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CLINICAL LYMPHOMA

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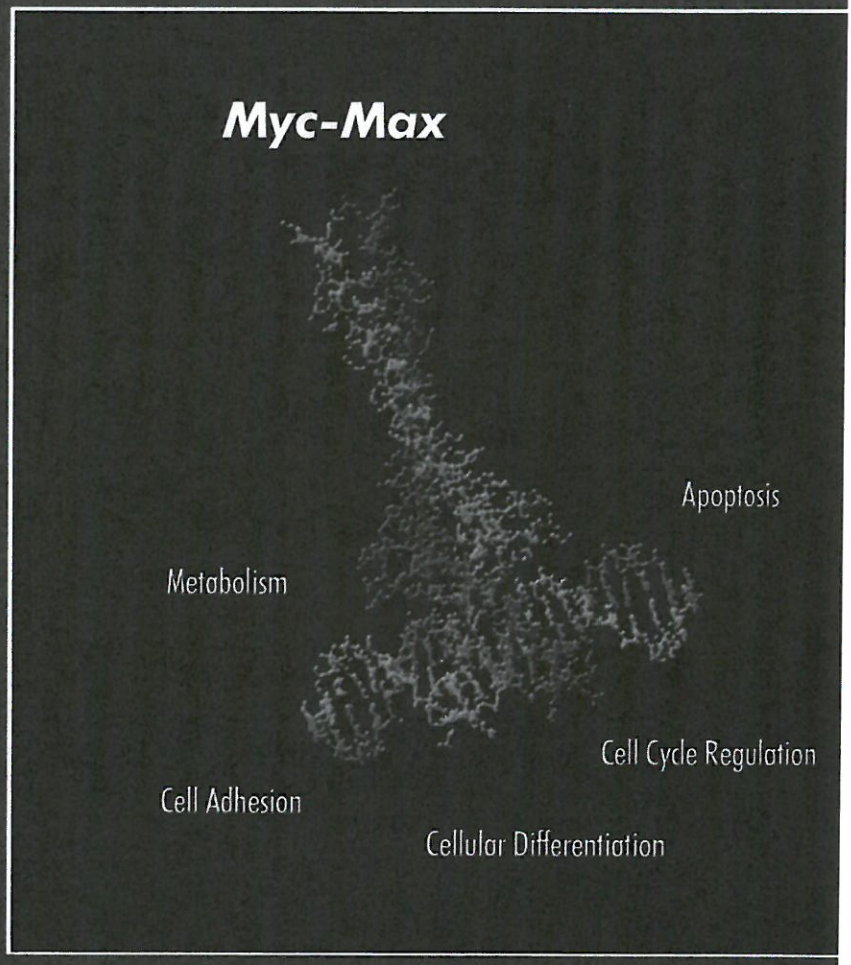

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Commentary on "Positron Emission Tomography in Lymphoma: Comparison with Computed Tomography and Gallium-67 Single Photon Emission Computed Tomography Imaging"

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Positron emission tomography (PET) using fluorine-18 fluorodeoxyglucose ([^{18}F]FDG)has emerged as a clinical method for staging and monitoring responses to treatment in a variety of cancers.[1] Lymphoma is one of the most FDG-avid tumors known. Since July 1, 1999, the Health Care Financing Administration has approved PET reimbursement for Medicare patients with Hodgkin's disease (HD) and non-Hodgkin's lymphoma (NHL) where PET substitutes for a gallium-67 (^{67}Ga) scan. However, although some small, single-institution studies have shown the superiority of [^{18}F]FDG-PET over computed tomography (CT) for staging of lymphoma at diagnosis,[2] it is too early to replace conventional staging procedures (CT, bone marrow biopsy) with [^{18}F]FDG- PET.

In our study including 60 patients (23 high-grade NHL, 21 low-grade NHL, 16 HD), PET detected more lymph nodes in 15 patients but upstaging was only observed in two patients and the treatment strategy was never changed based on PET.[3] On the other hand, [^{18}F]FDG-PET did not identify bone marrow infiltration demonstrated histologically in eight patients (four high-grade NHL, three low-grade NHL, one HD) and gastric infiltration in another patient (high-grade NHL).

Other recent studies confirmed the limitations of PET in the staging of some histological subtypes of NHL[4] and in the evaluation of extranodal lymphoma.[5] Further prospective multicenter studies are warranted to confirm the accuracy and cost-effectiveness of [^{18}F]FDG-PET for the staging of lymphoma. In particular, more information is needed about the sensitivity of PET for the various histological subtypes and for extranodal localizations before we can expect to use PET alone in this indication.

Defining a complete remission after treatment may be difficult in some patients, particularly those with an aggressive NHL and a large tumor mass at diagnosis or those with scleronodular HD. These patients may respond very well to treatment, with complete disappearance of all clinical or biological abnormalities, but CT scans may show residual masses. Recent studies indicate the high positive predictive value of [^{18}F]FDG-PET in this clinical situation (Table 1): patients with a positive PET at the end of therapy have a more than 95% chance of relapsing early. In addition, preliminary results suggest that [^{18}F]FDG-PET is superior to ^{67}Ga-scan, an alternative to PET for posttreatment evaluation.[2] [^{18}F]FDG-PET also offers greater convenience, with the whole procedure completed in 2 hours in a single visit.

