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FDG-PET for predicting the prognosis of malignant lymphoma

Junichi OKADA,* Hiroshi OONISHI,* Kyosan YOSHIKAWA,** Jun ITAMI,** Kimiichi UNO,** Keiko IMASEKI** and Noboru ARIMIZU**

*Department of Radiology, Narita Red Cross Hospital
**Department of Radiology, Chiba University Hospital

To evaluate the usefulness of FDG-PET as a predictor of prognosis, 34 patients with untreated malignant lymphoma in the head and neck region were studied. After FDG-PET and treatment, they were observed from 15 to 50 months. Tumors which were aggressive and resistant to treatment tended to show high uptake of FDG. The survival rate of patients with high uptake of FDG, DAR ≥ 8, was lower than the rate of the other patients. It is considered to be useful to add FDG uptake of the tumor to other prognostic factors for predicting the prognosis.

Key words: ^{18}F-fluoro-deoxy-glucose (FDG), positron emission tomography, malignant lymphoma, prediction of prognosis

INTRODUCTION

IN OUR EARLY EXPERIENCE, higher uptake of ^{18}F-fluoro-deoxy-glucose (FDG) and higher glucose metabolism was observed in lymphomas which showed poor response to treatment.[1] The uptake of FDG correlated with the proliferative activity of the lymphoma, which was pathologically estimated.[2] It was reported that the proliferative activity was helpful for grading and predicting prognosis.[3,4] Consequently, positron emission tomography with FDG (FDG-PET) is considered to be promising as a predictor of cancer prognosis.

FDG-PET is applied to various kinds of malignant tumors including musculo-skeletal tumors,[5,6] liver tumors[7] and melanoma,[8] lymphomas,[1,2,9] etc. FDG-PET was used as an imaging procedure, and FDG uptake was compared to histological grading and tumor viability. In gliomas, FDG uptake may predict the survival rate of patients.[10] However, relationship between the initial uptake of FDG and the long term survival rate has not been fully studied in malignant lymphoma.

We have accumulated FDG-PET and clinical experience. Thirty-four patients, in whom FDG uptake of lymphomas had been measured before anti-cancer treatment, were observed for at least 15 months after the end of the treatment. In this study, the PET and clinical data of patients with malignant lymphoma were studied to evaluate the usefulness of FDG-PET as a predictor of the prognosis.

PATIENTS AND METHODS

Thirty-four patients, from 15 to 85 years old, with untreated malignant lymphoma in the head and neck region were studied. Three patients had Hodgkin's disease, and the other 31 patients had non-Hodgkin's lymphomas (NHLs). The 31 patients were diagnosed according to the Working Formulation for clinical usage. They were divided into low, intermediate, and high-grade malignancies by fresh biopsies[11] (Table 1). The pathological diagnosis, clinical staging by Ann Arbor classification, and mean tumor diameter at the beginning of the treatment of all patients were also listed in Table 1. After FDG-PET and the other examinations, they were treated by radiotherapy and/or chemotherapy, including Bleomycin, Vincristine, Cyclophosphamide, Adriamycin, Dexamethasone and Etoposide. When tumors disappeared on CT images by the treatment, we regarded this as "remission". When a small lesion remained after the treatment, a biopsy was performed at the lesion, and whether a remission occurred or not was pathologically diagnosed. They were observed for at least 15 months to fifty months after

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For reprint contact: Junichi Okada, M.D., Department of Radiology, Narita Red Cross Hospital, 90–1, Iida-cho, Narita, Chiba 286, JAPAN.

