The Role of 18F-FDG-PET/CT Scan in the Management of Multiple Myeloma
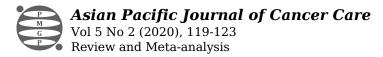
Shirin Haghighat

Shiraz University of Medical Science, Hematology and Medical Oncology

Bone lesion is a myeloma-defining event which is reported in 80% of multiple myeloma patients. Imaging of bone is essential in the evaluation of pattern and extent of bone involvement. Recently, whole body X ray (WBXR) has been replaced by more accurate imaging such as whole bode MRI and FDG-PET/CT scan. This review article provides the advantages and role of PET/CT scan in the diagnosis and management of multiple myeloma patients. Generally, PET/CT in diagnosis of bone involvement of newly diagnosed myeloma patients is more sensitive than WBXR. The prognostic value of PET/CT in newly diagnosed patients has been described as well. Different studies have demonstrated that several PET parameters such as the number of focal lesions (FL), SUV_{max} and extramedullary disease(EMD) may affect the outcome of multiple myeloma patients. Interstingely, the main role of PET/CT in myeloma patients is treatment response monitoring and to some extent assessment of MRD. PET/CT appears to be superior than MRI in evaluation of response due to its ability in differentiating active lesion from negative one.

Introduction

Infiltration and expansion of malignant monoclonal plasma cells, basically in the bone marrow causes multiple myeloma (MM) [1]. As indicated by the global cancer statistics 2018, MM represented 0.9% of all new malignancies and 1.1% of leading causes of cancer death worldwide in 2018 [2]. According to the global burden of multiple myeloma study, age-standardized incidence and mortality were highest in the Australasian, North American, and Western European regions and lowest in Asia, Oceania, and sub-Saharan Africa [3]. It is a proven fact that multiple myeloma develops from an asymptomatic premalignant condition clinically identified as monoclonal gammopathy of undetermined significance (MGUS) [4-5]. Hypercalcemia, anemia, renal function impairment, and bone lesions are classic CRAB features which are currently established diagnostic criteria for symptomatic MM [6]. Recently, International Myeloma Working Group has revised the criteria of diagnosis of MM and has mentioned the use of computed tomography (CT) scan and positron emission tomography (PET) scanning in addition to skeletal radiography to diagnose lytic bone lesions [7]. The most accepted staging system in patients affected by MM includes the international staging system (ISS) and Durie–Salmon staging system (DSS) [8]. The ISS is an easy risk scoring system that includes two parameters; serum β_2-microglobulin level and serum albumin level. This risk stratification system which is established in 2005, classified MM patients into three prognostic groups with different overall survival [9]. DSS predicts survival on the base of four parameters; M component production rate, hemoglobulin concentration, calcium value and the number of lytic bone lesions on X-ray [10]. Interpretation of bone lesions on X-rays have some limitation, so new Durie-salmon plus staging system was developed in 2006 which integrated new imaging techniques such as whole-body CT scan, magnetic resonance imaging (MRI) and whole-body FDG-PET scanning into anatomic and functional staging [11]. Bone involvement is one of the most frequent presentation of multiple myeloma, observed in about two-thirds of patients at the time of diagnosis and in approximately all patients in the course of their diseases [12]. Therefore imaging could be an essential part of the approach to multiple myeloma for detection of lytic bone lesions and identification of extramedullary disease to demonstrate the need for early treatment [12]. Although plain X-rays have been easily available skeletal surveys for a long time, it has a
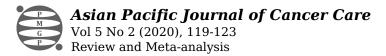
major limitation. Osteolytic bone lesions could be only detectable if at least 30% of trabecular bone is lost [13-14]. More sensitive imaging modalities such as CT, MRI, and PET can be used as an alternative to detect lytic bone lesions at the earlier stage of disease efficiently [15]. The European Society of Medical Oncology (ESMO) and European Myeloma Network (EMN) guidelines recommend a whole-body low dose CT scan as a new standard imaging for the detection of osteolytic bone lesions. These guidelines also recommend MRI and FDG-PET/CT scans to provide more details according to their availability [16-17]. In this article, I focus primarily on the role of FDG-PET/CT scan in the diagnosis, staging, therapy assessment and detection of minimal residual disease.

