Mini-review   **Open Access**

Current status and future prospects of PET/CT in NSCLC treated with checkpoint-based immunotherapy

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ABSTRACT

Immune checkpoint inhibitors play crucial roles in the treatment of advanced and recurrent non-small cell lung caner (NSCLC). As yet, there are no biomarkers to help select patients that would benefit from this treatment. Currently, evaluation of the efficacy of immune checkpoint inhibitors is performed using Response Evaluation Criteria In Solid Tumors (RECIST) or immune-related response criteria on the basis of computed tomography (CT) scans, which are based only on anatomical changes and exclude a metabolic assessment. 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) can add metabolic information, but is also subject to false-positive and false-negative findings in the presence of inflammation. In this review, we briefly discuss the optimal use of FDG-PET for the evaluation of checkpoint-based cancer immunotherapy and also discuss the relationship between immune checkpoint inhibitors and FDG-PET in NSCLC. We also introduce ongoing clinical studies and pre-clinical experiments involved in the development of diagnostic imaging and treatments for NSCLC.

Introduction

Lung cancer is the leading cause of cancer-related death worldwide[1]. Third-generation platinum doublets, epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKIs) in sensitized EGFR mutation-positive lung cancer, anaplastic lymphoma kinase (ALK) TKIs in ALK rearrangement-positive disease, anti-vascular endothelial growth factor (VEGF) antibody, anti-VEGF receptor (VEGFR) antibody, maintenance systemic therapy, and second- or third-line treatment have improved survival in patients with non-small cell lung cancer (NSCLC)[2-9]. To date, immune checkpoint inhibitors have been introduced[10-12]. Nivolumab, one of immune checkpoint inhibitors that is an antibody against programmed death-1 (PD-1), causes T cell activation and demonstrates antitumor activity through the blockade of combination between PD-1 and its ligand, programmed death ligand-1 (PD-L1). In some phase III trials, overall survival (OS), objective response rate (ORR), and progression free survival (PFS) were better with nivolumab than with chemotherapy in NSCLC (Checkmate 017 and Checkmate 057[13,14]). Furthermore, pembrolizumab, also an immune checkpoint inhibitor that is also an antibody against PD-1, has been reported in the KEYNOTE 024 phase III trial[15] to have superior PFS, OS, and ORR compared

Immunotherapy	Year	Target molecule	Phase	N	Primary endpoint	Results	Reference No.
Nivolumab	2015	PD-1	III	272	Overall survival	At 1 year, the overall survival rate was 42% (95% CI, 34 to 50) with nivolumab versus 24% (95% CI, 17 to 31) with docetaxel.	13
Nivolumab	2015	PD-1	III	582	Overall survival	At 1 year, the overall survival rate was 51% (95% CI, 45 to 56) with nivolumab versus 39% (95% CI, 33 to 45) with docetaxel.	14
Pembrolizumab	2016	PD-1	III	305	Progression-free survuval	Median progression-free survival was 10.3 months (95% confidence interval [CI], 6.7 to not reached) in the pembrolizumab group versus 6.0 months (95% CI, 4.2 to 6.2) in the chemotherapy group (hazard ratio for disease progression or death, 0.50; 95% CI, 0.37 to 0.68; P<0.001).	15
Ipilimumab	2012	CTLA-4	II	204	Immune-related progression-free survuval	Phased ipilimumab improved irPFS compared with the control (hazard ratio [HR], 0.72; P=.05).	24
Atezolizumab	2017	PD-L1	III	850	Overall survival and PD-L1 expression population	Overall survival in the TC1/2/3 or IC1/2/3 population was improved with atezolizumab (n=241) compared with docetaxel (n=222; median overall survival was 15·7 months [95% CI 12·6–18·0] with atezolizumab vs 10·3 months [8·8–12·0] with docetaxel; HR 0·74 [95% CI 0·58–0·93]; p=0.0102).	68
Durvalumab with or without tremelimumab	2016	PD-L1	Ib	102	Safety	Treatment-related serious adverse events occurred in 37 (36%) of 102 patients, and three deaths were related to treatment	70
PD-1: Programmed cell death-1, CTLA-4: Cytotoxic T lymphocyte antigen-4, PD-L1: Programmed cell death ligand-1, TC: Tumor cells, IC: Immune cells							

