Comparison of Fluorine-18-2-Fluorodeoxyglucose and Gallium-67 Citrate Imaging for Detection of Lymphoma

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Patients with lymphomas are conventionally imaged with [^{67}Ga]citrate for tumor detection and determination of dissemination. Fluorine-18-2-fluoro-2-deoxy-D-glucose ([^{18}F]FDG) is a radiopharmaceutical that accumulates into tissues where glucose utilization is enhanced, such as tumors. Six cancer patients (five non-Hodgkin's lymphomas, one endodermal retroperitoneal sinus carcinoma) were imaged with [^{18}F]FDG and [^{67}Ga]citrate whole-body scintigraphies in order to compare the sensitivities of these two tumor imaging radiopharmaceuticals. Among the five untreated lymphoma patients, two ^{67}Ga scans and four [^{18}F]FDG scans were positive; in the patient with the retroperitoneal carcinoma who had a positive [^{18}F]FDG scan before treatment, both scans were negative after treatment. Fluorine-18 FDG may be a more sensitive tumor-detecting radiopharmaceutical for non-Hodgkin's lymphoma than [^{67}Ga]citrate.

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Scintigraphy with gallium-67 (^{67}Ga) citrate is an established clinical method for detection of tumors, and it is widely used for evaluation of tumor spread, e.g., of lymphoma (*1–3*). There is some controversy concerning the mechanism of accumulation of ^{67}Ga into malignant cells—it has been suggested that the nuclide is transported intracellularly by transferrin (*4*), which may preferentially be taken up by malignant cells (*5*). Other observations indicate that ^{67}Ga incorporation into malignant cells may be due to altered plasma membranes (*6*). Accumulation of gallium may also be connected with the observation that gallium is cleared relatively slower from tumor cells than normal cells (*7*), which, in turn, may be allied to the frequent observation that gallium is located in lysosomelike granules of malignant cells (*8,9*).

The accumulation of the fluorine-18 (^{18}F) label of [^{18}F]-2-fluoro-2-deoxy-D-glucose ([^{18}F]FDG) is based on the intracellular trapping of [^{18}F]FDG 6-phosphate, which is the product of the hexokinase reaction of FDG (*10*). Further metabolism of FDG 6-phosphate is restricted in tissues devoid of glucose 6-phosphatase due to steric inhibition of enzyme activities by the fluorine atom in position 2 of the glucal ring. Thus, enhanced radioactivity will be detected in tissues that have a high glycolytic rate and lack glucose 6-phosphatase, such as the brain (*11,12*). Malignant tissue fulfills also these conditions (reviewed in *13*).

Before a new clinical method is introduced, controlled studies comparing the conventional and the new method have to be made. In this study, five patients with non-Hodgkin's lymphoma and one patient with carcinoma are presented that were scanned with [^{18}F]FDG and [^{67}Ga]citrate on consecutive days. Although the number of patients is small, the results indicate that [^{18}F]FDG may be superior to [^{67}Ga]citrate as an agent for detection of non-Hodgkin's lymphoma.

MATERIALS AND METHODS

The imaging apparatus consisted of a conventional gamma camera* equipped with a 15-cm-thick lead collimator (diameter 27 cm) with 1,000 parallel holes separated by septa 1.8 mm thick. One static whole-body image was obtained. The duration of image collection was 20 min.

The patients were first imaged with [^{18}F]FDG and on the following day with ^{67}Ga.

Fluorine-18 FDG was produced at our institution as described elsewhere (*14*). The substance has been found safe for

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use in humans by repeated tests for toxicity and pyrogenicity. Fluorine-18 FDG has been approved for clinical research by the local ethical committee, and the patients gave oral informed consent. Fluorine-18 FDG in saline solution was injected i.v. 60 min before scintigraphy at doses of 0.5 to 5.0 mCi (Table 1).

For ^{67}Ga imaging, 5 mCi of [^{67}Ga]citrate† was given as a standard i.v. dose on the day prior to scintigraphy, i.e., after the [^{18}F]FDG scanning was completed. Images were also obtained 48 hr after injection, but did not confer any additional information.

CASE REPORTS

Five of the patients had non-Hodgkin's lymphomas and one had a retroperitoneal carcinoma of endodermal origin (Table 1). All patients were imaged before treatment; however, the patient with carcinoma was imaged only with [^{18}F]FDG before treatment and with both radiopharmaceuticals after four courses of chemotherapy. All patients were in an unfasted state at the time of imaging.

