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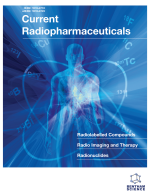
REVIEW ARTICLE

PET/CT and the Response to Immunotherapy in Lung Cancer



Laura Evangelista[1,*], Matteo Sepulcri[2] and Giulia Pasello[3]

[1]*Nuclear Medicine Unit, Department of Medicine – DIMED, University of Padua, 35128 Padua, Italy;* [2]*Radiation Oncology Unit, Veneto Institute of Oncology IOV - IRCCS, Padua, Italy;* [3]*Oncology 2 Unit, Veneto Institute of Oncology IOV - IRCCS, Padua, Italy*

Abstract: ***Objective:*** In recent years, the introduction of immune checkpoint inhibitors has significantly changed the outcome of patients affected by lung cancer and cutaneous melanoma. Although the clinical advantages, the selection of patients and the evaluation of response to immunotherapy remain unclear, the immune-related Response Evaluation Criteria in Solid Tumor (irRECIST) was proposed as an update of the RECIST criteria for the assessment of response to immunotherapy. However, morphological images cannot predict early response to therapy that represents a challenge in clinical practice. 18F-FDG PET/CT before and after immunotherapy has an indeterminate role, demonstrating ambiguous results due to inflammatory effects secondary to activation of the immune system. The aim of the present review was to analyze the role of PET/CT as a guide for immunotherapy, by analyzing the current status and future perspectives.

Methods: A literature search was conducted in order to select all papers that discussed the role of PET/CT with FDG or other tracers in the evaluation or prediction of response to immunotherapy in lung cancer patients.

Results: Many papers are now available. Many clinical trials have demonstrated the efficacy of immunotherapy in lung cancer patients. FDG PET/CT can be used for the prediction of response to immunotherapy, while its utility for the evaluation of response is not still clearly reported. Moreover, the standardization of FDG PET/CT interpretation is missing and different criteria, such as information, have been investigated until now.

Conclusion: The utility of FDG PET/CT for patients with lung cancer undergoing immunotherapies is still preliminary and not well addressed. New agents for PET are promising, but large clinical trials are mandatory.

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1. INTRODUCTION

The development of new agents, in the last years, that induce or potentiate the anti-tumor activity of the immune system has changed the management of cancer patients with a deep effect on the patient outcome. Immune checkpoint inhibitors have demonstrated an extraordinary result in a wide range of tumors, particularly in patients affected by lung cancer [1-3] and cutaneous melanoma [4-6]. However, other tumor types (*i.e.* squamous cell carcinoma of the head and neck cancer, renal cell carcinoma, urothelial cancer and others) have been treated with immunotherapy [7-9]. Ipilimumab has been the first checkpoint inhibitor approved in 2011 by the food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of advanced melanoma. Nivolumab was introduced also for the treatment of non-small cell lung cancer (NSCLC), demonstrating an improvement in overall survival (OS) when compared to docetaxel [1, 2, 10, 11]. Although these demonstrated clinical advantages, the selection of patients and the evaluation of response to immunotherapy remain unclear. The immune-related Response Evaluation Criteria in Solid Tumor (irRECIST) was proposed as an update of the RECIST criteria for the assessment of response to immunotherapy [12, 13]. However, morphological images cannot predict early response to therapy that represents a challenge in clinical practice. Recently, Cho *et al.* [14] reported preliminary data in 20 patients with cutaneous melanoma undergoing 18F-FDG PET/CT before and after immunotherapy. The authors combined the RECIST and Positron Emission Tomography Response Criteria in Solid Tumors (PERCIST) criteria in order to obtain a tool for the evaluation of response to immunotherapy, named PECRIT (PET/CT Criteria

*Address correspondence to this author at the Nuclear Medicine Unit, Department of Medicine – DIMED, University of Padua, Via Giustiniani, 2 35128 Padua, Italy; Tel: +39 049821310; Fax: +390498213008; E-mail: laura.evangelista@unipd.it

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for early prediction of Response to Immune Checkpoint Therapy). However, few data about the utility of FDG PET/CT in patients with lung cancer treated with immunotherapy are now available [15]. The aim of the present review was to analyze the role of PET/CT as a guide for immunotherapy in lung cancer, by analyzing the current status and future perspectives. The present paper is descriptive, with the objective of discussing current evidences and the future perspectives for research in this field; therefore, the search strategies such as those used for the systemic review were not applied.

