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Original Article

Fluorodeoxyglucose Detected Changes in Brain Metabolism After Chemotherapy in Pediatric Non-Hodgkin Lymphoma

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ABSTRACT

Background: Potential neurocognitive dysfunction after chemotherapy is a worrisome long-term outcome. Our objective was to evaluate the effect on brain metabolism in pediatric patients with non–central nervous system cancer treated with chemotherapy by analyzing brain data from serial whole-body fluorodeoxyglucose positron emission tomography/computed-tomography (FDG-PET/CT) scans taken before and sequentially after therapy.

Methods: Fourteen pediatric patients diagnosed with lymphoma and treated with systemic and prophylactic intrathecal chemotherapy were included. All patients had baseline pretreatment whole-body FDG-PET/CT and at least one post-therapy study preformed as part of standard surveillance. Brain positron emission tomography data were quantitatively analyzed for normalized fluorodeoxyglucose uptake in various brain regions. A generalized estimating equation approach was used to evaluate temporal changes after chemotherapy.

Results: Median time of follow-up surveillance positron emission tomography–computed-tomography was 456 days after chemotherapy course. Various brain regions demonstrated significant changes in fluorodeoxyglucose uptake as a function of time passed since chemotherapy. Increased fluorodeoxyglucose uptake was noted in the parietal and cingulate cortexes. Decreased fluorodeoxyglucose uptake was demonstrated in deep gray matter nuclei and in the brainstem.

Conclusions: Our study provides novel insights into long-standing and progressive changes in regional glucose metabolism after chemotherapy in pediatric cancer population, lasting long after the end of therapy and reaching clinical remission. Expanding the utility of regular surveillance fluorodeoxyglucose positron emission tomography to a detailed quantitative assessment of regional brain metabolism after chemotherapy can provide valuable information on individual chemotherapy-related neuromodulation and facilitate the development of strategies to minimize neurocognitive side effects.

Introduction

One consequence of recent advances in cancer diagnosis and treatment is more patients achieving complete recovery. Subsequently, there is growing concern about long-term effects of antineoplastic therapy. Longitudinal studies using neuropsychologic assessment of cancer survivors have shown growing evidence that chemotherapy is associated with long-term alterations of cognitive function.[1,2] "Chemobrain" is the term used to describe this cognitive impairment, assuming that chemotherapy is the causative factor.

Children with non-Hodgkin lymphoma (NHL) undergo treatment with central nervous system (CNS)-directed therapy, the potentially neurotoxic effects, which have not been reported in NHL survivors. Therapy may include cranial radiation, high-dose methotrexate, high-dose cytarabine, and intrathecal

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chemotherapy. Recently adult survivors of childhood NHL have been reported to experience impaired neurocognitive function, i.e., memory, executive function, processing speed, and academics impaired in comparison with both population norms and community control subjects.[3] Early detection and intervention strategies are required to evaluate and prevent possible neurocognitive effects.

Glucose is the brain's main metabolic substrate and its oxidation produces the necessary amount of energy needed for adequate cerebral activity. The positron emission tomography (PET) tracer ^{18}F-fluorodeoxyglucose (^{18}F-FDG) allows the *in vivo* study of glucose metabolism. The local glucose consumption, and thus ^{18}F-FDG cerebral uptake, strictly correlates with local neuronal activity, particularly at the synaptic connection level with neurotransmission and signal transduction being the processes with the highest energetic requirements.[4] Regional brain ^{18}F-FDG uptake differences are observed depending on scanning starting time after intravenous tracer injection.[5] Therefore in clinical oncological imaging, the interval between FDG administration and the start of acquisition is usually 60 minutes.[6] FDG-PET studies have shown that chemotherapy seems to change brain glucose metabolism. Sorokin et al.[7] demonstrated decreased overall glucose metabolism after chemotherapy. Chronic changes in glucose metabolism were also demonstrated in the cerebral cortex, basal ganglia, and in the cerebellum of adult breast cancer survivors.[8] Little is known about long-term metabolic alterations in pediatric cancer survivors, exposed to systemic chemotherapy during childhood.

