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Review Article

Recent advancements in ^{18}F-FDG PET/CT for the diagnosis, staging, and treatment management of HIV-related lymphoma

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Abstract: Infection with the Human Immunodeficiency Virus (HIV) is one of the most pressing issues facing public health on a worldwide scale. Currently, HIV-related lymphoma is the most common cause of death among people living with HIV, and warrants more attention. The unique challenges associated with HIV-related lymphoma management derive from the underlying HIV infection and its immunosuppressive effects. ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) has gained significant prominence in the past few years as a valuable diagnostic and therapeutic instrument for the treatment of HIV-related lymphoma. This review will start with an overview of the subtypes, risk factors, and therapeutic choices for individuals with HIV-related lymphoma. We will then briefly discuss the current application of ^{18}F-FDG PET/CT in the medical management of HIV-related lymphoma patients, followed by the initial staging of the disease, the evaluation of therapeutic response, the prediction of prognostic outcomes, the decision-making process for radiotherapy guided by PET findings, and the distinguishing of various diagnoses.

Keywords: Human immunodeficiency virus, diffuse large B-cell lymphoma, Burkitt's lymphoma, Hodgkin's lymphoma, ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography

Introduction

Infection with the Human Immunodeficiency Virus (HIV) is one of the most pressing issues facing public health on a worldwide scale. In 2022, there were 1.3 million new HIV infections and 39 million people living with the virus [1]. Almost 680,000 individuals died from infections related to Acquired Immunodeficiency Syndrome (AIDS) [2].

As life expectancy has increased due to the use of highly active antiretroviral treatment (HAART), cancer has become the primary reason for mortality and morbidity in HIV cases. Consequently, between 25 and 40 percent of HIV/AIDS patients develop malignancies. Malignant tumors are responsible for more than 28% of HIV-related mortality, and more than 40% of HIV cases are subsequently diagnosed with HIV-related lymphomas [3, 4].

HIV/AIDS-associated lymphomas, are caused by T and B lymphocytes during different phases of maturation. Nearly 90% of lymphomas are caused by B cells, with some lymphoma subtypes being more common than others. While some of these can appear in individuals who are not HIV-infected, others seem to be more prevalent among those who are HIV-positive. HIV/AIDS-associated lymphomas are cancers with aggressive features and a rapid rate of spread. Without treatment, mortality can occur within weeks to months of diagnosis [5]. HIV-related lymphomas were formerly classified based on their morphology and principal location, such as "systemic", "primary central nervous system", and "body cavity". However, the World Health Organization (WHO) currently categorizes diseases into separate entities according to their molecular, immunological, and morphological changes [6].

The correlation between lymphomas and acquired immunodeficiency was identified during the onset of the AIDS epidemic in the early 1980s [4]. In the present time, when lymphoma occurs in HIV-positive individuals, it constitutes a significant complication and one of the main causes of morbidity and mortality. On the basis of the immunological status of HIV-infected individuals, malignancy is categorized as AIDS-defining or non-AIDS-defining. More than half of all AIDS-defining cancers affect people who are HIV-positive [7, 8].

The management of HIV-related lymphoma presents unique challenges due to the underlying HIV infection and its impact on the immune system. In the past few years, ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) has proven to be an essential diagnostic and management tool in the treatment of this complicated disease [9]. For lymphoma treatment, this noninvasive method gives various quantitative metabolic indicators, including SUVmax, total lesion glycolysis (TLG), metabolic tumor volume (MTV), and SUV at lean body mass (SUL). The 2014 Lugano criteria recom-

