FDG-PET in the evaluation of myeloma in 2012

C. Bodet-Milin\textsuperscript{a,b}, T. Eugène\textsuperscript{a}, C. Bailly\textsuperscript{a}, M. Lacombe\textsuperscript{c}, E. Frampas\textsuperscript{b,d}, B. Dupas\textsuperscript{d}, P. Moreau\textsuperscript{e}, F. Kraeber-Bodéré\textsuperscript{a,*},b,c

\textsuperscript{a} Nuclear Medicine Department, Hôtel-Dieu, CHU de Nantes, 1 place Alexis-Ricordeau, 44093 Nantes cedex 1, France
\textsuperscript{b} CRCNA, Inserm UMR 892, Nantes cedex 1, France
\textsuperscript{c} Nuclear Medicine Department, ICO-Site Gauducheau, Saint-Herblain, France
\textsuperscript{d} Radiology Department, Hôtel-Dieu, CHU de Nantes, 1 place Alexis-Ricordeau, 44093 Nantes cedex 1, France
\textsuperscript{e} Haematology Department, Hôtel-Dieu, CHU de Nantes, 1 place Alexis-Ricordeau, 44093 Nantes cedex 1, France

Abstract
Multiple myeloma (MM) is a malignant haematological disease characterised by clonal proliferation of malignant plasma cells in the bone marrow. MM is expressed by diffuse infiltration of the bone marrow, focal bone lesions and extra-medullary lesions. Conventional staging follows the Salmon and Durie classification, which was recently revised (Salmon and Durie plus) to include MRI and FDG-PET examinations. FDG-PET is being evaluated for initial staging and therapeutic monitoring and its place still needs to be validated, particularly in comparison with MRI of the pelvis and spine, the reference examination for diagnosis, which is systematically combined with X-rays of the skeleton. Certain recent data in the literature suggest that FDG-PET provides better staging of the disease at the time of intervention than MRI, and that the examination has considerable prognostic value when it normalises after the initial courses of chemotherapy and at the end of treatment. As for the evaluation of lymphomas, the interpretation criteria should be standardised.

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Positron emission tomography using fluorine-18 labelled fluorodeoxyglucose (FDG-PET) is a three-dimensional non-invasive whole body imaging technique providing excellent diagnostic performance in terms of sensitivity and resolution. The technique has been validated in recent years in numerous oncological indications, for initial, end of treatment or early therapeutic evaluation of various solid tumours (bronchial, ENT and colorectal carcinomas, melanomas etc.) or haematological diseases (diffuse large B-cell lymphoma

* Corresponding author.

E-mail address: francoise.bodere@chu-nantes.fr (F. Kraeber-Bodéré).

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or Hodgkin’s disease) [1,2]. Semi-quantitative study of the consumption of FDG by determining the standardised uptake value (SUV) may have prognostic value in certain diseases (bronchial carcinomas, lymphomas) [3].

Multiple myeloma (MM) is a malignant haematological disease characterised by the clonal proliferation of malignant plasma cells in the bone marrow. It is expressed by diffuse infiltration of the bone marrow, focal bone lesions and extra-medullary lesions (EML). Conventional staging follows the Salmon and Durie classification, initially described in 1975, which was recently revised (the Salmon and Durie plus classification) to include MRI and FDG-PET results [4,5]. FDG-PET is being evaluated for initial staging and therapeutic monitoring of patients with multiple myeloma (MM), and its place still needs to be validated, particularly in comparison with MRI of the pelvis and spine, the current reference examination for diagnosis systematically combined with X-rays of the skeleton [6]. Certain recent data in the literature nevertheless suggest that FDG-PET provides better staging of the disease at the time of diagnosis than MRI and that the examination has considerable prognostic value when it normalises after the initial courses of chemotherapy and at the end of treatment. As for the evaluation of lymphomas, the interpretation criteria must be standardised for FDG-PET to be used in the routine evaluation of MM.

FDG-PET and initial staging

The clinical symptoms of MM are a combination of anaemia, hypercalcaemia, renal impairment, and above all multiple bone lesions, which are present in 80% of symptomatic patients. At the time of diagnosis, it is indispensable to evaluate these bone lesions by imaging techniques. In addition to exploring the whole body using standard X-rays, an MRI of the pelvis and spine is the reference examination for detecting both focal lesions (FL) and diffuse lesions of the disease [4–6]. Classic imaging shows one or more visible focal osteolytic lesions on standard X-rays, but systemic bone loss with the appearance of osteoporosis may also be found [7]. There are also very rare forms of osteosclerotic myeloma (POEMS syndrome: Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal gammopathy, and Skin lesions) which appear as diffuse or localised bone condensation. A minority of patients appear normal in imaging. Diffuse infiltration of the marrow by MM cells is often accompanied by FL, with or without osteolysis. These well delimited FL are shown by hyperfixation in a FDG-PET scan or an abnormal MRI signal. To avoid false-positives, only abnormalities of at least 5 mm diameter should be considered as focal lesions [8]. At the time of diagnosis, about 5% of patients are considered as having a solitary plasmacytoma (SP) of the soft tissues or bones, most of whom have under-staged MM. Additional bone marrow biopsy, MRI or FDG-PET examinations often re-establish a diagnosis of MM by showing other sites of disease [9–11]. Correct diagnosis is essential for deciding on appropriate treatment; patients with SP rarely require systemic treatment [12].

