Original

Comparison of ^{18}F-choline and ^{18}F-FDG accumulation in PET imaging of oral squamous cell carcinoma

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Abstract : Positron emission tomography (PET) with ^{18}F-choline was performed to examine squamous cell carcinomas in the oral cavity, and its usefulness in the diagnosis of oral cancers was investigated on the basis of comparison with [^{18}F] -2-fluoro-2-deoxy-D-glucose (^{18}F-FDG) PET. The subjects were 36 oral cancer patients, with 17 patients and 19 patients examined by ^{18}F-choline and ^{18}F-FDG PET, respectively. ^{18}F-choline and ^{18}F-FDG accumulation were analyzed in the primary lesions and in the brain, major salivary glands, liver, abdomen, and urinary bladder. ^{18}F-choline accumulated less than ^{18}F-FDG in the brain and bladder. For the remaining examined organs, ^{18}F-choline accumulation was greater than that of ^{18}F-FDG. The mean value of ^{18}F-choline accumulation in the primary lesions was not significantly different from that of ^{18}F-FDG. ^{18}F-choline accumulation by the primary lesions peaked within 10 minutes after administration. ^{18}F-FDG did not reach a maximum even after 50 minutes. In conclusion, ^{18}F-choline accumulated in the primary lesions of oral cancers, similar to ^{18}F-FDG. Furthermore, it is also useful for the diagnosis of cases that progress near the brain, which is difficult with ^{18}F-FDG. ^{18}F-choline shortens the PET examination time, markedly reducing the burden on patients more than ^{18}F-FDG PET.

Key words : ^{18}F-choline, ^{18}F-FDG, PET, oral cancer, physiological accumulation

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Introduction

Positron-emission tomography (PET) is a methodology of nuclear medicine that is widely used in oncology and neurology. A glucose analog, ^{18}F-labeled [^{18}F] -2-fluoro-2-deoxy-D-glucose (^{18}F-FDG), is mainly used to distinguish between benign and malignant lesions, to stage tumors, to detect recurrence, and to assess the effect of therapy[1, 2]. ^{18}F-FDG accumulation decreases in hyperglycemic patients[3]. It physiologically accumulates in the brain and urinary bladder, making diagnosing brain tumors and prostate cancer difficult[4, 5]. Normally, patients rest quietly for 1 hour to allow ^{18}F-FDG uptake followed by scanning. The usefulness of PET, using [methyl-^{11}C] choline (^{11}C-choline) as a tumor tracer to substitute for ^{18}F-FDG, has been reported[6, 7]. Since cell division is usually accelerated in tumors, the synthesis of cell membranes can be used as an imaging target. Choline is a major building block of cell membrane phospholipids and accumulates in tumor cells in proportion to the frequency of cell division[8]. The uptake rate of ^{11}C-choline into cells is rapid and, in contrast to ^{18}F-FDG, is unaffected by blood glucose levels or glucose metabolism. Its usefulness as a PET tumor tracer in the prostate and the brain has been reported[5, 9]. However, it has to be synthesized in a PET facility and must be immediately used because the half-life of ^{11}C is very short (20 minutes). If choline can be labeled with ^{18}F, which has a relatively long half-life (110 minutes), its delivery logistics become the same as those for ^{18}F-FDG. Studies on the synthesis method and clinical application of ^{18}F-choline have been performed[10]. Now, the usefulness of ^{18}F-choline as a tumor tracer in the prostate has been established[11]. But there have been few reports on its use in the oral cavity to assess squamous cell carcinoma, and it has not been sufficiently clarified whether or not ^{18}F-choline PET is clinically useful. In this study, ^{18}F-choline and ^{18}F-FDG PET were performed on patients with squamous cell carcinoma, and the differences in images and the usefulness of ^{18}F-choline PET were evaluated.

