Positron emission tomography/computed tomography surveillance in patients with lymphoma: a fox hunt?

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Despite improvements in survival rates, relapses after first-line therapy can occur in 20-50% of patients with advanced-stage Hodgkin's lymphoma (HL) or diffuse large-B-cell lymphoma (DLBCL).[1,2] In both diseases, treatment failures are usually observed within 3 years of completion of treatment with the majority of relapses occurring in the first 12 months for HL[3,4] and 18 months for DLBCL.[4] However, no consensus exists on an optimal surveillance strategy to determine a preclinical relapse after first remission, although routine [18F]fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) imaging has become a standard practice in many centers. The benefits of monitoring for recurrence depend on the probability of relapse in the population being tested as well as the sensitivity, specificity and the frequency of the test.[5] The prevalence of relapse in both HL and DLBCL is rare, with reportedly only one relapse per 68 visits in HL[6] and per 40–45 visits for patients with aggressive non-Hodgkin's lymphoma (NHL)[5] based on routine CT scans. While PET/CT has not been closely investigated in a surveillance setting, it has become clear that its accuracy is superior to that of CT imaging. According to results from a meta-analysis, FDG-PET predicts disease relapse with a sensitivity and specificity of 50-100% and 67-100%, respectively, for HL and 33-77% and 82-100%, respectively, for NHL, irrespective of the association of a residual mass on CT.[7] Even with its relatively high sensitivity, the risks and benefits of routine surveillance PET/CT imaging remain controversial, mainly, because of its cost, radiation burden and the high rate of false-positive results (30-80%)[3,8-12] with potential consequences of overtreatment. In this issue of the Journal, El-Galaly *et al.* report the value of surveillance PET/CT in a retrospective cohort of 161 HL patients who achieved a complete or partial remission after first-line treatment.[12] During a median follow-up of 34 months 14% of patients experienced a relapse. With an average of 1.9 PET/CT per patient, the positive predictive value (PPV) of routine PET/CT and clinically indicated PET/CT was 22% and 37%, respectively (P=0.02). However, in a subset of high-risk patients (with extranodal disease, a positive PET result at interim or therapy completion) the PPV increased to 36% while in those without risk factors the PPV was only 5%. Consequently, the authors concluded that the routine use of surveillance PET in HL patients entering complete remission after first-line treatment should be reserved for high-risk patients. These results were in line with those of Petrausch *et al.* who suggested that monitoring may be worthwhile in high-risk DLBCL populations.[11]

The weaknesses of the existing surveillance PET studies include retrospective design, the paucity of prospective data in distinct risk categories, non-standardized interpretation of PET/CT, and the lack of randomized multicenter setting, while the strength is that all data were obtained after achievement of first complete remission in both HL and DLBCL. In the study by El-Galaly *et al.*, the major limitation is the retrospective data procurement from existing reports from a period spanning 10 years without using up-to-date PET scanners, standard protocols, or interpretation criteria.[12] Notwithstanding major steps taken towards standardizing PET readings in lymphoma,[13,14] the reading schemes still vary across centers which may lead to more false positive findings than would be otherwise obtained.

One can readily deduce that frequent PET/CT monitoring is not justifiable for low-risk HL or DLBCL. However, based on the premise that treatment at relapse is more likely to be effective when the disease is in a preclinical stage with a small tumor burden,[15-17] routine surveillance imaging for patients in their first complete remission could be theoretically justified.

A multitude of variables should be considered in order to increase the benefits of surveillance PET/CT imaging in the proper population of patients.

(i) *Presence of clinical symptoms.* In a number of studies, relapses were reported to be associated with clinical symptoms in 55-80% of patients during follow-up.[6,11,15,18] The rate of symptomatology that accounts for recurrence preceding imaging tests could, however, have been overestimated since the development of symptoms usually prompts an imaging test which derails the surveillance scheme for routine imaging. Moreover, most of these studies were performed in the pre-PET era. In a large group of uniformly treated patients with aggressive NHL (n=108), 80% of relapses were diagnosed on the basis of clinical symptoms while planned surveillance imaging identified recurrence in 22% of the cases preceding symptoms.[15] Patients were 4.1 times more likely to have low-risk disease if relapse was diagnosed by routine imaging compared with those diagnosed by clinical findings with median overall 5-year survivals of 54% and 43%, respectively (P=0.13). It is clear that aggressive NHL is more clinically detected than is HL which has a more insidious course at relapse (as an example, see figure 1). Hence, aggressive NHL may be less conducive to surveillance imaging because of the aggressive biology of disease often causing symptoms.

(ii) *Pre-therapy risk for recurrence*. Stratifying patients based on their pre-therapy risk category and routinely monitoring only those who are at high-risk of recurrence could be a rational approach.[11,12] Among high-risk HL patients, three-quarters were found to have a PET-proven relapse during follow-up, whereas in the low-risk subset, only 20% had a PET-proven relapse.[3] These findings were supported by those of another study conducted in a mixed group of 125 patients with HL and aggressive NHL. The majority of relapses (62%) were diagnosed clinically, especially, in the subgroup with aggressive NHL and in cases with extranodal disease (P<0.05).[10] Similarly, in the current issue of the Journal, El-Galaly *et al.* report that the

