Metabolic Response of Non-Hodgkin's Lymphoma to ^{131}I-Anti-B1 Radioimmunotherapy: Evaluation with FDG PET

Tatsuo Torizuka, Kenneth R. Zasadny, Paul V. Kison, Stephen G. Rommelfanger, Mark S. Kaminski, and Richard L. Wahl

Division of Nuclear Medicine, Division of Hematology/Oncology, Department of Internal Medicine, and Department of Radiology, University of Michigan, Ann Arbor, Michigan

^{131}I-anti-B1 (CD20) radioimmunotherapy (RIT) is a promising approach for treatment of non-Hodgkin's lymphoma (NHL). We assessed the tumor metabolic response to RIT using FDG PET. **Methods:** We examined 14 patients with NHL, who were given first a tracer dose of ^{131}I-anti-B1 and then RIT, each preceded by infusion of unlabeled anti-B1. In 8 of 14 patients, PET was performed at baseline and 33–70 d after RIT. The other 6 patients underwent PET at baseline, 6–7 d after the tracer dose, and 5–7 d after RIT to estimate the early response to tracer dose and RIT. To assess tumor FDG uptake, standardized uptake value normalized for lean body mass (SUV-lean) was measured 1 h after FDG injection. **Results:** After RIT, complete response was observed in 6 patients, partial response in 6, and no response in 2. At 33–70 d after RIT, mean SUV-lean of 6 responders markedly declined to 41% of the baseline value ($P < 0.002$). Soon after tracer dose and after RIT, mean SUV-lean of the other 6 responders decreased to 79% and 62% of the baseline values, respectively ($P < 0.05$). In 2 nonresponders, SUV-lean did not significantly decline from the baseline value at 37 d after RIT. **Conclusion:** FDG PET metabolic data obtained 1–2 mo after RIT correlate well with the ultimate best response of NHL to RIT, more significantly than the early data after tracer dose or RIT. FDG uptake in NHL may decline gradually after RIT in responding patients.

Key Words: non-Hodgkin's lymphoma; radioimmunotherapy; FDG PET

J Nucl Med 2000; 41:999–1005

Non-Hodgkin's lymphoma (NHL) is increasing in frequency, and many cases are incurable. Most patients with low-grade lymphoma present with advanced-stage disease, which, although treatable, is generally considered incurable with conventional therapy. A review of 212 newly diagnosed patients with advanced-stage, low-grade lymphoma showed that a response rate to the first treatment was 88% and showed declines with successive recurrences, reaching 48% after the third treatment (*1*). Other studies have indicated that only 50% of intermediate- and high-grade lymphomas responded to conventional chemotherapy for primary treatment (*2,3*).

Received Nov. 24, 1998; revision accepted Jan. 19, 2000.

For correspondence or reprints contact: Richard L. Wahl, MD, Division of Nuclear Medicine, University of Michigan Medical Center, 1500 E Medical Center Dr., B1G412, Ann Arbor, MI 48109-0028.

^{131}I-anti-B1 (CD20) radioimmunotherapy (RIT) has been recognized as a promising approach for treatment of NHL. We have shown previously that 22 of 28 (79%) patients with non-Hodgkin's B-cell lymphoma responded to RIT and that 64% of those responses were complete (*4*). Before RIT, these patients had experienced 1 or more failures of different chemotherapy regimens, including those with the most active drugs. These findings suggest that the antitumor mechanisms of ^{131}I-anti-B1 are highly independent of those of most chemotherapeutic agents and are suited to the treatment of patients failing primary or salvage chemotherapy. In addition, this therapy ultimately may have a role in initial treatment of NHL.

PET with FDG has been used widely to show increased glucose metabolism in various types of malignant lesions (*5–9*). Several studies using FDG PET have successfully shown the feasibility of imaging, staging, and noninvasively predicting malignant grade in NHL (*10–13*). Notably, FDG PET has the ability to detect low-grade lymphoma, a disease in which lower sensitivity for detection is obtained with ^{67}Ga (*14*). The noninvasive measurement of FDG uptake with PET provides quantitative indices of tumor glucose metabolism, which might be appropriate indicators and predictors of tumor response to treatment, because cancer growth is typically characterized by an increased rate of glucose metabolism (*9,15–19*).

To evaluate a response of NHL to ^{131}I-anti-B1 RIT, we have examined CT scans of patients at intervals of 2–3 mo after therapy. However, CT after treatment is sometimes inconclusive because of distortion of morphologic structures. In this study, we examined FDG PET at 1–2 mo after RIT to estimate the feasibility of FDG PET in monitoring a response to RIT compared with the morphologic response observed on CT images. In addition, we assessed whether FDG PET data obtained early after tracer dose and RIT can predict outcomes for NHL patients.