We hypothesized that the pediatric developing brain is more sensitive to chemotherapy than the adult brain, and will show long-term metabolic changes after chemotherapy, which could be demonstrated using FDG-PET. The present study evaluates therapy-related effects on brain metabolism in pediatric patients with non-CNS cancer, treated with systemic chemotherapy, by analyzing serial whole-body FDG-PET/computed-tomography (FDG-PET/CT) studies before and sequentially after the therapy.

Material and Methods

Study design

Retrospective observational study was conducted by reviewing whole-body FDG-PET/CT studies of pediatric cancer patients clinically preformed for cancer staging or for monitoring response to treatment. This study was approved by the institutional review board and adhered to standards set forth by the Health Insurance Portability and Accountability Act. Waiver of patient informed consent was approved by the institutional review board for the purposes of this study.

Patients

Children aged less than 18 years with NHLs treated in our tertiary medical center (2007 to 2012) who underwent clinical surveillance with whole-body FDG-PET/CT studies were included in the study. Inclusion criteria included (1) an available baseline consisting of a pretreatment whole-body FDG-PET/CT study and (2) at least one follow-up post-treatment FDG-PET/CT study. Exclusion criteria were (1) resistant or relapsed disease that required salvage chemotherapy or bone marrow transplantation, (2) known CNS involvement by the underlying cancer, evaluated by CNS analysis and by surveillance FDG-PET/CT studies, (3) known underlying systemic syndromes or CNS abnormalities (e.g., ataxia telangiectasia, mental retardation, and so forth), or (4) craniospinal irradiation.

Imaging acquisition and analysis

FDG-PET/CT

^{18}F-FDG-PET/CT scanning was performed using a PET/CT scanner with a 16 detector row helical CT scanner (Philips Gemini GXL; Philips Medical Systems, Cleveland, OH, USA). The combined scanner allows for simultaneous acquisition of up to 45 transaxial PET images with interslice spacing of 4 mm in one-bed position and provides an image from vertex to thigh in ~10 bed positions. The transaxial field of view and pixel size of the PET images reconstructed for fusion were 57.6 cm and 4 mm, respectively, with a matrix size of 144 × 144. The technical parameters used for CT imaging were pitch 0.8, gantry rotation speed 0.5, 120 kVp, 250 mAs, 3-mm slice thickness, and specific breath-holding instructions. After 4 to 6 hours of fasting, patients received an intravenous injection 5.18 MBq/kg up to 370 MBq ^{18}F-FDG. Approximately 60 ± 10 minutes later, CT images were obtained without intravenous or oral contrast media from the vertex to the mid-thigh for ~32 seconds. An emission PET scan followed in three-dimensional acquisition mode for the same axial coverage, 1.5 minutes per bed position. The PET scan, which begins approximately 60 to 70 minutes after FDG injection, takes approximately 12 to 20 minutes in children (according to the age and the height of the child). Hence, the brain, which is the last window to be scanned, is being scanned less than 90 minutes after the FDG injection. CT images were used for fusion with the PET data and to generate an attenuation map for attenuation correction. PET images were reconstructed using a line of response protocol with CT attenuation correction, and the reconstructed images were generated for review on a computer workstation (EWB; Philips Medical Systems).

Evaluation of PET data

From the whole-body PET/CT studies, images of the head and vertex to the skull base were manually cropped using a multimodality viewer (IntelliSpace Portal 7.0; Philips Medical Systems). Quantitative analysis using NeuroQ software version 3.0 (Syntermed) was performed by an experienced neuroradiologist. Briefly, steps included preprocessing (removal of the scalp activity around the brain, spatial registration) and structurally reformatting the brain to a high quality standardized normal brain template. The NeuroQ output quantifies relative FDG uptake in 47 different brain regions of interest (ROIs). Mean FDG uptake values in various brain regions were normalized to the entire brain activity and does not represent absolute uptake.