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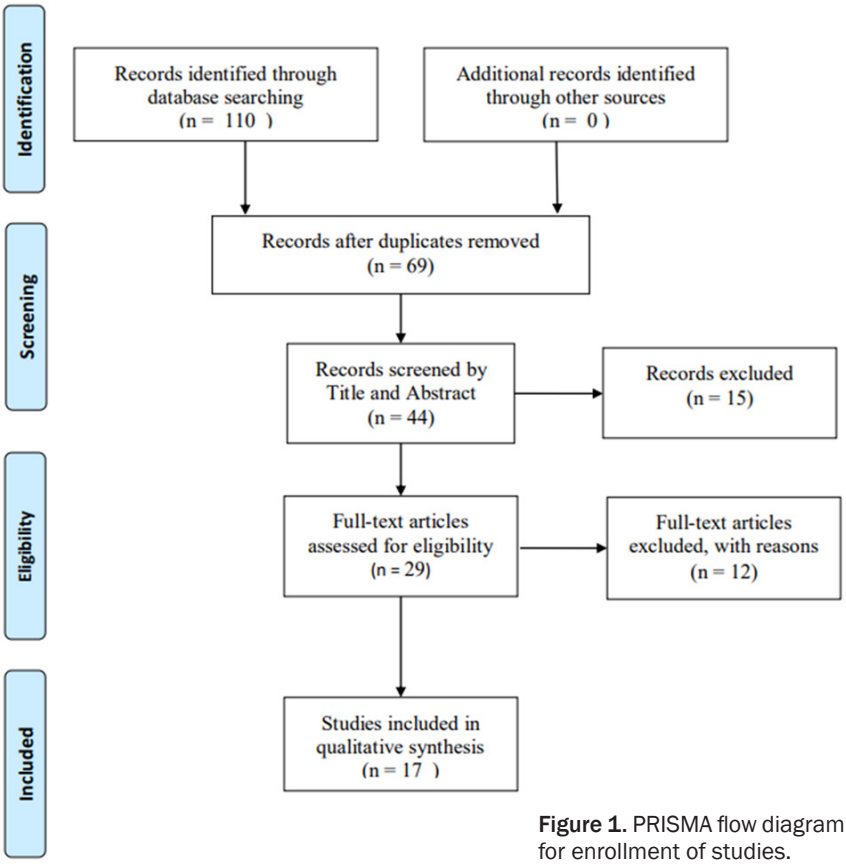

Figure 1. PRISMA flow diagram for enrollment of studies.

mend ^{18}F-FDG PET/CT for all FDG-avid lymphomas due to its strong sensitivity to lymph nodes and extranodal lymphoma involvement throughout the body [10]. Numerous randomized clinical trials have shown that changes in tumor metabolism can influence decisions about whether to increase or decrease treatment intensity during the course of lymphoma treatment [11, 12].

It is clear that lymphoma in the general population and HIV-related lymphoma are distinct entities. HIV-related lymphoma demonstrates a more severe Ann Arbor stage, a higher incidence of B symptoms (including fever, unintentional weight loss, and night sweats), and a poorer prognosis when compared to lymphoma in HIV-negative individuals, even during the HAART era [13]. An ^{18}F-FDG PET/CT false positive for HIV-related lymphoma is commonly caused by HIV-related benign lymphadenopathy. It remains debatable whether HIV infection increases tumor burden and decreases overall survival. Limited research has been conducted to date regarding the clinical utility of ^{18}F-FDG PET/CT in the context of HIV-related lymphoma [14].

This review will start with an overview of the Subtypes, risk factors, and therapeutic choices for individuals with HIV-related lymphoma. We will then briefly discuss the current application of ^{18}F-FDG PET/CT in the medical management of HIV-related lymphoma patients, followed by the initial staging of the disease, the evaluation of therapy response, the prediction of prognostic outcomes, the decision-making process for radiotherapy guided by PET findings, and the distinguishing of various diagnoses.

Materials and methods

Search strategy

We have conducted a literature review of the role of ^{18}F-FDG PET/CT in the medical management of AIDS/HIV-related lymphoma patients. The investigation was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) criteria; the flow diagram is demonstrated in **Figure 1**. The research was conducted in the PubMed, MEDLINE, Scopus, Web of Science, DOAJ, Science Direct, and Google Scholar databases between January 2003 and October 2023. The search was conducted using the Advanced Search Builder, with the keywords being entered into [Title OR Abstract]. We have filtered only research articles published in English language and using the terms '(^{18}F-fluorodeoxyglucose positron emission tomography combined with computed tomography [Mesh] OR FDG-PET/CT [Mesh]) AND (AIDS-Related [Mesh] OR AIDS-Associated [Mesh] OR HIV-Related [Mesh] OR HIV-associated [Mesh]) AND (Lymphoma [Mesh])'.

Inclusion and exclusion criteria

Original articles that evaluated the role of ^{18}F-FDG PET/CT for AIDS/HIV-related lymphoma were eligible for inclusion in the systematic review. References in selected research were reviewed for other relevant literature. There were both retrospective and prospective investigations, as well as blinded and non-blinded research. Case reports and case series, review articles lacking original data, editorials, letters, and conference papers were all excluded.

Data extraction and quality evaluation

An evaluation of the titles and abstracts was conducted by two authors (G.S. and A.H.). After implementing inclusion and exclusion criteria, data from studies were extracted based on the requirements of the survey.

