Scientific Research Publishing

Advances in Bioscience and Biotechnology, 2023, 14, 151-161
https://www.scirp.org/journal/abb
ISSN Online: 2156-8502
ISSN Print: 2156-8456

Value of ^{18}F-FDG PET/CT Based on PD-L1 to Predict Outcomes of Immunotherapy in NSCLC

Fuxia Xie, Mengdan Li, Xingguo Jing*

Department of Nuclear Medicine, The First Affiliated Hospital of Chongqing Medical University, Chongqing, China
Email: *2585546335@qq.com

How to cite this paper: Xie, F.X., Li, M.D. and Jing, X.G. (2023) Value of ^{18}F-FDG PET/CT Based on PD-L1 to Predict Outcomes of Immunotherapy in NSCLC. *Advances in Bioscience and Biotechnology*, **14**, 151-161.
https://doi.org/10.4236/abb.2023.144010

Received: February 2, 2023
Accepted: April 17, 2023
Published: April 20, 2023

Abstract

Immune checkpoint inhibitors (ICIs), targeting programmed cell death protein-1 (PD-1) and its ligand (PD-L1), have changed the treatment history of lung cancer, especially in the field of non-small cell lung cancer (NSCLC). ^{18}F-FDG PET/CT, as a noninvasive and effective examination technique, reflects the location and functional information of tumor lesions through the metabolic level of glucose. Studies have shown that PD-L1 may affect the sugar metabolism of tumor cells. Therefore, ^{18}F-FDG PET/CT can be used to predict the expression of PD-L1 and evaluate the efficacy of immunotherapy. This article mainly introduces the relationship between PD-L1 expression and NSCLC, the advantages of ^{18}F-FDG PET/CT, the imaging mechanism of ^{18}F-FDG PET/CT based on PD-L1 and its research progress in NSCLC, and the role of ^{18}F-FDG PET/CT in the response and efficacy evaluation of immunotherapy in NSCLC, aiming to provide a reference for the clinic.

Keywords

^{18}F-FDG PET/CT, PD-L1, Immune Checkpoint Inhibitors, Non-Small Cell Lung Cancer, Immunotherapy

1. Introduction

Lung cancer is the most common type of cancer worldwide and the leading cause of cancer death. It is also the area where cancer treatment has progressed most rapidly. Among them, 80% - 85% are non-small cell lung cancer (NSCLC), which can be treated with surgery, chemotherapy, radiotherapy, targeted therapy, and immunotherapy [1]. Especially inhibitors of programmed cell death protein 1 (PD-1) and its ligand 1 (PD-L1) greatly extend the overall survival of patients and offer new hope [2]. Currently, PD-L1 is the only approved biomarker used to evaluate the efficacy of PD-1/PD-L1 inhibitors by directly ob-

taining tumor tissue for immunohistochemical (IHC) analysis [3]. However, for patients who cannot undergo invasive examination and have concealed lesions, PD-L1 detection cannot be performed through puncture biopsy, and the positive rate of sputum exfoliated cells is also low, thereby limiting the chances for these patients to receive immunotherapy.

^{18}Fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) is a functional imaging modality that reflects the activity level of whole-body tumor lesions through glucose metabolism, providing important information on morphology and function for tumor management. It plays an important role in tumor diagnosis, staging, treatment planning, treatment response, recurrence monitoring, etc. [4]. Many studies [5] [6] [7] have revealed that quantitative parameters on ^{18}F-FDG PET/CT, such as maximum standardized uptake value (SUVmax), tumor metabolic volume (MTV) and total lesion glycolysis (TLG), etc., have important prognostic significance in the efficacy of immunotherapy for non-small cell lung cancer. Several recent studies [8] [9] have also shown the expression of PD-L1 in tumor cells is closely related to the accumulation of ^{18}F-FDG in PET/CT. The reason may be PD-L1 expressed on tumor cells can enhance glucose uptake in tumor tissue by inhibiting the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (AKT)/mammalian target of rapamycin (mTOR) pathway of T cells, and the increase in glucose uptake during glycolysis is the basis for ^{18}F-FDG PET/CT imaging [10]. As a result, metabolic parameters are altered. Therefore, ^{18}F-FDG PET/CT can be used to evaluate the efficacy of immunotherapy in NSCLC through PD-L1. This article provides a comprehensive review of the relationship between PD-L1 expression and NSCLC, the advantages of ^{18}F-FDG PET/CT, the imaging mechanism of ^{18}F-FDG PET/CT based on PD-L1 and its progress in NSCLC, and the predictive role of ^{18}F-FDG PET/CT in the response and efficacy of immunotherapy in NSCLC patients.

