The place of positron emission tomography imaging in the management of patients with malignant lymphoma

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Positron emission tomography (PET) is increasingly used for the evaluation of patients with Hodgkin's disease (HD) or non-Hodgkin's lymphoma (NHL). Despite recent advances, physicians should still interpret the results of PET studies cautiously. We critically discuss here the potential as well as the pitfalls of PET imaging for staging, prognostic appraisal, early response evaluation, post-treatment assessment and follow-up of patients with lymphoma.

PET imaging performed in addition to conventional imaging techniques, such as computed tomography (CT), improves the staging of lymphoma and thus may result in treatment modifications.[1,2] However, methodological problems have to be pointed out. Most previously unknown lesions detected by ^{18}F-FDG PET have not been confirmed by a biopsy. Biopsy of a single suspect lesion has usually been performed to obtain the diagnosis. Most patients have also undergone a bone marrow biopsy because ^{18}F-FDG PET cannot match its accuracy.[3,4] However, further biopsies have only been performed in the case of equivocal lesions when the results could potentially influence staging and treatment. Sometimes treatment modifications have even been done based on PET results without any proof that PET findings were actually true-positive or true-negative. Several studies attempted to calculate the sensitivity and specificity of PET. However, in the absence of histological proof (the gold standard) this is, by definition, impossible. Hence, most of these studies used a standard of reference. They examined the concordance between routine staging procedures and ^{18}F-FDG PET. Positive findings by both the standard of reference and ^{18}F-FDG PET were regarded as actual locations of disease. Negative findings by both methods were regarded as true-negative (no involvement by lymphoma). In the case of discrepancy, response to treatment and follow-up data were used to assess the exactness of the patient's original evaluation. However, this approach heavily biases results in favor of the least specific test, deceptively making it appear to be more accurate.

An even more important problem is that we do not know whether intensifying treatment based on PET results is really indicated. All our current treatment recommendations are based on studies using conventional imaging techniques. In certain situations, in particular in early stage HD, ongoing research is aimed at reducing long-term side effects. However, several papers reported that, based on PET results, more aggressive treatments have been administered by the clinicians. They justify the routine use of PET because of this suspected impact on treatment. However, is this really good evidence-based medicine? Do we really need to intensify the chemotherapy regimen when only PET imaging shows more advanced disease? Tumor masses identified by PET but not detected by conventional imaging techniques are rather small. One can estimate that many patients are overtreated. In this issue of the journal, Hutchings *et al.* report a substantial improvement of initial staging by ^{18}F-FDG PET and ^{18}F-FDG PET/CT.[5] They confirm previous studies showing that ^{18}F-FDG PET/CT offers advantages over ^{18}F-FDG PET.[6,7] More importantly, they show the first preliminary clinical data indicating that, if upstaging by PET alone was allowed, this could result in unnecessarily more intensive treatment. Of the ten patients who would have been upstaged to a more advanced treatment group by PET, only one progressed after a median follow-up of 24 months.

The problem is probably less critical for the definition of the field of radiation therapy based on PET when involved field radiation is part of the treatment. Theoretically, there is also a risk that we overtreat some small lesions but this is probably at least compensated by avoiding the irradiation of other non-involved but enlarged lymph nodes. Of course, only a prospective randomized trial could really answer the question whether PET-based radiation treatment improves outcome and long-term side effects, but this type of trial is unlikely to be conducted.

^{18}F-FDG PET is also the best non-invasive imaging technique for early response evaluation.[8] When performed after two or three courses of chemotherapy, it allows patients to be separated into two categories, one with and the other without residual ^{18}F-FDG uptake. However, ^{18}F-FDG PET is not a perfect indicator of response because some PET-positive patients still have a good outcome. The probability that PET remains positive depends on the sensitivity of the tomograph (smallest lesion that can be detected), the biology of the tumor (more rapid response to chemotherapy in aggressive tumors), the tumor mass at diagnosis (tumor shrinkage below the detection level occurs later in larger tumors), the drugs used (impact of monoclonal antibodies such as rituximab on the metabolic response rate remains unknown), the dose-intensity of chemotherapy (more rapid regression with higher dose-intensity) and the interval between the last day of chemotherapy and ^{18}F-FDG PET (transiently reduced metabolic activity early after chemotherapy).[8] Since our pilot study published in this Journal in 2000,[9] several studies have confirmed our findings in larger and more homogeneous patient populations. [10-12] In the largest study (90 patients) reported by Haioun *et al.* (including 41% of patients treated with rituximab), the probability of complete remission at the end of treatment was 58% if PET remained positive after two cycles compared with 83% if PET was negative.[11] They observed that the prognostic value of PET results

was independent of the International Prognostic Index (IPI) score and concluded that ^{18}F-FDG PET should be used in first-line chemotherapy to allow a more risk-adapted approach. However, an absolute difference of only 25% is clearly not optimal. Among the 58% of PET-positive patients who achieved a complete remission, many would have been overtreated. Therefore, there is still a long way to go before considering this approach in our routine practice. There are several reasons why it is not yet appropriate to change management based on residual ^{18}F-FDG uptake on interim PET scans in chemotherapy-sensitive patients with NHL. First, when a new drug combination is used routinely, the best timing for the PET evaluation must be re-defined. Hence, the prognostic value of PET after two cycles must be confirmed in a population where all patients receive rituximab. We also need confirmation of these results in prospective multicenter trials in which several nuclear medicine physicians interpret PET studies in different technical conditions. Furthermore, it remains unknown whether the prognosis of PET-positive patients can be improved by intensifying treatment after two cycles of chemotherapy.