2. LUNG CANCER AND IMMUNOTHERAPY

PD-1 and its ligands PD-L1 represent a key pathway in preventing loss of cytotoxic function in lymphocytes and consequently preventing tumor evasion from immune response. The first drug introduced for inhibiting the PD-1/PD-Ls immunosuppressive pathway, in lung cancer patients, was nivolumab [2]. Later, pembrolizumab and atezolizumab were included as therapeutic approaches in lung cancer, by also considering the expression of PD-L1 [16, 17]. However, the role of PD-L1 expression for the selection of patients who can be treated with immunotherapy is still debated [16, 18-20].

In Table **1** are reported the summary of the most important clinical trials about immunotherapy in lung cancer patients. All trials were phase III randomized controlled studies that showed significant improvement of outcomes, after the introduction of immunotherapy. As shown, by comparing the best standards of treatment (chemotherapy with docetaxel or

Table 1. Summary of clinical trials about immunotherapy in lung cancer.

Trials, Refs.	Drug (dose)	N of Patients	Phase study	Line	PD-L1/ALK Expression	OS HR	PFS HR
Checkmate 017, [1]	Nivolumab vs. Docetaxel (3 mg/kg/2wks vs. 75 mg/m2)	272	III	Second-line	large (from <1% to >10%)	0.69	0.67
Checkmate 057, [2]	Nivolumab vs. Docetaxel (3 mg/kg/2wks vs. 75 mg/m2)	582	III	Second-line	large (from <1% to >10%)	0.59	0.70
Keynote 010, [16]	Pembrolizumab vs. Docetaxel (2 mg/kg/3wks vs. 75 mg/m2) and (10 mg/kg/3wks vs. 75 mg/m2)	1033	II/III	Second-line	PDL-1 TPS >=1%	0.71 and 0.61	0.88 and 0.79
Keynote 024, [19]	Pembrolizumab vs. chemotherapy (carboplatin + pemetrexed (500 mg/m²), cisplatin (75 mg/m²) + pemetrexed (500 mg/m²), carboplatin (AUC 5 or 6) + gemcitabine (1250 mg/m²), cisplatin (75 mg/m²) + gemcitabine (1250 mg/m²), or carboplatin (AUC 5 or 6) + paclitaxel (200 mg/m²).	1934	III	First-line	PDL-1 TPS >=50%	0.60	0.50
Socinski *et al*. [50]	Atezolizumab + carboplatin plus paclitaxel and atezolizumab + bevacizumab + carboplatin + paclitaxel vs. bevacizumab + carboplatin + paclitaxel.	1202	III	First-line	EGFR <10% ALK <5%	0.78	0.62
OAK trial, [17]	Atezolizumab (1200 mg fixed dose every 3 weeks) vs. docetaxel (75 mg/m² every 3 weeks).	1225	III	Second-line	Large (comprised a sub-group PD-L1 expression analysis)	0.72 (0.41 in PD-L1>50%)	0.95
KEYNOTE-189, [51]	Cisplatin (75 mg/m²) or carboplatin + pemetrexed (500 mg/m²), followed by pemetrexed (500 mg/m²) + pembrolizumab vs. Cisplatin (75 mg/m²) or carboplatin + pemetrexed (500 mg/m²), followed by pemetrexed (500 mg/m²) + placebo	965	III	First-line	Large (comprised a sub-group PD-L1 expression analysis)	0.49	0.52
Govindan *et al*. [52]	Paclitaxel and carboplatin + blinded ipilimumab 10 mg/kg vs. paclitaxel and carboplatin + placebo	749	III	First-line	N.A.	0.91	0.87

N.A. Not available.

platinum) with immunotherapy (both pembrolizumab and nivolumab), a better progression-free survival and OS were found, by including immunotherapy, with a reduction of 30-40% of the death risk. These results represent a remarkable achievement in medical history.