2. The Correlation between PD-L1 Expression and NSCLC

PD-L1 is the ligand of PD-1, mainly expressed on the surface of tumor cells. The expression level is represented by the tumor positive proportion score (TPS) [11]. In the hypoxic microenvironment, tumor cells can also express hypoxia-inducible factor-1α (HIF-1α), upregulating glucose transporter (GLUT)-1 and vascular endothelial growth factor (VEGF) to promote anaerobic glycolysis and angiogenesis [12] [13]. The binding of PD-L1 with PD-1 on the surface of T cells, B cells, or NK cells is the main mechanism of inducing immune escape, playing a role in immune checkpoints during tumor growth [14]. HIF-1α is another important mediator of tumor immune response, which synergizes with PD-1/PD-L1 [15]. Immune inhibitors targeting PD-1/PD-L1 pathway can restore T cell immune function and are used in the treatment of malignant tumors, especially in NSCLC. ICIs, represented by Pembrolizumab, have been approved by the FDA for first-line treatment of advanced NSCLC patients [2].

Compared with conventional chemotherapy, PD-1/PD-L1 checkpoint inhibitors have shown promising results in the treatment of non-small cell lung cancer (NSCLC). Patients with higher PD-L1 expression level, such as TPS ≥ 50% for first-line treatment and TPS ≥ 1% for second-line treatment, have better objective response rate (ORR) to immunotherapy and longer overall survival (OS) [16] [17]. The expression level of PD-L1 in tumors may also provide a selection criterion for patients to predict immunotherapy response. A large multicenter study [18] found that NSCLC patients with PD-L1 TPS above 50% and continuous first-line Pembrolizumab therapy had an objective response rate (ORR) of 44.5%, median progression-free survival (mPFS) and OS were 7.9 and 17.2 months, respectively. Multivariate analysis has also shown that PD-L1 expression above 90% was significantly associated with higher ORR (P = 0.0204) and longer OS (P = 0.0346). It can be seen that first-line ICIs in NSCLC patients with high PD-L1 expression have better objective response rate and longer survival. PD-L1 may provide stratified evidence for immunotherapy programs in NSCLC patients.

Despite the predictive value of PD-L1, in addition to the dynamic and heterogeneous expression of PD-L1 during the cancer evolution and treatment of individual patients, there are some inherent limitations in tissue sampling and detection methods. Different antibody reagents and evaluation thresholds may lead to different results. Therefore, in addition to immunehistochemical detection of PD-L1 expression, biomarkers with better prognostic effect need to be discovered.

3. Advantages of ^{18}F-FDG PET/CT

The mechanism of immunotherapy is different from conventional chemotherapy. ICIs induce tumor infiltration and immune cell proliferation while restoring T lymphocyte activity, leading to a temporary increase in tumor burden. Therefore, new immune therapy reactions have been proposed, including pseudo-progression, hyper-progression or immune-related progression [19]. Morphological imaging is difficult to evaluate immunotherapy response in the early stages. Compared with traditional solid tumor efficacy evaluation criteria1.1 (RECIST 1.1) [20] based only on lesion size, ^{18}F-FDG PET/CT based on metabolic changes can capture changes in tumor volume and function earlier than CT through tumor metabolic volume load, which partially compensates for the blind spots in traditional imaging evaluation. In order to overcome the limitations of traditional efficacy evaluation criteria, various PET standards for evaluating tumor responses have emerged, such as PET response criteria in solid tumors (PERCIST) [20], immune response evaluation criteria in solid tumors (iPERCIST) [21], and immunotherapy-modified PERCIST (imPERCIST) [22].

Humbert O *et al*. [23] analyzed the role of ^{18}F-FDG PET/CT in evaluating early immune response in NSCLC patients. According to the PERCIST criteria, assessment was done at different time points: before immunotherapy, 7 weeks

and 3 months after immunotherapy. They found that patients who achieved complete or partial metabolic response and disease stability after 7 weeks of treatment could achieve long-lasting clinical benefits, with a sensitivity of 85.7%, specificity of 62.1% and accuracy of 72.0%. Additionally, for patients whose first evaluation showed disease progression, subsequent PET/CT scans could help identify more than half of patients with atypical response patterns, namely pseudoprogression and immune dissociation progression. Both of these immune response patterns can lead to persistent clinical benefits.

