The role of FDG-PET and bone marrow examination in lymphoma staging

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The introduction of positron emission tomography using [F-18]fluorodeoxyglucose (FDG-PET) has had a substantial impact on the management of patients with lymphoma. Increasing numbers of patients are having an FDG-PET study as part of their initial staging, despite FDG-PET cannot be considered yet a standard procedure for staging in many types of lymphoma. FDG-PET has demonstrated its superiority over conventional imaging to identify nodal and extra-nodal sites of disease and provides complementary information to that obtained with bone marrow biopsy. This can result in disparities in the staging and prognostication of patients based on the procedures used to assess the extension of the disease. The difficulty lies in how to use the information provided by FDG-PET to communicate effectively when using staging classifications and prognostic indices that were designed following conventional imaging.

**Key words:** bone marrow biopsy, FDG-PET, lymphoma, prognosis, stage

Achieving a correct histological diagnosis and an accurate determination of the extension of the disease are the first and most relevant steps in the management of patients with lymphoma. They influence subsequent strategy and have a clear impact on the chances of curing the disease. One of the most important advances in the management of patients with lymphoma in recent years is the introduction of positron emission tomography using [F-18]fluorodeoxyglucose (FDG-PET), to the point that at the last International Conference on Malignant Lymphoma (11-ICML, Lugano 2011) a workshop was held to address the relevance of the Ann Arbor staging system in the current FDG-PET era. Before discussing the impact the introduction of FDG-PET has made in the management of lymphoma (and its potential implication on the need to continue performing bone marrow biopsies—BMBx), it is essential to put these issues in context by reviewing the reasons that underline the importance of an accurate staging. (1) The treatment of patients with lymphoma depends on the extension of the disease. Historically, Ann Arbor staging classification was designed to help in defining radiotherapy fields for patients with Hodgkin lymphoma (HL) when this was the main modality of treatment [1]. It is obvious that in this scenario it is essential to know all areas of involvement by lymphoma to be able to adequately treat the patients. Hence, it might be argued that there is need for an accurate determination of all areas of disease if patients are to be treated with systemic chemotherapy. However, even in the immunochemotherapy era, staging determines treatment in specific circumstances. The typical example is the management of patients with HL, in whom specific protocols are designed for patients with ‘early’ stage and for those with ‘advanced’ stage disease. Similarly, although this might be changing, the standard treatment for patients with localized follicular lymphoma (FL) is involved field radiotherapy, whereas symptomatic patients with advanced stage receive systemic treatment. (2) The extension of the disease determines patients’ outcome. The extension of the disease, as reflected by the stage, is one of the most important predictors of outcome for almost any type of lymphoma. As such, the stage is included in the prognostic indices for aggressive lymphoma (IPI), FL (FLIPI and FLIPI2), mantle cell lymphoma (MIPI), T-NHL and advanced stage HL (Hasenclever index). Furthermore, the IPI includes the number of extra-nodal sites, the FLIPI includes the number of nodal sites and the FLIPI2 includes the size of the largest mass, all these emphasizing the importance of an accurate determination of the extension of the disease. Finally, bone marrow (BM) involvement, diagnosed by BMBx, is part of the MIPI and of the prognostic index for T-NHL. (3) Assessment of response. An accurate assessment of treatment response can only be performed if an adequate initial staging has been carried out and if the same imaging technique is used at baseline and at the end of treatment. The response to treatment is among the strongest predictors of outcome in patients with lymphoma and determines further management, especially in potentially curable diseases such as DLBCL or HL. There is strong evidence that the functional information provided by FDG-PET to assess response to therapy at the end of treatment increases substantially the accuracy of the assessment, so that the revised response criteria developed by the International Harmonization Project published in 2007 recommended the use of FDG-PET for the end-of-therapy response assessment in DLBCL and HL [2]. It should be noted that whereas these guidelines state that the use of FDG-PET for response assessment of ‘aggressive’ NHL subtypes other
than DLBCL and ‘indolent’ lymphomas is less clear, recent data from the PRIMA study support the poor prognostic impact of achieving a partial response defined by FDG-PET in patients with FL treated with immunochemotherapy [3].

The role of FDG-PET and BMBx in lymphoma staging will be reviewed against this background.

role of FDG-PET in the staging of lymphoma

It is generally accepted that imaging the metabolic activity of tumour provides more sensitive and more specific information about the extent of disease than anatomical imaging alone and, thus, FDG-PET has become a standard imaging procedure for staging many types of cancer. The major limitation in assessing the diagnostic accuracy of FDG-PET in lymphoma is the lack of a ‘gold standard’, as, given the multifocal nature of the disease, it is both impractical and unethical to obtain histopathological confirmation of all potential sites of disease. Therefore, most studies use clinical follow-up to confirm findings in lesions not biopsied. Thus, FDG-PET-positive foci that disappear with treatment are assumed to have been involved in spite of the lack of histological proof of malignancy.

Numerous studies using a combination of scan results, histology and clinical follow-up have demonstrated that FDG-PET is able to detect a greater number of involved sites of disease than CT. Specifically, FDG-PET has been found to be more accurate than CT in the assessment of nodal disease [4, 5]. In addition, the identification of extra-nodal involvement is of extreme importance, as it alters the stage and the prognosis of the disease, but CT shows no changes or only subtle changes on extra-nodal areas with disease infiltration. Several studies have reported FDG-PET to be superior to CT also in the detection of extra-nodal disease [5–7]. In a study in 81 patients with lymphoma comparing the ability of FDG-PET and CT to detect extra-nodal disease, FDG-PET revealed 24 additional sites of extra-nodal involvement not detected by CT [6]. In half of the patients up-staged by FDG-PET, this was due to splenic or extra-nodal disease not detected by CT in a similar study in newly diagnosed HL [7]. The superiority of FDG-PET over CT in identifying extra-nodal infiltration was further confirmed in a prospective study in patients with HL, in which the sensitivity of FDG-PET to detect the organ involvement was 86% in comparison with a sensitivity of 37% for CT [5].