Subjects and Methods

1. Subjects

The subjects were 36 oral cancer patients, who were examined with ^{18}F-choline or ^{18}F-FDG PET. The histologic type was well-differentiated squamous cell carcinoma. Seventeen oral cancer patients were examined

Table 1 Characteristics of the patients who performed ^{18}F-choline and ^{18}F-FDG PET in this study

	^{18}F-FDG	^{18}F-choline
Age (mean ± SD) (years)	66.5 ± 12.5	65.6 ± 12.1
Gender		
Male	10	10
Female	7	9
TNM classification		
T_1 N_0 M_0	2	5
T_2 N_0 M_0	12	10
T_2 N_1 M_0	1	0
T_4 N_0 M_0	2	3
T_4 N_2 M_0	0	1

There were no difference in the mean age ($p = 0.83$) and male-female ratio ($p = 0.97$) of the two groups in patients.

by ^{18}F-choline PET. Histological examination was performed within one month of PET. Their mean age was 66.5 ± 12.5 y (Table 1). The disease stage was determined by following the International Union Against Cancer (UICC) classification (6th ed.) [12]. The cancer location was the tongue in ten patients, the gingiva in three, the floor of the mouth in two, and the buccal mucosa and the hard palate in one patient each. ^{18}F-FDG PET was performed on 19 patients with a mean age of 65.6 ± 12.1 y ($p = 0.83$). The cancer location was the tongue in six patients, the gingiva in five, the floor of the mouth in three, the buccal mucosa and the lip in two patients each, and the hard palate in one. The primary lesion was evaluated by CT or MRI, and the product of the major axis and minor axis was taken as the size of the primary lesion. Cases with a major axis of < 10 mm in the axial plane were excluded from this study because evaluation by PET was difficult. This study was conducted in accordance with the Declaration of Helsinki. All study protocols were approved by the Ethics Committee at the School of Dentistry (no. 01083), Iwate Medical University.

2. PET scanning protocol

^{18}F-choline and ^{18}F-FDG were synthesized at the Cyclotron Center of Iwate Medical University. For ^{18}F-fluoromethyl choline (^{18}F-choline), [^{18}F] fluoromethyl triflate ([^{18}F] CH_2FOTf) was prepared using the synthesis method reported by Iwata et al.[13]. ^{18}F-FDG was synthesized using $H_2{}^{18}O$ water in the first step, followed by the ^{18}O (p, n) ^{18}F reaction. The blood glucose level did not exceed 150 mg/dL at the time of PET in any patient. Patients refrained from sugar ingestion starting from midnight on the day before examination, and fasted for 4 hours before examination. The tracer was administered via the median cubital vein.

We used a Head Tome IV (Shimadzu, Kyoto, Japan) PET scanner or a SET 3000GCT/M (Shimadzu, Kyoto, Japan) PET/CT scanner. Both scanners have a full width at half maximum (FWHM) of 6 mm. PET data was acquired under the following conditions: field of view, 256 mm × 256 mm; matrix, 128 × 128; pixel size, 2.0 × 2.0 mm^2; and section thickness, 2.6 mm. For PET, transmission scans were performed using ^{68}Ge/^{68}Ga standard sources, and absorptive correction of the obtained emission images was applied on the basis of the data. In ^{18}F-choline PET, 3.7 MBq/kg of ^{18}F-choline was administered before a whole-body PET scan, and an emission scan was initiated after 5 minutes. In ^{18}F-FDG PET, 3.7 MBq/kg of ^{18}F-FDG was administered and an emission scan was initiated after 60 minutes. PET and CT data were analyzed using the medical imaging analysis application Dr. View (AJS, Tokyo, Japan).