In CheckMate-17 [1] and CheckMate-57 [2], Nivolumab demonstrated a long-term clinical benefit and a favorable tolerability profile compared with docetaxel in previously treated patients with advanced NSCLC. In particular, in the CheckMate-57, a significant improvement in overall survival was found for the subgroup of patients with higher levels of tumor PD-L1 expression.

In the phase III KeyNote-010 trial, 1033 patients who were previously treated for metastatic NSCLC were randomized in two arms of treatment with pembrolizumab (different immunotherapy regimen) vs. docetaxel. The pembrolizumab therapy showed a significant improvement in overall survival as compared to those treated with docetaxel (median overall survival: 14.9 months vs. 17.3 months vs. 11.8 months, respectively for the pembrolizumab 2 mg/Kg vs. pembrolizumab 10 mg/Kg vs. Docetaxel) [16].

In phase III KeyNote-024, only patients with a PD-L1 expression >50% were included, differently from the KeyNote-010 that also included patients with a PD-L1 expression > 1%. The gain in survival rate against the standard of treatment was about 20%.

The expression of PD-L1 is considered to be the most influential biomarker at present. However, the first trials were performed independently of the expression of PD-L1, but the post-doc analysis showed a significant improvement in response rate for patients with a tumor proportion score (TPS) >50% than those with a TPS<=1% [16, 19].

However, the Food and Drug Administration (FDA) approved pembrolizumab for the first-line treatment of patients with a PD-L1 TPS of 50% or greater and pembrolizumab plus platinum combination therapy in patients regardless of PD-L1 expression.

The evaluation of response to immunotherapy represents a fertile field of research. With immunotherapy being a highly effective therapy, with an expensive profile, an early evaluation of response would be useful to avoid ineffective treatment regimens. However, the correct management of patients undergoing immunotherapy is still not determined. FDG PET/CT seems promising, but its role needs further investigations.

18F-FDG PET/CT has been widely used in clinical practice for the evaluation of response to therapies in patients with lung cancer [21-23]. Standardized uptake value (SUV) between baseline and follow-up studies is one of the most common parameters tested; however, it is affected by various factors, such as technical, physical and biological factors [24-26]. In order to facilitate the reproducibility of PET/CT results, in 1999, the European Organization for Research and Treatment of Cancer (EORTC) criteria were developed. These criteria were based on the SUV normalized to body surface area (SUVba) to reduce the influence of the body weight of SUV [27]. Later, in 2009, the American researches introduced an alternative protocol for the assessment of response to therapy in oncological patients: the Positron Emission Tomography Response Criteria in Solid Tumors (PERCIST 1.0). PERCIST 1.0 recommends using SUV corrected for lean body mass (SUL) to falsely avoid high organ SUV in obese patients [28-30]. By the way, FDG is able to monitor changes in glucose metabolism that is not present only in tumor cells, but also in inflammatory ones. As known, immunotherapy elicits a natural inflammatory response and therefore, traditional PET imaging using FDG has proven inadequate in examining responses to immunotherapy [31]. Few papers are now available about the role of FDG PET/CT for the prediction and assessment of response to immunotherapy in patients with lung cancer [15, 32-36]. Furthermore, the majority of them are clinical case presentations [32-35]. On the contrary, different data are now published about the evaluation of response to immunotherapy with FDG PET/CT in cutaneous melanoma [14] and lymphoma [37].

Eshghi *et al.* [32] described the ability of FDG PET/CT in the evaluation of dynamic adaptation of tumor immune response with Nivolumab. The authors described PET/CT results in a 61-year-old woman with stage IV NSCLC who was treated with Nivolumab. PET/CT was performed before and during immunotherapy, demonstrating continuous adaptation of the immune system for the fight against tumor. This paper highlights the hypothesis that changes in tumor metabolism can be associated with response of the immune system rather than a real progression of the disease.