MATERIALS AND METHODS

Patient Population

We studied 14 patients with NHL expressing the CD20 antigen (Table 1). Eight had relapsed after chemotherapy, radiation therapy,

TABLE 1
Summary of Patients

Patient no.	Tumor site	Grade	Size (cm)	Previous therapy	Duration between TD and PET* (d)	Duration between RIT and PET (d)	RIT dose (GBq)	Response to RIT
1	Abdomen	Low	5 × 4	CT	N/A	70	1.48	CR
2	L axilla	Low	2.5 × 2.5	CT	N/A	33	1.52	CR
3	Mediastinum	Low	3 × 5	CT, RT	N/A	69	2.63	CR
4	L kidney	IM	10 × 10	CT	N/A	34	3.07	PR
5	Mediastinum	Low	10 × 5	CT, RT	N/A	34	4.00	PR
6	Spleen	Low	9 × 10	CT, RT	N/A	56	2.05	PR
7	L axilla	IM	3 × 3	CT	N/A	37	2.00	NR
8	Mediastinum	IM	5 × 8	CT	N/A	37	2.29	NR
9	Pelvis	Low	4 × 4	None	7	7	4.77	CR
10	Pelvis	Low	3 × 5	None	6	7	2.41	CR
11	Pelvis	Low	3 × 3	None	6	5	3.29	CR
12	Abdomen	Low	15 × 10	None	6	6	2.15	PR
13	Liver	Low	2.5 × 2.5	None	7	7	3.26	PR
14	Mediastinum	Low	3 × 5	None	6	7	5.59	PR

*Patients 1–8 did not undergo PET between TD (tracer dose) and RIT.
CT = chemotherapy; CR = complete response; RT = radiation therapy; IM = de novo intermediate grade; PR = partial response; NR = no response.

or both, and were treated with RIT in the phase I trial, which enrolled only previously treated patients (*20*). These 8 patients had received no therapy for at least 1 mo before baseline PET scans. The other 6 patients had not been treated previously and received RIT in the next phase II trial enrolling untreated patients.

In each patient, we focused on the 1 tumor lesion that had the largest size within the field of view of the baseline PET scan. Tumor size was determined by measuring the largest perpendicular diameters of tumor on CT imaging. The duration between CT scan and PET scan was 0–16 d at baseline study. All patients provided written informed consent for the RIT and PET imaging studies. All studies were approved by the institutional review board of the University of Michigan. ^{131}I-anti-B1 and FDG were made under the guidelines of the Investigational New Drug exemptions approved by the U.S. Food and Drug Administration.

Preparation and Iodination of Anti-B1 Antibody

The anti-B1 mouse immunoglobulin G2a monoclonal antibody was provided by Coulter Corporation, Miami, FL. Radioiodination of the antibody with ^{131}I, purification of the radiolabeled product, verification of its immunoreactivity, and testing for its contamination by pyrogens were performed as described previously (*4,21*).

Tracer Dose and Dosimetry Studies

Before administering the therapeutic dose to each patient, we determined the radiation dose to the whole body delivered by a small dose of radiolabeled anti-B1. All patients were hospitalized to receive 15–20 mg anti-B1 antibody, trace-labeled with approximately 185 MBq (5 mCi) ^{131}I, over 30 min. Dosimetric estimates were then made according to the methods described previously (*21*).

To evaluate whether preinfusing unlabeled antibody could optimize radiolabeled antibody tumor targeting, patients 1–3 received 2 additional tracer doses on successive weeks, each of which was immediately preceded by an infusion of 95 mg unlabeled anti-B1, followed by 495 mg the next week. The next 11 patients received only 1 tracer dose, preceded by a single, unlabeled antibody dose (450–495 mg). Diphenhydramine (50 mg) and acetaminophen (650 mg) were given orally as premedication before each antibody infusion. Saturated potassium iodide was given orally for at least 14 d, beginning the day before the first antibody infusion, to inhibit uptake of radioactive iodine by the thyroid.

Radioimmunotherapeutic Dose

At least 1 wk after the last tracer dose, 15–20 mg anti-B1 labeled with a high amount of radioactivity (the radioimmunotherapeutic dose) was administered (Table 1). This dose was preceded by the infusion of 450–495 mg unlabeled antibody. The total radioactivity of the RIT dose was individualized, so that a patient would receive a specified dose of whole-body radiation (in cGy) predicted by the tracer doses and dosimetry. Patients were again premedicated with diphenhydramine and acetaminophen, and potassium iodide was given for 14 d. In addition, potassium perchlorate (200 mg, 3 times daily) was given for 7 d beginning the day of the infusion.

FDG PET Imaging Procedure

On patients 1–8, FDG PET was performed at baseline and 33–70 d after RIT. To estimate early responses of tumors to tracer doses and RIT, patients 9–14 underwent PET at baseline, 6–7 d after tracer dose, and 5–7 d after RIT. The interval between the baseline PET scan and the first tracer dose was 0 or 1 d, except for 2 patients, whose intervals were 35 d (patient 2) and 8 d (patient 8).