In a prospective study of 52 patients with NSCLC, Castello A *et al*. [24] found that in the first assessment during ICI treatment, the imPERCIST standard was more accurate than RECIST 1.1 in assessing treatment response and predicting OS. In addition, for patients who were judged to be disease-stable in CT, imPERCIST could identify patients with longer survival periods. Vekens K *et al*. [25] also came to the same conclusion that the reduction in tumor metabolic volume 8 to 9 weeks after immunotherapy was a better indicator of prolonging OS and forecasting post-therapy response. Therefore, ^{18}F-FDG PET/CT demonstrated an advantage in immunotherapeutic response assessment, which can identify clinically beneficial patients in the early stage, provide valuable information for early modification of treatment plan, stop inefficient treatment with adverse effects as soon as possible, and reduce the cost of immunotherapy.

Although the above literatures are small sample size studies, with the application of a variety of radionuclide molecular probe imaging targeting PD-1/PD-L1, fluorine-18-labeled PET/CT will become more sensitive and specific in evaluating tumor immune efficacy.

4. Relationship between the Expression Level of PD-L1 and ^{18}F-FDG PET/CT

4.1. Possible Mechanisms for PD-L1 Affecting ^{18}F-FDG Intake

PET/CT using fluorine-18 labeled FDG as a tracer has been widely used in tumor diagnosis and efficacy monitoring. FDG is a natural glucose analogue, and its distribution in the body can reflect glucose metabolism status. After entering tumor cells, FDG is phosphorylated into 6-phosphate deoxyglucose (FDG-6-PO4) under the action of hexokinase. Due to its structural differences from natural 6-phosphat glucides, it could not enter the next step of metabolism, thus concentrating in tumor cells, which clearly shows the increased glucose metabolism of tumor lesions [26]. However, FDG intake is closely related to GLUT-1, HIF-1α, VEGF and PI3K/AKT/mTOR signaling pathways, all of which are involved in the regulation of glucose metabolism [27]. Some of the findings [28] [29] [30] suggest that there is a metabolic competition between tumors and immune cells. Activated T cells induce AKT through its T cell receptor (TCR) and CD28 to activate and up-regulate GLUT1, which transfers glucose from the extracellular to the intracellular for glycolysis catalyzed by hexokinase. Interferon (IFN)-γ secreted by T cells induces tumor cells to express co-inhibiting li-

gand PD-L1. PD-L1 interacts with PD-1 to inhibit PI3K phosphorylation and TCR. Then the PI3K/AKT/mTOR pathway of T cells is inhibited and glycolysis is weakened. When glycolysis is enhanced in tumor cells, high ^{18}F-FDG uptake is shown on ^{18}F-FDG PET/CT. As a result, glucose in TIME is taken up by tumor cells in large quantities and produces lactic acid, a metabolic waste product, forming low glucose, low oxygen and low PH environment. The acidified microenvironment will promote glycolysis, allowing more lactic acid to be transported out of the cell into the microenvironment, and more H^+ to be retained outside the cell, leading to further acidification of the microenvironment and again promoting the glycolysis of cancer cells. TIME hypoxia leads to increased expression of HIF-1α, which binds to the anoxic response region in the PD-L1 promoter and up-regulates the expression of PD-L1, and so on, promoting each other.

Therefore, tumor cells can compete with T cells for glucose uptake by inhibiting PI3K/AKT/mTOR pathway through PD-L1, resulting in high uptake of ^{18}F-FDG [10]. However, further basic and clinical studies are needed to prove whether there are other mechanisms by which PD-L1 affects glucose metabolism.

4.2. Relationship between PD-L1 Expression and SUVmax

The maximum standardized uptake value (SUVmax) is the most widely used metabolic parameter in ^{18}F-FDG PET/CT. It is associated with tumor cell proliferation and poor prognosis. Many studies have shown that SUVmax is associated with PD-L1 expression [9] [31] [32].