Diagnostic value of FDG-PET CT scan

PET/CT scan by using FDG as a radiotracer can detect the glucose hypermetabolism of medullary and intramedullary lesions and gives properly both morphological and functional information [14-18]. It is widely accepted that whole-body PET/CT and MRI are equal in detecting focal bone lesions at diagnosis, however, MRI is more powerful at detecting diffuse disease and PET/CT is more reliable in detecting extramedullary diseases [19-20-21)]. National Oncologic PET Registry (NOPR) has recently published the impact of PET/CT on intended management of 16 different cancer types which reported the highest frequency of a change in intended treatment in multiple myeloma (48.7%) compared to other types of cancers [22]. A high impact of PET on the management of patients with plasma cell disorder has been also demonstrated in a Canadian retrospective study with a change in the planned approach in more than 2/3 of patients [15]. A significant correlation between 18F-FDG parameters (SUVs and kinetics) and bone marrow plasma cell infiltration was approved in 40 patients with primary symptomatic multiple myeloma by a German study in 2015 [23]. Several studies have illustrated the sensitivity and specificity ranging from 75% to 100% in detecting lytic bone lesions and staging by PET/CT scan [24-25]. In patients with nonsecretory multiple myeloma who do not have any measurable parameters, more sensitive skeletal survey methods like PET/CT scan can assess the stage of the disease [26]. Another condition in which PET/ CT scan continues to be a considerable topic is solitary plasmacytoma, a single bone or soft tissue mass of clonal plasma cell with no or small bone marrow plasmacytosis. A panel of expert European hematologists recommended PET/CT or MRI, at least one of them, as a mandatory imaging modalitiy in a case of solitary plasmacytoma to exclude the presence of additional lesions [27]. The last IMWG guideline also recommends the PET/CT scan for the first evaluation of patients with solitary extramedullary plasmacytoma [1].

The role of PET/CT in the assessment of prognosis

Several studies have shown the prognostic value of PET/CT in patients with smoldering multiple myeloma (SMM) and MM. A prospective study of a cohort of 120 patients with SMM has shown the probability of progression to MM in 2 years is 58% for patients with positive PET/CT versus 33% for PET/CT-negative patients [28]. Siontis et al. also showed that patients with SMM who have positive PET/CT scans are at higher (75%) risk of progression to symptomatic MM within 2 years [29]. These studies support the use of PET/CT scan to identifying the patients with SMM at higher risk of progression to symptomatic MM who are probably candidates for early initiation of treatment. Bartel et al. demonstrated the impact of PET/CT parameters such as the number of focal lesions (FL), presence of extramedullary disease (EMD), and SUV of lesions on the survival outcome of patients affected by MM [30]. Another Italian study has prospectively evaluated the prognostic significance of the same PET/CT parameters in patients with MM. This study revealed that FL≥3, SUV>4.2, and EMD in PET/CT associated with shorter PFS and OS [31]. Volume-based PET parameters such as metabolic tumor volume (MTV) and total lesion glycolysis (TLG) have been used
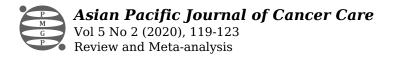
to measure the metabolic activity of the tumor. Fonti et al. reviewed retrospectively medical data of 47 patients with newly diagnosed untreated MM and measured MTV, determined by FDG-PET/CT. They demonstrated the value of MTV in the prediction of PFS and OS in myeloma patients [32]. Similarly, another study by McDonald et al. found the useful survival implication of MTV and TLG. They also demonstrated the superiority of these volumetric measurements on the number and SUV of focal lesions in the prediction of OS and PFS [33]. A Chinese study has found the correlation between ki-67 expression and increase in FDG uptake in PET/CT in patients with EMM. They have also shown the prognostic implication of combination of ki-67 expression and SUVmax in PET in EMM patients [34]. In another study, Cengiz et al. reported that there was a significant correlation between bone marrow FDG uptake and percentage of CD38- and CD-138 expressing plasma cell. They also revealed the correlation between FDG uptake and some prognostically relevant laboratory parameters such as β2M and CRP [35]. As well the correlation between SUVmax in bone lesions and clinical parameters related to tumor burden such as high M protein, plasma cell >20% in bone marrow, β2M>3.5mg/dl, hypercalcemia at the onset of disease, and increased LDH was reported by Li et al [36].

