Journal of Leukemia
ISSN: 2329-6917

Rios-Tamayo et al., J Leuk 2015, 3:1
DOI: 10.4172/2329-6917.1000e112

Editorial Open Access

# Positron Emission Tomography with Integrated Computed Tomography in Multiple Myeloma: A Silent Revolution

**Rafael Ríos-Tamayo[1,2*], Antonio Rodríguez Fernández[3], Juan Sáinz[1,2], Rocío Sánchez Sánchez[3], José Manuel Llamas Elvira[3] and Manuel Jurado Chacón[1,2]**

[1]*Monoclonal Gammopathies Unit, University Hospital Virgen de las Nieves, Granada, Spain*

[2]*Genomic Oncology Area, GENYO, Centre for Genomics and Oncological Research, Pfizer /University of Granada /Andalusian Regional Government, PTS, Granada, Spain*

[3]*Department of Nuclear Medicine, University Hospital Virgen de las Nieves, Granada, Spain*

[*]**Corresponding author:** Dr. Rafael Rios-Tamayo, Monoclonal Gammopathies Unit, University Hospital Virgen de las Nieves Granada, Genomic Oncology Area, Genyo, Granada, Spain, Tel: +34 671592298; Fax: +34958020655; E-mail: rriost33@gmail.com

**Rec date:** November 27, 2014, **Acc date:** November 29, 2014; **Pub date:** November 30, 2014



## Editorial

From time to time, the history of multiple myeloma (MM) has been marked by an event that has changed the way we face the management of this disease. The impact of new imaging techniques in the diagnosis, prognosis and treatment of MM could be considered "a silent revolution". For a long time, the valuation of bone disease in MM has been performed using conventional radiology. CRAB features (hypercalcemia, renal failure, anemia, and bone lesions) attributable to the clonal plasma cell proliferative disorder have been used to define active or symptomatic MM disease. MM-related bone disease, mainly in the form of osteolytic lesions, is detected in almost 80% of newly diagnosed MM patients [1]. However, the definition of positive bone disease depends on the technique used. In recent years, major advances have been made in imaging technology with the appearance of new techniques that have shown to have higher sensibility than radiographic bone survey in the detection of bone lesions [2-5]. Positron emission tomography (PET) with 18 fluorine-fluoro-deoxyglucose (FDG) integrated with computed tomography (PET/CT) is a functional imaging technique that can help to assess bone marrow infiltration as well as unsuspected disease sites involving the bones and/or extra-medullary sites. The widespread use of PET/CT as well as magnetic resonance imaging has improved the understanding of the impact of bone disease in MM [6].

The International Myeloma Working Group has recently updated the criteria for the diagnosis of MM [7]. From now on, the term MM refers to MM requiring therapy. One of more sites of osteolytic bone destruction (≥ 5 mm in size) on skeletal radiography, CT or PET/CT, does fulfil the criteria for bone disease in MM and should be regarded as meeting the CRAB requirement. However, in relation to PET/CT, evidence of underlying osteolytic bone destruction is needed on the CT portion of the examination. Although some uncertainty remains in some aspects of MM diagnosis, the boundaries between asymptomatic precursor diseases and CRAB-defined MM are now better defined. Nevertheless, the pathogenesis of MM-induced bone disease is only partially known. Mathematical models serve to better understand this process and could be applied to evaluate current therapies and even suggest new potential therapeutic targets [8].

A growing body of evidence supports the use of PET/CT in the assessment of diagnosis, prognosis and follow-up of MM patients, including concern about stem cell transplantation (SCT). The role of PET/CT in MM and related disorders has been recently reviewed [9] but little is known about the value of this technique in the assessment of monoclonal gammopathies other than active MM [10]. On the other hand, the correct diagnosis and risk of progression of precursor diseases can also be evaluated by PET/CT [11-13]. A study by the Spanish Group of Myeloma aiming to find the role of PET/CT on the risk of progression to MM is on-going. In a single institution study, we have analyzed the baseline findings of PET/CT in 158 patients with monoclonal gammopathies [10]. We were able to identify MM-related bone disease in 80% of symptomatic MM, but 100% of smoldering MM were negative. Interestingly, one of forty-six cases of monoclonal gammopathy of uncertain significance was positive. At the moment, the importance of baseline PET/CT positive findings in patients with true precursor diseases remains to be determined.

