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Fluorine-18-FDG and Iodine-131-Iodide Uptake in Thyroid Cancer

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We conducted a prospective study to define the sensitivity of ^{131}I scintigraphy and ^{18}FDG PET whole-body scanning in the detection of thyroid cancer and metastases. **Methods:** Forty-one patients with differentiated thyroid carcinoma who underwent thyroidectomy and ^{131}I elimination of the remaining thyroid were studied by ^{18}FDG whole-body PET in 52 examinations and by ^{131}I whole-body scanning. **Results:** Combined ^{18}FDG and ^{131}I imaging resulted in a senstivity of about 95%, with alternating uptake of ^{131}I and ^{18}FDG in the metastases: ^{131}I trapping metastases with no ^{18}FDG uptake and ^{18}FDG trapping metastases with no ^{131}I uptake. Five uptake types were differentiated. Alternating uptake was found in about 90% of the patients, which was nearly identical to the sensitivity of the combined ^{131}I/^{18}FDG investigation. In six patients with increasing human thyroglobulin levels, we found that ^{18}FDG whole-body PET localized positive neck metastases of papillary thyroid carcinomas that were histologically confirmed after extirpation. **Conclusion:** Combination ^{18}FDG and ^{131}I whole-body imaging protocol enables detection of local recurrence or metastases on whole-body scans that are often not shown by other imaging methods. Biochemical grading of thyroid cancer may also be possible with this method: Tumors with remaining functional differentiation for hormone synthesis and iodine uptake have low glucose metabolism in more than 95%; tumors without this functional differentiation of ^{131}I uptake show high glucose metabolism. Fluorine-18-FDG uptake seems to be an indicator of poor functional differentiation, and possibly higher malignancy, in thyroid cancer.

Key Words: fluorine-18-FDG PET; thyroid carcinoma; iodine-131

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Human thyroglobulin (hTg) determination for the detection of local tumor recurrence and metastases and ^{131}I whole-body scanning are well-established methods in the follow-up of patients with thyroid carcinoma (*1*). Other imaging procedures such as radiography, ultrasound, CT and MR offer additional control methods during follow-up. Newer scintigraphic examinations with ^{201}Tl-chloride, ^{99m}Tc-sestamibi and ^{111}In-octreotide, the latter for diagnosing C-cell carcinoma, have not been completely evaluated clinically (*2*).

After ^{131}I elimination of remaining thyroid tissue, increasing hTg levels need to be evaluated. In conventional diagnostic procedures, hTg-producing tissue cannot always be localized. With 2-[^{18}F]-fluorodeoxyglucose (^{18}FDG), it is possible to detect malignant tumors with a sensitivity of 80%–90% (*3*). However, a few published studies report absence of ^{18}FDG uptake in thyroid carcinoma (*4–6*).

This prospective study was designed to define the sensitivity of thyroid cancer and metastases detection with ^{18}FDG whole-body PET in combination with ^{131}I whole-body scanning.

MATERIALS AND METHODS

Forty-one patients with differentiated thyroid carcinoma after thyroidectomy and ^{131}I elimination of the remaining thyroid underwent follow-up ^{18}FDG whole-body PET studies from December 1993 to August 1995. Twelve patients had papillary carcinoma, 23 had follicular carcinoma and 6 had Hürthle-cell carcinoma. Three additional patients with C-cell carcinoma, all MEN II, and with elevated calcitonin levels had no uptake of ^{18}FDG and were not reported in this study. All patients underwent ^{131}I whole-body gamma camera imaging, neck and abdominal US, CT and hTg level determination. All patients gave informed consent for participation in the study.

The ^{18}FDG whole-body PET results were systematically compared with the results from the methods mentioned above, especially with ^{131}I whole-body scans. All examinations were performed not more than 4 wk before or after the PET study.

The ^{18}FDG studies were performed on a scanner with whole-body and high-sensitivity modes. The field of view (FOV) was 15 cm; 5–7 FOV = 75–105-cm body scan. The patients fasted 18 hr prior to the

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TABLE 1
^{18}FDG/^{131}I Uptake Type and Histology of Thyroid Cancer

Uptake type	Type	Number of patients			
		Papillary	Follicular	Hürthle cell	Total
I	^{18}FDG-positive/^{131}I-negative	7†	8	4	19
II	^{18}FDG-negative/^{131}I-positive	1	5	—	6
III	Mixed type*	1	4	—	5
IV	^{18}FDG- and ^{131}I-positive	1	3	—	4
V	^{18}FDG- and ^{131}I-negative	2‡	3§	2¶	7
	Total	12	23	6	41

*Type III: either ^{18}FDG-positive/^{131}I-negative or ^{18}FDG-negative/^{131}I-positive (mixed type).

