Case report

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PET-guided Switch from Immunotherapy to Targeted Therapy in a Metastatic Melanoma Patient: a personalized approach

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Abstract

An early identification of non-responders in oncology is of crucial importance to rapidly switch treatment regimens. Here we report a positron emission tomography, (PET)-guided switch from immunotherapy to targeted therapy in a patient affected by metastatic melanoma. We describe the case of a 78-years-old male patient diagnosed with nodular melanoma, submitted to baseline PET/CT with ^{18}fluorodeoxyglucose (^{18}F-FDG) that showed cutaneous and skeletal metastases (stage IV). The patients started immunotherapy with pembrolizumab. A PET/CT performed 3 months after the start of immunotherapy demonstrated progressive metabolic disease both at skeletal and cutaneous level, confirmed also by the biopsy. As patients resulted positive for BRAF V600k mutation, treatment regimen was rapidly switched to combined anti-BRAF/MEK targeted therapy. The PET/CT performed 3 months later, showed almost complete metabolic response. Ten months after the beginning of targeted therapy, the patient continues to present a durable metabolic response. PET/CT with ^{18}F-FDG may help in monitoring the response to treatment in metastatic melanoma thus defining personalized therapeutic pathways. ***Clin Ter 2020; 171 (4):e283-287. doi: 10.7417/CT.2020.2228***

Key words: *melanoma, positron emission tomography, immunotherapy, targeted therapy, BRAF mutation*

Introduction

Cutaneous malignant melanoma (MM) is a leading cause of cancer worldwide, with an increased predisposition to metastasize to other organs, after primary tumor excision. In about 30% of subjects affected by MM, distant metastases occur; with the sites of predominant colonization being skin, lung and lymph nodes (1). In spite of many advances in diagnosis and therapy, prognosis of patients with metastatic MM, especially those in stage IV with high serum level of lactate dehydrogenase (LDH), remains poor.

It has been demonstrated that 50% of MM patients harbor a mutation in the DNA sequence encoding BRAF, a serine/threonine protein kinase, that activates the MEK/ERK-signaling pathway (**2**). In 90% of cases, the mutation occurs at the codon 600 level, namely BRAF V600e mutation, which causes a constitutive activation of the MAP kinase pathway. This scientific evidence triggers the need of research for therapy aimed to block the BRAF/MEK mechanism in mutated MM. It has to be highlighted that anti BRAF/MEK targeted therapy has deeply conditioned the prognosis of MM. The introduction of immune-mediated therapies has required a novel diagnostic approach aimed at evaluating both the treatment response and the eventual disease progression.

Here we describe a case of MM in which the therapeutic pathway was defined through the appropriate use of molecular imaging with positron emission tomography (PET)/computed tomography (CT).

Case description

A Caucasian 78-years-old male without relevant medical history presented with a pigmented lesion of the left arm in March 2018. He was submitted to excisional biopsy and histology resulted positive for nodular melanoma, characterized by regression, ulceration and a 2.7 mm Breslow thickness. Afterwards, he was submitted to wide excision and sentinel lymph node biopsy that resulted positive for a sub-capsular metastasis in one node of the left axillary region. Subsequently, he underwent a follow-up.

In December 2018 he was admitted to our attention for the appearance of purplish cutaneous nodules in his left axilla, that were confirmed as melanoma metastases at histological examination. Five section of FFPE sample was used for DNA extraction with QIAmp DNA FFPE KIT (QIAGEN), the mutational analysis of BRAF were performed with the Real-Time PCR Kit EasyBRAF TM (DIATECH) and a V600K mutation was detected in BRAF gene.

The patient was submitted to PET/CT with ^{18}fluoro-deoxyglucose (^{18}F-FDG) that revealed multiple hypermetabolic focuses in bones and diffuse tracer uptake in the axillary region, thus the patient was categorized as stage IV. Furthermore, several PET-derived parameters were carried out such as the standardized uptake value (SUV) and the tumor metabolic volume (MTV), the latter was calculated through

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a SUV-based threshold algorithm (PETvCAR, General Electric, WI, USA). Every lesion was segmented and total lesion glycolysis (TLG) was calculated as the product of MTV x SUVmean. All the lesions in the body were considered, thus whole body TLG (wbTLG) was calculated as the sum of the TLG of each lesion with a result of 117.4 grams (g) (Fig. 1). In consideration of the burden of the disease, also consistent with LDH serum level (390 U/L), the patient was submitted to immunotherapy with a monoclonal antibody directed against the programmed death-1 protein (PD-1), pembrolizumab 200 mg, administered intravenously every 3 weeks, from December 2018.

