Lymphoid Organs' Metabolism and its Role in Predicting the Outcomes of Patients with Malignant Melanoma Treated with Immunotherapy – an Exploratory Study

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Abstract

Background.

This study aimed to evaluate the changes in 2-[18F]-FDG PET/CT parameters of lymphoid organs and their association with clinical outcomes in melanoma patients undergoing immunotherapy.

Materials and methods.

Ninety-two consecutive patients with malignant melanoma were enrolled in the study. Patients underwent serial 2-[18F]-FDG PET/CT scans at baseline (PET0), 6 months (PET1), 18 months (PET2), and 36 months after starting immunotherapy. Visual and semiquantitative analyses were performed by two experienced nuclear medicine specialists. Mean standardized uptake values (SUVmean) of the liver and spleen were measured, and the Spleen Liver Ratio (SLR) was calculated. Clinical assessments and disease outcomes were recorded based on physical examinations, routine blood work, serum chemistry studies, and conventional imaging. Progression-free survival (PFS) and overall survival (OS) were also determined.

Results.

Most patients received anti-PD1 therapy, and radiotherapy was combined with systemic treatment in some cases. After 6, and 18 months, clinical disease control was achieved in 74% and 74%, respectively. Patients without clinical disease control exhibited higher bone marrow FDG uptake and an increase in the sites of metabolic lesions. Median SLR values were slightly higher in patients without disease control after 6 and 18 months, but lower after 36 months. At PET0, the median SLR at PET0 was higher in alive patients than who died, while it was similar in the following scans. Patients with signs of inflammation on PET1 had a higher baseline SLR, which decreased in the subsequent PET2 scan.

Conclusions.

Changes in bone marrow FDG uptake may serve as potential indicators of treatment response and disease outcomes. SLR would be considered an interesting predictive and prognostic indicator. This study provides insights into the dynamic changes of metabolic parameters during immunotherapy and their clinical implications in malignant melanoma patients.

INTRODUCTION

The advent of immunotherapy in clinical practice has brought about a significant transformation in the prognosis of patients affected by malignant melanoma. The first agent to make an impact was the cytotoxic T lymphocyte-associated protein 4 (CTLA-4) inhibitor, ipilimumab, which demonstrated improved survival rates in melanoma patients [1]. Subsequently, programmed cell death protein (PD1) or PD1-ligand inhibitors, such as pembrolizumab and nivolumab, have been employed in the treatment of various solid cancers, including melanoma [2], showing promising clinical improvements and increased survival rates.

Despite the success of immune checkpoint inhibitors (ICIs), a significant proportion of patients with malignant melanoma do not respond at all to immunotherapy or require combination treatments. Consequently, one of the primary challenges in patients undergoing immunotherapy is to identify specific parameters capable of predicting treatment success or failure. In this context, medical imaging plays a crucial role.

18F-Fluorodeoxyglucose (2-[18F]-FDG) positron emission tomography/computed tomography (PET/CT) is an essential tool for staging malignancy based on tumor extent and identifying target lesions as reference points for future assessment of ICIs' antitumor activity [3]. According to Seban et al, [4] three main biomarkers can be derived from the analysis of 2-[18F]-FDG PET/CT, namely tumor burden, tumor glucose uptake, and nontumoral hematopoietic tissue metabolism. In melanoma patients, all these metabolic parameters have been correlated with both the response to therapy and the prognosis [5].

Anwar et al [6] demonstrated that the absolute number of metabolic lesions can predict the response to therapy during ICIs. Patients who showed an appearance of more than four lesions at PET exhibited disease progression and poor prognosis. Moreover, an increase in 2-[18F]-FDG uptake at the bone marrow level has been found to be correlated with the prognosis [4].

The mean spleen-to-liver ratio (SLRmean = spleen SUVmean/liver SUVmean) has been associated with a poor prognosis [7–10]. However, its role in predicting the response to therapy is still under evaluation [11–13].

The objective of the present study was to assess whether changes in mean SLR, bone marrow uptake, and the site of metabolic lesions at 2-[18F]-FDG PET/CT can predict the clinical response to ICIs and the outcomes of malignant melanoma patients.

MATERIALS AND METHODS

Study approval and patient population

The study protocol received approval from the institutional ethical committee at the "dei Colli" Hospital in Napoli, Italy, in July 2020 (Approval No. AOC-0020062-2020). The research involved collaboration from eight Italian centers, each possessing well-established experience in PET/CT and oncology. To facilitate data collection, a dedicated Microsoft Excel datasheet was created for the study. Any anomalies or inconsistencies found during the data collection process were addressed by conducting interviews with the respective centers involved before proceeding with the analysis.

Patient population

Between August 2013 and December 2020, data were collected for 92 consecutive patients diagnosed with malignant melanoma who underwent [18F]FDG PET/CT examinations. The study's inclusion criteria were as follows: 1) a confirmed diagnosis of malignant melanoma; 2) age greater than 18 years; 3) serial 2-[18F]-FDG PET/CT examinations conducted before and during ICIs therapy; and 4) a minimum follow-up period of 12 months after the initial PET/CT scan. Patients who were participating in clinical trials or lacked a confirmed diagnosis of malignant melanoma were excluded from the study. It is worth noting that some patients included in this study were previously analyzed in other reports [14–15].