Xv X *et al*. [33] discussed the correlation between metabolic parameters of ^{18}F-FDG PET/CT and PD-L1 expression in non-small cell lung cancer, and found that SUVmax was an independent predictor of PD-L1 in adenoma of NSCLC ($P < 0.05$). It was also an independent predictor of high PD-L1 expression ($P < 0.05$). In a retrospective analysis of 579 NSCLC patients, Takada K *et al*. [9] found that SUVmax in the PD-L1 positive group was significantly higher than in the PD-L1 negative group ($P < 0.0001$) and SUVmax also was an independent predictor of PD-L1 expression regardless of tumor size (OR = 5.46, $P < 0.0001$). Wu X *et al*. [31] also found that PD-L1 was not correlated with tumor size, only SUVmax was an independent predictor of PD-L1 expression in NSCLC (OR = 1.14, $P < 0.0001$), and the sensitivity, specificity and accuracy were 65.4%, 86.7%, 80.7% respectively. A retrospective analysis [34] involving 362 NSCLC patients found SUVmax is the only factor related to the expression level of PD-L1 and patients with SUVmax > 8.5 have higher PD-L1. As mentioned above, SUVmax should be positively correlated with PD-L1 expression, which may be related to tumor cells increasing their glucose uptake by inhibiting PI3K/AKT/mTOR pathway of T cells. However, the analysis of Jreige M *et al*. [35] in 49 patients with NSCLC showed that there was no significant correlation between PD-L1 and SUVmax. The reasons for the contradictory conclusions

may be that the sample size of cases is not large enough, the characteristics of the selected population are different, and the expression of tumor PD-L1 is also heterogeneous.

To sum up, SUVmax can predict the expression of PD-L1, but whether it can quantify the expression of PD-L1 needs more prospective large-scale research. At present, the research at home and abroad is basically limited to the correlation between the expression level of PD-L1 and SUVmax. However, whether tumor metabolic volume (MTV) or total lesion glycolysis (TLG) can predict the expression of PD-L1 and the advantages of different metabolic parameters are lacking.

5. The Role of ^{18}F-FDG PET/CT in the Response and Efficacy Evaluation of Immunotherapy in NSCLC

^{18}F-FDG PET/CT mainly quantifies tumor load through SUV, MTV, TLG and other parameters. SUVmax is a semi-quantitative parameter that provides the maximum standard concentration of radioactivity uptake by tumors. MTV is a volume index measured by a specific SUV threshold and mainly describes the metabolic volume of tumors. TLG is the product of the average SUV value of all voxels in the tumor and MTV, representing the uptake degree of ^{18}F-FDG and tumor size, as well as the overall metabolic and volumetric load of the tumor [36]. ^{18}F-FDG PET/CT is widely used in monitoring the efficacy of systemic chemoradiotherapy or targeted therapy for a variety of cancers, and plays an important role in monitoring the efficacy of immunotherapy in NSCLC patients in particular.

In a meta-analysis, the European Lung Cancer Working Group of the International Association for the Staging Study of Lung Cancer demonstrated the prognostic value of SUVmax in NSCLC [37]. Grizzi F *et al.* [38] reported that nearly all patients with rapid disease progression after immunotherapy had low baseline SUVmax in a preliminary analysis of 27 patients with NSCLC. However, in the retrospective study of Evangelista L, the higher the SUVmax before treatment, the lower the effective rate [39]. Clearly, the current knowledge of metabolic parameters obtained by ^{18}F-FDG PET/CT in immunotherapy of NSCLC patients is limited, and some published findings are contradictory, especially the relationship between SUVmax and immunotherapy response. Some researches [37] [39] have suggested that lower SUVmax is associated with better response rates, while other reports [38] [40] have claimed lower FDG intake is immune to "cold" tumors that are not sensitive to immunotherapy. The 7th Edition of the American Joint Board on Cancer Staging Manual also does not recommend SUVmax for risk stratification [41], the reason may be that SUVmax is a single voxel value, which does not represent the complete metabolic volume of the tumor [42]. In fact, MTV and TLG are considered to be more reliable markers of tumor burden and aggressiveness, and are more suitable as markers for predicting prognosis of multiple malignancies, including lung cancer, and have

been proposed for risk stratification in lung cancer patients [43]. A large prospective study [44] showed that high MTV was an important independent prognostic factor in patients with advanced NSCLC prior to immunotherapy, predicting early treatment discontinuation (ETD) and poor OS. The high MTV and TLG were also significantly correlated with short OS. Another retrospective, two-center study found that MTV value was significantly associated with treatment responses that achieved disease control. Patients with disease progression had a higher median MTV value than patients with disease control [45]. Similarly, Polverari G *et al*. [46] found similar results: the baseline MTV and TLG values were higher in patients with disease progression, although their analysis was limited to primary lesions. Dall'Olio FG *et al*. [47] found that the median OS was significantly reduced (P = 0.004) in patients with total MTV (tMTV) ≥ 75 cm^3 when they analyzed 34 patients receiving first-line Pembrolizumab. Which suggested tMTV ≥ 75 cm^3 is an independent biomarker for first-line poor prognosis in patients with NSCLC with high PD-L1 expression using Pembrolizumab.

