Early Treatment Response in Malignant Lymphoma, As Determined by Planar Fluorine-18-Fluorodeoxyglucose Scintigraphy

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Clinical oncology needs flexible techniques for routine monitoring of treatment response. We therefore compared planar ^{18}F-fluorodeoxyglucose (FDG) with a conventional gamma-camera and a special collimator to ^{67}Ga scintigraphy in 26 patients with malignant lymphoma during chemotherapy. The scintigraphic appearance of involved sites was essentially the same with both tracers: in patients eventually achieving complete remission, tracer distribution had normalized after two courses; high uptake reflected treatment failure; faint uptake was associated with variable outcome. For (re)staging, ^{67}Ga may be preferable (higher contrast). To document the initial response, we performed FDG scintigraphy during the first course (n = 11). Effective treatment sharply reduced metabolic tumor activity within days and prior to volume response, whereas abnormal uptake persisted in treatment failure. Planar FDG scintigraphy may be a tool to assess the potentially prognostic initial response rate, preventing overtreatment and allowing a timely switch to more aggressive therapy.

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Chemotherapeutic strategies in cancer patients are based on radiological criteria, although volume reduction is a late sign of effective therapy and radiological techniques cannot distinguish vital tumor from necrosis or fibrosis. Several potentially effective therapeutic options are available to treat malignant lymphoma. Imaging techniques should aim at detection of vital tumor in residual masses and, perhaps an even greater challenge, at prediction or early assessment of therapeutic (in)efficacy. The clinical outcome of patients with a high risk of relapse may improve if patients are treated primarily with high-dose chemotherapy. Volume-oriented criteria do not provide accurate prognostic information in this respect (*1–3*). During treatment for malignant lymphoma, there is no satisfactory way to identify patients at risk for relapse after chemotherapy (*1,2*) nor those overtreated. Early recognition of ineffective primary chemotherapy could imply less cumulative drug toxicity and tumor burden at the start of salvage therapy, which might improve clinical outcome (*4*).

Metabolic imaging using biological tracers may provide clinically relevant information not to be obtained with volume-oriented methods. Positron emission tomography (PET) allows quantitative assessment of regional blood flow (RBF), oxygenation and metabolism. However, PET technology is not fully established and access to PET facilities is limited so that this method is not used routinely. It remains to be established whether three-dimensional visualization and absolute quantification are obligatory for response monitoring. Alternatively, planar positron emission scintigraphy could be suited for large scale application; it can easily fit into regular chemotherapeutic schedules providing diagnostic information within 1 hr. We therefore developed a special 511-keV collimator for a conventional gamma-camera system for planar FDG scintigraphy. Phantom studies indicated that performance characteristics, in terms of spatial resolution, were at least comparable to other radiopharmaceuticals like ^{201}Tl and ^{67}Ga (*5*).

To determine whether planar FDG imaging provides clinically relevant diagnostic information, we compared FDG to the established lymphoma tracer ^{67}Ga in patients with malignant lymphoma. To document the initial response, we performed FDG scintigraphy during the first course in 11 patients treated with chemotherapy.

MATERIALS AND METHODS

We performed FDG (obtained from the Center for Radioisotope Research of the Free University, Amsterdam) and ^{67}Ga scintigraphies in 26 patients (13 with Hodgkin's disease, 13 with non-Hodgkin's lymphoma) according to the schedule in Table 1. Twelve patients had nodular sclerosing Hodgkin's disease and one had mixed, cellular type Hodgkin's disease. All non-Hodgkin's lymphomas were unfavorable, i.e., of intermediate and high-grade malignancy (*6*). To determine how soon after the start of chemotherapy uptake changes could be documented, we performed FDG scintigraphy in 11 of these patients, prior to treatment and during the first chemotherapeutic course. Volume re-

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TABLE 1
Gallium-67 and FDG Imaging Schedule

	^{67}Ga	FDG
Pretreatment	x	x
After one course	—	x (n = 11)
After two courses	x	x
After full therapy	x*	x*

*In case of residual mass in Hodgkin's disease (n = 8).

sponse was documented using standard clinical methods (palpation, chest x-ray and computed tomography (CT)).