PET/CT equipment and image acquisition protocol

Similar standard protocols, following the procedural guidelines of the European Association of Nuclear Medicine (EANM) [16], were implemented across all participating centers for PET/CT image acquisition. Prior to imaging, all patients fasted for a minimum of 6 hours, and their blood glucose levels were maintained below 200 mg/dL at the time of tracer injection. To minimize 2-[18F]-FDG uptake in skeletal muscle, patients were instructed to refrain from talking, chewing, or engaging in any muscular activity before the PET/CT scan.

The PET/CT studies were acquired and integrated using hybrid systems, in accordance with the specific protocols adopted at each participating center. Whole-body PET data on tracer distribution were acquired (3 minutes per bed) in 3-D mode, commencing 60 minutes after intravenous administration of 2-[18F]-FDG. Attenuation was corrected using CT images, and subsequently, the CT and PET images were matched and fused into transaxial, coronal, and sagittal images for further analysis.

Interpretation of PET/CT images

Serial 2-[18F]-FDG PET/CT scans were conducted at specific time points, namely PET0 (within 3 months before starting immunotherapy), PET1 (after a median time of 6 months from starting immunotherapy), PET2 (after a median time of 18 months from starting immunotherapy), and PET3 (after a median time of 36 months from starting immunotherapy). Each scan was analyzed by two experienced nuclear medicine specialists at each center using both qualitative (visual) and semiquantitative analyses.

The mean standardized uptake value (SUVmean) of the liver (SUVmean_L) and the spleen (SUVmean_spleen) was measured by employing an isocontour of the spherical volume of interest (VOI) of 3.0 cm3 in the right lobe of the liver and the upper lobe of the spleen, respectively. The value of 41% of SUVmax isocontour threshold was employed. The Spleen Liver Ratio (SLR) was then calculated as the ratio between SUVmean_spleen and SUVmean_L. In cases where liver or spleen metastases were present, the VOI was positioned away from the regions showing high 2-[18F]-FDG uptake to ensure accurate measurements.

Variability of SLR was calculated as following:

$$\frac{\text{PostPET} - \text{prePET} \times 100}{\text{PrePET}}$$

Bone marrow uptake was visually quantified using a scale system ranging from 1 to 5. The scale was defined as follows:

- Score 1: Absent uptake
- Score 2: Uptake equal to the mediastinal blood-pool
- Score 3: Uptake equal to the liver
- Score 4: Uptake moderately higher than the liver
- Score 5: Uptake markedly higher than the liver

This scale allowed for a subjective assessment of bone marrow uptake levels based on visual comparison to reference organs (mediastinal blood-pool and liver).

The definition of immuno-therapy-induced organ inflammation on 2-[18F]-FDG PET/CT relied on visual observations. It was characterized by a diffuse and homogeneous increase in the intensity of tracer uptake within a specific organ when compared to PET0 scan. This visual finding served as the criterion for identifying and assessing organ inflammation resulting from immunotherapy.

Clinical response to immunotherapy and follow-up

Patients in the study were monitored following current clinical guidelines. The clinical assessments involved physical examinations, routine blood work, serum chemistry studies, and conventional imaging, primarily CT scans. Clinical information was collected near each PET scan. The evaluation of disease control was based on the results of clinical and radiological assessments. Specifically, disease control was considered achieved if the patient exhibited complete or partial or stable disease at the time of assessment. Conversely, no-disease control was determined if there was confirmed progression of the disease.

Follow-up data were obtained from the patients' clinical charts or through telephone interviews. The date of the latest examination or consultation was utilized to determine the duration of each patient's follow-up. Progression-free survival (PFS) and overall survival (OS) were defined as follows: PFS represented the time elapsed between the PET0 and the occurrence of progressive disease, while OS indicated the time between PET0 and all-cause mortality.

Statistical analysis

Variables were expressed as number (percentage), or as means ± standard deviation (SD) or as medians and interquartile ranges (IQRs). Student’s t-test was used to compare continuous variables. Pearson’s chi-square test was used to compare categorical variables. The statistical analyses were performed using SPSS version 19 (IBM, Armonk, NY, USA), and MedCalc version 20.027 (MedCalc Software Ltd, Ostend, Belgium).

RESULTS

A total of 92 patients were enrolled in the study (Table 1). Most patients received anti-PD1 therapy (nivolumab or pembrolizumab), with 14 patients (15.2%) also undergoing radiotherapy in combination with systemic treatment. PET0 and PET1 data were available for all patients, while 70 (76%) and 34 (37%) patients underwent PET2 and PET3 scans, respectively. Table 2 demonstrates that the median values of SLR were similar across the scans, with a slight increase in bone marrow uptake observed between PET0 and PET1 (the score 4/5 increased from 2.2% to 6.5% in PET0 and PET1 scans, respectively), followed by stable levels in PET2 and PET3.

In patients with available data for the clinical evaluation, disease control was reported in 69/80 (74%), 43/58 (74%), and 26/30 (87%) patients after 6, 18, and 36 months, respectively. The relative stability of disease control of 74%, 74%, and 87%, respectively, was partly due to the drop of 80 scans at PET1 over 58 scans at PET2 to 30 scans at PET3. However, in many cases the patients discontinuing the immunotherapy, and in those who continued it, the rate of response remained stable. Patients without clinical disease control showed higher bone marrow FDG uptake (grade 3-4) both at PET0 and in the following PET scans compared to those with disease control (Table 3).

