

Advances in PET/CT Metabolic Imaging in Radiotherapy Combined with Immunotherapy for Non-Small Cell Lung Cancer

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Abstract: According to worldwide statistics, lung cancer is the leading cause of both morbidity and mortality among all forms of cancer, and the outcome of patients with non-small cell lung cancer (NSCLC) remains poor. Monotherapy with immune checkpoint inhibitors is not very effective; radiotherapy could sensitize immunity by altering the tumor microenvironment, but the optimal sequencing, dose fractionation, and identification of benefiting populations in combination therapy do not have standardized criteria yet. The ^{18}F -FDG PET/CT enables the non-invasive evaluation of the tumor metabolic load and provides possible application value in the overall management of combination therapy, which involves four fundamental areas including preliminary patient screening and prediction of beneficial populations, targeting volume definition of radiotherapy and dose fractionation optimization and sequence choices, the initial effectiveness evaluation during treatment, and the determination of immune-related adverse reactions and their distinction from actual progression. Existing body of evidence indicates that initial metabolic tumor volume and total lesion glycolysis are related to the immune state of the tumor microenvironment, and the initial alteration of these variables during therapy correlates moderately well with prognosis. In some immune-related adverse reactions, abnormal FDG uptake may occur prior to the emergence of clinical signs; nevertheless, it is difficult to differentiate between true progression, pseudoprogression, and post-radiotherapy inflammation. However, most of the recent studies are retrospective and of small populations and do not use standardized measures of metabolic parameters, and none of them are prospective interventional studies. In general, PET/CT metabolic imaging has the potential to be used as an auxiliary decision-making tool in the course of combined therapy, but there is still a significant gap before it can become a clinically actionable decision-making tool. The urgency of methodological standardization and prospective stratified studies is now paramount.

Keywords: NSCLC; Radiotherapy; Immunotherapy; ^{18}F -FDG PET/CT; Metabolic parameters

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1. Introduction

Lung cancer is the leading cause of both incidence (12.8 %) and death (19.1 %) in the world due to all types of cancer ^[1], and the vast majority of all lung cancers are non-small-cell lung cancers (NSCLC) ^[2]. Even with the ongoing progress of surgery, chemotherapy, and targeted therapy, the general outlook of NSCLC patients is not satisfactory ^[3]. Even though immune checkpoint inhibitors (ICIs) have completely changed the treatment landscape, the overall objective response rate (ORR) of single drugs is only 20-25% ^[4], and most patients develop primary or acquired resistance ^[5-6], which requires ICI-based combination approaches to overcome the efficacy barrier. Besides local control of the tumor, radiotherapy may reshape the tumor microenvironment via induction of immunogenic cell death (ICD) and activation of the cGAS-STING pathway, turning cold tumors into hot tumors and possibly sensitizing immune responses ^[7-8]. Nevertheless, the extent to which this synergistic mechanism can be applied to clinical practice is largely influenced by the sequence of treatment, dose, and fractionation pattern, as well as the accurate identification of populations benefiting from such combinations, but standard criteria for such critical factors do not exist yet ^[9]. As an example, the PACIFIC trial defined the paradigm of consolidation immunotherapy after concurrent chemoradiotherapy ^[10-11], but the PACIFIC-2 trial indicated that the concurrent combination did not provide additional benefit to survival ^[12], implying that this approach is not yet optimized and that effective biomarkers are urgently required to drive individualized decisions.

In this context, ¹⁸F-FDG PET/CT is a non-invasive metabolic imaging tool that may quantify the total tumor metabolic burden ^[13]. Earlier investigations have indicated that baseline PET metabolic measures and initial modifications during therapy have potential in stratification of patients and prediction of efficacy ^[14-16]. PET/CT-based radiomics models can also predict the response to immunotherapy non-invasively and dynamically ^[17].

Still, post-radiotherapy inflammation of normal tissues may cause high FDG uptake for up to 15 months, which severely complicates assessing residual tumor or recurrence ^[18-19]. Moreover, tumors might initially grow and then stabilize or regress ^[20], which makes conventional PERCIST criteria problematic in their ability to distinguish true progression from pseudoprogression ^[21-22] because immunotherapy can also lead to pseudoprogression. Even though metabolic parameters of PET/CT have been shown to predict results in monotherapy with immunotherapy, there are no standard criteria that help to determine the right combinations in the particular case of a combination of radiotherapy and immunotherapy, and systematic data on whether metabolic parameters can be actually converted into clinical action-oriented decision-making tools is not available yet.