†Four patients with postoperative histologically confirmed carcinomas. Two of them were hTG-negative prior to surgery.

‡One true-negative (hTG < 1 ng/ml) and one false-negative (hTG < 10 ng/ml).

§Two true-negative (hTG < 1 ng/ml) and one false-negative (hTG > 100 ng/ml) after radioiodine therapy.

¶True-negative (hTG < 1 ng/ml).

injection of ^{18}FDG (5 MBq/kg body weight). Imaging began 45 min postinjection. The scan time for one FOV was 5–7 min.

Transmission correction was performed for quantitative evaluation of tumor uptake in 31 examinations. Standardized uptake values (SUVs) were calculated and corrected for body weight (SUV_{bw}) and body surface area (SUV_{bsa}), as described by Kim et al. (*7*). A correction for the finite resolution with recovery coefficient was not necessary for the evaluated metastases because of metastases size (>18 mm) and the high resolution of the scanner (*8*). For ^{131}I whole-body scanning, we used a scanner with two opposite large-field gamma camera detectors and high-energy collimators. The ^{131}I dose was between 100 MBq and 6 GBq (therapy doses), and patients were scanned 48 hr to 5 days after tracer administration.

All thyroid carcinoma patients were examined for ^{131}I uptake without hormone substitution at high TSH levels. FDG-PET was performed before or after ^{131}I whole-body scanning; some ^{18}FDG whole-body scans were obtained after the patient began thyroxin substitution. Four patients examined with ^{18}FDG without thyroxin substitution received thyroxin substitution at a later time.

RESULTS

Thirty-four of 41 patients had increased hTg levels (>1 ng/ml), indicative of local recurrence or metastases. In nine patients, other imaging methods (CT, MR, ultrasound, ^{131}I whole-body scintigraphy, ^{201}Tl scintigraphy, ^{99m}Tc-MDP skeletal scintigraphy) and, in three patients, ^{99m}Tc-MIBI scintigraphy provided no satisfying explanation for the elevated hTg levels. Seven patients were hTg-negative (<1 ng/ml) but had suspicious findings after palpation or neck ultrasound or in follow-up after therapy.

We found alternating behavior between ^{131}I and ^{18}FDG uptake in the metastases of 30 patients: metastases that trapped ^{131}I showed no uptake of ^{18}FDG and non-^{131}I trapping metastases exhibiting high ^{18}FDG uptake. Moreover, the metastases with high ^{18}FDG uptake were easily differentiated from normal tissue and those metastases trapping ^{131}I. FDG whole-body PET detected non-^{131}I trapping metastases of thyroid carcinomas in papillary or follicular carcinoma as well as Hürthle cell thyroid carcinoma in about 95% of the patients. Four Hürthle cell carcinomas were also ^{18}FDG-positive/^{131}I-negative.

Table 1 presents the five different types of ^{18}FDG/^{131}I uptake and classifies the uptake patterns histologically. Figures 1 through 4 depict patients with types I–IV uptake.

Two of 19 patients with type I uptake had hTG levels <1 ng/liter, but palpation of the neck region revealed suspicious nodules. Ultrasound could not differentiate these nodules from benign alterations, but the ^{18}FDG scans were positive for metastases, which were histologically confirmed as papillary carcinoma.

In five of seven patients with ^{18}FDG- and ^{131}I-negative scans, other imaging methods or clinical parameters did not confirm metastases. Only two patients had ^{131}I- and ^{18}FDG-negative scans after completing ^{131}I therapy.

The ^{131}I and ^{18}FDG uptake patterns in 184 metastases of 26 patients are shown in Table 2. Standardized uptake values (SUV_{bw}) in ^{18}FDG trapping metastases of uptake pattern type I, were >3.79 (range 3.79–5.21) and <2.48 (range 0.77–2.48) for uptake pattern type II. These values confirm the good visual discrimination of the ^{18}FDG-positive metastases from normal tissue. The SUV_{bsa} yielded similar results and relations with the corresponding count values.

