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PET/CT in head and neck cancer

Correlation of ^{18}F-BPA and ^{18}F-FDG uptake in head and neck cancers

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ABSTRACT

Background and purpose: The aim of this study was to compare the accumulation of 4-borono-2-^{18}F-fluoro-phenylalanine (^{18}F-BPA) with that of ^{18}F-fluorodeoxyglucose (^{18}F-FDG) in head and neck cancers, and to assess the usefulness of ^{18}F-FDG PET for screening candidates for boron neutron capture therapy (BNCT).

Material and methods: Twenty patients with pathologically proven malignant tumors of the head and neck were recruited from March 2012 to January 2014. All patients underwent both whole-body ^{18}F-BPA PET/CT and ^{18}F-FDG PET/CT within 2 weeks of each other. The uptakes of ^{18}F-BPA and ^{18}F-FDG at 1 h after injection were evaluated using the maximum standardized uptake value (SUVmax).

Results: The accumulation of ^{18}F-FDG was significantly correlated with that of ^{18}F-BPA. The SUVmax of ^{18}F-FDG $\geqslant$5.0 is considered to be suggestive of high ^{18}F-BPA accumulation.

Conclusions: ^{18}F-FDG PET might be an effective screening method performed prior to ^{18}F-BPA for selecting patients with head and neck cancer for treatment with BNCT.

Boron neutron capture therapy (BNCT) is a targeted radiotherapy technique developed to treat patients with selected malignant tumors. It has been tested in brain *tumors*, head and neck cancers and melanoma which are radioresistant with infiltrative growth pattern [1–4].

This particular radiation therapy is based on the combined use of thermal neutrons and one of the two stable isotopes of boron (^{10}B) to destroy tumor cells via the ^{10}B(n,α)^{7}Li neutron capture reaction. Thermal neutrons cause the boron neutron capture reaction. Epithermal neutrons are slowed down in the body and are especially needed if deep seated tumors are intended to be treated. It requires a high-intensity epithermal neutron beam and a ^{10}B carrier that accumulates in target tumor cells. Interaction of neutrons with ^{10}B nuclei releases alpha particles and recoiling lithium-7 nuclei with very short range (<10 μm) that should kill the cell. The selectivity of the therapy is based on the fact that only tumor cells containing ^{10}B are destroyed, preserving normal tissues due to their low affinity for the boron drug [1,2,5]. The success of BNCT is dependent on the sufficient accumulation of ^{10}B in cancer tissue relative to adjacent tissues, with preferably a 3- to 5-fold greater concentration in the former [1,2]. Therefore, estimation of ^{10}B content in tumor and normal tissue helps predict the therapeutic potential of BNCT. Since ^{10}B accumulation varies by tumor type, and even tumors of the same grade may differ in their biochemical properties, it would be highly desirable to determine ^{10}B concentrations prior to performing BNCT.

The most frequently used ^{10}B carrier compound today is 4-^{10}B-borono-L-phenylalanine (^{10}BPA). An ^{18}F-labeled analog of ^{10}BPA, 4-borono-2-^{18}F-fluoro-phenylalanine (^{18}F-BPA) has been developed to predict ^{10}B concentrations in tumors [6]. Imahori et al. designed a method for quantitative measurement of ^{10}B concentrations using ^{18}F-BPA positron emission tomography (PET) [7,8]. ^{18}F-BPA PET is generally used to anticipate the therapeutic effects of BNCT performed using ^{10}BPA [5–9]. However, only certain hospitals have the capability to synthesize ^{18}F-BPA [9]. Synthesis of ^{18}F-BPA from ^{18}F$_2$ gas is limited because of low radio yield, low specific activity, and high cost. Therefore, the amount of ^{18}F-BPA, which can reasonably be synthesized is not sufficient to screen all potential BNCT candidates. Because of these limitations, it is often not easy to assay the ^{10}B concentrations in tumor and normal tissues using ^{18}F-BPA PET.