According to the stated background, the present review will systematically summarise the development of the use of ¹⁸F-FDG PET/CT metabolic imaging in whole-course management of NSCLC radiotherapy in combination with immunotherapy by discussing four main issues, including baseline patient selection, radiotherapy planning optimization, dynamic assessment of efficacy, and early warning of toxicity. The summary of the current evidence and its limitations is given to offer a theoretical basis for precision combination strategies based on imaging.

2. Overview of the biological basis of radiotherapy combined with immunotherapy and PET/CT metabolic parameters

2.1. Immunomodulatory effects of radiotherapy and the biological basis of combined immunotherapy

Radiotherapy has a double-sided role in addition to local tumor control when used with combined

immunotherapy. On the one hand, it is possible that the ionizing radiation causes direct damage to tumor cell DNA and promotes cell death ^[23]. On the other hand, radiotherapy has a modulating impact on the tumor immune microenvironment, which may be used as a sensitizing regimen in immunotherapy ^[24-25]. The mechanistic explanation of such an effect is the capability of radiotherapy to remodel the tumor immune microenvironment, providing a biological rationale for combination therapy. It has been shown experimentally that radiotherapy has the potential to change an immunologically unfavorable tumor microenvironment with inadequate T-cell infiltration into one that promotes T-cell recruitment and activation, and hence increases the effectiveness of immune checkpoint inhibitors ^[26-27]. In particular, radiotherapy can cause immunogenic cell death (ICD) in tumor cells, which release tumor-associated antigens and pro-inflammatory factors serving as antigens for T-cell recognition ^[28]; at the same time, radiotherapy can stimulate the cGAS-STING pathway, leading to the activation of the innate immune system, the development of dendritic cells, and T-cell activation and infiltration of tumors ^[29-30]. The modified microenvironment created by radiotherapy offers favorable immune response conditions for the immune checkpoint inhibitors that are delivered later.

The remodeling process has specific clinical relevance to non-small cell lung cancer (NSCLC). The tumor microenvironment of NSCLC shows a high degree of immunological heterogeneity, and there is a considerable interpatient difference in PD-L1 expression levels, as well as the number and activity of tumor-infiltrating lymphocytes, both of which restrict the effectiveness of immunotherapy as a monotherapy in a subpopulation of patients ^[31-33]. Radiotherapy-induced local immunomodulation provides a possible treatment breakthrough to address this challenge ^[34].

Nevertheless, the ability of radiotherapy to induce antitumor immune responses is variable and depends on various factors such as dose fractionation regimen, irradiation site, and overall dose. Besides, baseline immunity level, tumor mutational load, and other micro-environmental properties of various patients also have an impact on the results of the combination therapy ^[35-37]. These parameter dependencies and patient heterogeneity indicate that objective and dynamic assessment measures are required in clinical care to evaluate the inter-patient variability in immune response to radiotherapy and the inter-treatment changes. ¹⁸F-FDG PET/CT has the possibility of non-invasively determining the glucose metabolic activity and metabolic tumor burden of systemic tumor tissues; therefore, it might offer imaging-based information to address the above-mentioned evaluation requirements.

2.2. Definitions and imaging basis of Core Metabolic Parameters of ¹⁸F-FDG PET/CT

Positron emission tomography/computed tomography with ¹⁸F-fluorodeoxyglucose is a functional imaging technique that measures the glucose metabolism of the tumor tissue to quantify the amount of tumor burden in radiotherapy combined with immunotherapy. According to the Warburg effect, malignant cells have elevated glucose uptake compared to normal cells, and FDG PET/CT allows noninvasive metabolic imaging of systemic lesions ^[38]. Due to the high FDG avidity of NSCLC, metabolic activity of both primary cancers and metastases can be detected sensitively ^[39-40].

Of the metabolic parameters based on FDG PET/CT, the three most commonly used parameters are maximum standardized uptake value (SUVmax), metabolic tumor volume (MTV), and total lesion glycolysis (TLG). A summary of definitions, biological significance, strengths, and weaknesses of these three parameters is presented in **Table 1**.