Table 1 Patient list

Age	Disease grade*	Subtype**	Tumor diameter (mm)***	Stage (Ann Arbor)	Treatment	DAR	Complete remission	Relapse	Prognosls (observation period, months)
63	NHL intermediate	diffuse, mixed	20.2	2	Chemo	2.0	+	–	survive (41)
50	NHL intermediate	diffuse, large	30.4	2	Radiation	12.0	+	–	survive (49)
43	NHL intermediate	diffuse, large	24.3	2	Radiation	4.7	+	–	survive (48)
66	NHL intermediate	diffuse, large	14.0	2	Radiation	5.4	+	–	survive (24)
35	Hodgkin mixed cellularity		23.0	3	Chemo	4.8	+	–	survive (48)
56	NHL intermediate	diffuse, mixed	35.0	1	Radiation	4.1	+	–	survive (45)
77	NHL intermediate	diffuse, mixed	25.5	2	Chemo	5.3	+	–	died by other disease (4)
60	NHL intermediate	foll., large	19.0	1	Chemo	5.5	+	–	survive (38)
77	NHL intermediate	diffuse, large	33.9	2	Chemo Radiation	4.4	+	–	survive (43)
39	Hodgkin mixed cellularity		35.7	3	Chemo Radiation	5.7	+	–	survive (41)
56	NHL low	small, lympho	30.9	4	Radiation Chemo	2.4	+	–	survive (40)
54	NHL intermediate	diffuse mixed	32.4	2	Chemo	10.4	+	–	survive (35)
51	NHL intermediate	diffuse, mixed	21.8	1	Chemo Radiation	3.3	+	–	survive (32)
60	NHL intermediate	diffuse, large	34.0	1	Radiation	12.9	+	–	survive (31)
44	NHL intermediate	diffuse, large	50.0	2	Chemo Radiation	5.0	+	–	survive (31)
59	NHL intermediate	diffuse, large	19.0	2	Chemo	3.8	+	–	survive (27)
52	NHL intermediate	diffuse, large	85.0	1	Chemo	9.7	+	–	survive (22)
81	NHL intermediate	diffuse, large	69.0	2	Radiation Chemo	6.0	+	–	survive (22)
22	Hodgkin nodular sclerosis		90.0	2	Chemo Radiation	9.5	+	–	survive (21)
16	NHL intermediate	diffuse, mixed	32.0	1	Chemo Radiation	7.5	+	–	survive (22)
53	NHL intermediate	diffuse, large	25.0	1	Radiation	8.0	+	–	survive (15)
70	NHL low	foll., mixed	25.0	3	Radiation Chemo	8.0	+	–	survive (15)
42	NHL intermediate	diffuse, large	25.0	3	Chemo	5.0	+	+	survive (45)
69	NHL intermediate	diffuse small cleaved	66.3	1	Radiation	9.4	+	+	died (26)
84	NHL high	immuno	34.6	1	Radiation	9.8	+	+	died (15)
63	NHL intermediate	diffuse, large	42.4	1	Radiation	9.4	+	+	died (14)
71	NHL intermediate	diffuse, large	30.0	1	Chemo	5.4	+	+	died (7)
60	NHL intermediate	diffuse, mixed	33.0	4	Chemo	3.1	+	+	died (24)
85	NHL intermediate	diffuse, large	61.0	2	Radiation Chemo	12.6	–		died (2)

Age	Disease grade*	Subtype**	Tumor diameter (mm)***	Stage (Ann Arbor)	Treatment	DAR	Complete remission	Relapse	Prognosls (observation period, months)
84	NHL intermediate	diffuse, large	52.0	3	Chemo	12.4	–		died (4)
49	NHL high	immuno	28.2	4	Chemo	15.3	–		died (7)
78	NHL intermediate	diffuse, large	31.1	4	Chemo	24.5	–		died (5)
73	NHL intermediate	diffuse, mixed	53.0	4	Chemo	13.2	–		died (1)
58	NHL intermediate	diffuse, mixed	36.0	2	Radiation	8.3	–		died (6)

*NHL: non-Hodgkin's lymphoma, pathological grading classified by Working Formulation
**pathological subtype classified by Working Formulation
foll.; follicular, lympho; lymphocytic, immuno; immunoblastic
***mean tumor diameter

the treatment. The content of the treatment and the prognosis were listed in Table 1.

FDG-PET Techniques

In Chiba University Hospital, FDG was synthesized by CYPRIS and CUPID, a cyclotron system and drug-synthesizer system made by Sumitomo Heavy Industries. The patients were positioned to obtain PET images on the plane in which the tumors were shown at maximum size on X-ray CT. After transmission scan for attenuation correction, about 148 MBq (4 mCi) of FDG was injected intravenously in a fasting state longer than twelve hours. Beginning 60 minutes after the injection, a 5 minute scan was acquired by means of a Shimadzu-SET 130W (HEADTOME III) PET scanner, whose spatial resolution was 1.04 cm FWHM.

FDG Activity was measured by setting a 10 × 10-mm square region of interest (ROI) on the PET image. A tumor ROI was set in the area where FDG activity was highest in the tumor. From the tumor activity, the differential absorption ratio (DAR) of FDG-to-tumor was calculated. The DAR was derived from the following equation[12]:

DAR = tumor activity / (injected dose / body weight).