Additionally, the presence of more sites of metabolic disease was more prevalent in patients without clinical disease control. After 6 months from the start of immunotherapy, patients without clinical disease control showed a slightly higher median SLR compared to those with disease control (Figure 1A). The difference in

median SLR values was more pronounced after 18 months (Figure 1B). The variability of SLR among the serial PET scans resulted slightly different between patients with and without clinical beneficial only in the length of time between 6-month and 18-month from the start of immunotherapy (Supplemental Figure 1) (Figure 2, 3).

During the median follow-up period of 41 (1-312 months) months, 41 patients (44.6%) experienced progressive disease, and 32 patients (34.8%) died. Table 4 and Figure 4 illustrate the correlation between secondary lymphoid organs uptake and the outcomes. Although not statistically significant, there was a slight increase in bone marrow FDG uptake in patients who experienced progressive disease or death. Similarly, the appearance of new lesions on PET scans was more frequent in patients with a worse prognosis. The median SLR at PET0 was higher in alive patients than those died. However, similar values of median SLR were reported between the two groups of patients in the following PET scans after 6, 18, and 36 months (Supplemental Figure 2). Nevertheless, considering the SLR variability, the changes in values between PET0 and PET scans after 6 months were more evident compared to the other serial PET scans (Figure 4).

SLR and bone marrow uptake in case of signs of inflammation

Signs of inflammation were recorded after PET1 and PET2. In PET1, 12 out of 92 patients (13%) exhibited evidence of inflammation, while after PET2, 6 out of 70 patients (9%) showed inflamed lesions. The median value of SLR at PET0 was higher in patients with signs of inflammation in the first PET examination (after 6 months), but this difference became less pronounced in the subsequent scan (PET2). This suggests that the inflammation might have subsided or become less intense in some patients as treatment progressed.

DISCUSSION

The introduction of immunotherapy has revolutionized the management and prognosis of patients with malignant melanoma. In this study, we explored the role of 2-[18F]-FDG PET/CT in evaluating treatment response and predicting outcomes in melanoma patients undergoing immunotherapy. The results of our study demonstrate the potential of metabolic parameters derived from PET/CT scans as valuable prognostic indicators.

Our study cohort consisted of 92 consecutive patients with malignant melanoma who underwent serial 2-[18F]-FDG PET/CT scans at various time points after starting immunotherapy. The analysis of PET/CT scans provided valuable insights into the metabolic changes in melanoma patients during immunotherapy. We observed a slight increase in bone marrow FDG uptake between PET0 and the 6-month scan (PET1), which could be indicative of treatment-induced inflammation. However, this inflammation appeared to subside or decrease in intensity over time, as evidenced by a less pronounced difference in SLR between PET1 and subsequent scans (PET2, PET3). This suggests that the initial inflammatory response might resolve during the course of immunotherapy, possibly in response to treatment efficacy.

Clinical disease control, defined as complete, partial, or stable disease, was achieved in a significant proportion of patients after 6, 18, and 36 months. Notably, patients without clinical disease control exhibited higher bone marrow FDG uptake and a more widespread metabolic disease pattern. Additionally, the median SLR values were slightly higher in patients without disease control after 6 and 18 months. These findings suggest that the SLR may have predictive value in monitoring treatment response and prognosis, especially in the earlier stages of immunotherapy. Currently, data available in literature did not demonstrate any correlation between SLR and

the response to therapy [11–13], differently from the present study. However, in all three papers [11–13], the number of patients was lower than 50 and different PET parameters were used, such as SUVmax or SUVmean.

We further investigated the relationship between SLR and patient prognosis. The median SLR at PET0 was higher in patients who remained alive throughout the follow-up period compared to those who died. This finding suggests that a higher SLR at baseline might be indicative of better disease control and improved survival. Similar data were also reported by other researcher's group [4, 9]. However, the values of median SLR became more similar between the two groups of patients in the subsequent PET scans conducted after 6, 18, and 36 months. This observation suggests that the initial SLR might lose its predictive value over time and highlights the importance of monitoring SLR changes during of immunotherapy. However, as emerged from the present study, the changes in SLR between the baseline and the 6-month PET/CT scan differed between patients with a good prognosis and those with a poor prognosis. Indeed, the SLR increased during the first 6 months of immunotherapy in patients with a better prognosis compared to those with a worse prognosis. The most plausible hypothesis to explain this phenomenon is the increase in splenic function, given that the spleen is a lymphoid organ. However, the variability in SLR is not observed in subsequent scans, probably because it may be influenced by various factors, including treatment response and disease dynamics. In the study by Prigent et al [7], a change of SLRmean > 25% at 3 months from the start of ICIs compared to the baseline was associated with a poor prognosis. The authors explained this phenomenon by correlating the value of SLR with the immune system activation, although they suggested a validation of the changes in SLR with a large series.

The presence of signs of inflammation on PET1 was associated with higher baseline SLR values, further supporting the link between inflammation and metabolic parameters. However, this association became less evident in the subsequent PET2 scan, possibly indicating the dynamic nature of inflammation during treatment. The changes in SLR between PET1 and PET2 were more pronounced than in later scans, suggesting that early assessment of SLR may have greater prognostic significance.