Clinical data

Patient charts were reviewed for demographic data (gender and age), chemotherapy protocol, and for the presence of exclusion criteria.

Statistical analysis

Statistical analysis was done using SPSS software version 24 (IBM Corp, Armonk, NY, USA). Normalized brain FDG activity in various brain regions was presented as a function of time after chemotherapy treatment in scatterplot graphs to evaluate possible nonlinear trends. As all datasets show linear behavior, univariate and multivariate generalized estimating equation procedures were used to evaluate significant temporal changes in multiple measurements. $P < 0.05$ was used to define statistical significance.

Results

Study population

Of 46 NHL pediatric patients in the research period, 14 patients were eligible for the study (11 boys and three girls). The mean age of our patients was 12 years (age 2.6 to 17.3 years). Overall 61 FDG-PET/CT studies were analyzed. All patients had at least one post-treatment PET/CT study. One patient had one follow-up study, five patients had two follow-up studies, one patient had three follow-up studies, three patients had four follow-up studies, three patients had five follow-up studies, and one patient had six follow-up studies. The median time of the follow-up PET/CT surveillance was 456 days after chemotherapy course (interquartile range of 282 to 591 days). Nine patients were treated with LMB-group B,[9] three patients were treated with Euro-LB-02,[10] and two patients were treated with ALCL-99.[11] All patients were treated with prophylactic intrathecal chemotherapy, which includes methotrexate, cytarabine, and hydrocortisone (age adjusted dose).

Brain PET/CT imaging findings

Baseline relative FDG uptake in various brain regions can be seen in the Supplementary Material. Various brain regions have demonstrated significant changes in FDG uptake as a function of time passed since chemotherapy (Table 1). Bilateral parietal and cingulate cortices showed gradual annual increases in FDG uptake of approximately 2% to 3% compared with baseline uptake ($P < 0.002$). Basal ganglia and brainstem regions showed corresponding annual decreases in FDG uptake ($P < 0.04$). The right thalamus had the most prominent and significant reduction in FDG uptake of approximately 3% annually ($P = 0.002$). Representative scatterplots are presented in Fig.

Multivariate analysis adjusted to age, gender, and treatment protocol showed similar effects, with increased statistical significance (Table 2). A significant interaction was found between temporal metabolic changes in parietal and cingulate cortexes between boys and girls, with less prominent metabolic changes in boys (B values, i.e. the added effect over the overall effect for boys, were −0.008 ($P < 0.001$) in the left superior parietal cortex, −0.012 ($P < 0.001$) in the right superior parietal cortex, −0.010 ($P < 0.001$) in the right inferior parietal cortex, and −0.007 ($P = 0.024$) in the right posterior cingulate cortex). A weak, but significant, interaction was found between temporal changes in FDG uptake in the right caudate nucleus and thalamus and patients' age (B values, i.e. the added effect over the overall effect for older age, were 0.001($P < 0.001$) and −0.001 ($P = 0.02$), respectively). No interaction was found between temporal changes in FDG uptake and treatment protocol.

Discussion

Currently, most children and adolescents diagnosed with cancer achieve long-term survival.[12] Potential neurocognitive dysfunction is one of the most worrisome long-term outcomes, especially in the pediatric age group. Our study has shown ongoing changes in FDG uptake in various brain regions lasting much after therapy cessation. This finding might represent long-term sequela of systemic chemotherapy. Historically, significant neurocognitive and neuropsychologic deficits were reported in survivors of brain tumors and acute lymphoblastic leukemia (ALL), especially when cranial radiation was added. However, the evidence that chemotherapy alone causes lasting neurocognitive late effects is not consistent. In last two decades, several prospective trials described long-term neurocognitive deficits in survivors of childhood ALL after chemotherapy alone, involving mainly processes of attention and executive functioning, whereas global intellectual functions are relatively preserved.[13–16] In adults, several longitudinal neuropsychologic studies have described noticeable cognitive changes close to the end of therapy, tending to partially or fully resolve over time.[17,18] Several factors have been identified that generally increase the risk of developing cognitive neurotoxicity associated with chemotherapy. These include exposure to higher doses of chemotherapeutic agents, synergistic neurotoxic effects of multiagent chemotherapy, additive effects of cerebral radiation, and intrathecal administration of chemotherapy.[19]