The sensitivity of MRI is approximately 70% in MM and the number of lesions detected by MRI on diagnosis is an independent prognostic factor of survival, as was shown by the largest series in the literature published in 2007 concerning 611 patients treated in a uniform manner [13]. FDG-PET has been studied in MM more recently, but in 2010, international experts did not recommend its routine use for initial or prognostic evaluation of the disease [6]. Nevertheless, there are strong data in support of its use. Since with FDG-PET, the whole body and skeleton can be explored, its sensitivity is in the order of 90% for detecting myelomatous lesions [14–18], and it shows focal, diffuse or mixed lesions with variable glucose uptake giving variable SUVmax values (Fig. 1). PET combined with CT has shown itself to be superior to PET alone, since analysis of the CT slices improves the detection of bone lesions [13,18].

The sensitivity of FDG-PET is greater than whole body X-ray examinations: the technique shows additional lesions in half the patients but false negatives for small lesions detected by standard X-rays [14]. Small series have compared the sensitivity of FDG-PET with pelvic and spinal MRI [14,15]. The sensitivity of FDG-PET was comparable to or less than that of the MRI for diffuse spinal lesions but detected additional FLs. Moreover, FDG-PET detected additional bone marrow or extra-medullary lesions in the regions not explored by the MRI. In patients with SP, FDG-PET detected additional lesions, with sensitivity and specificity higher than that of MRI (Figs. 2 and 3).

A large series concerning 239 patients, given uniform first line treatment in the “total therapy” double autologous transplantation programme of the group in Little Rock, Arkansas, prospectively compared FDG-PET and MRI for assessing the respective prognostic value of these examinations [16]. In multivariate analysis, the only imaging examination significantly associated with poor prognosis both for survival and for event-free survival when the number of FL was greater than 3 on diagnosis, was FDG-PET. The number of FL on the initial MRI (seven or more) was associated with event-free survival, but not with overall survival [13].

Figure 1. FDG-PET in a patient with multiple myeloma: increase in diffuse bone marrow uptake associated with focal lesions.
The prognostic value of the number of FLs on the initial FDG-PET was confirmed in another recent large series of 192 patients with MM in a double autologous transplantation programme following induction consisting of thalidomide and dexamethasone [16]. In this study, having at least three FL (44% of cases), an SUV > 4.2 (46% of cases), and the presence of EMLs (6%) negatively affected progression-free survival at 4 years. An SUV > 4.2 and the presence of EMLs were also associated with shorter overall survival. It is known that EMLs are associated with poorer prognosis, above all if they are present in the initial staging [19]. Fig. 4 illustrates the case of a patient explored during initial pre-therapeutic staging of MM: PET detected EMLs and the SUV was measured as 22.4 on the skeleton, indicating the aggressiveness of the disease. The more prolonged the evolution of the disease, the more likely it is that low or non-secreting disease will develop, both of which are high risk for poor differentiation and aggressiveness.

FDG-PET is also very useful for evaluating the rare non- or low-secreting forms of MM, which cannot be evaluated by laboratory methods.

**FDG-PET and therapeutic evaluation**

As for malignant lymphoma, obtaining complete metabolic remission (CMR) in an intermediate evaluation before or after autologous transplantation is associated with better survival. In 2009, Bartel et al. showed that normalisation of FDG fixation in focal lesions of bone and the sites of EMLs after the initial course of chemotherapy and before autologous transplantation was associated with
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Figure 3. FDG-PET in a patient with solitary nasopharyngeal plasmacytoma.

Better event-free survival and overall survival [19]. When compared with the genetic profiles, CMR before autologous transplantation seemed to indicate better overall survival in low risk patients and better event-free survival in high-risk patients. In Zamagni’s series, the persistence of an SUV > 4.2 after induction of therapy was associated with lower progression-free survival [17]. Three months after the autologous transplant, CMR was obtained in 65% of patients, with PFS and overall survival at 4 years higher than that of PET-positive patients. Interestingly, 23% of patients obtaining CR according to conventional criteria were considered to be PET-positive. Multivariate analysis showed that the PET status after autologous transplantation was an independent prognostic factor for progression-free survival. Following this publication, in an editorial in Blood in 2011, Moreau discussed the possibility of a new definition of CR in patients being monitored for MM, integrating the data from metabolic imaging [18]. Additional studies and standardised interpreting criteria will be necessary.
Figure 4. FDG-PET in a patient with multiple myeloma: diffuse bone marrow hypermetabolism (a) with lytic lesions extending to the soft tissue (b), splenic (c) and lymph node involvement (d).
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Conclusion

Even if it is still not validated for routine clinical use, FDG-PET seems to be a promising imaging technique for evaluating MM and SP. Recent studies suggest excellent sensitivity, with the initial image, intermediate images after a few courses of chemotherapy and imaging after autologous transplantation having prognostic value for survival.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References