Evaluation of treatment response with F-FDG PET/CT

18F-FDG PET/CT is a superior imaging modality to evaluate the response to treatment because it can distinguish between active and inactive lesions [12]. Several studies have demonstrated that post-treatment PET negativity correlates with a significant response to therapy. They have found the correlation between FDG suppression before transplantation and better outcome [30-31]. Caldarrela et al. have confirmed the usefulness of FDG PET/CT in assessing the response to treatment in a systematic review of 10 studies involving 690 patients with multiple myeloma and solitary plasmacytoma. They also found that response to treatment could be shown by FDG-PET earlier than other imaging tools such as MRI and whole-body X-ray [37]. Another retrospective study of 282 patients with MM showed that in patients achieving conventionally complete response (CR), positive PET associated with two times higher risk of progression compared to negative PET [38]. Several studies have compared FDG-PET with whole-body MRI in post-treatment setting to provide information about the persistent disease. They confirmed that MRI may have falsely positive results due to persistent signal abnormalities in non-active lesions. While the unique role of PET/CT in the evaluation of response to treatment has been proved [39-40]. Another study on 19 patients with multiple myeloma has demonstrated that FDG-PET before and after the first cycle of chemotherapy may be helpful to identify the patients who would respond to this chemotherapy [41]. In recent years, modern combination therapies in newly diagnosed MM patients have improved the depth of response and have increased the minimal residual disease negativity [42]. several meta-analysis and reviews have shown that MRD negativity associated with increased OS and PFS [43-44]. Therefore, improving the currently employed assays to detect the MRD may be considered one of the major goals in the management of MM patients. Different studies have evaluated the complementary role of PET/CT to existing methods such as bone marrow techniques, multiparameter flow cytometry (MFC) and next-generation sequencing (NGS). They reported higher OS in MRD-/PET- or MRD+/ PET- patients (4-year OS 94.2 and 100 % respectively) compared to PET+ patients (4-year OS 73.8%) [45].

What are the limitations of the FDG-PET scan?

Although the usefulness of PET/CT in diagnosis, staging and treatment monitoring has been suggested by several studies some reviews have demonstrated the limitations of PET/CT in this issue. Limited availability and higher cost compared to conventional imaging are the major causes of less application of PET/CT in the diagnosis and management of multiple myeloma in some institutes. False-positive results may be observed in different inflammatory conditions (such as thyroiditis, inflammatory bowel disease, and esophagitis), chemotherapy within the past 4 weeks,

and radiotherapy within the past 2-3 months. Patients who received granulocyte colony-stimulating factors (GCSF) recently may show false positive uptake of FDG in the bone marrow [46]. Post-surgical and fracture areas can be other important causes of false-positive results in the FDG-PET scan [21]. False-negative results including hyperglycemia and recent use of high dose glucocorticoids are other limitations of FDG-PET for evaluation of patients with multiple myeloma. Sequestration phenomenon may be a potential pitfall in interpreting the post-therapy FDG-PET in myeloma patients. Heavily bone marrow infiltration by tumoral cells causes sequestration of 18F-FDG tracer in the bone marrow and lower availability of tracer to detect other sites of active disease. Successful treatment of bone marrow infiltration leads to an increase in the metabolic activity of residual disease then misinterpretation of the residual lesions as a progressive disease [47].

In conclusion, this mini-review shows that available evidence on the value of PET/CT in diagnosis, staging, prognosis and response monitoring is promising. PET/CT can detect myeloma bone lesions with a sensitivity higher than WBXR and comparable to MRI. It may also provide significant prognostic information in smoldering myeloma and solitary plasmacytoma. Interestingly, PET/CT could be a useful tool to monitor the treatment response due to its ability to detect the metabolic activity in lesions.

