

Role of PET/CT in diffuse large B-cell lymphoma (Review)

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Abstract. Diffuse large B-cell lymphoma (DLBCL) is the most common subtype of non-Hodgkin lymphoma, and its diagnosis and management are moving steadily toward personalization and precision. As a functional imaging modality, positron emission tomography-computed tomography (PET/CT) plays an irreplaceable role in the management of DLBCL. For diagnosis and staging, PET/CT corrects staging errors made with CT alone and improves the detection of bone marrow involvement; baseline metabolic parameters [metabolic tumor volume (MTV) and total lesion glycolysis] and measures of disease dissemination (Dmax) are independent prognostic factors, and MTV in particular refines the risk stratification provided by the International Prognostic Index. During therapy, an interim Δ SUVmax reduction of $\leq 66\%$ indicates high-risk patients, while a negative interim Deauville score (1-3) and a negative end-of-treatment PET/CT both predict favorable long-term survival. Before chimeric antigen receptor T-cell therapy and autologous hematopoietic stem cell transplantation, metabolic parameters also carry predictive value for both outcome and toxicity. In addition, radiomics combined with multiparametric data improves prognostic accuracy, and novel tracers and PET/MR offer complementary advantages for distinguishing tumor from inflammation and for assessing extranodal disease. Taken together, PET/CT provides a precise evaluation platform that spans the entire course of diagnosis and treatment. The present study systematically reviews the application of PET/CT to the diagnosis, prognostic prediction, response assessment and special clinical scenarios of DLBCL.

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1. Introduction

Diffuse large B-cell lymphoma (DLBCL), the most common aggressive subtype of non-Hodgkin lymphoma (NHL), accounts for ~30-40% of all NHL cases and is characterized by marked aggressiveness, biological heterogeneity and potential curability. Although 60-70% of newly diagnosed patients are cured with the R-CHOP regimen, up to 30-40% develop primary refractory disease or relapse (1). Outcomes in refractory disease remain extremely poor, although newer strategies, such as the FDA-approved Pola-R-CHP regimen, immunotherapy and targeted agents, have appreciably improved survival. Because the benefit of these strategies depends heavily on early and accurate risk stratification, reliable prognostic models that can inform individualized treatment decisions (TD) represent a core clinical need.

Positron emission tomography-computed tomography (PET/CT) is a radionuclide tracer imaging technique. Its principle is to track the metabolic activity of specific biological substrates using tracers labeled with positron-emitting radionuclides: Multiple rings of detectors capture the photons emitted after positron annihilation, and computer processing then generates images that combine anatomical information on target organs or diseased tissue with the corresponding physiological parameters, thereby supporting diagnosis (2). By integrating metabolic functional imaging with anatomical localization, this technique has substantially reshaped the diagnostic and therapeutic paradigm of DLBCL. The tracer most widely used in clinical practice is the glucose analog ^{18}F -fluorodeoxyglucose (^{18}F -FDG). After intravenous injection, ^{18}F -FDG enters cells through glucose transporters and is phosphorylated intracellularly; because it can be neither metabolized further nor transported back across the cell membrane, it remains trapped within the cell for several hours. Under conditions of stable glucose metabolism, the

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distribution of ^{18}F -FDG therefore reflects glucose utilization throughout the body. The core advantage of ^{18}F -FDG PET/CT lies in its ability to trace the glycolytic activity of tumor cells, allowing sensitive detection of metabolically active lesions that conventional examinations may miss and thereby improving the accuracy of staging (3). PET/CT also provides objective evidence for response assessment, prognostic stratification, and individualized treatment adjustment through quantitative measures, such as metabolic tumor volume (MTV), total lesion glycolysis (TLG), and the maximum distance between lesions (Dmax), and through dynamic parameters that capture metabolic change before and after treatment, such as the change in maximum standardized uptake value ($\Delta\text{SUV}_{\text{max}}$) and the Deauville score. PET/CT has thus become indispensable for the diagnosis, staging, interim monitoring, and prognostic prediction of DLBCL. The present study systematically reviews its role across the comprehensive management of the disease (Fig. 1).

2. Lesion extent and staging

PET/CT-assisted staging. PET/CT has become a pivotal component of the clinical management of DLBCL. Its particular value lies in the ability to identify, through metabolic imaging, extranodal lesions that conventional modalities such as contrast-enhanced CT and ultrasound readily miss. PET/CT can clearly delineate sites that appear negative or indeterminate on conventional examination, particularly extranodal or deep-seated disease such as microscopic splenic involvement and retroperitoneal or peritoneal lesions (4), and it provides precise localization for biopsy, thereby increasing the diagnostic yield of pathological sampling (5). Whereas conventional CT defines disease extent solely on the basis of lesion size, PET/CT distinguishes tumor from normal tissue on the basis of metabolic activity and thereby reclassifies the disease stage in ~30% of patients, most often by upstaging (6). In patients who relapse or progress after treatment, PET/CT also permits re-evaluation of disease extent and informs the adjustment of subsequent treatment strategies.

Detection of bone marrow involvement (BMI) by PET/CT. Accurate detection of BMI is important for TDs and prognostic assessment, both at initial staging and during response evaluation in DLBCL. No universally accepted gold standard for detecting BMI in lymphoma currently exists. Standard iliac crest bone marrow biopsy (BMB) has well-recognized limitations in identifying marrow involvement in DLBCL, and ancillary techniques such as flow cytometry are therefore often added in clinical practice to improve sensitivity. In recent years, PET/CT, as a non-invasive functional imaging modality, has shown substantial value for the assessment of BMI in DLBCL.

On PET/CT, bone marrow uptake in patients with DLBCL is broadly classified as diffuse homogeneous uptake (dPET; higher than liver uptake) or focal uptake (fPET) (7). Focal uptake can substitute directly for BMB in the diagnosis of BMI, whereas diffuse uptake, although it does not entirely exclude BMI, generally has no prognostic impact and may be regarded as PET-negative (7). Notably, marrow involvement in DLBCL

more often produces a focal pattern than diffusely increased uptake (8). Diffusely increased uptake may arise from reactive marrow hyperplasia, inflammation, or post-chemotherapy change, and may also reflect diffuse lymphomatous infiltration; its diagnostic specificity is nevertheless lower than that of focal uptake (9). Although markedly increased diffuse FDG uptake (with an SUV exceeding that of the liver) often suggests a high likelihood of marrow involvement, its clinical significance remains uncertain.