Structural and functional neuroimaging has been applied to examine effects of chemotherapy in pediatric cancer patients. FDG-PET is a major functional imaging modality, which provides information of the tumor's metabolic activity, providing insight into its malignant state and response to therapy. FDG-PET of the brain reflects real-time metabolic activity in various areas of the brain, and in cancer patients it can provide information on evolving metabolic changes after chemotherapy. There are inconclusive reports on brain regions, which are affected by systemic chemotherapy. These inconclusive reports could be because of, at least partially, the huge heterogeneity concerning experimental methodologies. Diffuse decrease in FDG uptake in the cortex and deep gray matter nuclei was reported in adult cancer patients after chemotherapy.[1,7] Chiaravalloti et al.[20] showed only transient global decrease, which resolves rapidly even when continuing chemotherapy. Long lasting reduced FDG uptake in deep gray matter structures observed in the present study was also reported in pediatric ALL survivors.[21,22] Reduced FDG activity in the basal ganglia was further observed in adult patients with pharyngeal carcinoma or rectal cancer receiving

TABLE 1.
Brain Regions Demonstrating Statistically Significant Changes in Fluorodeoxyglucose (FDG) Uptake as a Function of Time That Passed Since Chemotherapy (Univariate Generalized Estimating Equation)

Brain Region	Baseline Relative FDG Uptake	Temporal Effect (90 days)	Confidence Interval		Significance
			Lower	Upper	
Left superior parietal cortex	0.92	0.004	0.002	0.007	0.002
Right superior parietal cortex	0.98	0.005	0.001	0.008	0.009
Right inferior parietal cortex	1.10	0.005	0.000	0.011	0.047
Right posterior cingulate cortex	1.20	0.004	0.001	0.008	0.024
Right parietotemporal cortex	1.13	0.004	0.000	0.008	0.031
Left posterior cingulate cortex	1.23	0.004	0.002	0.006	0.000
Right caudate nucleus	0.97	−0.004	−0.008	0.000	0.043
Right thalamus	0.95	−0.008	−0.013	−0.003	0.002
Right lentiform nucleus	1.17	−0.005	−0.008	−0.002	0.002
Midbrain	0.71	−0.003	−0.005	−0.001	0.010
Pons	0.61	−0.005	−0.008	−0.001	0.007