We did not observe any significant difference in metastatic ^{18}FDG uptake in patients with or without thyroid hormone substitution (i.e., with high or low TSH levels). Additionally,

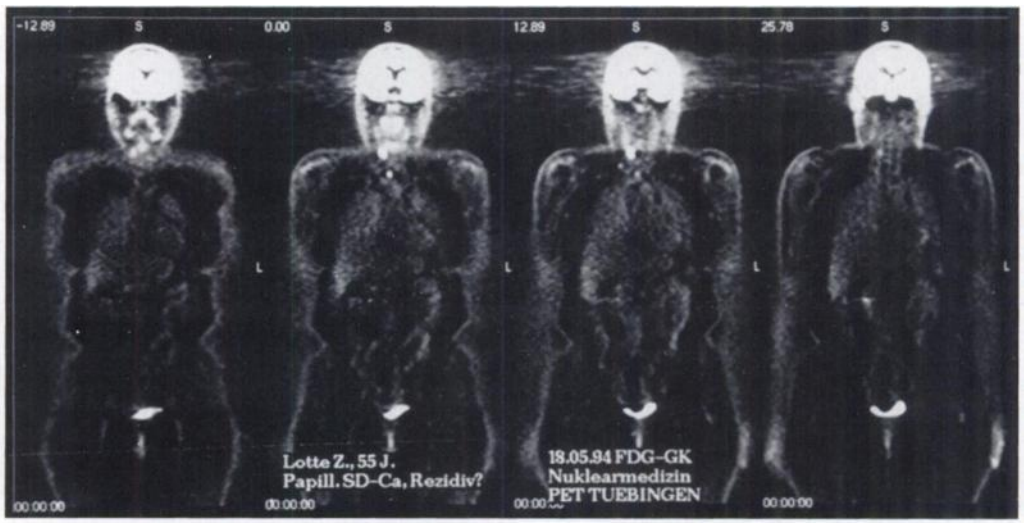

FIGURE 1. Uptake pattern type I in a 56-yr-old woman with papillary thyroid cancer, 8 yr after surgery and ^{131}I ablation of the remaining thyroid. Two locoregional recurrences were surgically removed, and there is now slight increase of hTg to 4.2 ng/liter. FDG whole-body PET shows three ^{18}FDG-positive nodules in the jugulum which were histologically confirmed as metastases of a papillary thyroid carcinoma.