Table 1 **Predictive Value of [^{18}F]-FDG PET for Posttreatment Evaluation in Patients with Lymphoma**

Authors	Number of patients	Median follow-up (months)	Positive predictive value	Negative predictive value
Jerusalem et al, 1999[6]	54	23	6/6 (100%)	40/48 (83%)
Zinzani et al, 1999[10]	44	20	13/13 (100%)	30/31 (97%)
Mikhael et al, 2000[11]	32	38	8/9 (89%)	21/23 (91%)
Spaëpen et al, 2000[7]	96	24	27/27 (100%)	55/69 (80%)

Although [^{18}F]FDG-PET is the best way to identify patients with an incomplete response to treatment and a very high risk of early relapse, some questions remain. Because of the higher cost of PET, should PET be performed in all patients or only in those with an abnormal CT scan? Is [^{18}F]FDG-PET a valid alternative to conventional radiological examination, or is [^{18}F]FDG-PET only complementary to CT for the noninvasive evaluation of residual masses? Some limitations of [^{18}F]FDG-PET are also well known. A negative [^{18}F]FDG-PET cannot exclude the presence of minimal residual disease possibly leading to a later relapse.[6,7]

On the other hand, although the positive predictive value of PET is very high, a histological confirmation of residual disease should be obtained before the start of salvage therapy because [^{18}F]FDG is not a tumor-specific tracer, and a false-positive result can never be excluded. The impact of an early diagnosis of residual disease by PET on long-term outcome is also unknown.

In the future, [^{18}F]FDG-PET may prove to be useful in the routine follow-up of asymptomatic patients after the end of therapy with the aim of diagnosing early relapses. We recently reported preliminary results in 36 patients with HD undergoing [^{18}F]FDG-PET every 4-6 months for 2-3 years after the end of chemotherapy and/or radiotherapy.[8] All five relapses were correctly identified early by [^{18}F]FDG-PET studies. Relapse was never diagnosed first based on clinical examination, laboratory findings, or CT studies, but two patients presented B symptoms at the time of relapse.

The major problem in our study was the high rate of false positivity: [^{18}F]FDG-PET incorrectly suggested relapse in six patients. Obviously, further studies are required to fully evaluate the potential of PET in the early detection of relapse and its impact upon outcome.

Finally, [^{18}F]FDG-PET may also be useful for monitoring response to treatment.[2] Chemotherapy causes a rapid decrease of [^{18}F]FDG uptake as early as 7 days after the first cycle of treatment. Our own data indicate that persistent tumoral [^{18}F]FDG uptake after a few cycles of polychemotherapy is predictive of treatment failure in NHL.[9] In a series of 28 patients, all five who still presented increased [^{18}F]FDG uptake in sites previously involved by lymphoma relapsed or reprogressed. Early identification of non-responders by [^{18}F]FDG-PET could possibly determine a change from an unsuccessful therapy to a more effective one. Patients whose tumors remain [^{18}F]FDG-PET positive in the course of chemotherapy may be candidates for alternative treatment such as high-dose chemotherapy with autologous stem-cell transplantation. However, only a large randomized trial will be able to determine if such an approach can change the outcome of these patients.

In conclusion, [^{18}F]FDG-PET is a new, exciting imaging modality in oncology. It provides information complementary to conventional radiological techniques, and it seems to be more accurate than a ^{67}Ga-scan. However, the most important question remains unanswered. Does the identification of more tumor sites or the earlier detection of residual disease permit more effective treatment? We do not need further data indicating that [^{18}F]FDG-PET is complementary to conventional radiological imaging. Time has come for large multicenter trials analyzing the real clinical impact for [^{18}F]FDG-PET on patient outcome.

1. Rigo P, Paulus P, Kaschten BJ, et al. Oncological applications of positron emission tomography with fluorine-18 fluorodeoxyglucose. *Eur J Nucl Med* 1996; 23:1641-1674.
2. Kostakoglu L, Goldsmith SJ. FDG-PET in lymphoma: comparison with CT and Ga-67 imaging. *Clin Lymphoma* 2000; 1:67-74.
3. Jerusalem G, Warland V, Najjar F, et al. Whole-body 18F-FDG PET for the evaluation of patients with Hodgkin's disease and non-Hodgkin's lymphoma. *Nucl Med Commun* 1999; 20:13-20.
4. Hoffmann M, Kletter K, Diemling M, 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.
5. Weidmann E, Baican B, Hertel A, et al. Positron emission tomography (PET) for staging and evaluation of response to treatment in patients with Hodgkin's disease. *Leuk Lymph* 1999; 34:545-551.
6. Jerusalem G, Beguin Y, Fassotte MF, et al. Whole-body positron emission tomography using 18F-fluorodeoxyglucose for posttreatment evaluation in Hodgkin's disease and non-Hodgkin's lymphoma has higher diagnostic and prognostic value than classical computed tomography scan imaging. *Blood* 1999; 94:429-433.
7. Spaepen K, Stroobants S, Dupont P, et al. Prognostic value of positron emission tomography with fluorodeoxyglucose (FDG-PET) after first line chemotherapy in non-Hodgkin's lymphoma (NHL). *Proc Am Soc Clin Oncol* 2000; 19:11a (Abstract #33).
8. Jerusalem G, Beguin Y, Fassotte MF, et al. Early detection of relapse by whole-body positron emission tomography (PET) using 18F-fluorodeoxyglucose (18F-FDG) in the follow-up of patients with Hodgkin's disease (HD). *Proc Am Soc Clin Oncol* 2000; 19:10a (Abstract #30).
9. Jerusalem G, Beguin Y, Fassotte MF, et al. Persistent tumoral 18F-FDG uptake after a few cycles of polychemotherapy is predictive of treatment failure in non-Hodgkin's lymphoma (NHL). *Haematologica* 2000; in press.
10. Zinzani PL, Magagnoli M, Chierichetti F, et al. The role of positron emission tomography (PET) in the management of lymphoma patients. *Ann Oncol* 1999; 10:1181-1184.
11. Mikhael NG, Timothy AR, Hain SF, et al. 18-FDG-PET for the assessment of residual masses on CT following treatment of lymphomas. *Ann Oncol* 2000; 11 (Suppl. 1):S147-S150.