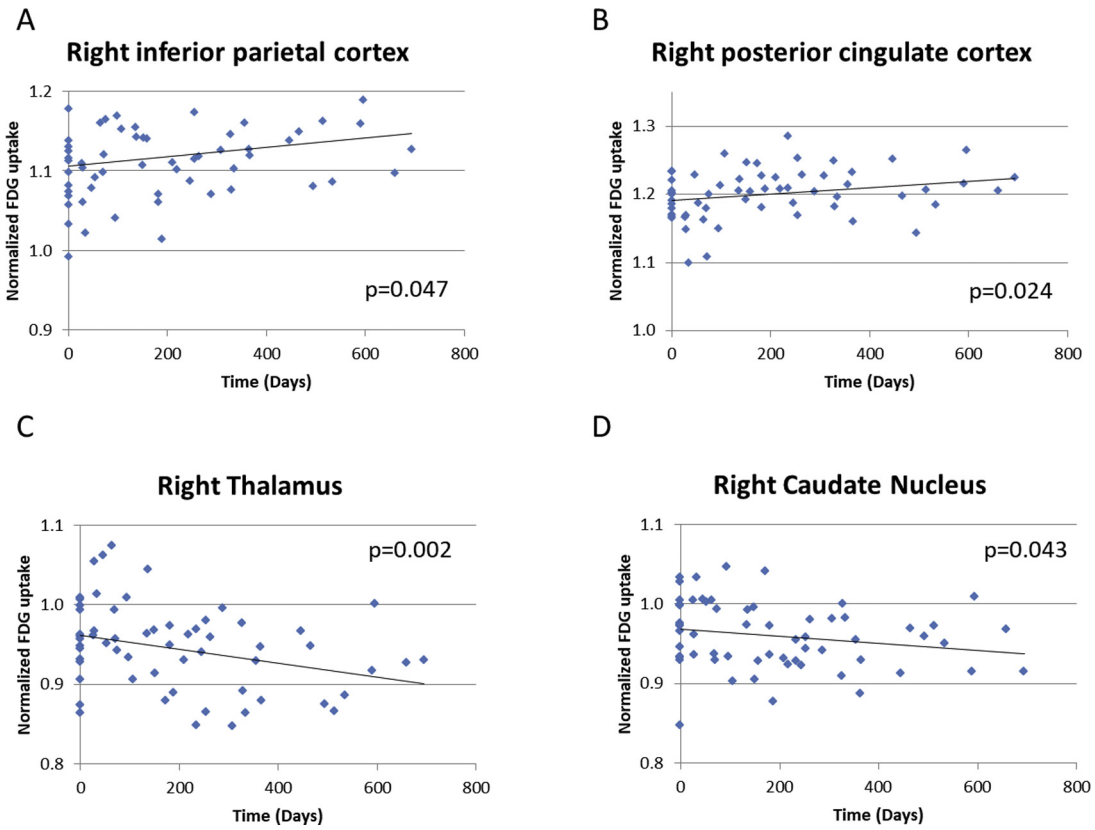

FIGURE. Representative scatterplots of normalized fluorodeoxyglucose (FDG) uptake in the (A) right inferior parietal cortex, (B) right posterior cingulate cortex, (C) right thalamus, and (D) right caudate nucleus. The color version of this figure is available in the online edition.

chemotherapy.[23,24] We have demonstrated increased FDG uptake in several cortical regions, such as the parietal and cingulate cortex, corresponding to earlier reports in adult patients.[20,24] Nevertheless, previously reported reduced metabolism in frontal lobes was not demonstrated in the present study.[25] Although some studies showed more substantial cognitive and white matter changes in younger patients,[26] in the present study the child's age during systemic therapy had a limited effect on evolving metabolic impairment, as has been previously reported.[22] A novel observation in the present study was gender differences in metabolic alterations after chemotherapy, suggesting girls are more prone than boys to metabolic changes after chemotherapy. This finding might represent underlying gender-related differences in brain structure and function.[27]

In clinical practice, visual inspection of PET images is the main tool for image interpretation. However, such analysis may miss changes in uptake such as increased uptake in background cortical and deep gray matter nuclei. Quantitative measures are routinely used for FDG-PET studies. The most commonly used absolute measure is the standardized uptake value. This value represents the ^{18}F-FDG uptake within evaluated tissue, measured over a certain time interval after ^{18}F-FDG administration and normalized to the injected FDG dose and to a factor (such as body weight) that takes into account distribution throughout the body.[28] Nevertheless, many physiological and technical factors can affect the measured standardized uptake value, such as blood glucose levels, patient motion, or delay between FDG injection and PET scanning. To overcome these limitations of absolute FDG uptake measurements,

TABLE 2.
Brain Regions Demonstrating Statistically Significant Changes in Fluorodeoxyglucose Uptake as a Function of Time That Passed Since Chemotherapy (Multivariate Generalized Estimating Equation, Adjusted to Age, Gender, and Treatment Protocol)