There are certain limitations that need to be acknowledged. The study cohort was relatively small, and the follow-up period varied among patients. Additionally, as with any observational study, there may be confounding factors that could influence the results.

CONCLUSIONS

In conclusion, our study highlights the potential of 2-[18F]-FDG PET/CT as a valuable tool in the management of malignant melanoma patients undergoing immunotherapy. The metabolic parameters derived from PET/CT scans, particularly SLR and bone marrow FDG uptake, offer promising insights into treatment response and prognosis. Further research with larger cohorts and longer follow-up periods is warranted to validate these findings and establish their clinical utility in guiding treatment decisions for melanoma patients undergoing immunotherapy.

Declarations

Funding: This research received no external funding.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of "dei Colli" Hospital in Napoli, Italy, in July 2020 (Approval No. AOC-

0020062-2020).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Conflicts of Interest: The authors declare no conflict of interest.

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Tables

Table 1. Characteristics of the population

Variables	
N of patients	92
Median age (range), years	66 (31-89)
Comorbidity, n (%)	
No	65 (70.6)
Yes	27 (29.4)
Therapies before immunotherapy, n (%)	
No	1 (1.1)
Surgery	58 (63)
Chemotherapy	1 (1.1)
Combination of treatments	32 (34.8)
Type of immunotherapy, n (%)	
Anti-CTLA4 (Ipilimumab)	20 (21.7)
Anti PD-1 (Nivolumab or Pembrolizumab)	72 (78.3)
Combination of immunotherapy with other therapies, n (%)	
No	78 (84.8)
Yes	14 (15.2)
BRAF-mutation, n (%)	
No	24 (26.1)
Yes	21 (22.8)
Not available	47 (51.1)

Table 2. Distribution of qualitative and quantitative PET parameters during the serial scans

	PET0 (n=92)	PET 1 (n=92)	PET 2 (n=70)	PET 3 (n=34)
Median SLR (range)	0.79 (0.60-1.23)	0.79 (0.51-1.32)	0.78 (0.42-1.58)	0.75 (0.50-1.06)
Bone marrow uptake, n (%)				
1	26 (28.3%)	26 (28.3%)	17 (24.6%)	9 (26.5%)
2	43 (46.7%)	41 (44.6%)	38 (55.1%)	15 (44.1%)
3	21 (22.8%)	19 (20.7%)	13 (18.8%)	9 (26.5%)
4	2 (2.2%)	5 (5.4%)	1 (1.4%)	1 (1.1%)
5	0	1 (1.1%)	0	0
Site of new lesions, n (%)				
None	-	58 (63%)	51 (72.9%)	27 (79.4%)
Lymph nodes	-	6 (6.5%)	6 (8.6%)	1 (2.9%)
Viscera	-	8 (8.7%)	5 (7.1%)	3 (8.8%)
Soft tissue	-	6 (6.5%)	3 (4.3%)	2 (5.9%)
Skeleton	-	2 (2.2%)	0	0
Skeleton+viscera	-	1 (1.1%)	1 (1.4%)	0
Lymph node+viscera	-	4 (4.3%)	2 (2.9%)	0
Lymph node+soft tissue	-	0	1 (1.4%)	0
Soft tissue+viscera	-	1 (1.1%)	0	0
More than 2 sites	-	6 (6.5%)	1 (1.4%)	1 (2.9%)

SLR=spleen-liver ratio

Table 3. Distribution of qualitative PET parameters during the serial scans based on the clinical disease control

	Disease control 1			Disease control 2			Disease control 3		
	Yes	No	*P value*	Yes	No	*P value*	Yes	No	*P value*
Bone marrow uptake_PET0									
1	21 (30%)	3 (27%)	*0.203*	11 (26%)	5 (33.3%)	0.836	8 (31%)	0	0.215
2	34 (49%)	3 (27%)		26 (60%)	9 (60%)		14 (54%)	2 (50%)	
3	13 (19%)	4 (36%)		5 (12%)	1 (6.7%)		3 (12%)	2 (50%)	
4	1 (1%)	1 (9%)		1 (2.3%)	0		1 (4%)	0	
5	0	0		0	0		0	0	
Bone marrow uptake_PET1									
1	21 (30%)	3 (27%)	*0.020*	13 (30%)	5 (33.3%)	0.843	9 (35%)	0	0.093
2	32 (46%)	3 (27%)		20 (47%)	9 (53%)		11 (42%)	1 (25%)	
3	14 (20%)	2 (18%)		9 (21%)	2 (13%)		6 (23%)	3 (75%)	
4	2 (3%)	3 (27%)		1 (2.3%)	0		0	0	
5	0	0		0	0		0	0	
Bone marrow uptake_PET2									
1	-	-	-	11 (26%)	5 (33.3%)	0.246	8 (31%)	1 (25%)	0.385
2	-	-		24 (56%)	8 (53%)		13 (50%)	1 (25%)	
3	-	-		8 (19%)	1 (7%)		5 (19%)	2 (50%)	
4	-	-		0	0		0	0	
5				0			0	0	
Bone marrow uptake_PET3									
1	-	-	-	-	-	-	9 (35%)	0	0.002
2	-	-		-	-		13 (50%)	0	
3	-	-		-	-			4 (100%)	