In February 2019, the patient was submitted to restaging through PET/CT with ^{18}F-FDG that showed increased grade of uptake in the skeletal lesions and extension of the cutaneous metastatization. The calculation of wbTLG resulted of 2950 g. The disease progression was confirmed by clinical examination, biopsy and histology (Fig. 2). In consideration of the clinical pattern and taking into account the positivity of the BRAF V600k mutation, in March 2019 the patient was rapidly switched to combined anti BRAF/MEK targeted therapy with dabrafenib 75 mg, 4 capsules (cp) daily and trametinib 2 mg, 1 cp daily.

The follow-up PET/CT was performed in May 2019 and showed an almost complete metabolic response to targeted therapy, with a significant reduction of wbTLG (10.7 g), with a good overall performance status (Fig. 3). The last follow-up in December 2019, confirmed stability of the metabolic response.

Discussion

In recent years, impressive progress has been made in the management of advanced MM. In particular, immunotherapy has been introduced in clinical practice with the aim of reactivating the immune system against malignant cells. Drugs belonging to the class of immune checkpoint inhibitors are capable of blocking immune checkpoint proteins, whose function is effectively inhibiting the immune system through various mechanisms. Immunotherapy has been proved effective in providing survival benefits in MM patients.

While in the *wild type* advanced MM immunotherapy with immune checkpoint inhibitors represents the first choice therapy, both immunotherapy and targeted therapy can be successfully used for the management of mutated MM.