Brain Region	Temporal Effect (90 days)	Confidence Interval		Significance
		Lower	Upper	
Left superior parietal cortex	0.004	0.002	0.007	0.002
Right superior parietal cortex	0.005	0.002	0.008	0.001
Right inferior parietal cortex	0.006	0.001	0.010	0.018
Right posterior cingulate cortex	0.004	0.001	0.007	0.009
Right parietotemporal cortex	0.004	0.001	0.008	0.026
Left posterior cingulate cortex	0.004	0.002	0.006	0.000
Right caudate nucleus	−0.004	−0.008	0.000	0.035
Right thalamus	−0.008	−0.013	−0.003	0.001
Right lentiform nucleus	−0.005	−0.008	−0.001	0.008
Midbrain	−0.003	−0.005	−0.001	0.006
Pons	−0.005	−0.008	−0.002	0.001

relative FDG uptake was used in the present study. Because no specific brain region is known to be protected from chemotherapy effects, all-brain uptake was selected as the normalization denominator rather than specific regions. Such analysis enables detection of relative brain region changes in FDG activity, although detection of diffuse absolute changes in glucose metabolism might be underestimated. Automated quantification of mean pixel values lying within standardized ROIs enables detection of subtle changes in brain FDG uptake (approximately 2% to 3% annual changes in FDG uptake), which cannot be detected on visual inspection.

Chemotherapeutic agents typically have limited penetration to brain tissue because of the blood-brain barrier. Mechanisms underlying neurotoxicity after systemic chemotherapy have not yet been clearly elucidated and include inflammatory changes, demyelination of white matter tracts, a reduction in neural stem cell proliferation, and changes in hormonal or growth factor levels.[29] Concurrent psychiatric morbidity might also have effects on regional brain FDG metabolism. It is known that being afflicted by cancer can cause substantial rate of anxiety, depression, and other psychosocial consequences, which unavoidably confound assessment by imaging methods. Treated patients with major depression have shown increased metabolism in the parietal cortex.[30] Relative hypermetabolism was noted in the posterior cingulate cortex in cancer patients in association with later development of depressive or adjustment disorders.[31] Future neuroimaging research should include also correlation with concurrent neuropsychologic morbidity, to clarify its confounding effects.

In the present study, a new method is suggested for assessment of the degree of neurotoxicity of systemic chemotherapy using whole-body FDG-PET/CT. FDG-PET/CT studies, routinely performed for staging, response evaluation, and surveillance can also be used to monitor “neurosafety” profiles of anticancer therapies. Expanding the utility of regular surveillance FDG-PET to a detailed quantitative assessment of regional brain metabolism after chemotherapy may provide valuable information on individual chemotherapy-related neuromodulation and may facilitate the development of strategies to prevent and minimize neurocognitive long-term effects.

A significant limitation of our study, which stems from its retrospective design, is the absence of neurocognitive correlation of brain metabolic alterations found in FDG-PET imaging. Thus clinical significance of the alterations found in regional FDG uptake changes was not determined. As PET/CT involves radiation, data on normal pediatric control subjects are sparse. Therefore we used the prechemotherapy PET as an internal control. Fitting pediatric brain, especially in a relative low resolution of all-body PET/CT acquisition, to a standardized normal adult template may have introduced a measuring error because of effects of spatial transformation on various brain ROIs, especially in younger age group. This introduction of error could have been improved through the use of age-dependent normalization templates, which were not available in the application used in the present study. Our study is a preliminary report with a relatively small number of patients that limits the evaluation of both contributing and protective factors, which may have influence on brain glucose metabolism after chemotherapy. Further prospective studies are needed to determine the roles of psychological and other confounders and to provide a more conclusive correlation between quantitative metabolic assessments and cognitive effects. Once the clinical significance of the regional brain FDG uptake changes will be better characterized, individual analysis of brain FDG uptake in surveillance all-body PET studies might be used to modulate treatment protocols to reduce adverse cognitive effects.

