^{18}F-FDG PET/CT Can be Used to Predict Progression in Smoldering Multiple Myeloma Patients

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Introduction

- There is a need to refine smoldering multiple myeloma (SMM) risk stratification, to identify high-risk patients that may benefit from early intervention.
- In multiple myeloma (MM) increased uptake on ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) is a poor prognostic marker.

In SMM, 2 prior studies have shown that FDG uptake can have prognostic value:

1. Focal lesions with FDG uptake and without osteolysis are associated with an increased risk of progression to active MM [1]
2. SMM patients with PET/CT scans post-diagnosis, an increased mean standardized uptake value (SUV) at L4 has been shown to increase the risk of progression to MM or death [2]

However, these studies have not been validated in an independent cohort of patients with SMM.

Study Aim

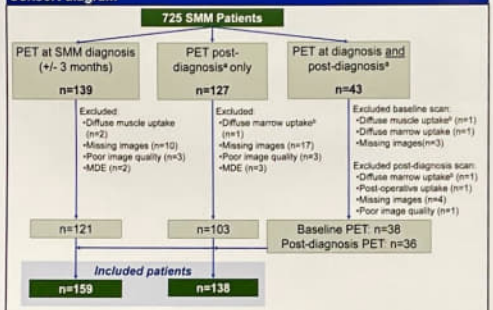
Validate prior studies assessing the prognostic utility of focal lesions without osteolysis and the L4 SUV update as indicators of progression risk in patients with SMM.

Methods

- Retrospectively study
- Inclusion criteria
  - SMM patients diagnosed between January 2000 to January 2020
  - Available 18F-FDG PET/CT images either within 3 months of SMM diagnosis, or between diagnosis and treatment for MM.
- Exclusion criteria
  - Baseline FLCr ≥100 and involved FLC ≥ 10 mg/dL or bone marrow plasma cells ≥ 60% were excluded
  - Baseline osteolytic or extramedullary lesions.
  - PET/CT scans conducted within 3 months of progression to MM or last follow-up
- PET/CT scans were evaluated by two independent reviewers, including a radiologist with nuclear radiology specialization.
- Focal lesions were defined as FDG-avid lesions without underlying osteolysis on CT.
- The mean and maximum SUV of L4 and the liver were determined using MIM software (MIM Software Inc., Cleveland, OH, USA).
- Statistical analysis
  - Kaplan Meier survival analysis was used to assess the time to progression (TTP)
  - TTP was calculated from the date of PET/CT imaging acquisition to progression.
  - Progression was defined as MM with end organ damage (hypercalcemia, renal failure, or lytic bone lesions).
  - Cox proportional hazards models were used to estimate hazard ratios.

Results

Consort diagram



Abbreviations: (18)F-fluorodeoxyglucose positron emission tomography (PET), computed tomography (CT), myeloma defining event (MDE)
*Post-diagnosis PET scans were conducted >3 months post-diagnosis and >12 months prior to last follow up in patients without progression and >3 months prior to last progression in patients with progression
§Patients with a known myeloproliferative neoplasm were excluded (n=1 chronic myeloid leukemia, n=1 chronic neutrophilic leukemia)