Patient 1

A male aged 26 yr had felt discomfort and pain to the left in his back for 2 mo before admission. He also developed general symptoms (fever of unexplained origin, itching, and lassitude). At presentation a tumor was felt in the upper left quadrant of his abdomen, and ultrasonography revealed a retroperitoneal tumor. At laparotomy a large tumor was found that filled the left retroperitoneal space. Histologially the tumor was centrocytic lymphoma (diffuse small cleaved follicular center cell lymphoma). The [^{67}Ga]citrate scan was normal (Fig. 1A); in the [^{18}F]FDG scan there was an accumulation that corresponded to the tumor at laparotomy (Fig. 1B).

Patient 2

A woman aged 72 yr had complained of pain in the left hip for 12 mo. Six weeks before admission a tumor had appeared in the inguinal region. A radiograph showed acetabular destruction, and a tumor that extended from the inguinal region to the umbilicus was palpable. A biopsy was taken. The tumor was a histiocytic (immunoblastic) lymphoma of the inguinal lymph nodes that had extended into the pelvis. Gallium-67 scintigraphy showed accumulation of radioactivity in the hip, but not in the inguinal region, whereas [^{18}F]FDG corresponded closely to the clinical extension of the tumor.

Patient 3

A male aged 68 yr had observed enlarged cervical nodes bilaterally for 4 mo before admission. Biopsy revealed a well differentiated lymphocytic lymphoma. Clinically the patient was well and only the cervical lymph nodes were pathologically enlarged. The [^{67}Ga]citrate scan was normal. The [^{18}F]FDG scan did not show any accumulations in the neck, but there was enhanced activity in the abdomen, corresponding to what subsequent lymphography showed to be lymphomatous involvement of the para-aortic nodes.

Patient 4

A male aged 24 yr had noticed an enlarged lymph node to the left of his neck and in his left groin 9 mo before presentation. Five months before presentation he became acutely disoriented and was admitted to a psychiatric hospital where he received antipsychotic medication. Two months later the psychosis had cleared, but a visible tumor had appeared to the left in his neck. On admission enlarged lymph nodes were palpated in all lymph node regions, and the spleen extended 8 cm below the left costal curvature. A biopsy of the cervical tumor was taken, and histologically the disease was a diffuse small lymphocytic lymphoma. The ^{67}Ga scan (Fig. 2A) was positive for the cervical and splenic involvement, and equivocal for the inguinal region; the [^{18}F]FDG scan (Fig. 2B) showed the extension of the cervical involvement more exactly than the [^{67}Ga]citrate scan and the inguinal accumulations were clearly pathological.

TABLE 1
Patient Data and Scintigraphy Results*

Patient no.	Age/sex	Diagnosis	[^{18}F]FDG dose (mCi)	^{67}Ga	[^{18}F]FDG
1	26/M	Retroperitoneal diffuse small cleaved follicular center cell lymphoma (low grade) (stage IIB)	1.9	–	+
2	72/F	Immunoblastic lymphoma of left inguinal nodes (high grade) (stage IIB)	2.0	+	+
3	68/M	Diffuse small lymphocytic lymphoma of cervical and para-aortic nodes (low grade) (stage IIIA)	0.5	–	+
4	42/M	Diffuse small lymphocytic lymphoma of cervical and inguinal nodes, spleen and liver (low grade) (stage IVB)	5.0	+	+
5	49/M	Immunoblastic lymphoma of cervical and inguinal nodes (high grade) (stage IIIA)	3.2	–	–
6	29/M	Retroperitoneal endodermal carcinoma	I: 2.0 II: 2.0	not done –	+ –

* Patient 6 underwent both scans after chemotherapy; before treatment only a [^{18}F]FDG scan was obtained.