Table 1: Clinical studies of checkpoint-based immunotherapy for NSCLC

to platinum-based cytotoxic chemotherapy as a first-line treatment for NSCLCs with ≥ 50% positive PD-L1 expression. We showed previous clinical studies of checkpoint-based immunotherapy for NSCLC in Table 1.

Contrast-enhanced computed tomography (CT) and magnetic resonance imaging (MRI) have been used to stage and follow up various malignancies before and after treatment[16-18]. 18F-fluorodeoxyglucose-positron emission tomography (FDG-PET) is an effective tool for metabolically assessing treatment response and surveillance of disease status. However, it sometimes shows increased FDG uptake at sites of local inflammatory changes caused by the accumulation of inflammatory cells[19]. Many researchers have reported the utility of FDG-PET or FDG-PET/CT in evaluating therapeutic response to date[20-23]. In this review, the role of PET/CT after treatment with immune checkpoint inhibitors is highlighted and the following topics are discussed: (a) Use of immune checkpoint inhibitors in NSCLC; (b) Tumor microenvironment and metabolic variables; (c) Imaging comparison between FDG-PET and CT scan; (d) Development of molecular imaging criteria for staging and surveillance; (e) Pitfalls and clinical questions; (f) Clinical trials using PET imaging for evaluating immune checkpoint inhibitors; and (g) Conclusions and future directions.

Use of immune checkpoint inhibitors in NSCLC;

In patients with recurrence after surgery for NSCLC or advanced NSCLC, who have relapsed after previous platinum-based chemotherapy, docetaxel monotherapy is considered to be the current standard treatment regimen[5,7]. Recent prospective studies including CheckMate 017[13] and CheckMate 057[14] showed that nivolumab was superior to docetaxel for squamous cell carcinoma[13] and non-squamous cell carcinoma[14] previously treated with platinum-based agents. Based on these randomized controlled trials, one of the current second line chemotherapies in patients failing platinum-based chemotherapy is considered to be nivolumab. Pembrolizumab is a humanized monoclonal antibody against PD-1. A recent prospective study showed that in patients with advanced NSCLC and PD-L1 expression by at least 50% of tumor cells, pembrolizumab was associated with significantly longer PFS and OS (KEYNOTE 024[15]). Based on these results, in patients with advanced NSCLC and recurrent NSCLC after surgery with PD-L1 expression ≥ 50%, pembrolizumab is recommended as first-line immunotherapy. Ipilimumab is a fully humanized IgG1 anti-cytotoxic T lymphocyte antigen-4 (CTLA-4) monoclonal antibody that blocks the binding of CTLA-4 to its ligand, B7.1. A randomized phase II clinical study assessed treatment effects with paclitaxel and carboplatin with or without ipilimumab in treatment-naïve stage IV NSCLC patients[24]. In that study the patients showed improvement in immune-related PFS when ipilimumab was administered after chemotherapy (5.7 versus 4.6 months, respectively, P = 0.05). A phase III clinical trial to investigate whether ipilimumab plus paclitaxel and carboplatin will extend the OS of patients with squamous NSCLC compared to placebo plus paclitaxel and carboplatin is ongoing (NCT01285609).