Acknowledgments

Conflict of interest

References

References

1. Hillengass Jens, Usmani Saad, Rajkumar S Vincent, Durie Brian G M, Mateos María-Victoria, Lonial Sagar, Joao Cristina, Anderson Kenneth C, García-Sanz Ramón, Riva Eloísa, Du Juan, van de Donk Niels, Berdeja Jesús G, Terpos Evangelos, Zamagni Elena, Kyle Robert A, San Miguel Jesús, Goldschmidt Hartmut, Giralt Sergio, Kumar Shaji, Raje Noopur, Ludwig Heinz, Ocio Enrique, Schots Rik, Einsele Hermann, Schjesvold Fredrik, Chen Wen-Ming, Abildgaard Niels, Lipe Brea C, Dytfeld Dominik, Wirk Baldeep Mona, Drake Matthew, Cavo Michele, Lahuerta Juan José, Lentzsch Suzanne. International myeloma working group consensus recommendations on imaging in monoclonal plasma cell disorders. *The Lancet Oncology.* 2019; 20(6)[DOI](DOI)
2. Bray Freddie, Ferlay Jacques, Soerjomataram Isabelle, Siegel Rebecca L., Torre Lindsey A., Jemal Ahmedin. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians.* 2018; 68(6)[DOI](DOI)
3. Cowan Andrew J., Allen Christine, Barac Aleksandra, Basaleem Huda, Bensenor Isabela, Curado Maria Paula, Foreman Kyle, Gupta Rahul, Harvey James, Hosgood H. Dean, Jakovljevic Mihajlo, Khader Yousef, Linn Shai, Lad Deepesh, Mantovani Lorenzo, Nong Vuong Minh, Mokdad Ali, Naghavi Mohsen, Postma Maarten, Roshandel Gholamreza, Shackelford Katya, Sisay Mekonnen, Nguyen Cuong Tat, Tran Tung Thanh, Xuan Bach Tran, Ukwaja Kingsley Nnanna, Vollset Stein Emil, Weiderpass Elisabete, Libby Edward N., Fitzmaurice Christina. Global Burden of Multiple Myeloma. *JAMA Oncology.* 2018; 4(9)[DOI](DOI)
4. Rajkumar S. Vincent, Kumar Shaji. Multiple Myeloma: Diagnosis and Treatment. *Mayo*
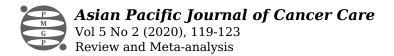
Clinic Proceedings. 2016; 91(1)[DOI]

5. Rajkumar S. Vincent. Evolving diagnostic criteria for multiple myeloma. *Hematology.* 2015; 2015(1)[DOI]

6. Hussain Azhar, Almenfi Hana Farag, Almehdewi Abdelfattah M, Hamza Mohammed S, Bhat Malpe Surekha, Vijayashankar Narasimha Prasad. Laboratory Features of Newly Diagnosed Multiple Myeloma Patients. *Cureus.* 2019. [DOI]

7. Rajkumar S Vincent, Dimopoulos Meletios A, Palumbo Antonio, Blade Joan, Merlini Giampaolo, Mateos María-Victoria, Kumar Shaji, Hillengass Jens, Kastritis Efstathios, Richardson Paul, Landgren Ola, Paiva Bruno, Dispenzieri Angela, Weiss Brendan, LeLeu Xavier, Zweegman Sonja, Lonial Sagar, Rosinol Laura, Zamagni Elena, Jagannath Sundar, Sezer Orhan, Kristinsson Sigurdur Y, Caers Jo, Usmani Saad Z, Lahuerta Juan José, Johnsen Hans Erik, Beksac Meral, Cavo Michele, Goldschmidt Hartmut, Terpos Evangelos, Kyle Robert A, Anderson Kenneth C, Durie Brian G M, Miguel Jesus F San. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. *The Lancet Oncology.* 2014; 15(12)[DOI]