The FDG imaging was performed with a conventional gamma camera (Sigma 410S, Technicare, OH), equipped with a collimator especially designed for 511-keV photons (Nuclear Fields, Boxmeer, the Netherlands). We used a 20% energy window around the photopeak. We established that ^{67}Ga photons did not interfere with 511-keV imaging. Planar images of documented masses were made 45 min after 185 MBq of FDG was administered and 1 wk after 185 MBq of ^{67}Ga was administered (128 × 128 matrix). For both tracers, the acquisition time was 15 min. During FDG imaging, patients were in the nonfasting state. An experienced radiologist and two nuclear medicine physicians interpreted the radiological and scintigraphic studies. Tracer uptake was graded visually according to a visual grading scale: − = negative, ± = faint, + = moderate and ++ = high uptake. Clinical decisions were taken independently of the results of FDG studies during chemotherapy. Restaging after completed chemotherapy included a CT scan and ^{67}Ga-scintigraphy in case of a residual mass in Hodgkin's disease treated with MOPP/ABV (negative planar followed by single photon emission computed tomography (SPECT)). Positive ^{67}Ga uptake at that stage was considered to represent vital tumor.

RESULTS

Prior to treatment, all radiologically documented lymphoma sites were visualized with ^{67}Ga as well as FDG (Fig. 1), except for 1-cm cervical nodes in a patient with non-

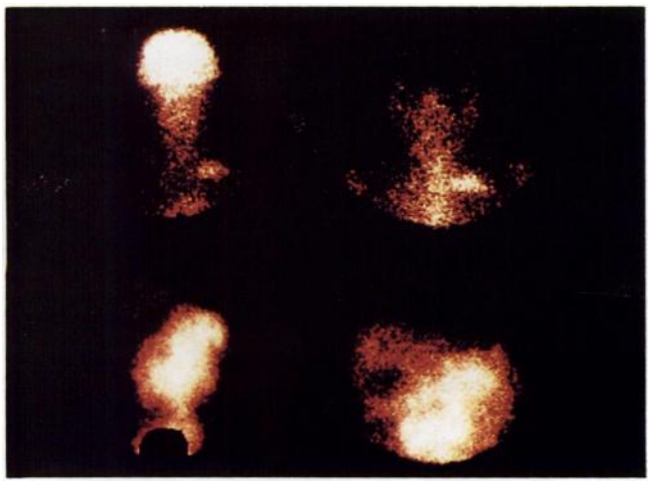

FIGURE 1. Biodistribution of FDG (left) and ^{67}Ga (right) in a patient with supraclavicular (top row) and retroperitoneal (bottom row) localizations of non-Hodgkin's lymphoma.

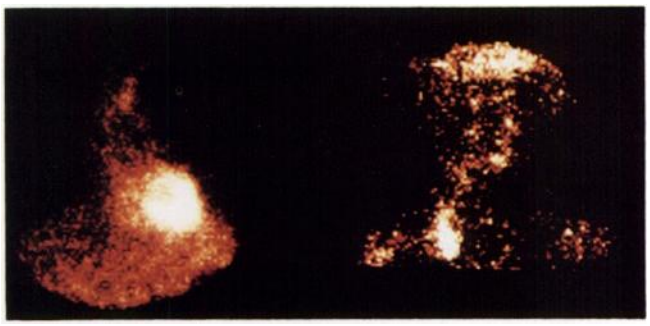

FIGURE 2. Abnormal mediastinal (left) and retroperitoneal (right) FDG uptake in a patient suspected of relapsed Hodgkin's disease (B-symptoms). CT scans of thorax and abdomen had been inconclusive (multiple nodes of approximately 1 cm). Mediastinoscopy confirmed active disease.

Hodgkin's lymphoma of intermediate malignancy (Table 3, Patient 9). Tracer uptake was similar in Hodgkin's disease and non-Hodgkin's lymphoma. In patients with suspected relapse (B-symptoms), metabolic imaging proved especially useful to confirm clinical suspicion of active disease and localize the involved sites (Fig. 2). In general, contrast was highest with ^{67}Ga. Anatomical overlap of tumor site and tissue with physiological tracer uptake impaired interpretation in two cases: costophrenic nodes were obscured by splenic ^{67}Ga accumulation but readily depicted with FDG, whereas a ^{67}Ga-positive presternal site could hardly be detected with FDG because of myocardial FDG uptake. Tomographic ^{67}Ga studies were sometimes needed to differentiate faint costal and hilar uptake.