An ECAT 921/EXACT scanner or an ECAT 931/08 scanner (CTI, Knoxville, TN) was used in this study. The ECAT 921 scanner permits simultaneous acquisition of 47 transverse planes of 3.4-mm thickness encompassing a 15.0-cm axial field of view. The ECAT 931 scanner permits simultaneous acquisition of 15 transverse planes of 6.75-mm thickness and a 10.3-cm axial field of view. All patients fasted for at least 4 h before undergoing PET. Initial transmission scanning of the region of interest (ROI) was performed for 10 min with a ^{68}Ge ring source. Acquired data were used later for attenuation correction in image reconstruction. Static images were obtained at 60–70 min after intravenous administra-

tion of ~370 MBq FDG, produced as described previously (22). Serum glucose levels measured before each PET scanning session were normal.

Data Analysis

Cross-sectional sinogram data were corrected for dead time, decay, random coincidences, and attenuation. Image reconstruction was performed by means of a filtered backprojection algorithm using a Hanning filter with a cutoff frequency of 0.3 and a 128 × 128 matrix. The average reconstructed and filtered x–y spatial resolution was about 1.2-cm full width at half maximum in-plane for both scanners.

ROIs for analysis of uptake of ^{18}F activity were defined in a tumor that was detectable as a hot area relative to the normal background. To minimize the influence of partial-volume effect associated with decreasing tumor volumes resulting from treatment, a small, square ROI (2 × 2 pixels = ~1.2 × 1.2 cm) was placed over the region of maximum FDG uptake in the tumor, using a computerized semiautomatic algorithm. The ROIs over all planes covering tumor were reviewed, and counts were averaged in the 3 (ECAT 921 scanner) or 2 (ECAT 931 scanner) contiguous sections with the highest activities. Standardized uptake value (SUV) calculated on the basis of lean body mass (SUV-lean) was determined in this maximal uptake ROI. SUV-lean is defined as tissue concentration (MBq/mL) divided by injected dose/lean body mass (MBq/g) (*23*).

Tumor Response

Evaluation for tumor response, including physical examination, CT (chest, abdomen, and pelvis), bone marrow biopsies (if positive for lymphoma at last evaluation), and blood counts and chemistries, was performed during the tracer studies before RIT, 4–6 and 12 wk after therapy, and every 2–3 mo thereafter. As previously described, a complete response (CR) was defined as a complete disappearance of all detectable disease for at least 1 mo or as lack of change in a minimal, residual radiographic abnormality for at least 6 mo (*4,21*). A partial response (PR) was defined as a reduction of at least 50% in the sum of the products of the largest perpendicular diameters of all measurable lesions for at least 1 mo.

Statistical Analysis

Statistical comparisons of PET data were performed using paired or unpaired t tests. $P < 0.05$ was considered to be statistically significant.

RESULTS

Of the 14 patients given an RIT dose, 6 (44%) achieved CR and 6 (44%) achieved PR (Table 1). Baseline SUV-lean was not significantly different among patients showing complete, partial, and no responses (8.58 ± 2.02, 8.12 ± 2.31, and 8.65 ± 4.06, respectively). All 11 patients with low-grade lymphoma responded to RIT, whereas 2 of 3 patients who had de novo intermediate-grade lymphoma did not respond to the therapy. These 2 patients (patients 7 and 8) were also resistant to the final course of chemotherapy (a response lasting for <3 mo after treatment). In contrast, all patients responding to chemotherapy for 1 y were also sensitive to RIT. All 6 patients with untreated low-grade lymphoma responded to RIT.

At 33–70 d after RIT, SUV-lean of 6 responding patients markedly decreased from the baseline value ($P = 0.0013$), whereas SUV-lean of 2 nonresponders was essentially unchanged (Table 2; Fig. 1). In 4 of the 6 responders, RIT reduced SUV-lean to 30%–38% of the baseline values (Fig. 2). Figure 3 shows a high correlation between the percentages of SUV-lean and tumor size after RIT, relative to the baseline values ($r = 0.952$; $P < 0.001$). In 5 responders, however, SUV-lean showed values about 10%–20% higher than tumor size. In patient 7, a nonresponder, SUV-lean was reduced to 89%, whereas tumor size decreased to 56%, compared with the baseline values. CT performed 2 mo later showed tumor regrowth in this patient.

At 6–7 d after a tracer dose, mean SUV-lean of 6 responding patients was modestly but significantly decreased to 79% of the baseline value ($P = 0.025$) (Table 2). However, in 2 of 6 responders (patients 9 and 14), SUV-lean declined by only 0.4% and 5.1%, respectively, with the tracer dose (Fig. 4). At 5–7 d after RIT, mean SUV-lean of these 6 responding patients was significantly decreased to 62% of the baseline values ($P = 0.031$). Three of 6 responders (patients 9, 11, and 12) showed relatively rapid decreases in SUV-lean with RIT (Fig. 5). However, 1 CR patient (patient 10) had an increase in SUV-lean, and 1 PR patient (patient 14) showed only a 19% decrease in SUV-lean (Fig. 6) compared with the baseline values.

