Annals of Nuclear Medicine Vol. 20, No. 10, 689–693, 2006

# Findings of fluorine-18-FDG PET in extranodal origin lymphoma —In three cases of diffuse large B cell type lymphoma—

Takashi NIHASHI,* Kazumasa HAYASAKA,* Toshihide ITOU,** Kengo ITO,*,*** Rikio KATO,* Toshiharu OKAE**** and Takeo ISHIGAKI*****

*Department of Radiology, National Center for Geriatrics and Gerontology
**Department of Hematology, National Center for Geriatrics and Gerontology
***Department of Brain Science and Molecular Imaging, National Institute for Longevity Sciences
****Department of Radiology, Anjo General Hospital
*****Department of Radiology, Nagoya University Graduate School of Medicine

F-18 fluorodeoxyglucose (FDG) positron emission tomography (PET) is an excellent modality for non-invasive functional imaging of malignant lymphoma and is highly sensitive and specific for the detection of lymphoma lesions. Here, we report the findings of FDG-PET for three cases of diffuse large B cell type lymphoma (DLBCL) with extranodal tumors in the breast, stomach, and liver plus spleen, respectively. The whole body FDG-PET findings showed no evidence of lymph node (LN) involvement or distant metastasis. Strong FDG accumulations were observed in the only extranodal sites by whole body FDG-PET. Therefore, we could confirm that these cases were extranodal primary origins. Whole body PET is useful to determine the primary sites, that is, extranodal origin DLBCL with its clear images.

**Key words:** extranodal lymphoma, FDG-PET, DLBCL

## INTRODUCTION

THE REMARKABLE FEATURES of F-18 fluorodeoxyglucose (FDG) positron emission tomography (PET) make it possible to determine whether tumors are malignant or benign by detecting the level of glucose metabolism in tumor tissues.[1–4]

It is very important when choosing a therapeutic strategy for malignant lymphoma (ML), to accurately evaluate the spread and the stage of the disease. Computed tomography (CT), ultrasound (US), and gallium 67 scintigraphy ($^{67}$Ga) have been used as non-invasive imaging tools that enable the evaluation of almost all regions of the whole body. Recently, the usefulness of PET, including PET-CT, for the staging and treatment-monitoring of ML has been discussed.[4–8] It appears that PET is the most promising imaging tool with respect to the potential to improve the accuracy of the staging of ML.[1,5]

ML, especially non-Hodgkin's lymphoma, may occur outside the lymph nodes and extranodal lymphoma occurs in about 40% of ML patients.[4,9–11] Extranodal involvement is divided into two types. In the first type, extranodal lymphoma is the origin of the disease, while in the second type, the extranodal lymphoma results from the regional spread of nodal disease or hematogenous dissemination. For both types, it is very important to accurately determine the number and location of extranodal lesions, because the existence of extranodal disease is a key factor in the prognosis of patients.[12,13]

Lopez-Guillermo et al. reported that the primary sites of the disease were associated with particular clinicopathologic features and with the outcome in a large number of diffuse large B cell type lymphoma (DLBCL) patients from a single institution. They reported that the patients with lesions in Waldeyer's ring or gastrointestinal (GI) showed better overall survival (OS) than patients with lesions in nodal or other extranodal sites.[12] Therefore, when extranodal DLBCL is diagnosed, it is important to determine not only how many lesions exist, but also, whether the lesion is the primary site or not.

Received April 29, 2006, revision accepted August 11, 2006.
For reprint contact: Takashi Nihashi, M.D., Department of Radiology, National Center for Geriatrics and Gerontology, 36–3, Gengo, Morioka-cho, Ohbu 474–8522, JAPAN.
E-mail: dr284@hotmail.com