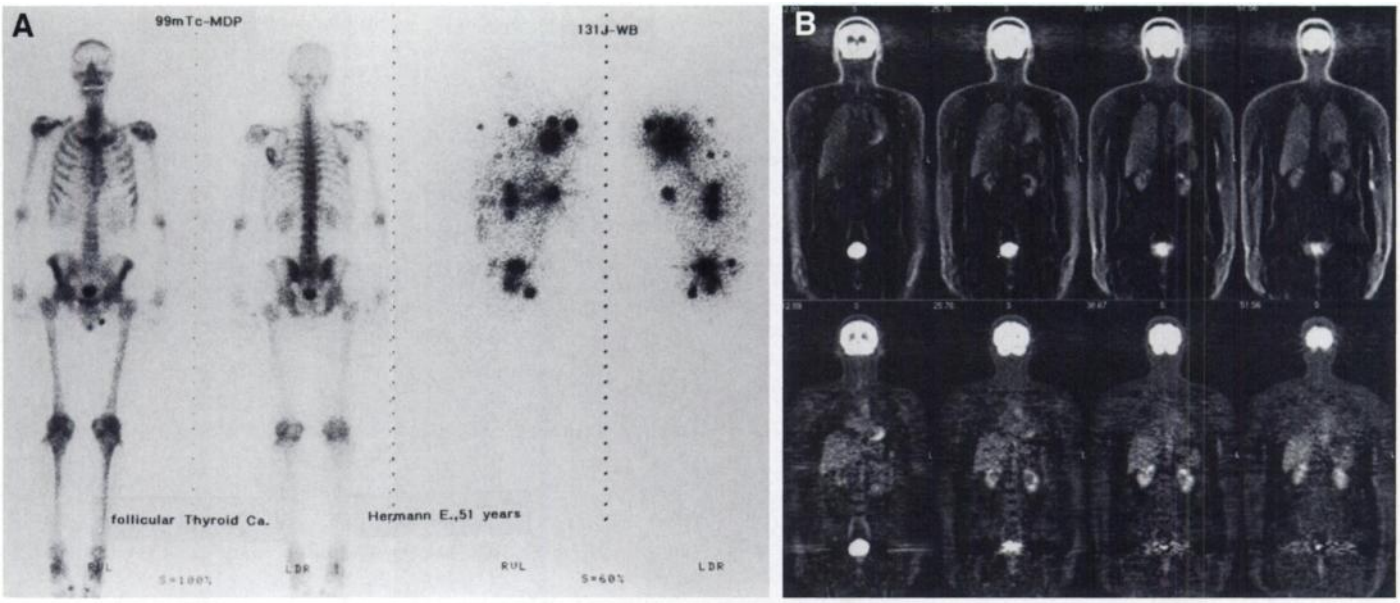

FIGURE 2. Uptake pattern type II in a 48-yr-old man with follicular carcinoma. The patient underwent the first ^{131}I therapy 3 mo ago and is now undergoing a second ^{131}I therapy. (A) Technetium-99m-MDP bone scan (left) shows only one small focus in the spine which is suspicious for fracture. Iodine-131 scan (right) after second radioiodine therapy session shows resting multiple uptake foci. (B) FDG whole-body, PET-negative scan. Noncorrected scans above, corrected scans below.

four patients, controlled with and without thyroxin substitution and with low or respectively high TSH levels, did not exhibit significantly different uptake patterns.

To date, we have not performed FDG-PET studies before and after thyroid ablation in patients who had recurring metastases after thyroid removal to compare with ^{131}I scans to determine changes, if any, in ^{18}FDG uptake.

DISCUSSION

In patients with elevated or increasing hTg who had no metastases with ^{131}I uptake, we could detect ^{18}FDG-positive metastases with a sensitivity of about 94%. In patients with ^{131}I-positive metastases, only a few metastases also exhibited ^{18}FDG uptake. In five patients with ^{131}I-negative metastases, CT, MRI, US or ^{201}Tl scintigraphy could not detect metastases. All positive ^{18}FDG-PET studies resulted in tumor extirpation and histological confirmation of the metastases. Seven of 41 patients had negative ^{131}I and ^{18}FDG metastases. Only two patients with metastases confirmed by chest radiography and neck ultrasound had false-negative ^{131}I and ^{18}FDG results. Both patients had undergone repeat ^{131}I therapy. Therefore, the combination of ^{131}I and ^{18}FDG whole-body scanning has the highest sensitivity in the detection of thyroid carcinoma metastases.

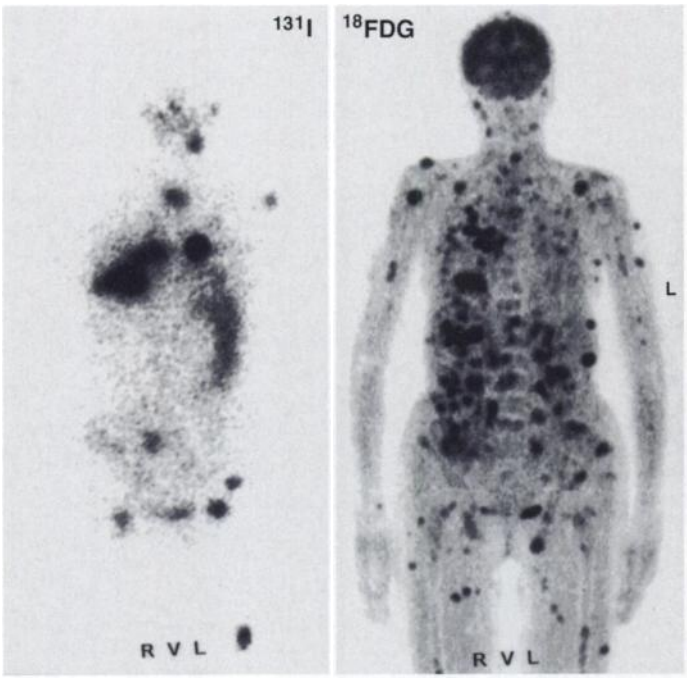

FIGURE 3. Uptake pattern type III in a 63-yr-old woman with varying differentiated papillary thyroid carcinoma. Iodine-131 scan shows high ^{131}I uptake in the metastases but no uptake in lung and other metastases which were depicted on radiographs. FDG whole-body PET shows three times more marked metastases, none which trapped ^{131}I. (Left) ^{131}I whole-body scan and (right) ^{18}FDG whole-body PET scan (sinogram projection).