Considering the importance of bone disease in relation to the diagnosis of MM, PET/CT can highlight the baseline pattern of bone disease (diffuse or focal), the number and intensity of bone lesions, as well as the presence of extra medullary disease (EMD). The number of focal lesions and EMD give strong prognostic information [14-15]. The prognostic impact of the standardized uptake value (SUV) has been also pointed out in some studies. Serial PET/CT can add useful prognostic information [16-17]. The role of PET/CT in the assessment of response to therapy, including SCT, has been emphasized [18-21]. In our recent study analyzing 88 MM patients [10], we demonstrated a significant impact of PET/CT in overall survival curves when patients who achieved partial or complete response to induction therapy were compared with those who showed disease progression. Although patients with baseline PET/CT positive findings (EMD, more than three focal lesions or diffuse involvement) usually show worse survival curves than negative cases, the difference did not reach statistical significance, likely due to a short follow-up.

PET/CT findings have even questioned the current definition of complete response in MM, [18,22], but, although an important step forward has been recently given [7], standardization of disease definitions according to PET/CT is still needed. Virtually all MM patients will suffer either biological or clinical relapse. Clinical relapse occurs frequently at bones, showing a wide range of possibilities, from a pathological fracture to an asymptomatic or mildly symptomatic bone relapse or progression. Although early diagnosis of bone relapse is still a challenge, the timely use of PET/CT can help to achieve this goal, along with a high degree of clinical suspicion and a proper valuation of biomarkers of biological relapse. Any clinician involved in the care of MM patients has to face the difficulty of some scenarios dealing with patients that may move in a short period of time from a stringent complete response to a relapse or progression. PET/CT can unravel a relapse/progression that might have passed unnoticed. Obviously, this fact has a great clinical impact, allowing early treatment and helping to plan a more definitive approach, such as

reduced-intensity conditioning allogeneic SCT. The importance of PET/CT lies on the ability to help us to make the right decisions at the right time.

Minimal residual disease (MRD) is currently a hot topic in the global care of MM patients and it is commonly assessed in clinical trials by multiparameter flow cytometry or molecular techniques [23,24]. MRD is increasingly used in daily clinical practice owing to its great clinical impact. However, this technique has also limitations and some patients with negative MRD can relapse. At the moment, a debate is open about the role of imaging techniques to help in the assessment of MRD. Therefore, PET/CT could be considered potentially as a complementary technique for the assessment of the MRD status.

PET/CT cannot be considered as a perfect imaging technique for MM, but its increasing use is allowing us to better understand the behavior of MM-related bone disease and to take appropriate action at the right time, thus contributing to improve the care of our patients. The more we know about PET/CT, the more we realize that we have a new ally in the fight against MM. Almost without realizing it, PET/CT is starring a silent revolution in the history of MM. As in other revolutions, time will tell.

