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Evaluation of a Surgical Gamma Probe for Detection of ^{18}F-FDG

Seiei YASUDA, Hiroyasu MAKUUCHI, Hirofumi FUJII*, Hisao NAKASAKI, Masaya MUKAI, Sotaro SADAHIRO, Tomoo TAJIMA, Michiru IDE*, Akira SHOHTSU* and Yutaka SUZUKI**

Department of Surgery, Tokai University School of Medicine,
** HIMEDIC Imaging Center at Lake Yamanaka,*
*** Department of Nuclear Medicine, Tokai University School of Medicine*

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Because fluorine-18 fluorodeoxyglucose (^{18}F-FDG) is an excellent tumor-localizing radiopharmaceutical, a hand-held radiation detection probe capable of localizing an area with high ^{18}F-FDG uptake would make radioguided surgery possible. In this laboratory study, we investigated the capability of a widely used intraoperative gamma probe with a cadmium zinc telluride (CdZnTe) detector for detection of ^{18}F-FDG. For sensitivity tests, an 0.1- ml ^{18}F-FDG preparation was made to act as a point source with radioactivities of 1.0, 2.0, and 3.0μ Ci (37 kBq, 74 kBq, 111 kBq). Relative transmission across the side wall of the probe and sensitivity at each source-to-probe distance were measured. For simulation studies, 2 l of ^{18}F-FDG solution (0.02μ Ci, 0.74 kBq /ml) served as normal background. One ml of ^{18}F-FDG was prepared to simulate tumors with radioactivities of 0.05, 0.1, 0.2, and 0.4μ Ci (1.85 kBq, 3.7 kBq, 17.4 kBq, and 14.8 kBq). The ratios of the radioactive concentration of tumor to that of the background were 2.5, 5, 10, and 20:1, respectively. The tested gamma probe was shown to be sensitive to ^{18}F. The high-energy annihilation radiation was detected from the side wall of the probe despite application of a supplementary collimator. The count rate decreased markedly as the source-to-probe distance increased, owing to the effects of the inverse-square law. In the simulation studies, the probe detected a considerable amount of background activity. However, the measured count rate increased with the increasing source-to-background ratio. In our setting, the probe was capable of distinguishing the ^{18}F-FDG source from the background when the source-to-background ratio was no less than 5 : 1. To make a surgical application feasible, however, collimation or shielding against high background radiation is necessary.

Key words : Fluorine-18 fluorodeoxyglucose (FDG), Intraoperative probe, Gamma probe, Radioguided surgery

INTRODUCTION

Radioguided surgery has a history of more than 50 years. Several hand-held radiation-detection probes used with radioactive isotopes have been tested for surgical assist. The first intraoperative use of a probe was reported in 1949 by Selverstone et al., who used a Geiger-Mueller probe with radioactive phosphorus, ^{32}P, in brain tumor surgery [1]. In 1984, Aitken et al. first reported use of a gamma probe with radiolabeled monoclonal antibody in surgery for colorectal cancers; the technique is now called radioimmunoguided surgery (RIGS) [2]. Since 1993, a gamma probe with ^{99m}Tc-sulfur colloid has been employed for detecting sentinel nodes during surgery [3, 4]. The sentinel node technique has led to widespread use of the intraoperative probe [5]. Not a few surgeons are now accustomed to using the intraoperative probe [6].

Concurrent with the improvement in probe systems [7–9], new tumor-seeking radiopharmaceuticals have emerged. The isotope ^{18}F is used in the form of fluorine-18 fluorodeoxyglucose (^{18}F-FDG) in positron emission tomography (PET). By coincidence detection with the PET scanner, malignant tumors with increased glycolysis are imaged with high object contrast [10, 11]. Relatively high tumor-to-normal tissue ratios of

Seiei YASUDA, Department of Surgery, Tokai University School of Medicine, Bohseidai, Isehara, Kanagawa 259–1193, Japan
Tel: 0463-93-1121, FAX: 0463-95-6491, e-mail: yasuda@is.icc.u-tokai.ac.jp

^{18}F-FDG uptake has been demonstrated. Because ^{18}F-FDG is an excellent tumor localizing radiopharmaceutical, a probe capable of detecting areas of high ^{18}F-FDG uptake would make probe-guided surgery possible. We investigated the ability of a gamma probe to detect tumor accumulation of ^{18}F-FDG.