Baseline characteristics of study cohort

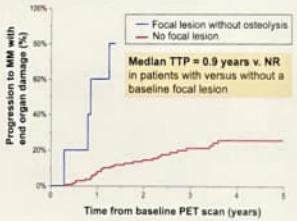
	Baseline PET/CT at SMM diagnosis (n=159)	PET/CT post SMM diagnosis (n=138)
Median age at SMM diagnosis - n (IQR)	66.3 (57.3-72.9)	67.4 (58.4-74.8)
Sex – n (%)		
Male	99 (62)	67 (49)
Female	60 (38)	71 (51)
Median time from SMM diagnosis to PET/CT (months) - n(IQR)	0.7 (0.2-1.8)	32 (12.6-61.6)
SMM diagnosis		
Median BMPC - % (IQR)	20 (13-27)	15 (10-20)
Median MCP - g/dL (IQR)	1.7 (1.1-2.5)	1.6 (1-2.5)
Median involved:uninvolved FLCr - n (IQR)	9 (4-24.4)	8.1 (2.5-23.8)
Median Hb - g/dL (IQR)	12.8 (11.7-13.9)	12.9 (11.3-13.9)
At PET/CT imaging date		
Median MCP - g/dL (IQR)	-	2.1 (1.2-3)
Median involved:uninvolved FLCr - n (IQR)	-	15.3 (3.3-39.9)
Median Hb - g/dL (IQR)	-	12.6 (11.4-13.7)
Baseline Mayo 2018 risk*		
Low (score 0) - n(%)	63 (40)	57 (41)
Intermediate (score 1) - n(%)	47 (30)	45 (33)
High (score ≥2) - n(%)	49 (30)	36 (26)
Location of imaging		
Mayo Clinic - n(%)	100 (63)	97 (70)
External institution - n(%)	60 (37)	41 (30)

Abbreviations: bone marrow plasma cell percentage (BMPC), monoclonal protein (MCP), free light chain ratio (FLCr)
*The Mayo 2018 SMM risk score incorporates 3 risk factors, with a point for each risk factor present: involved to uninvolved FLCr >20, MCP >2 g/dL, and BM PC >20% [3]

Focal lesions without osteolysis on PET

- 5 (3.1%) patients with a baseline PET/CT scan (n=159) had a focal lesion (n=1 with 5 focal lesions, n=1 with 2 focal lesions, n=3 with 1 focal lesion).
- The median SUVmax of focal lesions was 4.6 (range 3.6-6.9).
- **The TTP to symptomatic MM was significantly higher in SMM patients with a focal lesion** on **baseline PET/CT** imaging versus those without **(HR 12.7, 95% CI 4.2-38.3, p<0.001)**, even after **adjusting** for baseline Mayo 2018 SMM risk score, sex, PET/CT location (images acquired at Mayo Clinic vs. an external institution) and age at SMM diagnosis **(HR 6.1, 95% CI 1.9-20.3, p=0.003)**.

Progression to multiple myeloma with end organ damage, stratified by the presence or absence of focal lesions without underlying osteolysis on **baseline** PET imaging.



L4 vertebral body SUV uptake

- Among the 138 patients with a PET/CT scan post-diagnosis, the median L4 SUV_{mean} was 1.9 (IQR 1.6-2.2).
- There was no correlation between the L4 SUV_{mean} and biomarkers of tumor burden (serum monoclonal protein [MCP] level or free light chain ratio at time of PET/CT imaging).
- The **risk of progression was significantly higher in patients with an L4 SUV_{mean} above versus below the liver SUV_{mean}** in patients with:
  - PET/CT imaging **at SMM diagnosis (HR 2.7, 95% CI 1.1-6.2, p=0.02)**
  - PET/CT imaging **post-SMM diagnosis (HR 3.7, 95% CI 1.6-8.2, p=0.001)**
  - PET/CT imaging **post-SMM diagnosis after adjusting for sex, hemoglobin level, serum MCP, and age at the time of follow up PET/CT imaging (HR 4.3, 95% CI 1.8-10.3, p<0.001).**

Conclusion

- Our results validate the findings that in SMM patients, focal lesions without underlying osteolysis on baseline ^{18}F-FDG PET/CT imaging and an SUV_{mean} at L4 that is higher than the liver are associated with an increased risk of progression to active multiple myeloma.
- These markers could be incorporated into SMM risk stratification models to further optimize risk prognostication

References

1. Zamagni et al., Leukemia 2016; 30: 417-422
2. Amini et al., Skeletal Radiology 2021; 50: 79-85
3. Lakshman et al., BCJ 2018; 8: 59

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