Table 1. Definitions, biological implications, advantages, and limitations of core metabolic parameters of ^{18}F -FDG PET/CT

Parameter	Definition	Biological Implication	Advantages	Parameter
SUVmax (maximum standardized uptake value)	Maximum ^{18}F FDG uptake value based on a single voxel within the tumor.	Reflects the glucose uptake level of the “hot spot” region with the highest metabolic activity within the tumor; the metabolic activity of this region has been associated with tumor aggressiveness in studies.	Simple to measure, does not require precise delineation of the region of interest, and has relatively high reproducibility.	Represents only the single highest voxel value; susceptible to image noise, partial volume effect, and physiological uptake. Cannot reflect the overall tumor metabolic burden.
MTV (metabolic tumor volume)	Volume of the region with increased FDG uptake within the tumor lesion (usually defined by a threshold of SUV = 2.5 or 40% of SUVmax). Wholebody (wb) or total MTV is defined as the sum of volumes of all positive lesions.	Reflects the volume of the region with increased FDG uptake within the overall tumor, i.e., the total volume of metabolically active tumor tissue throughout the body.	Integrates metabolic information with spatial volume, and better represents the total capacity of systemically metabolically active lesions compared to SUVmax.	Measurement results are highly dependent on the delineation method of the region of interest and the threshold setting criteria, limiting comparability across different studies ^[41] .
TLG (total lesion glycolysis)	Product of MTV and mean SUV (SUVmean).	Simultaneously integrates metabolic activity intensity and metabolically active volume, reflecting the total glycolytic activity of all systemic lesions.	Combines the dual information of SUV and MTV, theoretically providing a more comprehensive reflection of the overall tumor metabolic burden than a single parameter.	Calculation depends on accurate acquisition of MTV and SUVmean, and is also affected by delineation methods. There is currently no unified standardized measurement protocol ^[42] .

Note: Parameter definitions are detailed in this reference and all its sources^[42].

The information dimensions provided by these three parameters differ—SUVmax reflects the single-point uptake value of the region with the highest metabolic activity within the tumor, whereas MTV and TLG reflect the overall systemic metabolic burden from the perspectives of metabolically active volume and the product of volume and intensity, respectively. Since NSCLC is frequently associated with multi-station metastatic lymph nodes and distant metastases, MTV and TLG can measure the entire burden of systemically metabolically active lesions, thereby offering more elaborate tumor metabolic data than SUVmax^[43–45]. It must also be said that precise measurement of MTV and TLG is very sensitive to the choice of the region-of-interest delineation algorithm and the threshold setting rules, and variations in methods between studies are likely to influence the comparability of outcomes^[41]. Accordingly, each study ought to explicitly state its particular measurement parameters as well as delineation procedures to allow the interpretation of the findings.

3. Application of PET/CT in baseline patient selection and prediction of benefiting populations

3.1. The value of metabolic burden parameters in the immune status mapping of the tumor microenvironment

Quantifiable associations exist between baseline ^{18}F FDG PET/CT metabolic burden parameters and the

immune status of the tumor microenvironment in NSCLC, which is the condition enabling the application of metabolic imaging to identify populations that would benefit before combination therapy. At the overall level of metabolic load, wb-MTV and wb-TLG have been shown in various studies to be statistical predictors of PD-L1 expression, whereas SUVmax could not be predictive in these studies, implying that the total volume of metabolically active tissue and overall glycolytic activity are more representative of the systemic immunosuppressive state associated with the total tumor burden than is the single-point maximum uptake value ^[46-47]. Other researchers have expanded the analytical aspect to include not only overall burden but also the spatial distribution homogeneity of metabolic activity in the tumor. Heterogeneity index (HI), defined as the ratio of the area under the cumulative uptake-volume histogram curve to the peak value, is used to measure the spatial dispersion of FDG uptake ^[48]. In a retrospective study of 270 NSCLC patients, it was demonstrated that HI was positively correlated with PD-L1 expression, with an AUC of 0.674 in predicting PD-L1 positive status, which suggests that high metabolic heterogeneity may indicate the coexistence of multiple clonal subpopulations with different metabolic activities in the tumor, with concomitant heterogeneity in the functional activity and distribution of infiltrating immune cells ^[49]. The relationship between metabolic active burden and tumor mutational burden also offers support in another dimension; standardized maximum uptake value (SULmax) has been found to be an independent predictor of TMB-High status, adding to the chain of evidence that metabolic parameters reflect immune status in terms of neoantigen load ^[50]. With the introduction of radiomics methods, these insights have gone even deeper; A habitat model that was created using the spatial distribution of metabolic-density subregions had a PD-L1 prediction of up to 0.83, which indicates that spatial distribution data on metabolic heterogeneity can have more immune microenvironment features than individual parameters ^[51]. Nevertheless, all of the aforementioned evidence comes from the framework of immunotherapy or immunochemotherapy, and there are not yet any studies that have confirmed the correlation between metabolic parameters and the immune status of the tumor microenvironment in the particular case of radiotherapy combined with immunotherapy. Besides, the strength of the associations is typically weak, unable to translate into clinical practice.

