Fluorine-18 Fluorodeoxyglucose Positron Emission Tomography for Lymphoma: Incorporating New Technology into Clinical Care

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Fluorine-18 fluorodeoxyglucose (^{18}FDG) positron emission tomography (PET) is a functional imaging technique that takes advantage of the increased glycolytic activity associated with neoplastic disease. It has been demonstrated to be useful in the initial staging of non-small cell lung cancer (1) and other neoplasms. Gallium scanning, often used as a supplement to initial staging for both Hodgkin's and non-Hodgkin's lymphoma, can be predictive of clinical outcome following therapy, but has several disadvantages. For example, gallium is excreted into the bowel, making interpretation of abdominal scans difficult. There is also a 3- to 5-day delay after injection before scanning can be performed. Nonspecific hilar uptake and enhancement of regenerating thymus in younger patients can lead to false-positive results, and a pretreatment scan is necessary to confirm that the tumor is gallium avid. In comparison, PET allows for superior resolution, can be performed in 1 day, but is more expensive than gallium scanning.

The key questions that must be answered before determining how to incorporate this new technology into the management of patients with lymphoma include the following: does PET upstage patients at the time of diagnosis, and does this alter therapy? Does PET during therapy predict outcome? And, does PET predict residual disease in patients with persistent computed tomographic (CT) abnormalities following therapy?

In this issue of *The American Journal of Medicine* (2), Wirth et al. attempt to answer the first of these questions regarding the use of PET in the staging of lymphoma, and to compare PET with gallium scanning in this setting. In this study, the medical records of 50 patients who had PET, gallium scanning, or conventional staging of Hodgkin's, indolent Non-Hodgkin's, or aggressive non-Hodgkin's lymphoma were reviewed. Of 36 patients classified as stage I or II on conventional assessment, 4 were reclassified as stage III or IV by each of PET and gallium scanning. Management, in terms of treatment strategy or radiotherapy field, was altered by PET in 9 patients (18%) and by gallium scanning in 7 (14%). Positron emission tomography appeared to be more sensitive than gallium scanning in identification of additional sites of disease, with a difference in site positivity rate of 13%. Gallium scanning was not significantly different from conventional assessment in this regard. The authors concluded that PET should be indicated for staging based on the higher site positivity rate and because results altered choice of therapy in 9 patients. However, the lack of central radiographic review and the retrospective design create problems in interpretation. The retrospective design creates a bias in that PET may have been performed only on patients who were difficult to stage conventionally. Certainly, that many of these patients had both PET and gallium scans performed would tend to support this conclusion.

The higher site positivity rate observed with PET may upstage patients with early disease and thus provide an advantage over gallium scanning; a change from stage I/II to III/IV will make a therapeutic difference for most patients with either Hodgkin's or non-Hodgkin's lymphoma, as was demonstrated by Bangerter et al. (3). In their study (3), 5 patients were upstaged, resulting in treatment changes. There were no alterations in radiotherapy in this group. Positron emission tomography missed sites of documented disease in 4 patients.

In the United States, the standard of care for patients with stage I or II non-bulky Hodgkin's disease is an abbreviated course of chemotherapy, followed by involved-field radiotherapy (4). For aggressive histology non-Hodgkin's lymphoma patients with stage I or non-bulky stage II disease, treatment with three cycles of CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone), followed by involved-field radiotherapy, is usual (5). Those with more advanced-stage disease, or other poor prognostic factors, are treated with more extended courses of chemotherapy. The primary decision point is limited (stage I or II) versus advanced (stage II or IV) disease. Positron emission tomography, while clearly sensitive, is an expensive test. For example, at the University of California, San Francisco, a whole-body PET scan costs approximately $3000. Limiting its use to those who are more likely to have a therapeutic change resulting from upstaging (i.e., patients with stage I or II disease) would therefore be more appropriate than would functional scanning as part of routine pretreatment staging for all patients with lymphoma.

Of even greater potential utility is the use of post-treatment scanning to identify persons who are at high risk of

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recurrent disease. Jerusalem et al. (6) compared PET with CT in 54 patients with Hodgkin's disease or aggressive non-Hodgkin's lymphoma. All patients underwent PET scanning 1 to 3 months after completion of chemotherapy. Relapse occurred in all 6 patients with positive PET scans, 26% of patients with residual CT masses but negative PET, and 10% with negative CT and PET. One-year disease-free survival was 0% for those with positive PET versus 86% for those with negative scans.

In a recent study by Spaepen et al. (7), of patients with aggressive histology non-Hodgkin's lymphoma who underwent PET scanning 1 to 3 months following completion of chemotherapy (and before radiotherapy), 53 of the 67 patients with negative post-treatment PET scans were also CT negative. With a median follow-up of 653 days, there were 10 recurrences (20%) in this group and only 1 recurrence among the 14 with positive CT and negative PET. All 26 post-treatment PET-positive patients relapsed, including 14 who had negative post-treatment CT scans. The 2-year actuarial progression-free survival rate for PET-negative patients was 85%, compared with 4% for those who were PET positive. These data support the routine use of post-treatment PET scanning in aggressive non-Hodgkin's lymphoma, and question the value of post-treatment CT scanning.

These conclusions were reinforced and extended by the same authors at the 2001 annual meeting of the American Society of Hematology, during which they presented the results of a study of early (mid-treatment) restaging PET following three to four cycles of chemotherapy in 70 patients with aggressive non-Hodgkin's lymphoma. None of the 33 patients with persistent ^{18}FDG uptake had durable remissions, while 31 of the 37 with negative scans remained in remission, with a median follow-up of 1107 days. There was a statistically significant association between PET findings and both progression-free and overall survival.

Another presentation at this meeting, by Naumann et al., evaluated residual CT abnormalities following chemotherapy in 58 patients with Hodgkin's or non-Hodgkin's lymphoma. The number of patients with non-Hodgkin's lymphoma was too small to evaluate. However, of the 43 patients with Hodgkin's disease and residual CT abnormalities, 36 had negative post-treatment scans. None of these patients relapsed (median follow-up, 39 months), indicating a strong negative predictive value for PET in this setting.

It is still relatively early to determine how to incorporate ^{18}FDG PET into the management of patients with Hodgkin's or non-Hodgkin's lymphoma. This is a sensitive functional imaging technique that is more convenient than gallium scanning. No doubt it is more expensive than gallium scanning, but if all patients with lymphoma do not require pretreatment scans, as with gallium scanning, cost may not be a substantial factor. The study in this issue of the *Journal* suggests utility in pretreatment PET scanning as a small number of patients will be upstaged, thus resulting in treatment changes. However, this approach may be used most effectively in those who are most likely to have therapy changed due to upstaging—that is, those with early-stage disease. The most convincing data, however, indicate that PET is beneficial in the post- or mid-treatment period for patients receiving chemotherapy for aggressive non-Hodgkin's lymphoma. Early identification of persistent disease may allow some patients to switch to more effective therapy without having to complete a full course of initial treatment. There are limited data on those with Hodgkin's disease, although preliminary results suggest that post-treatment PET scanning may be useful in this setting as well. Should post-treatment PET be reserved only for those with residual CT lesions? The study by Spaepen et al. (7) suggests otherwise, as one half of those with post-treatment positive PET scans had complete remission by CT scan, and all of them relapsed subsequently. Further evaluation of this approach and of the use of PET in Hodgkin's disease will have to await the results of other studies, but clearly, PET is a valuable tool that can help clinicians to identify patients whose prognosis is poor following the use of standard first-line therapies.

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