Imaging of Metastases of Thyroid Carcinoma with Fluorine-18 Fluorodeoxyglucose

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Three patients with multiple metastases of thyroid carcinoma were studied with ^{18}F-2-fluoro-2-deoxy-D-glucose (FDG) and iodine-131 (^{131}I) imaging. Metastases that accumulated only FDG, only ^{131}I, or both FDG and ^{131}I could be demonstrated. Metabolic heterogeneity was seen between different metastases in all patients. The accumulation of FDG may also differ between different metastases of the same patient. The uptake of FDG in metastases was shown to increase parallel with their progression. Metastases of thyroid carcinoma that have ceased to accumulate ^{131}I after treatment with radioiodine may still be demonstrated with FDG. Metastases that accumulate FDG, but not ^{131}I, may behave more aggressively than metastases that accumulate ^{131}I, but not FDG.

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Fluorine-18-2-fluoro-2-deoxy-D-glucose (FDG) is a D-glucose analog, which is converted in cells to FDG-6-PO_4 by hexokinase (*1*). FDG-6-PO_4 is metabolically trapped and accumulates in tissue where glucose 6-phosphatase is lacking (*2,3*), because the other enzymes acting on glucose 6-phosphate have only a negligible affinity for FDG 6-phosphate and it has low membrane permeability. The rate of accumulation of FDG 6-phosphate is proportional to the phosphorylation rate of exogenous glucose and the D-glucose utilization of the tissue. Fluorine-18 has a half-life of only 109 min, which entails tolerable radiation doses to the patient (*4*). In the human body FDG accumulates mainly in the heart and the brain, reflecting the high glycolytic rate of these tissues. Further, ^{18}F is a positron-emitting radionuclide, which allows quantitative imaging with positron emission tomography (PET) (*3*).

The mechanism of accumulation of FDG in malignant tissue is based on the enhanced rate of glycolysis (*5*). Malignant tissue may also lack glucose 6-phosphatase (*6*). FDG has been shown to accumulate in human brain and bone tumors (*7,8*), and in primary and metastatic carcinomas of the liver (*9, 10*). FDG is retained more by high-grade than low-grade brain cancer, and in these tumors the accumulation of FDG may correlate with length of survival (*7*).

Iodine-131 (^{131}I) has been widely used to detect and treat metastases of differentiated thyroid carcinoma. However, not all metastases accumulate ^{131}I (*11*) and, thus, are not involved in hormone synthesis. It has been suggested that these metastases are less differentiated (*12*), and therefore they may determine the ultimate prognosis of the patient. Because the accumulation of FDG in tumors may be proportional to the degree of tumor differentiation (*7*), it would be interesting to know if metastases that do not accumulate ^{131}I could be demonstrated with FDG. To our knowledge, advanced human thyroid carcinoma has not been studied with FDG imaging before, and herein we present the results of FDG imaging of three patients with advanced thyroid carcinoma.

MATERIALS AND METHODS

Three patients with advanced thyroid carcinoma were studied with FDG and ^{131}I imaging. In all cases the thyroid gland had been removed and the histologic diagnosis established. (For further details see Case Reports.)

FDG was synthesized after production of ^{18}F by a 103 AVF cyclotron with triacetyl glucal as the precursor. The synthesis followed the method of Haaparanta et al. (*13*). FDG was injected intravenously as a bolus through a cannula; the patient doses ranged 2–4 mCi (74–148 MBq). The imaging

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device for FDG was a conventional Anger gamma camera with a 1-in. crystal and a special collimator for 511 keV photons. One-minute frames representing the "dynamic" circulatory phase were collected during the first 30 min, and after this a steady-state image of 200,000 counts was collected 30–55 min after the injection.

Scanning with ^{131}I was done with an ordinary gamma camera. A 2-mCi (74 MBq) dose of ^{131}I was given orally 48 hr before imaging. Thyroxine feeding was interrupted for 3–4 wk before ^{131}I scanning, but scannings with FDG were performed during thyroxine replacement therapy.

RESULTS

All patients had metastases visible in FDG scan. The metastases became visible in the steady state (30–55 min) phase, but in one case metastases could also be detected during the dynamic circulatory phase (Fig. 1).