4	-	-		-	-		3 (12%)	0	
5							1 (3.8%)	0	
							0		
Site of new lesions_PET1									
None	51 (74%)	2 (18.2%)		34 (79%)	7 (46%)		22 (85%)	4 (100%)	
Lymph nodes	4 (5.8%)	0		3 (7%)	0		2 (7.7%)	0	
Viscera	3 (4.3%)	4 (36.4%)		3 (7%)	2 (13.3%)		1 (3.8%)	0	0.871
Soft tissue	6 (8.7%)	0	*0.0001*	0	2 (13.3%)	0.019	1 (3.8%)	0	
Skeleton	0	0		0	0		0	0	
Skeleton+viscera	1 (1.4%)	1 (9.1%)		0	1 (6.7%)		0	0	
Lymph node+viscera	3 (4.3%)	0		0	2 (13.3%)		0	0	
Lymph node+soft tissue	3 (4.3%)	2 (18.2%)		0	0		0	0	
Soft tissue+viscera	1 (1.4%)	2 (18.2%)			1 (6.7%)		0		
More than 2 sites	0								
Site of new lesions_PET2									
None	-	-		35 (81%)	6 (40%)		22 (85%)	4 (100%)	
Lymph nodes	-	-		4 (9.3%)	2 (13.3%)		2 (7.7%)	0	
Viscera	-	-		0	3 (20%)		1 (3.8%)	0	0.871
Soft tissue	-	-	-	2 (4.7%)	1 (6.7%)		1 (3.8%)	0	
Skeleton	-	-		0	0	0.011	0	0	
Skeleton+viscera	-	-		0	1 (6.7%)		0	0	
Lymph node+viscera	-	-		1 (2.3%)	0		0	0	
Lymph node+soft tissue	-	-		1 (2.3%)	0		0	0	
Soft tissue+viscera				0	1 (6.7%)		0		
More than 2 sites				0					

Site of new lesions_PET3									
None	-	-		-	-		23 (89%)	2 (50%)	
Lymph nodes	-	-		-	-		1 (3.8%)	0	
Viscera	-	-		-	-		1 (3.8%)	0	0.045
Soft tissue	-	-	-	-	-	-	1 (3.8%)	1 (25%)	
Skeleton	-	-		-	-		0	0	
Skeleton+viscera	-	-		-	-		0	0	
Lymph node+viscera	-	-		-	-		0	0	
Lymph node+soft tissue	-	-		-	-		0	0	
Soft tissue+viscera							0	1 (25%)	
More than 2 sites							0		

Table 4. Distribution of qualitative PET parameters during the serial scans based on the outcomes

	Progressive disease			Alive		
	No	Yes	*P value*	No	Yes	P value
Bone marrow uptake_PET0						
1	18 (35.3%)	8 (19.5%)		18 (33.3%)	7 (21.9%)	
2	19 (37.3%)	24 (58.5%)	*0.051*	24 (44.4%)	18 (56.3%)	*0.649*
3	14 (27.5%)	7 (17.1%)		11 (20.4%)	6 (18.8%)	
4	0	2 (4.9%)		1 (1.9%)	1 (3.1%)	
5	0	0		0	0	
Bone marrow uptake_PET1						
1	17 (33.3%)	9 (22%)		19 (35.2%)	6 (18.8%)	
2	22 (43.1%)	19 (46.3%)	*0.578*	22 (40.7%)	17 (53.1%)	*0.230*
3	10 (19.6%)	9 (22%)		11 (20.4%)	6 (18.8%)	
4	2 (3.9%)	3 (7.3%)		1 (1.9%)	3 (9.4%)	
5	0	0		0	0	
Bone marrow uptake_PET2						
1	11 (29.7%)	6 (18.8%)		11 (28.2%)	5 (20.8%)	
2	20 (54.1%)	18 (56.3%)	*0.512*	22 (56.4%)	15 (62.5%)	*0.547*
3	6 (16.2%)	7 (21.9%)		6 (15.4%)	3 (12.5%)	
4	0	1 (3.1%)		0	1 (4.2%)	
5	0	0		0	0	
Bone marrow uptake_PET3						
1	7 (35%)	2 (14.3%)		7 (30.4%)	1 (12.5%)	
2	9 (45%)	6 (42.9%)	*0.316*	12 (52.2%)	3 (37.5%)	*0.176*
3	4 (20%)	5 (35.7%)		3 (13%)	4 (50%)	
4	0	1 (7.1%)		1 (4.3%)	0	
5	0	0		0	0	
Site of new lesions_PET1						
None	38 (74.5%)	20 (48.8%)		38 (70.4%)	15 (46.9%)	
Lymph nodes	5 (9.8%)	1 (2.4%)		6 (11.1%)	0	
Viscera	3 (5.9%)	5 (12.2%)		4 (7.4%)	4 (12.5%)	
Soft tissue	0	6 (14.6%)		1 (1.9%)	4 (12.5%)	
Skeleton	1 (2%)	1 (2.4%)	*0.019*	2 (3.7%)	0	*0.015*

