PET/CT molecular imaging in the era of immune-checkpoint inhibitors therapy

Yuan Gao†, Caixia Wu†, Xueqi Chen, Linlin Ma, Xi Zhang, Jinzhi Chen, Xuhe Liao and Meng Liu*†

Department of Nuclear Medicine, Peking University First Hospital, Beijing, China

Cancer immunotherapy, especially immune-checkpoint inhibitors (ICIs), has paved a new way for the treatment of many types of malignancies, particularly advanced-stage cancers. Accumulating evidence suggests that as a molecular imaging modality, positron emission tomography/computed tomography (PET/CT) can play a vital role in the management of ICIs therapy by using different molecular probes and metabolic parameters. In this review, we will provide a comprehensive overview of the clinical data to support the importance of 18F-fluorodeoxyglucose PET/CT (18F-FDG PET/CT) imaging in the treatment of ICIs, including the evaluation of the tumor microenvironment, discovery of immune-related adverse events, evaluation of therapeutic efficacy, and prediction of therapeutic prognosis. We also discuss perspectives on the development direction of 18F-FDG PET/CT imaging, with a particular emphasis on possible challenges in the future. In addition, we summarize the researches on novel PET molecular probes that are expected to potentially promote the precise application of ICIs.

KEYWORDS
positron emission tomography/computed tomography (PET/CT), molecular imaging, immune-checkpoint inhibitors (ICIs), tumor microenvironment (TME), metabolic parameter, molecular probe

Introduction

Cancer immunotherapy has paved a new way for the treatment of many types of malignancies, particularly advanced-stage cancers, by intervening in the abnormal immune processes, reshaping the tumor microenvironment (TME), and restoring immune surveillance (1). Immune-checkpoint inhibitors (ICIs), such as the blocking antibodies of programmed cell death protein-1 (PD-1), programmed death-ligand 1 (PD-L1), and cytotoxic T lymphocyte-associated protein 4 (CTLA-4), have brought considerable clinical benefits to cancer patients. However, only a subset of patients can benefit from ICIs therapies, and some might even experience severe immune-related
adverse events (irAEs) and detrimental hyperprogressive disease (2). Emerging preclinical and clinical evidence indicates that the reciprocity between ICIs and TME may play a complex and important influence on ICIs therapy, but the specific mechanism is still unclear. How to characterize TME noninvasively and effectively, so as to deeply elucidate its potential mechanisms in immunotherapy and precisely guide the use of ICIs, is continually attracting research interest worldwide.

It is well-known that positron emission tomography (PET)/computed tomography (CT) can reflect the biological information of the living body noninvasively and dynamically by using different kinds of imaging agents. Fluorine-18 fluorodeoxyglucose ($^{18}$F-FDG), the most commonly used PET/CT imaging agent, has been increasingly applied in the immunotherapeutic management. It can reflect the level of glucose accumulation in both primary tumor tissues and metastatic lesions by tracking glucose uptake through a single scan. The metabolic parameters obtained from $^{18}$F-FDG PET/CT arguably provide useful indications of the tumor burden (3). Accumulating evidence suggests that $^{18}$F-FDG PET/CT imaging can play a vital role in ICIs therapy, including TME characterization, irAEs assessment, efficacy evaluation, prognosis prediction, and so on.

In this review, we focus on the characteristics of TME associated with immunotherapy, and provide an overview of the clinical data associated with the application of $^{18}$F-FDG PET/CT imaging in the treatment of ICIs. Furthermore, we discuss perspectives on the development direction of $^{18}$F-FDG PET/CT imaging, with a particular emphasis on possible challenges in the future. We also summarize the researches on novel PET/CT molecular imaging, which may potentially promote the precise application of ICIs.

**Characteristics and classifications of TME**

Compared with traditional treatments, such as radiotherapy and chemotherapy, ICIs treatment is more closely related to TME. The efficacy of ICIs may be influenced by various mechanisms related to the tumor or the host, among which TME is being widely investigated as a critical factor. The characteristics of TME vary in different individuals and cancer types, which will affect the immune response to ICIs treatment.

**Compositions and metabolism of TME**

TME is composed of tumor cells, immune cells, stromal cells, extracellular matrix, and exosomes (4), thus forming a microenvironment with the characteristics of inflammation, hypoxia, acidity, and immunosuppression. Different types of cells in TME have their preferred metabolic phenotypes (Figure 1).

Tumor cells generally experience metabolic reprogramming, especially glucose metabolism, to adapt to immunosuppressive TME. Even under aerobic conditions, tumor cells are typically characterized by glycolysis, resulting in high rates of glucose intake with high lactate excretion, which is known as the Warburg effect (5). There are fundamental differences between the metabolic programs of cancer cells and immune cells, as well as between different immune cells (6).