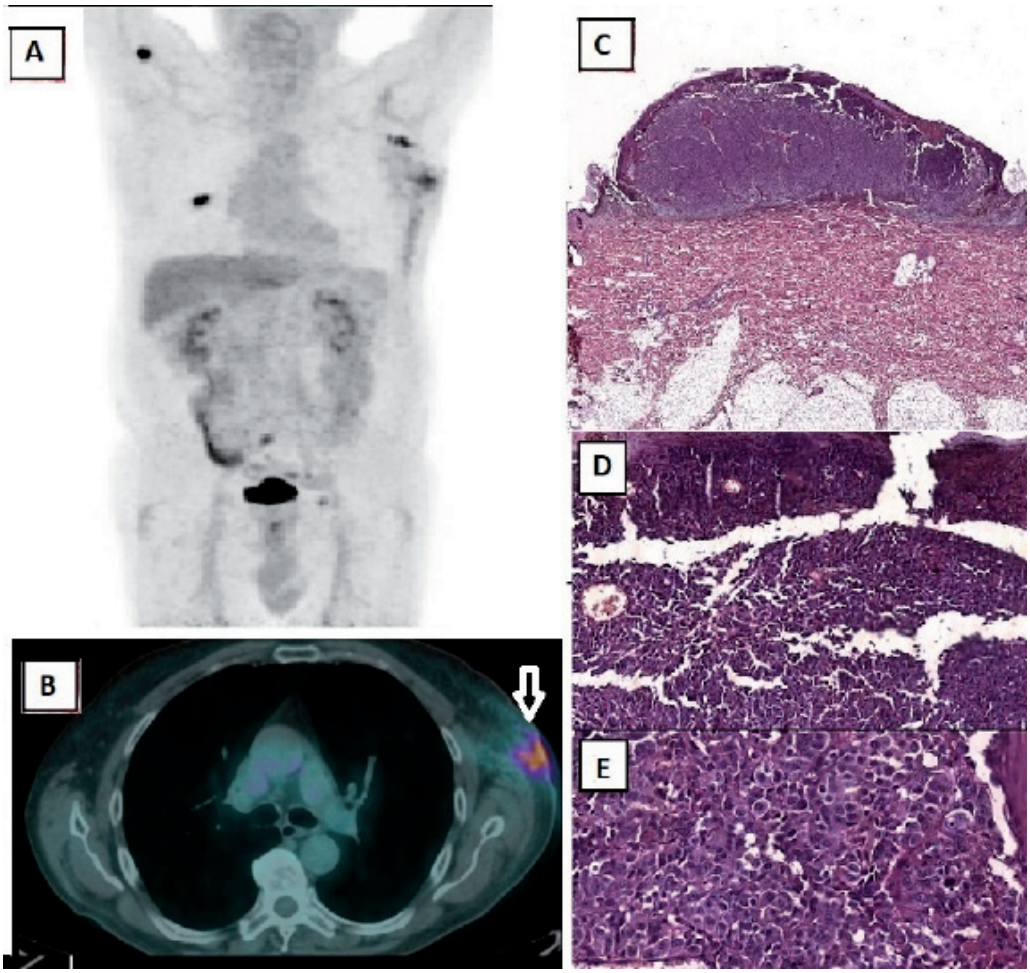

Fig. 1. (A) Whole Body PET capture of the initial staging, demonstrating increased tracer uptake in bones and in the cutaneous tissue of the left axillary region. (B) Transaxial fused PET/CT images detailing a hypermetabolic tissue in the left axilla (arrow). (C) Macroscopic aspect of the pigmented lesion of the left arm that appears nodular and ulcerated. (D) Low-power photomicrograph showing solid nests and cords composed by a proliferation of epitheliomorphic cells. (E) High-power photomicrograph showing cells characterized by widespread polymorphism and polymetry.

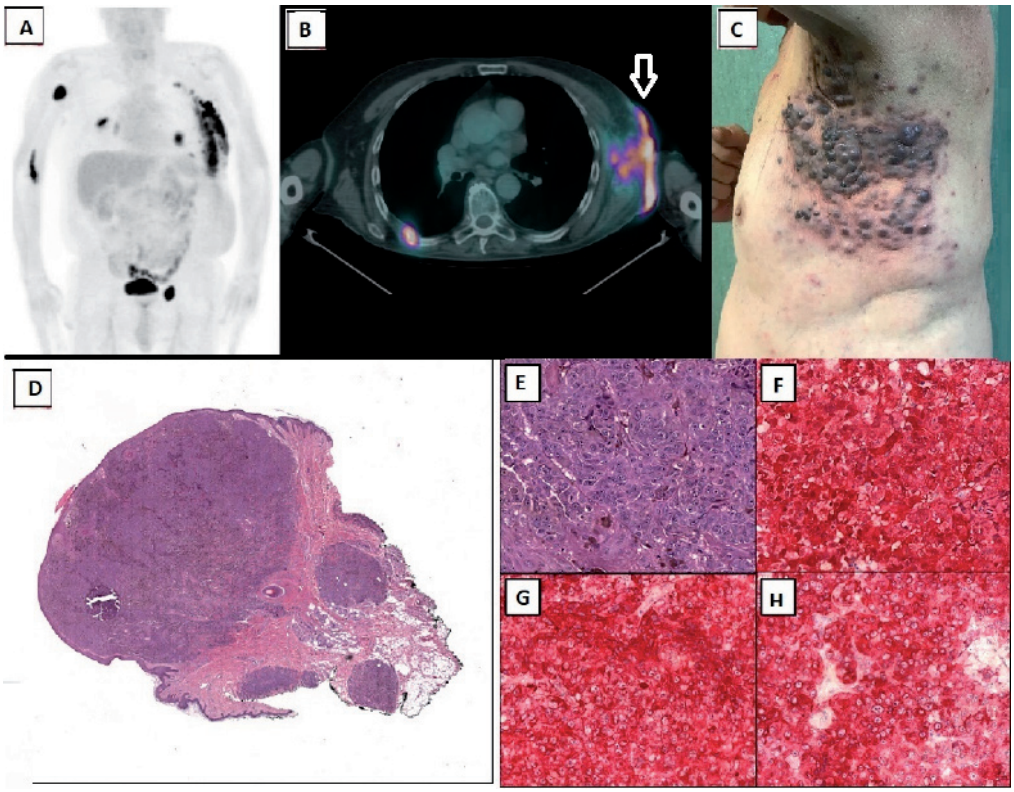

Fig. 2. (A) Whole Body PET acquired 3 months after immunotherapy, depicting a significantly increased extension of the metastatic involvement in bones and left axillary. (B) Transaxial fused PET/CT images detailing the extension of the metastatization in the left axillary region (arrow), also demonstrating a rib localization. (C) Clinical examination showing multiple purplish cutaneous nodules in the same region. (D) Macroscopic aspect of the cutaneous metastasis. (E) High-power photomicrograph showing cells characterized by widespread polymorphism and polymetry, with immunoreactivity for S-100 (F), Melan-A (G) and HMB-45 (H).