Early during chemotherapy for Hodgkin's disease (after two courses), ^{67}Ga and FDG uptake had decreased considerably in most cases (Table 2). The relative change of tracer uptake generally exceeded volume reduction (tumor volume estimations were available in 8/13 patients; Fig. 3). Normal distribution of ^{67}Ga and FDG after two courses preceded complete remission as established after full chemotherapy. Patients with reduced uptake, but still abnormal tracer distribution after two courses had a variable outcome; moderate uptake was found in two patients clinically suspected of therapeutic inefficacy (Table 2). Scintigraphic appearance of 8/8 residual masses was similar and negative with ^{67}Ga and FDG. Early relapse in the primary site occurred in one patient (Table 2, Patient 2).

In non-Hodgkin's lymphoma (Table 3), normalized ^{67}Ga and FDG distribution after two chemotherapeutic courses preceded complete remission in 7/13 patients. According to clinical staging criteria, a residual mass was considered to harbor vital tumor. Pertinent accumulation of both tracers in three patients suggested the presence of vital tumor tissue, which was confirmed by clinical evidence of progression (Fig. 4). In 2 of 3 patients who had small residual masses, moderate and faint tracer uptake (FDG as well as ^{67}Ga) had been found after two courses, respectively (Table 3, Patients 7, 8). Some ^{67}Ga uptake and negative FDG scintigraphy were observed in a patient with a 1-cm residual cervical mass and inflammatory changes of the overly-

TABLE 2
Clinical and Scintigraphic Characteristics of Patients with Hodgkin's Disease

Patient	Stage	Outcome FDG/^{67}Ga pretreatment		FDG/^{67}Ga after two courses	Additional therapy	Follow-up (mo)
First treatment (MOPP-ABV)						
1	IV,s*	CR†‡	++/++	−/−	—	16, EF¶
2	IIIS	CR‡	++/++	±/± (s)	—	13, relapse
3	IIE,s	CR‡	++/++	±/−	—	16, EF
4	II,s	PR‡	++/++	±/−	RT	7, abdominal relapse**
5	II,s	CR‡	++/++	−/−	RT***	17, EF
Relapse (MOPP-ABV)						
6	II,i	CR	++/++	−/−	—	15, EF
7	IV	PR§	++/++	−/−	2nd line, AuBMT***	12, EF
8	II,i	CR	++/++	−/−	—	13, EF
9	III	CR‡	+/++	−/−	AuBMT***	18, EF
10	III	CR‡	++/++	−/−	—	13, EF
11	II,i	CR‡	+/++	−/−	—	15, EF
Treated with bone marrow ablative chemotherapy and transplantation						
12	III	PR	++/++	+/+ (s)	RT	11, EF
13	III	PR	++/++	+/+ (s)	RT	12, EF

*s = supradiaphragmatic, i = infradiaphragmatic localizations.
†CR and PR = complete and partial remission, respectively.
‡Residual mass and negative ^{67}Ga SPECT.
§No ^{67}Ga SPECT available.
¶EF = event free.
**No abdominal FDG scan available during primary chemotherapy.
***Standard additional therapy; RT = radiotherapy, AuBMT = bone marrow ablative chemotherapy and autologous bone-marrow transplantation.

ing skin, either of which may have accumulated ^{67}Ga (Table 3, Patient 6).

In three patients with Hodgkin's and in eight patients with non-Hodgkin's lymphoma, FDG imaging was performed after the first cycle. Compared to the pretreatment situation, clear reductions of tracer uptake were documented in 9 of 11 (Fig. 5); in the 5 of 11 who were studied within the first week of chemotherapy, this was evident within days after the start. In two patients, high FDG uptake suggested therapeutic failure, confirmed by the clinical course.

DISCUSSION

In malignant lymphoma, planar FDG imaging generally provided the same diagnostic information as ^{67}Ga. Within