Immune cells can be divided into immune-activating cells and immunosuppressive cells. The characteristics of TME might inhibit antitumor immune cells and lead to their exhaustion or senescence (7), but tumor-promoting immune cells mostly show tolerance (8). Immune-activating cells include CD8$^+$ effector T (Teff) cells, CD8$^+$ memory T (Tmem) cells, CD4$^+$ T helper 1 (Th 1) cells, dendritic cells (DCs), natural killer (NK) cells, inflammatory tumor-associated macrophages (M1-TAM), B cells, and neutrophils. Immunosuppressive cells include regulatory T (Treg) cells, myeloid-derived suppressor cells (MDSCs), and immunosuppressive macrophages (M2-TAM), which subvert antitumor immunity by secreting cytokines or interfering with metabolism (5).

Stromal cells include cancer-associated fibroblasts (CAFs), endothelial cells, and pericytes. Like immune cells, stromal cells could interact with tumor cells, modulate their metabolic behavior, and contribute to migration, invasion, and evasion of immune surveillance (9). CAFs can carry out aerobic glycolysis and secrete lactate and pyruvate as fuels for neighboring tumor cells. A metabolic cross-talk exists between tumor cells and CAFs, referred to as a reverse-Warburg effect. CAFs are also characterized by increased synthesis and secretion of glutamine, which is consumed by cancer cells, thus allowing them to sustain nucleotide generation and oxidative phosphorylation (OXPHOS) to obtain high proliferation (10).

**Classifications of TME associated with ICIs therapy**

With the continuous understanding of the dynamic interaction (promote or hinder) between the status of TME and the treatment with ICIs, several TME classifications based on immunotherapeutic rationale have been proposed. These types are associated with therapy response and might be helpful in selecting the appropriate immunotherapy strategy and suitable patients.

Tumor immune microenvironment (TIME) refers to the immunological characteristics of TME, mainly including the cell types, infiltration degrees, and molecular expression levels of immune cells. Based on the degree and location of tumor-infiltrating lymphocytes (TILs) in TIME, tumors can be classified into “cold” or “hot” ones, or more precisely, divided into three types of immune-inflamed, immune-excluded, and immune-desert (11). In addition, PD-L1 expression and TILs...
infiltration are essential features of TIME related to ICIs (12, 13). Hence, TIME can be divided into four tumor immune microenvironment types (TIMTs) according to these two characteristics, i.e., PD-L1−/TIL−, PD-L1+/TIL+, PD-L1−/TIL+, and PD-L1+/TIL− (14).

Considering that the metabolic and immune characteristics of TME are important theoretical bases for tumor immunotherapy, Siska et al. recommended the metabolic-tumor-stroma score (MeTS) to describe the characteristics of tumor metabolism and cell heterogeneity (15): (1) OXPHOS metabolic type and high T cell infiltration; (2) reverse Warburg type; (3) mixed type; and (4) Warburg type and low T cell infiltration.

**Application of ¹⁸F-FDG PET/CT imaging in ICIs treatment**

Due to the Warburg effect, tumor cells are usually characterized by high glucose metabolism, i.e., increased FDG uptake is often induced in the case of over-expression of glucose transporters (GLUT), such as GLUT1 and GLUT3. A set of studies have shown that GLUT1 expression is correlated with tumor size and hypoxia of TME, and the latter activates hypoxia-inducible factor 1-alpha (HIF-1α) to trigger the Warburg effect and upregulate GLUT expression (16). It has also been elucidated that HIF-1α could directly bind to the hypoxia response element in the PD-L1 proximal promoter and control its expression under hypoxic conditions (17). Besides, activation of some immune cells, including CD4+ and CD8+ T cells, is accompanied by increased metabolism, such as upregulated aerobic glycolysis, tricarboxylic acid (TCA) cycle, and OXPHOS (6). The above mechanisms may provide a theoretical basis for the role of ¹⁸F-FDG PET/CT imaging in ICIs therapy, including characterization of TIME, assessment of irAEs, evaluation of therapeutic efficacy, and prediction of prognosis (Figure 2).

**Characterization of TIME**

Delineation of TIME characteristics can help treatment formulation, efficacy evaluation, and prognosis prediction (18). Due to the complexity of TIME components and their dynamic changes during the treatment process of ICIs, traditional methods such as biopsy have limitations in reflecting TIME. As a non-invasive and functional whole-body imaging modality, ¹⁸F-FDG PET/CT imaging has some potential advantages in characterizing the overall glucose metabolism of tumor cells, activated immune cells, and stromal cells in the TME of the primary lesions.
The majority of researches on the application of 18F-FDG PET/CT imaging on TIME characterization focused on non-small-cell lung cancer (NSCLC) (Table 1). Zhao et al. carried out two studies with the largest sample sizes (419 cases and 428 cases) to investigate the relationship between PD-L1 expression and 18F-FDG uptake, using 22C3 and SP142 assays, respectively (19, 20). They both showed that maximum standardized uptake value (SUVmax) was significantly associated with PD-L1 expression in NSCLC. A meta-analysis across seven studies (473 patients) showed that the predictive sensitivity of the SUVmax for the expression of PD-L1 in NSCLC patients was 75%, and the specificity was 73% (41). Other metabolic parameters, such as mean standardized uptake value (SUVmean) and the ratio of metabolic to morphological lesion volumes (MMVR), have been reported to be correlated with PD-L1 or PD-L1 expression (26, 27). 18F-FDG PET/CT radiomics have also been used to explore predictive models based on images and clinical information for PD-L1+/TIL+ tumors (AUC: 0.869, sensitivity: 77.27%, specificity: 82.61%) (42). Wu et al. analyzed the correlation between SUVmax and TIMT classification in patients with clear renal cell carcinoma (ccRCC) and suggested that SUVmax might be used as an indicator for TIMTs and thus help guide the treatment with ICIs (32).