To quantitate the local accumulation of the radiotracers, regions of interest (ROIs) (round, 10 mm in diameter) were set and the maximum radioactivity in the ROI was measured. The value was corrected with the dose and body weight of the patient, and the maximum standardized uptake value (SUVmax) was determined using the following calculation formula:

SUVmax = Maximum radioactivity concentration in the ROI [Bq/ml] / (injected dose of ^{18}F-choline or ^{18}F-FDG) [Bq] / patient body weight [g])

In addition to the primary lesion, SUVs were measured in the brain, parotid gland, submandibular gland, sublingual gland, liver, abdomen, and bladder. Patients showed no abnormalities in these organs by CT/MRI and

clinical examination, except at the primary lesion.

3. Time-course changes in ^{18}F-choline and ^{18}F-FDG accumulations

To clarify the time course of ^{18}F-choline and ^{18}F-FDG accumulations in the primary site, a dynamic scan was performed every 5 minutes in 2 cases of tongue cancer to compare their SUVmax.

4. Statistical analysis

The statistical differences in mean value between the two populations were assessed by the Student's t-test if the variances were equal as determined by the Kolmogorov–Smirnov test, or by the unpaired t-test with Welch correction. Linear regression analysis was performed to investigate the relationship between ^{18}F-choline or ^{18}F-FDG accumulation and tumor size. A p value < 0.05 was regarded as significant. Statistical analyses were performed with InStat (GraphPad Software, San Diego, CA, USA).

Results

1. Physiological accumulation of ^{18}F-choline and ^{18}F-FDG

The SUVmax of regions with physiological accumulation was compared between the 17 oral cancer patients who were examined by ^{18}F-choline PET and 19 oral cancer patients who were examined by ^{18}F-FDG PET. Fig. 1 shows the head and neck regions of a PET/CT fusion image, and Fig. 2 shows a whole-body PET image. Areas with high ^{18}F-choline