In conclusion, our study provides novel insights into long-standing and progressive changes in regional glucose metabolism after chemotherapy in the pediatric cancer population, lasting long after the end of therapy and clinical remission. Future prospective studies combining neuroimaging with longitudinal neurocognitive assessment will allow further characterization of the long-term consequences of chemotherapy in pediatric cancer patients and identify potential imaging biomarkers of neurotoxicity associated with chemotherapy.

Supplementary Material

Supplementary material to this article can be found online at doi.org/10.1016/j.pediatrneurol.2018.10.019.

References

1. Horky LL, Gerbaudo VH, Zaitsev A, et al. Systemic chemotherapy decreases brain glucose metabolism. Ann Clin Transl Neurol. 2014;1:788–798.
2. Simo M, Rifa-Ros X, Rodriguez-Fornells A, Bruna J. Chemobrain: a systematic review of structural and functional neuroimaging studies. Neurosci Biobehav Rev. 2013;37:1311–1321.
3. Ehrhardt MJ, Mulrooney DA, Li C, et al. Neurocognitive, psychosocial, and quality-of-life outcomes in adult survivors of childhood non-Hodgkin lymphoma. Cancer. 2018;124:417–425.
4. Berti V, Mosconi L, Pupi A. Brain: normal variations and benign findings in fluorodeoxyglucose-PET/computed tomography imaging. PET Clin. 2014;9:129–140.
5. Ishii K, Sakamoto S, Hosaka K, Mori T, Sasaki M. Variation in FDG uptakes in different regions in normal human brain as a function of the time (30 and 60 minutes) after injection of FDG. Ann Nucl Med. 2002;16:299–301.
6. Boellaard R, Delgado-Bolton R, Oyen WJ, et al. FDG PET/CT: EANM procedure guidelines for tumour imaging: version 2.0. Eur J Nucl Med Mol Imaging. 2015;42:328–354.
7. Sorokin J, Saboury B, Ahn JA, Moghbel M, Basu S, Alavi A. Adverse functional effects of chemotherapy on whole-brain metabolism: a PET/CT quantitative analysis of FDG metabolic pattern of the “chemo-brain”. Clin Nucl Med. 2014;39:e35–e39.
8. Silverman DH, Dy CJ, Castellon SA, et al. Altered frontocortical, cerebellar, and basal ganglia activity in adjuvant-treated breast cancer survivors 5-10 years after chemotherapy. Breast Cancer Res Treat. 2007;103:303–311.
9. Patte C, Auperin A, Michon J, et al. The Societe Francaise d'Oncologie Pediatrique LMB89 protocol: highly effective multiagent chemotherapy tailored to the tumor burden and initial response in 561 unselected children with B-cell lymphomas and L3 leukemia. Blood. 2001;97:3370–3379.
10. Landmann E, Burkhardt B, Zimmermann M, et al. Results and conclusions of the European Intergroup EURO-LB02 trial in children and adolescents with lymphoblastic lymphoma. Haematologica. 2017;102:2086–2096.
11. Wrobel G, Mauguen A, Rosolen A, et al. Safety assessment of intensive induction therapy in childhood anaplastic large cell lymphoma: report of the ALCL99 randomised trial. Pediatr Blood Cancer. 2011;56:1071–1077.
12. Kadan-Lottick NS, Zeltzer LK, Liu Q, et al. Neurocognitive functioning in adult survivors of childhood non-central nervous system cancers. J Natl Cancer Inst. 2010;102:881–893.
13. Buizer AI, de Sonneville LM, Veerman AJ. Effects of chemotherapy on neurocognitive function in children with acute lymphoblastic leukemia: a critical review of the literature. Pediatr Blood Cancer. 2009;52:447–454.
14. Copeland DR, Moore III BD, Francis DJ, Jaffe N, Culbert SJ. Neuropsychologic effects of chemotherapy on children with cancer: a longitudinal study. J Clin Oncol. 1996;14:2826–2835.
15. Moleski M. Neuropsychological, neuroanatomical, and neurophysiological consequences of CNS chemotherapy for acute lymphoblastic leukemia. Arch Clin Neuropsychol. 2000;15:603–630.
16. von der WN, Mosimann I, Hirt A, et al. Intellectual outcome in children and adolescents with acute lymphoblastic leukaemia treated with chemotherapy alone: age- and sex-related differences. Eur J Cancer. 2003;39:359–365.
17. Collins B, Mackenzie J, Stewart A, Bielajew C, Verma S. Cognitive effects of chemotherapy in post-menopausal breast cancer patients 1 year after treatment. Psychooncology. 2009;18:134–143.
18. Wefel JS, Lenzi R, Theriault RL, Davis RN, Meyers CA. The cognitive sequelae of standard-dose adjuvant chemotherapy in women with breast carcinoma: results of a prospective, randomized, longitudinal trial. Cancer. 2004;100:2292–2299.
19. Schagen SB, Wefel JS. Chemotherapy-related changes in cognitive functioning. EJC Suppl. 2013;11:225–232.
20. Chiaravalloti A, Pagani M, Di PB, et al. Is cerebral glucose metabolism affected by chemotherapy in patients with Hodgkin's lymphoma? Nucl Med Commun. 2013;34:57–63.
21. Kahkonen M, Harila-Saari A, Metsahonkala L, et al. Cerebral blood flow and glucose metabolism in long-term survivors of childhood acute lymphoblastic leukaemia. Eur J Cancer. 1999;35:1102–1108.