Statistical Analysis

Student's t-test was used to compare mean values between the groups. Survival was measured from the beginning of treatment until death or the time of the last follow-up. The survival rate was estimated by the Kaplan-Meier method, and the statistical difference between survival curves was determined by the log-rank test.[13] Multivariate analysis by means of the Cox proportional hazards model[14] was used to test whether the following covariates had a significant impact on survival: DAR, age, histological grading by Working Formulation, tumor size, and staging by Ann Arbor classification. Covariates were included in the model by means of the maximum partial likelihood ratio test. Covariates were tested for their independent effects.

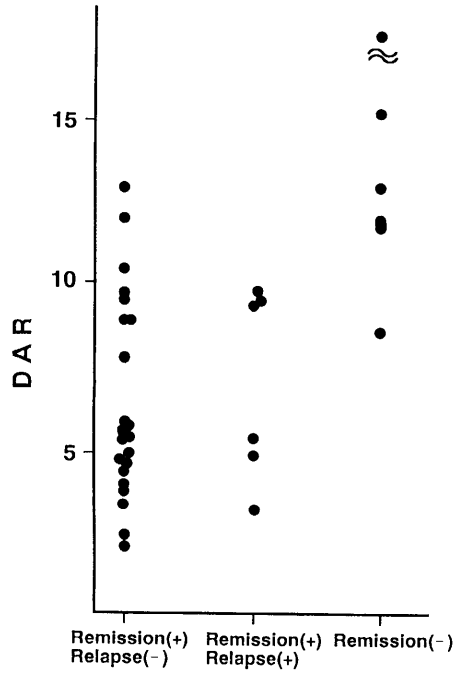

Fig. 1 Plot of FDG uptake (DAR) in patients with lymphoma. The patients were divided into three groups. Group 1: remission was obtained and relapse have not been observed. Group 2: remission was obtained but relapse occurred. Group 3: remission was not obtained. The FDG uptake (DAR) of group 1, 2 and 3 was 6.4 ± 3.0, 7.0 ± 2.9 and 14.4 ± 5.5. The FDG uptake of group 3 was higher than the other groups ($p < 0.02$).

RESULTS

According to the prognosis after the treatment, all patients were divided into three groups. Group 1 (22 patients): complete remission was obtained and no sign of tumor relapse was observed. Group 2 (six patients): remission was obtained by the treatment, but relapse occurred. Group 3 (6 patients): remission was not obtained. Death occurred in five patients in Group 2 and in six patients in Group 3. The DAR of all patients was plotted in Figure 1.

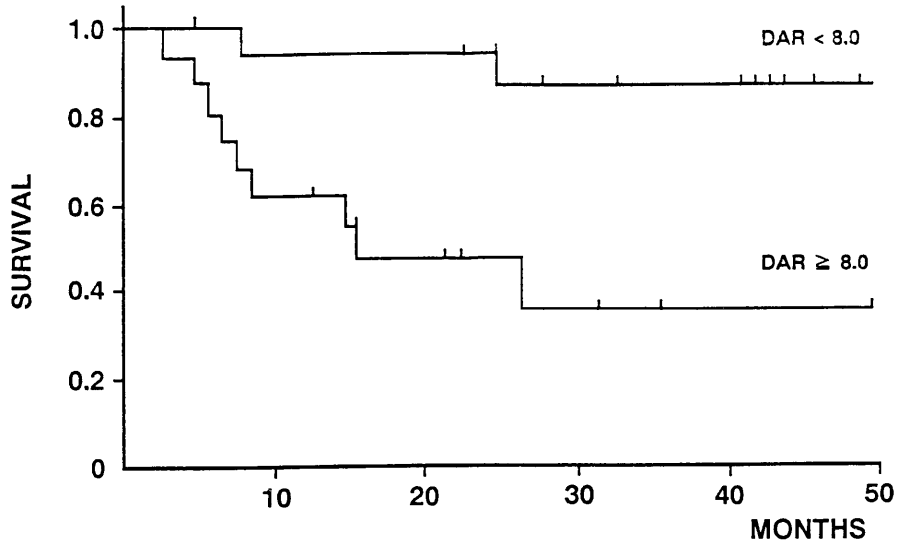

Fig. 2 Survival rate of patients with malignant lymphoma. The patients were divided into two groups according to initial FDG uptake before treatment; DAR < 8 (n = 18), DAR ≥ 8 (n = 16).

Table 2 Cox proportional hazards models: prognostic factors influencing survival

Covariate	Coefficient
Age	0.0702 ($p < 0.01$)
Pathological grading	0.294 ($p = 0.63$)
Size	0.0228 ($p = 0.29$)
Staging by TNM	0.833 ($p = 0.033$)
DAR	0.195 ($p = 0.016$)

The mean value ± standard deviation for Groups 1, 2, and 3 was 6.4 ± 3.0, 7.0 ± 2.9, and 14.4 ± 5.5, respectively. The DAR of Group 3 was statistically higher than that of the other groups ($p < 0.02$). The difference between Group 1 and Group 2 was not significant.