Fewer studies have been performed in the field of HD.[13,14] In this issue of the Journal, Gallamini *et al.*[15] present the largest prospective multicenter evaluation so far. They show that PET was able to predict treatment outcome correctly after only two cycles of chemotherapy in in 103 of 108 patients (95%) with advanced stage HD. If other groups are able to confirm these excellent results, a prospective evaluation of early treatment intensification in patients presenting residual ^{18}F-FDG uptake after two cycles would be warranted. Early response evaluation by ^{18}F-FDG PET could also help to select patients with a better prognosis, thereby allowing a less aggressive approach with reduced long-term toxicity. A very interesting multicenter trial (*Chairman Prof JA Radford, Manchester*) in early stage HD is ongoing in the UK. Patients in complete remission, based on PET evaluation, after three cycles of standard chemotherapy (ABVD) are randomized to receive either involved field radiotherapy or no further treatment. Patients with residual ^{18}F-FDG uptake are not randomized and receive further chemotherapy and involved field radiotherapy. The rate of false-negative PET at the end of chemotherapy may be a problem because microscopic disease cannot be detected by PET. If involved field radiotherapy is still needed in many patients to eliminate residual microscopic disease after standard chemotherapy, then the relapse rate in the experimental arm without radiotherapy will be significantly higher. The trial will also show whether PET is able to identify a population of high-risk patients who can be cured by additional chemotherapy and radiotherapy. In any case this PET study will contribute to a better definition of the treatment strategy in early stage HD, a context in which long-term toxicity is clearly an important issue. It will also evaluate the feasibility of undertaking large multicenter trials that integrate PET for treatment stratification.

High-dose chemotherapy followed by autologous stem cell transplantation (ASCT) is the treatment of choice for chemosensitive NHL patients relapsing after conventional chemotherapy. It is also the best treatment option for most HD patients progressing or relapsing after standard chemotherapy. Several studies have shown that ^{18}F-FDG PET during or after reinduction chemotherapy has an important prognostic role in the pretransplantation evaluation of patients with lymphoma.[16-20] Only patients with a negative PET scan have a good long-term disease-free survival rate. However, some patients with residual but decreased ^{18}F-FDG uptake also have a good outcome after autologous transplantation. These high-risk patients may be candidates for trials testing the role of modified and more intensive treatment approaches that still include high-dose chemotherapy followed by ASCT. An important challenge for the future is the development of successful treatment strategies for chemotherapy-refractory patients. These patients have no change in ^{18}F-FDG uptake or even progressive disease based on metabolic response criteria. They may benefit from more experimental treatment options in an ultimate attempt to overcome their poor clinical outlook. The study presented by Schot *et al.* in this issue of the Journal shows that serial PET response assessment has a better predictive accuracy than a single PET evaluation.[21] Unfortunately, they found that exclusion from ASCT was only indicated if PET after stem cell mobilisation showed non-responsive disease. However, for practical, economic and psychological reasons, selection for ASCT should preferably take place before stem cell collection. ^{18}F-FDG PET after allogeneic stem cell transplantation could also be useful for monitoring response to adoptive immunotherapy and deciding on further donor lymphocyte infusions[22] but this remains to be confirmed.

^{18}F-FDG PET is now considered as the non-invasive imaging technique of choice for the detection of residual disease after treatment.[8] Zijlstra *et al*. performed a meta-analysis of the reported sensitivity and specificity of relevant studies published up to January 2004.[23] In this issue of the Journal, they report a pooled sensitivity and specificity for detection of residual disease in HD of 84% and 90%, respectively. For NHL, pooled sensitivity and specificity were 72% and 100%, respectively. According to the clinical situation, PET-positive patients need either directed biopsies to confirm residual disease or further salvage treatment.[8] However, it is important to remember that increased ^{18}F-FDG uptake is not observed only in tumoral tissue. In particular, when abnormal ^{18}F-FDG uptake is seen outside initially involved sites, infectious or inflammatory lesions must be excluded. Consequently, it is always indicated to correlate PET findings with clinical data, other imaging modalities and/or a biopsy before starting salvage therapy.[24] On the other hand, a negative ^{18}F-FDG PET study cannot exclude minimal residual disease leading later to a clinical relapse. Some investigators prefer to combine ^{18}F-FDG PET and conventional imaging response criteria to define the end-of-treatment status of the disease.[25] Indeed, we also found a higher relapse rate in PET-negative patients with residual masses shown by conventional imaging techniques compared to PET-negative patients without residual masses.[26] However, relapse occurred outside of the residual masses in most patients. They had more advanced disease at diagnosis and their initial IPI score indicated that they must be followed more closely because of their higher risk of relapse. We understand that it is difficult for large co-operative groups to

define response based on PET alone because of limited access to PET facilities in the past and lack of experience of recent PET units, thereby reducing confidence in this imaging modality. However, we are convinced that clinical studies will use mainly or exclusively PET-based response criteria in the near future and this approach should thus be validated.

Patients with a high risk of recurrence but an excellent chance of salvage should be observed closely. Good clinical judgment and a careful history and physical examination are the most important components for monitoring patients after treatment. Routine imaging studies are generally not performed. Relapse of lymphoma is usually identified as a result of investigation of symptoms. We performed a pilot study of routine follow-up by PET in patients with HD.[27] We were able to detect residual tumor or relapse up to 9 months before confirmation by biopsy or conventional imaging techniques, but we also found a high rate of false-positive results. More recently, we also analyzed our data for NHL.[28] Based on disappointing results, we have stopped such routine follow-up in unselected patients with aggressive NHL. In contrast, PET could detect relapse several months before the development of clinical symptoms in low-grade NHL. Further studies examining the impact of PET on outcome and a cost-benefit analysis are warranted before using PET routinely in the follow-up of selected patient populations suffering from lymphoma.

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