MATERIALS AND METHODS

This laboratory study was conducted with a commercially available intraoperative gamma probe (neo2000, Neoprobe Corporation, Dublin, OH, USA) [9]. The hand-held surgical probe uses semiconductor detectors made of cadmium zinc telluride (CdZnTe) with a built-in tungsten shield. The diameter of the probe head is 14 mm. A detachable collimator is supplementary. The side of the collimator consists of plastic. The front face is covered with a 7 mm-thick lead with a round window (7 mm in diameter) in the center. The lower energy threshold was set to 150 KeV.

Sensitivity tests

A 0.1-ml ^{18}F-FDG preparation was put into a plastic syringe to act as the point source with different radioactivities of 1.0, 2.0, and 3.0μ Ci (37, 74, and 111 kBq).

1. Measurement of relative transmission across the side wall of the probe.

The high-energy annihilation radiation (511 KeV) emitted from the ^{18}F was expected to penetrate the side wall of the probe. The supplementary collimator provided for detecting ^{99m}Tc seemed inefficient when used to detect ^{18}F. To confirm these assumptions, an ^{18}F-FDG source was positioned at the outer surface of the probe head, and the count rate was measured with and without the supplementary collimator (Fig. 1).

2. Measurement of sensitivity at each source-to-probe distance (in air and in water).

For this purpose, an ^{18}F-FDG source was positioned in contact with the center of the probe head, and the probe was moved at 1-cm increments for source-to-probe distances ranging from 0 to 5 cm (Fig. 2).

3. Measurement of angular sensitivity (in air and in water).

An ^{18}F-FDG source was positioned at the level of the center of the probe with a source-to-probe distance of 3 cm (Fig. 3). The probe was then moved. The corresponding count rate was measured for source-to-probe angles between 0 and 90 degrees. The collimator was not used.

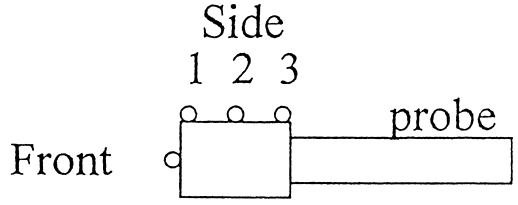

Fig. 1 Each ^{18}F-FDG source was placed on the probe head and counts were measured.

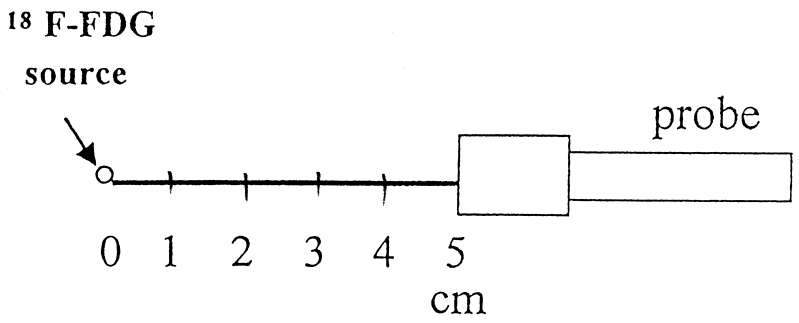

Fig. 2 Counts were measured for source-to-probe distances ranging from 0 to 5 cm.

Simulations

For simulating abdominal surgery, 2 l of an ^{18}F-FDG solution (0.02μ Ci/ml, 0.74 kBq) were made to mimic normal abdominal background. One ml of ^{18}F-FDG preparation was placed in a plastic syringe to act as "tumor" with four different radioactivities, 0.05, 0.1, 0.2, and 0.4 μ Ci (1.85, 3.7, 17.4, and 14.8 kBq, respectively). The ratios of radioactive concentration of "tumor" to that of background were 2.5, 5, 10, and 20:1, respectively. An ^{18}F-FDG source was placed on the surface of the background solution, simulating tumor deposits or metastatic lymph nodes on the abdominal cavity surface. The probe was placed in contact with the^{18}F-FDG source, and the count rate was measured.

Considering the short half life of ^{18}F, each study was performed within a few minutes, and a decay correction was not made. Count rates were acquired for 2 seconds, and the mean count rate per second was recorded as counts per second (cps).