3.2. Existing evidence for baseline metabolic imaging in predicting benefiting populations from combined therapy

The preliminary studies conducted in various retrospective studies have shown that baseline PET/CT metabolic parameters could differentiate potential benefiting populations based on radiotherapy combined with immunotherapy before treatment, but the consistency of the evidence is weak. Within the framework of immunotherapy monotherapy, wb-MTV and wb-TLG have demonstrated a significant correlation with shorter progression-free survival (PFS) and overall survival (OS), implying that metabolic load indicates the overall condition of tumor biological aggressiveness and the immunosuppressive microenvironment ^[52]. Nevertheless, in particular, in the situation where the combination of radiotherapy and immunotherapy is used, there are reports stating that the prognostic predictive value of baseline MTV could be reduced, and it has not always been recognized as an independent predictor since the advent of immunotherapy ^[53]. There have also been other studies that have shown at the molecular level that metabolic heterogeneity is correlated with the immunosuppressive microenvironment, indicating that non-uniformity of the metabolic activity across the tumor can indicate the complexity of spatial immune avoidance and thus undermine the effectiveness of combination therapy ^[54].

As seen in the above studies, there is a consistency in the direction of results, i.e., both high metabolic burden and high heterogeneity indicate poor prognosis, though there is much variability between the designs of studies. Furthermore, many of them are retrospective with a few cases and do not contain independent external validation groups; furthermore, multifactorial analyses have not compensated for the confounding effects of known prognosticators, such as PD-L1 expression status and clinical stage. Thus, the available evidence indicates that the preliminary data show that the baseline metabolic parameters have the ability to identify the benefiting population; however, there are no prospective interventional studies to confirm whether patients chosen by metabolic parameters can achieve better survival benefits from combination therapy compared to conventional regimens.

4. Application of PET/CT in individualized decisionmaking of combination therapy regimens

4.1. Metabolic active target delineation and optimization of radiotherapy dose/fractionation patterns

The fundamental principle behind ^{18}F -FDG PET/CT in radiotherapy planning is that it enables the expansion of target definition beyond anatomical limits to metabolically active limits, a step which is particularly relevant in individualized dose and fractionation strategy optimization in the context of radiotherapy plus immunotherapy^[55]. Traditional radiotherapy target delineation relies largely on anatomical structures as seen on CT, but the metabolically active extent of tumors may not necessarily be fully overlapping with the anatomic boundaries seen on CT, particularly when tumors are associated with atelectasis, obstructive pneumonitis, or post-treatment anatomical alterations^[56]. The biological target volume (BTV) defined using PET is likely to better outline sub-regions of tumor with greater proliferative and invasive potential and thus, in some studies, the delivery of simultaneous integrated boost (SIB) to the most metabolically active area of the BTV has been found to have the potential to enhance local control rates^[57-58].