Two of the patients (Patients 1 and 2, see Case Reports) had multiple metastases, which did not accumulate ^{131}I, but retained FDG. On the other hand, lung (Patient 3) and neck (Patient 1) metastases that accumulated ^{131}I, but not FDG, could be demonstrated. In one case (Patient 3) a mediastinal metastasis retained both FDG and ^{131}I. Metabolic heterogeneity was seen between different metastases in all patients.

The progression of metastases could be followed in one case (Patient 1) with serial FDG scans. The FDG image of the metastases enlarged and intensified as the size of the metastases increased in chest x-ray (Fig. 2). Metastases that have ceased to accumulate ^{131}I after treatment with radioiodine could still be demonstrated with FDG (bone and lung metastases of Patient 2).

CASE REPORTS

Patient 1

A male patient, aged 66 yr, underwent total thyroidectomy in April 1975. A well differentiated papillary carcinoma with a regional lymph node metastasis was found and surgically removed. Postoperatively 80 mCi ^{131}I was administered. In 1985 an elevated serum thyroglobulin value (62 μg/l) was measured and the patient was asked to return for further examination. In February 1985 no palpable metastases were present and scanning with ^{131}I was negative, but large metastases were found at the suprasternal notch and in the upper mediastinum in the chest x-ray. In August 1985 ^{131}I accumulated in the thyroid region ~5 cm above the suprasternal notch, after which the patient received 100 mCi radioiodine in October 1985. The metastases at the suprasternal notch and in the upper mediastinum did not accumulate ^{131}I, either before or after treatment with radioiodine.

Scanning with FDG was performed three times (September and November 1985, March 1986). FDG accumulated in all three scans in the metastases at the suprasternal notch and the upper mediastinum, but not in the neck region (Fig. 1), whereas, ^{131}I continued to accumulate in the neck in spite of therapy with radioiodine, but not in the other metastases.

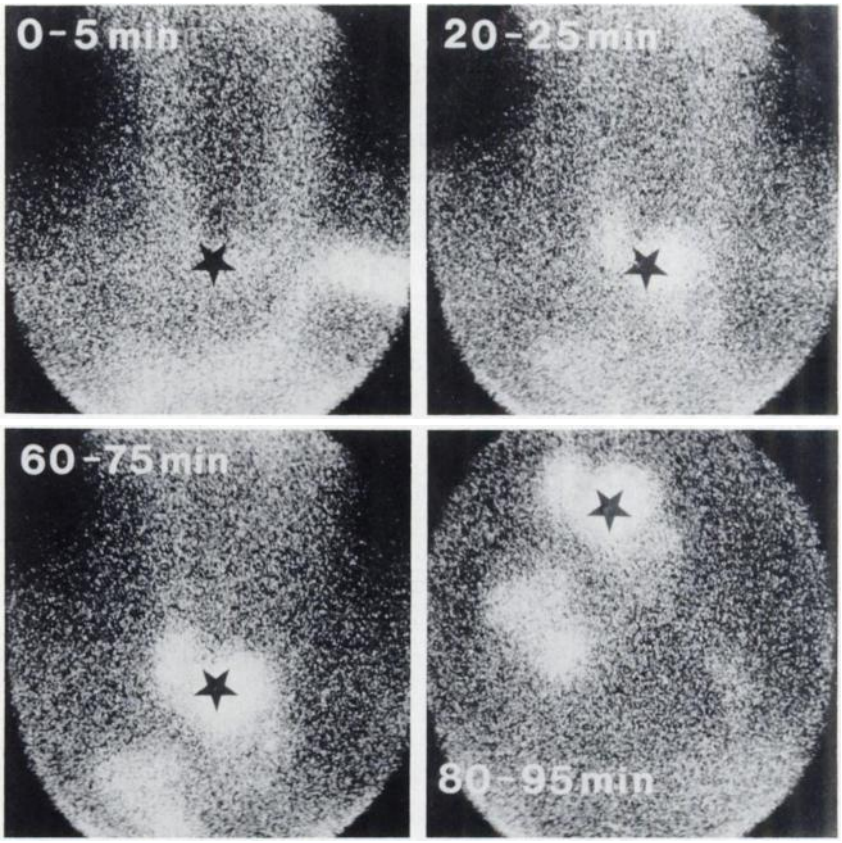

FIGURE 1
Accumulation of FDG in metastases of thyroid carcinoma at different time intervals after the injection of FDG. The suprasternal notch is marked with a star. The metastases are located at the suprasternal notch and the upper mediastinum.

