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Novel Interpretation Criteria (Italian Myeloma Criteria for Positron Emission Tomography Use) Its Prognostic Significance for Fluorodeoxyglucose Labeled with Fluorine-18 Positron Emission Tomography / Computed Tomography in Multiple Myeloma

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ABSTRACT

Background: Multiple Myeloma (MM) is a hematologic malignancy characterized by the proliferation of abnormal plasma cells. Despite advancements in treatment, the management of MM remains challenging due to varying bone marrow involvement, Extramedullary disease (EMD), and the need for standardized imaging evaluation.

Objectives: This study aimed to evaluate the prognostic significance of the Italian Myeloma Criteria for positron emission tomography (PET) Use (IMPeTUs) in MM patients receiving High-Dose Chemotherapy (HDT).

Patients and methods: This prospective study was performed on 42 recently diagnosed symptomatic MM patients at Benha University Hospitals between October 2023 and October 2024. All patients underwent whole-body Fluorodeoxyglucose labeled with Fluorine-18 Positron Emission Tomography/ Computed Tomography [18F] FDG PET/CT imaging before and after treatment, with assessments based on the IMPeTUs criteria.

Results: Significant improvements were observed at follow-up, including a decrease in Deauville score (DS) and hypermetabolic lesions. The occurrence of spine lesions and the uptake of the most intense focal lesion significantly decreased. The number of lytic lesions decreased, and there was a notable reduction in the number of lesions in patients treated with chemotherapy compared to baseline. However, there were no significant changes in EMD, Para Medullary Disease (PMD), or fractures.

Conclusion: Follow-up PET/CT imaging using IMPeTUs criteria offered valuable prognostic information and provided insight into treatment response in MM patients undergoing HDT, supporting its potential for clinical application in improving patient management.

Keywords: IMPeTUs, [18F] FDG, Multiple myeloma, PET imaging criteria, DS.

INTRODUCTION

Multiple myeloma (MM), recognized as the second most prevalent hematologic malignancy, predominantly affects the elderly population. It represents approximately 1% of all diagnosed cancers and accounts for nearly 10% of hematologic neoplasms [1]. MM is defined by the uncontrolled proliferation of abnormal plasma cells that secrete monoclonal immunoglobulins. These pathological plasma cells accumulate within the Bone Marrow (BM), leading to overproduction of immunoglobulins, which can be detected through laboratory testing of serum and/or urine samples [2].

The hallmark clinical manifestations of MM are summarized by the acronym CRAB, which stands for hypercalcemia (C), renal impairment or dysfunction (R), anemia (A), and bone-related damage (B), primarily resulting from the increased activity of osteoclasts induced by the disease [3]. Both the extent of BM involvement and the presence of Extramedullary Disease (EMD) are considered vital in assessing disease prognosis and determining appropriate therapeutic strategies [4].

A pivotal imaging modality in the management of MM is Fluorodeoxyglucose labeled with Fluorine-18 PET/CT, commonly abbreviated as [18F] FDG PET/CT. This hybrid imaging technique is widely utilized due to its high sensitivity and specificity in detecting disease manifestations, including both medullary and extramedullary lesions [5].

One of the major advantages of [18F] FDG PET/CT lies in its ability to differentiate between metabolically active lesions and those that are inactive, thereby establishing its role as the preferred imaging standard for evaluating therapeutic response and disease progression [6]. Nevertheless, [18F] FDG PET/CT is not without limitations. It may produce false-positive or false-negative findings, which can hinder accurate diagnosis and assessment [7].

Interpreting PET/CT scans in patients with MM poses specific challenges, largely due to the heterogeneous nature of BM involvement, the coexistence of MM-related conditions such as EMD and para medullary disease (PMD), and the frequent presence of pathological bone fractures. The typically low proliferation rate of MM cells contributes to inconsistencies in scan interpretation, a lack of universally accepted evaluation criteria, and reduced reproducibility between different observers [8].