Several studies have compared PET/CT and BMB for the detection of BMI in DLBCL. PET/CT has greater sensitivity for focal marrow lesions (10); in one series (8), the sensitivity of PET/CT was 94%, compared with only 24% for BMB. In patients with a negative BMB but focal marrow uptake on PET/CT, the involvement indicated by PET/CT carries independent prognostic value and helps identify disease missed by biopsy (11). PET/CT also has a high negative predictive value (NPV) at post-treatment restaging, up to 100% in one study (12), suggesting that patients with a negative PET/CT result may not require repeat BMB to confirm complete remission.

Other studies have found that PET/CT can still miss marrow involvement detected by BMB, particularly when infiltration is diffuse rather than focal or when an indolent lymphoma component is present (13,14). Histological examination therefore remains important for staging and TDs in patients with early-stage disease. Moreover, visual assessment and quantitative metabolic parameters do not consistently outperform BMB for prognostication, and BMB has been reported to remain an independent predictor of progression-free survival (PFS) and overall survival (OS) in some patients (14).

In summary, PET/CT has high sensitivity and a high NPV for the evaluation of BMI in DLBCL, and it is a valuable complement to BMB, particularly for the detection of focal lesions and the assessment of treatment response. Because false-negative results occur and findings are inconsistent across studies, however, PET/CT cannot fully replace BMB, especially in newly diagnosed high-risk patients and in those with clinically suspected diffuse infiltration, in whom the combined use of both methods is more prudent. The respective indications for the two modalities can be defined more precisely. When BMB is unavailable or the patient declines an invasive procedure, focal uptake on PET/CT provides a reliable basis for diagnosing BMI; at post-treatment restaging, the very high NPV of a negative PET/CT result can obviate unnecessary repeat biopsy; and when a comprehensive assessment of total tumor burden at both nodal and extranodal sites is required, PET/CT provides markedly more information than BMB. Conversely, BMB remains irreplaceable in several settings: In newly diagnosed DLBCL in which PET/CT shows only diffuse uptake without definitive evidence of tumor infiltration, BMB with histology and flow cytometry is still required for confirmation; when clinical suspicion of marrow involvement is high but PET/CT is negative (for example, an indolent lymphoma component or minimal diffuse infiltration), BMB is a necessary complement; and when TDs depend closely on marrow pathology [for example, whether to add central nervous system (CNS) prophylaxis or to modify chemotherapy intensity], BMB remains the gold standard. For patients with high-risk disease at baseline staging [for example, an IPI score ≥ 3 , markedly

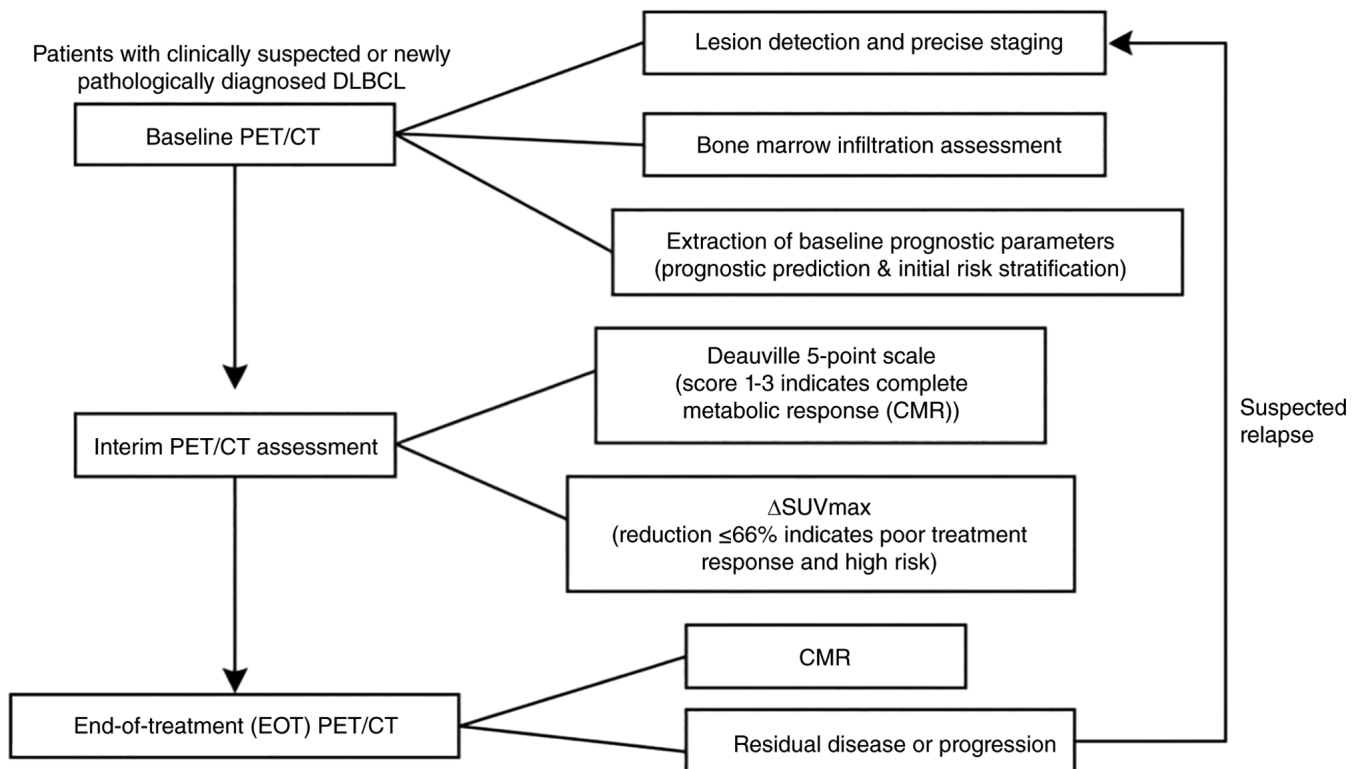


Figure 1. Standardized PET/CT management algorithm for patients with DLBCL across three key phases: Baseline, interim (I-PET2), and EOT. Baseline: Metabolic tumor volume, TLG, and Dmax refine IPI-based risk stratification and guide initial treatment decisions. Interim: the Deauville five-point scale (scores 1-3 indicate response; scores 4-5 indicate residual metabolic activity) and $\Delta\text{SUV}_{\text{max}}$ (a reduction of $\leq 66\%$ indicates high risk) allow dynamic early response assessment and treatment adaptation. EOT: a negative result (score 1-3) predicts favorable long-term survival, whereas a positive result (score 4-5) indicates a high risk of relapse and guides subsequent management. The algorithm spans the entire clinical course, from staging and response prediction to individualized treatment adjustment. PET/CT, positron emission tomography-computed tomography; DLBCL, diffuse large B-cell lymphoma; EOT, end of treatment.

elevated lactate dehydrogenase (LDH), or multiple extranodal lesions], concurrent PET/CT and BMB are recommended, because the two modalities are complementary and their combined use minimizes the rate of missed diagnosis: Focal uptake on PET/CT can replace BMB for diagnosis, whereas BMB should still be performed when only diffuse uptake is observed or when PET/CT is negative but clinical suspicion remains high.

