Annals of Nuclear Medicine Vol. 16, No. 5, 337–345, 2002

Clinical impact of whole body FDG-PET on the staging and therapeutic decision making for malignant lymphoma

Masayuki SASAKI, Yasuo KUWABARA, Hirofumi KOGA, Makoto NAKAGAWA, Tao CHEN, Kouichirou KANEKO, Kazutaka HAYASHI, Katsumasa NAKAMURA and Kouji MASUDA

Department of Clinical Radiology, Graduate School of Medical Sciences, Kyushu University

Objectives: The aim of this study is to evaluate the clinical impact of whole-body FDG-PET for the pre-therapeutic evaluation of malignant lymphoma and compared to that of ^{67}Ga-scintigraphy when added to non-RI examinations. ***Methods:*** We examined 46 patients with malignant lymphoma including 42 newly diagnosed cases and 4 relapsed cases. Whole-body FDG-PET was started 63 minutes after the administration of FDG with ECAT EXACT HR^{+}. The clinical stage of each patient was determined based on the results of a non-RI examination (consisting of physical examination, CT, gastrointestinal studies and bone marrow aspiration), ^{67}Ga planar images and FDG-PET. Discrepant findings were verified based on the response to treatment and the findings of a follow-up examination more than 6 months after treatment. Finally, 152 nodal regions and 19 extranodal tissues were found to be involved by disease. ***Results:*** In the 152 nodal lesions, FDG-PET detected 54 nodal lesions in addition to 98 lesions detected by non-RI examinations, whereas ^{67}Ga-scintigraphy detected 14 additional lesions. The sensitivity of non-RI, non-RI + ^{67}Ga and non-RI + FDG was 64.5%, 73.7% and 100.0%, respectively. In 19 extranodal lesions, FDG-PET detected 5 extranodal lesions in addition to 13 lesions detected by non-RI examinations, whereas ^{67}Ga-scintigraphy detected 1 additional lesion. The sensitivity of non-RI, non-RI + ^{67}Ga and non-RI + FDG was 68.4%, 73.7% and 94.7%, respectively. When combining the FDG-PET findings with the non-RI findings, the improvement of the detectability was much higher than that when ^{67}Ga findings were combined to the non-RI findings. For the staging of lymphoma, the non-RI and non-RI + ^{67}Ga findings accurately diagnosed 76.1% and 80.4%, respectively, whereas the non-RI + FDG findings accurately diagnosed 82.6%. Finally, FDG-PET resulted in changes in the clinical management of 8 patients (17.4%). ***Conclusions:*** FDG-PET offers more information in addition to the findings of conventional diagnostic methods than ^{67}Ga-scintigraphy in order to accurately detect malignant lymphoma. FDG-PET can therefore play an important role in therapeutic decision making on lymphoma.

Key words: malignant lymphoma, FDG (^{18}F-fluorodeoxyglucose), PET (positron emission tomography), staging, management

INTRODUCTION

MALIGNANT LYMPHOMA is one of the potentially curable malignancies. Improvements in the treatment of this disease depend not only on new therapeutic techniques but also on the development of diagnostic techniques for staging. Accurate primary staging therefore remains an important prerequisite for selecting the appropriate therapeutic approach. Clinically, the usual approach for diagnosing malignant lymphoma is mainly with ^{67}Ga-scintigraphy and non-RI imaging studies including conventional radiography, CT and/or MRI, ultrasonography and gastrointestinal studies which provide both anatomic and morphologic information. Limitations to anatomical imaging arise due to the fact that those diagnostic

Received March 18, 2002, revision accepted June 3, 2002.

For reprint contact: Masayuki Sasaki, M.D., Ph.D., Department of Clinical Radiology, Graduate School of Medical Sciences, Kyushu University, 3–1–1 Maidashi, Higashi-ku, Fukuoka 812–8582, JAPAN.

E-mail: msasaki@radiol.med.kyushu-u.ac.jp

criteria are mainly based on lesion size and not on the biological behavior of the lesions. ^{67}Ga-scintigraphy plays an important role in evaluating patients with malignant lymphoma because it provides biological information independent of the lesion size. Although ^{67}Ga-scintigraphy can detect more lesions than CT in some cases, ^{67}Ga-scintigraphy has not been shown to be superior to CT for the primary staging of lymphoma.[1,2]

Fluorine-18-2-fluoro-2-deoxy-D-glucose (FDG)-positron emission tomography (PET) has shown promising results in diagnosing many malignant tumors with an increased glucose metabolism. FDG-PET has also been reported to be effective for the detection,[3,4] staging and restaging,[5–11] management[12,13] and monitoring therapy [14–16] of malignant lymphoma. Although the usefulness of FDG-PET for the staging of malignant lymphoma has so far been reported in comparison to other examinations, some anatomical imaging methods cannot be clinically excluded because anatomical information is required to select the optimal therapeutic strategy for some tumors. As a result, the additional information obtained by FDG-PET when used in addition to anatomical imaging is considered to play an important role in patient management.

In this study, we examined the usefulness of FDG-PET for the detection and staging of malignant lymphoma and compared its findings to those of ^{67}Ga-scintigraphy and non-RI examinations. Furthermore, we also evaluated and compared the clinical impact of FDG-PET on the staging and management of malignant lymphoma with that of ^{67}Ga-scintigraphy when added to non-RI examinations.

MATERIALS AND METHODS

Patients

We examined 46 patients with histologically confirmed malignant lymphoma including 3 patients with Hodgkin's disease (HD) and 43 with non-Hodgkin's lymphoma (NHL): male/female = 28/18, age range, 23–90 years; mean age, 60.4 years. Four patients with recurrent disease were included in this study, and all 4 of these patients had once obtained a complete remission after previous therapy which had been performed at least 6 months before. The classification of all 46 patients was made based on the Ann Arbor system and the histological findings are shown in Table 1. All examinations were performed within 27 days (mean 14.3 days).