In an effort to create a standardized framework for interpreting PET/CT scans in MM, a group of Italian experts developed the Italian Myeloma Criteria for PET Use (IMPeTUs), which incorporates clinically relevant parameters specific to MM imaging [9]. Although, early results with IMPeTUs have been encouraging [10], its

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broader implementation is still limited. This study investigated the prognostic value of IMPeTUs in MM patients receiving high-dose chemotherapy (HDT).

PATIENTS AND METHOD

This prospective cohort study was performed in the Radiology Surgery Department at Benha University Hospitals from October 2023 to October 2024. The study enrolled 42 patients with recently diagnosed, symptomatic MM who were undergoing treatments such as chemotherapy or Bmtrans+.

Inclusion criteria: Patients with a confirmed diagnosis of MM, demonstrated by the presence of an M-component in serum and/or urine along with clonal plasma cells in the BM and/or a documented clonal plasmacytoma. Patients who had digital image data available for retrospective analysis. Patients with a time interval of less than 3 weeks between the assessment of hematological and immunologic parameters and 18F-FDG PET/CT.

Exclusion criteria: Participate who were not committed with follow up. Patients with additional comorbidities. Patients who had underwent treatment before 18F-FDG PET/CT acquisition.

All patients were subjected to: Complete history and physical examination: Personal history (Age, gender, residence, occupation, socioeconomic status, education level and special habits). Primary disease: Asking about any complaint. Past medical: The participants were asked about any concurrent disease or medications uptake. Past surgical history: The participants were asked about any prior surgical procedures. Family medical history.

Clinical examination: Heart rate, systolic and diastolic blood pressure, respiratory rate and oxygen saturation under non-invasive monitoring was done.

Radiological investigations: Whole-body PET/CT scan.

Procedure: Following the standard technique, whole-body PET/CT imaging was conducted sixty minutes after the injection of [18F] FDG. The imaging covered the whole body, from the head to the feet. In accordance with the European Association of Nuclear Medicine (EANM) Linear Scheme, the participants were required to abstain from food for a minimum of six hours before receiving their FDG doses. CT 64-, 128-, and 16-section PET/CT scanners were used in order to gather scans, which covered the full body and were performed utilizing bed positions that lasted for two minutes. On static whole-body PET/CT scans, imaging assessment was performed in accordance with IMPeTU's criteria.

IMPeTUs criteria: In order to reconstruct the images, the OSEM technique was used, although time-of-flight optimization was not utilized. The criteria consisted of an evaluation of the metabolic condition of the bone marrow using the Deauville five-point scale, localized PET-positive lesions (with or without osteolysis), EM and PM illness, and fractures. Both target and EM lesions were visually evaluated to determine their amounts of uptake.

Follow-up: A post-treatment PET/CT examination was carried out on each and every subject. Without regard to the dispersion of the lesion in the first imaging, the Deauville score (DS) was used in order to determine which lesion had the greatest uptake during the subsequent scans. In addition, the anatomical region of the warmest baseline lesion was taken into consideration throughout the DS assessment, independent of the FDG avidity seen in subsequent scans.

Ethical considerations: The study was done after being accepted by The Research Ethics Committee, Benha University. All patients provided written informed consents prior to their enrolment after a comprehensive explanation of the study's aims, procedures, risks, and potential benefits. The consent form explicitly outlined their agreement to participate in the study and for the publication of data, ensuring protection of their confidentiality and privacy. This work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans.

Statistical analysis

Statistical analysis was performed using SPSS software, version 26 (IBM Inc., Chicago, Illinois, USA). Quantitative variables following a parametric distribution were expressed as mean and standard deviation (SD), and comparisons between two independent groups were conducted using the unpaired Student's *t*-test. Non-parametric data were reported as medians along with their interquartile ranges (IQR). Categorical (qualitative) variables were presented as frequencies and percentages (%) and analyzed using either the Chi-square (χ^2) test or Fisher's exact test, depending on the sample size and distribution characteristics. To evaluate the predictive accuracy of specific variables for identifying the presence of cerebral edema in the study population, a receiver operating characteristic (ROC) curve analysis was employed. A two-tailed P value of ≤ 0.05 was considered statistically significant throughout the analysis.