PET/CT-guided target volume delineation for radiotherapy. The contribution of PET/CT to lesion detection extends beyond staging. In radiotherapy, PET/CT allows the extent of tumor infiltration to be delineated more precisely, reduces the dose delivered to normal tissue, and improves both the safety and the efficacy of treatment. In DLBCL, PET/CT has substantially improved the accuracy of target volume delineation: By displaying tumor metabolic activity, it distinguishes active disease from post-treatment fibrosis or necrosis more clearly than conventional CT and therefore defines the extent of infiltration more accurately. Radiotherapy guided by this functional metabolic information achieves a more conformal dose distribution, concentrating high doses within the true tumor volume while sparing the surrounding normal organs as far as possible. In mediastinal disease, for example, PET/CT can effectively separate tumor from the adjacent pericardium and lung, markedly reducing the dose delivered to these critical structures and lowering the risk of late complications

such as radiation pneumonitis and myocardial injury (15). Radiotherapy plans based on PET/CT have been shown to maintain, and possibly to improve, local tumor control while enhancing treatment safety, ultimately offering patients improved outcomes and quality of life.

3. Prognostic prediction and response assessment by PET/CT

Early identification of patients with DLBCL who respond poorly to R-CHOP is essential if more effective alternative treatments are to be explored. The International Prognostic Index (IPI), the traditional and most widely used prognostic tool in DLBCL, stratifies patients according to five clinical variables: Age, performance status, LDH level, Ann Arbor stage and the number of extranodal sites involved, and provides clinicians with an initial basis for risk assessment. The IPI nevertheless has important limitations in the era of precision medicine: As a static clinical score, it captures neither the intrinsic biological heterogeneity of the tumor nor its metabolic burden, and it does not permit dynamic monitoring of response. By revealing tumor functional metabolism non-invasively and dynamically, PET/CT enables precise management throughout the treatment course, from baseline risk assessment through interim response monitoring to end-of-treatment (EOT) evaluation and has become a key tool for predicting survival outcomes in DLBCL.

Baseline prognostic parameters on PET/CT

SUVmax. The standardized uptake value (SUV) is a semi-quantitative measure of FDG uptake, reported as SUVmax, SUVmean, or SUVpeak, that reflects tumor metabolic activity by relating the radioactivity concentration within the tumor to the injected dose. The prognostic value of baseline SUV in DLBCL is complex. Some studies support a predictive role on grounds of biological plausibility, in that a high SUV may indicate a more aggressive tumor and have reported an association between high baseline SUVmax and both PFS and OS (16). More detailed evidence (17), however, indicates that the predictive power of SUV alone is limited and unstable, mainly because SUVmax represents the metabolic activity of only the single most active point within the tumor and captures neither total tumor burden nor spatial heterogeneity. In current prognostic models, SUV therefore serves primarily as a basic measurement, whereas parameters that characterize the disease more comprehensively, such as MTV and TLG, have proved to be more robust and independent prognostic indicators. In short, although baseline SUV is biologically meaningful, it is generally insufficient to predict long-term outcome reliably on its own; it must be incorporated into composite models that also include tumor burden, clinical indices such as the IPI, and molecular features if risk stratification is to be precise.

At the level of biological mechanism, ^{18}F -FDG uptake is clearly linked to tumor cell proliferative activity. Ki-67, the most widely used marker of cellular proliferation, indicates the proportion of cells in the G1, S, G2 and M phases of the cell cycle. Several studies have demonstrated a significant positive correlation between SUVmax and the Ki-67 index in DLBCL lesions (18,19). Papajk *et al* (20) analyzed 149 patients with newly diagnosed NHL and found that Ki-67 correlated positively with SUVmax, with the DLBCL subtype showing the highest level of FDG uptake. Mechanistically, rapidly proliferating tumor cells require large amounts of glucose to meet the demands of glycolytic energy production and biosynthesis, which upregulates glucose transporter 1 and hexokinase 2 and thereby drives high FDG uptake. The strength of the correlation between SUVmax and Ki-67 nevertheless varies among studies, because SUVmax reflects glucose metabolic flux whereas Ki-67 measures the proliferative fraction at a single time point; the two do not capture identical biological dimensions, which helps explain why SUVmax alone has limited prognostic value. Studies directly examining the relationship between SUVmax and other proliferation markers, such as proliferating cell nuclear antigen (PCNA) and argyrophilic nucleolar organizer regions, remain scarce in DLBCL, and the available evidence remains strongest for Ki-67.

MTV and TLG. MTV is the total volume of disease delineated at a given standardized uptake value threshold, whereas TLG is the sum, across all lesions, of the product of MTV and SUVmean. Baseline MTV and TLG are established independent risk factors for PFS and OS (21-23).

MTV improves the risk stratification provided by the IPI and by the National Comprehensive Cancer Network IPI (24-26), particularly in identifying patients at genuinely high risk. Although the traditional clinical indices are widely used, they discriminate poorly within a heterogeneous patient population. By quantifying the total metabolic tumor burden, MTV

identifies truly high-risk patients more accurately, patients who often have poor outcomes even when the international prognostic indices place them in a low- or intermediate-risk category.