8. Deng Shengming, Zhang Bin, Zhou Yeye, Xu Xin, Li Jihui, Sang Shibiao, Zhang Wei. The Role of18F-FDG PET/CT in Multiple Myeloma Staging according to IMPeTUs: Comparison of the Durie–Salmon Plus and Other Staging Systems. *Contrast Media & Molecular Imaging.* 2018; 2018[DOI]

9. Palumbo Antonio, Avet-Loiseau Hervé, Oliva Stefania, Lokhorst Henk M., Goldschmidt Hartmut, Rosinol Laura, Richardson Paul, Caltagirone Simona, Lahuerta Juan José, Facon Thierry, Bringhen Sara, Gay Francesca, Attal Michel, Passera Roberto, Spencer Andrew, Offidani Massimo, Kumar Shaji, Musto Pellegrino, Lonial Sagar, Petrucci Maria T., Orlowski Robert Z., Zamagni Elena, Morgan Gareth, Dimopoulos Meletios A., Durie Brian G.M., Anderson Kenneth C., Sonneveld Pieter, San Miguel Jésus, Cavo Michele, Rajkumar S. Vincent, Moreau Philippe. Revised International Staging System for Multiple Myeloma: A Report From International Myeloma Working Group. *Journal of Clinical Oncology.* 2015; 33(26)[DOI]

10. Hari P N, Zhang M-J, Roy V, Pérez W S, Bashey A, To L B, Elfenbein G, Freytes C O, Gale R P, Gibson J, Kyle R A, Lazarus H M, McCarthy P L, Milone G A, Pavlovsky S, Reece D E, Schiller G, Vela-Ojeda J, Weisdorf D, Vesole D. Is the international staging system superior to the Durie–Salmon staging system? A comparison in multiple myeloma patients undergoing autologous transplant. *Leukemia.* 2009; 23(8)[DOI]

11. Durie Brian G.M.. The role of anatomic and functional staging in myeloma: Description of Durie/Salmon plus staging system. *European Journal of Cancer.* 2006; 42(11)[DOI]

12. Zamagni Elena, Tacchetti Paola, Cavo Michele. Imaging in multiple myeloma: How? When?. *Blood.* 2019; 133(7)[DOI]

13. Derlin Thorsten. Imaging of multiple myeloma: Current concepts. *World Journal of Orthopedics.* 2014; 5(3)[DOI]

14. Kosmala Aleksander, Bley Thorsten, Petritsch Bernhard. Imaging of Multiple Myeloma. *RöFo - Fortschritte auf dem Gebiet der Röntgenstrahlen und der bildgebenden Verfahren.* 2019; 191(09)[DOI]

15. Shachar Ben, Prica Anca, Anconina Reut, Hawsawy Asmaa, MacCrostie Pamela, Langer Deanna, Metser Ur. Impact of 18F-fluorodeoxyglucose PET/CT in the management of patients with plasma cell disorders. *Nuclear Medicine Communications.* 2020; 41(1)[DOI]

16. Moreau P., San Miguel J., Sonneveld P., Mateos M.V., Zamagni E., Avet-Loiseau H., Hajek R., Dimopoulos M.A., Ludwig H., Einsele H., Zweegman S., Facon T., Cavo M., Terpos E., Goldschmidt H., Attal M., Buske C.. Multiple myeloma: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology.* 2017; 28[DOI]

17. Caers Jo, Garderet Laurent, Kortüm K. Martin, O'Dwyer Michael E., van de Donk Niels W.C.J., Binder Mascha, Dold Sandra Maria, Gay Francesca, Corre Jill, Beguin Yves, Ludwig Heinz, Larocca Alessandra, Driessen Christoph, Dimopoulos Meletios A., Boccadoro Mario, Gramatzki Martin, Zweegman Sonja, Einsele Hermann, Cavo Michele, Goldschmidt Hartmut, Sonneveld Pieter, Delforge Michel, Auner Holger W., Terpos Evangelos, Engelhardt Monika. European Myeloma Network recommendations on tools for the

diagnosis and monitoring of multiple myeloma: what to use and when. *Haematologica.* 2018; 103(11)DOI