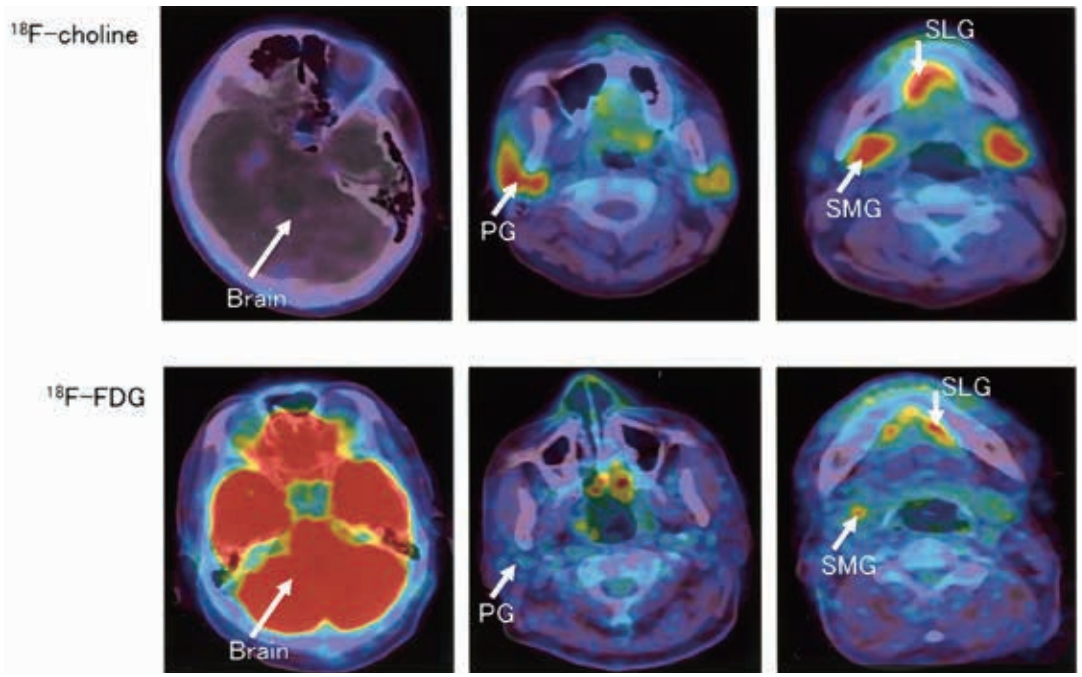

Fig. 1 : Typical head and neck PET/CT fusion images using ^{18}F-choline and ^{18}F-FDG. The upper and lower rows show ^{18}F-choline and ^{18}F-FDG, respectively. ^{18}F-choline hardly accumulated in the brain, but high-level accumulation of ^{18}F-FDG was noted. In the major salivary glands, ^{18}F-choline showed significantly increased accumulation compared with ^{18}F-FDG. Areas with high accumulation are displayed as red. (PG: Parotid gland, SMG: Submandibular gland, SLG: Sublingual gland)

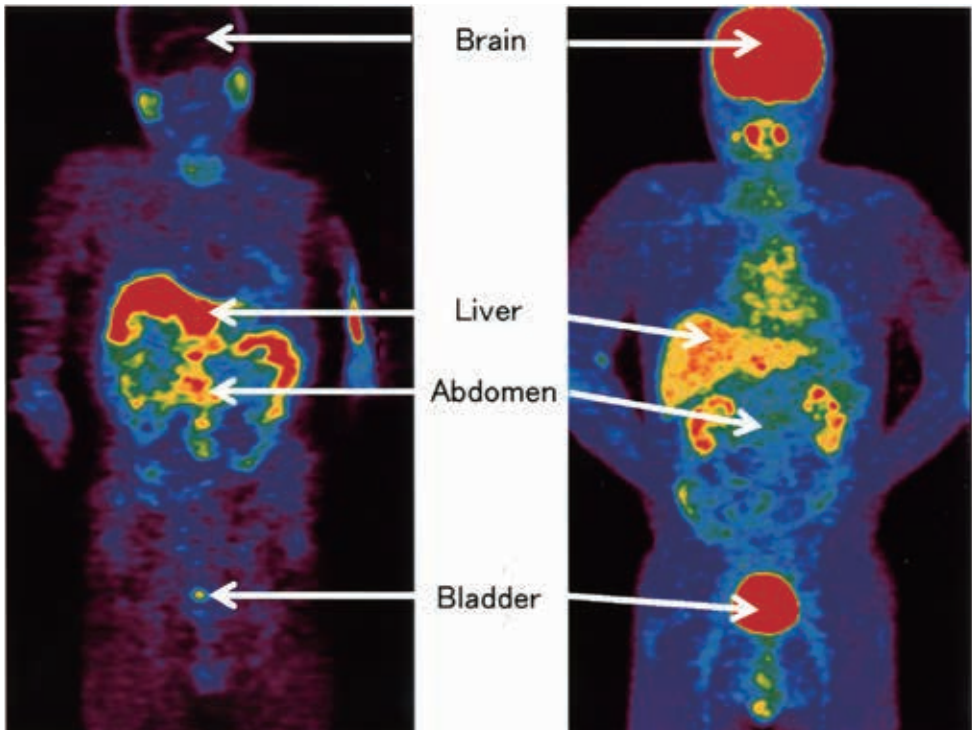

Fig. 2 : Typical whole-body PET images (Maximum Intensity Projection) using ^{18}F-choline (left) and ^{18}F-FDG (right). Physiological accumulation of ^{18}F-choline is observed in the liver and abdomen. High-level accumulation of ^{18}F-FDG is observed in the brain and bladder.