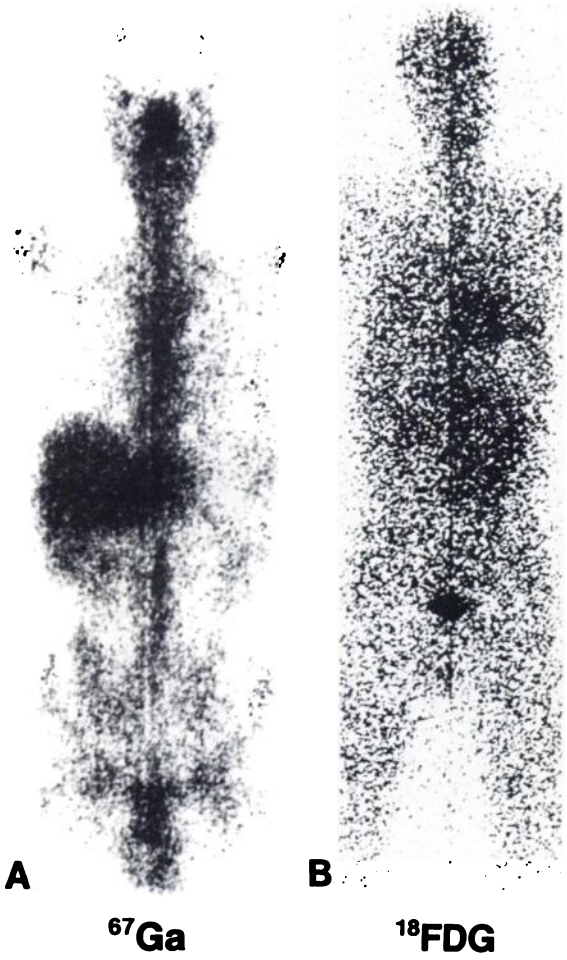

FIGURE 1
A,B: Patient 1, centrocytic retroperitoneal lymphoma. A pathologic accumulation of [^{18}F]FDG activity can be seen in the abdomen to the left of the midline. AP-view.

Patient 5

A male aged 49 yr attended for routine check-up at his private physician who found enlarged lymph nodes in the right axilla and left groin. The patient was subjectively well. There was one pathological lymph node (diameter 2 cm) cervically and several smaller ones in both axillas and inguinal regions. Biopsy of a cervical node revealed the tumor to be histologically an immunoblastic lymphoma. A clinical workup revealed no other sites of lymphomatous involvement. Both scans were normal.

Patient 6

A male aged 29 yr had had abdominal pain for 10 mo before presentation. A large tumor was palpated in the upper left quadrant of his abdomen. At laparotomy the tumor was found to extend retroperitoneally 25 cm from the left kidney inferiorly. The alpha-fetoprotein titer was high (9,350 μg/l), and histologically the tumor was a germinal, highly undifferentiated carcinoma. No metastases were diagnosed. The [^{18}F]FDG scan before chemotherapy showed a pathological accumulation corresponding to the clinical findings (Figure 3A). No [^{67}Ga]citrate scan was obtained at this time. After four courses of chemotherapy and almost complete clinical regression of the tumor, the [^{18}F]FDG scan (Figure 3B) was normal. A [^{67}Ga]citrate scan was also normal at this time.

DISCUSSION

The gallium scan is generally reported to be positive in 50% to 70% of patients with lymphoma, although rates as low as 40 and as high as 90% to 100% have been reported (for review see *15.*). Thus a detection rate in the present study of 2/5 is comparable to these reports, although the rather low yield of positive ^{67}Ga images may be incidental in a small series like the present one. The [^{18}F]FDG images were positive in 4/5 lymphoma patients. In the patient where no accumulation was seen (Patient 5), the tumors were <2 cm in diameter, which is below the detection limit of the imaging apparatus. Patient 3 had also cervical tumors below the detection limits of the imaging device, although the [^{18}F]FDG scan revealed previously undetected lymphomatous involvement para-aortally.

It appears that [^{18}F]FDG is a suitable radiopharmaceutical for detection of non-Hodgkin's lymphomas.

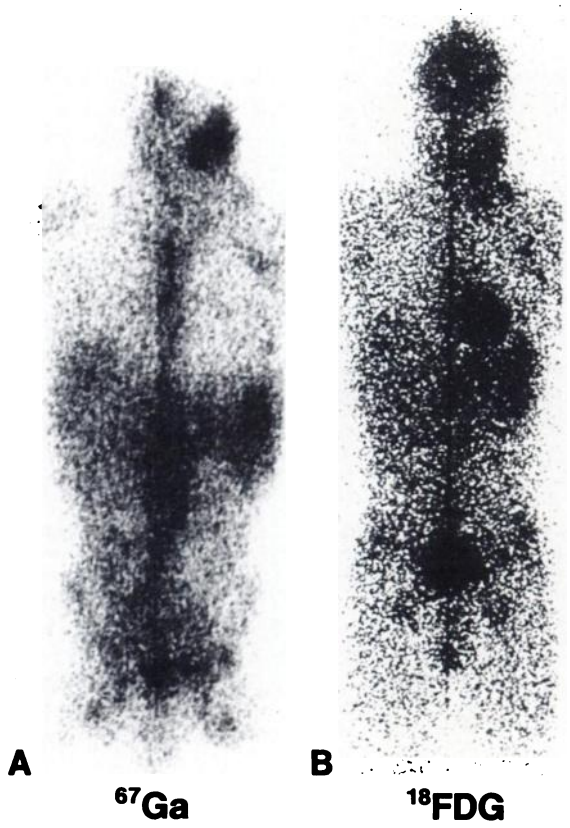

FIGURE 2
A,B: Patient 4, lymphoma of the cervical and inguinal nodes, liver, and spleen. The left cervical tumors are clearly demonstrated in both images, but the [^{18}F]FDG scan points to disease also sub- and supraclavicularly. Accumulations in the spleen and inguinal nodes are seen in both images. AP-view.