Any pertinent papers were added after a thorough analysis of the references in earlier review articles. We obtained 17 eligible published research articles in their final version. We selected to include just the primary findings that were relevant to the goal of this study for some of them (**Figure 1**).

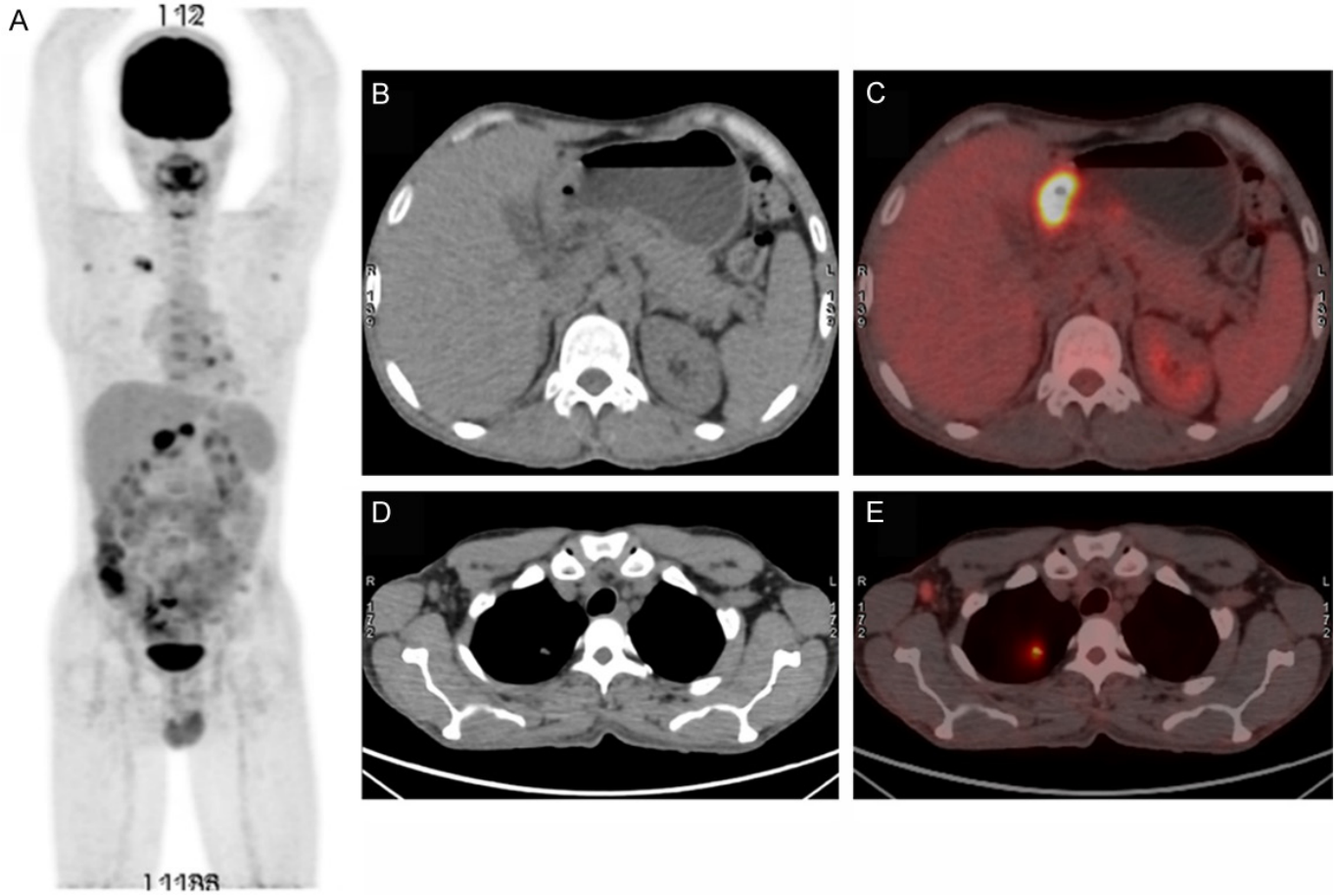

Figure 2. A: A whole-body ^{18}F-FDG PET-CT scan of a 36-year-old HIV-positive man with upper gastrointestinal symptoms as well as endoscopic and histopathologic findings of diffuse large B-cell lymphoma (DLBCL). Abnormal radionucleotide uptake in the stomach, left mediastinum, right lung apex, and bilateral axilla was found. B, C: Evidence of multifocal infiltrative mucosal thickening is noted in the antrum and distal lesser curvature of the stomach, which appears to be of high radionucleotide uptake (SUVmax = 17.5), compatible with the biopsy-proven diagnosis of gastric lymphoma in an HIV-positive patient. Also, a few perigastric lymph nodes are seen, which show no obvious abnormal radionucleotide uptake, favoring the inflammatory rather than malignant nature of the nodes. D, E: A solid hypermetabolic (SUVmax = 6) nodule with a speculated border is depicted in the apical segment of the right lung, which is highly in favor of the malignant nature of the nodule. A small-sized but slightly hypermetabolic (SUVmax = 2) right axillary lymphadenopathy is also illustrated, which proved to be a reactive lymph node after histopathologic assessment.

The significance of ^{18}F-FDG PET/CT in HIV-related lymphoma staging and diagnosis

Diagnosis and staging of HIV lymphoma with ^{18}F-FDG PET CT is an essential application of this imaging technique. The utilization of ^{18}F-FDG PET/CT has been suggested for the purposes of prognostic prediction, response evaluation, initial staging, and restaging of HIV-related lymphoma [15]. ^{18}F-FDG PET/CT is more effective than contrast-enhanced CT in the early stages of lymphoma detection, particularly for lesions involving the gastrointestinal tract, spleen, and bone marrow that lack or have minimal anatomical abnormalities. ^{18}F-FDG PET/CT can produce a reliable map of probable disease and detect previously unrecognized areas of disease in the first stage of AIDS-related Burkitt's lymphoma (BL) [14]. A retrospective examination of 13 HIV-positive BL patients who had at least one ^{18}F-FDG PET/CT scan was done by Just et al. [16]. ^{18}F-FDG PET/CT revealed high SUVmax sites in 5 out of 5 patients scanned before therapy, including the spleen (1/5), peritoneum (2/5), bone (1/5), and lymph nodes (4/5), in addition to all sites found by conventional imaging. Fifty-four percent of individuals had lymph node involvement, rare in endemic or sporadic BL. In addition, the parotid lymph nodes were the primary site of BL in three of the cases.