In addition, the correlation between 18F-FDG PET/CT imaging and TIME in breast cancer, gastric cancer, colorectal cancer, bladder cancer, nasopharyngeal cancer, and oral squamous cell carcinoma has also been observed (Table 1).

Assessment of irAEs

The perturbation of ICIs on the balance of the immune system can lead to a loss of self-tolerance and excessive immune activation of normal tissues, resulting in irAEs (43). The irAEs can affect nearly all organ systems, such as the neurologic, pulmonary, cardiovascular, gastrointestinal, endocrine, genitourinary, integumentary, skeletal and joint systems, and...
The irAEs resulting from different ICIs may vary. A systematic review found that deaths from CTLA-4 inhibitors were mainly caused by the irAEs of colitis (70%), and deaths from PD-1/PD-L1 inhibitors were mainly pneumonia (35%), hepatitis (22%), and neurotoxicity (15%) (46). For different types of tumors, the most commonly affected sites of irAEs are also different. For example, patients with NSCLC mainly show endocrine system and skin irAEs, and patients with melanoma mostly involve the skin and liver, while irAEs occur in patients with RCC are more common in the skin and gastrointestinal tract (47).

A number of current reports support that some irAEs seem to be associated with improved tumor response and better survival (48). This association may stay robust in certain cancer types (NSCLC, melanoma, RCC, and advanced urothelial cancer) and organ-specific irAEs (the skin and endocrine system) (49–52). But some reports pointed out that grade 3-5 irAEs (severe irAEs) are not associated with increased overall survival (OS) and progression-free survival (PFS) in NSCLC patients (53, 54). Oncologists should weigh the risk of irAEs against the benefit of ICIs before immunotherapy and take appropriate management once irAEs occur.

Therefore, it is necessary to judge the appearances of irAEs timely by noninvasive imaging methods. CT or magnetic resonance imaging (MRI) has been widely used to detect irAEs, especially in the lung, pancreas, liver, and nervous system (55). However, the utility of 18F-FDG PET/CT imaging in irAEs screening and monitoring is largely under-recognized currently (2).

18F-FDG PET/CT imaging may be a sensitive method to identify the development and severity of irAEs, which usually present as a new non-neoplastic lesion with increased FDG accumulation after ICI treatment (56). For instance, elevated thyroid SUVmax commonly suggests ICI-related thyroiditis (57), while a diffuse increase of FDG uptake in the pancreas is a characteristic manifestation of ICI-related pancreatitis (58). A study on patients with metastatic melanoma treated with ICIs found that novel quantitative imaging biomarkers, i.e. the SUV percentiles (SUVX%) of 18F-FDG uptake within the target organs, could be predictive of irAEs in the bowel, stomach, and thyroid (56). This study also demonstrated that some irAEs could be detected on 18F-FDG PET/CT imaging before the onset of clinical symptoms, which showed increased 18F-FDG uptake in the affected organs. The typical 18F-FDG PET/CT manifestations of irAEs can be seen in Figure 3.

### Table 1: Tumor microenvironment evaluation by 18F-FDG PET/CT imaging.

| Histology                  | Parameters | Conclusions                              | References |
|----------------------------|------------|------------------------------------------|------------|
| NSCLC                      | SUVmax     | positively associated with PD-L1 expression | (19–25)    |
|                            |            | positively associated with CD8+ T cells, CD163+ TAMs and Foxp3+ Treg cells; negatively associated with CD57+ cells |            |
|                            | SUVmean    | positively associated with PD-L1 expression | (21, 22, 26) |
|                            | MMVR       | negatively correlated with PD-L1 expression in TCs | (26)      |
|                            | radiomics  | models based on radiomics and/or clinicopathological characteristics showed good accuracy in predicting PD-L1 expression level | (28–30)    |
|                            |            | showed good performance in predicting PD-L1+/TIL+ tumors | (31)      |
| ccRCC                      | SUVmax     | positively associated with PD-L1+/TIL+ and PD-L1+/TIL+ tumors | (32)      |
| breast cancer              | SUVmax     | positively associated with TIL levels | (33–35) |
|                            |            | positively associated with PD-L1 expression | (33)      |
| gastric cancer             | SUVmax     | positively associated with CD3+ and Foxp3+ T cell counts | (36)      |
| colorectal cancer          | SUVmax     | positively associated with PD-L1 expression | (37)      |
| bladder cancer             | SUVmax     | positively associated with PD-L1 and PD-1 expression | (38)      |
| nasopharyngeal carcinoma   | SUVmax     | negatively correlated with PD-L1 expression in TIICs and positively associated with PD-L1 expression in TCs | (39)      |
| oral squamous cell carcinoma | SUVmax     | negatively correlated with cold tumors (low tumoral PD-L1 and low stromal CD8+TILs) | (40)      |