RESULTS

According to the demographic data, the ages of the cases that were investigated varied from 48 to 83 years, with mean 62.33 years. Regarding sex, 52.4% were male. Type of treatment showed that 90.5% of the

studied cases received chemotherapy, while only 9.5% took Bmtrans+ (Table 1).

Table (1): Demographic data and type of treatment among the studied cases.

Variable		(n=42)	
Age: (years)	Median Range	62.33±8.5 48-83	
Variable		**No**	**%**
Sex:	Female Male	20 22	47.6 52.4
Type:	Chemo Bmtrans+	38 4	90.5 9.5

BMtrans+: Bone Marrow Transplant Positive (Patients who have undergone bone marrow transplantation) No: Number (Refers to the count of patients in each category) %: Percentage (Proportion of patients in each category) Chemo: Chemotherapy (Patients who received chemotherapy).

There was a statistically significant decrease in DS score at follow up compared to baseline among the studied cases, where frequency of scores 2, 3, 4 & 5 at base line versus follow up were 9.5%, 33.3%, 38.1% & 19% versus 78.6%, 16.7% 0% & 4.8% respectively.

There was a statistically significant decrease in number of hypermetabolic lesions at follow up compared to baseline among the studied cases, where frequency of F1, F2, F3, F4 & F5 at base line versus follow up were 0%, 16.7%, 50%, 33.3% and 0% versus 21.4%, 57.1%, 11.9% 4.8% & 4.8% respectively. There was a statistically significant decrease in uptake of the hottest focal lesion, DS at follow up compared to baseline among the studied cases, where frequency of score 0, 1, 2, 3 & 4 at base line versus follow up were 4.8%, 73.8%, 7.1%, 9.5% and 4.8% versus 50%, 40.5%, 4.8% 4.8% & 0% respectively. There was a statistically significant decrease in number of lytic lesions by CT at follow up compared to baseline among the studied cases, where frequency of L1, L2, L3, L4 & L5 at base line versus follow up were 0%, 16.7%, 50%, 33.3% and 0% versus 26.2%, 52.4%, 11.9% 4.8% & 4.8% respectively (Table 2).

Table (2): Bone marrow uptake, DS, number of focal, hypermetabolic lesions, uptake of the hottest focal lesion, DS, number of lytic lesions by CT among the studied cases before and after treatment

Variable		Baseline (n=42)		Follow up (n=42)		W	P
		No	**%**	**No**	**%**		
DS:	2	4	9.5	33	78.6	5.18	<0.001**
	3	14	33.3	7	16.7		
	4	16	38.1	0	0		
	5	8	19	2	4.8		
Hypermetabolic lesions:	F1 (no lesions)	0	0	9	21.4	4.63	<0.001**
	F2 (1-3 lesions)	7	16.7	24	57.1		
	F3 (4-10lesions)	21	50	5	11.9		
	F4 (>10 lesions)	14	33.3	2	4.8		
	F5	0	0	2	4.8		
Uptake of the hottest focal lesion, DS:	0	2	4.8	21	50	4.60	<0.001**
	1	31	73.8	17	40.5		
	2	3	7.1	2	4.8		
	3	4	9.5	2	4.8		
	4	2	4.8	0	0		
Number of lytic lesions by CT:	L1 (no lesions)	0	0	11	26.2	5.35	<0.001**
	L2 (1-3 lesions)	7	16.7	22	52.4		
	L3 (4-10lesions)	21	50	5	11.9		
	L4 (>10 lesions)	14	33.3	2	4.8		
	L5	0	0	2	4.8		

W: Wilcoxon test statistic (used for comparing paired data), P: P-value (statistical significance value), DS Deauville Score (used for PET/CT response assessment), F: Focal hypermetabolic lesion category (classification based on lesion count), Uptake of the hottest focal lesion, DS: Deauville Score for the most active lesion, L – Lytic lesion category (classification based on number of lytic lesions on CT), CT: Computed Tomography.