This study was approved by the Committee for the Clinical Application of Cyclotron-Produced Radionuclides in Kyushu University Hospital, and written informed consent was obtained from all patients before the study.

FDG-PET

Whole body FDG-PET studies were performed with ECAT EXACT HR$^+$ (Siemens, Knoxville, USA). The data acquisition was started 63 minutes after the intravenous administration of FDG with 94.4–484.2 MBq (mean ± SD = 270.6 ± 102.5). Emission scans were obtained in a 3-dimensional mode from the head to the thigh in 9 bed positions with an acquisition time of 3 minutes each. The images were reconstructed with a filtered back projection by means of a Hanning filter (cutoff = 0.4 cycle/pixel) without attenuation correction. The axial spacial resolution was 4.2 mm of full width at half maximum. All patients fasted for at least 4 hours and their blood glucose level was 85.5–128.0 mg/d*l* (mean ± SD = 105.7 ± 11.1).

Table 1 Classification of 46 patients with lymphoma

Histology & Grade		Stage				Total
		I	II	III	IV	
HD		2	0	0	1	3
NHL	Low	0	0	1	0	1
	Intermediate	11	3	13	6	33
	High	4	1	2	1	8
	Unclassified	1	0	0	0	1
Total		18	4	16	8	46

HD: Hodgkin's disease, NHL: non-Hodgkin's lymphoma

^{67}Ga-scintigraphy

^{67}Ga scanning was performed 72 hours after the intravenous injection of 111 MBq of ^{67}Ga-citrate. Both anterior and posterior whole body planar images were simultaneously obtained with a dual-headed gamma camera GCA901A/WB (Toshiba Corp, Tokyo, Japan).

Non-RI examinations

Bolus contrast enhancement and incremental CT scans with a thickness of 10 mm were obtained with either conventional or multi-detector CT scanners. The face, neck, chest, abdomen and pelvis were systematically investigated. Lymph nodes 1 cm in size or larger were defined as lymph nodes suspected to be involved by lymphoma.

Gastrointestinal (GI) studies were performed with barium meal studies for upper GI series from the esophagus to the terminal ileum and barium enema studies for the colon and rectum.

Bone marrow biopsy specimens were obtained from either the sternum or iliac crest in order to diagnose the presence of any bone marrow infiltration.

Data analysis and standard reference

The FDG-PET images and ^{67}Ga-scintigraphy findings were visually evaluated by 3 nuclear medicine physicians without any clinical information. Non-RI examinations were evaluated by 2 radiologists.

The standard reference for the lesion was determined based on the results of non-RI examinations (consisting of

a physical examination, CT, gastrointestinal studies and bone marrow aspiration), ^{67}Ga-scintigraphy and FDG-PET. Any discrepant findings were verified based on the response to treatment and the findings of follow-up examinations performed more than 6 months after treatment. In some cases, other examinations such as MRI, ultrasonography and bone scintigraphy were also used to obtain standard reference data.

The nodal regions were classified into the following 19 regions: Waldeyer's ring [#1], right and left cervical, paraclavicular, occipital & pre-auricular [#2, #3], right and left axillar & pectral [#4, #5], mediastinal [#6], right and left hilar [#7, #8], right and left epitrochlear & brachial [#9, #10], spleen [#11], para-aortic [#12], mesenteric [#13], right and left para-iliac [#14, #15], right and left inguinal and femoral [#16, #17], right and left popliteal regions [#18, #19]. Finally, 152 out of 874 nodal regions in 46 patients were determined to be involved by lymphoma.

Nineteen extranodal tissues in 46 patients were diagnosed to be involved by lymphoma, consisting of 2 in the nasal cavity, 3 in the stomach, 3 in the intestines, 3 in the liver, 2 in the adrenal gland, 1 in the kidneys, 1 in the skin and 4 in the bone marrow.

Table 2 Detectability of nodal involvement

	^{67}Ga only	FDG only	non-RI only	non-RI + ^{67}Ga	non-RI + FDG
Sensitivity (n = 152)	44.1% (n = 67)	92.1% (n = 140)	64.5% (n = 98)	73.7% (n = 112)	100.0% (n = 152)
Specificity (n = 722)	99.7% (n = 720)	99.0% (n = 715)	99.4% (n = 718)	99.4% (n = 718)	98.8% (n = 713)
Accuracy (n = 874)	90.0% (n = 787)	97.8% (n = 855)	93.4% (n = 816)	95.0% (n = 830)	99.0% (n = 865)

^{67}Ga: ^{67}Ga-scintigraphy, FDG: FDG-PET, non-RI: non-RI examinations consisting of physical examinations, CT, gastrointestinal studies and bone marrow aspiration

RESULTS

Nodal involvement

In the 152 nodal lesions, the sensitivities of ^{67}Ga only, FDG only and the non-RI examinations were 44.1%, 92.1% and 64.5%, respectively (Table 2). In comparison to the non-RI examinations, 14 additional lesions in 10 patients were detected by the ^{67}Ga-scintigraphy findings,