On top of these considerations, conventional fractionation radiotherapy (1.8-2.0 Gy per fraction) results in less damage to normal tissues but has the potential to eliminate circulating effector T cells and lead to lymphopenia. In contrast, high-dose hypofractionated radiotherapy (≤ 5.0 Gy per fraction) has been shown to promote immune synergy via various mechanisms, including greater release of antigens and upregulation of MHC class I molecules. However, when large-volume targets are irradiated with high-dose hypofractionated regimens, the risk of normal tissue complications is greatly increased^[59]. This trade-off can also be helped by the three-dimensional distribution information of metabolic activity given by PET/CT in cases where there is a small BTV and well-defined spatial relation to critical normal structures like the esophagus and heart; a high-dose hypofractionated treatment may be used to achieve maximum immune activation effects. However, when there is significant BTV involvement of the mediastinum or both sides of the hilus, an evaluation of the balance between immune synergistic advantages and the likelihood of radiation pneumonitis is needed. Nevertheless, the clinical proof of the aforementioned strategies largely comes in the form of single-arm or small-sample retrospective studies; no prospective studies have confirmed the non-inferiority or superiority of various dose-fractionation approaches in patients with PET-defined metabolically active targets, and there are no systematic comparisons of the ideal dose limit of high-dose hypofractionated regimens and the temporal course of immune activation at different fractionation patterns.

4.2. Reference value of imaging for sequencing of combination therapy

One of the main factors determining the effectiveness of combination therapy is the optimal sequencing of radiotherapy and immunotherapy, and PET/CT-based metabolic evaluation may offer indirect indications of this choice on two levels: tumor load and post-radiotherapy metabolic changes. The time-dependence of radiotherapy-induced immunogenic cell death and the cGAS-STING pathway is time-dependent; animal studies have indicated that 48 hours to 2 weeks following radiotherapy is a viable window to activate the immune system, but the exact time frame of this window in human NSCLC has not been clinically defined by imaging methods^[60-61]. In this regard, it seems reasonable to suppose that preliminary post-radiotherapy PET reassessment prior to starting immunotherapy could offer useful information about sequencing choices, although this hypothesis does not have any direct clinical proof yet^[62-63]. A multicenter study compared survival differences between concurrent and sequential sequencing patterns with baseline selection bias caused by the non-randomized assignment, which makes it hard to relate efficacy differences to sequencing per se at the level of clinical evidence^[64]. All in all, the role of PET/CT in sequencing decisions regarding combination therapy remains in the exploration stage, and there is no prospect of proving that sequencing approaches developed on the basis of metabolic indicators will be associated with positive outcomes in terms of survival.

5. Application of PET/CT in early efficacy evaluation during treatment

5.1. Predictive value of early changes in metabolic parameters for treatment response

The ability to forecast the final efficacy of radiotherapy and immunotherapy using early alterations in ¹⁸F-FDG PET/CT metabolic parameters throughout the course of treatment is one of the current most focused areas of evidence gathering in this area. The extent of the change in MTV and TLG has been found to be significantly correlated with PFS among patients receiving immunotherapy monotherapy at 4 -6 weeks following treatment initiation by several studies^[14]. In radiotherapy plus immunotherapy, there have been a few reports that have considered the effect of residual metabolic burden on subsequent efficacy in the post-radiotherapy window period and prior to the start of consolidation immunotherapy. A particular study demonstrated that residual metabolic tumor volume (rMTV) possessed significant prognostic value in those patients who did not undergo consolidation immunotherapy, but it was no longer significant in patients who underwent consolidation immunotherapy^[65]. So far, clinical data are insufficient to determine the quantitative association between the size of changes in metabolic parameters in such a window period and the effectiveness of follow-on immunotherapy, as well as to compare predictive performance across different evaluation time points. Moreover, the implementation of radiomics methods has created new opportunities to enhance predictive precision. Pre- and post-treatment delta-radiomics feature-based models have demonstrated their potential predictive power in some studies where the concept that high-dimensional features have the ability to detect subtle texture changes that cannot be detected by conventional features has been used^[66-67]. Nevertheless, there are no direct head-to-head comparison studies yet to prove that Delta-radiomics models are consistently better than single metabolic factors.

5.2. Interference of treatment-related inflammation in efficacy interpretation and corresponding strategies

The increase in FDG uptake following combination therapy represents an interpretative problem in clinical practice. The difficulty is that both inflammation caused by treatment, such as post-radiation effects on normal tissues, and inflammation caused by immune mechanisms can also result in very high FDG

metabolism in lesions or normal organs, which can be misinterpreted as disease progression when using traditional single-time-point metabolic imaging assessment methods such as PERCIST (i.e., so-called false-positive results) ^[20]. In the combination therapy scenario, this inflammatory metabolic increase appears similar to imaging, making the efficacy assessment criteria potentially vulnerable to failure. Consequently, the correct determination of the biological origin of the increased metabolism is a very important part of the efficacy evaluation in the course of combination therapy.