Earlier investigations have only reported irregular ^{18}FDG uptake in thyroid tumors and metastases, but these findings were not correlated to ^{131}I uptake (*5,6,12,13*).

The alternating uptake pattern of ^{131}I/^{18}FDG we observed in 30 patients with thyroid carcinoma and metastases enabled us to identify five uptake patterns (*9*).

In 90% of the metastases, there was no continuous, reverse relationship in ^{18}FDG or ^{131}I uptake levels. There was, however, a "yes/no" or "no/yes" state in visual analyses that can be confirmed quantitatively (SUV_{bw}).

Within these five uptake patterns, we could identify three uptake levels in 34 patients with metastases:

1. At the patient level, type I and II (25 patients).
2. At the metastasis level, type I–III (30 patients).
3. At the cellular level (hypothetical), type I–IV (34 patients).

TABLE 2
Comparison ^{18}FDG/^{131}I Uptake in 184 Metastases in 26 Thyroid Cancer Patients

Uptake type	Papillary thyroid carcinoma	Follicular thyroid carcinoma	Hürthle-cell carcinoma:
I	62 metastases	59 metastases	8 metastases
II	18 metastases, (2 partially ^{18}FDG-positive)	30 metastases	
IV	3 metastases	4 metastases	

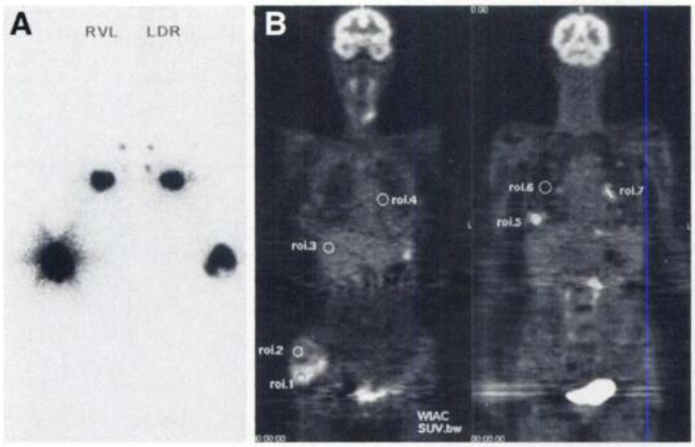

FIGURE 4. Uptake pattern type IV in a 58-yr-old woman who had a large tumor in the right hip for more than 15 yr that progressed in the last months and was not treated before with ^{131}I. Two metastases had ^{18}FDG and ^{131}I uptake but in different areas of the metastases. (A) ^{131}I whole-body scan and (B) ^{18}FDG whole-body PET scan corrected for attenuation with ROIs. ROI 1 (SUV_{bw}: 3.79) and ROI 2 (SUV_{bw}: 1.86) showed different uptake regions in one metastasis. ROI 4 (SUV_{bw}: 4.07) showed a lung metastasis without ^{131}I uptake. ROIs 4 (SUV_{bw}: 1.54) and 7 (SUV_{bw}: 4.30) seem to be in the same metastasis but in two other differentiated regions.

Thirty-four patients showed ^{18}FDG and/or ^{131}I uptake: 30 of them exhibited the flip-flop phenomenon at the patient level, five had the mixed type III; and 4 both uptake of ^{18}FDG and ^{131}I. Five percent of the metastases had both ^{131}I and ^{18}FDG uptake. In those patients with simultaneous uptake of ^{18}FDG and ^{131}I, the SUV_{bw} were relatively low and might be caused by a mixture of different tumor cells in these metastases. It is not yet clear whether the same cells can take up iodine and FDG or whether there are two different cell types in one metastasis. We observed alternating ^{131}I and ^{18}FDG uptake in different regions of the same metastasis in two larger metastases (Fig. 4). This phenomenon may be explained by the hypothesis that functionally more differentiated thyroid carcinoma cells with normal low glucose metabolism and remaining ^{131}I uptake can later change to a high glucose metabolic state that corresponds to the newly dedifferentiation of the cells.