22. Phillips PC, Moeller JR, Sidtis JJ, et al. Abnormal cerebral glucose metabolism in long-term survivors of childhood acute lymphocytic leukemia. Ann Neurol. 1991;29:263–271.
23. Hsieh TC, Wu YC, Yen KY, Chen SW, Kao CH. Early changes in brain FDG metabolism during anticancer therapy in patients with pharyngeal cancer. J Neuroimaging. 2014;24:266–272.
24. Machado AMC, Fagundes TC, Mafra A, Silva RG, Castro ACG, Mamede M. Effects on 18F-FDG PET/CT brain glucose metabolism in rectal cancer patients undergoing neoadjuvant chemotherapy. Clin Nucl Med. 2017;42:e484–e490.
25. Baudino B, D'agata F, Caroppo P, et al. The chemotherapy long-term effect on cognitive functions and brain metabolism in lymphoma patients. Q J Nucl Med Mol Imaging. 2012;56:559–568.
26. Wilson DA, Nitschke R, Bowman ME, Chaffin MJ, Sexauer CL, Prince JR. Transient white matter changes on MR images in children undergoing chemotherapy for acute lymphocytic leukemia: correlation with neuropsychologic deficiencies. Radiology. 1991;180:205–209.
27. de Court. The human cerebral cortex: gender differences in structure and function. J Neuropathol Exp Neurol. 1999;58:217–226.
28. Boellaard R. Standards for PET image acquisition and quantitative data analysis. J Nucl Med. 2009;50:11S–20S.
29. Wigmore P. The effect of systemic chemotherapy on neurogenesis, plasticity and memory. Curr Top Behav Neurosci. 2013;15:211–240.
30. Kennedy SH, Evans KR, Kruger S, et al. Changes in regional brain glucose metabolism measured with positron emission tomography after paroxetine treatment of major depression. Am J Psychiatry. 2001;158:899–905.
31. Kumano H, Ida I, Oshima A, et al. Brain metabolic changes associated with predisposition to onset of major depressive disorder and adjustment disorder in cancer patients—a preliminary PET study. J Psychiatr Res. 2007;41:591–599.