There was statistically significant decrease in frequency of spine lesions when comparing baseline with follow up where frequency of lesions was 73.8% at baseline versus 42.9% at follow up. No difference was founded in skull & other sites where frequency at baseline versus follow up was 26.2% & 90.5% versus 14.3% and 81% respectively. There was a decrease in frequency of presence of at least one fracture among the studied cases at follow up versus baseline (26.7% versus 28.6%) but without statistical significance. The frequency of presence of PMD was comparable among the studied cases when comparing baseline with follow up (4.8% in both). There was a decrease in frequency of presence of EMD among the studied cases at follow up versus baseline (23.8% versus 28.6%) but without statistical significance (Table 3).

Table (3): Site of lesions, presence of at least one fracture, presence of PMD, presence of EMD among the studied cases before and after treatment

Variable		Baseline (n=42)		Follow up (n=42)		P^
		No	%	No	%	
Site:	Spine	31	73.8	18	42.9	<0.001**
	Skull	11	26.2	6	14.3	0.06 NS
	Other	38	90.5	34	81	0.13 NS
Presence of at least one fracture:	No	30	71.4	35	83.3	0.06
	Yes	12	28.6	7	16.7	NS
Presence of PMD:	No	40	95.2	40	95.2	1
	Yes	2	4.8	2	4.8	NS
Presence of EMD:	No	30	71.4	32	76.2	0.50
	Yes	12	28.6	10	23.8	NS

P^: P-value (statistical significance value), NS: Not Significant (indicates no statistically significant difference), PMD – Para medullary Disease (disease occurring near the bone marrow), EMD – Extramedullary Disease (disease occurring outside the bone marrow), No: Number (refers to the count of patients in each category), %: Percentage (proportion of patients in each category).

DISCUSSION

MM is a complex and aggressive hematologic malignancy defined by the unchecked proliferation of monoclonal plasma cells, predominantly within the BM. Its clinical course is remarkably diverse, shaped by a wide spectrum of cytogenetic abnormalities, biological behaviors, and clinical features, which often complicate both staging and prognostic assessment [11].

Among imaging tools, [18F] FDG PET/CT has emerged as the gold standard for monitoring treatment response and disease progression, owing to its high sensitivity and specificity in detecting both medullary and EMD lesions [12]. Yet, despite its value, PET/CT interpretation in MM remains a diagnostic puzzle—clouded by variable patterns of BM involvement, the frequent presence of EMD and PMD, and the typically slow-growing nature of MM cells, all contributing to inconsistencies and low inter-observer reliability [13].

To standardize evaluation, Italian experts developed the Italian Myeloma Criteria for PET Use (IMPeTUs), a structured framework aimed at standardizing PET/CT evaluation by addressing key disease parameters. While promising, these criteria have yet to gain widespread clinical traction [14]. Against this backdrop, our study was conducted at Benha University to explore the prognostic potential of IMPeTUs in MM patients undergoing HDT. Using whole-body PET/CT scans acquired 60 minutes after the administration of [18F] FDG and interpreted in accordance with the EANM Linear Scheme and IMPeTUs criteria, we observed a compelling trend: A statistically significant decline in DS at follow-up compared to baseline, with a clear shift toward lower scores and reduced intensity of the hottest focal lesions.

In the present study, a statistically significant decrease in DS scores was observed at follow-up compared to baseline, with higher frequencies of lower scores at follow-up and the intensity of the hottest focal lesion showed a significant decrease in DS scores at follow-up compared to baseline. These findings are in agreement with a study conducted by multiple authors to comprehensively assess the prognostic significance of the IMPeTUs criteria in MM patients who underwent HDT followed by ASCT. In that study, a total of 47 newly diagnosed MM patients underwent [18F] FDG PET/CT imaging prior to the initiation of therapy (baseline PET/CT), and out of this cohort, 34 patients also underwent follow-up PET/CT scans upon the completion of ASCT. A statistically significant reduction in DS scores was observed when comparing pre-treatment and post-treatment PET/CT scans, particularly in anatomical regions where the most metabolically active lesions, referred to as the hottest lesions, had initially been detected during baseline imaging [15].