DISCUSSION

^{131}I-anti-B1 (CD20) RIT has been shown to be a promising treatment in patients with B-cell NHL (*4,21*). In this treatment, radionuclide-labeled monoclonal antibodies recognizing tumor-associated antigens are administered systemically to selectively target radioactivity to cancer cells. In our initial study, an RIT dose achieved a high response rate, even in a group of patients who had been resistant to primary chemotherapy (*4*). Patients with low-grade lymphoma were particularly responsive to this treatment. Recently, this

TABLE 2
SUV-Lean Before and After Tracer Dose and Radioimmunotherapy

Patient no.*	Response	Baseline†	5–6 d after TD†	After RIT†‡
1–6	CR/PR	8.58 ± 2.02	N/A	3.5 ± 1.05 ($P = 0.0013$)
7–8	NR	8.65 ± 4.06	N/A	8.32 ± 4.48 ($P = 0.467$)
9–14	CR/PR	6.91 ± 1.3	5.47 ± 1.28 ($P = 0.025$)	4.29 ± 1.07 ($P = 0.031$)

*Data for patients 1–8 at 33–70 d after RIT; data for patients 9–14 at 5–7 d after RIT.

†SUV-lean data show mean ± SD.

‡P calculated vs. baseline values.

TD = tracer dose; CR = complete response; PR = partial response; NR = no response.

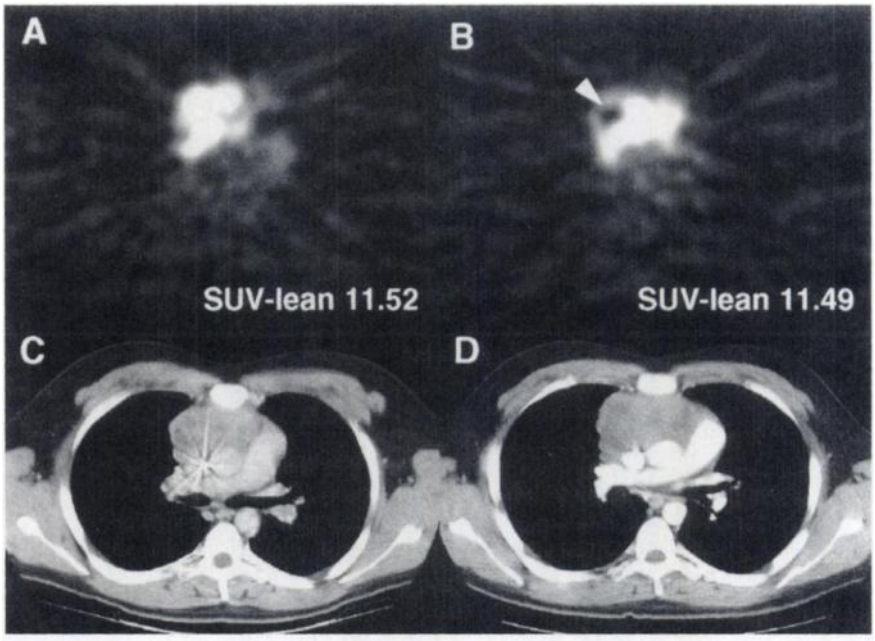

FIGURE 1. PET scans of nonresponding patient (patient 8) show maximum FDG uptake in tumor unchanged after RIT (baseline [A]; 37 d after RIT [B]), although small region of decreased FDG uptake was observed (arrowhead). CT scans show mediastinal tumor almost unchanged in size from pretreatment (C) to 37 d after RIT (D).

approach has been extended to large patient populations and to patients with previously untreated NHL.

To evaluate the response to RIT, we have performed CT at 2- to 3-mo intervals after the therapy. However, it is sometimes difficult to differentiate posttherapeutic scar tissue from viable residual tissue on CT imaging, potentially leading to incorrect management of patients. CT images after treatment are often equivocal or inconclusive because of distortion of anatomic structures (*24*). Identification of nodal involvement with CT imaging is largely based on lymph node size, but even small nodes may harbor tumor and large nodes may be benign (*25,26*).

In the past several years, FDG PET has been used successfully to assess noninvasively the metabolic activity in cancers (*5–9*). The principle of this application is based on the observation that malignant cells are characterized by increased glucose metabolism, which can be shown on PET imaging. The FDG PET technique offers potential advantages over anatomic imaging methods for monitoring treatment response, including the abilities to characterize tumor tissue essentially independently of morphologic parameters and to measure tissue glucose metabolism quantitatively.