NSCLC, non-small cell lung carcinoma; ccRCC, clear cell renal cell carcinoma; TCs, tumor cells; TIICs, tumor-infiltrating immune cells; TME, tumor microenvironment; TIMT, tumor immune microenvironment type; TIL, tumor-infiltrating lymphocyte; PD-L1, programmed death-ligand 1; PD-1, programmed cell death protein-1; SUVmax, maximum standardized uptake value; SUVmean, mean standardized uptake value; MTV, metabolic tumor volume; TLG, total lesion glycolysis; MMVR, ratio of metabolic to morphological lesion volumes.

so on (44, 45). The irAEs resulting from different ICIs may vary. A systematic review found that deaths from CTLA-4 inhibitors were mainly caused by the irAEs of colitis (70%), and deaths from PD-1/PD-L1 inhibitors were mainly pneumonia (35%), hepatitis (22%), and neurotoxicity (15%) (46). For different types of tumors, the most commonly affected sites of irAEs are also different. For example, patients with NSCLC mainly show endocrine system and skin irAEs, and patients with melanoma mostly involve the skin and liver, while irAEs occur in patients with RCC are more common in the skin and gastrointestinal tract (47).

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### Evaluation of therapeutic efficacy

ICIs treatment can achieve antitumor effects by eliminating immunosuppression and reinvigorating Tmem cells, which are good for the patient's long-term survival. However, ICIs can also lead to atypical response patterns, including pseudoprogression, hyperprogression, and mixed response.
In order to standardize the imaging evaluation of tumor treatment efficacy, a series of tumor treatment response evaluation criteria have been proposed. The CT-based evaluation criteria, i.e. Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) (59), were initially used directly. The typical cases evaluated by RECIST 1.1 were displayed in Figure 4. RECIST 1.1 was later adjusted for better ICI response evaluation. The modified RECIST 1.1 for immune-based therapeutics, i.e. iRECIST, classify the initial discovery of the suspected progression as initially unrevealed progressive disease (iUPD) (60). Immune-modified RECIST (imRECIST) includes the measurable new lesions in the total tumor burden (61).

Meanwhile, the 18F-FDG PET (PET/CT)-based evaluation criteria have also been successively proposed (Table 2). The European Organization for Research and Treatment of Cancer 1999 criteria (EORTC) is the first metabolism criterion using SUVmax changes to determine antitumor treatment response (62). In 2009, Wahl et al. proposed the PET Response Criteria in Solid Tumors (PERCIST) (63), which has also been modified further. Immune PERCIST (iPERCIST) introduced the concept of unconfirmed progressive metabolic disease (UPMD) (64). Since immunotherapy may induce new inflammatory lesions that are detectable on 18F-FDG PET/CT, immunotherapy-modified response classification (imPERCIST5) was introduced. According to imPERCIST5, progressive metabolic disease (PMD) was defined only by an increase of the sum of peak standardized uptake values normalized for body lean body mass (SULpeak) by 30% (65). In 2018, Anwar et al. proposed PET Response Evaluation Criteria for Immunotherapy (PERCIMT) to evaluate clinical benefit based on the number and size of new lesions (66). According to PERCIMT, 4 or more new lesions (regardless of size), or 3 or more new lesions (diameter > 1 cm), or 2 or more new lesions (diameter > 1.5 cm), are all defined as no-clinical benefit, while the other cases are considered clinically benefited.

The comparative studies of different response evaluation criteria are shown in Table 3. In short, the continuous adjustment of immunotherapy response evaluation criteria aims to guide immunotherapy management more precisely and effectively.

**Prediction of prognosis**

Since only a certain proportion of patients can benefit from ICIs therapy, how to conduct pretreatment assessments and identify eligible patients has important clinical significance. Up to now, some potentially prognostic biomarkers have been explored, including tumor PD-L1 expression, tumor mutation burden (TMB), microsatellite instability (MSI), gene expression profiles, gastrointestinal microbiome, and so on (73). Nevertheless, the values of these biomarkers remain controversial, and some biomarkers (such as TMB and MSI) require complex, expensive, and time-consuming analyses. Despite imperfection, PD-L1 expression is still the most commonly used biomarker in clinic, especially for NSCLC patients (74).

There have been a variety of studies committed to discovering the prognostic value of 18F-FDG PET/CT imaging on ICI treatment, but the results are inconsistent. The researches mainly focus on patients with NSCLC and melanoma, and the
metabolic parameters include SUVmax, SUVmean, metabolic tumor volume (MTV), total MTV (tMTV), total lesion glycolysis (TLG), and so on (Table 4). Although SUVmax is the most commonly used metabolic parameter, its prognostic value may be controversial (81, 87). Some researchers have also advocated that SUVmean may be suggestive (83). Other studies support the prognostic value of MTV and TLG for immunotherapy, indicating that high MTV and TLG are associated with poor clinical outcomes.