One of the defining features of IMPeTUs is its integration of the 5-point DS, a standardized scoring system that was originally designed for the evaluation of Hodgkin lymphoma but has since been adapted to assess skeletal involvement in MM. Despite its implementation, when the Deauville criteria were applied to reference BM and focal MM lesions before the start of treatment, no significant association was found between the DS and PFS, indicating that this scoring system may have limited predictive utility in determining disease progression. These findings are consistent with those of a prior retrospective analysis investigating the role of IMPeTUs in a cohort of 47 MM patients before treatment, where the 5-point DS similarly failed to serve as a reliable predictor of either disease progression or mortality [16]. However, at follow-up, PET/CT scans revealed a marked reduction in the DS of reference BM, reflecting a clear metabolic response to therapy. Two methods were used to assess focal lesions: The first focused on estimating the DS of the most clearly defined focal lesion with the highest uptake on follow-up PET/CT, regardless of the location of the hottest lesion in the baseline imaging [17]. This approach yielded a non-significant decrease in DS as a response to treatment, indicating that while a reduction

in metabolic activity was observed, the change was insufficient to reach statistical significance. Conversely, the second approach centered on the evaluation of DS during follow-up PET/CT, specifically targeting the anatomical regions where the hottest lesion had been identified on the baseline PET/CT, irrespective of whether a clearly defined [18F] FDG-avid lesion remained in those regions following therapy. By focusing on these specific regions of interest, this method revealed a statistically significant reduction in DS after treatment [18].

In the present investigation, a significant decrease in the number of hypermetabolic lesions at follow-up was noted, with a prominent reduction in the higher-frequency lesions (F3, F4, and F5) and a corresponding increase in the lower-frequency lesions (F1 and F2). This shift in lesion frequency suggests a favorable therapeutic response, with the higher-grade lesions showing a marked reduction and the lower-grade lesions becoming more prevalent. These findings are in alignment with multiple studies that have reported a significant reduction in the number of focal, medullary, hypermetabolic lesions at follow-up compared to baseline. In these studies, the majority of patients showed no detectable lesions at follow-up, while a smaller subset continued to exhibit at least one lesion. Among patients with clearly defined, hypermetabolic lesions at follow-up, the median DS of the hottest lesions remained consistent with baseline, suggesting a lack of significant change in the intensity of these lesions [19]. Furthermore, several studies have highlighted the prognostic significance of hypermetabolic soft-tissue components, such as EMD and PMD, with evidence linking their presence to poorer survival outcomes in MM [20].

EMD is a well-established indicator of poor prognosis in MM, and our findings corroborate this in the pre-treatment phase, as evidenced by both univariate and multivariate survival analyses. However, it is noteworthy that the presence of EMD on follow-up PET/CT did not correlate with worse progression-free survival (PFS) in our cohort. This lack of association may be explained by the possibility that these lesions are not true manifestations of EMD but rather represent inflammatory responses induced by treatment. Such inflammatory reactions may result in the appearance of FDG-avid lesions that are not indicative of disease progression, thereby not correlating with PFS [21]. This reasoning is substantiated by two significant factors. rst, the PET findings demonstrate a nearly symmetrical pattern of mediastinal/hilar lymphadenopathy, along with widespread bilateral lymphadenopathy affecting the mediastinal, iliac, and inguinal lymph nodes, and a lung infiltration pattern resembling pneumonitis. Second, the patients' clinical response following ASCT aligns with the clinical gold standard [22]. Although histopathological validation of the imaging findings was not available, such validation would have been essential to conclusively rule out false positives. As a result, in situations where there is inconsistency between imaging and clinical or laboratory findings—particularly in the presence of measurable residual disease—a histopathological examination of ambiguous findings is strongly advised [23].

This observation is consistent with a study conducted by several researchers, which presented a series of cases illustrating the phenomenon of 18F-FDG sequestration by BM heavily infiltrated by myeloma at diagnosis. This sequestration can lead to the misinterpretation of residual disease as PD on follow-up PET/CT scans, even when patients have had a significant response to treatment. Their case series included three patients diagnosed with MM according to the IMWG criteria, all of whom underwent staging based on the Revised International Staging System. In the first case, the post-treatment PET/CT showed minimal 18F-FDG uptake in the BM, with significant improvement in the numerous previously identified axial lesions [24].