This study estimated the metabolic response of non-

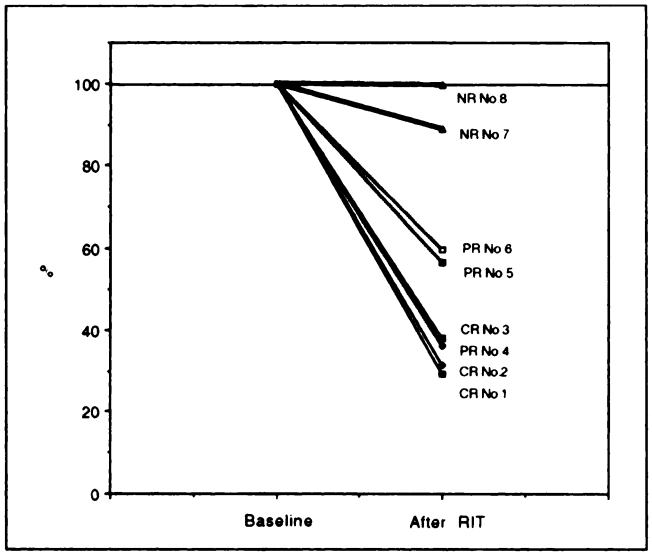

FIGURE 2. Percentages of SUV-lean after RIT relative to baseline value (patients 1–8). PET was performed at baseline and at 33–70 d after RIT. NR = no response; PR = partial response; CR = complete response.

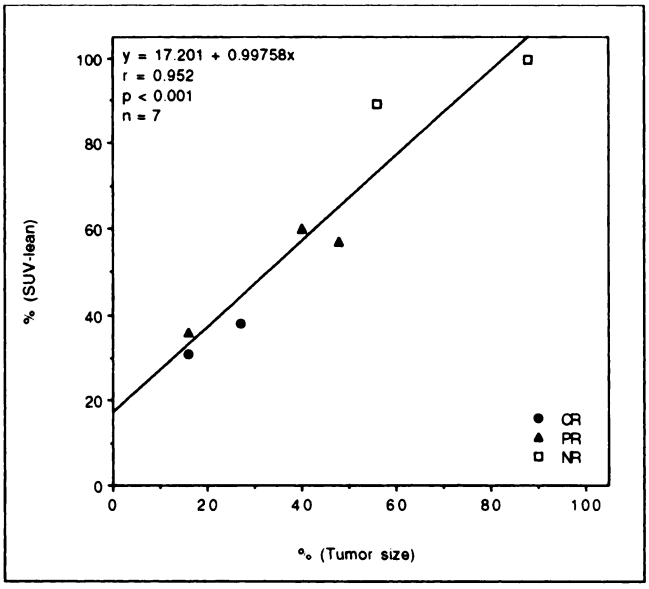

FIGURE 3. Correlation between percentage of SUV-lean and tumor size after RIT, relative to baseline values (patients 2–8). PET was performed at baseline and at 33–69 d after RIT. Time between PET and CT scans was 0–16 d. In patient 1, tumor size was not available after RIT. PR = partial response; CR = complete response; NR = no response.

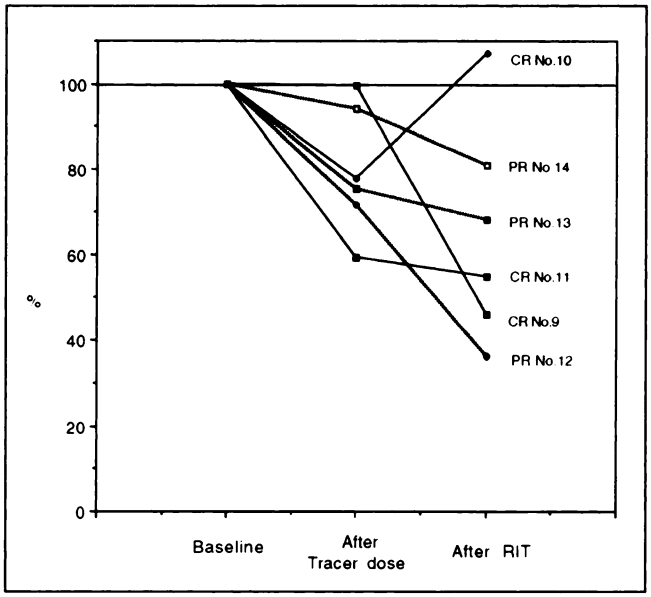

FIGURE 4. Percentages of SUV-lean after tracer dose and after RIT relative to baseline values (patients 9–14). PET was performed at baseline, at 6–7 d after tracer dose, and at 5–7 d after RIT. CR = complete response; PR = partial response.