18. Messiou Christina, Kaiser Martin. Whole-Body Imaging in Multiple Myeloma. *Magnetic Resonance Imaging Clinics of North America.* 2018; 26(4)DOI

19. van Lammeren-Venema Danielle, Regelink Josien C., Riphagen Ingrid I., Zweegman Sonja, Hoekstra Otto S., Zijlstra Josée M.. 18F-fluoro-deoxyglucose positron emission tomography in assessment of myeloma-related bone disease: A systematic review. *Cancer.* 2011; 118(8)DOI

20. Moreau Philippe, Attal Michel, Caillot Denis, Macro Margaret, Karlin Lionel, Garderet Laurent, Facon Thierry, Benboubker Lotfi, Escoffre-Barbe Martine, Stoppa Anne-Marie, Laribi Kamel, Hulin Cyrille, Perrot Aurore, Marit Gerald, Eveillard Jean-Richard, Caillon Florence, Bodet-Milin Caroline, Pegourie Brigitte, Dorvaux Veronique, Chaleteix Carine, Anderson Kenneth, Richardson Paul, Munshi Nikhil C., Avet-Loiseau Herve, Gaultier Aurelie, Nguyen Jean-Michel, Dupas Benoit, Frampas Eric, Kraeber-Bodere Françoise. Prospective Evaluation of Magnetic Resonance Imaging and [18F]Fluorodeoxyglucose Positron Emission Tomography-Computed Tomography at Diagnosis and Before Maintenance Therapy in Symptomatic Patients With Multiple Myeloma Included in the IFM/DFCI 2009 Trial: Results of the IMAJEM Study. *Journal of Clinical Oncology.* 2017; 35(25)DOI

21. Sachpekidis Christos, Goldschmidt Hartmut, Dimitrakopoulou-Strauss Antonia. Positron Emission Tomography (PET) Radiopharmaceuticals in Multiple Myeloma. *Molecules.* 2019; 25(1)DOI

22. Hillner B. E., Siegel B. A., Shields A. F., Liu D., Gareen I. F., Hunt E., Coleman R. E.. Relationship Between Cancer Type and Impact of PET and PET/CT on Intended Management: Findings of the National Oncologic PET Registry. *Journal of Nuclear Medicine.* 2008; 49(12)DOI

23. Sachpekidis C, Mai EK, Goldschmidt H, Hillengass J, Hose D, Pan L, et al. 18F-FDG Dynamic PET/CT in Patients with Multiple Myeloma Patterns of Tracer Uptake and Correlation With Bone Marrow Plasma Cell Infiltration Rate. *Clin Nucl Med.* 2015; 40:e300-e307.

24. Zamagni Elena, Cavo Michele. The role of imaging techniques in the management of multiple myeloma. *British Journal of Haematology.* 2012. DOI

25. Bailly C, Leforestier R, Jamet B, Carlier T, Bourgeois M, Guérard F, et al. PET Imaging for Initial Staging and Therapy Assessment in Multiple Myeloma Patients. *Int. J. Mol. Sci.* 2017; 18:445.

26. Corso Alessandro, Mangiacavalli Silvia. NON-SECRETORY MYELOMA: READY FOR A NEW DEFINITION?. *Mediterranean Journal of Hematology and Infectious Diseases.* 2017; 9(1)DOI

27. Caers J., Paiva B., Zamagni E., Leleu X., Bladé J., Kristinsson S. Y., Touzeau C., Abildgaard N., Terpos E., Heusschen R., Ocio E., Delforge M., Sezer O., Beksac M., Ludwig H., Merlini G., Moreau P., Zweegman S., Engelhardt M., Rosiñol L.. Diagnosis, treatment, and response assessment in solitary plasmacytoma: updated recommendations from a European Expert Panel. *Journal of Hematology & Oncology.* 2018; 11(1)DOI