Curioni-Fontecedro *et al.* [34] reported a case of a 72-year-old woman with lung cancer undergoing Nivolumab. FDG PET/CT was made before and after 6-weeks from the end of immunotherapy. An increase in FDG uptake for the lymph node and visceral metastasis was shown between the scans, indiscriminate for progression and pseudoprogression. For a further analysis, a lymph node biopsy was done, demonstrating the presence of metabolically active effector lymphocytes, rather than tumor pseudoprogression.

Higuchi *et al.* [33] reported an example of a 75-year-old man with metastatic NSCLC who underwent Nivolumab treatment as second line chemotherapy. FDG PET/CT was performed before and after 6-courses of immunotherapy, showing a decrease in FDG uptake in each recurrent lesion. The authors were in favor of the use of FDG PET/CT in monitoring the response to Nivolumab. In this case, T cell activation and infiltration into the tumor tissue did not affect the results of FDG PET/CT, but larger data would be mandatory.

Fakhri *et al.* [35] described a clinical case of a 74-year-old male patient undergoing neoadjuvant therapy with pembrolizumab and chemotherapy for a stage IIIA NSCLC. The patient was staged with FDG PET/CT before and after treatment. The images showed the appearance of mildly FDG-avid lymph nodes in the paratracheal and hilar areas, and the reduction in FDG uptake in the primary lesion. The histopathological analysis revealed noncaseating granulomatous inflammation probably due to immunotherapy [38, 39].

Friedrickson *et al.* [36] reported some preliminary data about the role of FDG PET/CT in predicting response to Atezolizumab in a cohort of 103 patients with lung cancer. The preliminary data concluded that the baseline whole-body

metabolic tumor volume was a strong negative prognostic factor for overall survival, while SUVmax was not.

A recent paper by Kaira *et al.* [15] reported that the metabolic responses by FDG PET/CT evaluating by TLG or MTV are associated with therapeutic response and survival 1 month after nivolumab administration in 25 patients with NSCLC. The authors encouraged the implementation of FDG PET/CT in clinical practice, for the assessment of response to nivolumab therapy.

Eshghi *et al.* [40] described the role of FDG PET/CT in predicting the development of thyroiditis with subsequent hypothyroidism in patients with lung cancer treated by nivolumab. The authors reported data from 18 patients who underwent PET/CT before and during treatment. SUVmax and TLG in the thyroid were measured, in order to assess their changes during nivolumab. Patients who developed hypothyroidism, as an immune-related adverse effect, have a higher FDG uptake (in terms of SUVmax and TLG). Moreover, those with hypothyroidism were able to continue treatment with nivolumab for a more long time than the counterpart. This study highlights how FDG PET/CT can be interchangeably used for the prediction of response to Nivolumab.

A very recent paper published by Goldfarb *et al.* [41] reported the role of a new criterion for the evaluation of response to immunotherapy, so-called iPERCIST in 28 patients affected by NSCLC undergoing PET/CT before (scan-1) and 2-months (scan-2) later nivolumab therapy. iPERCIST was defined as a dual-point evaluation of unconfirmed progressive metabolic disease status at scan-2 confirmed/non-confirmed by a third scan (scan-3) performed 4-weeks later from scan-2. The authors found a significant difference in terms of overall survival in patients who were considered responders and non-responders based on the iPERCIST criteria. Therefore, this new instrument would be useful and should be tested in a large series of patients.

Fig. (**1**) shows an example of FDG PET/CT before and after immunotherapy.

3. BEYOND FDG AND IMMUNOTHERAPY IN LUNG CANCER

Table **2** reports some promising radiopharmaceutical agents for the evaluation and prediction of response to immunotherapy [42-47].