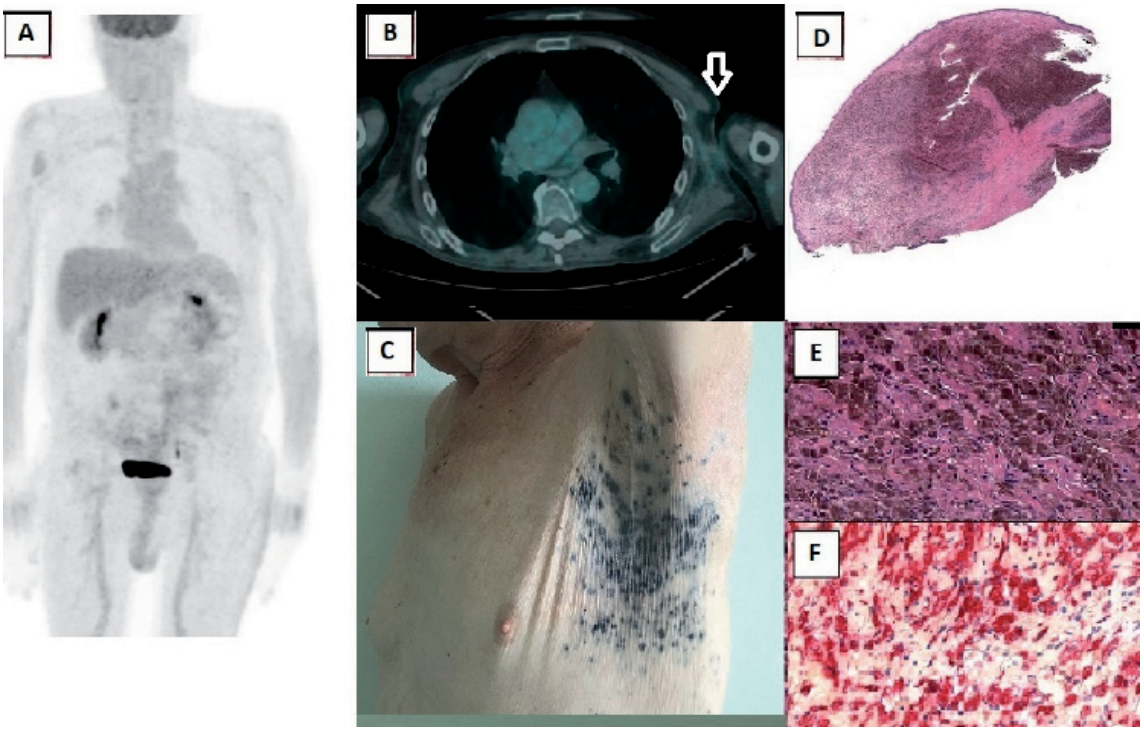

Fig. 3. (A) Whole Body PET acquired 3 months after the start of the anti BRAF/MEK targeted therapy, depicting significantly and almost complete regression of the hypermetabolic metastases. (B) Transaxial fused PET/CT images showing no 18F-FDG uptake in the left axilla (arrow). (C) Clinical examination showing regression of the cutaneous nodules with residual skin dyschromia. (D) Macroscopic aspect of the cutaneous metastasis after targeted therapy. (E) High-power photomicrograph showing numerous large monomorphic cells with abundant intracytoplasmic brown. (F) Immunoreactivity for CD68 confirming that these cells were macrophages.

The results of a clinical trial performed on a large cohort of patients demonstrated that the combination of nivolumab (a programmed death 1 (PD-1) checkpoint inhibitor) and ipilimumab (a cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) checkpoint inhibitor) resulted in a significant improvement of progression-free survival. On the other hand, anti-BRAF therapy with dabrafenib and trametinib also proved clinically effective in subjects with BRAF V600e mutation, as ruled out by the phase 2 multi-centric clinical trial performed on 174 patients affected by mutated MM with cerebral metastases (3).

The best sequence for placing these two therapeutic options (immunotherapy before/after targeted therapy) in mutated MM therapeutic workflow is still a debated issue. In our specific case, considering the low burden of the disease, it has been decided to promptly start anti PD-1 immunotherapy.

