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[18]F FDG PET/CT Metabolic Volumetric Parameters Versus Deauville Scoring for Therapy Response in Multiple Myeloma Patients.

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ABSTRACT:

Introduction: 18F-FDG PET/CT is an efficient modality to monitor minimal residual disease (MRD), assess disease burden and therapy response. **Purpose:** The aim of this study to assess therapy response in MM patient using either the Deauville scoring (DS) and metabolic volumetric parameters and detect their predictive value. **Patients and methods:** A total of 50 adult patients newly diagnosed with multiple myeloma (MM) were prospectively evaluated. Initial and interim FDG-PET/CT scan were be analyzed using DS and metabolic volumetric parameters then their prognostic value was detected. **Results:** NO statistically significant were be detected for DS either in initial and interim PET/CT studies. Regarding the metabolic parameters, initial MTV and TLG between responder and non-responder categories showed notable significance with p value 0.004. moreover, interim MTV, TLG and SUV peak determined p value 0.021, 0.009 and 0.007 respectively.

Conclusion: Metabolic volumetric parameters were promising tools to predict outcome in MM patient. Cutoff of initial MTV more than 70 showed sensitivity of 78 % and specificity of 71.4 %. The sensitivity of 56 % and specificity of 93 % for cutoff more than 350 for of initial TLG. Interim SUV peak level with cutoff point of more than 3, showing sensitivity of 86 % and specificity of 73 %.

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INTRODUCTION:

Multiple myeloma is currently ranked as the second most prevalent hematological malignancy, it accounts for 1-2% of all diagnosed malignancies and 10-15% of all blood malignancies [1, 2]. Multiple myeloma is mostly at an average age of 69. Fifty percent of patients are over 65, and fifteen percent are under 55 [1]. Abnormal monoclonal plasma cell proliferation in the bone marrow is a characteristic of multiple myeloma causing lytic changes, that primarily affect the axial skeleton, 49% of vertebral bodies, 35% of cranial bones, 34% of pelvic bones, 33% of ribs, and shafts of long bones [3]. The treatment of multiple myeloma is difficult and has seen a lot of progress with the introduction of new treatment lines that aim to achieve minimal disease residual or complete remission in order to move forward with bone marrow transplantation. The primary objective is to identify treatment response early on, whether it is through disease progression or regression [1,2]. Nowadays, PET-CT is the preferred diagnostic technique for evaluating treatment response. It also has a promising future in the identification of active residual disease; early negative PET-CT results following chemotherapy induction are associated with improved survival and a lower relapse rate [4]. **Aim of Work** Examine the predictive value or significant value of Deauville scoring when evaluating therapy response. Correlation between the patient's therapy outcome and metabolic volumetric parameters extracted from PET-CT. Suggesting cut off values for the metabolic parameters extracted to be prognostic discriminators from initial & interim PET-CT

PATIENTS and METHODS:

Fifty adult patients with pathologically confirmed multiple myeloma were enrolled in our prospective study. Between March 2021 and November 2023, all of them were referred to the National Cancer Institute's (NCI) Nuclear Medicine unit.

(18-F) FDG PET/CT imaging: Imaging protocol: PET-CT was done at initial staging. Interim PET-CT was done after completion of 12 weeks of treatment before BMB. Post-therapy PET-CT was done at the end of treatment after completion of 18 weeks of treatment after BMB was done. Patients who achieved complete remission at interim PET-CT, proceeded with BMT and no post-treatment PET-CT was done. **Patient preparation:** Fasting for 4-6 hours prior to the study.

Avoidance of severe muscles exercise for 24 hours prior to the study

Blood glucose level before the F18 FDG administration should not exceed 160 mg/dl. Injected dose is approximately 0.14 mCi/kg body weight of 18-F FDG

max in initial & interim PET-CT, then its value was correlated according to hepatic and blood pool reference activity in both studies. Bone marrow activity was assessed upon drawing ROI over lumbar vertebrae and measuring its SUV max, then its value was also correlated to hepatic and blood pool

Image acquisition: Whole body CT study scanning extended from the level of the skull base till toes when the examined patients in the supine position with elevated arms. FDG PET/CT study was conducted using a dedicated using Discovery PET-CT scanner (GE Medical System, USA) (5).

Qualitative assessment: Initial & interim PET-CT were assessed according to Deauville scoring system where patients as

reference activity in both studies. Finally, a ratio between highest SUV max and bone marrow SUV max was detected in initial and interim studies.

Quantitative assessment: A spherical volume of interest (VOI) is drawn over the regions of interest and then recorded the maximum standardized uptake value (SUV max), mean standardized uptake value (SUV mean), Total lesion glycolysis (TLG), & Metabolic Tumor volume (MTV) in the follow (6); **Score I**: No uptake. **Score II**: Less than or equal mediastinum **Score III**: More than mediastinum, but less than hepatic reference activity **Score IV**: Moderately more than hepatic reference activity **Score Va**: Markedly more than hepatic reference activity **Score Vb**: New lesions. ROI was drawn over the lesion with the highest SUV VOI.