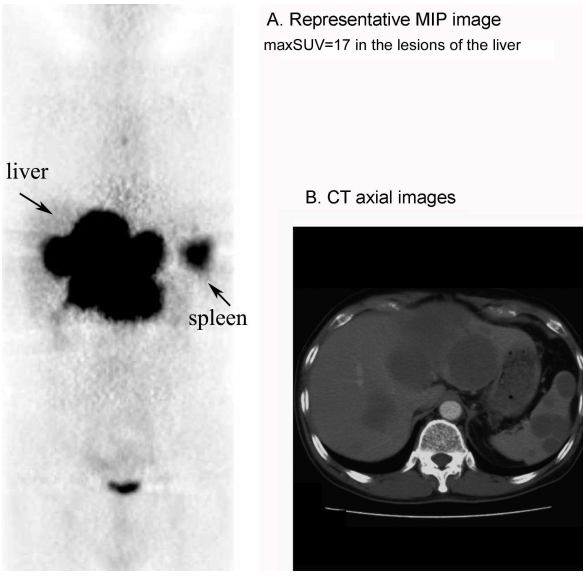


**Fig. 1** A, MIP image. B, Representative axial CT images. Strong FDG accumulation was observed in multiple regions in the liver and spleen, corresponding to the tumor detected by CT. (A and B). $SUV_{max}$ was approximately 17 in the affected liver tumor. The pattern of the accumulation was homogeneous, round and very intense. Black arrows show the uptake in liver and spleen. In addition, FDG uptake was increased in front of the thoracic vertebrae; however, this region was examined by CT and the lesion was determined to be due to degeneration of the vertebral body because there were no apparent enlarged lymph nodes. Whole-body PET scan did not show any evidence of lymph node involvement or distant metastases, and this was confirmed by CT.

Recently, Schoder et al. reported that the intensity of FDG uptake distinguishes between indolent and aggressive non-Hodgkin's lymphoma.[14]

In the present study, we experienced three cases of extranodal origin DLBCL localized in the breast, stomach, and liver plus spleen, and in the initial diagnosis FDG-PET was useful because of its clear findings. Therefore, we report these cases and also review some literature about extranodal DLBCL.

## CASE REPORT

*Case 1*

A 63-yr-old Japanese man was admitted for examination and treatment of abdominal pain and vertigo. US examination was performed first, and many tumors were found in the liver and spleen. Blood examination showed a high level of lactate dehydrogenase (LDH), soluble interleukin 2 receptor (sIL2R) and impaired liver function. Fine-needle cytological biopsy of the liver was attempted; however, a diagnosis could not be made. Next, FDG-PET and CT scan with contrast medium were performed to evaluate the disease.

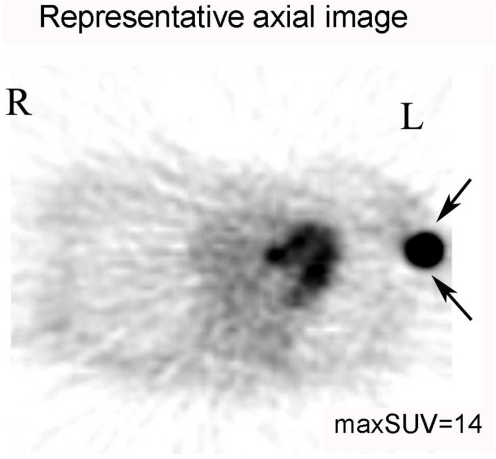


**Fig. 2** Representative axial image. Strong FDG accumulation was observed in the mass in the left breast and $SUV_{max}$ was approximately 14. The pattern of the accumulation was homogeneous, round and very intense. Black arrows show the uptake in the tumor of the left breast.

Strong FDG accumulation was observed in multiple regions in the liver and spleen, corresponding to the tumors detected by CT (Fig. 1A and B). Maximum of standardized uptake value ($SUV_{max}$) was approximately 17 in the liver tumors. The pattern of the accumulation was homogeneous, round and very intense. In addition, FDG uptake was increased in front of the thoracic vertebrae; however, CT examined this area and the lesion was determined to be due to degeneration of the vertebral body because there were no apparent enlarged lymph nodes. Whole-body PET scan did not show any evidence of lymph node involvement or distant metastases, which was confirmed by CT. From the results of a blood examination and the findings of PET, the possibility of a malignant lymphoma was suspected strongly. Biopsy of the liver was tried again, and the disease was diagnosed as DLBCL.

After systemic chemotherapy, partial remission (PR) was obtained and autologous blood stem cell transplantation (auto PBSCT) was planned for further therapy.