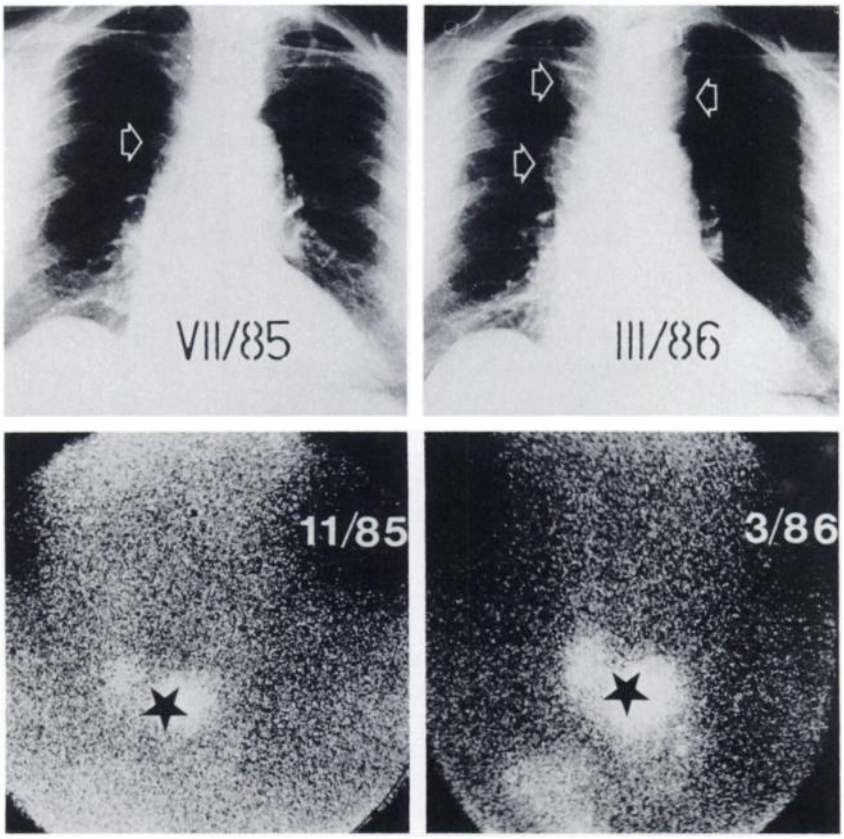

FIGURE 2
Two chest x-ray films and FDG scans showing progression of metastases at the suprasternal notch (star) and the upper mediastinum.

During the follow-up the metastases at the suprasternal notch and the upper mediastinum progressed strikingly, which could also be verified by FDG scanning (Fig. 2), but no palpable tumor has appeared in the neck (June 1986). FDG also accumulated in the superior lobe of the left lung in all three scans, but during the 8-mo follow-up no sign of metastasis appeared in chest x-ray films of the left lung.

Thyroxine feeding was interrupted for 3–4 wk before the ^{131}I scans and radioiodine therapy. The patient had been on thyroxine feeding for 3, 5, and 1 wk, respectively, when the three scans with FDG were performed. Serum thyroxine (S-T_4) was measured 1 wk before the second FDG scan (when the patient had been on thyroxine for 4 wk), and was found to be 100 nmol/l (reference values in this hospital 70–150 nmol/l). At the same time serum thyroid stimulating hormone (S-TSH) was 1.5 mU/l (reference value <7 mU/l).

Patient 2

A female patient, aged 59 yr, had a total thyroidectomy in February 1980. A moderately differentiated follicular carcinoma invading adjacent muscles with regional lymph node metastases was found and removed. In 1981 a metastasis was removed from the thyroid region. Iodine-131 continued to accumulate in the thyroid region, although the patient was given radioiodine therapy twice (80 mCi and 100 mCi). In 1982 multiple lung metastases were discovered in ^{131}I scan and in chest x-ray films, and the tumors were histologically verified malignant at mediastinoscopy. In 1983 ^{131}I also accumulated in the pelvis. During 1982–1985 the patient received radioiodine therapy three times (100 mCi, 150 mCi, and 150 mCi, respectively), and external palliative radiotherapy to the lung metastases on two occasions. After these treatments accumulation of ^{131}I in the thyroid region, the lungs, and the pelvis ceased, but the lung metastases continued to progress; in 1985 multiple bone metastases were also detected in x-ray films.