Hodgkin's B-cell lymphoma to ^{131}I-anti-B1 (CD20) RIT using FDG PET. This is a new form of treatment using both immunologic effects and radiation damage as methods to kill tumors. In our results, baseline tumor glucose metabolism (SUV-lean) did not predict the response of NHL to treatment. This finding, albeit based on a small sample size, was not completely consistent with data reported by Okada et al. (*27*), who showed that the prognoses of patients with newly diagnosed lymphoma seem to correlate with the degree of tumor FDG uptake before chemotherapy or radiation therapy. The discrepancy between our results and those of Okada et al. is partly caused by differences in treatment methods and probably because many of our patients had received prior treatment. We also showed that SUV-lean at 1–2 mo after RIT correlated well with the ultimate best response of NHL to RIT, and that the decreases in SUV-lean in responders were almost parallel to the decreases in tumor size measured by CT (Fig. 3). In contrast, SUV-lean obtained early after tracer dose or RIT often, but not consistently, declined in responding patients (Fig. 4). These findings suggest that tumor metabolic response to RIT may be relatively gradual in responding patients and that PET imaging very early after treatment may fail to reliably assess the long-term therapeutic effect.

Hoekstra et al. (*18*) estimated the response to chemotherapy in patients with malignant lymphoma using planar FDG imaging (i.e., using the same radiotracer with an imaging method less sensitive than PET) and showed that effective treatment sharply reduced tumor metabolic activity within days and before volume response, whereas abnormal uptake persisted in patients with treatment failure. In studies of patients with breast cancer (*16,28*), FDG PET scans predicted the response to chemohormonotherapy or chemotherapy more rapidly than present conventional radiologic and clinical methods. These data show that tumor glucose metabolism may decline rapidly after effective chemotherapy.

In contrast, with radiation therapy, metabolic changes appear to be more gradual than those after chemotherapy. PET studies at 4 mo after completion of radiation therapy more accurately reflected disease status than those at 1 mo after treatment in patients with head and neck cancers, because the early responses were often quite small (*19*). Haberkorn et al. (*15*) performed FDG PET before and after radiation therapy in patients with recurrent colorectal cancers and showed that a significant decrease in FDG uptake was observed only in 50% of patients, despite good palliative results. They explained these findings as the result of "inflammatory reactions" caused by radiation injury, which may last for the first 6 mo after the end of treatment (*29*). Therefore, the time course of metabolic response to treatment may vary in different types of cancer and in different kinds of treatment.

In our results, FDG uptake in NHL decreased relatively gradually after effective RIT. It is possible that this decline in FDG uptake is more gradual than has been reported previously as a result of chemotherapy and may be because of the mechanism at cell death after RIT. The decline rate of FDG uptake after RIT suggests that tumor cell death may be

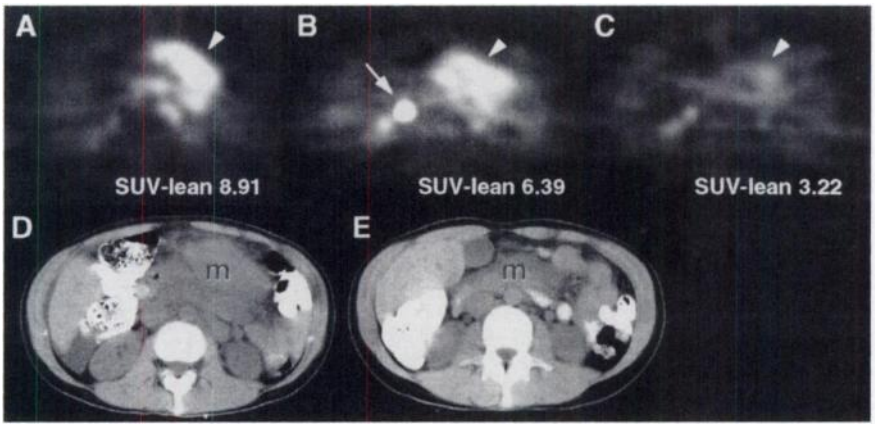

FIGURE 5. PET scans of patient 12 with partial response show rapid metabolic response to RIT in abdominal tumor (arrowheads) (baseline [A]; 6 d after tracer dose [B]; 6 d after RIT [C]). Arrow indicates FDG uptake in normal right kidney. CT scans show tumor size (m) has decreased markedly and ascites has disappeared after treatment (baseline [D]; 41 d after RIT [E]).