Combining MTV with other clinical or imaging features is an effective way to refine risk stratification further. One study integrated MTV with a measure of spatial tumor dissemination and thereby improved risk stratification in DLBCL (27): By combining MTV with the maximum distance between the two farthest lesions (Dmax), the investigators separated patients into three prognostic groups, and the high-risk group, with both high MTV and high Dmax, had a significantly lower 4-year PFS rate. Combining the two measures therefore identifies genuinely high-risk individuals within conventional stage groupings more precisely and optimizes risk stratification. MTV can also be combined with molecular subtyping. Within the cell-of-origin (COO) classification, the germinal center B-cell-like (GCB) and non-GCB subtypes carry inherently different prognoses. As early as 2016, Cottreau *et al* (1) showed, in 81 patients with newly diagnosed DLBCL treated with R-CHOP or a CHOP-like regimen, that patients with a high MTV had significantly lower 5-year PFS and OS than those with a low MTV; more importantly, high MTV still distinguished patients with a poor prognosis from those with a favorable prognosis within the molecularly low-risk group. These findings indicate that integrating molecular and PET/CT imaging features at diagnosis can produce a more refined, individualized prognostic model.

Risk stratification models have not remained confined to static baseline parameters. In a pioneering study, Eertink *et al* (28) extended the approach to dynamic assessment during treatment, combining baseline PET radiomics features (including age, MTV, and the distance between the largest lesion and the farthest lesion, Dmax-bulk) with a quantitative measure of interim metabolic response (ΔSUVmax as a continuous variable) to construct a dynamic prediction model. This model significantly improved risk stratification in DLBCL, increasing the accuracy of risk reclassification by 22% relative to conventional models and providing a sound basis for decisions on early treatment intensification with, for example, chimeric antigen receptor (CAR) T cells or bispecific antibodies.

In summary, the use of PET/CT in DLBCL has evolved from simple response assessment to prognostic prediction and precise risk stratification. Baseline MTV, a powerful quantitative index, together with the IPI, molecular subtyping, and even early dynamic metabolic response, now forms part of a multidimensional, modern system of risk stratification.

Dmax. Cottreau *et al* (1) were the first to propose that dissemination features, the maximum distance between the two farthest lesions (Dmax-patient) and the distance between the largest lesion and the farthest lesion (Dmax-bulk), are prognostic factors in DLBCL (27), and these measures have since been widely adopted. Dmax and the spatial dissemination index (SDmax) are independent predictors of PFS and OS (29) and reflect the spatial spread of disease. SDmax and MTV characterize the disease in complementary ways: The former describes the pattern of dissemination, the latter the tumor burden. Notably, SDmax carries significant value for baseline risk stratification in DLBCL independently of MTV.

Cottreau *et al* (30) also found that a revised prognostic index based on Dmax and Eastern Cooperative Oncology Group performance status (ECOG PS), the Dmax-revised prognostic index, identified an ultra-high-risk population, with an area under the curve significantly greater than that of the IPI. Dmax is thus a quantitative measure of lymphoma dissemination that is significantly associated with prognosis in DLBCL and that stratifies patient risk effectively (Fig. 2).

Interim PET/CT assessment. Interim PET/CT is a critical tool for assessing the response to first-line therapy in DLBCL. To minimize false-positive and false-negative results, international lymphoma organizations and investigators worldwide have continued to refine the interpretation criteria, successively proposing visual methods such as the International Harmonization Project criteria and the Deauville five-point scale, as well as semi-quantitative measures such as the Δ SUVmax. Current guidelines nevertheless remain cautious about the routine clinical use of interim PET/CT and state explicitly that treatment should not be changed on the basis of interim PET/CT findings alone unless there is clear evidence of disease progression.

Timing of interim PET/CT. Response assessment during treatment for DLBCL is categorized by timing: Early PET after two cycles of chemotherapy (I-PET2), interim PET after four cycles (I-PET4), and EOT PET after completion of all therapy. I-PET2 mainly reflects the initial chemosensitivity of rapidly proliferating cells and helps identify, at an early stage, patients with a favorable or a poor response, including those with no response. I-PET4 better captures the regrowth of lymphoma cells, reflected in a high proliferation index at that time point, and is therefore used mainly to identify patients likely to progress or relapse. In DLBCL, the first interim PET/CT is recommended after two rather than four cycles of treatment. When the I-PET2 result is negative, subsequent PET/CT scans add little to the monitoring of relapse (31), whereas a positive I-PET2 result warrants repeat imaging.

In a study of 1,692 patients with DLBCL that examined the timing of interim PET, Eertink *et al* (32) found that, during R-CHOP therapy, I-PET2 and I-PET4 predicted a favorable response with comparable accuracy. The optimal time point and criteria should therefore be chosen according to the clinical question: The best time to assess response is after two cycles; patients with a good response on I-PET2 are suitable candidates for de-escalation trials; and those with an unfavorable response, as defined by the Δ SUVmax criterion at I-PET4, may be enrolled in randomized trials of novel therapies.

Yuan *et al* (33) explored an even earlier time point and showed that interim PET/CT after a single cycle of chemotherapy is feasible in DLBCL and has predictive value similar to that of I-PET2. The Deauville score and MTV measured after one cycle could not, however, predict the final treatment response or one-year disease-free status.

Interpretation criteria for interim PET/CT

Deauville score. The Deauville scoring system, a key tool for response assessment, has been examined extensively. A negative interim PET/CT result [Deauville score 1-3, indicating complete metabolic response (CMR)] is generally associated with a favorable prognosis (33,34); its core value lies in

distinguishing treatment-sensitive from potentially resistant patients according to the degree of metabolic response. In one study of patients with low-risk DLBCL, interim PET/CT after four cycles of R-CHOP identified favorable responders (Deauville score 1-3) in whom the number of chemotherapy cycles could be reduced from six to four without compromising the 2-year PFS rate; this approach also significantly reduced the risk of adverse events such as neutropenia, febrile neutropenia and infection (35).

Yuan *et al* (33) further reported that a Deauville score of 4 on interim PET/CT has limited prognostic value in DLBCL, whereas a score of 5 carries considerably greater prognostic significance. The Deauville system is thus not only an effective prognostic tool but also an important quantitative basis for individualizing treatment and optimizing therapeutic strategy.

Δ SUVmax. The Δ SUVmax is a core quantitative measure for interim PET/CT and reflects the relative change in tumor metabolic activity between baseline and interim imaging. It is calculated as Δ SUVmax=[(baseline SUVmax-interim SUVmax)/baseline SUVmax] x100%. A reduction of $\leq 66\%$ at interim assessment identifies patients at very high risk (36-38). By quantifying dynamic changes in metabolic activity, Δ SUVmax overcomes the qualitative limitations of the Deauville score and provides a key tool for the precise adjustment of treatment in DLBCL. As an independent predictor, it has proved superior to visual assessment in several studies (39,40).