*Case 2*

A 68-yr-old Japanese female visited our hospital with the chief complaint of tumor in the left breast.

Cytological fine-needle biopsy of the breast mass showed DLBCL. Next, FDG-PET was performed for further examination. Strong FDG accumulation was observed in the mass in the left breast and $SUV_{max}$ was approximately 14. The pattern of the accumulation was homogeneous, round and very intense (Fig. 2).

Whole-body PET scan did not show any evidence of lymph node involvement or distant metastases. We diagnosed this as a rare case of primary breast lymphoma based on the FDG-PET scan. After surgical resection,

**Table 1** Summary of three cases

| Case | Age | Sex | Location | Histological diagnosis | Surface marker | | | | | FDG-PET scan | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | CD5 | CD10 | CD20 | LDH | sIL2R | Stage | Findings | $SUV_{max}$ |
| 1 | 63 | m | liver, spleen | DLBCL | (−) | (−) | (+) | H | H | $IV_E$ | HR | 17 |
| 2 | 68 | f | breast | DLBCL | (−) | (−) | (+) | N | H | $I_E$ | HR | 14 |
| 3 | 55 | m | stomach | DLBCL | NA | NA | (+) | H | H | $IV_E$ | HR | 17 |

DLBCL: diffuse large B cell type lymphoma, NA: not available, H: high, N: normal, HR: homogeneous and round.
* These cases were diagnosed according to the American Joint Committee on Cancer (AJCC) stage.[30]
** Early and delayed scan were performed. The delayed scan showed an increase of $SUV_{max}$ to 22.

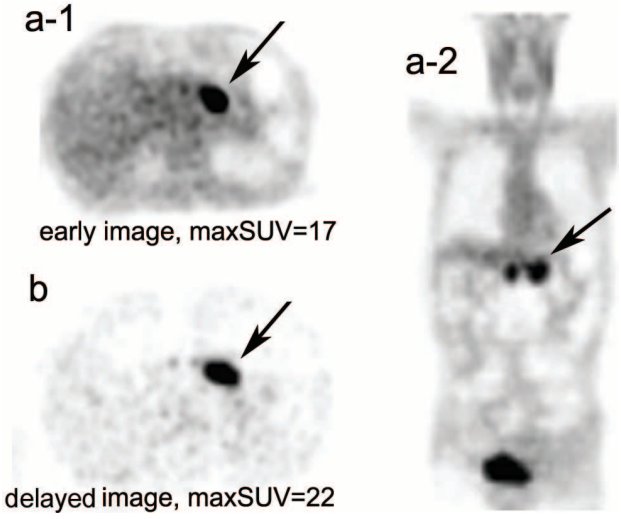


**Fig. 3** Representative axial (a-1) and coronal images (a-2). FDG-PET showed accumulation in the stomach (*black arrows*). $SUV_{max}$ was approximately 17 in the early image (a-1), and 22 in the delayed image (b). Black arrows show the uptake in the tumor of the stomach. In coronal image (a-2), there were two accumulations of FDG in the stomach side by side, and both lesions were confirmed to be primary lesions of ML of operation.

radiotherapy and concurrent chemotherapy, PR was obtained. Blood examination did not show a high level of LDH, but a high level of sIL2R.

*Case 3*

A 55-yr-old Japanese man visited our hospital with the chief complaint of motor weakness in the left leg. In the department of neurology, multiple sclerosis (MS) was suspected from his neurological findings. About 8 months after the onset, this patient was admitted to our hospital for motor weakness in the bilateral legs. During this hospitalization, gastroendoscopy was performed because of appetite loss and anemia. This examination revealed a submucosal mass of the stomach. Due to the findings of gastroendoscopy, diffuse invasion in the submucosa of the stomach was suspected.

Cytological fine-needle biopsy of this lesion showed DLBCL. Next, FDG-PET was performed for further examination. Strong FDG accumulation was observed in the mass in the stomach and $SUV_{max}$ was approximately 17. The pattern of the accumulation was homogeneous, and very intense. The delayed scan showed an increase of $SUV_{max}$ to 22 (Fig. 3).