The development of these new agents is essential for preliminary evaluation of PD-L1 expression in all metastatic sites of disease that is useful in order to: 1) avoid multiple biopsies; 2) better select patients who will benefit from immunotherapy; and 3) reduce the costs (by avoiding unnecessary treatments).

Ehlerding *et al.* [43] tested the utility of radiolabeled CTLA-4 PET/CT in mice with NSCLC. Ipilimumab is the only FDA-approved CTLA-4 antibody. By blocking the co-inhibitory receptor CTLA-4 using checkpoint-blocking antibodies, T-cells remain active and lead to a greater cytotoxic immune response in the tumor microenvironment [48]. 64Cu-DOTA-ipilimumab in mice bearing CTLA-4 expressing tumor was able to correctly localize the tumor, but a link was found with the receptor on the cell surface rather than in

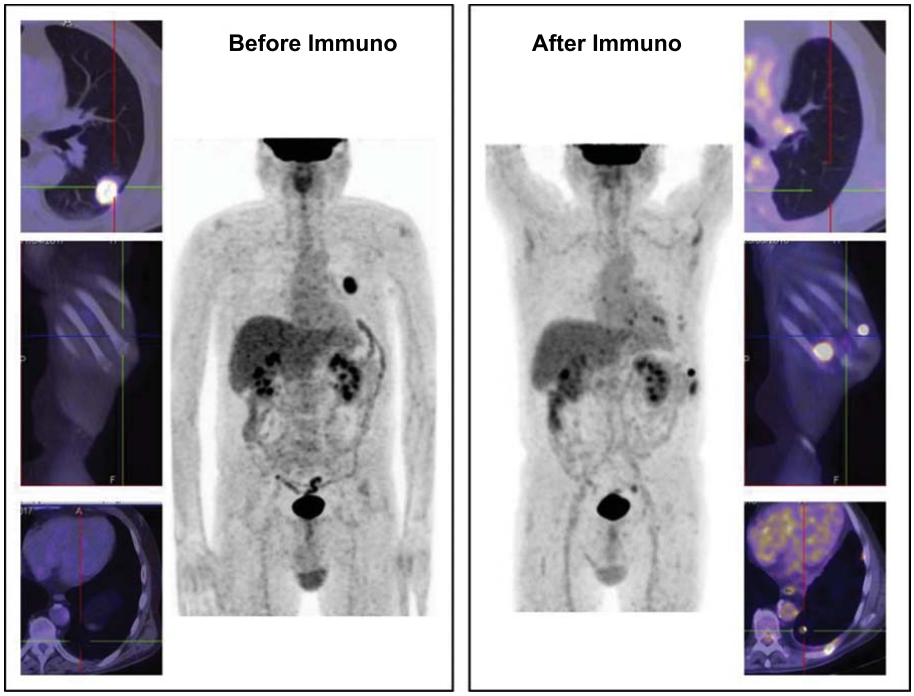

Fig. (1). A 64-year old male affected by non-small cell lung cancer underwent FDG PET/CT before and after immunotherapy (SPER trial; ClinicalTrials.gov Identifier: NCT02273375). (Left) Baseline PET/CT demonstrated a high FDG uptake into a single lesion located in the left lung. (Right) Post-treatment PET/CT showed the appearance of FDG uptake in the lung (two lesions in the posterior and anterior segment of the inferior lobe of the left lung), and in the left pleural spaces (two lesions), compatible with progression of disease. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Table 2. New radiopharmaceutical agents for immuno-PET.