Obviously, baseline tumor metabolic volume load measured by ^{18}F-FDG PET/CT is a strong predictor of immunotherapy, whether limited to primary or systemic lesions. Volume index MTV and TLG can be used to stratify patients to make precise and personalized immunotherapy plans.

6. Summary and Prospect

In a word, immunotherapy based on PD-1/PD-L1 inhibitors has pushed cancer treatment into a new era, with the potential to dominate the field of cancer in the next 10 years, and hopes to turn NSCLC into a chronic disease. Screening patients with the greatest benefit and realizing precision medicine are inseparable from various tests and biomarkers. Although PD-L1 can select immunotherapy-advantaged patients, the detection method has some limitations, and only PD-L1 seems to be insufficient. ^{18}F-FDG PET/CT, as a representative of molecular imaging, has gradually been recognized for its value in evaluating immune efficacy. In view of the relationship between PD-L1 level and ^{18}F-FDG uptake, PET/CT may become a noninvasive alternative predictor of PD-L1. ^{18}F-FDG PET/CT can also identify patients who respond well to immunotherapy earlier than conventional imaging. However, ^{18}F-FDG PET/CT also has some controversies. For example, in terms of efficacy evaluation criteria, domestic and foreign studies are slightly insufficient, and the prognostic value of different metabolic parameters is worth further exploration. Therefore, more large-scale clinical trials and studies are urged to promote its application in the evaluation of immune efficacy. More radionuclides need to be developed to improve the accuracy of predictions and provide new evidence for immunotherapy.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

References

[1] Wang, Y., Zhao, N., Wu, Z., *et al*. (2020) New Insight on the Correlation of Metabolic Status on ^{18}F-FDG PET/CT with Immune Marker Expression in Patients with Non-Small Cell Lung Cancer. *European Journal of Nuclear Medicine and Molecular Imaging*, **47**, 1127-1136. https://doi.org/10.1007/s00259-019-04500-7

[2] Herbst, R.S., Baas, P., Kim, D.W., *et al*. (2016) Pembrolizumab versus Docetaxel for Previously Treated, PD-L1-Positive, Advanced Non-Small-Cell Lung Cancer (KEYNOTE-010): A Randomised Controlled Trial. *The Lancet*, **387**, 1540-1550. https://doi.org/10.1016/S0140-6736(15)01281-7

[3] Incorvaia, L., Fanale, D., Badalamenti, G., *et al*. (2019) Programmed Death Ligand 1 (PD-L1) as a Predictive Biomarker for Pembrolizumab Therapy in Patients with Advanced Non-Small-Cell Lung Cancer (NSCLC). *Advances in Therapy*, **36**, 2600-2617. https://doi.org/10.1007/s12325-019-01057-7

[4] Castello, A., Rossi, S. and Lopci, E. (2020) ^{18}F-FDG PET/CT in Restaging and Evaluation of Response to Therapy in Lung Cancer: State of the Art. *Current Radiopharmaceuticals*, **13**, 228-237. https://doi.org/10.2174/1874471013666191230144821

[5] Eude, F., Guisier, F., Salaün, M., *et al*. (2022) Prognostic Value of Total Tumour Volume, Adding Necrosis to Metabolic Tumour Volume, in Advanced or Metastatic Non-Small Cell Lung Cancer Treated with First-Line Pembrolizumab. *Annals of Nuclear Medicine*, **36**, 224-234. https://doi.org/10.1007/s12149-021-01694-5

[6] Hashimoto, K., Kaira, K., Yamaguchi, O., *et al*. (2022) Visual Assessment of ^{18}F-FDG Uptake on PET to Predict Survival Benefit to PD-1 Blockade in Non-Small Cell Lung Cancer. *Clinical Nuclear Medicine*, **47**, 108-116. https://doi.org/10.1097/RLU.0000000000004009

[7] Tao, X., Li, N., Wu, N., *et al*. (2020) The Efficiency of ^{18}F-FDG PET-CT for Predicting the Major Pathologic Response to the Neoadjuvant PD-1 Blockade in Resectable Non-Small Cell Lung Cancer. *European Journal of Nuclear Medicine and Molecular Imaging*, **47**, 1209-1219. https://doi.org/10.1007/s00259-020-04711-3

[8] Chen, R., Zhou, X., Liu, J., *et al*. (2019) Relationship between the Expression of PD-1/PD-L1 and (18)F-FDG Uptake in Bladder Cancer. *European Journal of Nuclear Medicine and Molecular Imaging*, **46**, 848-854. https://doi.org/10.1007/s00259-018-4208-8

