($d = 0.26$) and Nausea ($d = 0.23$) and the parents' reports for Nausea ($d = 0.28$), Procedural Anxiety ($d = -0.22$), and Treatment Anxiety ($d = -0.32$) (Table 3). The scores for Pain and Hurt and Nausea were higher for children with brain tumors than for children with other cancers, indicating better HRQOL. However, the scores for Procedural Anxiety and Treatment Anxiety were lower for children with brain tumors than for children with other cancers, indicating worse HRQOL. The direction of the effects was the same for the scales reported by parents and children.