Skeleton+viscera	1 (2%)	0		0	1 (3.1%)	
Lymph node+viscera	1 (2%)	3 (7.3%)		1 (1.9%)	3 (9.4%)	
Lymph node+soft tissue	0	0		0	1 (3.1%)	
Soft tissue+viscera	1 (2%)	0		0	1 (3.1%)	
More than 2 sites	1 (2%)	5 (12.2%)		2 (3.7%)	4 (12.6%)	
Site of new lesions_PET2						
None	33 (86.8%)	18 (56.3%)		34 (85%)	11 (45.8%)	
Lymph nodes	1 (2.6%)	5 (15.6%)		3 (7.5%)	3 (12.5%)	
Viscera	2 (5.3%)	3 (9.4%)		1 (2.5%)	4 (16.7%)	
Soft tissue	0	3 (9.4%)		1 (2.5%)	2 (8.3%)	
Skeleton	0	0	*0.076*	0	0	*0.056*
Skeleton+viscera	1 (2.6%)	0		0	1 (4.2%)	
Lymph node+viscera	1 (2.6%)	1 (3.1%)		1 (2.5%)	1 (4.2%)	
Lymph node+soft tissue	0	1 (3.1%)		0	1 (4.2%)	
Soft tissue+viscera	0	0		0	0	
More than 2 sites	0	1 (3.1%)		0	1 (4.2%)	
Site of new lesions_PET3						
None	16 (80%)	11 (78.6%)		21 (91.3%)	4 (50%)	
Lymph nodes	1 (5%)	0		1 (4.3%)	0	
Viscera	0	3 (21.4%)		0	3 (37.5%)	
Soft tissue	2 (10%)	0		1 (4.3%)	0	
Skeleton	0	0	*0.131*	0	0	*0.009*
Skeleton+viscera	0	0		0	0	
Lymph node+viscera	0	0		0	0	
Lymph node+soft tissue	0	0		0	0	
Soft tissue+viscera	0	0		0	0	
More than 2 sites	1 (5%)	0		0	1 (12.5%)	

PFS=progression free survival; OS=overall survival

Figures

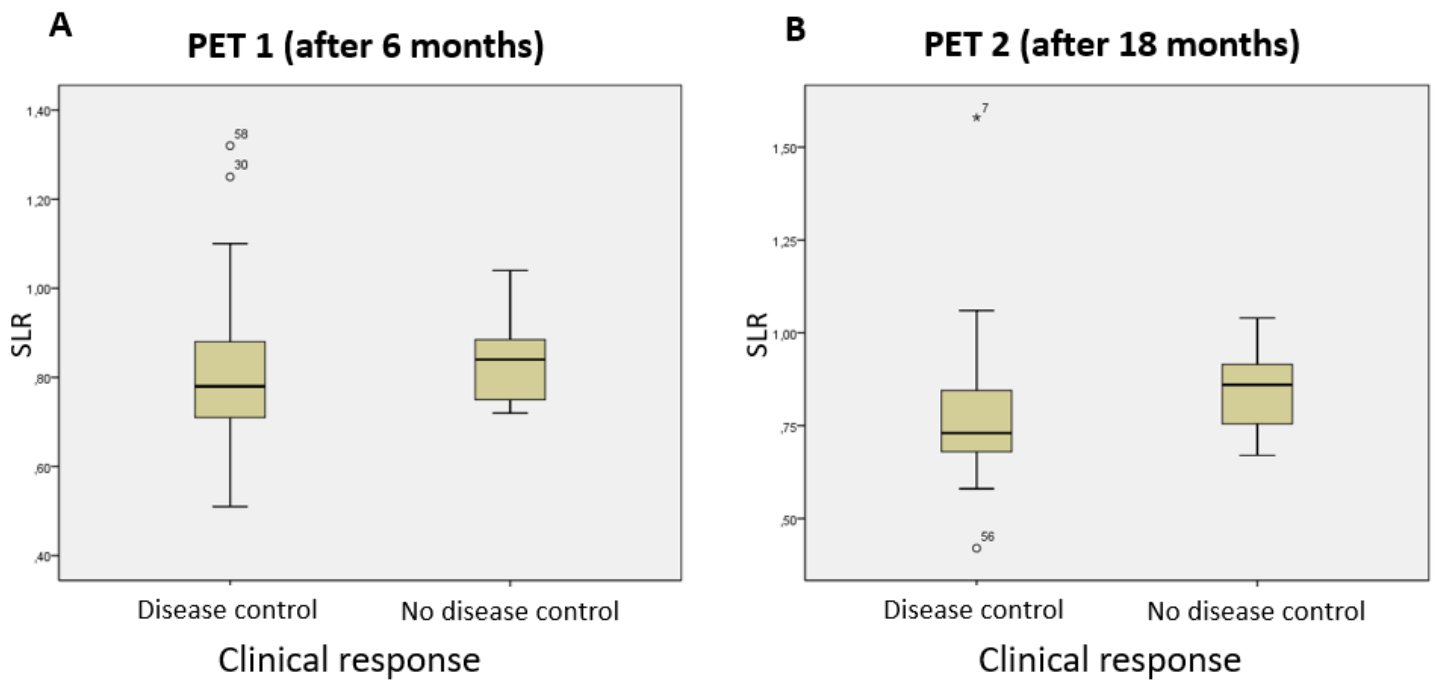

Figure 1

Range of values for spleen-to-liver ratio (SLR) in patients with and without disease control at clinical evaluation, after 6 months (A) and 18 months (B) from the start of immunotherapy. Clinical response was defined as disease control (stable+improvement) and no disease control (worsening).