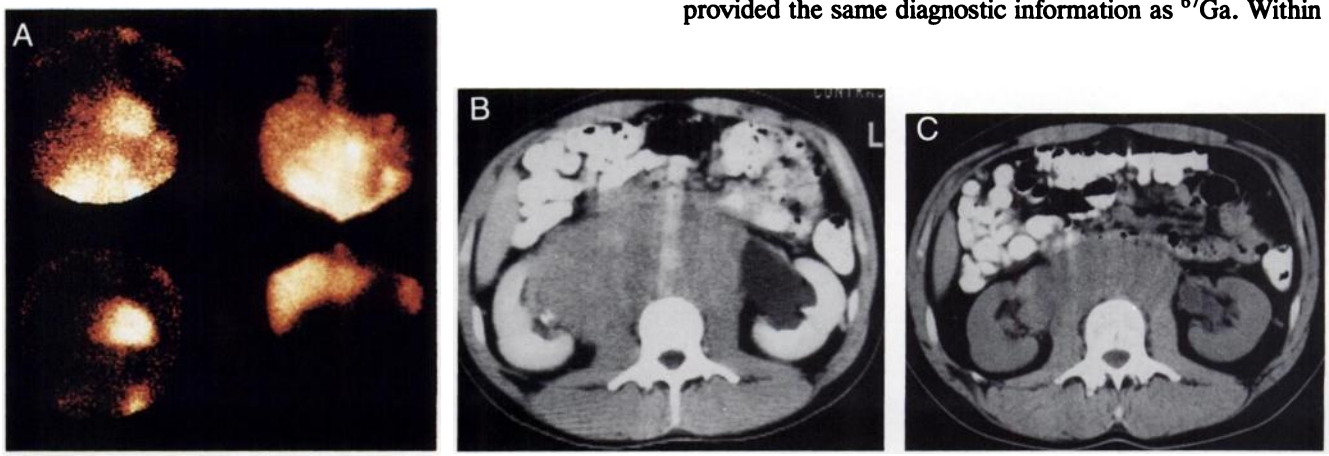

FIGURE 3. (A) Planar views of upper abdomen/thorax show similar FDG (top, left) and ^{67}Ga (top, right) uptake in retroperitoneally relapsed Hodgkin's disease (B, pretreatment CT at the renal pelvis level). Planar views of upper abdomen/thorax show similar intrapulmonal uptake (right, paracardially) indicated vital tumor tissue in a lesion previously considered to be residual fibrotic tissue. After two chemotherapeutic courses, tracer uptake was near normal (FDG, bottom left; ^{67}Ga bottom right), thus predicting volume response (C, CT after four courses at the same level as in B). FDG accumulation in the left part of the abdomen represents urinary stasis in the left kidney. This patient was classified as a partial remission on morphological grounds.

TABLE 3
Clinical and Scintigraphic Characteristics of Patients with Non-Hodgkin's Lymphoma

Patient	Stage	Outcome	FDG/^{67}Ga pretreatment	FDG/^{67}Ga after 2 courses	Additional therapy	Follow-up (mo)
First treatment (CHOP-MTX)						
1	II,i*	CR	++/++	−/−	—	20, EF†
2	IIE,i	CR	++/++	−/−	—	17, EF
3	IV	CR	++/++	−/−	RT‡	14, EF
4	IE,s	CR	+/++	−/−	—	13, EF
5	II,s	CR	++/++	−/±§	—	17, EF
6	II,s	PR	++/++	−/±	RT	11, EF
7	II,s	PR	++/+	+/+	RT	7, relapse
8	II,s	PR	++/++	±/±	2nd line, auBMT¶, RT	6, EF
9	III	CR	−/−	−/−	—	12, EF
Treated with second line chemotherapy and auBMT						
10	III	PR	++/++	++/++	RT	Died of tumor
11	II,s	CR	++/++	−/−	—	Died during auBMT
12	IIE,s	PR	na/na**	++/++	RT, third line, auBMT	Died of tumor
13	II,s	PR	++/++	++/++	Third line, auBMT, RT	Died of tumor

*i = infradiaphragmatic, s = supradiaphragmatic localizations.
†EF = event free.
‡Standard additional therapy.
§Unexplained bihilar ^{67}Ga-uptake outside primarily affected sites.
¶AuBMT = bone marrow ablative chemotherapy and autologous bone-marrow transplantation.
**Na = not available.

days after the start of chemotherapy, profound metabolic changes could be visualized with FDG.

Several PET studies have indicated the potential of biological tracers for tumor detection (*7–10*), mostly using enhanced glycolysis of vital tumor cells (*11*) as defined by FDG-uptake. Although aspecific FDG accumulation in macrophages (*12*) and hypoxia-induced FDG uptake (*13*) could be confounding factors, FDG seems to be an attractive radiopharmaceutical for monitoring response to therapy.