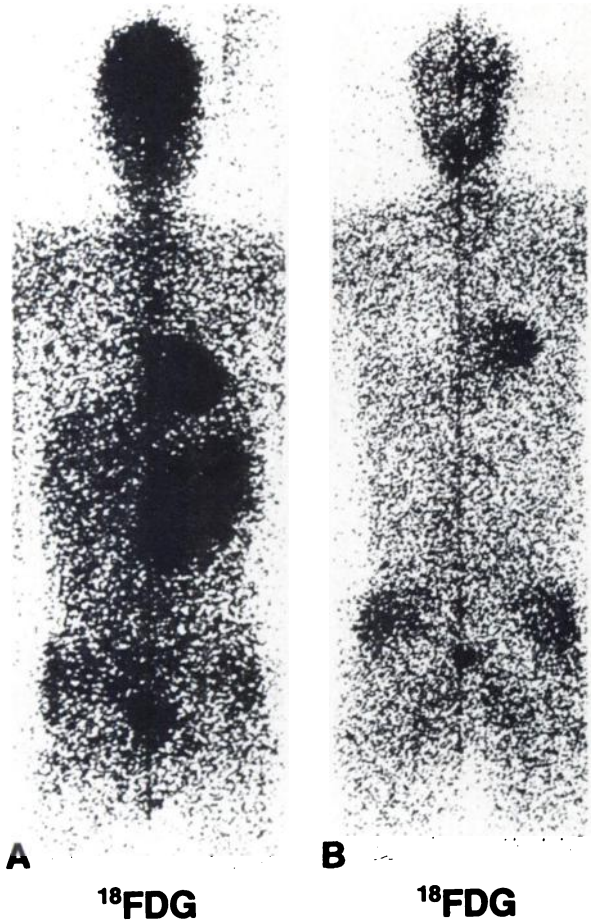

FIGURE 3
Patient 6, sinus endodermalis carcinoma in the left retroperitoneum; A: Before treatment; B: After four courses of chemotherapy. The [^{18}F]FDG image before treatment coincides with the clinical status, a tumor 20 cm in diameter was palpable under the left costal curvature. After treatment, the tumor had shrunk to a diameter of 8 cm and the patient was clinically well. At laparotomy, only necrotic tumor tissue was found. AP-view.

Fluorine-18 FDG fulfills the criteria of the "ideal tumorophilic radiocompound" as stated by Ito and Muranaka (*16*), i.e., rapid clearance from the blood (the study can be made soon after administration of the radiopharmaceutical); high accumulation in the viable part of the tumor; higher affinity for tumor than normal tissue; emits photons suitable for detection; and a short physical half-life.

Other studies have shown that [^{18}F]FDG accumulates preferentially into malignant tumors, and not in benign tumors or inflammatory foci (*17*). Patient 5 who had a germinal carcinoma, shows that [^{18}F]FDG is probably useful for detecting other malignancies as well. This is in agreement with previous results in animals (*18*) and man (*19*).

The circumstance that tumors generally take up [^{18}F]FDG does not, of course, mean that [^{18}F]FDG is a tumor-specific radiopharmaceutical. Fluorine-18 FDG accumulates physiologically into the heart, brain, and urine, and tumors in these regions may not be discernible in an [^{18}F]FDG image.

Thus, [^{18}F]FDG may be used as a clinical imaging agent for studying the dissemination of lymphoma, as shown in Patients 1–4. This application of [^{18}F]FDG as a radiopharmaceutical is possible with a gamma camera and does not demand positron emission tomograph. A disadvantage of [^{18}F]FDG is that it is expensive to produce. This obstacle may, however, be overcome, as the compound proves to be sufficiently valuable for routine clinical purposes.

NOTES

* (Searle Pho gamma V) Siemens Medical Systems, Iselin, NJ.

† Amersham International, Buckinghamshire, United Kingdom.

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