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Special Theme Topic:
Treatment of Malignant Brain Tumor

Usefulness of FMISO—PET for Glioma Analysis

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Abstract

Glioma is one of the most common brain tumors in adults. Its diagnosis and management have been determined by histological classifications. It is difficult to establish new paradigms because the pathology has matured and a great deal of knowledge has accumulated. On the other hand, we understand that there are limitations to this gold-standard because of the heterogeneity of glioma. Thus, it is necessary to find new criteria independent of conventional morphological diagnosis. Molecular imaging such as positron emission tomography (PET) is one of the most promising approaches to this challenge. PET provides live information of metabolism through the behavior of single molecules. The advantage of PET is that its noninvasive analysis does not require tissue sample, therefore examination can be performed repeatedly. This is very useful for capturing changes in the biological nature of tumor without biopsy. In the present clinical practice for glioma, ^{18}F-fluorodeoxyglucose (FDG) PET is the most common tracer for predicting prognosis and differentiating other malignant brain tumors. Amino acid tracers such as ^{11}C-methionine (MET) are the most useful for detecting distribution of glioma, including low-grade. Tracers to image hypoxia are under investigation for potential clinical use, and recently, ^{18}F-fluoromisonidazole (FMISO) has been suggested as an effective tracer to distinguish glioblastoma multiforme from others.

Key words: glioma, positron emission tomography (PET), hypoxia, ^{18}F-fluoromisonidazole (FMISO)

Introduction

In glioma management, particularly in surgery, precise diagnosis before the initial operation is quite important because the treatment strategy and prognosis differ widely with histological grade. Gliomas diffusely infiltrate neighboring brain structures and are characterized by regional variations of histological malignancy.[38] Therefore, detection of the highly malignant region and delineation of the extent of the tumor are critical for preoperative evaluation.

Gliomas often present with different degrees of malignancy in different parts of the tumor. Therefore, surgical biopsies may miss the most malignant tumor sample and underestimate the grade. Preoperative diagnostic information is thus extremely important in planning of precise treatment. In this regard, the role of positron emission tomography (PET) has been increasing in practical situations. PET has been used for evaluation of glioma metabolism, and the most popular radiolabeled tracers are ^{18}F-fluorodeoxyglucose (FDG), ^{18}F-fluorothymidine (FLT), and ^{11}C-methionine (MET). Previous research using these traces has addressed whether alterations presented by PET reveal prognostic value, and whether it detects malignant transformation from low-grade to high-grade. Moreover, tracers for imaging hypoxia, including ^{18}F-fluoromisonidazole (FMISO), are under investigation to address these clinical issues. Hypoxia is a very important phenomenon when considering tumor malignancy. It has been suggested that hypoxia makes the tumor resistant to radiation therapy and allows the tumor to be more aggressive, and indeed, malignant glioma tissues often develop hypoxia.

Development of hypoxia PET tracer is not new.

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Although Valk et al. reported the first use of FMISO for glioma imaging,[51] it was not frequently used during the 1990s. An explosive increase in the prevalence of PET scanners in the last decade, especially PET-CT integrated scanners, encouraged researchers and clinicians to apply FMISO for different types of tumors, including gliomas. Our group demonstrated that FMISO could distinguish glioblastoma from less malignant gliomas.[17] FDG PET visualizes the glucose metabolism of the tumor, and it has been demonstrated since the 1980s that FDG uptake of gliomas is highly correlated with histological malignancy and with patient survival.[1,4,15,19,35,37]

However, FDG PET is often unsuitable for detection of gliomas because the glucose consumption of a normal brain cortex is relatively high,[3,7] and when a hypermetabolic lesion is near the cortical or subcortical gray matter, it is difficult to differentiate FDG uptake in tumor and in normal brain.[11] Although several experiments addressing this weak point have been reported,[45] new analytic concepts are necessary to utilize FDG PET for management of gliomas. MET, an amino acid tracer, is one of the most widely used tracers because there is less uptake in healthy brain, resulting in better contrast between tumor and normal brain than with FDG PET.[43] MET PET has been suggested to delineate both benign and malignant gliomas more accurately than conventional imaging methods such as computed tomography (CT) or magnetic resonance imaging (MRI).[39,50] Although previous studies have shown positive correlations between MET uptake and histological grade,[19,21,27], MET uptake of gliomas with oligodendroglial components is significantly higher than that of astrocytic gliomas, even in histologically low-grade tumors.[5,10,16,20,24,33,42] In oligodendrocytic tumors, MET uptake ratio does not always correlate with histological tumor grade and proliferative activity.[20] Moreover, MET uptake ratio in grade II oligodendrogliomas is not significantly different from that in grade IV glioblastomas.[33]

Tracers to image hypoxia are under investigation for potential clinical use, and recently, FMISO has been suggested as a useful tracer for diagnosis of GBM. In this article, we describe FMISO PET with a new aspect in management of glioma.

^{18}F-fluoromisonidazole (FMISO)

Why and how to image hypoxia?