We believe that uptake type II, ^{131}I-positive/^{18}FDG-negative, seems to represent functionally better differentiated low-grade tumor cells; whether the prognosis for the patient is better must still be evaluated. Conversely, type I uptake, ^{18}FDG-positive/^{131}I negative, represents higher malignancy of the tumor cells with lower functional differentiation. The mixed type III seems to represent metastases of type I and type II [i.e., different degrees of differentiation occur in metastases in the same patient (see Fig. 3)].

The relative benignancy of tumors with high ^{131}I uptake and no ^{18}FDG uptake was demonstrated in three patients with follicular thyroid carcinoma, in whom the metastases had already been detected for 31, 15 and 6 yr, respectively.

Multiple bone metastases exhibiting ^{131}I uptake and typical radiographs were not visible on ^{99m}Tc-MDP bone scans or ^{18}FDG scans. This indicates the relative benignancy of the tumor in the four patients with uptake pattern type II (Fig. 2). The absence of phosphonates trapping in bone metastases seems to provide similar information about tumor malignancy as does the absence of ^{18}FDG uptake. This low sensitivity (~60%) in bone metastases for trapping phosphates/phosphonates was described by Castillo et al. (*14*) for differentiated thyroid carcinoma metastases.

Furthermore, as an additional diagnostic tool in 360 patients with nonthyroid cancer tumors, ^{18}FDG whole-body PET detected benign thyroid adenomas in five patients. There was ^{18}FDG uptake in the cold nodules (^{99m}Tc-pertechnetate/^{131}I-negative). Three of these histologically confirmed benign adenomas were Hürthle cell adenomas without signs of malignancy but exhibiting high hTg levels (258; 530; 460 ng/ml). The adenomas in the other two patients were not examined histologically. Bloom et al. (*10*) also described eight patients who had ^{18}FDG-positive benign thyroid adenomas with an FDG dose uptake ratio (DUR) <7.5. The PET data, on the basis of these DURs, could differentiate between benign (<7.5) and malignant (>8) thyroid adenomas. We did not find any hot nodules that were ^{18}FDG-positive. Voth et al. (*13*) also reported elevated ^{18}FDG thyroid uptake in Basedow disease.

We did not observe significance correlation between ^{18}FDG uptake and thyroid hormone levels (TSH stimulation or suppression). A similar correlation between glucose uptake and cell differentiation has been demonstrated in other malignant tumors such as astrocytomas and glioblastomas (*15*). We also observed this correlation in eight patients with neuroblastoma: The two better differentiated ganglioneuroblastomas were ^{18}FDG-negative and ^{123}I-MIBG-positive, as were the eight neuroblastomas. We also observed five hepatocellular carcinomas, of which two fibrolamellar carcinomas did not exhibit ^{18}FDG uptake, possibly because of their higher differentiation.

Therefore, ^{18}FDG uptake appears to permit grading of tumor differentiation and malignancy in thyroid cancer as well as other carcinomas. Increased glucose metabolism could be a general indicator for higher graded tumors in oncology.

CONCLUSION

A dual study with ^{18}FDG and ^{131}I provides a sensitivity of 95% for the detection of recurrent thyroid cancer. This sensitivity rate enables detection of local recurrence or metastases with whole-body imaging that are often not revealed by other imaging methods. It also appears possible that a lack of ^{18}FDG uptake and residual ^{131}I uptake in metastases represents higher functional tumor differentiation. Additional studies with larger patient populations may show whether this diagnostic test also indicates better prognosis. It seems that we could obtain a biochemical grading for the functional differentiation of thyroid carcinomas with the alternating uptake of ^{131}I and ^{18}FDG.