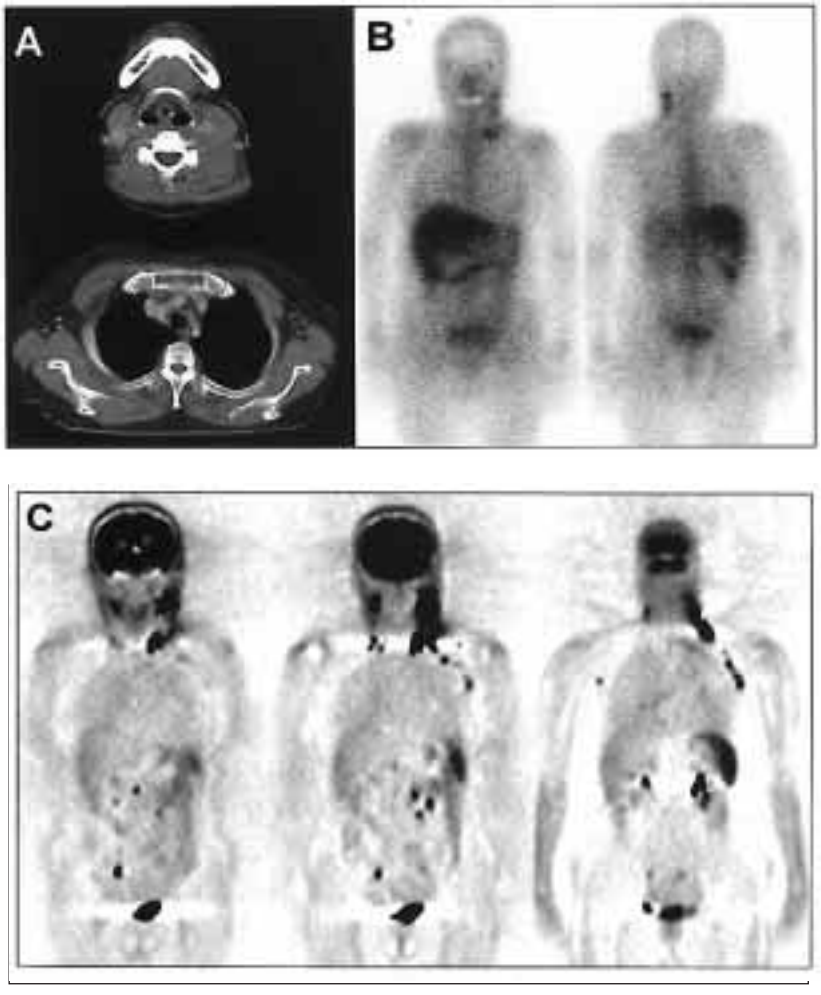

Fig. 1 A 70-year-old female patient with extensive, intermediate-grade NHL. A: CT scans demonstrated lymphadenopathy in the left cervical region while only small lymph nodes were shown in the right cervical and left axillary region. B: ^{67}Ga-scintigraphy showed a high uptake in the left cervical and left paraclavicular regions. C: FDG-PET demonstrated an abnormally high uptake in the bilateral cervical, paraclavicular, axillary, mesenteric and right parailiac nodal regions and the spleen.

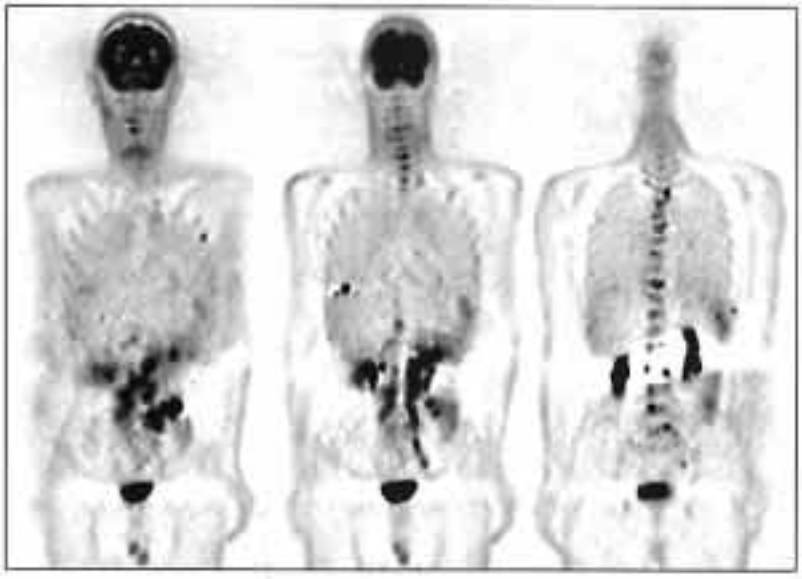

Fig. 2 A 43-year-old male patient with extensive, intermediate-grade NHL. FDG-PET demonstrated abnormally high uptakes in the abdominal para-aortic, parailiac and mesenteric regions and spleen. Multiple bone marrow involvement is also demonstrated in the spine and ribs.

and 54 additional lesions in 21 patients were detected by the FDG-PET findings. Fourteen additional lesions detected by ^{67}Ga-scintigraphy were also detected by FDG-PET. All 54 additional lesions detected by FDG-PET were smaller than 1 cm in diameter (Fig. 1). Such additional information noticeably improved detectability and resulted in 73.7% and 100% of sensitivity with non-RI + ^{67}Ga and non-RI + FDG, respectively.

In FDG-PET, twelve false-negative lesions were observed in 7 patients including 2 with high-grade and 5 with intermediate grade disease: 2 lesions in Waldeyer's ring, 2 in axillary, 1 in mediastinal, 1 in hilar, 3 in para-aortic, 1 in mesenteric, 1 in inguinal regions and 1 in the spleen. All these lesions were detected by non-RI examinations and disappeared after the completion of treatment. In 2 lesions in Waldeyer's ring, the FDG uptake in the lesions were comparable to the contralateral normal region and could not be differentiated from physiological FDG uptake in the pharyngeal region. In a patient with bulky tumors in the bilateral cervical, bilateral axillary, right hilar, para-aortic and mesenteric regions, the FDG-PET missed 5 nodal lesions and a high FDG uptake was seen only in the bilateral cervical lesions. The histological grade of this patient was intermediate. Five bulky lesions in 4 other patients did not accumulate any FDG either.