Hypoxia is a phenomenon that has interested oncologists for a long time. Malignant tumor tissues often develop hypoxia. By means of hyperexpression of hypoxia inducible factor (HIF)-1 alpha, which enhances a number of genes related to proliferation, hypoxia makes the tumor resistant to radiation therapy and allows the tumor to be more aggressive. Previously, the sole method for measuring intratumoral oxygen partial pressure was the use of needle electrodes.[30] However, this procedure is too invasive to use as a preoperative evaluation, and it could also alter the microenvironment in the tumor, possibly giving an inaccurate oxygen concentration.

PET is expected to be an ideal noninvasive tool for visualizing hypoxic condition in vivo. Development of hypoxia PET tracers has been researched for years. The first radiotracer developed for hypoxia imaging was ^{14}C misonidazole in 1981.[6] It was followed by the introduction of FMISO as a PET tracer.[18] Although Valk et al. reported the first use of FMISO for glioma imaging,[51] it was not frequently used during 1990s. An explosive increase in the prevalence of PET scanners in the last decade, especially PET-CT integrated scanners, has encouraged researchers and clinicians to apply FMISO to different kinds of tumors, including brain tumors.

Mechanisms of FMISO uptake

The mechanisms of FMISO accumulation in hypoxic tissues have been described previously.[28] Briefly, intravenously injected FMISO is first distributed to the cells via blood flow. Then, the FMISO molecules capture electrons in the mitochondrial electron transfer system. In normoxic cells, namely cells without hypoxia, the FMISO electron is taken by O_2. In hypoxic cells, on the other hand, FMISO keeps the extra electron in the molecule because of O_2 shortage. FMISO with an extra electron is allowed to stay in the cell whereas FMISO with no extra electron is excreted from the cell. Therefore, FMISO is cleared from the normoxic cells but not from the hypoxic cells. Note that FMISO in necrotic cells is also excreted because there is no functioning mitochondrion from which FMISO can take electrons. The threshold of O_2 partial pressure that determines whether or not FMISO is excreted is believed to be ~10 mmHg.[22,41] This suggests that FMISO accumulates only in severely hypoxic tissues, which we should pay attention.

Hypoxia imaging for differential diagnosis

Theoretically, FMISO PET can differentiate tumors with severe hypoxia from those without. Studies using direct needle electrodes suggested that the hypoxic condition of gliomas depends on its degree of malignancy.[9,14,26] We examined 23 preoperative glioma patients of different World Health Organization (WHO) grades using FMISO PET and FDG PET.[17] The PET findings were compared with histological findings. We found that FMISO uptake was seen

only in glioblastoma multiforme (GBM), but not in less malignant gliomas (grade II or grade III). In the WHO definition, GBM has necrosis in the tumor, although grade III or lower grade gliomas do not develop necrosis.[29] Therefore, it is reasonable that only GBM has severe hypoxia beyond the FMISO threshold and thus shows FMISO uptake. We concluded that FMISO PET may be able to clearly distinguish GBM from lower grade gliomas.

On the other hand, several articles reported apparently different results from ours. Cher et al. reported FMISO PET findings of glioma patients of various grades.[8] In that paper, all grade IV tumors showed high FMISO uptake, which is consistent with ours. However, they observed that one of the three grade III gliomas showed positive FMISO uptake. Yamamoto et al. also observed FMISO uptake in some grade III gliomas, although the uptake in grade IV was significantly higher than in grade III or lower.[52] FMISO uptake in grade III glioma was observed by these two research groups probably because the images were acquired earlier at 2 hours after intravenous FMISO injection, whereas we acquired the PET images 4 hours after injection. In fact, protocols with 2 hours as uptake time are often used for FMISO studies.

However, Thorwarth et al. discussed a problem with two-hour imaging of FMISO.[49] Showing the results of kinetic analysis for the dynamic dataset of FMISO PET, this article reported that some of the hot spots on two-hour FMISO images disappeared on four-hour FMISO images. This suggested that the high uptake on two-hour images may have reflected high initial influx of the tracer due to increased blood flow rather than hypoxia. In other words, four-hour images should represent hypoxia alone, whereas two-hour images should represent increased blood flow with or without hypoxia. We understand that two-hour imaging has advantages: (1) less time is required for the entire examination, reducing patients' stress and (2) approximately twice the number of photons is detected by the PET scanner compared to four-hour imaging, due to 110 minutes half-life of ^{18}F, by which the image quality of two-hour protocol should be better than that of four-hour protocol. To further optimize the procedure, we need direct comparison between these protocols for the same patient group.

Reproducibility

One may argue that hypoxia condition is not stable, but rather fluctuating to some extent. In fact, hypoxia in tumor can be divided into acute hypoxia and chronic hypoxia.[2] This raises concerns about a lack of reproducibility of the hypoxia imaging leading to insufficient reliability for clinical usage.[32] However, using four-hour imaging, our colleagues attempted to compare FMISO images of the same patients with head and neck cancer, which were acquired at 48-hour intervals.[36] They demonstrated that the image parameters reproduced; the difference of tumoral SUVmax of FMISO between first and second scanning was 7.0% ± 4.6% (range, 1.2–11.7%), and that of tumor-to-muscle ratio was 7.1% ± 5.3% (range, 0.4–15.3%). This high reproducibility of FMISO imaging justifies a clinical application.