The survival rate of patients was calculated by the Kaplan-Meier method. The patients with a DAR higher than 8 showed a lower survival rate than the patients with a lower DAR (Fig. 2). The difference between the two groups was significant ($p < 0.005$). We set the cutoff at 6, 7, 8, 9 and 10 and tested the differences between the two groups. The statistical difference was largest when we use the 8 cutoff.

A Cox proportional hazards model was used to test the prognostic factors of DAR, age, pathological grading of malignancy, tumor size measured by X-ray CT and staging by the Ann Arbor classification (Table 2). DAR was confirmed as a prognostic factor as well as age and staging.

DISCUSSION

In our early experience, we reported that low accumulation of FDG was observed in low-grade NHL and high accumulation was observed in high-grade NHL. FDG-PET seemed to be useful for grading lymphomas.[1] In Japan, the number of intermediate-grade NHL was much larger than the number of other lymphomas. Besides pathological grading, useful methods for grading and predicting prognosis were expected to be developed. Ki-67 immunostainning is one of the methods. A monoclonal antibody, Ki-67, reacts with a nuclear antigen present in cells in the Gl, S, G2 and M phases of the cell cycle but not in the G0. The number of Ki-67 positive cells showed tumor proliferative activity and it was reported that patients with a high number had lower survival rates. This has been helpful in the prognosis of malignant lymphoma.[3,4] In a previous report by us,[2] the tumor accumulation of FDG correlated with Ki-67 positivity ($r = 0.67$). Ki-67 immunostainning was performed with fresh biopsy specimens. On the other hand, PET can be examined *in vivo*.

In the study, we also obtained the value given by kinetic rates of glucose, $k_1k_3/(k_2+k_3)$, by means of the graphic method demonstrated by Patlak and Gjedde et al.[15,16] The value was closely connected with glucose metabolism.[17] In our study, the kinetic rate correlated well with the DAR measured at 60 minute after injection in lymphomas. The DAR, which is obtained without arterial blood sampling, can be used as an indicator of glucose metabolism in the tumor.[2] An optimal time point for measuring the tumor activity of FDG has not been defined.[18] In all of our patients, the activities increased continuously for 60 minutes. Considering limited machine time and the good correlation between $k_1k_3/(k_1+k_2)$ and the DAR measured at 60 minute after the injection, we have been using the latter value.

To evaluate the usefulness of FDG-PET in predicting the prognosis, the tumor uptake of FDG before treatment was compared with the prognosis in 34 patients with lymphoma in the head and neck region. Six lymphomas,

which were not controlled by the initial series of treatment, showed significantly higher uptake of FDG. Cancer death occurred in all cases during the period of observation. Remission was observed in the other 28 patients.

In six of the 28 patients, tumor relapse was observed during the period of observation. Death occurred in five of the 6 patients. Before beginning the treatment, FDG-PET seemed to be helpful for detecting tumors which are very aggressive and resistant to treatment. However, in patients with remission, no significant difference in FDG uptake was observed between patients with and without tumor relapse. It was unable to differentiate relapsers from non-relapsers.

When we set a cut-off value for DAR = 8, the survival rates of patients in whom tumor showed higher uptake of FDG (DAR $\geq$ 8) was significantly lower than those of the other patients. To the impact on survival of the uptake of FDG, we used the Cox proportional hazards model. Age, pathological grading by Working Formulation, tumor size and staging by the Ann Arbor system were included. Age, staging and DAR showed significant impact on survival. In clinical practice, many factors, for example age, stage, tumor size, pathological subtype, LDH, B symptom and the number of extranodal sites, are evaluated in predicting prognosis for a patient with malignant lymphoma. Many immunohistological tumor marker techniques have also been examined. One of them is Ki-67 staining. A useful method and a useful combination of some prognosticators are expected to be developed. In this study, the number of materials, especially Hodgkin's disease and NHL, except intermediate grade, is limited. However, it is considered to be useful to add FDG-PET to other prognostic factors for the prediction of prognosis.

In summary, tumors which were aggressive and resistant to treatment tended to show high uptake of FDG. The survival rate for the patients with high uptake of FDG was lower than that for the other patients. FDG uptake had a significant impact on survival in the Cox proportional hazards model. FDG-PET is considered to be useful for predicting prognosis before treatment.

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