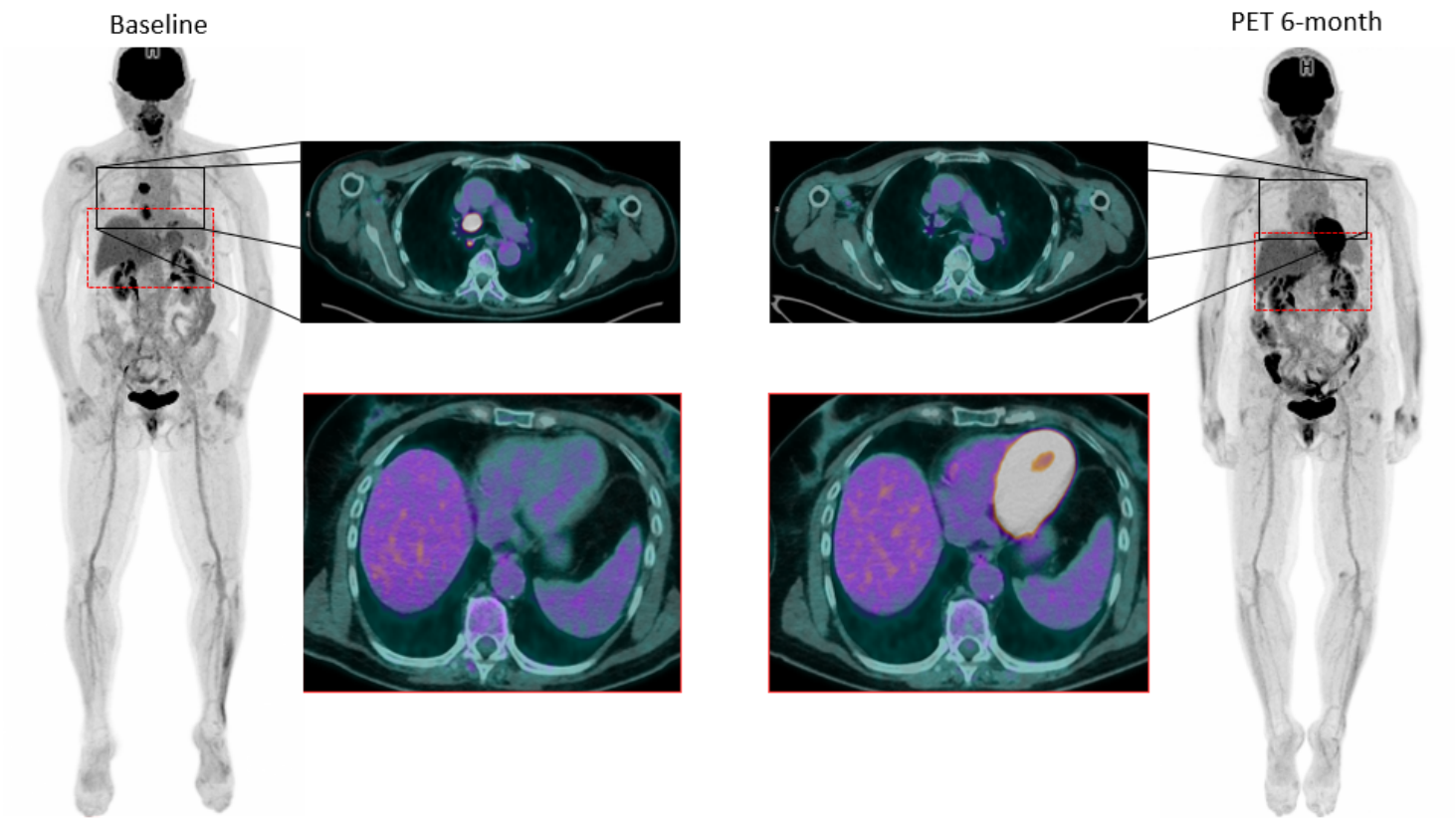

Figure 2

A 69 years-old female with malignant melanoma, treated with Nivolumab. PET0 showed a presence of right hilar lymph node and homolateral lung metastases. After 6 months from the start of immunotherapy, a new PET/CT scan showed a complete metabolic response to therapy. Spleen-Liver-Ratios were 1.29 and 1.29, respectively at PET0 and at the second PET/CT scan. The uptake at bone marrow level reported a grade equal to 2.