[9] Takada, K., Toyokawa, G., Okamoto, T., Baba, S., Kozuma, Y., *et al*. (2017) Metabolic Characteristics of Programmed Cell Death-Ligand 1-Expressing Lung Cancer on ^{18}F-Fluorodeoxyglucose Positron Emission Tomography/Computed Tomography. *Cancer Medicine*, **6**, 2552-2561. https://doi.org/10.1002/cam4.1215

[10] Kaira, K., Serizawa, M., Koh, Y., *et al*. (2014) Biological Significance of ^{18}F-FDG Uptake on PET in Patients with Non-Small-Cell Lung Cancer. *Lung Cancer*, **83**, 197-204. https://doi.org/10.1016/j.lungcan.2013.11.025

[11] Thunnissen, E., de Langen, A.J. and Smit, E.F. (2017) PD-L1 IHC in NSCLC with a Global and Methodological Perspective. *Lung Cancer*, **113**, 102-105. https://doi.org/10.1016/j.lungcan.2017.09.010

[12] Semenza, G.L. (2010) HIF-1: Upstream and Downstream of Cancer Metabolism. *Current Opinion in Genetics and Development*, **20**, 51-56. https://doi.org/10.1016/j.gde.2009.10.009

[13] Zimna, A. and Kurpisz, M. (2015) Hypoxia-Inducible Factor-1 in Physiological and Pathophysiological Angiogenesis: Applications and Therapies. *BioMed Research International*, **2015**, Article ID: 549412. https://doi.org/10.1155/2015/549412

[14] Xia, L., Liu, Y. and Wang, Y. (2019) PD-1/PD-L1 Blockade Therapy in Advanced Non-Small-Cell Lung Cancer: Current Status and Future Directions. *The Oncologist*, **24**, S31-S41. https://doi.org/10.1634/theoncologist.2019-IO-S1-s05

[15] Noman, M.Z., Desantis, G., Janji, B., *et al*. (2014) PD-L1 Is a Novel Direct Target of HIF-1alpha, and Its Blockade under Hypoxia Enhanced MDSC-Mediated T Cell Activation. *Journal of Experimental Medicine*, **211**, 781-790. https://doi.org/10.1084/jem.20131916

[16] Reck, M., Rodriguez-Abreu, D., Robinson, A.G., *et al*. (2016) Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer. *The New England Journal of Medicine*, **375**, 1823-1833. https://doi.org/10.1056/NEJMoa1606774

[17] Corsini, L.R., Fanale, D., Passiglia, F., *et al*. (2018) Monoclonal Antibodies for the Treatment of Non-Hematological Tumors: A Safety Review. *Expert Opinion on Drug Safety*, **17**, 1197-1209. https://doi.org/10.1080/14740338.2018.1550068

[18] Cortellini, A., Tiseo, M., Banna, G.L., *et al*. (2020) Clinicopathologic Correlates of First-Line Pembrolizumab Effectiveness in Patients with Advanced NSCLC and a PD-L1 Expression of >/= 50. *Cancer Immunology, Immunotherapy*, **69**, 2209-2221. https://doi.org/10.1007/s00262-020-02613-9

[19] Lopci, E. (2021) Immunotherapy Monitoring with Immune Checkpoint Inhibitors Based on [(18)F]FDG PET/CT in Metastatic Melanomas and Lung Cancer. *Journal of Clinical Medicine*, **10**, 5160. https://doi.org/10.3390/jcm10215160

[20] Wahl, R.L., Jacene, H., Kasamon, Y., *et al*. (2009) From RECIST to PERCIST: Evolving Considerations for PET Response Criteria in Solid Tumors. *Journal of Nuclear Medicine*, **50**, 122S-150S. https://doi.org/10.2967/jnumed.108.057307

[21] Goldfarb, L., Duchemann, B., Chouahnia, K., Zelek, L. and Soussan, M. (2019) Monitoring Anti-PD-1-Based Immunotherapy in Non-Small Cell Lung Cancer with FDG PET: Introduction of iPERCIST. *EJNMMI Research*, **9**, Article No. 8. https://doi.org/10.1186/s13550-019-0473-1

[22] Ito, K., Teng, R., Schoder, H., *et al*. (2019) (18)F-FDG PET/CT for Monitoring of Ipilimumab Therapy in Patients with Metastatic Melanoma. *Journal of Nuclear Medicine*, **60**, 335-341. https://doi.org/10.2967/jnumed.118.213652