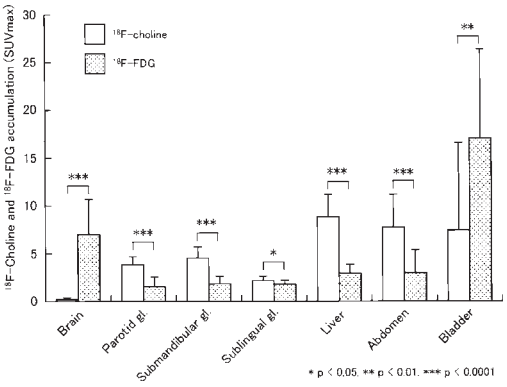

Fig. 3 : Mean SUVmax for each organ of physiological accumulation of ^{18}F-choline and ^{18}F-FDG. Means are separated in the bar chart with T-bars indicating standard deviation. A p-value of < 0.05 was regarded as significant.

or ^{18}F-FDG are indicated by red on the color scale. In Fig. 3, the SUVs (mean ± S.D.) of the respective organs are displayed as bar graphs. In the brain, the SUVmax of ^{18}F-choline was 0.19 ± 0.18, whereas that of ^{18}F-FDG was 6.96 ± 3.75, which shows a lower mean SUVmax of ^{18}F-choline ($p < 0.0001$). The SUVmax of ^{18}F-choline in the parotid, submandibular, and sublingual glands was 3.84 ± 0.84, 4.54 ± 1.17, and 2.17 ± 0.46, respectively; the SUVmax of ^{18}F-FDG was 1.52 ± 1.03, 1.84 ± 0.79, and 1.80 ± 0.39, respectively. The physiological accumulation level of ^{18}F-choline in the major salivary glands (parotid gland, submandibular gland and sublingual gland) was significantly higher than that of ^{18}F-FDG ($p < 0.0001$ for parotid and submandibular glands, and $p = 0.013$ for sublingual gland).

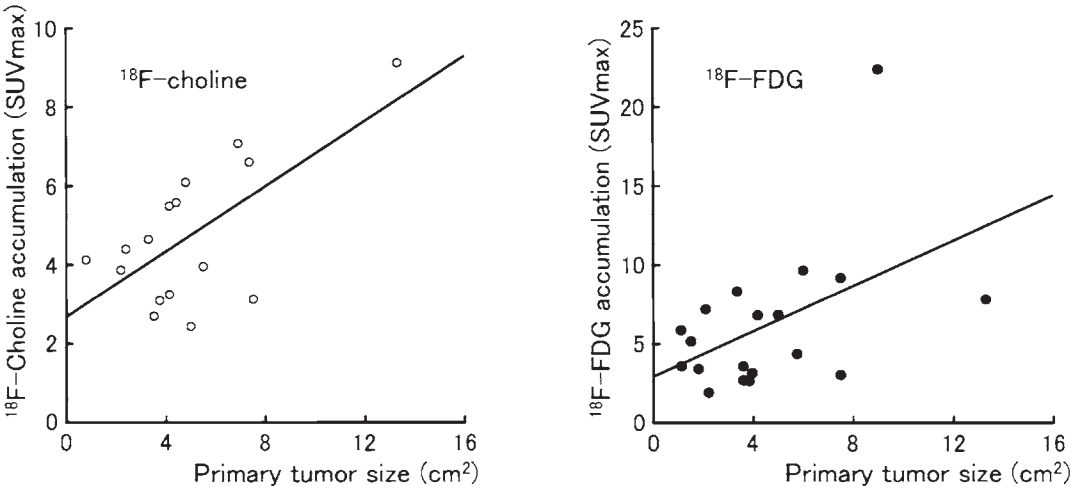

Fig. 4 : Relationship between ^{18}F-choline (left) and ^{18}F-FDG (right) accumulation and primary tumor size. Linear regression analysis of ^{18}F-choline accumulation and tumor size measured by CT or MRI provided a y-intercept of 2.72 and a slope of 0.41. The correlation was significant ($r = 0.67$; 95% confidence interval 0.16 to 0.66, $p = 0.003$). In the case of ^{18}F-FDG, they were 2.94 and 0.72, respectively. The correlation was significant ($r = 0.48$; 95% confidence interval 0.05 to 1.38, $p = 0.036$).