The specificity of ^{67}Ga only, FDG only and non-RI examinations was 99.7%, 99.0% and 99.4%, respectively, whereas that of non-RI + ^{67}Ga and non-RI + FDG was 99.4% and 98.8%, respectively. The FDG-PET decreased the specificity of non-RI examination because of the false-positive findings.

In FDG-PET, seven false-positive lesions were observed in 5 patients including 1 with high grade and 4 with intermediate grade: 3 in cervical, 3 in mediastinal and 1 in hilar regions. In a patient with silicosis, high FDG uptake was observed in both the mediastinal and hilar lymph nodes. CT also demonstrated enlarged lymph nodes at these sites. A follow-up CT did not show any morphological changes after the completion of treatment for lymphoma and, as a result, these lesions were diagnosed to be false-positive. In a patient, who had only one lesion located in the left cervical region, additional FDG uptake was observed in the right cervical region where CT showed small lymph nodes measuring 5 mm in size. Radiotherapy was only performed on the left cervical lesion without any adjuvant therapy because she was an aged patient. A follow-up examination after the completion of therapy did not show any evidence of a tumor in the right cervical region. A high FDG uptake in 2 cervical regions in 1 patient and 2 mediastinal regions in 2 patients was also diagnosed as false-positive. These false-positive findings were considered to be due to non-specific

Table 3 Detectability of extranodal involvement

	^{67}Ga only	FDG only	non-RI only	non-RI + ^{67}Ga	non-RI + FDG
Sensitivity (n = 19)	42.1% (n = 8)	73.7% (n = 14)	68.4% (n = 13)	73.7% (n = 14)	94.7% (n = 18)
PPV	100.0% (8/8)	87.5% (14/16)	100.0% (13/13)	100.0% (14/14)	94.7% (18/19)

^{67}Ga: ^{67}Ga-scintigraphy, FDG: FDG-PET, non-RI: non-RI examinations consisting of physical examinations, CT, gastrointestinal studies and bone marrow aspiration.
PPV: positive predictive value

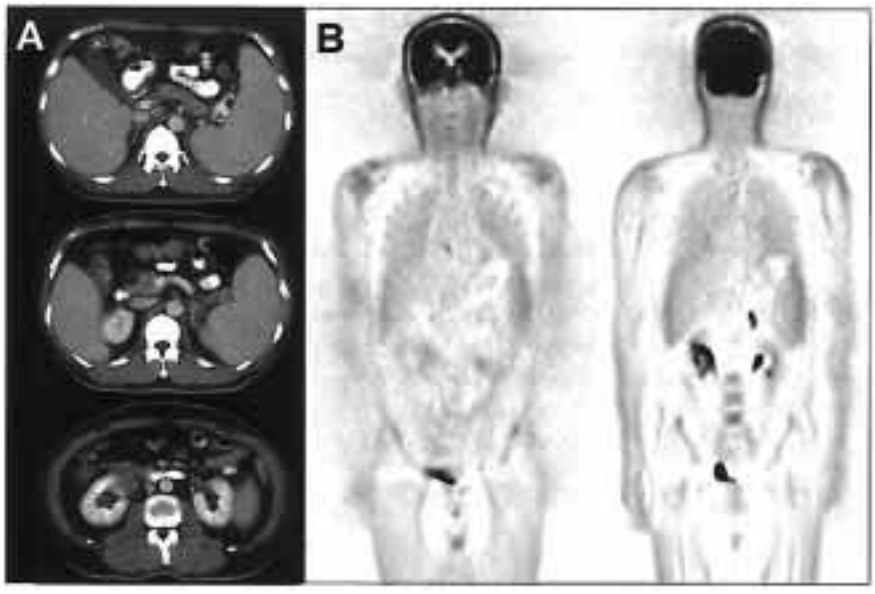

Fig. 3 A 56-year-old male patient with extensive, intermediate-grade NHL. A: CT images demonstrate splenomegaly, a left adrenal tumor and a right renal tumor. These findings disappeared after treatment. B: FDG-PET demonstrated an abnormally high uptake only in the left adrenal gland.

inflammatory change based on the clinical course and non-RI examinations which were negative at these sites.

Finally, the overall accuracy for diagnosing nodal lesions in non-RI, non-RI + ^{67}Ga and non-RI + FDG was 93.4%, 95.0% and 99.0%, respectively.

Extranodal involvement

In 19 extranodal lesions, the sensitivities of ^{67}Ga only, FDG only and the non-RI were 42.1%, 73.7% and 68.4%, respectively (Table 3). ^{67}Ga-scintigraphy detected 1 additional lesion in the occipital bone, but FDG-PET did not. This lesion was confirmed by subsequent MRI and bone scintigraphy, and it disappeared after treatment. FDG-PET detected 5 additional lesions in 4 patients: 2 in bone marrow (Fig. 2), 1 in the skin and 1 in the liver. The sensitivity of non-RI + ^{67}Ga and non-RI + FDG was 73.7% and 94.7%, respectively. Additional information obtained by FDG-PET greatly improved the sensitivity for detecting extranodal lesions.