Whole-body PET scan did not show any evidence of lymph node involvement or distant metastases. We diagnosed this as primary stomach lymphoma and surgical resection was planned for the initial therapy. Blood examination did not show a high level of LDH and sIL2R in this case. After surgical resection, radiotherapy and concurrent chemotherapy, PR was obtained.

Table 1 shows a summary of the findings in these three cases (Table 1).

*FDG-PET scan protocol*

The procedure for FDG-PET was as follows: An ECAT EXACT HR 47 PET camera (Siemens/CTI) was used, and imaging was performed using 3-D acquisition at 60 minutes after the intravenous administration of 250 MBq $^{18}$F-FDG. In case 3, we performed two scans, that is, the first scan was started at 60 minutes after the administration, and the second scan was started at 120 minutes. The collected data were reconstructed into a 128 × 128 pixel image matrix. Tissue attenuation of annihilation photons was corrected by transmission scans using rotating $^{68}$Ge/$^{68}$Ga line sources. Six bed positions of the body trunk were applied, which covered areas from the neck to the pelvis. The total time for one bed position was 6 minutes (mins), with a transmission scan of 2 min and an emission scan of 4 mins. The patient fasted for at least 6 hours prior to the examination. Normal glucose level was confirmed prior to the PET scan. Regional FDG uptake in the affected area was expressed as SUV.

## DISCUSSION

Non-Hodgkin's lymphoma may be of extranodal origin in some cases, and extranodal origin sites exist in about 40% of DLBCL patients.[4,9–12] DLBCL is the most common type of non-Hodgkin's lymphoma, and occurs in approximately 30% of total non-Hodgkin's lymphoma patients.[15]

It was reported that extranodal sites might be lung, pleura, thymus, breast, spleen, liver, pancreas, musculoskeletal system, and central nervous system.[4]

The International Prognostic Index (IPI) is widely used as a prognosis prediction factor for choosing a treatment strategy.[13] IPI includes five factors, i.e. (1) age (>60 years), (2) clinical stage (III/IV), (3) performance status (PS) (2–4), (4) serum LDH (>normal), and (5) the number of extranodal lesions (two or more lesions). Thus, the number of lesions outside of lymph nodes is important for the prognostic evaluation of patients and is considered to be very important for choosing appropriate treatment. When the extranodal involvement is observed, there are two possibilities. First, the extranodal lymphoma is the origin, and second, the extranodal lymphoma is the result of regional spread of nodal lymphoma and/or hematogenous dissemination. In fact, it is difficult to judge this problem in some cases.

Whether the spleen should be included as a nodal or extranodal site is controversial, and in the present study, in case 1, we considered that the liver was the main affected organ, although there was lymphoma in the spleen. Therefore, case 1, in which there was lymphoma in both the liver and spleen, was considered to be extranodal origin lymphoma.

The intensity of FDG uptake was evaluated as $SUV_{max}$. In the present study, every patient showed high $SUV_{max}$, that is, more than 10. Schoder et al. showed that patients with NHL (SUV > 10) have a high likelihood for aggressive disease.[14]

Primary hepatic lymphoma is a very rare disease.[16,17] Noronha et al. reported that primary hepatic lymphoma is a rare malignancy and constitutes about 0.016% of all cases of non-Hodgkin's lymphoma. In addition, the predominant histology is B-cell lymphoma, most commonly diffuse large cell type. The patients with lymphoma with liver involvement also have spleen lesions.[18] Bangerter et al. reported a case report that showed high glycolytic activity of a solitary mass in the liver with central necrosis.[19]

Primary breast lymphoma is also a very rare disease. Giardini et al. reported that these cases represented 0.1% of the more than 25,000 primary malignant tumors of the breast treated during over a 30-year period in their institution.[20] Vignot et al. reported that non-Hodgkin's lymphoma of the breast represented 0.04–0.05% of malignant lesions of the mammary gland in a single institution.[21] Most breast lymphomas are B-cell lymphoma.[22,23] There are only a few reports of FDG-PET findings of extranodal breast lymphoma.[24,25] Kumar et al. reported the findings of FDG-PET in a case of DLBCL, namely, intense and diffuse FDG uptake in dense breast tissue that might have been missed by CT and mammography. Bakheet et al. reported ring-shaped FDG uptake in a patient with breast lymphoma. In the present case 2, the FDG uptake was intense, round and homogeneous.