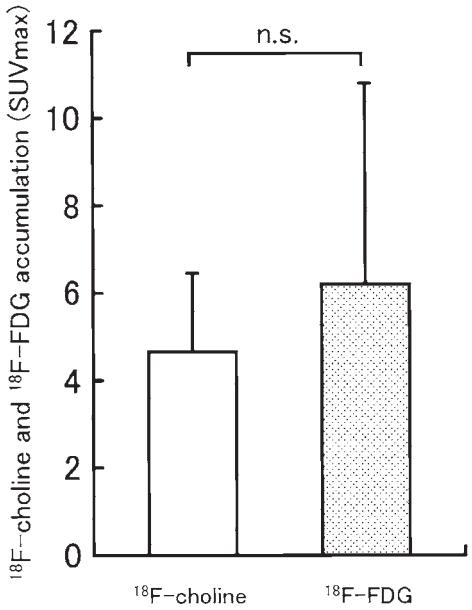

Fig. 5 : ^{18}F-choline and ^{18}F-FDG SUVmax in oral cancer
The mean ^{18}F-choline ($n = 17$) and ^{18}F-FDG ($n = 19$) was 4.65 and 6.20, respectively. There was no significant difference in SUVmax between the two groups by the unpaired t-test.

The SUVmax of ^{18}F-choline in the liver and abdomen was 8.83 ± 2.36 and 7.77 ± 3.42, respectively, and those of ^{18}F-FDG were 2.92 ± 0.95 and 2.97 ± 2.42, respectively, showing significantly higher mean SUVmax of ^{18}F-choline ($p < 0.0001$). In the urinary bladder, the SUVmax of ^{18}F-choline and ^{18}F-FDG was 8.43 ± 9.16 and 17.06 ± 9.33, respectively, which shows a lower mean SUVmax of ^{18}F-choline ($p = 0.009$).

2. Comparison of ^{18}F-choline and ^{18}F-FDG accumulation for oral cancer

The relationship between ^{18}F-choline and ^{18}F-FDG accumulation and primary tumor size was examined. The SUVmax increased with the increasing size of the primary lesion with both radiotracers ($r = 0.67$; $p = 0.003$ for ^{18}F-choline, $r = 0.48$; $p = 0.036$ for ^{18}F-FDG) (Fig. 4). In addition, ^{18}F-choline and ^{18}F-FDG accumulation for oral cancer was compared. The mean SUVmax of ^{18}F-choline was 4.65 ± 1.80, whereas that of ^{18}F-FDG was 6.20 ± 4.60.

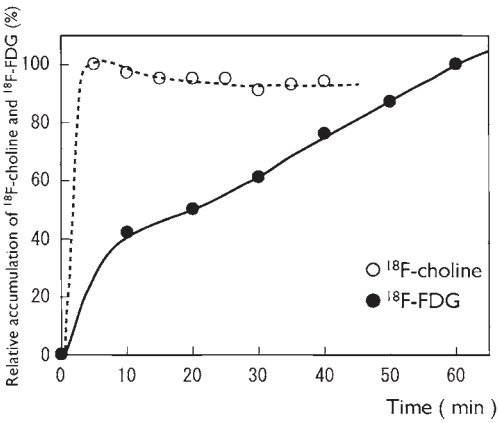

Fig. 6 : Time-course changes in ^{18}F-choline and ^{18}F-FDG accumulations in primary lesions (tongue carcinoma) . The horizontal axis is the elapsed time from administration of each radiopharmaceutical, and the vertical axis is the relative value of the accumulation amount to the primary site. ^{18}F-choline accumulated in tumor tissue rapidly, peaking within 10 minutes. In contrast, ^{18}F-FDG accumulation gradually increased with time.

The mean SUVmax of ^{18}F-choline in the primary site was lower than that of ^{18}F-FDG, but there was no statistical difference ($p = 0.201$) (Fig. 5) .