**Table 2: Metabolism evaluation criteria for immunotherapy response.**

| Criterion | CMR | PMR | SMD | PMD |
|-----------|-----|-----|-----|-----|
| EORTC (1999) (62) | complete resolution of 18F-FDG uptake within the tumor volume | SUV is reduced by at least 15% ~25% after 1 cycle of chemotherapy, and > 25% after more than one treatment cycle | not SUV increase > 25%, visible increase in the extent of tumor 18F-FDG uptake (> 20% in the longest dimension), or appearance of new 18F-FDG uptake in metastatic lesions | CMR, PMR, or PMD |
| PERCIST (2009) (63) | 18F-FDG uptake completely disappeared | SUVpeak decrease by >30% in the target lesions, and absolute drop in SUV by at least 0.8 SUV units | not SUVpeak in the target lesions increase ≥ 30%, with ≥ 0.8 SUV unit increase; 75% increase in TLG, new 18F-FDG-avid lesions that are typical of cancer and not related to treatment effect or infection | CMR, PMR, or PMD |
| iPERCIST (2019) (64) | 18F-FDG uptake completely disappeared | SUVpeak decrease by >30% in the target lesions | not SUVpeak increase ≥ 30% or new 18F-FDG-avid lesions (UPMD) | CMR, PMR, or PMD |
| imPERCIST5 (2019) (65) | 18F-FDG uptake completely disappeared | SUVpeak decrease by >30% in the target lesions, and absolute drop in SUV by at least 0.8 SUV units | not SUVpeak in the target lesions increase ≥ 30%, with ≥ 0.8 SUV unit increase in tumor SUVpeak; New lesions were included in the sum of SUVpeak if they showed higher uptake than existing target lesions or if fewer than 5 target lesions were detected on the baseline scan | CMR, PMR, or PMD |

EORTC, European Organization for Research and Treatment of Cancer 1999 criteria; PERCIST, PET Response Criteria in Solid Tumors; imPERCIST5, immunotherapy-modified PERCIST, 5-lesion analysis; iPERCIST, immune PERCIST; CMR, complete metabolic response; PMR, partial metabolic response; SMD, stable metabolic disease; PMD, progressive metabolic disease; UPMD, unconfirmed progressive metabolic disease; CPMD, confirmed progressive metabolic disease; SUV, standard uptake value; SUVpeak, peak standardized uptake value; SULpeak, peak standardized uptake values normalized for body lean body mass; SUV, standardized uptake value of lean body mass; TLG, total lesion glycolysis; SUVpeak, peak standardized uptake value.
Seban et al. demonstrated that tMTV > 75 cm³ was associated with poor prognosis (dNLR > 3 and tMTV > 75 cm³), moderate (2019) et al. (64). Goldfarb (2019) et al. (68). Sachpekidis (2020) provides a good indication of the total cancer burden (3). correlation between TLG and OS (88). In addition, tMTV death protein-1; CTLA-4, cytotoxic T lymphocyte-associated protein 4. stratiﬁed neutrophil-to-lymphocyte ratio (dNLR) and tMTV, which proposed a metabolic scoring system based on the derived prognosis (dNLR > 3 or tMTV > 75 cm³) and good prognosis (dNLR ≤ 3). However, Vekens et al. discovered that tMTV and TLG did not have a predictive effect (87). Servan et al. (2021) established a nomogram including multi-parameter PET/CT images, namely the EGFR-deep learning score (EGFR-DLS), to classify patients into three groups with different prognosis: poor prognosis (dNLR > 3 and tMTV > 75 cm³), moderate prognosis (dNLR > 3 or tMTV > 75 cm³) and good prognosis (dNLR ≤ 3 and tMTV ≤ 75 cm³) (77). However, Vekens et al. discovered that tMTV and TLG did not have a predictive effect (87).

The main reasons for the inconsistent results may lie in the heterogeneity of patients included and the difference of treatment schemes in the study cohorts. The discrepancies between adopted end-point events and treatment response evaluation criteria may be other confounding issues. Further researches should be carried out to establish an ideal and universal method from the metabolism perspective for predicting the prognosis of pan-cancer, which would be validated in a large dataset. In recent years, the rapid development of artiﬁcial intelligence has further promoted the application of 18F-FDG PET/CT radiomics, which extracts a large number of quantitative features from PET/CT images through automated and high-throughput methods, in the prognosis evaluation after surgery, chemoradiotherapy, targeted therapy or immunotherapy. Mu et al. (91) constructed a deep learning model based on PET/CT images, namely the EGFR-deep learning score (EGFR-DLS), to provide non-invasive decision support for targeted therapy or immunotherapy for patients with NSCLC. Moreover, Mu et al. (92) established a nomogram including multi-parameter PET/CT radiomic features, Eastern Cooperative Oncology Group (ECOG) score, and distant metastasis to predict the prognosis of patients with stage IIB-IV NSCLC receiving ICIs therapy.