The gastrointestinal tract is the most common site of primary extranodal lymphoma.[4,26] Any part of the gastrointestinal tract may be involved, from the oral cavity to rectum. However, the stomach is the most frequent organ, followed by the small intestine and colon. Gastrointestinal tract lymphomas account for 4–20% of all cases of non-Hodgkin's lymphoma and 30–40% of all extranodal lymphomas.[26,27] One-half to two-thirds of gastrointestinal tract non-Hodgkin's lymphomas are DLBCL.[27] Kumar et al. reported intense and homogeneous uptake in the region of the ascending colon and intense irregular uptake in bowel loops. In the present case 3, the FDG uptake was very intense and homogeneous. In terms of therapy, surgical resection generally plays an important role for localized non-Hodgkin's lymphoma in terms of initial therapy.[29]

In these three cases, we could easily evaluate the distribution of the disease because of strong and localized accumulation of FDG-PET. These clear findings leaded to accurate diagnosis, that is, primary extranodal lymphoma. Further, it was possible to evaluate that the masses were not indolent but aggressive since the accumulation was intense. Therefore, we considered that FDG-PET was a useful functional imaging tool to evaluate extranodal origin lymphoma.

## CONCLUSION

We report the findings of FDG-PET for extranodal origin lymphoma in cases with involvement of the breast, stomach, and liver plus spleen. We conclude that whole-body PET is a useful imaging tool in terms of defining the primary sites of the cases of malignant lymphoma, that is, extranodal origin or not.

## REFERENCES


1. 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.
2. Dizendorf EV, Baumert BG, von Schulthess GK, Lutolf UM, Steinert HC. Impact of Whole-Body $^{18}$F-FDG PET on Staging and Managing Patients for Radiation Therapy. *J Nucl Med* 2003; 44: 24–29.
3. Friedberg JW, Chengazi V. PET scans in the staging of lymphoma: current status. *Oncologist* 2003; 8: 438–447.
4. Metser U, Goor O, Lerman H, Naparstek E, Even-Sapir E. PET-CT of extranodal lymphoma. *AJR* 2004; 182: 1579–1586.
5. 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.
6. Bar-Shalom R, Yefremov N, Haim N, Dann EJ, Epelbaum R, Keidar Z, et al. Camera-based FDG PET and $^{67}$Ga SPECT in evaluation of lymphoma: comparative study. *Radiology* 2003; 227: 353–360.