RESULTS

Sensitivity tests

1. The probe achieved the highest count

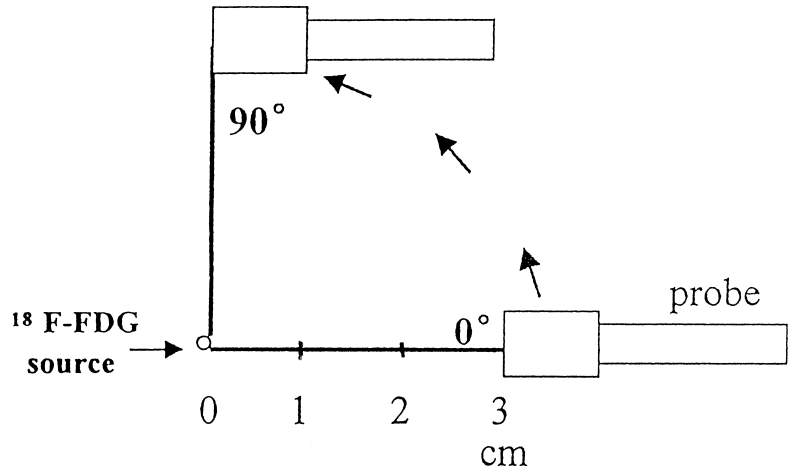

Fig. 3 Angular sensitivities were measured for source-to-probe angles between 0 and 90 degrees.

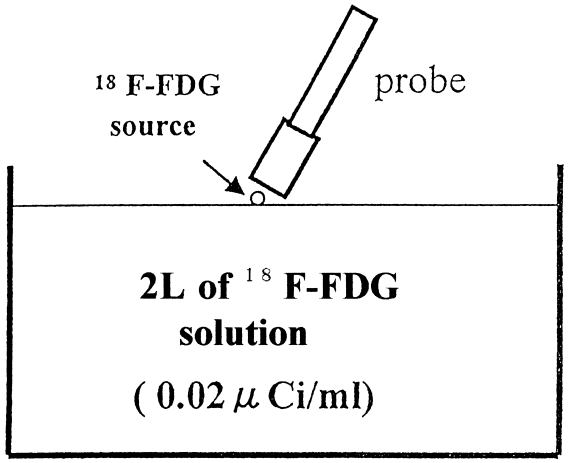

Fig. 4 For simulation relevant to abdominal surgery, a ^{18}F-FDG source was placed on the surface of the background solution. Counts were measured by positioning the probe to contact the source.

rate with the ^{18}F-FDG source at the center of the probe head when the supplementary collimator was not used. With the source at the side wall of the probe, a substantial count rate was obtained. The relative transmission across the side wall was between 5% and 35% of the rate with the source at the center of the probe. The probe detected lower counts with the collimator than without it when the ^{18}F-FDG source was placed at the center of the probe head. This occurred because the distance between the detector in the probe and the ^{18}F-FDG source was increased by the intervening collimator. In spite of the collimator, the probe detected high counts from the side wall of the probe (Table 1).

2. With an increase in the distance between the probe head and the ^{18}F-FDG source, the count rate decreased markedly (Table 2). When the 3μCi/0.1ml- ^{18}F-FDG source was used and the source was placed in contact with the probe, the count rate in air (846 cps) was lower than in water (1293 cps) and lower than the count listed in Table 1 (1270 cps). We considered this due to random errors.

3. Because it was thought that the supplementary collimator would be ineffective in shielding transmission across the side wall of the probe, angular sensitivity was measured without the collimator. The count rate differed inappreciably for source-to-detector angles between 0 and 90 degrees (Table 3).

Simulations

Background activity was measured by positioning the probe head at the surface of the ^{18}F-FDG solution serving as background, and the measured count rate was 114 cps. As shown in Table 3, the measured count rate increased with the increase in

Table 1 Count rate (cps) at each position of the ^{18}F-FDG source

^{18}F-FDG source*	Collimator	Front	Side 1	Side 2	Side 3
3	(−)**	1270	441	247	64
	(+)	344	322	209	71
2	(−)	1044	301	133	52
	(+)	270	235	159	53
1	(−)	501	153	90	24
	(+)	100	118	86	18

* μCi/0.1ml
**Collimator absent (−) or present (+)

Table 2 Count rate (cps) at each source-to-probe distance

(in air)

^{18}F-FDG source*	0 cm	1 cm	2 cm	3 cm	4 cm	5 cm
3	846	246	125	62	41	29
2	815	192	83	42	29	20
1	453	85	40	20	15	8

(in water)

^{18}F-FDG source	0 cm	1 cm	2 cm	3 cm	4 cm	5 cm
3	1293	311	157	80	41	27
2	1091	257	105	59	33	21
1	400	100	47	22	14	8

* μCi/0.1ml

radioactivity of the ^{18}F-FDG source. Random errors exist in nuclear radiation counting measurements, and a true count rate is obtained by the measured count rates $\pm 2\sqrt{\text{measured count rates}}$ at 95% confidence level [12]. At a tumor-to-background ratio equal to or larger than 5 : 1, the count rates were higher than the background by 2 standard deviations ($p < 0.05$). This result shows that at a high tumor-to-background ratio, the ^{18}F-FDG source was discernible from the surrounding background.