Prediction of prognosis

Is FMISO PET predictive of prognosis for GBM patients? According to Cher et al., positive FMISO uptake was suggested to be associated with patient's survival.[8] Spence et al. analyzed FMISO PET performed before radiotherapy and compared the findings with time to progression.[46] They found that those patients who had greater hypoxia volume or greater tumor-to-blood uptake ratio showed earlier progression. In another article, they also evaluated the predictive performance of several parameters derived from FMISO PET and MR imaging.[47] They found that the most significant predictors of survival were hypoxia volume,[30] hypoxia surface area,[6] and tumor-to-blood uptake ratio measured on FMISO PET images.[18]

Other clinical options

One of the expected roles of FMISO imaging is therapy monitoring. It may be possible to see how fractionated radiotherapy damages tumor cells more effectively, because FMISO images can visualize the reoxygenation process. In a report of two cases, we observed a considerable decrease of FMISO accumulation in GBM after chemoradiotherapy, as compared to that before therapy.[31]

Other hypoxia tracers being examined

As we mentioned above, one of the shortcomings of FMISO as a PET tracer is slow clearance of nonspecific activity of FMISO from plasma and non-hypoxic tissues, by which it requires 4 hours to acquire adequate "hypoxia" images but not perfusion images. Although this is not a crucial disadvantage, if the uptake time could be shortened, hypoxia imaging would be more widely used than ever. Researchers have been looking for other hypoxia tracers; nothing has more evidence than FMISO so far, but some are reported to be promising.

Recently, Kurihara et al. wrote a comprehensive review article on preclinical and clinical data for hypoxia PET tracers including FMISO, ^{18}F-fluoroerythronitroimidazole (FETNIM), ^{18}F-fluoroazomycin-arabinofuranoside (FAZA), and ^{62}Cu or ^{64}Cu-diacetyl-bis(N^4-methylthiosemicarbazone) (Cu-ATSM).[25]

Among these radiotracers, FETNIM has not been used for brain tumor. FAZA is less lipophilic than FMISO and thus non-specific activity is expected to be washed out more quickly. Sorger et al. showed its faster clearance than FMISO, but tracer uptake in the tumor was lower for FAZA than FMISO in the animal study.[44] Postema et al. evaluated FAZA PET for 50 patients with various malignant tumors, including seven GBMs.[40] The images were acquired 2–3 hours after injection. The image quality was reported to be good, but its superiority to FMISO was not clear.

A great advantage of Cu-ATSM is that the radionuclide ^{62}Cu is produced by a ^{62}Zn/^{62}Cu generator, which allows the institutes without a nearby cyclotron to image hypoxia. In a study using a R3327-AT tumors model, the late images of Cu-ATSM (acquired at 19 hours) were correlated with FMISO images (acquired at 2–4 hours) and oxygen probe measurement.[34] However, they found a lack of correlation between the early images of Cu-ATSM (acquired at 1 hour) and the FMISO images. They also used a FaDu tumor model and reported that both early and late images of Cu-ATSM were correlated with FMISO image. More recently, Dence et al. compared ATSM with FMISO, FDG, and FLT in a study of a 9L gliosarcoma model. Cu-ATSM was highly correlated with FMISO in the study using autoradiography.[12] Clinically, Tateishi et al. reported the use of Cu-ATSM for glioma patients and found a correlation between Cu-ATSM uptake and glioma grading.[48] Further studies are necessary to establish the clinical significance of Cu-ATSM PET.

Finally, we would like to mention ^{18}F-EF5 or 2-(2-nitro-1[H]-imidazol-1-yl)-N-(2,2,3,3,3-pentafluoropropyl)-acetamide. This radiotracer was first used in an animal study by Ziemer et al.[53] Evans et al. applied EF5 for glioma patients, and found that EF5 uptake was correlated with poor prognosis.[14] They also compared EF5 uptake with microscopic findings of vasculature.[13] Animal studies suggest that EF5 uptake is correlated with radiation response.[23]

Summary

The most common tracer, FDG, has a potential role in providing prognostic information. But the detectability of tumors is still a frustrating issue. On one hand, amino acid tracers including MET provide better sensitivity and distinction from normal brain for gliomas. However, on the other hand, their usefulness is limited regarding the distinction between low-grade and high-grade tumors. Perhaps in the future, hypoxia tracers such as FMISO may become a strong tool for determining histological grading. Because it is important that we predict each positive and negative point of the tracers in order to achieve appropriate diagnosis before biopsy.

Conflicts of Interest Disclosure

The authors have no personal, financial, or institutional interest. All authors (except KH and TS) are members of the Japan Neurosurgical Society (JNS), and have registered online Self-reported COI Disclosure Statements forms through website for JNS members.

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