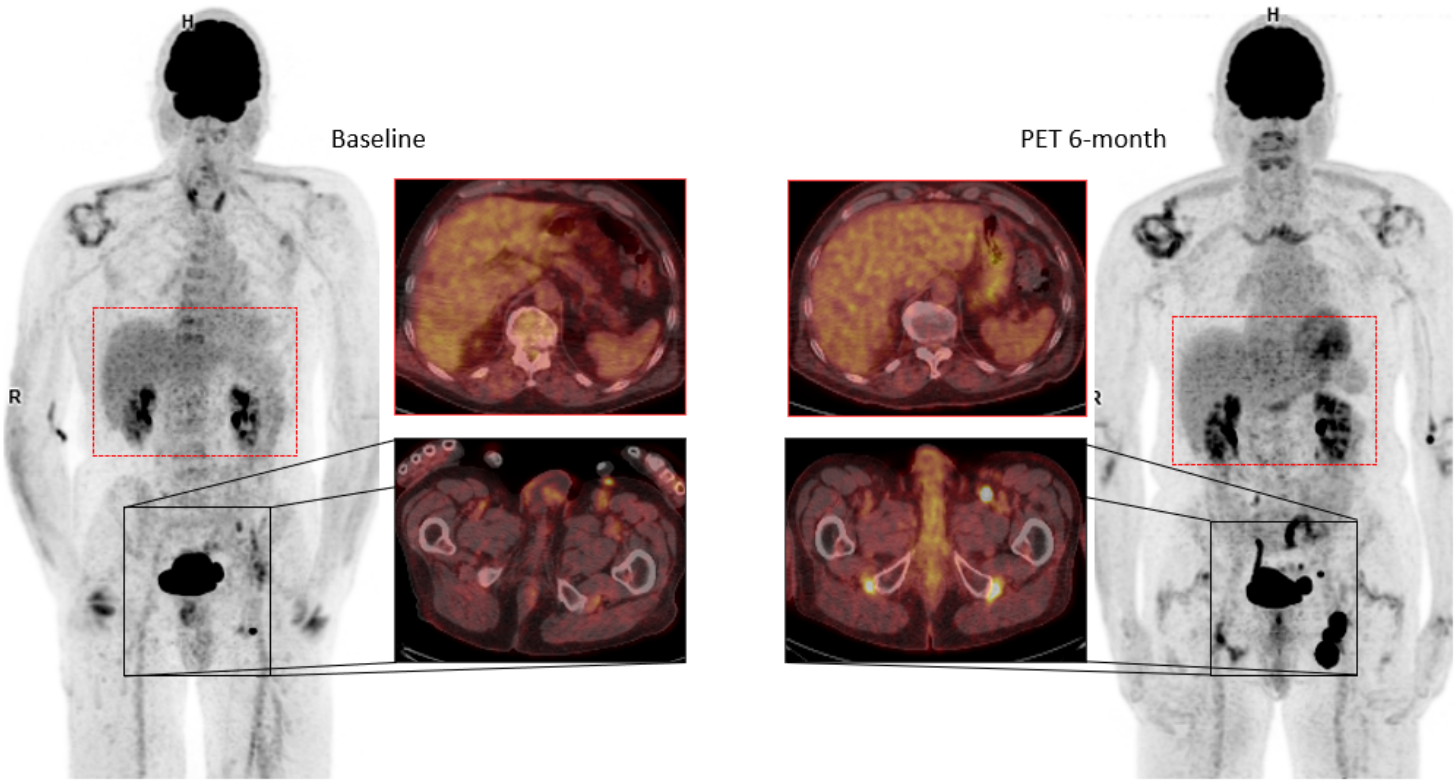

Figure 3

A 74-years old male with a malignant melanoma, treated with Pembrolizumab. PET0 demonstrated the presence of a focal uptake in left inguinal lymph nodes compatible with a recurrent disease. A second PET scan (PET1) performed after 6 months from the start of immunotherapy demonstrated an increase FDG uptake in the left inguinal lymph nodes compatible with progressive disease that was later confirmed by a further PET/CT imaging. Therefore, immunotherapy was stopped and a local treatment based on radiation therapy was started. Spleen-Liver-Ratios were equal to 0.845 and 0.775, respectively in the PET0 and PET1, with a SUL variability of -8%.

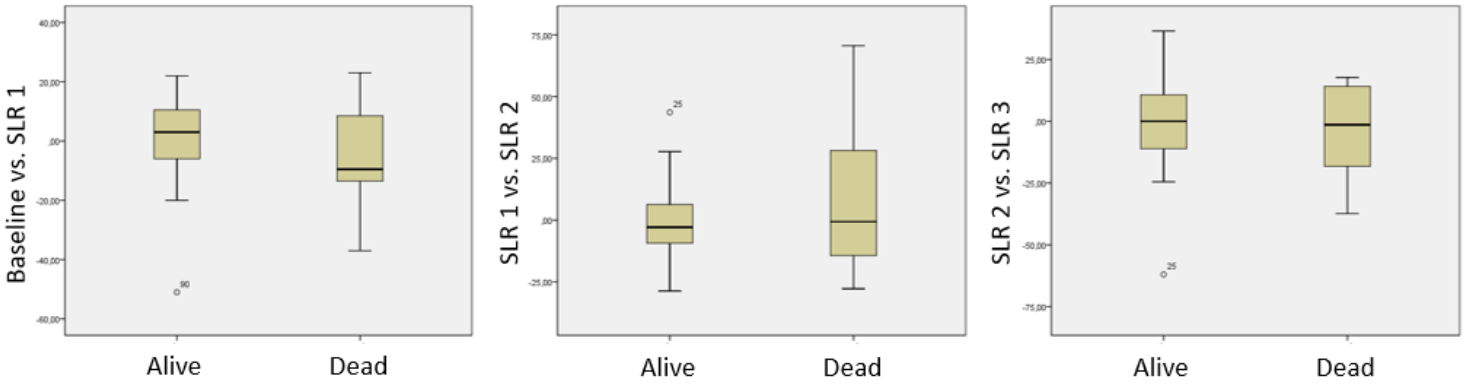

Figure 4

Range of the variability for spleen-to-liver ratio (SLR), in sequential PET/CT scan (PET1, PET2 and PET3), in alive and died patients.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Figure1Supplemental.pptx
- Figure2Supplemental.pptx