3. Time-course changes in ^{18}F-choline and ^{18}F-FDG accumulations in primary lesions

To clarify differences in the time course of ^{18}F-choline and ^{18}F-FDG accumulation in the primary lesions, uptake in two tongue cancer patients was measured over 60 minutes after each radiopharmaceutical administration (Fig. 6) . The time after the administration was plotted on the horizontal axis. The values relative to the maximum, regarded as 100% within the 60-minute period, were plotted on the vertical axis. ^{18}F-choline accumulated in tumor tissue beginning immediately after administration and peaked within 10 minutes. In contrast, ^{18}F-FDG accumulation in tumor tissue increased over a longer time.

Discussion

Currently, a glucose analog, ^{18}F-FDG, is widely used for PET, and its usefulness for diagnosing oral cancer has been reported[1, 14] . Generally, overexpression of the glucose transporter protein and reduced glucose-6-phosphatase activity on the cell membrane are observed in malignant tumor cells. ^{18}F-FDG is incorporated into cells through this enhanced glucose metabolism[15] . Since ^{18}F-FDG incorporation reflects glucose metabolism in cells, it accumulates not only in tumor cells but also in the brain, in which glucose metabolism is physiologically enhanced, and in the urinary bladder, which is the route of ^{18}F-FDG excretion. These conditions are likely to interfere with diagnosing brain tumors and prostate tumors that are located close to the urinary bladder[11, 14] . Moreover, ^{18}F-FDG is not appropriate for diagnosing patients with a high blood glucose level because it competes with blood glucose[3] .

The agent of choline preparation has recently been developed as a new drug for tumor-diagnostic PET, and has been attracting attention. Since choline is the substrate of synthesis of phosphatidylcholine, which is the typical constituent of cell membranes, choline accumulation in tumor tissue is considered to reflect phosphatidylcholine synthesis; phosphatidylcholine synthesis has been reported to accumulate in close relation to the cell cycle[16] . In a previous clinical application of choline PET, it was used for tumors that were difficult to diagnose using^{18}F-FDG, mainly prostate cancer[17, 18] . Since choline does not reflect glucose metabolism, unlike ^{18}F-FDG, it may be applicable for the examination of hyperglycemic diabetes patients. However, a

few clinical applications of choline PET for oral cancer have been reported. Choline preparations for PET include ^{11}C and ^{18}F labels. Only limited facilities can use ^{11}C because its physical half-life is very short (about 20 minutes). In contrast, the physical half-life of ^{18}F (about 110 minutes) is much longer, which enables its supply through a delivery system. ^{18}F-fluoroethyl-choline and ^{18}F-fluoromethyl-choline are known as ^{18}F-labeled choline analogs, and DeGrado et al. clarified the superiority of the latter as an oncologic tracer[19]. The choline radiopharmaceutical used in our study was ^{18}F-fluoromethyl-choline that was prepared by employing the chemical synthesis method by Iwata et al.[13], and it is assumed to favorably accumulate in the target primary lesions.

The maximum standardized uptake value (SUVmax) was adopted for the parameter of accumulation of each radioactive drug on PET. It has been reported that the SUVmax does not accurately reflect the overall metabolism of tumors because it is an evaluation of one voxel[20]. Studies showing a high usefulness of the metabolic tumor volume (MTV), in which ^{18}F-FDG accumulation is calculated from the tumor volume and total lesion glycolysis (TLG), have been increasingly reported[14, 21, 22]. However, at present, MTV and TLG are not used in general medical practice because they require specialized analysis. Thus, we adopted the SUVmax, which is frequently used as a simple index.