Authors (year), ref	Radiopharmaceutical	Target	Experimental phase
Pool *et al.* (2206), [42]	89Zr-imgratuzumab	EGFR	Preclinical
Sun *et al.* (2016), [47]	64Cu-anti CD 146	CD 146	Preclinical
Ehlerding *et al.* (2017), [43]	64Cu-DOTA-ipilimumab	Cytotoxic T lymphocyte associated protein (CTLA-4)	Preclinical
Cole *et al.* (2017), [44]	89Zr-nivolumab	PD-L1	Preclinical
Truillet *et al.* (2018), [46]	89Zr-C4	Human IgG1	Preclinical
England *et al.* (2018), [45]	89Zr-df-nivolumab	PD-L1	Preclinical

the intracellular domain. 64Cu-DOTA-ipilimumab was injected in mice (5-10 MBq) by an intravenous infusion. In order to assess tracer accumulation in the tumor, the CTLA-4 receptor was blocked by injecting excess cold ipilimumab 24h prior to injection of radiolabeled ipilimumab in A549 tumor-bearing mice. A great accumulation of tracer was noted in the liver.

Cole *et al.* [44] and England *et al.* [45] reported preclinical data about a nivolumab-based radiopharmaceutical in small animals. Cole *et al.* reported increased uptake of tracer in the spleen that was reduced by co-administration of excess nivolumab (carrier-added 3 mg/kg). England *et al.* tested the biodistribution of 89Zr-df-Nivolumab in NOD scid gamma (NSG) and hu-PBL-SCID-model (PBL) mice bearing A549 tumor. The uptake of the radiopharmaceutical agent was significantly higher in the tumor for the PBL mice and in the spleen for the NSG mice. The authors underlined the advantages to use 89Zr, thanks to the long half-life that allows to track PD-1 expressing T-cells infiltration into the tumor over the course of 168 h. PET images were performed after 3, 6, 12, 24, 48, 72 and 168h post-injection. Biodistribution images revealed that the tracer had a higher uptake in the salivary gland in PBL mice than NSG.

Truillet *et al.* [46] evaluated the biodistribution of immunoPET with 89Zr-C4 in mice, demonstrating a high accumulation of tracer in the spleen and in the liver and maximum uptake in the tumor after 48h from the administration. Interestingly, the authors noted an acute change in PD-L1 expression on the tumor cells due to standard chemotherapies with immuno PET underlying the utility of serial images in order to predict the response to some immunotherapies. Because patients with as little as 5% of antigen-positive cells on biopsy can experience a response to cancer immunotherapy, imaging tools with high specificity and low background in antigen-negative tissue are essential. Biodistribution studies were performed after 8, 24, 48, 72 and 120 h after the injection of the radiopharmaceutical agent. The clearance of the tracer by the tumor appeared after 48h from the injection at PET images.

Despite a large number of data and the small number of animals in each study, the variability concerning the anti-PD-L1-mAbs used is large. A recent review by Vaz *et al.* [49] suggests a high radiopharmaceutical sensitivity and specificity for PD-L1 detection and described clear identification of the tumor on images. Therefore, Nuclear Medicine investigations using radiolabeled targeting monoclonal antibodies may provide a useful imaging biomarker.

CONCLUSION

In conclusion, the utility of FDG PET/CT for patients with lung cancer undergoing immunotherapies is still preliminary and not well addressed. Despite its low specificity, FDG PET/CT can predict the response to therapy, monitor the development of immune related events, and provide prognostic information. Alternative radiopharmaceutical agents for PET/CT are under evaluation, although still in preclinical phase. However, they seem promising for the selection of patients who will benefit from these promising immune-stimulated therapies. New trials are mandatory in order to understand the utility of PET/CT in patients treated with immunotherapy.

LIST OF ABBREVIATIONS

irRECIST	=	immune-related Response Evaluation Criteria in Solid Tumor
FDG	=	Fluorodeoxyglucose
PET	=	Positron Emission Tomography
CT	=	Computed Tomography
PD-L1	=	Programmed Death-Ligand 1
SUV	=	Standardized Uptake Value
PERCIST	=	Positron Emission Tomography Response Criteria in Solid Tumors
PECRIT	=	PET/CT Criteria for early Prediction of Response to Immune Checkpoint Therapy
NSCLC	=	Non-Small Cell Lung Cancer
EORTC	=	European Organization for Research and Treatment of Cancer
CTLA-4	=	Cytotoxic T-Lymphocyte Antigen 4
MBq	=	megabequerel

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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