Tumor microenvironment and metabolic variables;

In addition to neoplastic cells, the tumor microenvironment consists of various cell types such as tumor infiltrating lymphocytes (TILs) and tumor-associated macrophages (TAMs)[25,26]. It has been shown that tumor infiltrating leukocytes may display opposite functions and a wide extent of heterogeneity, depending on the primary tumor location and stage of disease[27,28]. The potential ability of immune cells for tumor control is reflected in the behavior of TILs in some solid tumors[29,30]. And immune-related variables could be helpful biomarkers of prognosis and surrogate endpoints of treatment responses[31,32]. FDG is actively incorporated in neoplastic tissue and tumor-related activated immune cells such as TILs and TAMs as a glucose analogue[33,34]. Therefore, FDG-PET could provide valuable information on the metabolic status of the tumor microenvironment. Chang et al.[35] suggested that glucose consumption had restricted T cells metabolically, weakening their effector functions. Lopci, et al.[36] reported an association between metabolic parameters on FDG-PET and the expression of tumor-related immunity markers. That study suggested a potential role for FDG-PET to characterize the tumor microenvironment and select NSCLC candidates to checkpoint inhibitors[36].

Imaging comparison between FDG-PET and CT scan;

FDG-PET can evaluate viable cells and it is considered to be more sensitive than CT for detection of solitary primary lung tumors[37,38]. Some previous prospective studies showed that FDG-PET/CT had 96% sensitivity and 82–88% specificity when compared with sensitivity and specificity of 96% and 53% of CT[37,39]. In identification of pulmonary tumor, metabolic assessment with FDG-PET is considered to be superior to clinical and morphological criteria[40]. FDG-PET is accurate in differentiating benign from malignant lesions as small as 1 cm[41], and overall sensitivity of 96% (range, 83–100%), specificity of 79% (range, 52–100%), and accuracy of 91% (range, 86–100%) can be expected by previous studies[42-44]. We previously showed the usefulness of maximum standardized uptake value (SUVmax) for the prognosis of patients with pathological stage I lung adenocarcinoma. In that report, we calculated SUVmax cut-off value as 2.5 according to receiver operating characteristic (ROC) curve, and also showed that disease-free survival (DFS) after surgery less than 2.5 of SUVmax was significantly better compared with the patients more than 2.5 of SUVmax[45]. However, these results are dependent on SUVmax cut-off values, which differed in each institution, and there is no universal value. To resolve this problem, Shiono, et al.[46] demonstrated a corrected SUV, which they termed the SUV index, and calculated this as the ratio of tumor SUVmax to liver mean SUV (SUVmean). They reported this SUV index was reproducible and was a significant predictor of NSCLC recurrence. Many investigators have also reported the utility of FDG-PET in evaluating therapeutic response[20-22]. Complete disappearance of FDG accumulation is an indicator of a low probability of local recurrence and better prognosis after local treatments such as surgery and radiation therapy, and systemic chemotherapy in patients with lung cancer[47-51].

The optimal follow-up schedule by FDG-PET scan during immunotherapy is controvertial. Some prospective studies (Checkmate 017[13] and Checkmate 057[14]) have suggested an evaluation schedule of immune checkpoint inhibitors of every eight weeks. In the KEYNOTE024 trial[15], imaging studies of the tumor were scheduled every nine weeks. However, these intervals are somewhat short for FDG-PET. In practice, the physician might evaluate the effects of immune checkpoint inhibitors by CT scan every eight or nine weeks and by FDG-PET every 16 to 18 weeks.

Zhang L, et al.[52] evaluated the diagnostic performance of dual time point FDG-PET/CT in the diagnosis of pulmonary nodules. Dual time point imaging technique conducts additional measurements at a second time point after the single time point, with 1.5 to 4 hours. They showed that dual time point and single time point studies had similar accuracy in the differential diagnosis of pulmonary nodules. They did conclude, however, that dual time point examinations appear to be more specific than single time point examinations. Therefore they recommended dual time point imaging for more accurate diagnosis. There are also some interesting reports[53,54], which demonstrated that pretreatment values of metabolic tumor volume (MTV) and total lesion glycolysis (TLG) were the prognostic factors in patients with some solid cancer. These parameters are quantitative volume parameters calculated from glucose uptake. MTV was defined as total tumor volume with FDG uptake segmented by fixed threshold methods at various rates of SUVmax. TLG values were calculated by multiplying the MTV and SUVmean values. These parameters also have potential to provide prognostic information in NSCLC patients treated with immune checkpoint inhibitors as well as chemotherapy and radiotherapy.