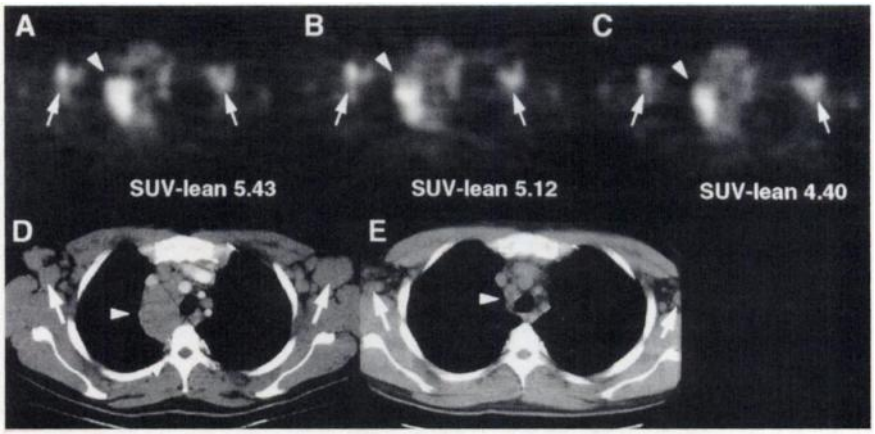

FIGURE 6. PET scans of patient 14 with partial response show gradual metabolic response to RIT in mediastinal tumor (arrowheads) and bilateral axillary lymph nodes (arrows) (baseline [A]; 6 d after tracer dose [B]; 6 d after RIT [C]). SUV-lean data show FDG uptake of mediastinal tumor. CT scans show reduction of size in mediastinal tumor (arrowheads) and bilateral axillary lymph node enlargement (arrows) after treatment (baseline [D]; 50 d after RIT [E]).

a gradual process. This is consistent with our clinical observations that tumor shrinkage can be gradual, but continuous, for extended times after RIT. In 4 of the 6 responding patients who underwent PET 3 times, FDG uptake significantly declined after the tracer dose. This observation was consistent with our previous data and probably was the result of unlabeled antibody effects, which may be mediated by anti-B1 recruitment of immune effectors or antiproliferative signals mediated directly through CD20 binding (*4*). In patient 10, who went into CR, it is possible that the transient increase in FDG uptake seen on PET after RIT was the result of antibody-induced inflammation at the tumor site. This would agree with our clinical observations that erythema and urticaria developed at the tumor sites in some patients soon after infusion of the unlabeled antibody predose (*20*).

Of the 14 NHL patients studied, the first 8, who had relapsed after previous treatment, underwent PET twice over 33–70 d, whereas the next 6 patients, who had been untreated previously, were scanned 3 times within 2 wk. We assume that these differences in the history of treatment do not significantly affect statistical analysis of PET data, because the 8 patients had been given no therapy for at least 1 mo before baseline PET studies and showed high tumor activity at the baseline PET. Another potential limitation of our study, in addition to the relatively small sample size, is that we estimated FDG uptake in 1 dominant lesion in each patient. Our clinical criteria defining the tumor response to treatment were based on all detectable lesions. Thus, in a patient with multiple lesions, it is possible that the metabolic response to RIT measured in a single lesion is not always identical to the anatomic criteria. However, the excellent correlation between metabolic response on PET and anatomic response on CT suggests our method of analysis to be valid. Furthermore, with our PET scanner, quantitative measurement of FDG uptake at all lesions was not possible. Moog et al. (*11*) reported that whole-body FDG PET may be more accurate for detecting nodal lymphoma than CT. Although the role of whole-body FDG PET during and after treatment is evolving, whole-body PET is likely to be very helpful for monitoring tumor metabolic activity after RIT and other treatments.

CONCLUSION

FDG PET data obtained 1–2 mo after RIT correlated well with the response of NHL to RIT, whereas early PET data after tracer dose and after RIT did not appear to be consistently useful for early predictions of response, because tumor metabolic response to RIT is relatively gradual. FDG PET appears to be a useful tool for monitoring response to RIT, based on this initial study. More extensive clinical evaluation is recommended.

ACKNOWLEDGMENT

This study was supported by the National Cancer Institute, grants CA52880, CA53172, CA56731, and MO1-RR-00042.

REFERENCES

1. Johnson PW, Rohatiner AZ, Whelan JS, et al. Patterns of survival in patients with recurrent follicular lymphoma: a 20-year study from a single center. *J Clin Oncol.* 1995;13:140–147.
2. Fisher RI, Gaynor ER, Dahlberg S, et al. Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma. *N Engl J Med.* 1993;328:1002–1006.
3. Armitage JO. Treatment of non-Hodgkin's lymphoma. *N Engl J Med.* 1993;328: 1023–1030.
4. Kaminski MS, Zasadny KR, Francis IR, et al. Iodine-131-anti-B1 radioimmunotherapy for B-cell lymphoma. *J Clin Oncol.* 1996;14:1974–1981.
5. Avril N, Dose J, Janicke F, et al. Metabolic characterization of breast tumors with positron emission tomography using F-18 fluorodeoxyglucose. *J Clin Oncol.* 1996;14:1848–1857.
6. Inokuma T, Tamaki N, Torizuka T, et al. Evaluation of pancreatic tumors with positron emission tomography and F-18 fluorodeoxyglucose: comparison with CT and US. *Radiology.* 1995;195:345–352.
7. Kubota K, Matsuzawa T, Fujiwara T, et al. Differential diagnosis of lung tumor with positron emission tomography: a prospective study. *J Nucl Med.* 1990;31: 1927–1932.
8. Torizuka T, Tamaki N, Inokuma T, et al. In vivo assessment of glucose metabolism in hepatocellular carcinoma with FDG PET. *J Nucl Med.* 1995;36:1811–1817.
9. Wahl RL, Quint LE, Greenough RL, Meyer CR, White RI, Orringer MB. Staging of mediastinal non-small cell lung cancer with FDG PET, CT, and fusion images: preliminary prospective evaluation. *Radiology.* 1994;191:371–377.
10. Lapela M, Leskinen S, Minn HR, et al. Increased glucose metabolism in untreated non-Hodgkin's lymphoma: a study with positron emission tomography and fluorine-18-fluorodeoxyglucose. *Blood.* 1995;86:3522–3527.
11. Moog F, Bangerter M, Diederichs CG, et al. Lymphoma: role of whole-body 2-deoxy-2-[F-18]fluoro-D-glucose (FDG) PET in nodal staging. *Radiology.* 1997;203:795–800.