DISCUSSION

The purpose of this study was to determine whether a widely used hand-held gamma probe can be applied during surgery to identify the tumor accumulation of ^{18}F-FDG. Prior to this laboratory study, we tested the probe by applying it to the skin of two patients who had just undergone a PET study. At 80 min after the intravenous administration of 260 MBq ^{18}F-FDG, the measured count rate was between 515 cps (lower leg) and 5117 cps (head); a measurable count rate was acquired at the usual dose of ^{18}F-FDG. Desai et al. used a CdZnTe detector probe and ^{18}F-FDG during surgery of 15 patients with colorectal cancer [13]. All lesions imaged in preoperative PET studies were correctly identified by the gamma probe at surgery in this preliminary study.

Several findings were obtained in our laboratory study. First, as was expected, the 511 KeV annihilation radiation was detected from the side wall of the probe despite application of the supplementary collimator. The high energy radiation of ^{18}F is more tissue-penetrating than are the lower energy gamma rays of ^{99m}Tc. Thus, the problem of background activity will arise when a gamma probe is used for detecting ^{18}F [14]. Second, the observed count rate decreased

Table 3 Count rate (cps) at each source-to-probe angle

(in air)

^{18}F-FDG source*	0°	10°	20°	30°	40°	50°	60°	70°	80°	90°
3	77	55	60	69	72	66	61	59	47	50
2	45	48	46	51	55	42	45	35	39	34
1	21	23	20	21	19	20	22	20	19	20

(in water)

^{18}F-FDG source	0°	10°	20°	30°	40°	50°	60°	70°	80°	90°
3	60	74	62	85	69	71	74	63	56	64
2	58	52	50	51	50	44	49	39	40	41
1	28	26	25	23	22	23	20	20	19	15

*μCi/0.1ml

Table 4 Results of the simulation study

^{18}F-FDG source*	Source-to-background ratio	Count rate (cps)
(background)		114
0.05	2.5	136
0.1	5	163
0.2	10	184
0.4	20	245

*μCi/1.0ml

markedly as the source-to-probe distance increased and was considered due to the inverse-square law effect [12]. This means that if a probe is employed in surgery, it should be close to or in contact with the target tissue. As for angular sensitivity, the count rate was not affected by a source-to-probe angle between 0 and 90 degrees. Third, in the simulation study, the probe detected a considerable amount of background activity. However, the measured count rate increased with the increase of source-to-background ratio. In our setting, a source-to-background ratio of not less than 5 : 1 seemed to be necessary for the source to be discernible by the gamma probe.

One problem is that the gamma probe has a large distal field of view [9], and highly penetrating annihilation radiation can be detected from distant background sources. The detection of background radiation would seriously hamper the ability to localize tumors. The tumor-to-background ratio of ^{18}F-FDG uptake is variable, depending on the tumor. In breast cancer , for example, the ratio is reported at 8.1 [15]. There are, however, many tumors with a ratio less than the 5 : 1 we obtained. One possible countermeasure against high background activity is to wait until the activity decreases. After intravenous administration of ^{18}F-FDG, the rate of uptake decreases in both normal tissue and in tumors over time. In delayed PET images, reduction of the ^{18}F-FDG uptake in normal tissue results in a high contrast image of the tumor [16]. There may be an appropriate timing for use of the intraoperative gamma probe. Another countermeasure is to shield the probe against background activity. This may require, however, a large and unwieldy detector with heavy shielding [9, 17]. Furthermore, changes in probe angle or position could cause changes in the count rate because of differences in the volume of tissue seen by the probe [18]. Further studies are clearly needed before use of an intraoperative gamma probe for the detection of ^{18}F will become practical.

To avoid the problem caused by detecting background activity, probe systems sensitive to positrons are under investigation [13, 19]. Unlike 511 KeV radiation emitted by positron annihilation, positrons have a short range ($\sim$1.8 mm in soft tissue), thus, only radiation emitted near a probe can be detected. In a simulation study using real standardised uptake value (SUV) with a tumor (SUV = 4.2) and background (SUV = 1), the detector was able to localize the tumor [19]. However, positron-sensitive probes are not yet in use, and their actual clinical utility remains to be determined.