Combining visual assessment using the Deauville score with Δ SUVmax to classify response on a 0-3 scale further improves predictive accuracy: Patients with a score of 0 have a significantly improved prognosis than all other groups, with improved positive predictive value (PPV) and specificity (41). Another study assessed the prognostic value of several PET parameters, including the Deauville score, at baseline and at interim assessment, and found that baseline MTV and Δ SUVmax were independent predictors of PFS and OS and that the EOT Deauville score was also significantly associated with PFS (42). Notably, the combination of an interim Deauville score of 4-5 with a Δ SUVmax reduction of $\leq 70\%$ identified a subgroup with a particularly poor prognosis.

Interim PET/CT across molecular subtypes. DLBCL is molecularly heterogeneous, and the greatest differences in biological behavior and treatment response lie between the GCB and non-GCB subtypes. Sun *et al* (43) found that interim PET/CT interpreted with the Deauville score independently predicted PFS in patients with GCB DLBCL but had no predictive value for OS. In patients with non-GCB disease, by contrast, the I-PET-negative group had significantly improved PFS and OS than the I-PET-positive group. Receiver operating characteristic analysis showed that interim PET based on Δ SUVmax predicted PFS and OS effectively in the non-GCB subtype but not in the GCB subtype; after stratification by the optimal Δ SUVmax threshold, this measure predicted both PFS and OS in patients with non-GCB disease.

These findings highlight the subtype-dependent prognostic value of interim PET and underline the need to take the pathological subtype of DLBCL into account in clinical practice. In patients with GCB disease, an interim Deauville score of 3 may indicate a relatively favorable prognosis, so that the original regimen can reasonably be continued. In patients

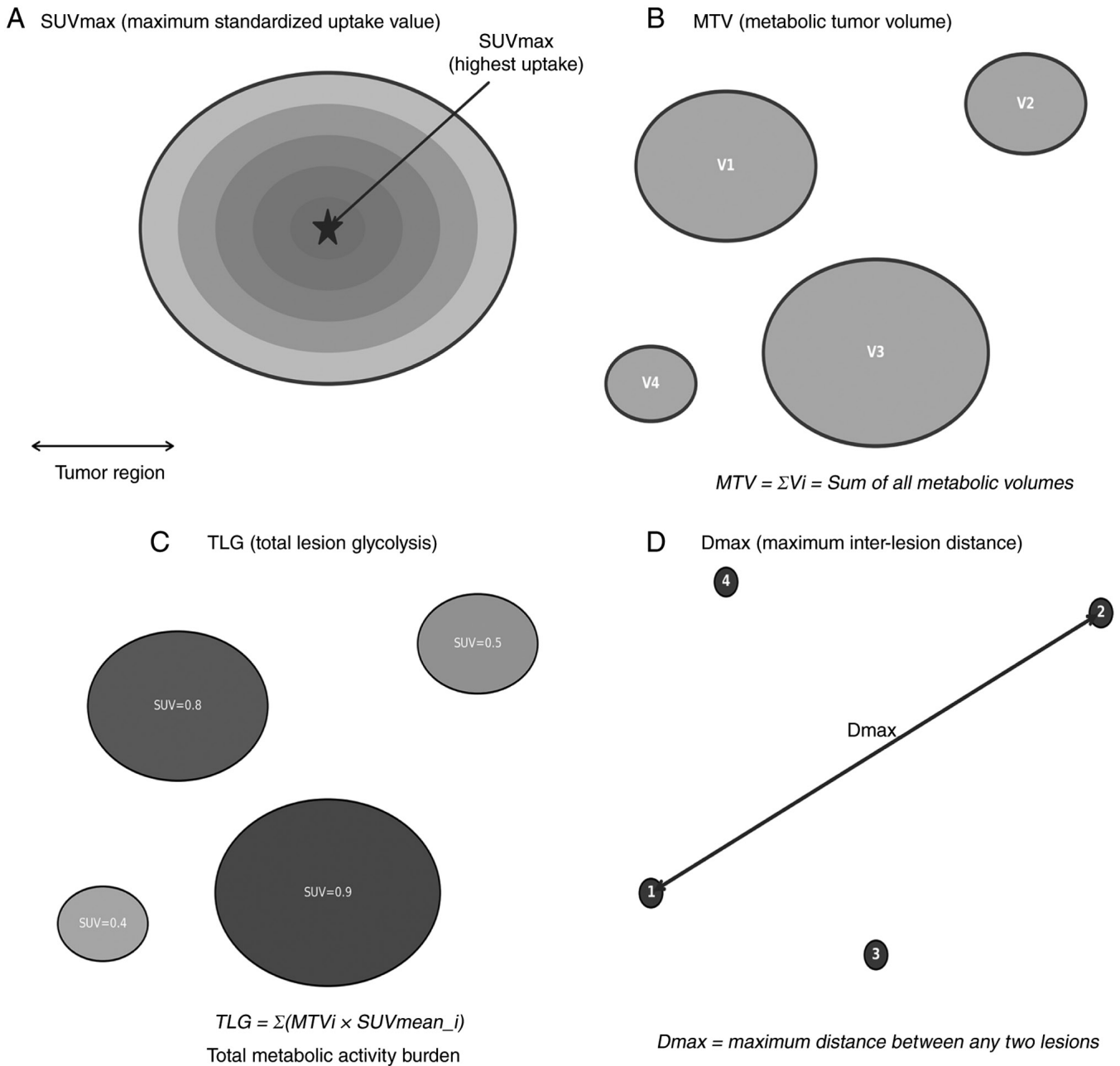


Figure 2. Key quantitative positron emission tomography-computed tomography parameters used for prognostic assessment in DLBCL. (A) SUVmax: The highest metabolic activity within a lesion; it reflects tumor aggressiveness but is limited as a measure of global disease burden. (B) MTV: the total volume of metabolically active tumor; an independent predictor of progression-free and overall survival that enhances IPI/NCCN-IPI risk stratification. (C) TLG: The product of volume and metabolic activity ($MTV \times SUV_{mean}$), reflecting the total glycolytic burden. (D) Dmax: The maximum distance between any two lesions, characterizing disease dissemination; combined with MTV in the Dmax-revised prognostic index, it identifies ultra-high-risk patients with poor outcomes. Used together, these four complementary parameters allow multidimensional and precise risk stratification. DLBCL, diffuse large B-cell lymphoma; MTV, metabolic tumor volume; TLG, total lesion glycolysis.

with non-GCB disease, failure to achieve a ΔSUV_{max} reduction of $\geq 66\%$ strongly suggests that the original regimen is insufficiently effective and that treatment should be modified early, for example, by switching to a novel therapy such as Pola-R-CHP or CAR T-cell therapy.