Scanning with ^{131}I was performed in June 1985 and with FDG in October 1985. Thyroxine replacement therapy was continued during FDG scanning (S-T_4 93 nmol/l, S-TSH <1 mU/l, serum free thyroxine 13.3 pmol/l, reference values 9–23 pmol/l). FDG was retained in the basilar parts of both lungs, which were crowded with metastases in chest x-ray. FDG also accumulated in the sacral and right iliac crest regions, which accumulated ^{99m}TcDPD (3,3-diphosphono-1,2-propanedicarboxylic acid, tetrasodium salt) in bone scan, and where lytic lesions compatible with osseous metastases were present in x-ray films. No accumulation of ^{131}I was seen in these locations, but this time ^{131}I accumulated in the metastases of the upper part of the left pulmonary hilus.

Patient 3

A male patient, aged 59 yr, had a partial lobectomy of the thyroid in October 1971, at which time a well differentiated follicular carcinoma was found. Total thyroidectomy was performed in 1975 after a recurrence. In addition to external radiotherapy the patient received radioiodine in 1971–1985 on 11 occasions up to the cumulative dose of 920 mCi. Pulmonary and mediastinal metastases were discovered and histologically confirmed in 1981.

FDG was retained in a 4-cm metastasis in the upper mediastinum, which also accumulated strongly ^{131}I in a scan performed 4 wk earlier. Thyroxine feeding was continued during FDG scan. One metastasis in the hilus of the left lung and another in the right lung accumulated only ^{131}I.

DISCUSSION

Like radioiodine, FDG can be used in imaging of metastases of advanced thyroid carcinoma. All patients had metastases that retained FDG, and two of the patients had multiple metastases that accumulated FDG but could not be detected by ^{131}I. Metastases that accumulate both FDG and ^{131}I, only FDG, or only ^{131}I were found. Metabolic heterogeneity could be seen between different metastases in all patients. In patient 1, metastases were followed with serial FDG and ^{131}I scans, and the metabolic behavior of different metastases remained similar during the observation time of 6 mo. The metastases that accumulated FDG continued to do so, whereas ^{131}I continued to accumulate in the neck.

It may be postulated that metastases that accumulate ^{131}I are involved in hormone synthesis and are more differentiated than those that do not retain ^{131}I (*12*). Patients with lung metastases that take up radioiodine have a high survival rate, ~50% of them survive 15 yr after the first administration of radioiodine, whereas, the survival of patients without significant radioiodine uptake after thyroid ablation is much shorter (*14*). In another study (*15*) ~60% of patients with pulmonary or osseous metastases of papillary or follicular carcinoma of the thyroid were alive at 5 yr, if the metastases accumulated radioiodine, whereas, only 30% of these patients were alive at 5 yr if the metastases did not retain radioiodine. On the other hand, metastases that retain FDG utilize more glucose than those that do not. Di Chiro et al. (*7*) found that FDG accumulates more in human high-grade brain cancer than in low-grade cancer. Taken together, metastases that accumulate FDG might behave more aggressively than those retaining ^{131}I. The metastases at the suprasternal notch and the upper mediastinum of patient 1, which accumulated FDG but not ^{131}I, grew rapidly in a few months (Fig. 2), whereas, no palpable tumor appeared in the neck where ^{131}I was retained instead of FDG.

All our patients were treated with radioactive iodine at least twice. A repetitive treatment with large doses of ^{131}I may lead to survival of cells, which are not involved in hormone synthesis and are less differentiated, because the cells that take up ^{131}I receive a larger dose of irradiation and are more likely to be destroyed. The ^{131}I and FDG scans of Patient 2 with metastases of a follicular carcinoma support this theory. This patient initially had an accumulation of ^{131}I in lung and bone metastases, which ceased after treatments with radioiodine and external radiotherapy to the lung metastases. The metastases, however, continued to progress according to x-ray films and also clearly accumulated FDG, but not ^{131}I.

Metastases of thyroid carcinoma can be detected with FDG while the patient is on thyroxine replacement therapy (Patients 1, 2, and 3). However, the possible effect of thyroxine feeding on accumulation of FDG in metastases of thyroid carcinoma has not yet been studied.

We conclude that FDG scanning may be useful in the follow-up of patients with advanced thyroid carcinoma, because it may reveal metastases that do not accumulate ^{131}I, and that therefore should be treated with external radiotherapy or chemotherapy rather than with radioiodine. FDG scanning may also be useful to confirm complete remission after treatment with radioiodine.

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