## References

1. Terpos E, Morgan G, Dimopoulos MA, Drake MT, Lentzsch S, et al. (2013) International Myeloma Working Group recommendations for the treatment of multiple myeloma-related bone disease. J Clin Oncol 31: 2347-2357.
2. Tan E, Weiss BM, Mena E, Korde N, Choyke PL, et al. (2011) Current and future imaging modalities for multiple myeloma and its precursor states. Leuk Lymphoma 52: 1630-1640.
3. Zamagni E, Cavo M (2012) The role of imaging techniques in the management of multiple myeloma. Br J Haematol 159: 499-513.
4. Regelink JC, Minnema MC, Terpos E, Kamphuis MH, Raijmakers PG, et al. (2013) Comparison of modern and conventional imaging techniques in establishing multiple myeloma-related bone disease: a systematic review. Br J Haematol 162: 50-61.
5. Waheed S, Mitchell A, Usmani S, Epstein J, Yaccoby S, et al. (2013) Standard and novel imaging methods for multiple myeloma: correlates with prognostic laboratory variables including gene expression profiling data. Haematologica 98: 71-78.
6. van Lammeren-Venema D, Regelink JC, Riphagen II, Zweegman S, Hoekstra OS, et al. (2012) Â¹â¸F-fluoro-deoxyglucose positron emission tomography in assessment of myeloma-related bone disease: a systematic review. Cancer 118: 1971-1981.
7. Rajkumar SV, Dimopoulos MA, Palumbo A, Bladé J, Merlini G, et al. (2014) International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol 15: e538-48.
8. Ji B, Genever PG, Patton RJ, Fagan MJ (2014) Mathematical modelling of the pathogenesis of multiple myeloma-induced bone disease. Int J Numer Method Biomed Eng 30: 1085-1102.
9. Dammacco F, Rubini G, Ferrari C, Vacca A, Racanelli V (2014) 18F-FDG PET/CT: a review of diagnostic and prognostic features in multiple myeloma and related disorders. Clin Exp Med.
10. Ríos-Tamayo R, Sáinz J, Puerta JM, Leyva R, Moatassim Y, et al. (2014). The role of PET/CT in the full range of monoclonal gammopathies. Blood 124: abstract 3365.
11. Fouquet G, Guidez S, Herbaux C, Van de Wyngaert Z, Bonnet S, et al. (2014) Impact of initial FDG-PET/CT and serum-free light chain on transformation of conventionally defined solitary plasmacytoma to multiple myeloma. Clin Cancer Res 20: 3254-3260.
12. Zamagni E, Nanni C, Gay F, Pezzi A, Bello M, et al. (2014) The presence of FDG PET/CT focal not osteolytic lesions identifies a subgroup of patients with smoldering multiple myeloma with high-risk of progression into symptomatic disease. Blood 124: abstract 3371.
13. Dykstra BL, Kumar S, Dispenzieri A, Lacy MQ, Buadi F, et al. (2014) PET/CT has major diagnostic value in the evaluation of smoldering multiple myeloma. Blood 124: abstract 3382.
14. Haznedar R, Aki SZ, Akdemir OU, Ozkurt ZN, Ceneli O, et al. (2011) Value of 18F-fluorodeoxyglucose uptake in positron emission tomography/computed tomography in predicting survival in multiple myeloma. Eur J Nucl Med Mol Imaging 38: 1046-1053.
15. Caers J, Withofs N, Hillengass J, Simoni P, Zamagni E, et al. (2014) The role of positron emission tomography-computed tomography and magnetic resonance imaging in diagnosis and follow up of multiple myeloma. Haematologica 99: 629-637.
16. Usmani SZ, Mitchell A, Waheed S, Crowley J, Hoering A, et al. (2013) Prognostic implications of serial 18-fluoro-deoxyglucose emission tomography in multiple myeloma treated with total therapy 3. Blood 121: 1819-1823.
17. Caldarella C, Treglia G (2013) Treatment Response Monitoring in Patients with Multiple Myeloma: The Role of Positron Emission Tomography-Computed Tomography using Fluorine-18-Fluorodeoxyglucose. J Bone Marrow Res 1: e103.
18. Zamagni E, Patriarca F, Nanni C, Zannetti B, Englaro E, et al. (2011) Prognostic relevance of 18-F FDG PET/CT in newly diagnosed multiple myeloma patients treated with upfront autologous transplantation. Blood 118: 5989-5995.
19. Derlin T, Peldschus K, Münster S, Bannas P, Herrmann J, et al. (2013) Comparative diagnostic performance of 18F-FDG PET/CT versus whole-body MRI for determination of remission status in multiple myeloma after stem cell transplantation. Eur Radiol 23: 570-578.
20. Derlin T, Weber C, Habermann CR, Herrmann J, Wisotzki C, et al. (2012) 18F-FDG PET/CT for detection and localization of residual or recurrent disease in patients with multiple myeloma after stem cell transplantation. Eur J Nucl Med Mol Imaging 39: 493-500.
21. Lapa C, Lückerath K, Malzahn U, Samnick S, Einsele H, et al. (2014) 18 FDG-PET/CT for prognostic stratification of patients with multiple myeloma relapse after stem cell transplantation. Oncotarget 5: 7381-7391.
22. Moreau P (2011) PET-CT in MM: a new definition of CR. Blood 118: 5984-5985.
23. Paiva B, Chandia M, Puig N, Vidriales MB, Perez JJ, et al. (2014) The prognostic value of multiparameter flow cytometry minimal residual disease assessment in relapse multiple myeloma. Haematologica .
24. Martinez-Lopez J, Lahuerta JJ, Pepin F, González M, Barrio S, et al. (2014) Prognostic value of deep sequencing method for minimal residual disease detection in multiple myeloma. Blood 123: 3073-3079.