### Challenges and perspectives

With unprecedented advances in ICIs in cancer treatment, the value of 18F-FDG PET/CT has been especially emphasized. Nevertheless, several challenges associated with 18F-FDG PET/CT imaging need to be addressed to broaden its application in ICIs treatment. One major shortcoming is the lack of recognized

**TABLE 3** Comparative studies on evaluation criteria of immunotherapy response.

| Author/Year       | Study/number | Histology | ICI Treatment | Criteria               | Conclusion                                                                 |
|-------------------|--------------|-----------|---------------|------------------------|-----------------------------------------------------------------------------|
| Sachpekidis et al. (67). (2018) | prospective 41 patients | melanoma | ipilimumab     | EORTC, PERCIMT           | The sensitivity of PERCIMT was signiﬁcantly higher than EORTC, but the speciﬁcity was not significantly different. |
| Sachpekidis et al. (68). (2019) | prospective 16 patients | melanoma | ipilimumab     | EORTC, PERCIMT           | PERCIMT shows more correct classiﬁcation (15/16 patients) than EORTC (13/16 patients). |
| Goldfarb et al. (64). (2019) | retrospective 28 patients | NSCLC | nivolumab     | iRECIST, PERCIMT         | iPERCIST can reclassify 39% of patients assessed by iRECIST. |
| Beer et al. (69). (2019) | prospective 42 patients | NSCLC | nivolumab, pembrolizumab or durvalumab | RECIST 1.1, iRECIST, PERCIST   | The three criteria are only moderately consistent, but there is no signiﬁcant difference in the ability to assess PFS and OS after 12 months. |
| Castello et al. (70). (2020) | prospective 35 patients | NSCLC | nivolumab or pembrolizumab | RECIST 1.1, imRECIST, PERCIST, imPERCIST, PERCIMT | Fair agreement between imRECIST and EORTC, and PERCIST, and moderate for imRECIST and PERCIMT were detected. All criteria are signiﬁcantly related to PFS, but only PERCIMT and imPERCIST are related to OS. |
| Dimitriou et al. (71). (2021) | retrospective 104 patients | melanoma | anti-PD-1 with or without anti-CYT-4 treatment | EORTC, PERCIMT | EORTC is better than RECIST in predicting progress, effectively assessing residual lesions on CT, and predicting long-term beneﬁts. |
| Kitaizama et al. (72). (2022) | retrospective 27 patients | melanoma | nivolumab or pembrolizumab | EORTC, PERCIST, imPERCIST | All the three FDG-PET criteria showed accuracy for response evaluation of ICI therapy and prediction of malignant melanoma patient prognosis. |

**Notes:**
- RECIST, Response Evaluation Criteria in Solid Tumor; iRECIST, a modiﬁed RECIST 1.1 for immune-based therapeutics; EORTC, European Organization for Research and Treatment of Cancer 1999 criteria; PERCIMT, PET Response Evaluation Criteria for Immunotherapy; PERCIST, PET Response Criteria in Solid Tumors; iPERCIST, immune PERCIST, imPERCIST, immunotherapy-modiﬁed PERCIST, PFS, progression-free survival; OS, overall survival; NSCLC, non-small-cell lung cancer; PD-L1, programmed death-ligand 1; PD-1, programmed cell death protein-1; CTLA-4, cytotoxic T lymphocyte-associated protein 4.
TABLE 4 Prognosis predictive role of 18F-FDG PET/CT in immunotherapy.