28. Zamagni E, Nanni C, Gay F, Pezzi A, Patriarca F, Bellò M, Rambaldi I, Tacchetti P, Hillengass J, Gamberi B, Pantani L, Magarotto V, Versari A, Offidani M, Zannetti B, Carobolante F, Balma M, Musto P, Rensi M, Mancuso K, Dimitrakopoulou-Strauss A, Chauviè S, Rocchi S, Fard N, Marzocchi G, Storto G, Ghedini P, Palumbo A, Fanti S, Cavo M. 18F-FDG PET/CT focal, but not osteolytic, lesions predict the progression of smoldering myeloma to active disease. *Leukemia.* 2015; 30(2)DOI

29. Siontis B, Kumar S, Dispenzieri A, Drake M T, Lacy M Q, Buadi F, Dingli D, Kapoor P, Gonsalves W, Gertz M A, Rajkumar S V. Positron emission tomography-computed tomography in the diagnostic evaluation of smoldering multiple myeloma: identification of patients needing therapy. *Blood Cancer Journal.* 2015; 5(10)DOI

30. Bartel Twyla B., Haessler Jeff, Brown Tracy L. Y., Shaughnessy John D., van Rhee Frits, Anaissie Elias, Alpe Terri, Angtuaco Edgardo, Walker Ronald, Epstein Joshua, Crowley John, Barlogie Bart. F18-fluorodeoxyglucose positron emission tomography in the context of other

imaging techniques and prognostic factors in multiple myeloma. *Blood.* 2009; 114(10)DOI

31. Zamagni Elena, Patriarca Francesca, Nanni Cristina, Zannetti Beatrice, Englaro Emanuela, Pezzi Annalisa, Tacchetti Paola, Buttignol Silvia, Perrone Giulia, Brioli Annamaria, Pantani Lucia, Terragna Carolina, Carobolante Francesca, Baccarani Michele, Fanin Renato, Fanti Stefano, Cavo Michele. Prognostic relevance of 18-F FDG PET/CT in newly diagnosed multiple myeloma patients treated with up-front autologous transplantation. *Blood.* 2011; 118(23)DOI

32. Fonti R., Larobina M., Del Vecchio S., De Luca S., Fabbricini R., Catalano L., Pane F., Salvatore M., Pace L.. Metabolic Tumor Volume Assessed by 18F-FDG PET/CT for the Prediction of Outcome in Patients with Multiple Myeloma. *Journal of Nuclear Medicine.* 2012; 53(12)DOI

33. McDonald James E., Kessler Marcus M., Gardner Michael W., Buros Amy F., Ntambi James A., Waheed Sarah, van Rhee Frits, Zangari Maurizio, Heuck Christoph J., Petty Nathan, Schinke Carolina, Thanendrarajan Sharmilan, Mitchell Alan, Hoering Antje, Barlogie Bart, Morgan Gareth J., Davies Faith E.. Assessment of Total Lesion Glycolysis by 18 F FDG PET/CT Significantly Improves Prognostic Value of GEP and ISS in Myeloma. *Clinical Cancer Research.* 2016; 23(8)DOI

34. Li Qian, Ma Jing, Li Han, Xu Wengui, Cao Zeng, Liu Su, Chen Lin, Gao Shuang, Yan Tinghui, Li Dongying, Wang Xue, Yue Yuanfang, Zhao Zhigang, Wang Xiaofang, Yang Hongliang, Zhao Haifeng, Yu Yong, Zhang Yizhuo, Fan Feiyue, Wang Yafei. Correlation Between Uptake of 18F-FDG During PET/CT and Ki-67 Expression in Patients Newly Diagnosed With Multiple Myeloma Having Extramedullary Involvement. *Technology in Cancer Research & Treatment.* 2019; 18DOI

35. Cengiz Arzu, Arda Hayri Üstün, Döğer Firuzan, Yavaşoğlu İrfan, Yürekli Yakup, Bolaman Ali Zahit. Correlation between baseline 18F-FDG PET/CT findings and CD38, CD138 expressing myeloma cells in bone marrow and clinical parameters in patiens with multiple myeloma. *Turkish Journal of Hematology.* 2018. DOI