In FDG-PET, five false-negative lesions were observed in 4 patients including 1 with high grade and 3 with intermediate grade disease: including 1 lesion in the stomach, 1 in the kidneys, 2 in the liver and 1 in the skull. All these lesions were detected by non-RI examinations and disappeared after completion of treatment. Bone marrow involvement in the occipital bone in a patient with intermediate grade lymphoma was not detected by FDG-PET because an extremely high brain uptake obscured the lesion. In a patient with high grade lymphoma, an upper GI study demonstrated a submucosal tumor in the gastric body. The lesion was found to be involved by lymphoma based on the findings of gastrointestinal endoscopy and a biopsy, and this lesion disappeared after treatment. FDG-PET could not detect any abnormalities because the FDG uptake in the stomach was homogeneous and not intense. In one patient, hepatic involvement was suggested by CT because of a diffuse hepatomegaly but there were no focal lesions. The FDG uptake in the liver was neither high nor heterogeneous (Fig. 3). In one patient, several small low density areas in the liver demonstrated by CT were considered to indicate hepatic involvement. The lesions were smaller than 1 cm and FDG-PET did not show any abnormalities. In a patient with intermediate grade lymphoma, right renal involvement measuring 3 cm in diameter was false-negative although a left adrenal lesion was positive on FDG-PET (Fig. 3).

In FDG-PET, two false-positive lesions were observed in 2 patients with intermediate-grade disease: including 1 lesion in the intestines and 1 in the liver. The FDG uptakes in these lesions were heterogeneous but not highly intense. Non-RI examinations did not show any abnormalities at these sites. They were finally determined to be inhomogeneous physiological uptakes based on the clinical follow-up. As a result, the positive predictive value of FDG-PET was 87.5% which was lower than that for either ^{67}Ga only or non-RI (100%).

Staging and management

Regarding the staging of lymphoma, ^{67}Ga only, FDG only and the non-RI findings resulted in an accurate diagnosis in 58.7%, 78.3% and 76.1%, respectively. By adding the ^{67}Ga-scintigraphy findings to the non-RI examination findings (non-RI + ^{67}Ga), two patients were accurately upstaged and the accuracy of the diagnosis improved to

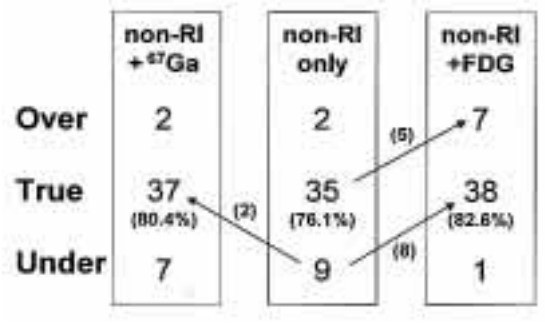

Fig. 4 Influence of the FDG-PET and ^{67}Ga-scintigraphy on the staging of lymphoma. ^{67}Ga-scintigraphy more accurately staged 2 patients than non-RI examinations did. FDG-PET accurately upstaged 8 patients but falsely upstaged 5 patients.

80.4% (Fig. 4). By adding FDG-PET to the non-RI examination findings (non-RI + FDG), eight patients were accurately upstaged and 5 patients were falsely upstaged, and thus the non-RI + FDG findings resulted in an accurate diagnosis in 82.6% of the cases.

Finally, ^{67}Ga-scintigraphy resulted in changes in the clinical management of 2 patients. On the other hand, FDG-PET resulted in changes in the clinical management of 8 patients (17.4%) including 6 patients with intermediate-grade NHL and 2 with high-grade NHL. In 5 patients, consolidation therapy with 3 additional cycles of chemotherapy was performed after completing the initial chemotherapy. In the other 3 patients, the radiation field was expanded based on the FDG-PET findings. The management plans were not changed in the 5 falsely upstaged patients.

DISCUSSION

Increased FDG uptake in lymphoma was first reported by Paul et al.[17] Since then, many reports have demonstrated the clinical usefulness of FDG-PET for the detection,[3,4] staging,[5–11] management[12,13] and monitoring the treatment response[14–16] of lymphoma.

For detecting nodal involvement, the sensitivity of FDG-PET has been reported to range from 80 to 100%.[3–13] The sensitivity of FDG-PET has also been reported to be superior to that of both CT scans (ranging from 82 to 95%)[6,7,11] and ^{67}Ga-scintigraphy (ranging from 40 to 95%).[2,3,17–20] In this study, the sensitivity of FDG-PET for the detection of nodal involvement was 92.1% and it was higher than that for both non-RI examinations and the ^{67}Ga-scintigraphy. Although the detectability of FDG-PET was superior to non-RI examinations, non-RI examinations cannot be excluded because anatomical information is necessary for planning patient management. In comparison to the non-RI examinations, FDG-PET detected 54 additional nodal lesions and improved sensitivity from 64.5% to 100%. Most of these lesions were detected in non-RI examinations, though they were diagnosed to be negative because they were smaller than 1 cm in diameter. These results were consistent with previous studies and therefore emphasize the importance of metabolic imaging by FDG-PET for accurately diagnosing lymphoma. Furthermore, FDG-PET was superior to ^{67}Ga-scintigraphy because ^{67}Ga-scintigraphy detected only 14 additional lesions, so that there was a +8.8% improvement in sensitivity. FDG-PET should therefore be used as a complementary method for non-RI examinations rather than ^{67}Ga-scintigraphy in order to accurately diagnose lymphoma.

The superiority of FDG-PET for the detection of extranodal lesions has also been demonstrated.[8,9,11, 21] The sensitivity of FDG-PET has been reported to be 67–100%. In our study, the sensitivity of FDG-PET was 73.7% and it was higher than that of non-RI examinations. This result is consistent with previous reports. Furthermore, FDG-PET noticeably improved sensitivity when added to non-RI examinations, and improvement was minimal when ^{67}Ga-scintigraphy was added.