| Author/Year | Study/number | Histology | ICI treatment | Conclusion |
|-------------|--------------|-----------|---------------|------------|
| Seban et al. (75) | retrospective, 55 patients | melanoma | anti-PD-1 IgG | Higher tMTV and BLR correlated with shorter survival |
| Ito et al. (76) | retrospective, 142 patients | melanoma | ipilimumab | wMTV was negatively correlated with OS |
| Seban et al. (77) | retrospective, 80 patients | NSCLC | anti-PD-1/PD-L1 | tMTV > 75 cm$^3$ was associated with shorter OS and absence of disease clinical benefit |
| Hashimoto et al. (78) | retrospective, 85 patients | NSCLC | pembrolizumab or nivolumab | TLG and MTV were negatively correlated with PFS and OS |
| Castello et al. (79) | prospective, 50 patients | NSCLC | nivolumab or pembrolizumab | High TLG and MTV were significantly associated with hyperprogression and MTV remained a negatively independent predictor for OS |
| Yamaguchi et al. (80) | retrospective, 48 patients | NSCLC | pembrolizumab | Higher MTV correlated with worse outcomes for patients with PD-L1 expression ≥50% |
| Polverari et al. (81) | retrospective, 57 patients | NSCLC | pembrolizumab | Patients with higher MTV and TLG values were more likely to have disease progression and poor response to immunotherapy. |
| Chardin et al. (82) | prospective, 75 patients | NSCLC | pembrolizumab or nivolumab | MTV and TLG were negatively correlated with OS and could reliably predict early treatment discontinuation |
| Seban et al. (83) | retrospective, 63 patients | NSCLC | pembrolizumab | Both high tMTV and high SUVmean were independent predictors for decreased PFS, and tMTV was also negatively correlated with OS. |
| Wong et al. (84) | retrospective, 90 patients | melanoma | ipilimumab, pembrolizumab or nivolumab | High pre-treatment SLR was associated with short PFS and OS |
| Seban et al. (85) | retrospective, 56 patients | melanoma | ipilimumab and/or pembrolizumab | In patients with mucosal melanoma, increased tumor SUVmax was correlated with shorter OS, while in patients with cutaneous melanoma, increased tMTV and BLR were independently correlated with shorter OS, PFS, and lower response |
| Dall'Olio et al. (86) | retrospective, 34 patients | NSCLC | pembrolizumab | tMTV ≥ 75cm$^3$ could be a prognostic predictor of inferior outcomes in patients with PD-L1 expression ≥ 50% |
| Vekens et al. (87) | retrospective, 30 patients | NSCLC | pembrolizumab | SUVmax was positively related to PFS. Clinical response and survival were independent of tMTV and TLG. Reduction of tMTV and TLG after 8 to 9 weeks of treatment was a better predictor of prolonged survival than RECIST 1.1. |
| Bauckneht et al. (88) | prospective, 45 patients | NSCLC | nivolumab | MTV was negatively related to OS |
| Awada et al. (89) | retrospective, 183 patients | melanoma | pembrolizumab | Elevated tMTV was associated with worse PFS and OS. |
| Gulturk et al. (90) | retrospective, 32 patients | RCC | nivolumab | Pre-treatment SUVmax was negatively related to PFS |

SUVmax, maximum standardized uptake value; SUVmean, mean standardized uptake value; MTV, metabolic tumor volume; TLG, total lesion glycolysis; tMTV, total metabolic tumor volume; tMLV, total metabolic lesion volume; SLR, spleen-to-liver SUVmax ratio; BLR, bone marrow-to-liver SUVmax ratio; wMTV, whole-body metabolic tumor volume; PD-L1, programmed death-ligand 1; PD-1, programmed cell death protein-1; NSCLC, non-small-cell lung cancer; RCC, renal cell carcinoma; RECIST 1.1, Response Evaluation Criteria in Solid Tumors version 1.1; OS, overall survival; PFS, progression-free survival.

Guidelines to instruct the application of 18F-FDG PET/CT imaging in immunotherapy. On the other hand, although glucose metabolism parameters, such as SUVmax, have been shown to be significantly related to the immune characteristics of TME or prognosis, related studies were mostly retrospective, single-center and small-sample size, and there are controversies between the results of different studies. So, further prospective and large-sample cohort studies are still needed. Moreover,
current studies mainly focus on NSCLC and melanoma. With the extensive development of ICIs treatment and the accumulation of cases, researches concentrating on other cancers can be investigated. Besides, there remains a challenging area of investigations on biological mechanisms of the association between TME and 18F-FDG PET/CT imaging, and basic and translational studies are encouraged to unravel the unknowns.

New PET molecular probe imaging for ICIs treatment

In addition to 18F-FDG, researchers are also committed to developing a series of new PET molecular probes targeting the compositions of TME, some of which have entered preclinical or clinical applications (Figure 5). The principles of these designs are mostly based on the specific binding of radiolabeled antibodies, peptides, or small molecules with the corresponding targets. The emergence of new molecular imaging agents is expected to provide more accurate means to obtain dynamic information about TME for promoting individualized treatment.

PD-1/PD-L1 targeting

PD-L1 or PD-1 expression is reported to be related with prognosis after immunotherapy, and the detection of the two biomarkers mainly depends on immunohistochemistry (IHC) of biopsy or surgery materials. However, this invasive and snap-shot approach has some limitations, including the inability to reflect the heterogeneity and spatio-temporal dynamic expression of PD-L1 or PD-1 in tumor tissues, different antibody detection platforms and different thresholds leading to different results, and difficulties in obtaining histological specimens for some patients. Targeted molecular imaging can detect PD-L1 or PD-1 expression noninvasively and dynamically in vivo to compensate for the above shortcomings.

PD-1 imaging agents used in clinical trials include 89Zr-pembrolizumab, 64Cu-pembrolizumab, and 89Zr-nivolumab. The first-in-humans study of 89Zr-pembrolizumab in patients with advanced-stage NSCLC confirmed its safety and feasibility for immunotherapy. The findings indicated that patients with higher tumor uptake for 89Zr-pembrolizumab showed a tendency for better response to pembrolizumab (93). A later study showed that 89Zr-pembrolizumab uptake was positively associated with PFS and OS in melanoma and NSCLC patients (94).