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Comparison of Fluorine-18-Fluorodeoxyglucose and Carbon-11-Methionine PET in Detection of Malignant Tumors

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Two commonly used tumor-seeking agents for PET are 2-deoxy-2-^{18}F-fluoro-D-glucose (FDG) and L-methyl-^{11}C-methionine (Met). This study compared FDG and Met in detecting residual or recurrent malignant tumors in the same patients. **Methods:** Thirty-four lesions in 24 patients with clinically suspected recurrent or residual tumors were studied with PET using Met as well as FDG. FDG scans were conducted 1 hr after the completion of PET with Met. The color-coded superimposed images of standardized uptake values (SUVs) and transmission data were produced, and the peak SUVs in the lesions were then evaluated. Lesions above 2.5 SUV were interpreted as positive results for active tumor. **Results:** The sensitivity of FDG-PET and Met-PET were 64.5% (20/31 lesions) and 61.3% (19/31 lesions), respectively. The mean SUV of FDG in residual or recurrent malignant tumors (n = 31) was significantly higher than that of Met but there was a significant correlation ($r = 0.788$, $p < 0.01$) between FDG and Met SUVs in all lesions (n = 34). **Conclusion:** PET using FDG and Met appear equally effective in detecting residual or recurrent malignant tumors although FDG uptakes were slightly higher than Met uptakes. Both showed a limited diagnostic sensitivity for small (<1.5 cm) tumors.

Key Words: PET; fluorine-18-FDG; carbon-11-methionine; recurrent tumor

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Recent development of high-resolution imaging modalities, such as CT, MRI and ultrasonography, has contributed to the early detection of malignant tumors because of the precise morphological information about the lesion and surrounding normal tissue. These noninvasive modalities, however, often cannot provide helpful information in detecting recurrent or residual tumors because of their limitation in differentiating recurrent or residual tumors from post-treatment changes (*1*).

On the other hand, PET with tumor-seeking agents may provide useful functional or biologic information of tumors, especially regarding viable tumor cells or cell proliferation (*2*). The most widely used tumor-seeking agent with PET is 2-^{18}F-fluoro-deoxy-D-glucose (FDG). This agent is transported, phosphorylated and metabolically trapped into tumor cells as a glucose substitute (*3*). L-methyl-^{11}C-methionine (Met) is an also widely used tumor-seeking agent for PET studies, which reflects the amino acid metabolism in tumors. The accumulation of Met in malignant tumors is primarily related to its increased transport system (*4*). These different mechanisms of FDG and Met may provide a different role for clinical PET in detecting various malignant tumors with different metabolic or biologic behavior. Only a few clinical studies, however, have compared FDG and Met in detecting untreated tumor (*5,6*). The present study compared FDG and Met as tumor-detecting tracers in detecting malignant residual or recurrent tumors in the same patients.

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MATERIALS AND METHODS

Patients

Twenty-four patients (14 women, 10 men; aged 19–74 yr) were treated for malignant tumors before the PET study and are included in this study. Pathological diagnoses of the primary tumor were established in all patients: 7 of 24 patients had breast cancer; 9 had malignant soft-tissue tumors; 3 had lung cancer, 3 had bone tumor; 1 had colon cancer and 1 had ovarian cancer. Treatment conducted before the PET study was as follows: 10 patients had systemic chemotherapy; 5 surgery and systemic chemotherapy, 5 surgery, systemic chemotherapy and radiation therapy; 2 surgery and radiation therapy; 1 surgery alone, and 1 radiation therapy alone. Since one patient (Patient 23) had repeated the PET study, 25 PET studies in 24 patients were analyzed and 34 lesions were evaluated (31 lesions were recurrent or residual malignant tumors; 26 of them were diagnosed based on pathological findings and 5 were diagnosed based on follow-up clinical findings including tumor marker levels and radiographic evidence of disease progression). Three lesions in three patients were non-malignant tumors; one was diagnosed based on pathological findings and the other two diagnosed based on results of follow-up clinical and radiological examinations performed for more than 2 yr.

Only one patient (Patient 23) had diabetes mellitus and his blood glucose level was well controlled during the PET study.

PET Imaging

FDG was produced in the cyclotron facility at The University of Texas M.D. Anderson Cancer Center by proton irradiation of enriched ^{18}O-water in a low-volume titanium target. 2-Deoxy-D-glucose was labeled with ^{18}F to produce FDG by the Hamacher method (*7*) using an automated system developed in our institute. Carbon-11-Met was also produced by an automated system developed at our cyclotron facility and $^{11}CO_2$ was produced by a $^{14}N(p, \alpha)^{11}C$ reaction and then trapped with liquid nitrogen. From a series of chemical reactions, $^{11}CO_2$ was converted to methyliodine, $^{11}CH_3I$ and then reacted with homocystein to produce ^{11}C-Met.