12. Newman JS, Francis IR, Kaminski MS, Wahl RL. Imaging of lymphoma with PET with 2-[F-18]-fluoro-2-deoxy-D-glucose: correlation with CT. *Radiology.* 1994;190:111–116.
13. Rodriguez M, Rehn S, Ahlstrom H, Sundstrom C, Glimelius B. Predicting malignancy grade with PET in non-Hodgkin's lymphoma. *J Nucl Med.* 1995;36: 1790–1796.
14. Paul R. Comparison of fluorine-18-2-fluorodeoxyglucose and gallium-67 citrate imaging for detection of lymphoma. *J Nucl Med.* 1987;28:288–292.
15. Haberkorn U, Strauss LG, Dimitrakopoulou A, et al. PET studies of fluorodeoxyglucose metabolism in patients with recurrent colorectal tumors receiving radiotherapy. *J Nucl Med.* 1991;32:1485–1490.
16. Jansson T, Westlin JE, Ahlstrom H, Lilja A, Langstrom B, Bergh J. Positron emission tomography studies in patients with locally advanced and/or metastatic breast cancer: a method for early therapy evaluation? *J Clin Oncol.* 1995;13:1470–1477.
17. Torizuka T, Tamaki N, Inokuma T, et al. Value of fluorine-18-FDG-PET to monitor hepatocellular carcinoma after interventional therapy. *J Nucl Med.* 1994;35:1965–1969.
18. Hoekstra OS, Ossenkoppele GJ, Golding R, et al. Early treatment response in malignant lymphoma, as determined by planar fluorine-18-fluorodeoxyglucose scintigraphy. *J Nucl Med.* 1993;34:1706–1710.
19. Greven KM, Williams DW, Keyes JW Jr, et al. Positron emission tomography of patients with head and neck carcinoma before and after high dose irradiation. *Cancer.* 1994;74:1355–1359.
20. Wahl RL, Zasadny KR, MacFarlane D, et al. Iodine-131 anti-B1 antibody for B-cell lymphoma: an update on the Michigan Phase I experience. *J Nucl Med.* 1998;39:21S–27S.
21. Kaminski MS, Zasadny KR, Francis IR, et al. Radioimmunotherapy of B-cell lymphoma with [^{131}I]anti-B1 (anti-CD20) antibody. *N Engl J Med.* 1993;329:459–465.
22. Toorongian SA, Mulholland GK, Jewett DM, Bachelor MA, Kilbourn MR. Routine production of 2-deoxy-2-[^{18}F]fluoro-D-glucose by direct nucleophilic exchange on a quaternary 4-aminopyridinium resin. *Int J Rad Appl Instrum [B].* 1990;17:273–279.
23. Zasadny KR, Wahl RL. Standardized uptake values of normal tissues at PET with 2-[fluorine-18]-fluoro-2-deoxy-D-glucose: variations with body weight and a method for correction. *Radiology.* 1993;189:847–850.
24. Mukherji SK, Mancuso AA, Kotzur IM, et al. Radiologic appearance of the irradiated larynx. Part II. Primary site response. *Radiology.* 1994;193:149–154.
25. Arita T, Kuramitsu T, Kawamura M, et al. Bronchogenic carcinoma: incidence of metastases to normal sized lymph nodes. *Thorax.* 1995;50:1267–1269.
26. Bailet JW, Abemayor E, Jabour BA, Hawkins RA, Ho C, Ward PH. Positron emission tomography: a new, precise imaging modality for detection of primary head and neck tumors and assessment of cervical adenopathy. *Laryngoscope.* 1992;102:281–288.
27. Okada J, Yoshikawa K, Imazeki K, et al. The use of FDG PET in the detection and management of malignant lymphoma: correlation of uptake with prognosis. *J Nucl Med.* 1991;32:686–691.
28. Wahl RL, Zasadny K, Helvie M, Hutchins GD, Weber B, Cody R. Metabolic monitoring of breast cancer chemohormonotherapy using positron emission tomography: initial evaluation. *J Clin Oncol.* 1993;11:2101–2111.
29. Hellman S. Principles of cancer management: radiation therapy. In: DeVita VTJ, Hellman S, Rosenberg SA, eds. *Cancer: Principles and Practice of Oncology.* 5th ed. Philadelphia, PA: Lippincott-Raven; 1997:307–332.