

# Assessment of Lymphoma Therapy Using $^{18}\text{F}$ -FDG PET

The evaluation of tumor response during and after cancer therapy using PET is frequently discussed. In the last 10–20 y, most hematologists and oncologists have used CT to assess the response of lymphoma to therapy; however, CT does not consistently distinguish between dividing tumor cells and posttherapy fibrosis. Patients with aggressive non-Hodgkin's lymphoma (NHL) have positive CT findings in approximately 50% of cases after chemotherapy, and long-term follow-up shows that only 50% or fewer of those with positive CT findings have disease relapse or other evidence of residual tumor (1–5). CT is a poor predictor of clinical outcome after treatment of aggressive NHL, and a posttherapy CT scan positive for NHL does not indicate that the time to progression for that patient will be significantly different from that for a patient with normal CT findings (6–8).

One primary consideration for choosing a test to detect early response to therapy should be the existence of an alternate therapy. Aggressive NHL is potentially curable, with 20%–40% of patients having a “cure” or long-term disease-free intervals, whereas most indolent cases of NHL are not curable with currently available therapies. Early assessment of response to tumor therapy will likely be more important in aggressive lymphoma or, particularly, in predicting lack of response or time to progression. Imaging viable residual tumor in a patient with aggres-

sive NHL not only would alter the management but also could potentially change the prognosis of the patient by allowing earlier use of alternative therapies and discontinuation of therapy that will not lead to a significant tumor response. In addition, early discontinuation of therapy that is not working will avoid the associated toxicity.

Patients not achieving a response from the initial chemotherapy based on cyclophosphamide, hydroxydaunorubicin, vincristine (Oncovin; Eli Lilly and Co., Indianapolis, IN), and prednisone (CHOP) for advanced-stage aggressive NHL are candidates for salvage chemotherapy or autologous bone marrow transplantation. Salvage chemotherapy can induce a long-term response, with a 5%–10% long-term disease-free survival for diffuse, large B-cell NHL (9–11). Autologous bone marrow transplantation performed on patients with aggressive, chemotherapy-responsive NHL at first relapse results in long-term survival for many. Patients who have an initial complete remission from chemotherapy and a later relapse have a better prognosis with autologous bone marrow transplantation than do patients who are resistant to the initial chemotherapy. Autologous bone marrow transplantation has been shown to be superior to salvage chemotherapy at usual doses and leads to long-term disease-free survival in ~40% of patients whose lymphoma remains chemotherapy sensitive after relapse (12–13).

It is clear that  $^{18}\text{F}$ -FDG uptake decreases during therapy in responding tumors and, in this case, lymphoma. Critical issues still need to be resolved about the use of PET for therapeutic assessment. At what point during chemotherapy will PET be useful for directing a new course of therapy if it is

believed that a change should or can be made? In concert, at what point will PET show optimal sensitivity and prediction of progression-free survival? Kostakoglu et al. (14) are responding to some of these questions in their article in this issue of *The Journal of Nuclear Medicine*.

The article by Kostakoglu et al. (14) reviews their experience with  $^{18}\text{F}$ -FDG PET in lymphoma. They look at the accuracy of detecting lymphoma resistant to treatment regimens of CHOP or CHOP variants (in the case of new NHL, 10 patients) or of dexamethasone, ifosfamide, cisplatin, and etoposide (in the case of treatment for NHL relapse, 7 patients). For Hodgkin's disease (13 patients) the chemotherapy used was adriamycin, bleomycin, vinblastine, and dacarbazine. The investigation used a dual-head gamma camera with attenuation correction for  $^{18}\text{F}$ -FDG imaging. The results show accurate prediction by coincidence PET after 1 cycle of chemotherapy but poor sensitivity for resistant disease (or disease that will relapse) after the last cycle. Sensitivity, specificity, and accuracy for first cycle versus completion of chemotherapy were 82%, 85%, and 97%, respectively, versus 46%, 90%, and 70%, respectively. These results are similar to others for early chemotherapy assessment but dramatically lower for posttherapy assessment (13,15–17).