[23] Humbert, O., Cadour, N., Paquet, M., *et al*. (2020) (18)FDG PET/CT in the Early Assessment of Non-Small Cell Lung Cancer Response to Immunotherapy: Frequency and Clinical Significance of Atypical Evolutive Patterns. *European Journal of Nuclear Medicine and Molecular Imaging*, **47**, 1158-1167. https://doi.org/10.1007/s00259-019-04573-4

[24] Castello, A., Rossi, S., Toschi, L., *et al*. (2020) Comparison of Metabolic and Morphological Response Criteria for Early Prediction of Response and Survival in NSCLC Patients Treated with Anti-PD-1/PD-L1. *Frontiers in Oncology*, **10**, 1090. https://doi.org/10.3389/fonc.2020.01090

[25] Vekens, K., Everaert, H., Neyns, B., *et al*. (2021) The Value of ^{18}F-FDG PET/CT in Predicting the Response to PD-1 Blocking Immunotherapy in Advanced NSCLC Patients with High-Level PD-L1 Expression. *Clinical Lung Cancer*, **22**, 432-440. https://doi.org/10.1016/j.cllc.2021.03.001

[26] Fowler, J.S. and Ido, T. (2002) Initial and Subsequent Approach for the Synthesis of ^{18}FDG. *Seminars in Nuclear Medicine*, **32**, 6-12. https://doi.org/10.1053/snuc.2002.29270

[27] Kaira, K., Serizawa, M., Koh, Y., *et al*. (2012) Relationship between ^{18}F-FDG Uptake on Positron Emission Tomography and Molecular Biology in Malignant Pleural Mesothelioma. *European Journal of Cancer*, **48**, 1244-1254.

https://doi.org/10.1016/j.ejca.2012.01.016

[28] Chang, C., Qiu, J., Sullivan, D., *et al*. (2015) Metabolic Competition in the Tumor Microenvironment Is a Driver of Cancer Progression. *Cell*, **162**, 1229-1241. https://doi.org/10.1016/j.cell.2015.08.016

[29] Scharping, N.E. and Delgoffe, G.M. (2016) Tumor Microenvironment Metabolism: A New Checkpoint for Anti-Tumor Immunity. *Vaccines* (*Basel*), **4**, 46. https://doi.org/10.3390/vaccines4040046

[30] Chaker, M., Minden, A., Chen, S., *et al*. (2018) Rho GTPase Effectors and NAD Metabolism in Cancer Immune Suppression. *Expert Opinion on Therapeutic Targets*, **22**, 9-17. https://doi.org/10.1080/14728222.2018.1413091

[31] Wu, X., Huang, Y., Zhao, Q., *et al*. (2020) PD-L1 Expression Correlation with Metabolic Parameters of FDG PET/CT and Clinicopathological Characteristics in Non-Small Cell Lung Cancer. *EJNMMI Research*, **10**, Article No. 51. https://doi.org/10.1186/s13550-020-00639-9

[32] Zhao, L., Liu, J., Shi, J., *et al*. (2020) Relationship between SP142 PD-L1 Expression and ^{18}F-FDG Uptake in Non-Small-Cell Lung Cancer. *Contrast Media & Molecular Imaging*, **2020**, Article ID: 2010924. https://doi.org/10.1155/2020/2010924

[33] Xv, X., Li, J.H., Dai, N., *et al*. (2022) Correlation between Metabolic Parameters of (18)F-FDG PET/CT and PD-L1 Expression in Non-Small Cell Lung Cancer. *Chinese Journal of Clinical Oncology*, **49**, 338-344.

[34] Hu, B., Chen, W., Zhang, Y., *et al*. (2020) ^{18}F-FDG Maximum Standard Uptake Value Predicts PD-L1 Expression on Tumor Cells or Tumor-Infiltrating Immune Cells in Non-Small Cell Lung Cancer. *Annals of Nuclear Medicine*, **34**, 322-328. https://doi.org/10.1007/s12149-020-01451-0

[35] Jreige, M., Letovanec, I., Chaba, K., Renaud, S., *et al*. (2019) ^{18}F-FDG PET Metabolic-to-Morphological Volume Ratio Predicts PD-L1 Tumour Expression and Response to PD-1 Blockade in Non-Small-Cell Lung Cancer. *European Journal of Nuclear Medicine and Molecular Imaging*, **46**, 1859-1868. https://doi.org/10.1007/s00259-019-04348-x