6. Role of PET/CT in toxicity identification and treatment response differentiation

6.1. Early metabolic imaging recognition of immune-related adverse events

The immune checkpoint inhibitors facilitate systemic T-cell immune responses and may cause damage to normal tissues due to immune-mediated effects, known as immune-related adverse events (irAEs). The metabolic signal features of irAEs on FDG-PET offer a possible way of early detection. IrAEs are usually seen on FDG-PET as either focal or diffuse increases in FDG uptake of organs that are normally metabolically inactive, and this metabolic change may occur prior to the onset of clinical signs because the immune-mediated tissue inflammation will affect the cellular and metabolic activities before it generates clinically visible signs in patients ^[68-70]. Increased FDG uptake commonly manifests itself as scattered patchy or ground-glass distribution in both lungs, which is most often observed outside the radiation field, but the intensity of uptake is usually less than that seen in primary tumors (Figure 1). Diffuse linear increased FDG uptake on the colonic wall, with or without CT evidence of bowel wall thickening, is a sign of immune-related colitis, which most commonly affects the descending and the sigmoid colon ^[71]. Other organs have also shown metabolic signals of irAEs, including bilateral symmetric increased uptake in the thyroid region in immune-related thyroiditis, focal increased uptake in the sellar region with pituitary enlargement in immune-related hypophysitis, and symmetric multi-articular uptake in immune-related arthritis ^[72-74]. Nevertheless, the identification of such metabolic signals has limitations concerning their limited specificity; infections, non-infectious inflammation, and physiological uptake may all cause increased FDG activity in normal organs, which overlaps with the manifestation of irAEs. Thus, it is necessary to interpret them comprehensively using clinical symptoms, laboratory results, and endoscopies.

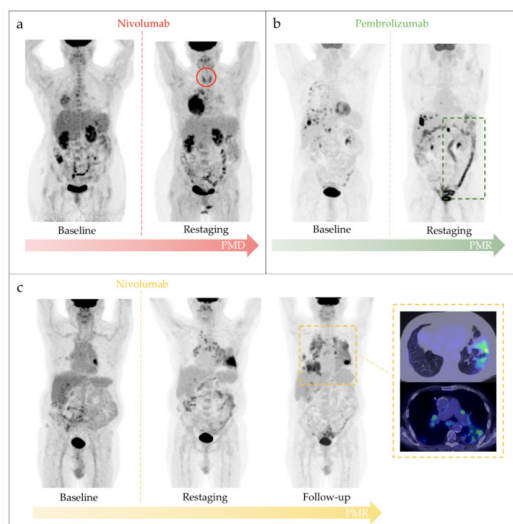


Figure 1. ¹⁸F-FDG PET/CT manifestations of immune-related pneumonitis and sarcoid-like reaction ^[75].

6.2. Comprehensive differentiation of true progression, pseudoprogression, and post-radiotherapy inflammation

The process of increased FDG uptake after combined therapy needs a multidimensional evaluation that should involve dynamic evolution, spatial distribution, morphological characteristics, and treatment timing. Dynamic evolution may be used as a key indicator: true progression is shown as a continuously increasing FDG uptake trend, pseudoprogression as a rise in FDG uptake followed by a plateau or spontaneous decrease (the turning point usually happens between 6-12 weeks since treatment), and the metabolic peak of post-radiotherapy inflammation is likely to occur 3-6 months following the end of radiotherapy and slowly decrease ^[20,76,77]. Ancillary discriminative value is also offered by morphological and spatial distribution features of post-radiotherapy inflammation, typically as diffuse, linear, or patchy distribution restricted to the radiation field, with morphology of isodose line patterns; pseudoprogression more frequently as heterogeneously increased uptake of pre-existing lesions with few new lesions; true progression more commonly as new nodules outside the radiation field or significant increase in size of existing lesions ^[78-80].