RESULTS:

Fifty MM patients were referred for initial staging by FDG PET/CT, interim PET-CT after 12 weeks of interrupted treatment and after 24 weeks at end of treatment PET-CT.

The patients' average age was 57 +/- 10 years. Sixty-four percent of the patients were older than fifty. The male to female ratio was 1.3:1, with 22% being female and 56% being male.

Comparison between Deauville scoring in initial and interim FDG PET/CT studies:

Out of 50 patients included in the study; 13 patients died during therapy. Median of SUV max in interim PET/CT scans showed decline in its value more than 50% compared to initial studies. 3.4 was the median bone marrow uptake in initial PET-CT that declined to 2 at interim scans. The median ratio of lesion (SUV max) to bone marrow (SUV max) is 1.9 (ranging from 0.9 to 11.1), where lower ratios are associated with higher bone marrow uptake than highest SUV max. Regarding the lesion/liver ratio, 48 patients presented with SUV max of the highest lesion more than liver (24 Deauville 4 and 24 Deauville 5) in initial PET/CT decreased to 20 patients at interim PET/CT scans. While the SUV max of remaining 17 patients became less than liver reference (7 patients with Deauville scoring 3, 7 patients with Deauville scoring 2 and three patients with Deauville scoring 1). 28 patients in initial scans presented with BM uptake higher than liver (24 presented with Deauville scoring 4 and 4 presented with Deauville 5) declined to 7 patients at interim studies

Table (1) Deauville scoring in initial and Interim PET-CT

	Median (range) for initial PET/CT	Median (range) for Interim PET/CT
SUV max	6.7 (3.1-41.1)	3 (2-12)
BM uptake	3.4 (1.8-10)	2 (1-6)
lesion to BM ratio	1.9 (0.9-11.1)	1.4 (0.7-6.9)
Lesion to liver (DS)	**n =50 (%)**	**n=37 (%)**
1	-	3 (8.1)
2	2 (4)	7 (18.9)
3	-	7 (18.9)
4	24 (48)	18 (48.6)
5	24 (48)	2 (5.4)
BM to liver		
1	3 (6)	12 (32.4)
2	14 (28)	14 (37.8)
3	5 (10)	4 (10.8)
4	24 (48)	7 (18.9)
5	4 (8)	

Volumetric parameters in initial and interim FDG PET/CT studies:

Baseline FDG PET/CT scans were retrieved, and PET volumetric images were analyzed for metabolic parameters SUV max, MTV and TLG and SUV peak. The patients showed decline in all volumetric parameters **(table 2)**.

at interim PET/CT studied as follow: Median MTV of 47 at initial studies declined to 22 at interim scans. 134 of median TLG at baseline scans decreased to 32.6 at interim studies.

Table (2): Median for volumetric parameters at initial and interim PET CT.

	Median for initial PET/CT parameters	Median for interim PET/CT parameters
MTV	47	22
TLG	134	32.6
SUV peak	6	2.8

At end of therapy (after 24 weeks) in patients with multiple myeloma: 14 patient (37.8%) achieved complete response, similar percentage show partial response. Only three patients (8.1%) were stationary and 16.2% (about 6 patient) had progressive disease. Patients who attained CR or PR were further categorized as responder, while non-responders are those with SD or PD.

Prognostic value of Deauville scoring and volumetric parameters in multiple myeloma patients:

A- **For Deauville scoring**, there was no statistically significant difference in response in relation to initial and interim PET CT data.

B- Regarding the metabolic parameters:

Initial PET/CT:
It was significantly notable that initial PET derived primary **MTV** non-respondent (median value of 186.5) compared to respondent (P value 0.012). **TLG** as well was significantly higher among non-respondent (median value of 358) compared to respondent (P value 0.004). The rest of initial PET-CT parameters (SUVmax, and SUVpeak) showed no statistically significant difference between respondent and non-respondent.

Interim PET/CT: It was significantly notable that interim PET derived **MTV, TLG and SUV peak non-responders** (P value 0.021, 0.009 and 0.007 respectively). **ROC curve** was used to mark a prognostic cut off points from the extracted primary volumetric parameters that could discriminate responders from non-responders.

Initial TLG level was the most important predictor for response with cutoff point of **more than 350**, showing sensitivity of 56 % and specificity of 93 %. For every unit increase in TLG level the risk of non-responsiveness increases by 2%. **Initial MTV** was also significant in detection of early responders with cutoff point **more than 70**, showing sensitivity of 78 % and specificity of 71.4 %. (**Figure 1,2**). **Interim SUV peak** level was the most important predictor for response with cutoff point of **more than 3**, showing sensitivity of 86 % and specificity of 73 % (**Figure 3).**
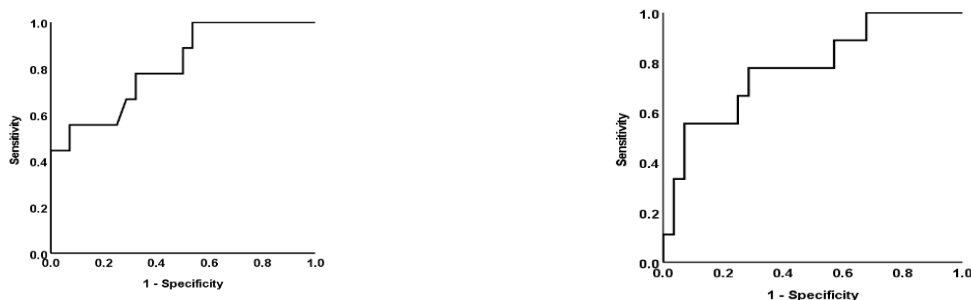
Figure 1. ROC Curve for initial TLG (on the right side) & MTV level