In conclusion, the tested gamma probe was sensitive to ^{18}F, and sensitivity decreased markedly with the increase in source-to-probe distance. At a high tumor-to-normal tissue ratio of ^{18}F-FDG uptake, the probe was capable of distinguishing the source from the background. To make surgical applications feasible, however, collimation or shielding against background radiation is necessary.

REFERENCES

1) Selverstone B, Sweet WH, Robinson CV. The clinical use of radioactive phosphorus in the surgery of brain tumors. Ann Surg 130: 643–651, 1949.
2) Aitken DR, Hinkle GH, Thurston MO, Tuttle SE, Martin DT, Olsen J, et al. A gamma-detecting probe for radioimmune detection of CEA-producing tumours: successful experimental use and clinical case report. Dis Colon Rectum 27: 279–282, 1984.
3) Alex JC, Krag DN. Gamma-probe guided localization of lymph nodes. Surg Oncol 2: 137–143, 1993.
4) Alex JC, Weaver DL, Fairbank JT, Rankin BS, Krag DN. Gamma-probe-guided lymph node localizaiton in malignant melanoma. Surg Oncol 2: 303–308, 1993.
5) Keshtgar MRS, Waddington WA, Lakhani SR, Ell PJ: The sentinel node in surgical oncology. Berlin Heielberg, Springer, 1999.
6) Schneebaum S, Even-Sapir E, Cohen M, Shacham-Lehrman H, Gat A, Brazovsky E, et al. Clinical application of gamma-detection probes-radioguided surgery. Eur J Nucl Med 26 (Suppl): S26–S35, 1999.
7) Tiourina T, Arends B, Huysmans D, Rutten H, Lemaire B, Muller S. Evaluation of surgical gamma probes for radioguided sentinel node localisation. Eur J Nucl Med 25: 1224–1231, 1998.
8) Britten AJ. A method to evaluate intra-operative gamma probes for sentinel lymph node localisation. Eur J Nucl Med 26: 76–83, 1999.
9) Hoffman EJ, Tornai MP, Janecek M, Patt BE, Iwanczyk JS. Intraperative probes and imaging probes. Eur J Nucl Med 26: 913–935, 1999.
10) Rigo P, Paulus P, Kaschten BJ, Hustinx R, Bury T, Jerusalem G, et al. Oncological application of positron emission tomography with fluorine-18 fluorodeoxyglucose. Eur J Nucl Med 23: 1641–1674, 1996.
11) Ruhlmann J, Oehr P, Biersack HJ (eds). PET in oncology: basics and clinical application, Berlin Heidelberg New York, Springer, 1999.
12) Sorenson JA, Phelps ME. Physics in Nuclear Medicine. 2nd ed., Philadelphia, US, WB Saunders

Company, 1987.
13) Desai D, Arnold M, Saha S, Hinkle G, Soble D, Frye J, et al. Intraoperative gamma detection of FDG distribution in colorectal cancer. 11th ICP Conference, Poster Abstract, pp. 49–50, 1999.
14) Daghighian F, Mazziotta JC, Hoffman EJ, Shenderov P, Eshaghian B, Siegel S, et al. Intraoperative beta probe: a device for detecting tissue labeled with positron or electron emitting isotope during surgery. Med Phys 21: 153–157, 1994.
15) Wahl RL, Cody RL, Hutchins GD, Mudgett EE. Primary and metastatic breast carcinoma: initial clinical evaluation with PET with the radiolabeled glucose analogue 2-[F-18]-fluoro-2-deoxy-D-glucose. Radiology 179: 765–770, 1991.
16) Kubota K, Yamaguchi K, Itoh M, Ohira H, Yamada K, Fukuda H. Whole-body FDG-PET for tumor detection should be imaged at 2hr after injection. J Nucl Med 40 (supple): 141P (abstract), 1999.
17) Perkins A. Peroperative nuclear medicine. Eur J Nucl Med 20: 573–575, 1993.
18) Woolfenden JM, Barber HB. Radiation detector probes for tumor localization using tumor-seeking radioactive tracers. AJR 153: 35–39, 1989.
19) Raylman RR, Wahl RL. Evaluation of ion-implanted-silicon detectors for use in intraoperative positron-sensitive probes. Med Phys 23: 1889–1895, 1996.