Nevertheless, when making TDs based on interim PET/CT, it is critical to recognize that molecular subtyping does not fully capture DLBCL's biological aggressiveness. High-grade B-cell lymphomas with MYC and BCL2 and/or BCL6 rearrangements ('double-hit' or 'triple-hit' lymphomas), as defined by the WHO classification, constitute a distinct

histological entity with an aggressive course and poor response to R-CHOP, irrespective of COO. These patients often require intensified regimens or early trial referral, and their management should not be guided by interim PET results alone, since chemosensitivity on imaging does not guarantee durable remission. Thus, the integration of interim PET/CT into therapeutic decision-making must be accompanied by comprehensive histopathological and genetic evaluation, including fluorescence *in situ* hybridization for MYC, BCL2 and BCL6 rearrangements, to ensure that the most aggressive variants are identified and treated accordingly.

Table I. Emerging PET tracers and advanced imaging technologies in diffuse large B-cell lymphoma.

Category	Tracer/Technology	Key Features
Cell proliferation tracers	^{18}F -FLT (Fluorothymidine)	• Higher tumor specificity • Correlates with Ki-67 • Improved PPV for early response
Antigen-targeted tracers	$^{68}\text{Ga}/^{89}\text{Zr}$ -CD20, Ga-PentixaFor	• Assess CD20 expression • Predict rituximab efficacy • CXCR4-targeted imaging
Amino acid tracers	^{11}C -MET (Methionine)	• High tumor-to-background • Unaffected by inflammation • Short half-life (20 min)
PET/MR technology	Integrated PET/MR	• Reduced radiation exposure • Superior soft tissue contrast • DWI for early response

PPV, positive predictive value; DWI, diffusion-weighted imaging; CXCR4, C-X-C chemokine receptor 4.

Interim PET/CT is a pivotal tool for assessing the response to treatment in DLBCL. With respect to timing, I-PET2 and I-PET4 have comparable predictive value: A negative I-PET2 result indicates a favorable prognosis, whereas a positive result warrants re-evaluation. With respect to interpretation, the Deauville score is widely applied, whereas quantitative measures such as $\Delta\text{SUV}_{\text{max}}$ (a reduction of $\leq 66\%$ indicating high risk) may predict outcome more precisely and may outperform visual assessment. The molecular subtype of DLBCL also influences the value of assessment, interim PET/CT being of greater prognostic utility in non-GCB disease. Clinical application should therefore integrate the timing of assessment, the interpretation criteria used, the molecular subtype, and the histological characteristics in order to guide individualized TDs.

EOT PET/CT assessment. A negative EOT PET/CT result (Deauville score 1-3) is closely associated with significantly prolonged PFS and OS (44,45), whereas a positive result (Deauville score 4-5) indicates a high risk of relapse. CMR at the end of treatment is an independent predictor of PFS and OS and a reliable prognostic biomarker in DLBCL, and its predictive value remains stable in long-term survival analyses. Han *et al* (34) showed that PET/CT parameters measured after a single cycle of chemotherapy were unrelated to long-term survival, whereas a negative EOT PET/CT result was the key predictor of long-term outcome; early chemotherapy-induced tumor regression therefore has considerably less prognostic value than EOT assessment.

In summary, PET/CT provides a dynamic monitoring network across the entire course of DLBCL management, with routine imaging recommended at baseline, interim, and end of treatment. At baseline, MTV, TLG and Dmax reflect tumor burden and dissemination, offering prognostic value beyond the IPI and guiding initial treatment intensity; however, no universally validated cut-offs exist for these parameters, reported thresholds vary widely with segmentation methods,

populations and regimens, so they should be used for risk stratification rather than binary classification. At interim, the Deauville scale and $\Delta\text{SUV}_{\text{max}}$ enable early identification of high-risk patients; a $\Delta\text{SUV}_{\text{max}}$ reduction of $\leq 66\%$ is the most validated threshold for predicting poor outcomes, whereas the Deauville score lacks a standardized semi-quantitative cut-off, and its PPV varies with timing and context. At end of treatment, a negative PET/CT strongly predicts long-term survival, while a positive result indicates high relapse risk and warrants further investigation.

For clinical decision-making: Elevated baseline MTV, TLG and Dmax in patients with high-risk IPI further stratify prognosis within this already high-risk group, suggesting closer monitoring or risk-adapted strategies. At interim, $\Delta\text{SUV}_{\text{max}}$ reduction $>66\%$ with Deauville 1-3 supports continuing current therapy, whereas $\Delta\text{SUV}_{\text{max}} \leq 66\%$ or Deauville 4-5, without clear progression, should not routinely modify first-line therapy; these findings should prompt multidisciplinary discussion to exclude false-positives (for example, inflammation and infection), and patients should continue planned therapy until EOT reassessment. At end of treatment, negative scans allow surveillance, while positive scans require biopsy confirmation before salvage therapy due to false-positive rates. Only the $\Delta\text{SUV}_{\text{max}} \leq 66\%$ threshold is consistently validated across cohorts; MTV, TLG and Dmax lack internationally accepted cut-offs, with reported values varying considerably by segmentation methods, populations and protocols. All PET/CT findings must therefore be interpreted cautiously, integrated with clinical and pathological data, and applied in local context rather than mechanistically, with further standardization and prospective validation needed.

4. PET/CT-based radiomics models

PET/CT-based radiomics has shown considerable value in the diagnosis and treatment of DLBCL in recent years. Radiomics

permits the high-throughput extraction and quantification, from standard PET/CT images, of features that are imperceptible to the human eye, and thereby reveals tumor heterogeneity more comprehensively.

Construction of prognostic models. Several studies have confirmed that radiomics features extracted from baseline PET/CT have independent prognostic value. In one study, semi-automatic segmentation was used to extract 490 radiomics features, and a model incorporating MTV, SUVmax and Dmax substantially outperformed the conventional IPI (46). Combining radiomics features with clinical factors such as the IPI refined risk stratification further and allowed more precise identification of high-risk patients (47,48).