(on the lift side) that predict treatment response.
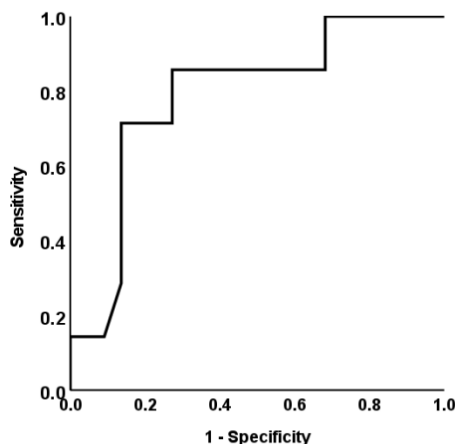
Figure 2. ROC Curve for interim SUV peak level that detect response in patients with MM.

DISCUSSION:

18F-FDG PET/CT is dramatically used for the detection of myeloma bone disease and extra-medullary sites of metabolically active myeloma foci with relatively high sensitivity and specificity. Furthermore, follow-up PET/CT scans can be utilized to monitor treatment response [4].

Trials have been focusing in enhancing the sensitivity and/or specificity of PET-CT as an initial prognostic tool for detection of early responders or non-responder, creating visual scoring system. By evaluating Deauville scoring for initial PET-CT in our study; most patients presented with highest focal lesions showing Deauville scoring IV and V. Median bone marrow uptake in initial PET-CT was 3.4 where 24 patients presented with BM Deauville 4.

Interim PET-CT showed regression of median SUVmax~3.5, most patients presented with Deauville scoring IV and II. For bone marrow uptake, median SUV max~ 2, with most patients show Deauville scoring I and II. PET-CT can identify minimal residual disease and an early therapy response by measuring the change in FDG

avidity in myelomatous lesions. [7]. **Dimitrakopoulou et al.** have examined the usefulness of a follow-up PET-CT scan following the initial chemotherapy cycle in 19 patients with MM. a median initial SUV max of 2.24 and post 1st cycle of SUVmax~1.74 was obtained. This study concluded that short term FU PET-CT is a powerful prognostic tool [8].

Nowadays, FDG-PET-CT volumetric quantifications are thought to be an important tool for determining the aggressiveness of bone marrow infiltration and early treatment response during the initial staging process. Evaluation of initial PET-CT volumetric parameters showing median SUV max of 6.7, further parameters are extracted including MTV, SUV mean, SUV peak and TLG with median ranges of (47, 2.8, 6 and 134) respectively. Regarding initial PET-CT predictive value of early treatment response, in the present study only primary MTV and TLG shows higher level among non-respondents (median MTV value of 186.5 with P value 0.012) and (median TLG value of 358 with P value 0.004). the cutoff values for MTV and TLG were (> 70 and > 350 respectively), with sensitivity of (78 and 56 respectively) and specificity of (71.4 and 93 respectively). Our study illustrated the additional value of initial and interim (after 12 weeks of treatment) PET-CT volumetric parameters as a prognostic tool in patients with multiple myeloma for the detection of therapy response. MTV, TLG and SUV peak parameters of interim PET-CT shows significant value in detection of treatment response. They show **higher levels among non-responders** (P value 0.021, 0.009 and 0.007 respectively). Considering Deauville scoring of initial and interim PET-CT; no statistically significant difference in response detection could be determined. Similarly; 47 patients with multiple myeloma were collected in a study done **by Fonti et al**. the median range of SUVmax was 8.1, median MTV of 23.7 mL and median TLG of 91.4 g. No statistical significance determined for PET-CT volumetric parameters such as SUVmax and SUVmean. However, **MTV and TLG** exhibits significant higher values in recognition of disease progression with cutoff points of **77.6 mL and 201.4** g respectively [9].

Moreover, retrospective study comprised forty-seven patients experienced for evaluation of PET/CT. A statistically significant difference was noticed between SUV max, MTV, TLG, and number of lytic lesions [10].

CONCLUSION:

Initial and interim FDG PET/CT volumetric parameters are useful tools for prediction of early treatment response in multiple myeloma patients. Deauville scoring showed significant reduction in its value during interim PET-CT compared to initial one; however, it has no significant role in early treatment response evaluation. Further studies including higher number of patients are recommended.

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