PD-L1 targeting imaging agents mainly include 89Zr-atezolizumab, 89Zr-durvalumab, and 18F-BMS-986192, all of which have been in clinical trials (95). Researchers uncovered that 89Zr-atezolizumab uptake performed better than IHC or RNA sequencing-based predictive biomarkers in evaluating clinical responses for ICIs (96). 89Zr-atezolizumab is also reported to be helpful in identifying RCC patients who may benefit from anti-PD-1/PD-L1 therapy (97). Meanwhile, a number of preclinical studies on PD-L1-targeting molecular
probes (including antibodies, peptides, and small molecules) using nuclear medicine, MRI, or optical imaging, have been documented (98, 99).

**CTLA-4 targeting**

CTLA-4 is another well-known immunosuppressive checkpoint. It is expressed on T cells and binds with CD80/86 ligands on DCs with a high affinity to prevent uncontrolled expansion of activated T cells. Accordingly, the blockade of CTLA-4 with antibodies has been used in clinic as a promising option for cancer patients. CTLA-4 targeting imaging agents include $^{64}$Cu-NOTA-ipilimumab-F(ab’)2, $^{64}$Cu-NOTA-ipilimumab, and $^{64}$Cu-DOTA-ipilimumab (100, 101), and all of them have not yet entered clinical trials.

**Other immune checkpoints targeting**

Apart from PD-1, PD-L1, and CTLA-4, several novel immune checkpoint molecules, both the inhibitory and stimulatory ones, have been discovered over the past decade (43). The former molecules include lymphocyte activation gene-3 (LAG-3), T cell immunoglobulin and mucin-domain containing-3 (TIM-3), T cell immunoglobulin and ITIM domain (TIGIT), sialic acid-binding immunoglobulin-like lectin 15 (Siglec-15), and V-domain Ig suppressor of T cell activation (VISTA), which express on a variety of immune cells and exhibit inhibitory roles in the context of malignancy. The positive immune regulators, such as glucocorticoid-induced TNFR-related gene (GITR) and tumor necrosis factor receptor superfamily member 4 (OX40), are co-stimulatory molecules expressed on T cells. In addition, inducible T-cell co-stimulator (ICOS) is an indicator of T-cell-mediated immune response, and some animal experiments showed that $^{89}$Zr-DFO-ICOS mAb targeting ICOS could monitor immunotherapy response (102, 103). With the discovery of new immune checkpoints, molecular probes targeting these targets are emerging.

**T cell targeting**

CD8+ TILs are an important feature reflecting TIME and significantly impact the tumorigenesis and development of tumors. Responders showed higher numbers of pre-existing CD8+ T cells within the tumor and at tumor margins prior to ICIs therapy (104). Therefore, targeted imaging of CD8+ T cells is of great significance for immunotherapy.

$^{89}$Zr-Df-IAB22M2C, a new molecular probe targeting CD8+ TILs, is used to assess CD8+ TILs in tumors accurately. The first human trial of $^{89}$Zr-Df-IAB22M2C has proven its safety and validity in patients with solid malignancies (105). $^{89}$Zr-PEGylated VHh-X18 has also been confirmed to have the potential for CD8+ TIL targeting imaging (106). Iravani et al. demonstrated that $^{18}$F-FDG and other new imaging agents, such as those targeting CD8+ TILs or T cell function, can be used for PET/CT imaging to guide ICI treatment in the future (107). However, due to the complexity of lymphocyte subsets, CD8+ TILs imaging agents can only reflect part of the overall immune effect (108). Another problem with T cell targeting imaging is to determine the optimal timing of evaluation to reasonably reflect the activation degree of T cells.

**Secretory substance targeting**

Secretory substances exist in the extracellular environment and participate in information transmission and effect exertion. Imaging targeting such substances, such as granzyme B and interferon-gamma (IFN-γ), has potential advantages in showing the immune treatment response. With regards to granzyme B targeted imaging, $^{18}$F-Ara-G and $^{68}$Ga-NOTA-GZP can reflect the activation of CD8+ T cells and help to distinguish between pseudoprogression and true progression (107). Another study showed that the detection of granzyme B with $^{68}$Ga-NOTA-GZP helps differentiate the responders from non-responders to immunotherapy (109). $^{89}$Zr-DFO-AN-18, a novel probe targeting IFN-γ, has been indicated to monitor the response to immunotherapy in mouse mammary tumors (110).

**Conclusion**

In summary, an in-depth understanding of the underlying mechanisms of cancer immunotherapy is an important cornerstone for expanding the benefits of ICIs treatment to a larger cancer population. Hence, diagnostic approaches, especially PET/CT molecular imaging, should be vigorously developed to identify patients who might benefit from ICIs treatment. Concurrently, under the guidance of PET/CT molecular imaging, clinicians can shift the paradigm to improve the outcome of cancer patients, and even facilitate the development of novel therapeutic strategies to enhance therapeutic effectiveness. It is believed that with the extensive availability of standardized protocols, various affordable imaging agents, and user-friendly analysis platforms, PET/CT imaging will play a more important role in the era of immuno-oncology.
Author contributions

Conceptualization, ML. Methodology, ML, YG, and CW. Material preparation, YG, CW, XC, LM, XZ, JC, and XL. Writing—original draft preparation, YG and CW. Writing—review and editing, ML and XC. Funding acquisition, ML. Supervision, ML. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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