As shown in Fig. 1, there was marked accumulation of ^{18}F-FDG in the brain, but ^{18}F-choline did not accumulate in the brain. The uptake of a radiotracer by brain and tumor tissue may disturb the estimation of whether the skull base is invaded. The advantages of ^{11}C-choline PET/CT for tumor staging of nasopharyngeal carcinoma and other diseases in the skull base compared to ^{18}F-FDG PET have been reported[23, 24]. However, the difficulty of producing ^{11}C-choline and the short half-life of the radionuclide are the limitations of its extension in clinical practice. These disadvantages are not applicable to ^{18}F-choline that is supplied by a delivery system. On ^{18}F-choline PET, physiological accumulation higher than that of ^{18}F-FDG was noted in the major salivary glands. Since the ^{18}F-choline accumulation level in the submandibular gland is higher than that of ^{18}F-FDG, metastatic submandibular lymph nodes located close to the mandibular gland should be carefully diagnosed by combining other modalities such as CT, MRI and Ultrasonography. Despite the accumulation of choline in the normal liver, by elevating the background signal, choline PET was appropriate for diagnosing hepatocellular carcinoma (HCC) in a reported study. Noordzij et al. reported that ^{18}F-choline is capable of detecting HCC lesions[25]. However, liver diseases other than HCC were not mentioned, and the usefulness of ^{18}F-choline in the liver region was not sufficiently evaluated.

A study by Nakasone et al. analyzing the relationship between ^{18}F-FDG-uptake and the size of primary oral cancers has reported that the larger the infiltration area, the higher the SUV[26]. In this study, ^{18}F-choline accumulation increases with an increase in the size of the primary lesion, similarly to ^{18}F-FDG. It is possible that phosphatidylcholine synthesis is enhanced as the tumor size increases, or the SUVmax increases due to the attenuation of the partial volume effect. But details are unclear, and further studies are necessary. Some studies reported that malignant tumors in the head and neck region are detectable by using ^{11}C-choline

and that it is comparable to detection using ^{18}F-FDG[27, 28]. Also, in this study, the average ^{18}F-choline accumulation in the primary site of oral cancer was a little lower than that of ^{18}F-FDG, but there was no statistical difference, thus suggesting that the usefulness of ^{18}F-choline PET for this region is high.

In ^{18}F-FDG PET imaging, patients have to wait for 50–60 minutes after the ^{18}F-FDG injection to reach an optimum tumor-to-background ratio because of its relatively slower clearance from the circulation. ^{18}F-FDG PET of oral cancers was more accurate at 1.5–2 hours after administration in some studies[29]. However, when the beginning of acquisition is delayed, the number of patients who are testable per day decreases and the waiting time of patients increases. Thus, many PET facilities perform emission scans 50–60 minutes after ^{18}F-FDG administration. For ^{18}F-choline, however, the retention time in the circulation is very short and the tumor uptake reaches a maximum at about 5 minutes, as shown in Fig. 6. Due to this characteristic of ^{18}F-choline accumulation, the total time required for examination was markedly shortened to about 30 minutes. Emission scans can be performed before excretion of ^{18}F-choline into the urinary bladder in patients in whom prostate cancer is suspected, enabling a more accurate diagnosis compared to that of ^{18}F-FDG PET. In our study, ^{18}F-choline accumulated in the urinary bladder. This may have been due to our scanning from the head down on PET, which allowed excretion into the urinary bladder. In Japan, there are several facilities that synthesize ^{11}C-choline and assess brain cancer and prostate cancer. Since ^{18}F-choline can be supplied through a delivery system, similarly to ^{18}F-FDG, it will become a new useful drug for PET.

Conclusion

In this study, we examined oral cancers with PET using ^{18}F-choline, comparing it with ^{18}F-FDG. ^{18}F-choline accumulated in the primary lesions of oral cancers, similar to ^{18}F-FDG. Furthermore, it is also useful for the diagnosis of cases that progress near the brain. However, it physiologically accumulates in the salivary glands. Thus, the submandibular region should be carefully diagnosed by combining several modalities. ^{18}F-choline shortens the PET examination time, markedly reducing the burden on patients.

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COI Disclosure

We have no financial relationships to disclose.

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