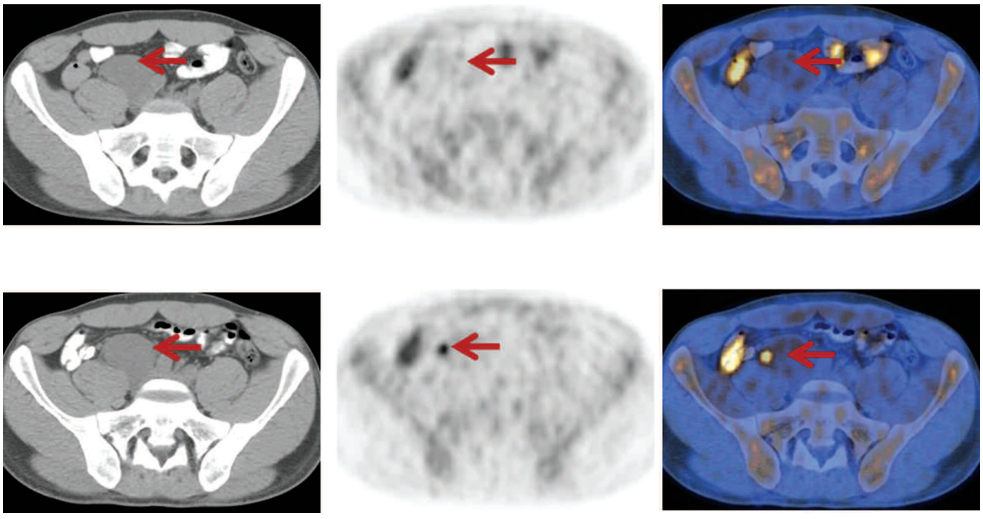

Figure 1. Patient with stage IIB abdominal HL (unfavorable) referred for a routine follow-up 6 months after completion of therapy, with no clinical symptoms. Post-completion PET/CT study (upper panel) shows a mass in the right common iliac region (arrows) with no appreciable FDG uptake consistent with treated lymphoma. However, the 6-month follow-up PET/CT study (lower panel) shows a focus of FDG uptake (arrows) within the mass, consistent with recurrent lymphoma.

highest incidence of relapse occurred in the higher-risk population which included patients with extranodal disease and a positive interim-PET scan.[12] In another retrospective study of 75 DLBCL patients, a risk score on the basis of signs of relapse, age above 60 years, or a combination of these factors identified patients with a high probability of PET-detected recurrence (P=0.04) which supported the use of a follow-up protocol including PET/CT in this subgroup.[11]

(iii) *Early response profile*. There is mounting evidence showing that a positive PET/CT result is associated with a high pre-test likelihood of recurrence which is dictated not only by clinical and biochemical risk factors but also by the early response profile as evidenced by interim PET imaging. Interim PET/CT after two chemotherapy cycles in both HL and DLBCL has been proposed as a surrogate test for chemosensitivity,[14,19-21] proving to be the most powerful independent prognosticator for treatment outcome. In keeping with these observations, 74% of interim PET-positive HL patients and only 20% of interim PET-negative ones had a PET-proven relapse within the first 18 months of follow-up.[3] Similar findings were made by El-Galaly *et al.*[12]

(iv) *Cost-benefit ratio and survival benefit*. Surveillance strategies are intended to detect early relapses in order to be able to institute potentially more effective second-line therapy quickly. The cost associated with indiscriminate routine imaging for HL or DLBCL patients proves prohibitive with today's restrictions in allocations of healthcare resources.[5,9,15,23] The cost of detecting a single event in HL patients was approximately $100,000.[9] The cost of detecting one asymptomatic relapse in patients with aggressive NHL by surveillance imaging, over a 5-year period, was between $42,750 and $85,500.[15] It should be emphasized that the missing link is the unequivocally proven issue of whether or not an early detection of relapse translates into a survival benefit. There is, however, some data indicating that salvage therapy for relapsed DLBCL and HL is more effective in patients with minimal disease burden, suggesting that early detection of relapse might increase the chance of long-term survival.[12,22] These early results should, however, be supported by data from larger populations, particularly high-risk groups.

(v) *Site of relapse.* One important issue to consider in an attempt to decrease false positive readings is that approximately 75% of relapses involve the initial disease sites although new sites of disease can also arise in 25% of patients.[3,12,18] It is, therefore, crucial to interpret the follow-up PET scans with the full knowledge of the extent of the original disease.

(vi) *Persistence of a residual mass at the end of treatment*. Although both HL and DLBCL are chemosensitive diseases, 65-85% of HL patients, especially those with a bulky mediastinal mass, and close to 60% of DLBCL patients presenting with an abdominal bulky lesion will have a residual mass on CT after completion of therapy.[6] Overall, a lymphoma relapse is more likely in those with a PET-positive finding, associated with a concomitant positive result on CT.[3,11,12] In a group of 192 HL patients the factors that were found to significantly improve the PPV in detecting recurrent HL included PET and CT concordance, involvement of a prior site of disease, and the occurrence of a radiographic abnormality within 12 months.[9] In a multivariate analysis of data from 134 HL patients, a morphological residual mass was the only significant risk factor for early follow-up (<24 months) (P=0.002, HR 7.6).[11] Briefly, there are data suggesting that all PET abnormalities are associated with a CT finding in cases with early relapsed disease,[12] but this issue should be further investigated to obtain definitive results from prospective data in a sufficiently large number of patients.

In conclusion, the preponderance of evidence suggests that in the majority of cases surveillance shortens progression-free survival without translating into a prolonged overall survival. One can confidently state that given both economic and psychological impacts on the patient, routine imaging after first complete remission is not indicated in patients with a low-risk profile including favorable interim response profile. Nonetheless, the debate on the role of surveillance FDG-PET cannot be complete without discrete data on patients with high-risk HL and DLBCL. Although the low PPV of FDG-PET raises important questions about this latter's clinical value in identifying patients for immedi-

ate salvage treatment, the, thus far, unproven survival benefit of such an approach should be addressed in a well-designed prospective, multicenter study employing standardized interpretation criteria to address the dilemma in the high-risk subgroup.

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