Various strategies for feature selection and fusion have been explored in order to optimize radiomics models. Jiang *et al* (49) used a cross-combination approach to generate 49 candidate feature-selection pipelines and derived radiomics features (R-features) significantly associated with PFS and OS. Another study compared several methods of feature reduction and found that, irrespective of the approach to lesion selection or dimensionality reduction, patient-level conventional PET features such as MTV, together with measures of disease dissemination, consistently showed the best predictive value (50).

Although different PET segmentation methods (for example, a fixed SUV threshold or a percentage threshold) alter the calculated values of individual radiomics features, the discriminative performance of models built with different segmentation methods does not differ substantially (51), which supports the robustness of the radiomics approach.

Models for subtyping and identification of transformation. Beyond prognostication, PET/CT radiomics has shown considerable promise in supporting the molecular subtyping of DLBCL, particularly the distinction between the GCB subtype and the non-GCB subtype [chiefly the activated B-cell-like (ABC) subtype]. This distinction is clinically important, because the GCB and ABC subtypes differ in pathogenesis and prognosis and often require different treatment strategies. Work in this field is moving from conventional metabolic parameters such as SUVmax toward more complex radiomics features.

In a retrospective study of lymphomas presenting with bulky mediastinal masses, classical Hodgkin lymphoma, primary mediastinal B-cell lymphoma and gray zone lymphoma, Abenavoli *et al* (52) found significant differences among these subtypes in FDG PET texture features and metabolic heterogeneity, providing proof of concept for the use of PET/CT radiomics to differentiate lymphoma subtypes.

Jiang *et al* (53) developed and validated a baseline PET/CT radiomics model for the non-invasive identification of histological transformation of indolent follicular lymphoma into aggressive DLBCL, demonstrating that radiomics features can capture the profound changes in tumor biology that accompany transformation. Clinically, such a model offers a valuable non-invasive alternative for patients who, for various reasons, cannot undergo repeat tumor tissue sampling for genetic sequencing. PET/CT is therefore likely to extend beyond staging and response assessment and to become embedded in the decision-making loop of precision medicine, with

non-invasive analysis of tumor biology providing key evidence to guide individualized treatment.

In summary, PET/CT radiomics improves the accuracy of prognostic stratification in DLBCL and extends the role of imaging to molecular subtyping and the identification of histological transformation, reflecting a shift from conventional metabolic parameters toward multidimensional, high-throughput features. Standardization of image acquisition and segmentation, the development of automated analysis workflows, and large-scale prospective studies are still needed before radiomics can move from a research tool to routine clinical use in the individualized management of DLBCL.

5. Applications in special clinical scenarios

PET/CT in CAR T-cell therapy. In the setting of CAR T-cell therapy, patients with DLBCL typically undergo PET/CT at the time of the TD, at CAR T-cell infusion (TT), and 1 month (M1) and 3 months (M3) after treatment. Metabolic parameters derived from these examinations have considerable value for predicting both survival and toxicity. Cohen *et al* (54) found, on univariate analysis, that a TD SUVmax >17.1 and a TT SUVmax >12.1 were significantly associated with shorter OS; on multivariate analysis, three factors were significantly associated with shorter OS: a TD SUVmax >17.1, an LDH level >450 U/l, and an ECOG performance status >1. At early response assessment (M1), patients with a Deauville score >3 had a significantly shorter median OS, and a Δ SUVmax of $\leq 66\%$ relative to the TD baseline also indicated a poor prognosis. With respect to toxicity, the pre-infusion SUVmax correlates strongly with the grade of cytokine release syndrome (CRS) (Spearman $r=0.806$, $P<0.001$) and the pre-infusion TLG moderately so ($r=0.534$, $P<0.001$), indicating that metabolic parameters acquired before infusion can give advance warning of toxicity (55). Taken together, these findings suggest that pre-treatment SUVmax helps select patients likely to benefit from CAR T-cell therapy, that the Deauville score and Δ SUVmax at 1 month allow early identification of patients at high risk of treatment failure, and that pre-infusion SUVmax provides an early warning for toxicity management.

PET/CT in autologous hematopoietic stem cell transplantation (auto-HSCT). Pre-transplant PET/CT effectively predicts survival in patients with DLBCL undergoing auto-HSCT (56). Sauter *et al* (57) found that patients with a pre-transplant Deauville score of 1-3 had significantly higher 3-year PFS (77% vs. 49%) and OS (86% vs. 54%) than those with a score of 4. Qiao *et al* (58) showed that, although the magnitude of the change in SUVmax (using a threshold of 66%) predicted neither PFS nor OS, a higher pre-transplant SUVmax (>6) was significantly associated with shorter PFS. Pre-transplant PET/CT therefore not only predicts survival in DLBCL but is also clinically useful for identifying patients at high risk of transplant failure and for selecting those who require intensified intervention.

6. Emerging alternative technologies

^{18}F -FDG PET/CT is the cornerstone of staging and response assessment in DLBCL, but it has intrinsic limitations in

distinguishing tumor from inflammation or infection and in characterizing tumor heterogeneity. These gaps have driven the development of novel tracers and of PET/MR, which aim to compensate for the shortcomings of ^{18}F -FDG PET/CT and to provide richer molecular imaging information for precision medicine (Table I).

Novel PET tracers. Among the tracers currently available, ^{18}F -FDG is the conventional metabolic agent. Proliferation tracers include 3'-deoxy-3'- ^{18}F -fluorothymidine (^{18}F -FLT), which is phosphorylated by thymidine kinase 1 (TK-1) and thereby retained within the cell; TK-1 activity peaks during the DNA synthesis phase. Uptake of ^{18}F -FLT correlates well with classic markers of tumor proliferation such as the Ki-67 index, PCNA expression, and the S-phase fraction, while remaining low in inflammatory lesions. ^{18}F -FLT can therefore distinguish tumor tissue from inflammation more specifically than ^{18}F -FDG and has considerable potential for early response assessment and treatment monitoring. Because FLT may have greater tumor specificity than FDG (59,60), FLT PET offers a particular advantage for the early assessment of response to chemotherapy, chemioimmunotherapy, radiotherapy, or combinations of these. Minamimoto *et al* (61) demonstrated that, in DLBCL, the PPV of interim FLT PET/CT was significantly higher than that of interim FDG PET/CT with both qualitative and semi-quantitative interpretation; even with simple visual assessment, the PPV of FLT PET/CT remained superior to that of FDG PET/CT.