One of the most crucial issues in oncology is represented by the use of imaging biomarkers for assessing the response to treatments in order to promptly identify responders from non-responders. In this context, standard Response Evaluation Criteria in Solid Tumors (RECIST) and RECIST 1.1 criteria present limitations for evaluating tumor treated with the recently introduced immune checkpoint inhibitors (4). To overcome these drawbacks, the immune-RECIST (iRECIST) have been developed to correctly identify the different possible patterns of response after treatment with immune checkpoint inhibitors (5).

PET/CT with ^{18}F-FDG represents a well-established tool in oncology for both diagnosis and restaging after treatments. In particular, PET images can be assessed either qualitatively or through quantitative evaluation, the latter approach often being carried out according to the PET Response Criteria In Solid Tumours (PERCIST) (6).

As far as it concerns the response to targeted therapy in advanced MM, it has been demonstrated that a down-regulation of extra-cellular signal regulated kinase, due to the combined anti BRAF/MEK therapy, entails a rapid reduction of the glycolytic rate in the neoplastic cells. Therefore, a reduction in ^{18}F-FDG uptake, as measured by SUV and other PET-derived parameters, results in a response to the treatment and survival benefit. The assessment of the response to immune checkpoint inhibitors is, on the other hand, more challenging. The immune-activation entails an increased accumulation of tumor infiltrating lymphocytes into sites of disease. Therefore, in some subjects, malignant tissues submitted to immunotherapy can present an enlargement prior to a subsequent shrinkage, a phenomenon also called "pseudo-progression". From a metabolic point of view, since both melanoma cells and activated lymphocytes are characterized by an increased glucose consumption, the differentiation between progression and pseudo-progression with PET may be difficult. In a cohort of 27 MM patients submitted to therapy with anti-PD-1 antibodies, PET/CT with ^{18}F-FDG was performed after a median of 15.2 months since the starting of the treatment (7). Fifteen out of the 27 examined patients had a positive PET scan, eight of whom underwent biopsy that showed immune cell infiltration in 3/8 cases (i.e. 38%). These preliminary data suggested that immune infiltration can represent an important confounding factor in PET interpretation. In order to distinguish progression from pseudo-progression in PET scan reading, it has been suggested to pay particular attention to signs of immune-flair, such as symmetric hilar and mediastinal nodal uptake and diffuse spleen activation (8).

Other studies support the evidence that ^{18}F-FDG-PET/CT may predict eventual response in patients treated with imunocheckpoint inhibitors with advanced melanoma. In particular, Cho and colleagues performed PET/CT scan in 20 patients submitted to therapy with immune checkpoint inhibitors at 3 different point-times: prior to treatment (SCAN-1), at 21-28 days (SCAN-2) and after 4 months (SCAN-3) (9). At each point-time of evaluation, response was assessed according to RECIST 1.1, irRC, PERCIST and European Organisation for Research and Treatment of Cancer (EORTC) criteria. Of note, the best overall response at the 4 month evaluation resulted to be associated with an increased tracer uptake (>15.5%), as measured by SUV normalized for lean body mass (SUL), at the SCAN-2. These results suggest that an increased metabolic activity of the lesions at the early PET evaluation might be linked to immune-activation, thus being predictive of a favorable long-term patients' outcome. These preliminary data, although they are intriguing, need to be supported by further studies with larger series. In particular, it has be pointed out that in the previously cited paper, the authors considered only the grade of ^{18}F-FDG uptake and did not take into account any functional volumetric parameter.

In this regard, Anwar et al. introduced the PET Response Evaluation Criteria for Immunotherapy (PERCIMT), based on the absolute number of new lesions detected by PET/CT in patients undergoing immunotherapy (10). A cohort of 41 patients affected by MM and treated with immune checkpoint inhibitors was dichotomized according to clinical response in those with clinical benefit (CB) and those without (no-CB). Of note, SUV changes after therapy did not correlate with patients' outcome. On the contrary. the application of a threshold of four newly emerged ^{18}F-FDG-avid lesions on the post-therapy PET/CT scan led to a sensitivity of 84% and a specificity of 100%. The cut-off was lower in patients with larger functional diameters, measured on PET/CT scan.