Regarding the detection of bone marrow involvement, FDG-PET identified 2 additional lesions in comparison to the non-RI examinations in our study. The usefulness of FDG-PET for detecting bone marrow involvement has been reported,[8,9,11,21] and it is consistent with our results. A faint and diffuse FDG uptake in bone marrow is normally observed in the central skeleton, so that an intense and/or heterogeneous uptake is considered to represent involvement. Although the results of the bone marrow biopsy remain the gold standard for identifying bone marrow involvement, the problem is that it is routinely performed in either the sternum or iliac bone. It may miss some lesions when they are distributed heterogeneously or peripherally. Whole-body FDG-PET is considered to be a useful tool because it does not miss such lesions in either the central or peripheral regions.

The staging correctly changed in 10.9% of patients based on the FDG-PET findings in our study, and a change in the therapeutic strategy was observed in 17.4% of patients in our study. Although Jerusalem reported that FDG-PET did not offer much improvement for the staging of lymphoma,[9] many reports have demonstrated that FDG-PET plays an important role in the staging of lymphoma because from 8 to 17% of patients had their staging correctly modified based on the results of FDG-PET.[5,6,8,11] They also demonstrated that most of these patients had their therapeutic strategies changed based on the FDG-PET findings. Our results are in agreement with these previous studies. Shah et al. reported that FDG-PET resulted in a change in clinical management in 34% of patients.[12] Recently, Schöder et al. examined the usefulness of FDG-PET on the staging and management of patients with lymphoma by mailing questionnaires to the referring physicians. They observed that FDG-PET resulted in a change in the clinical staging in 44% of patients and in the therapeutic management in 62% of all

patients.[13] Although 51.9% of questionnaires were not returned, FDG-PET was found to alter staging in 21% and therapeutic management in 30% of patients even if all remaining questionnaires did not show any changes. Because accurate primary staging is important in appropriate therapeutic decision making, FDG-PET is considered to be useful for the clinical management of patients.

In this study, 7 false-positive nodal regions were observed in 5 patients, 3 in the cervical, 3 in the mediastinal and 1 in the hilar regions. In one patient, high FDG uptake was observed in both the mediastinal and hilar regions due to silicotic lymphadenopathy. Five regions in 4 patients were finally considered to be non-specific inflammatory regions based on the clinical course and non-RI examinations. A relatively high FDG uptake in inflammatory lesions could produce false-positive results in FDG-PET.[22,23]

Considering extranodal tissue, relatively intense and inhomogeneous physiological FDG uptake in several organs can result in false-positive findings. Normal physiological FDG uptake in the bowel wall, which is usually intense and irregular in shape, cannot be differentiated from abnormal uptake. Inhomogeneous FDG uptake in the liver, mimicking abnormal uptake, is sometimes observed even in a morphologically and functionally normal liver.

In this study, 2 lesions in Waldeyer's ring were false-negative. Because relatively intense physiological FDG uptake is observed in the pharyngeal region, either extremely high uptake or the apparent laterality of FDG uptake is required to diagnose it as abnormal. Neither of these findings was observed in these patients. The physiological FDG uptake could result not only in false-positive findings but also in false-negative findings.

In extranodal tissues, the physiological FDG uptake in tissue can also result in false-negative findings. Extremely high FDG uptake in the brain obscured adjacent skull bone invasion in this study. Although a retrospective reevaluation found an abnormal uptake in the skull, a routine examination could not detect any lesion. A lesion in the renal hilum could not be differentiated from an intense FDG uptake in the urine that was excreted from the kidneys. Streak artifacts due to the intense radioactivity can also result in false-negative findings when the images are reconstructed by the filtered back projection method. The normal physiological FDG uptake in the liver and the stomach, which is usually intense, especially in the gastric body and the fornix, can also obscure such lesions.

Ten bulky nodal lesions did not accumulate any FDG. Although FDG-PET showed high sensitivity for detecting lymphoma, some lesions did not show any FDG uptake. Tatsumi et al. reported FDG-PET negative bulky lesions in a patient with indolent lymphoma.[24] The FDG uptake in lymphoma has been reported to correlate with the grade of malignancy.[25–27] Leskinen-Kallio et al. also showed that the FDG uptake in low-grade lymphoma was lower than that in high and intermediate grade lymphoma.[28] Recently, sufficient or prominent FDG uptake has also been reported in low-grade lymphoma,[4,6,7,29] except for MALT-type lymphoma.[10,29,30] Only 1 patient with low-grade lymphoma was included in our study, but all his 11 nodal lesions were positive in FDG-PET. On the other hand, 10 FDG-PET negative bulky lesions were observed in 5 patients consisting of 2 patients with high grade lymphoma and 3 patients with intermediate grade lymphoma. In these patients, a high FDG uptake was observed in other lesions from the same patient. The coexistence of FDG-positive lesion and FDG-negative lesions in individual patients was reported in patients with multiple metastases from thyroid cancer.[31] This phenomenon is considered to be associated with the different degrees of differentiation in tumors which tend to occur in metastases found in the same patient. A similar phenomenon may also occur in patients with lymphoma. Further investigations, examining both the transport mechanism and the enzyme activity related to FDG uptake, may be required to clarify this phenomenon.

In this study, the detectability of ^{67}Ga-scintigraphy was extremely low in both nodal and extranodal lesions, although some lesions were additionally detected, in comparison to non-RI examinations. For ^{67}Ga-scintigraphy, the recommended activity of ^{67}Ga-citrate in adults is 370 MBq in the evaluation of malignant disease.[32] Anderson et al. observed a significant improvement in the diagnostic ability of ^{67}Ga-scintigraphy for the detection of malignant lymphoma by using an adult dose of 259–370 MBq of ^{67}Ga-citrate.[18] The dose of 111 MBq of ^{67}Ga-citrate used in this study may be insufficient to detect lymphoma, but a dose of more than 111 MBq is not covered by medical insurance in Japan. Furthermore, we obtained only planar images but not SPECT images because of the limited examination time. The application of SPECT scanning is considered to improve the sensitivity and specificity of ^{67}Ga-scintigraphy.[1,19] Although examinations with ^{67}Ga-SPECT images with high-dose ^{67}Ga-citrate are expected to improve the detectability of lymphoma, FDG-PET is still considered to be superior to ^{67}Ga-scintigraphy.[20] Furthermore, ^{67}Ga-scintigraphy is considered to be more inconvenient and costly for patients because the scanning must be performed 3 (2–4) days after administration of ^{67}Ga-citrate, whereas FDG-PET can be performed within 2 hours after administration.