We know that  $^{18}\text{F}$ -FDG accumulation in lymphoma diminishes as successful therapy progresses. In a study by Romer et al. (17) on a group of 11 patients with newly diagnosed NHL,  $^{18}\text{F}$ -FDG uptake was measured by dedicated PET at 7 d (after 1 course) and 42 d (after 2 courses) after the start of chemotherapy. PET at 42 d was superior to PET at 7 d in the prediction of long-term outcome. The authors sug-

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gested that evaluation of tumor  $^{18}\text{F}$ -FDG uptake at as early as 7 d can predict the primary outcome to chemotherapy.  $^{18}\text{F}$ -FDG uptake parameters at days 7 and 42 were correlated with long-term clinical outcome. Seven days after the initiation of chemotherapy, the parameters of tumor  $^{18}\text{F}$ -FDG uptake decreased by 60% of initial values for standardized uptake value (SUV[*max*]) and by 67% for metabolic rate for  $^{18}\text{F}$ -FDG (MRFDG). From day 7 to day 42, all lesions exhibited a further decrease of tracer uptake: 42% for SUV[*max*] and 71% for MRFDG. The total decrease from baseline to day 42 was 79% for SUV[*max*] and 89% for MRFDG. Other authors have shown PET to have good sensitivity for detecting resistant disease after the completion of chemotherapy. In a study by Spaepen et al. (16) on 93 patients with NHL undergoing first-line chemotherapy,  $^{18}\text{F}$ -FDG PET had a 70% sensitivity for detecting residual disease after the completion of chemotherapy (6–8 courses). Progression-free survival was shorter for patients who had persistent  $^{18}\text{F}$ -FDG uptake. All patients with persistent uptake did have disease relapse. This study was performed using a dedicated, full-ring PET scanner. Also, in a group of 37 Hodgkin's disease patients, De Wit et al. (13) showed that PET undertaken at the completion of chemotherapy was 91% sensitive for predicting disease relapse.

The data the authors analyzed must be considered in light of a few important variables that may explain the differences between their results and other published data. The trial patients had different diseases, were being treated differently, and were at different points in their treatment. It is difficult to analyze the patients separately as, for example, an initial disease group or a relapse group, because the groups become very small. It is also difficult to view these data with relapse and initial-diagnosis patients lumped together, because the disease response characteristics may be different. This difficulty makes the data somewhat problematic. Also, there must certainly

have been some lymphoma patients who were seen at that center but were not enrolled in the trial. The trial was open for 3.5 y, and only 30 consecutive patients were enrolled. One would hope that during such a period a large referral center could enroll many more patients. A larger enrollment would give the authors data that could be more easily separated into subgroups. The low enrollment also raises the question of referral bias and the possibility that the trial may have enrolled a higher percentage of patients with advanced, resistant disease.

Another issue that needs to be addressed about the data is the use of coincidence PET for the detection of subtle disease persistence or resistance, especially after therapy. The disease sensitivity of dedicated PET scanners is well known to surpass that of coincidence PET scanners, and this superiority may be another circumstance in which the difference can be limiting (18). The authors' scanner does use attenuation correction, which improves the performance of the scanner but not to a level equivalent to that of dedicated PET. The article reports post-therapy coincidence PET to have a sensitivity of 46% for disease that relapses, compared with a sensitivity of 70%–91% for dedicated PET (13,15,16). If we assume that the most probable time for resistant disease to be at its smallest volume is after therapy, the most sensitive PET imaging method would be optimal at that time. This may explain the discrepancy between the results of Kostakoglu et al. (14) and other reports.

Management of therapy using PET is a topic of discussion in almost all oncology settings, in addition to the setting of lymphoma. Large, prospective trials with consistent patient groups are needed to answer questions on the predictive nature of PET for therapy assessment. The article by Kostakoglu et al. (14) does confirm that early therapeutic assessment of lymphoma treatment using coincidence PET can predict which patients will respond. Small, heterogeneous patient groups make the study somewhat prob-

lematic, however, relative to its generalizability and statistical power. The study is likewise not indicative of, or consistent with, the accuracy of dedicated PET of the posttherapeutic lymphoma patient. The article gives us an early look at therapeutic assessment using coincidence PET and may best be served by a direct comparison with dedicated PET before coincidence PET can be considered to be of limited utility for assessing the response of lymphoma after chemotherapy.

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