^{18}F-fluorodeoxyglucose (^{18}F-FDG) is the most popular PET tracer and is available in many hospitals. ^{18}F-FDG PET is a highly sensitive tool capable of yielding considerable information on glucose metabolism [10]. It has been used in the assessment of various cancers, as several malignant tumors consume large amounts of glucose [11]. The use of ^{18}F-FDG PET as a surrogate marker for ^{18}F-BPA could have wider applicability. Thus far no reports have directly compared ^{18}F-FDG with ^{18}F-BPA.

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Though the majority of patients undergoing BNCT have brain tumors such as high-grade gliomas and cerebral metastasis [1,2], the role of ^{18}F-FDG in brain tumors is limited because of high gray matter uptake. Recently, however, use of BNCT has extended to head and neck cancers [12–14]. In this study, we used PET to examine the uptake of both ^{18}F-BPA and ^{18}F-FDG in head and neck cancers. Our aim was to compare the accumulation of ^{18}F-BPA with that of ^{18}F-FDG in head and neck cancers, and to evaluate the usefulness of ^{18}F-FDG PET for screening potential candidates for BNCT.

Materials and methods

General

All chemical reagents were obtained from commercial sources. The study protocol was approved by the institutional review board and independent ethics committee of our hospital. All patients signed written informed consent before inclusion in the trial.

Subjects

Patients included in this study had histologically confirmed head and neck tumors, at least 1 site of disease measurable via PET, Eastern Cooperative Oncology Group performance status (PS) of 0–1, adequate organ function (neutrophil count $\geqslant$1500/μL, platelet count $\geqslant$75,000/μL, hemoglobin concentration $\geqslant$9.0 g/dL, serum bilirubin $\leqslant$1.5 mg/dL, AST and ALT $\leqslant$100 IU/L, serum creatinine $\leqslant$1.5 mg/dL, baseline left ventricular ejection fraction (LVEF) >60%), and were over 20 years old. The main exclusion criteria were congestive heart failure, uncontrolled angina pectoris, arrhythmia, symptomatic infectious disease, severe bleeding, pulmonary fibrosis, obstructive bowel disease or severe diarrhea, and symptomatic peripheral or cardiac effusion.

Radiosynthesis of ^{18}F-BPA and ^{18}F-FDG

^{18}F-BPA was synthesized by direct electrophilic radiofluorination of BPA (Sigma–Aldrich, St. Louis, MO, USA) using ^{18}F-acetyl hypofluorite as described previously [15]. Purification of ^{18}F-BPA was performed by HPLC using a YMC-Pack ODS-A column (20 × 150 mm; YMC, Kyoto, Japan) eluted with 0.1% acetic acid at a flow rate of 10 mL/min. The radiochemical purity of ^{18}F-BPA, determined by HPLC, was >99.5%, and its specific activity was 25 MBq/μmol. ^{18}F-FDG was prepared using an automated ^{18}F-FDG-synthesis system (F-200, Sumitomo Heavy Industries, Ltd.).

PET/CT scanner and protocol

The examination schedule is shown in Fig. 1. Images were acquired with Discovery 600 scanner (GE Healthcare, Milwaukee, WI, USA). A whole-body ^{18}F-FDG PET/CT image was obtained 1 h after the injection of ^{18}F-FDG (ca. 4 MBq/kg). For the ^{18}F-FDG PET/CT studies, patients were requested to fast for at least 4 h before the scheduled ^{18}F-FDG injection. Whole-body ^{18}F-BPA PET/CT imaging was also carried out within 2 weeks. ^{18}F-BPA PET/CT images were acquired 1 h after the injection of ^{18}F-BPA (ca. 4 MBq/kg).