However, after a decade of PET, the technique is still not a routine procedure in clinical oncology, which probably relates to its complexity and limited availability (*14*). The planar alternative is definitely much more flexible but needs to be established beyond phantom studies (*5*). In the present clinical study, the planar FDG approach allowed pretreatment visualization of affected lymphoma sites similar to ^{67}Ga, as has been found with PET (*8*).

For investigation of residual masses and pretreatment staging, we suggest that ^{67}Ga is the preferable tracer because of higher contrast. In areas with considerable physiological ^{67}Ga uptake, FDG scintigraphy may provide complementary information. The detection limit of planar FDG is apparently in the order of magnitude of ^{67}Ga. The apparent predictive power of FDG uptake needs to be confirmed in a larger study, since prevalence of treatment failure in front-line chemotherapy was relatively low. Clearly abnormal FDG uptake seemed to imply the presence of vital tumor (*11*) and a bad prognosis, as is the case for ^{67}Ga (*15,16*). Our data do not support the impression obtained from a small number of patients that the diagnostic information of planar FDG imaging is superior to ^{67}Ga (*17*).

Experience with in vivo monitoring of treatment response during therapy is limited. The present study was not designed to investigate the impact of FDG scintig-

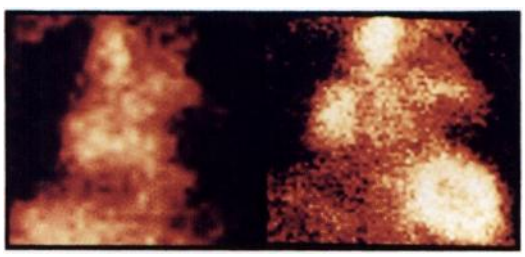

FIGURE 4. Mediastinal and hilar FDG uptake prior to treatment (left) and after two chemotherapeutic courses (right) in a patient with non-Hodgkin's lymphoma. Clinical course confirmed the presence of vital tumor.

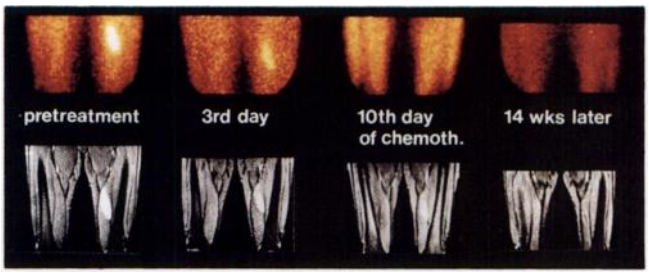

FIGURE 5. FDG scintigraphy and MRI in a patient previously treated for non-Hodgkin's lymphoma, presenting with pain in the left thigh. There was no palpable mass, CT was negative. MRI and FDG clearly depicted the tumor. Within days after the start of chemotherapy, profound metabolic changes were observed exceeding changes in volume and signal intensity. A complete remission was achieved after completed chemotherapy.

raphy prospectively, so that some patients with "partial remissions," received additional therapy according to clinical criteria. Presence of vital tumor cannot be excluded by negative planar FDG and ^{67}Ga scintigraphy, as is shown by some relapses in our patients. In these cases, PET's superior detection capacity might provide clinically relevant information, but this remains to be established.

Microscopic disease will remain beyond the grasp of any imaging modality. The initial response rate to chemotherapy could be an alternative way to predict therapeutic efficacy (*18–20*). The prolonged physical half-life of ^{67}Ga precludes its application for this purpose. Our data show that within days after the start of chemotherapy, major alterations of FDG uptake were easily recognized visually. Sequential studies are needed to define the optimal imaging schedule accounting for reversible phenomena (*21*).

Its unpredictable and heterogeneous response to chemotherapy suggests that malignant lymphoma is a good model to assess the value of metabolic imaging. Metabolic changes during chemotherapy were easily recognized using the planar technique. This approach allows a much larger patient turnover than PET contributing to study the clinical relevance of the "FDG signal." The technique may select patients for absolute quantitation with PET and may guide PET acquisitions because of the larger planar field-of-view. Comparison with FDG-SPECT and PET may reveal to what extent lower contrast with FDG (compared to ^{67}Ga) relates to collimator-camera characteristics or tracer biodistribution.

CONCLUSIONS

In malignant lymphoma, FDG can be imaged effectively and at low cost, with a conventional camera system and a special collimator. The FDG (glycolysis) and ^{67}Ga (transferrin-receptor density) appear to be equally useful in functional staging of malignant lymphoma. Early response rates should be determined with FDG.

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