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In vivo hypoxia imaging of brain tumors can visualize microscopic necrosis and anaerobic glycolysis.

（脳腫瘍に対するインビボ低酸素イメージングによって腫瘍内の顕微鏡的壊死
や嫌気性糖代謝を可視化する）

【Introduction】

Hypoxia is well known as one of the major factors that affect tumor malignancy. Hypoxic conditions stimulates translating many proteins concerning about the glycolytic system, cell migration, angiogenic signaling, and cell proliferation. In addition, hypoxia is well known to induce radiation or chemotherapy resistance. It is reasonable that tumor hypoxia causes poor prognosis by means of such treatment resistance. Fluoromisonidazole (FMISO) is the most widely used tracer of positron emission tomography (PET) to visualize severe hypoxia *in vivo*. We previously showed that FMISO accumulation related with presence of necrosis and allow distinguishing glioblastoma from other lower-grade gliomas. Thus, in chapter 1, we focus on the relationship between hypoxia and necrosis not only for astrocytic glioma but also for other types of brain tumor. We tested the diagnostic performance of FMISO to predict pathological diagnosis in terms of present/absent necrosis.

In chapter 2, we focus on the FMISO-and-fluorodeoxyglucose (FDG) double positive area, where we assume anaerobic glycolysis may be dominant for energy production. We tested whether the parameters from FMISO-and-FDG double positive area have a potential to predict prognosis.

Chapter 1

【Materials and methods】

The chapter 1 population included 66 patients (M:F=36:30, age: 27–85 years) who had brain tumor and underwent FMISO PET and magnetic resonance imaging (MRI) before radiation therapy, chemotherapy, and surgical intervention. According to the pathological diagnosis, brain tumors were divided into three groups astrocytic tumors (group 1), neuroepithelial tumors other than astrocytic tumors (group 2), and other histopathological tumors (group 3).

The FMISO PET of tumor-to-normal cerebellum ratio (TNR) was calculated for semi-quantitative analysis. The average values of cerebellar cortex of the standard uptake value (SUV) were defined as normal references. The maximum SUV (SUVmax) of the tumor was divided by averaging the cerebellar SUV as the TNR.

Two experienced neuropathologists assessed each specimen and evaluated the presence of necrosis in consensus. The diagnosis and evaluation were determined by agreement of the two pathologists.

【Results】

Histopathological necroses were observed in 23/23 glioblastomas (100%), 5/5 glioblastomas with oligo (100%), 1/8 AOs (12.5%), 1/1 AE (100%), 4/7 PCNSLs (57.1%), and 1/2 metastatic brain tumors (50%), and 1/1 atypical meningioma (100%). Necroses were found in 17/31 cases in group 1, 7/20 cases in group 2, and 6/15 cases in group 3. The TNR in group 1 was 3.45 ± 0.97 vs. 1.43 ± 0.42 (with vs. without necrosis), the TNR in group 2 was 2.91 ± 0.83 vs. 1.44 ± 0.20 , and the TNR in group 3 was 2.63 ± 1.16 vs. 1.36 ± 0.22 . The TNRs of cases with necrosis were significantly higher than those of cases without necrosis in

each group (group 1, 2, and 3: $p < 0.00001$, $p < 0.005$, and $p < 0.05$, respectively). The lowest TNR in necrosis positive cases was 1.65.

【Discussion】

Results indicated a strong correlation between the FMISO uptake status and the presence of necrosis. The correlations were significant not only in astrocytic tumors, but also in various histological types of brain tumor. It appears that both the presence of intratumoral micro-necrosis and FMISO uptake have certain thresholds of pO₂ pressure. Our results of strong agreement between necrosis and FMISO uptake suggest that the thresholds are close to each other.

Chapter 2

【Materials and methods】

The chapter 2 population consisted of 17 male and 15 female glioblastoma patients (age, 63.5 ± 14.8 years). All of the 32 glioblastoma patients underwent FDG PET, FMISO PET, and MRI before any treatments. FDG and FMISO PET images and MR images were co-registered using SPM8 software. For FMISO, we averaged cerebellar uptake for the normal reference, and for FDG we adopted contralateral cortex average uptake for FDG normal reference. Within the tumor volume of interests (VOIs), a voxel that had an FMISO TNR ≥ 1.3 or 1.65 was defined as FMISO-positive, and FDG TNR ≥ 1.0 was defined as FDG-positive. From these parameters we calculated the hypoxia volume (HV), hypoxic metabolic tumor volume (hMTV), hypoxic total lesion glycolysis (hTLG), hypermetabolic fraction of hypoxia volume (HMF). We tested the correlation between patients' PFS or OS and those parameters using the Cox regression model for univariate analysis and with the Cox proportional hazard model for multivariate analysis.

【Results】

The TNR for FDG was 1.55 ± 0.52 (range, 1.08–3.96). All (100%) of the lesions had a higher FDG SUV_{max} than the reference value (i.e., TNR ≥ 1.0). The TNR for FMISO was 3.29 ± 0.81 (range, 1.48–4.85). In volumetric assessment, the hMTV_{1.3} and HV_{1.3} were 7.98 ± 8.85 ml (range, 0.12–35.27 ml) and 29.78 ± 18.90 (range, 0.84–81.95 ml), respectively. The hTLG_{1.3} was 41.69 ± 37.65 (range, 0.66–126.26), and the HMF_{1.3} was $25.15 \pm 18.03\%$ (range, 0.89–61.80%).

At these cutoff values, the hMTV_{1.3}, hTLG_{1.3}, and extent of resections (EOR) were significantly correlated with PFS ($p=0.007$, $p=0.04$, and $p=0.01$, respectively). A significantly shorter OS was also suggested by higher HV_{1.3}, higher hMTV_{1.3}, higher hTLG_{1.3}, and lower EOR ($p=0.04$, $p=0.0028$, $p=0.037$, and $p=0.014$, respectively).

The Cox proportional hazard model indicated that patients' PFS and OS were independently influenced by the hMTV_{1.3} or hTLG_{1.3}.

【Discussion】

We conducted a study involving the independent detection of hypermetabolic and hypoxic volumes using FDG PET and FMISO PET, respectively. We found that the patients who had a larger hMTV_{1.3} or larger hTLG_{1.3}, or had undergone a more extensive surgical procedure, survived significantly longer than the other patients. In addition, multivariate analysis indicated that both the hTLG_{1.3} and hMTV_{1.3} were significant prognostic factors that were independent from the EOR. The FDG/FMISO double-positive fraction may reflect 'signal transmission efficiency' initiated from hypoxia to anaerobic glycolysis.

【Summary and Conclusion】

FMISO PET could visualize intratumoral microscopic necrosis in vivo and could provide important information for treatment decisions and surgical strategies of any type of brain tumor. The combination of FDG and FMISO PET may allow evaluate tumoral anaerobic glycolysis.