Development of molecular imaging criteria for staging and surveillance

Although we usually evaluate the tumor response with RECIST[55] or immune-related Response Criteria (irRC)[56] after cancer treatment, there are two sets of response criteria using PET. The European Organization for Research and Treatment of Cancer (EORTC) criteria are the first metabolic criteria for solid tumors, which were published in 1999[57]. EORTC criteria are based on the most FDG-avid lesions at baseline that are followed on each subsequent scan. Wall, et al.[58] proposed PET Response Criteria in Solid Tumors (PERCIST), which operates with a fixed ROI of 1

Higuchi M, Nemoto T, Matsuida H, Oshibe I, Soeta N, Takeshige T, Saito T, Suzuki H.
J Rare Dis Res Treat. (2017) 2(2): 43-49

Journal of Rare Diseases Research & Treatment

cm³ to assess the most FDG-avid part of the single most metabolically active tumor in the patient at each PET/CT scan. In these criteria, tumor responses are divided into four categories: complete metabolic response (CMR), partial metabolic response (PMR), stable metabolic disease (SMD), and progressive metabolic disease (PMD). Although some previous reports demonstrated that there was concordance between EORTC criteria and PERCIST in the assessment of the tumor response in patients with solid tumors[59,60], prospective studies using EORTC criteria and PERCIST are lacking. However, the metabolic evaluation criteria by both EORTC and PERCIST would be also helpful to evaluate the metabolic treatment effects in the cases of FDG-PET as well as anatomical evaluation by RECIST in the future, even in the patients with immunotherapy.

Pitfalls and clinical questions;

Immune checkpoint inhibitors has a potential problem, because the inflammatory changes caused by the accumulation of neutrophils, lymphocytes and macrophages[15] may lower the specificity because these cells take up FDG. Furthermore, immune checkpoint inhibitors activate T cells, which infiltrate tumor tissue. However, these TILs have been considered to be a potential biomarker for both selection of candidates and monitor of checkpoint-based immunotherapy. In this way, T cells have both positive effects of anti-cancer activity and adverse effects for the evaluation of immunotherapy with PET. We need to recognize these phenomena affected by T cells.

In fact, there are only few reports, which showed the usefulness of FDG-PET/CT to evaluate the efficacy of immune checkpoint inhibitor[61,62]. Kong BY, et al.[63] also reported that patients with residual metastases, which were no FDG uptake but detected anatomically by CT scan , after a prolonged period without progression on anti-PD-1 therapy might have metabolically inactive lesions.

If the TILs are an important factor and biomarker for predicting the efficacy of immune checkpoint inhibitors, the question follows as to whether the efficacy of immune checkpoint inhibitors might be higher in metastatic lymph nodes because of their rich populations of lymphocytes. We have previously shown more effective reduction of FDG accumulation in involved lymph nodes compared with other metastatic sites[62]. We need more detailed studies to elucidate this question.

PD-L1 expression is thought to be a dynamic marker during some treatments, as the expression of PD-L1 has been changed over time according to the microenvironmental changes. Because of these phenomena, the lack of imaging tools to accurately assess this dynamic immune checkpoint expression can create a barrier to validating some biomarkers for the prediction and monitoring of responders to clinical checkpoint inhibit.

An urgent issue to be resolved is to explore more specific biomarkers of this treatment and to develop better imaging systems for accurate surveillance, as checkpoint-based immunotherapy shows promise to improve the prognosis of patients with advanced or recurrent NSCLC.