However, the crucial question, regarding the role of FDG-PET to assess the initial extension of the disease to determine treatment and prognosis, is whether the ability of FDG-PET to detect additional areas of involvement results in a subsequent change in the stage of the disease and, more importantly, in a change in the management of the patients. The increased accuracy of FDG-PET and the additional lesions visualized contribute to a change in the stage of patients, in a percentage that ranges from 18% to 45% [7–11]. A subsequent change in management has been found in 18%–31% of the patients [8–11]. The wide range is likely to be due to different study populations, with FDG-PET results less likely to impact on the management in those populations with more advanced disease, whilst studies reporting a higher impact may reflect referral biases with FDG-PET being utilized for difficult cases. An early study in 38 patients with HL which aim at obtaining pathological confirmation of positive sites at CT and FDG-PET showed that FDG-PET correctly up-staged 21 patients and down-staged 1, in comparison with CT [12]. In a prospective multi-centre study published by Scott et al. on ‘indolent’ lymphomas, the management plans for the patients were decided on conventional staging methods before reviewing the FDG-PET, and compared with the management plans after the FDG-PET had been reviewed. FDG-PET detected additional involved lesions in 50% of the patients in comparison with conventional CT staging. A change in stage was seen in 32% of patients, who were mostly up-staged. FDG-PET altered the management in 34% of patients. Furthermore, progression-free survival after 12 months of follow-up was found to be significantly shorter in patients with additional lesions detected by FDG-PET [9]. This is consistent with FDG-PET having a prognostic value by identifying patients with a larger tumour burden. Along the same lines, a retrospective study by Wirth et al. including only patients with stage I–II FL reported a 45% change in management when staged by FDG-PET. In this study, widening of the radiotherapy field due to the involvement of further lymph nodes was reported as a change of therapy in patients who did not have a change in stage, partially explaining the high proportion of patients with a change in their management [13]. All these studies demonstrate an important contribution by FDG-PET in revealing disease sites that would have been overlooked by conventional staging, resulting in patients being under-treated. Nonetheless, a related relevant issue, such as how the additional information provided by FDG-PET at diagnosis impacts of the prognostication of the patients altering the prognostic scores, has been much less studied.

role of BMBx in the staging of lymphoma

Bone marrow aspirate and trephine (BMBx) is the current gold standard for the assessment of BM involvement and is an essential part of staging in patients with lymphoma. The presence of disease in the BM leads to a change in the stage, prognosis and, frequently, in the management of patients with different types of lymphoma. However, BMBx is, to say the least, an unpleasant procedure that can potentially miss disease not present in the biopsy area, given the patchy infiltration of BM in many cases or if the biopsy is inadequate in quality. Performing a bilateral BMBx can increase the sensitivity of the procedure by 10%–22%, but given its morbidity most centres, including St Bartholomew’s Hospital, perform only unilateral BMBx. There are several studies examining the role of FDG-PET in the detection of BM involvement in patients with lymphoma. There are no defined criteria for the interpretation of BM involvement on PET studies. In most clinical studies, a ‘positive’ BM on a staging FDG-PET is reported visually if there is diffuse increased activity relative to background tissues, such as background liver activity, or focal non-physiological FDG uptake. A meta-analysis published in 2004 examined the
role of FDG-PET in the assessment of BM involvement in both HL and NHL. It included data from 13 clinical studies and a total of 587 patients. FDG-PET was found to have a high specificity for the detection of a negative BM in HL (92%) and in NHL (88%). However, the sensitivity, although slightly better for HL (76%), was disappointing for NHL (43%). As a result, the authors concluded that FDG-PET could complement a BMBx in the staging of lymphoma, but it cannot replace it [14]. In this sense, most studies report a significant rate of false-negative FDG-PET in patients with ‘indolent’ NHL with a positive BMBx, resulting in a low sensitivity of 39% for FDG-PET to detect BM involvement [15]. This might be due to the focal involvement of the BM in patients with FL, making it difficult to visualize it on FDG-PET, contrasting with the diffuse extensive infiltration seen in patients with ‘aggressive’ lymphoma [16]. Of note, FDG-PET might be able to detect BM involvement in patients with ‘aggressive’ lymphoma but cannot discriminate whether this is due to ‘concordant’ involvement or ‘discordant’ infiltration with ‘indolent’ lymphoma in the BM, so that a BMBx cannot be obviated. More importantly, a BMBx can provide crucial information not available by FDG-PET: the haematopoietic reserve of the BM. Whereas this information is less relevant at diagnosis, it might be essential at the time of relapse. Conversely, there might be cases of focal bone involvement in patients with ‘indolent’ NHL that cannot be detected on a BMBx and would potentially lead to a change in the treatment if identified. Whereas conventional imaging with CT has a low sensitivity for bone involvement, FDG-PET could detect such cases. In summary, the consensus is that, at present, FDG-PET has a complementary role to play in the assessment of BM involvement in patients with lymphoma but cannot replace a BMBx.

In summary, FDG-PET has demonstrated its superiority over CT to identify both nodal and extra-nodal sites of disease, which has a clear impact on the staging and prognostication of patients with lymphoma. This calls into question the usefulness in the FDG-PET era of staging classifications and prognostic indices defined based on conventional staging. In addition, FDG-PET provides complementary information to that obtained with a BMBx, but it cannot replace this procedure.

disclosure

The authors have declared no conflicts of interest.

references