In the case we report, as far as it concerns the interpretation of the PET/CT scan acquired 3 months after the starting of anti PD-1 therapy, we were aided in our diagnosis by the impressive increase in TLG parameter, which combines both metabolic and volumetric features, and proved to be an emerging powerful prognostic factor in many oncological scenarios (11). The increased TLG was strongly suggestive of disease progression, as subsequently confirmed by histology, thus leading to a switch in the treatment regimen. In this regard, Annovazzi et al. recently evaluated the usefulness of PET-derived parameters (i.e. MTV and TLG) in a group of 57 patients treated with immune checkpoint inhibitors (ipilimumab or nivolumab) and submitted to PET/CT before therapy (PET0) and 12 to 18 weeks later (PET1) (12). Response at PET1 was assessed according to RECIST 1.1, EORTC, PERCIMT and by percentage change of MTV and TLG of up to 5 target lesions. As specifically concerns those subjects treated with nivolumab, the authors found that the best predictors of response were EORTC, MTV and TLG. Our results are substantially in agreement with

those reported in the aforementioned paper but. in contrast to Annovazzi's group, we included in TLG calculation not only the 5 target lesions but all the hypermetabolic focuses detected by PET/CT (i.e. wbTLG). In our experience, wbTLG resulted easy to be carried out through a dedicated software and may provide a helpful surrogate biomarker of the overall tumor burden.

This case suggests that PET/CT may represent a useful tool for the management of advanced MM in the era of targeted therapy and immunotherapy. In particular, as far as it concerns mutated MM, metabolic imaging, also supported by the accurate evaluation of the changes in PET-derived parameters, can be of great value for rapidly switching non-responding subjects to a potentially more effective regimen, thus allowing to define personalized therapeutic pathways.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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References

1. Sandru A, Voinea S, Panaitescu E, et al. Survival rates of patients with metastatic malignant melanoma. J Med Life 2014; 7:572-576
2. Ascierto PA, Kirkwood JM, Grob JJ, et al. The role of BRAF V600 mutation in melanoma. J Transl Med 2012; doi: 10.1186/1479-5876-10-85
3. Long GV, Trefzer U, Davies MA, et al. Dabrafenib in patients with Val600Glu or Val600Lys BRAF-mutant melanoma metastatic to the brain (BREAK-MB): a multicentre, open-label, phase 2 trial. Lancet Oncol 2012; 13:1087-1095
4. Milano A, Perri F, Ciarmiello A, et al. Targeted-therapy and imaging response: a new paradigm for clinical evaluation? Rev Recent Clin Trials 2011; 6:259-265
5. Seymour L, Bogaerts J, Perrone A, et al. iRECIST: guidelines for response criteria for use in trials testing immunotherapeutics. Lancet Oncol 2017;18:e143-e152
6. Skougaard K, Nielsen D, Jensen BV, et al. Comparison of EORTC criteria and PERCIST for PET/CT response evaluation of patients with metastatic colorectal cancer treated with irinotecan and cetuximab. Nucl Med 2013; 54:1026-1031
7. Kong BY, Menzies AM, Saunders CA, et al. Residual FDG-PET metabolic activity in metastatic melanoma patients with prolonged response to anti-PD-1 therapy. Pigment Cell Melanoma Res 2016; 29:572-577
8. Wong ANM, McArthur GA, Hofman MS, et al. The Advantages and Challenges of Using FDG PET/CT for Response Assessment in Melanoma in the Era of Targeted Agents and Immunotherapy. Eur J Nucl Med Mol Imaging 2017; 44:67-77
9. Cho SY, Lipson EJ, Im HJ, et al. Prediction of Response to Immune Checkpoint Inhibitor Therapy Using Early-Time-Point 18F-FDG PET/CT Imaging in Patients with Advanced Melanoma.J Nucl Med 2017;58:1421-1428
10. Anwar H, Sachpekidis C, Winkler J, et al.Absolute number of new lesions on 18F-FDG PET/CT is more predictive of clinical response than SUV changes in metastatic melanoma patients receiving ipilimumab. Eur J Nucl Med Mol Imaging. 2018;45:376-383
11. Filippi L, Di Costanzo GG, Tortora R, et al. Prognostic value of neutrophil-to-lymphocyte ratio and its correlation with fluorine-18-fluorodeoxyglucose metabolic parameters in intrahepatic cholangiocarcinoma submitted to 90Y-radioembolization. Nucl Med Commun 2020; 41:78-86
12. Annovazzi A, Vari S, Giannarelli D, et al. Comparison of 18F-FDG PET/CT Criteria for the Prediction of Therapy Response and Clinical Outcome in Patients With Metastatic Melanoma Treated With Ipilimumab and PD-1 Inhibitors. Clin Nucl Med 2020; 45:187-194