18F-FDG PET/CT is a vital tool in MM, as it combines the functional imaging provided by PET with the anatomical insights from CT. This synergy allows for the identification of metabolically active plasma cells both within the BM and extramedullary, helping to predict patient outcomes. The accuracy of 18F-FDG PET/CT is influenced by several factors, including proper patient preparation, individual metabolic variations, and the pharmacokinetics of 18F-FDG, which together determine how well the tracer is taken up. In cases of large, metabolically active tumors or heavily infiltrated marrow, the tracer can accumulate in these malignant regions, leading to sequestration [25]. As a result, less tracer is available for uptake by normal or other pathological sites. A diffuse increase in 18F-FDG uptake in the marrow can notably affect the availability of 18F-FDG to other tissues, including extramedullary tumors, due to the large volume of the BM space. Studies have shown that the activation of the marrow by pegfilgrastim can reduce the amount of 18F-FDG available to the tumor, leading to a decrease in tumor SUV, even though the tumor's metabolic rate remains unchanged [26]. Some researchers developed a correction factor to compute tumor SUV when there is significant marrow 18F-FDG uptake. A similar issue can occur with a higher rate of false negative tumor detection caused by increased muscular uptake due to a non-fasting condition [27]. Following therapy-induced eradication of myeloma-infiltrated marrow, there is an increased availability of 18F-FDG tracer, which can lead to an artificial rise in 18F-FDG uptake at remaining tumor sites. This can complicate the interpretation of 18F-FDG PET/CT scans after treatment [28].

MM treatment eliminates tracer sequestration, causing an artificial rise in metabolic activity at residual disease sites that could be wrongly interpreted as PD, despite a significant treatment response by other criteria. Such situations often lead clinicians to adjust treatment approaches. Therefore, it is essential for

oncologists to recognize this potential issue and interpret 18F-FDG PET/CT findings alongside other clinical and biomedical disease markers [29]. The exact frequency of this sequestration phenomenon is unknown, mainly because PET/CT assessments in MM patients are not conducted frequently. There is a need for prospective trials to explore the extent of 18F-FDG sequestration at diagnosis, identify disease and host factors influencing this process (like increased anaerobic glycolysis), and assess how different anti-myeloma treatments impact the tumor metabolism of myeloma cells (including the reversal of the 'Warburg effect') and the resulting 18F-FDG uptake [30].

In the current study, the number of lytic lesions identified by CT significantly decreased at follow-up, with a reduction in higher frequency lesions (L3, L4, and L5) and an increase in lower frequency lesions (L1 and L2). On the contrary, some authors found that there are no significant differences in the number of lytic lesions (Lx) were observed after follow-up period [31].

The contrary findings between the current study and the studies by several researchers may be attributed to differences in study design, imaging protocols, or patient characteristics. In the current study, significant reductions in the number of lytic lesions identified by CT at follow-up could reflect effective treatment responses, potentially influenced by stricter inclusion criteria or more advanced therapeutic regimens [32]. Conversely, few investigators reported no significant changes in the number of lytic lesions, which may indicate differences in follow-up duration, the sensitivity of imaging techniques, or the criteria used for evaluating lytic lesions. Additionally, variations in the baseline disease burden or the use of concurrent therapies, such as bisphosphonates or bone-modifying agents, could have impacted the progression or resolution of lytic lesions in their cohort. These discrepancies highlight the importance of standardizing imaging evaluation protocols and ensuring homogeneous patient populations in future studies to improve comparability and interpretability of findings [33].

Limitations: This study had some limitations including its single-center design, which may limit generalizability and also the relatively small sample size.

CONCLUSION

In conclusion, our study showed that follow-up PET/CT imaging reveals significant improvements in multiple myeloma patients, including reduced DS, hypermetabolic and lytic lesions, and decreased spine lesion frequency and uptake of the hottest focal lesion. These findings emphasize the role of PET/CT in monitoring disease progression and treatment response, providing valuable insights for patient management and therapy optimization.

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