The cross-over between immune-related pneumonitis and radiation pneumonitis makes differentiation even more difficult. FDG uptake in radiation pneumonitis is restricted to within the radiation field, and the magnitude of the metabolic increase has a dose-response relationship with irradiation dose, where higher-dose areas are associated with greater amounts of FDG uptake; the metabolic increase of the immune-related pneumonitis is multifocal or multi-lobar in distribution across both lungs, outside the radiation field, without spatial correlation to the radiotherapy plan, and may occur de novo at any stage of the combination therapy ^[81-84]. In cases where the metabolic elevations of the two injury types overlap on images, the spatial reference frame used in differentiation relies on the radiation field boundaries: the metabolic increase inside the radiation field and regular morphology is attributed to the radiation-induced injury first, whereas the diffuse uptake outside the radiation field or crossing the boundaries is more indicative of the immune-related pneumonitis ^[82]. Discriminative value is also given by temporal information. Priority may be given to radiation-induced injury in case of metabolic elevation within the projected post-radiotherapy period and with the same morphology of the isodose line, but if it is found several months after the end of radiotherapy or not temporally linked to the radiotherapy time point, it is necessary to strongly suspect immune-related pneumonitis ^[83].

Radiomics is also considered a secondary source for differentiation. A multicenter NSCLC immunotherapy group demonstrated that a classification model using baseline CT radiomic variables had an AUC of 0.875 in differentiating pseudoprogression and true progression, which indicated good discriminative capacity ^[85]. The model, however, has not been tested in the combined radiotherapy-immunotherapy situation. Moreover, healthy tissues following radiotherapy may have differing levels of FDG uptake lasting up to 6-12 months, though in later stages it mostly indicates fibrosis and not active inflammation, and PET metabolic data alone might be misleading ^[86]. The result underscores the importance of combined evaluation with CT morphology. However, there are still few direct comparative studies of longitudinal long-term metabolic patterns after radiotherapy and overlapping them with lung pneumonitis related to immune processes, and urgent multidisciplinary integrative research is required to systematically integrate imaging, dosimetric, and clinical data in order to develop a more discriminative evaluation system ^[87].

7. Summary and perspectives

In general, the utility of ^{18}F -FDG PET/CT metabolic imaging has been shown to have potential use in all stages of radiotherapy with immunotherapy in NSCLC. Baseline metabolic burden indices (especially MTV and TLG) exhibit some correlation with the immune profile of the tumor microenvironment, offering possible hints at the identification of probable responders prior to treatment; metabolic active target volume definition provides a functional approach to personalized modification of radiation dose and fractionation schemes; early changes in metabolic indicators during treatment are indicative of long-term prognosis; and the presence of abnormal FDG uptake in normal organs can be considered as early signs of irAEs. According to the available evidence, the relationship between early alterations in MTV and TLG during treatment and prognostic outcomes has demonstrated fairly consistent results in various retrospective analyses, which is the strongest line of evidence in the current knowledge base. The prognostic usefulness of baseline metabolic parameters has been frequently documented, but the uniformity of results found in different studies is rather unsatisfactory. All of the above evidence is more correlation-based and generally comes through small-sample retrospective research done at a single center and has no independent external validation groups. It is uncertain whether metabolic variables could actually act as clinically actionable decision aids to inform dose reduction, timing maximization, or regimen choice in combined therapy due to lack of direct evidence in prospective intervention studies.

With such constraints, further improvement of research can be made in the following ways. To begin with, there is an urgent requirement to standardize MTV and TLG measurement methodologies through clearly defining threshold settings, rules of region-of-interest delineation, and strategies of combining multiple lesions to increase the level of comparability among different findings of the study and establish a methodological base for further evidence synthesis and clinical translation. Next, the systematic collection of dynamic metabolic parameter data at various time points in the combination therapy setting should be initiated with the use of prospective observational cohort designs, and later, stratified randomized controlled trials based on metabolic parameters might be developed to confirm that metabolic imaging-assisted decision-making leads to survival benefits in patients. Also, one should pay attention to the application of artificial intelligence methods; it is likely that by developing multimodal models combining PET metabolism, CT morphology, radiation dose distribution, and clinical variables, the ability to differentiate true progression, pseudo-progression, and post-radiotherapy inflammation can be enhanced, and additional support can be provided to make individualized decisions over time. The further development of the above research will enable assessing the feasibility of transforming ^{18}F -FDG PET/CT from a biomarker into a clinical decision-making tool, and will offer a discoverable imaging trajectory towards the accuracy of radiotherapy combined with immunotherapy applied to NSCLC.

Disclosure statement

The authors declare no conflict of interest.

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