36. Li Ying, Liu Junru, Huang Beihui, Chen Meilan, Diao Xiangwen, Li Juan. Application of PET/CT in treatment response evaluation and recurrence prediction in patients with newly-diagnosed multiple myeloma. *Oncotarget.* 2016; 8(15)DOI

37. Caldarella Carmelo, Treglia Giorgio, Isgrò Maria Antonietta, Treglia Ivan, Giordano Alessandro. The Role of Fluorine-18-Fluorodeoxyglucose Positron Emission Tomography in Evaluating the Response to Treatment in Patients with Multiple Myeloma. *International Journal of Molecular Imaging.* 2012; 2012DOI

38. Zamagni E., Nanni C., Mancuso K., Tacchetti P., Pezzi A., Pantani L., Zannetti B., Rambaldi I., Brioli A., Rocchi S., Terragna C., Martello M., Marzocchi G., Borsi E., Rizzello I., Fanti S., Cavo M.. PET/CT Improves the Definition of Complete Response and Allows to Detect Otherwise Unidentifiable Skeletal Progression in Multiple Myeloma. *Clinical Cancer Research.* 2015; 21(19)DOI

39. Derlin Thorsten, Peldschus Kersten, Münster Silvia, Bannas Peter, Herrmann Jochen, Stübig Thomas, Habermann Christian R., Adam Gerhard, Kröger Nicolaus, Weber Christoph. Comparative diagnostic performance of 18F-FDG PET/CT versus whole-body MRI for determination of remission status in multiple myeloma after stem cell transplantation. *European Radiology.* 2012; 23(2)DOI

40. Kumar Shaji, Glazebrook Katrina N., Broski Stephen M.. Fludeoxyglucose F 18 PET/Computed Tomography Evaluation of Therapeutic Response in Multiple Myeloma. *PET Clinics.* 2019; 14(3)DOI

41. Dimitrakopoulou-Strauss Antonia, Hoffmann Martin, Bergner Raoul, Uppenkamp Michael, Haberkorn Uwe, Strauss Ludwig G.. Prediction of Progression-Free Survival in Patients With Multiple Myeloma Following Anthracycline-Based Chemotherapy Based on Dynamic FDG-PET. *Clinical Nuclear Medicine.* 2009; 34(9)DOI

42. Lonial S, Anderson K C. Association of response endpoints with survival outcomes in multiple myeloma. *Leukemia.* 2013; 28(2)DOI

43. Landgren O, Devlin S, Boulad M, Mailankody S. Role of MRD status in relation to clinical outcomes in newly diagnosed multiple myeloma patients: a meta-analysis. *Bone Marrow*

Transplantation. 2016; 51(12)DOI

44. Romano Alessandra, Palumbo Giuseppe Alberto, Parrinello Nunziatina Laura, Conticello Concetta, Martello Marina, Terragna Carolina. Minimal Residual Disease Assessment Within the Bone Marrow of Multiple Myeloma: A Review of Caveats, Clinical Significance and Future Perspectives. *Frontiers in Oncology.* 2019; 9DOI

45. Alonso Rafael, Cedena María Teresa, Gómez-Grande Adolfo, Ríos Rafael, Moraleda José María, Cabañas Valentín, Moreno María José, López-Jiménez Javier, Martín Fernando, Sanz Alejandro, Valeri Antonio, Jiménez Ana, Sánchez Ricardo, Lahuerta Juan José, Martínez-López Joaquín. Imaging and bone marrow assessments improve minimal residual disease prediction in multiple myeloma. *American Journal of Hematology.* 2019; 94(8)DOI

46. Dammacco Franco, Rubini Giuseppe, Ferrari Cristina, Vacca Angelo, Racanelli Vito. 18F-FDG PET/CT: a review of diagnostic and prognostic features in multiple myeloma and related disorders. *Clinical and Experimental Medicine.* 2014; 15(1)DOI

47. Sundaram S, Driscoll J, Fernandez-Ulloa M, Lima M, Malek E. FDG PET imaging in multiple myeloma: implications for response assessments in clinical trials. *Am J Nucl Med Mol Imaging.* 2018; 8(6):421-427.