Tracers of amino acid metabolism, such as ^{11}C -methionine (^{11}C -MET), offer another perspective, since tumor cells require abundant amino acids for protein synthesis. ^{11}C -MET provides high tumor-to-background contrast and is unaffected by inflammation, and it is significantly superior to ^{18}F -FDG for imaging cerebral lymphoma and for delineating tumor margins precisely. Its clinical application is limited, however, by the very short physical half-life of ^{11}C (20 min), which requires on-site cyclotron production.

Antigen- and receptor-targeted tracers. Tracers directed against antigens on the surface of DLBCL cells, such as ^{68}Ga - or ^{89}Zr -labeled anti-CD20 antibodies (for example, ^{89}Zr -DFO-rituximab), allow CD20 expression to be assessed *in vivo* across all lesions, providing an intuitive means of predicting the efficacy of rituximab and of conducting pharmacokinetic studies. Radiolabeled antibodies against CD22 can similarly be used to assess suitability for the corresponding targeted therapies. Particularly promising is ^{68}Ga -PentixaFor, a PET molecular probe directed at C-X-C chemokine receptor 4 (CXCR4). CXCR4 is highly expressed in a range of tumors, including multiple myeloma, lymphoma and aldosterone-producing adenoma, and in inflammatory disease, and ^{68}Ga -PentixaFor binds it specifically, permitting highly sensitive imaging of these conditions. This agent may assist not only in prognostic stratification and the identification of high-risk patients but also in selecting patients suitable for CXCR4-antagonist therapy.

^{68}Ga -labeled prostate-specific membrane antigen (PSMA) ligands warrant a note of caution: although developed for prostate cancer, PSMA is also expressed in the neovascular

endothelium of tumors, so that some highly vascularized extranodal DLBCL lesions may show non-specific uptake that must be recognized during image interpretation.

PET/MR. Integrated PET/MR has emerged as a more advanced molecular imaging technology than PET/CT and offers several advantages in DLBCL. First, it substantially reduces radiation exposure, which is particularly important for young patients who require repeated follow-up imaging. Second, MR is more sensitive for the detection of extranodal disease, especially involvement of the CNS, liver, bone, and bone marrow; combined with diffusion-weighted imaging, it can reveal treatment-induced changes in cellularity at an earlier stage and thus provide both functional and metabolic evidence for response assessment. Although PET/CT remains the standard for staging, the multiparametric capability of PET/MR gives it considerable potential for precise staging, response monitoring, and prognostic assessment.

In summary, ^{18}F -FLT, ^{11}C -MET, the various antigen-targeted tracers, and PET/MR are powerful complements to ^{18}F -FDG PET/CT and hold considerable promise for specific clinical challenges in DLBCL. Future work will need to overcome the limitations of existing tracers and to move these novel molecular probes from clinical studies into routine practice, ultimately enabling the personalized and precise management of DLBCL.

7. Limitations

Several limitations of PET/CT in clinical practice deserve attention. First, its sensitivity for CNS lesions is relatively low, chiefly because the high physiological FDG uptake of normal brain tissue masks lymphomatous lesions; such cases require cerebrospinal fluid examination or MRI to improve diagnostic accuracy. Second, physiological FDG uptake in other normal structures, such as the gastrointestinal tract and bone marrow, can interfere with image interpretation and produce false-positive results. Third, in the assessment of BMI, PET/CT has limited ability to detect heterogeneous or indolent disease, for which BMB remains necessary for definitive diagnosis.

More fundamental problems are shared across the field. i) There is no uniform standard for image segmentation, which directly affects the comparability of parameters and the generalizability of prognostic models. ii) Parameter measurement is not standardized across centers: Differences in scanners, reconstruction algorithms and patient preparation limit the cross-center comparability of semi-quantitative measures such as SUV and hinder the pooling and dissemination of results from multicenter studies. iii) Visual assessment is subjective: interpretation of the Deauville score depends on the reader's experience, and inter-observer variability is substantial, particularly at the boundary between scores 3 and 4; semi-quantitative parameters compensate only in part, since their thresholds and measurement procedures are also not standardized. These limitations point to an urgent need for internationally accepted, standardized guidelines covering PET/CT acquisition, reconstruction, segmentation and interpretation, in order to improve the reliability and reproducibility of the technique in the precision management of DLBCL.

8. Summary and outlook

PET/CT has become a core tool in the comprehensive management of DLBCL, with value spanning diagnosis, response assessment and prognostic prediction. At diagnosis and staging, its high metabolic sensitivity refines clinical staging and significantly improves the detection of BMI. At interim assessment, dynamic monitoring using visual interpretation and semi-quantitative parameters effectively identifies high-risk patients. For prognosis, a negative PET/CT result at the end of treatment is a strong predictor of long-term survival, whereas baseline MTV, TLG and Dmax are established independent prognostic indicators, MTV in particular being combinable with clinical and imaging measures to optimize risk stratification. In special settings such as CAR T-cell therapy and auto-HSCT, PET/CT provides key evidence for patient selection, early warning of toxicity and survival prediction.

Several priorities must be addressed if PET/CT is to be applied more precisely and more widely in DLBCL. First, internationally unified standards for image acquisition, reconstruction, segmentation and quantitative measurement should be established, including definition of the optimal thresholding algorithm for MTV and improved quality-control procedures for Deauville scoring and standardized SUV measurement, so as to enhance the reproducibility of clinical data and the comparability of multicenter studies. Secondly, because most machine-learning-based prognostic models are currently derived from retrospective studies, multicenter prospective cohort studies with large samples are required to validate rigorously the predictive value of radiomics features combined with clinical parameters, to establish automated and standardized analytical workflows, and to translate these models into clinical decision-making. Third, the particular advantages of novel tracers such as ^{18}F -FLT, ^{11}C -MET, and ^{68}Ga -PentixaFor for discriminating tumor from inflammation and for assessing proliferative activity and receptor expression should be exploited by overcoming current limitations in production technology, cost and evidence base, by conducting multicenter clinical trials, by establishing standardized protocols for administration and interpretation, and by exploring theranostic strategies that pair these tracers with targeted agents.

In summary, through the coordinated advancement of standardization, prospective validation, translation of novel tracers and multimodal imaging, PET/CT and its derived imaging biomarkers are expected to form a more powerful, precise, and generalizable system for prognostic prediction and therapeutic decision-making, ultimately supporting the continued development of individualized precision medicine for DLBCL.

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Authors' contributions

HJ, HS, DZ and LB made substantial contributions to the conception and design of the study, drafted the article and revised it critically for important intellectual content, and read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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