[36] Takahashi, M., Lorand-Metze, I., de Souza, C.A., *et al*. (2021) Metabolic Volume Measurements in Multiple Myeloma. *Metabolites*, **11**, 875. https://doi.org/10.3390/metabo11120875

[37] Paesmans, M., Berghmans, T., Dusart, M., *et al*. (2010) Primary Tumor Standardized Uptake Value Measured on Fluorodeoxyglucose Positron Emission Tomography Is of Prognostic Value for Survival in Non-Small Cell Lung Cancer: Update of a Systematic Review and Meta-Analysis by the European Lung Cancer Working Party for the International Association for the Study of Lung Cancer Staging Project. *Journal of Thoracic Oncology*, **5**, 612-619. https://doi.org/10.1097/JTO.0b013e3181d0a4f5

[38] Grizzi, F., Castello, A. and Lopci, E. (2018) Is It Time to Change Our Vision of Tumor Metabolism Prior to Immunotherapy? *European Journal of Nuclear Medicine and Molecular Imaging*, **45**, 1072-1075. https://doi.org/10.1007/s00259-018-3988-1

[39] Evangelista, L., Cuppari, L., Menis, J., Bonanno, L., *et al*. (2019) ^{18}F-FDG PET/CT in Non-Small-Cell Lung Cancer Patients: A Potential Predictive Biomarker of Response to Immunotherapy. *Nuclear Medicine Communications*, **40**, 802-807. https://doi.org/10.1097/MNM.0000000000001025

[40] Takada, K., Toyokawa, G., Yoneshima, Y., *et al*. (2019) ^{18}F-FDG Uptake in PET/CT Is a Potential Predictive Biomarker of Response to Anti-PD-1 Antibody Therapy in Non-Small Cell Lung Cancer. *Scientific Reports*, **9**, Article No. 13362.

https://doi.org/10.1038/s41598-019-50079-2

[41] Edge, S.B. (2010) AJCC Cancer Staging Handbook: From the AJCC Cancer Staging Manual. 7th Edition, Springer, New York, 718.

[42] Im, H.J., Pak, K., Cheon, G.J., *et al*. (2015) Prognostic Value of Volumetric Parameters of (18)F-FDG PET in Non-Small-Cell Lung Cancer: A Meta-Analysis. *European Journal of Nuclear Medicine and Molecular Imaging*, **42**, 241-251. https://doi.org/10.1007/s00259-014-2903-7

[43] Romesser, P.B., Qureshi, M.M., Shah, B.A., *et al*. (2012) Superior Prognostic Utility of Gross and Metabolic Tumor Volume Compared to Standardized Uptake Value Using PET/CT in Head and Neck Squamous Cell Carcinoma Patients Treated with Intensity-Modulated Radiotherapy. *Annals of Nuclear Medicine*, **26**, 527-534. https://doi.org/10.1007/s12149-012-0604-5

[44] Chardin, D., Paquet, M., Schiappa, R., *et al*. (2020) Baseline Metabolic Tumor Volume as a Strong Predictive and Prognostic Biomarker in Patients with Non-Small Cell Lung Cancer Treated with PD1 Inhibitors: A Prospective Study. *Journal for Immunotherapy of Cancer*, **8**, e000645. https://doi.org/10.1136/jitc-2020-000645

[45] Monaco, L., Gemelli, M., Gotuzzo, I., *et al*. (2021) Metabolic Parameters as Biomarkers of Response to Immunotherapy and Prognosis in Non-Small Cell Lung Cancer (NSCLC): A Real World Experience. *Cancers* (*Basel*), **13**, 1634. https://doi.org/10.3390/cancers13071634

[46] Polverari, G., Ceci, F., Bertaglia, V., *et al*. (2020) ^{18}F-FDG Pet Parameters and Radiomics Features Analysis in Advanced Nsclc Treated with Immunotherapy as Predictors of Therapy Response and Survival. *Cancers*, **12**, 1163. https://doi.org/10.3390/cancers12051163

[47] Dall Olio, F.G., Calabrò, D., Conci, N., *et al*. (2021) Baseline Total Metabolic Tumour Volume on 2-Deoxy-2-[18F]fluoro-d-glucose Positron Emission Tomography-Computed Tomography as a Promising Biomarker in Patients with Advanced Non-Small Cell Lung Cancer Treated with First-Line Pembrolizumab. *European Journal of Cancer*, **150**, 99-107. https://doi.org/10.1016/j.ejca.2021.03.020