Clinical trials using PET imaging for evaluating immune checkpoint inhibitors;

Some clinical studies (UMIN000020707 and UMIN000020814) have been ongoing to evaluate the efficacy of FDG-PET in nivolumab therapy for NSCLC (Table 2). In the other fields, there are also some ongoing trials

Identifier	Official title	Condition	Phase	Estimated enrollment	primary endpoint	Status	Region
UMIN000020707	FDG-PET/MRI imaging for the evaluation of early response to nivolumab in patients with previously treated non-small cell lung cancer	Previously treated non-small cell lung cancer	N.A.	25	Relationship between serial FDG-PET/MRI findings and progression free survival and tumor response	Recruit	Japan
UMIN000020814	Usefulness of FDG-PET/CT to predict the response after nivolumab in patients with previously treated advanced non-small cell lung cancer	Previously treated advanced non-small cell lung cancer	N.A.	30	Changing of SUVmax, MTV and TLG, and the efficacy of nivolumab	Recruit	Japan
NCT02716077	Early FDG-PET/CT imaging as a measure of response in patients with melanoma on pembrolizumab	Clinical stage III nodal or intransit disease or resectable stage IV melanoma	I	20	Disease-free survival	Recruit	United States
NCT02791594	Imaging the flare response with FDG-PET/CT in patients with advanced metastatic melanoma on pembrolizumab	Matastatic melanoma	N.A.	30	Number of complete response or partial response or nonresponders to CT	Recruit	United States

FDG-PET/MRI: 18F-fluorodeoxyglucose-positron emission tomography/magnetic resonance imaging, CT: Computed tomography, MTV: Metabolic tumor volume, TLG: Total lesion glycolysis

Table 2: Ongoing clinical trials using PET imaging for evaluating checkpoint-based immunotherapy

Higuchi M, Nemoto T, Matsuida H, Oshibe I, Soeta N, Takeshige T, Saito T, Suzuki H.
J Rare Dis Res Treat. (2017) 2(2): 43-49

Journal of Rare Diseases Research & Treatment

for the evaluation of FDG-PET imaging, including a trial for the evaluation of early FDG-PET/CT imaging in predicting response to treatment with pembrolizumab in patients with advanced melanoma (NCT02716077) and another trial for measuring early response to pembrolizumab in patients with advanced metastatic melanoma (NCT02791594). We expect these prospective studies would resolve whether or not a PET/CT scan after one treatment is an accurate predictor of response.

Conclusions and future directions

To resolve the lack of imaging tools to assess the dynamic PD-L1 expression, non-invasive immunoPET imaging of human PD-L1 expression was designed using a small high-affinity engineered protein scaffold in a pre-clinical model[64]. Some small-engineered protein radiotracers enabled much earlier detection of human PD-L1 expression than previously reported radiolabeled antibodies, and small high-affinity engineered proteins will eventually be used to predict and monitor responders to clinical immune checkpoint inhibitors[64].

There are also some reports of pre-clinical cancer immunotherapy studies such as photoimmunotherapy based on a monoclonal antibody conjugated to a highly specific photosensitizer that uses a near-infrared phthalocyanine dye[65,66], and combinatorial PD-1 blockade therapy with mitochondrial activation chemicals[67]. The former photoimmunotherapy induced immediate cytotoxic effects, which were detected as decreased glucose uptake using FDG-PET even before changes in tumor size became evident.

The latter combination therapy may pave a way to developing new combination therapies in the future; however, the combination therapy might also affect the image evaluation and immune-related adverse events in clinical practice.

Other immune checkpoint inhibitors may be clinically indicated in the future, such as PD-L1 antibody[68] and CTLA-4 antibody[69] in NSCLC treatment and the combination therapies with immune checkpoint inhibitors[70], EGFR-TKI, ALK TKI, anti-VEGF antibody, and anti- VEGFR antibody in combination with cytotoxic anti-cancer agents. The relationship between these combinations and the local metabolic milieu of each lesion is unclear, and these combination therapies might affect microenvironment and glucose metabolism, possibly with their own signature pattern on PET. More research in this area is needed.

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Higuchi M, Nemoto T, Matsuida H, Oshibe I, Soeta N, Takeshige T, Saito T, Suzuki H.
J Rare Dis Res Treat. (2017) 2(2): 43-49

Journal of Rare Diseases Research & Treatment

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