For whole-body PET/CT imaging, a scout image was acquired to determine the scanning field ranging from head to pelvis, using settings of 10 mA and 120 kV. Next, whole-body 16-slice helical computed tomography (CT) and whole-body 3D PET were performed. PET images were acquired in 7–8 bed positions with a 2 min acquisition period per bed position, so that the imaging covered the same field as that of whole-body CT. The acquired data were reconstructed as 192 × 192 matrix images (3.65 × 3.65 mm) using a 3D ordered subsets-expectation maximization (3D OS-EM) algorithm.

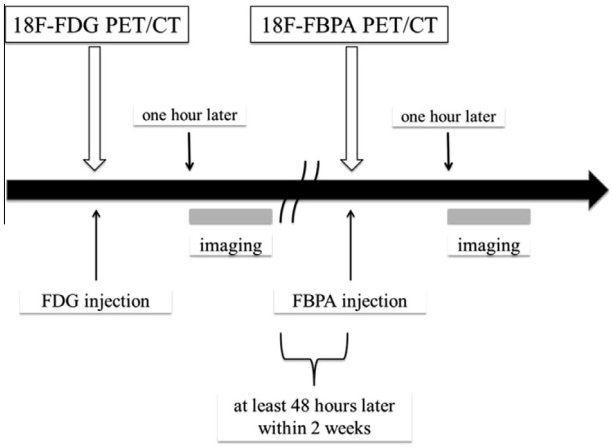

Fig. 1. Schedule of PET/CT examinations.

Tumor uptake of ^{18}F-BPA and ^{18}F-FDG

PET image evaluation and quantification of the standardized uptake value (SUV) were performed using AW Volume Share 4.5 software (GE Healthcare, Milwaukee, WI, USA). Regions of interest (ROIs) were delineated on the PET/CT images, and the maximum SUV in each ROI (SUVmax) was determined. Tumor ROIs were defined as the areas of highest activity. SUV was defined as the regional radioactivity divided by the injected radioactivity normalized to the body weight. Both the ^{18}F-BPA and ^{18}F-FDG uptake 1 h after injection were evaluated using SUVmax. At the corresponding level on ^{18}F-BPA PET, ROIs were then placed onto the normal tissue region surrounding the tumor to calculate the lesion to normal ratio (L/N) of ^{18}F-BPA. Clinically, dose planning was performed based on L/N ratio prior to initiation of BNCT. Tumor sizes were also measured on CT.

Statistical analysis

A linear regression analysis was performed for the correlation study. As previously reported, patients were determined eligible for BNCT when the L/N ratio of ^{18}F-BPA was more than 2.5 [1,8,16], so we used a L/N ratio of ^{18}F-BPA $\geqslant$2.5 to differentiate positive from negative. We then performed a receiver operating characteristic (ROC) analysis for SUVmax of ^{18}F-FDG to determine the optimal threshold values for quantitative discrimination. The area under the curve (AUC) was also calculated. For estimating concordance of cutoff value of the 2 tracers, Fisher's exact test was performed. Probability values of $P < 0.05$ were considered significant.

Results

Patient and tumor characteristics are summarized in Table 1. A total of 20 patients (17 male, 3 female, age range 30–76 years, mean age 62 years) with pathologically proven head and neck malignant tumors were enrolled in this study from March 2012 to January 2014. All patients had unresectable advanced or recurrent head and neck tumors. The majority of primary tumor sites were the pharynx or parotid gland. Tumor histological types varied: 9 patients had squamous cell carcinoma, 5 had adenoid cystic carcinoma and the remaining 6 had other types of malignant tumors. Fourteen of the 20 patients had local recurrent tumors, 5 had metastatic tumors and one had a newly diagnosed tumor.

Typical PET/CT images of ^{18}F-BPA and ^{18}F-FDG are shown in Fig. 2. SUVmax and L/N ratio of ^{18}F-BPA, SUVmax of ^{18}F-FDG and measured tumor size are summarized in Table 1. The tumor SUVmax of ^{18}F-BPA ranged from 1.79 to 8.19 (average, 4.13), whereas