Limitations

One limitation of this study is the difficulty of determining the presence of lesions because a histological diagnosis could not be obtained in most lesions. Most discrepant findings were verified based on the response to treatment and the findings of follow-up examinations performed more than 6 months after treatment, but not based on a histological analysis. Although the standard reference for

the lesions in this study may be less than perfect, it is difficult to perform biopsies on every suspected lesion. This is an unavoidable problem for such investigations.

FDG-PET without attenuation correction does not truly reflect the FDG uptake especially in regions located in the center of the body, though it has been reported to be useful for detecting lymphoma.[5,7,9,11,13] Kotzerke et al. reported that the attenuation correction did not improve the diagnostic accuracy of FDG-PET for lymphoma.[33] Furthermore, non-attenuation corrected FDG-PET was shown to provide a higher contrast between the lesion and the background which was independent of tumor localization.[34] One disadvantage of non-attenuation corrected FDG-PET is considered to be the distortion of the foci and the difficulty in assessing the anatomical localization, though they may not affect patient management because FDG-PET should be used as a method complementary to anatomical imaging methods. FDG-PET without attenuation correction shortens the examination time, so that the number of examinations can be increased. But attenuation correction is required for quantification in cases to assess the FDG uptake either for tumor characterization or therapy monitoring. As a result, the attenuation correction is not considered to be necessary when FDG-PET is performed only to detect lymphoma.

CONCLUSIONS

In conclusion, FDG-PET is superior to ^{67}Ga-scintigraphy in order to make an accurate diagnosis of lymphoma when used complementary to conventional diagnostic methods. FDG-PET is therefore considered to be useful for the detection and management of lymphoma and it also plays an important role in selecting the optimal therapeutic strategy.

ACKNOWLEDGMENTS

The authors thank Dr. Brian T. Quinn for his editorial assistance, and the technologists in the Division of Nuclear Medicine at Kyushu University Hospital for their valuable technical assistance.

REFERENCES

1. Front D, Israel O, Epelbaum R, Ben Haim S, Even Sapir E, Jerushalmi J, et al. Ga-67 SPECT before and after treatment of lymphoma. *Radiology* 1990; 175: 515–519,
2. Delcambre C, Reman O, Henry-Amar M, Peny AM, Macro M, Cheze S, et al. Clinical relevance of gallium-67 scintigraphy in lymphoma before and after therapy. *Eur J Nucl Med* 2000; 27: 176–184.
3. Okada J, Yoshikawa K, Imazeki K, Minoshima S, Uno K, Itami J, 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.
4. Newman JS, Francis IR, Kaminski MS, Wahl RL. Imaging of lymphoma with PET with 2-[^{18}F]fluoro-2-deoxy-D-glucose: correlation with CT. *Radiology* 1994; 190: 111– 116.
5. Hoh CK, Glaspy J, Rosen P, Dahlbom M, Lee SJ, Kunkel L, et al. Whole-body FDG-PET imaging for staging of Hodgkin's disease and lymphoma. *J Nucl Med* 1997; 38: 343–348.
6. Moog F, Bangerter M, Diederichs CG, Guhlmann A, Merkle E, Frickhofen N, et al. Lymphoma: Role of whole-body 2-deoxy-2-[^{18}F]fluoro-D-glucose (FDG) PET in nodal staging. *Radiology* 1997; 203: 795–800.
7. Stumpe KD, Urbinelli M, Steinert HC, Glanzmann CH, Buck A, von Schulthness GK. Whole-body positron emission tomography using fluorodeoxyglucose for staging of lymphoma: Effectiveness and comparison with computed tomography. *Eur J Nucl Med* 1998; 25: 721–728.
8. Bangerter M, Moog F, Buchmann I, Kotzerke J, Griesshammer M, Hafner M, et al. Whole-body 2-[^{18}F]-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) for accurate staging of Hodgkin's disease. *Ann Oncol* 1998; 9: 1117–1122.
9. Jerusalem G, Warland V, Najjar F, Paulus P, Fassotte MF, Fillet G, et al. Whole-body ^{18}F-FDG PET for the evaluation of patients with Hodgkin's disease and non-Hodgkin's lymphoma. *Nucl Med Commun* 1999; 20: 13–20.
10. Jerusalem G, Beguin Y, Najjar F, Hustinx R, Fassotte MF, Rigo P, et al. Positron emission tomography (PET) with ^{18}F-fluorodeoxyglucose (^{18}F-FDG) for the staging of low-grade non-Hodgkin's lymphoma (NHL). *Ann Oncol* 2001; 12: 825–830.
11. Buchmann I, Reinhardt M, Elsner K, Bunjes D, Altehoefer C, Finke J, et al. 2-(fluorine-18)fluoro-2-deoxy-D-glucose positron emission tomography in the detection and staging of malignant lymphoma. A bicenter trial. *Cancer* 2001; 91: 889–899.
12. Shah N, Hoskin P, McMillan A, Gibson P, Lowe J, Wong WL. The impact of FDG positron emission tomography imaging on the management of lymphomas. *Br J Radiol* 2000; 73: 482–487.
13. Schöder H, Meta J, Yap C, Ariannejad M, Rao J, Phelps ME, et al. Effect of whole-body ^{18}F-FDG PET imaging on clinical staging and management of patients with malignant lymphoma. *J Nucl Med* 2001; 42: 1139–1143.
14. Römer , Hanauske AR, Ziegler S, Thödtmann R, Weber W, Fuchs C, et al. Positron emission tomography in non-Hodgkin's lymphoma: assessment of chemotherapy with fluorodeoxyglucose. *Blood* 1998; 91: 4464–4471.
15. Mikhaeel NG, Timothy AR, O'Doherty MJ, Hain S, Maisey MN. 18-FDG-PET as a prognostic indicator in the treatment of aggressive non-Hodgkin's lymphoma—comparison with CT. *Leukemia and Lymphoma* 2000; 39: 5–6.
16. Spaepen K, Stroobants S, Dupont P, van Steenweghen S, Thomas J, Vandenberghe P, et al. Prognostic value of positron emission tomography (PET) with fluorine-18 fluorodeoxyglucose ([^{18}F]FDG) after first-line chemotherapy in non-Hodgkin's lymphoma: is [^{18}F]FDG-PET a valid alternative to conventional diagnostic methods? *J Clin Oncol* 2001; 19: 414–419.
17. Paul R. Comparison of fluorine-18-2-fluorodeoxyglucose and gallium-67 citrate imaging for detection of lymphoma. *J Nucl Med* 1987; 28: 288–292.
18. Anderson KC, Leonard RC, Canellos GP, Skarin AT,