7. Schaefer NG, Hany TF, Taverna C, Seifert B, Stumpe KD, von Schulthess GK, et al. Non-Hodgkin lymphoma and Hodgkin disease: coregistered FDG PET and CT at staging and restaging—do we need contrast-enhanced CT? *Radiology* 2004; 232: 823–829.
8. Metser U, Miller E, Kessler A, Lerman H, Lievshitz G, Oren R, et al. Solid splenic masses: evaluation with $^{18}$F-FDG PET/CT. *J Nucl Med* 2005; 46: 52–59.
9. Zucca E, Roggero E, Bertoni F, Cavalli F. Primary extranodal non-Hodgkin's lymphomas. Part 1: Gastrointestinal, cutaneous and genitourinary lymphomas. *Ann Oncol* 1997; 8: 727–737.
10. Zucca E, Roggero E, Bertoni F, Conconi A, Cavalli F. Primary extranodal non-Hodgkin's lymphomas. Part 2: Head and neck, central nervous system and other less common sites. *Ann Oncol* 1999; 10: 1023–1033.
11. Zucca E, Cavalli F. Extranodal lymphomas. *Ann Oncol* 2000; 11: 219–222.
12. Lopez-Guillermo A, Colomo L, Jimenez M, Bosch F, Villamor N, Arenillas L, et al. Diffuse large B-cell lymphoma: clinical and biological characterization and outcome according to the nodal or extranodal primary origin. *J Clin Oncol* 2005; 23: 2797–2804.
13. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. A Predictive Model for Aggressive Non-Hodgkin's Lymphoma. *N Engl J Med* 1993; 329: 987–994.
14. Schoder H, Noy A, Gonen M, Weng L, Green D, Erdi YE, et al. Intensity of $^{18}$Fluorodeoxyglucose Uptake in Positron Emission Tomography Distinguishes between Indolent and Aggressive Non-Hodgkin's Lymphoma. *J Clin Oncol* 2005; 23: 4643–4651.
15. The Non-Hodgkin's Lymphoma Classification Project. A Clinical Evaluation of the International Lymphoma Study Group Classification of Non-Hodgkin's Lymphoma. *Blood* 1997; 89: 3909–3918.
16. Ziarkiewicz-Wroblewska B, Gornicka B, Suleiman W, Wroblewski T, Morton M, Wilczynski GM, et al. Primary lymphoma of the liver—morphological and clinical analysis of 6 cases. Success of aggressive treatment. *Neoplasma* 2005; 52: 267–272.
17. Noronha V, Shafi NQ, Obando JA, Kummar S. Primary non-Hodgkin's lymphoma of the liver. *Crit Rev Oncol Hematol* 2005; 53: 199–207.
18. Sandrasegaran K, Robinson PJ, Selby P. Staging of lymphoma in adults. *Clin Radiol* 1994; 49: 149–161.
19. Bangerter M, Moog F, Griesshammer M, Merkle E, Hafner M, Ellenrieder V, et al. Usefulness of FDG-PET in diagnosing primary lymphoma of the liver. *Int J Hematol* 1997; 6: 517–520.
20. Giardini R, Piccolo C, Rilke F. Primary non-Hodgkin's lymphomas of the female breast. *Cancer* 1992; 69: 725–735.
21. Vignot S, Ledoussal V, Nodiot P, Bourguignat A, Janvier M, Mounier N, et al. Non-Hodgkin's Lymphoma of the Breast: A Report of 19 Cases and a Review of the Literature. *Clin Lymphoma* 2005; 6: 37–42.
22. Topalovski M, Crisan D, Mattson JC. Lymphoma of the breast. A clinicopathologic study of primary and secondary cases. *Arch Pathol Lab Med* 1999; 123: 1208–1218.
23. Domchek SM, Hecht JL, Fleming MD, Pinkus GS, Canellos GP. Lymphomas of the breast: primary and secondary involvement. *Cancer* 2002; 94: 6–13.
24. Bakheet SM, Bakheet R, Ezzat A, Tulbah A, Durakovic A, Hussain S. F-18 FDG positron emission tomography in primary breast non-Hodgkin's lymphoma. *Clin Nucl Med* 2001; 26: 299–301.
25. Kumar R, Xiu Y, Dhurairaj T, Yu JQ, Alavi A, Zhuang H. F-18 FDG positron emission tomography in non-Hodgkin lymphoma of the breast. *Clin Nucl Med* 2005; 30: 246–248.
26. Kumar R, Xiu Y, Potenta S, Mavi A, Zhuang H, Yu JQ, et al. $^{18}$F-FDG PET for Evaluation of the Treatment Response in Patients with Gastrointestinal Tract Lymphomas. *J Nucl Med* 2004; 45: 1796–1803.
27. d'Amore F, Brincker H, Gronbaek K, Thorling K, Pedersen M, Jensen MK. Non-Hodgkin's lymphoma of the gastrointestinal tract: a population-based analysis of incidence, geographic distribution, clinicopathologic presentation features, and prognosis. Danish Lymphoma Study Group. *J Clin Oncol* 1994; 12: 1673–1684.
28. Cogliatti SB, Schmid U, Schumacher U, Eckert F, Hansmann ML, Hedderich J, et al. Primary B-cell gastric lymphoma: a clinicopathological study of 145 patients. *Gastroenterology* 1991; 101: 1159–1170.
29. Fleming ID, Turk PS, Murphy SB, Crist WM, Santana VM, Rao BN. Surgical implications of primary gastrointestinal lymphoma of childhood. *Arch Surg* 1990; 125: 252–256.
30. AJCC cancer staging manual. Sixth Edition. Springer, 2001: 393–403.