Kaplan WD. High-dose gallium imaging in lymphoma. *Am J Med* 1983; 75: 327–331.
19. Tumeh SS, Rosenthal DS, Kaplan WD, English RJ, Holman BL. Lymphoma: evaluation with Ga-67 SPECT. *Radiology* 1987; 164: 111–114.
20. Kostakoglu L, Goldsmith SJ. Positron emission tomography in lymphoma: comparison with computed tomography and gallium-67 single photon emission computed tomography. *Clin Lymphoma* 2000; 1: 67–74.
21. Moog F, Bangerter M, Diederichs CG, Guhlmann A, Merkle E, Frickhofen N, et al. Extranodal malignant lymphoma: detection with FDG PET versus CT. *Radiology* 1998; 206: 475–481.
22. Sasaki M, Ichiya Y, Kuwabara Y, Otsuka M, Tahara T, Fukumura T, et al. Ringlike uptake of [^{18}F]FDG in brain abscess: a PET study. *J Comput Assist Tomogr* 1990; 14: 486–487.
23. Ichiya Y, Kuwabara Y, Sasaki M, Yoshida T, Akashi Y, Murayama S, et al. FDG-PET in infectious lesions: the detection and assessment of lesion activity. *Ann Nucl Med* 1996; 10: 185–191.
24. Tatsumi M, Kitayama H, Sugahara H, Tokita N, Nakamura H, Kanakura Y, et al. Whole-body hybrid PET with ^{18}F-FDG in the staging of non-Hodgkin's lymphoma. *J Nucl Med* 2001; 42: 601–608.
25. Okada J, Yoshikawa K, Itami M, Imazeki K, Uno K, Itami J, et al. Positron emission tomography using fluorine-18-fluorodeoxyglucose in malignant lymphoma: A comparison with proliferative activity. *J Nucl Med* 1992; 33; 325–329.
26. Rodriguez M, Rehn S, Ahlström H, Sundström C, Glimelius B. Predicting malignancy grade with PET in non-Hodgkin's lymphoma. *J Nucl Med* 1995; 36: 1790–1796.
27. Lapela M, Leskinen S, Minn HRI, Lindholm P, Klemi PJ, Söderström KO, 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.
28. Leskinen-Kallio S, Ruotsalainen U, Någren K, Teräs M, Joensuu H. Uptake of carbon-11 methionine and fluorodeoxyglucose in non-Hodgkin's lymphoma: A PET study. *J Nucl Med* 1991; 32: 1211–1218.
29. Hoffmann M, Kletter K, Diemling M, Becherer A, Pfeffel F, Petkov V, et al. Positron emission tomography with fluorine-18-2-fluoro-2-deoxy-D-glucose (F18-FDG) does not visualize extranodal B-cell lymphoma of the mucosa-associated lymphoid tissue (MALT)-type. *Ann Oncol* 1999; 10: 1185–1189.
30. Rodriguez M, Ahlström H, Sundín A, Rehn S, Sundström C, Hagberg H, et al. [^{18}F]FDG PET in gastric non-Hodgkin's lymphoma. *Acta Oncologica* 1997; 36: 577–584.
31. Grünwald F, Schomburg A, Bender H, Klemm E, Menzel C, Bultmann T, et al. Fluorine-18 fluorodeoxyglucose positron emission tomography in the follow-up of differentiated thyroid cancer. *Eur J Nucl Med* 1996; 23: 312–319.
32. Bartold SP, Donohoe KJ, Fletcher JW, Haynie TP, Henkin RE, Silberstein EB, et al. Procedure guideline for gallium scintigraphy in the evaluation of malignant disease. *J Nucl Med* 1997; 38: 990–994.
33. Kotzerke J, Guhlmann A, Moog F, Frickhofen N, Reske SN. Role of attenuation correction for fluorine-18 fluorodeoxyglucose positron emission tomography in the primary staging of malignant lymphoma. *Eur J Nucl Med* 1999; 26: 31–38.
34. Bengel FM, Ziegler SI, Avril N, Weber W, Laubenbacher C, Schwaiger M. Whole-body positron emission tomography in clinical oncology: comparison between attenuation-corrected and uncorrected images. *Eur J Nucl Med* 1997; 24: 1091–1098.