Additionally, ^{18}F-FDG PET/CT is used in patients with diffuse large B-cell lymphoma (DLBCL) related to HIV in order to promote initial staging, response assessment, and prognostic prediction. **Figure 2** demonstrated a 36-year-old HIV-positive man with upper abdominal pain and vomiting who underwent ^{18}F-FDG PET/CT due to accurate staging of DLBCL.

As previously mentioned, employing factors such as size, location, and enhancing mode to identify benign lymph nodes against malignant lymph nodes remains challeng-

Table 1. Key points about the significance of ^{18}F-FDG PET/CT in HIV-related lymphoma staging and diagnosis

Key points
● Diagnosis and staging of HIV lymphoma with ^{18}F-FDG PET/CT is an important application of this imaging technique.
● ^{18}F-FDG PET/CT is recommended for initial staging, restaging, response assessment, and prognostic prediction of HIV-associated lymphoma.
● ^{18}F-FDG PET/CT is superior to contrast-enhanced CT for the initial staging of lymphoma, especially for detecting lesions with no or minor anatomical abnormalities.
● ^{18}F-FDG PET/CT imaging can effectively determine the location of undetected disease sites and map suspected disease during the initial staging of HIV-related BL.
● Functional and morphological information from integrated ^{18}F-FDG PET/CT improves malignancy diagnosis, staging, restaging, and treatment monitoring. However, it's difficult to distinguish benign from malignant lymph nodes by size, location, and enhancement mode.

ing. When using ^{18}F-FDG PET/CT for early detection of HIV-related lymphoma, the possibility of false-positive results owing to benign lymphadenopathy must be fully considered [14, 17]. In establishing the potential etiology of lymphadenopathy, valuable indicators include clinical manifestations, CD4 counts, radiological characteristics, and PET metabolic parameters. However, there are incredibly few ^{18}F-FDG PET/CT studies with small statistical populations available currently for the early staging of HIV-related lymphoma. More extensive sample sizes will be needed for future research [14]. A summary of the significance of ^{18}F-FDG PET/CT in HIV-related lymphoma staging and diagnosis is provided in **Table 1**.

Differentiating between benign lymphadenopathy and HIV-related lymphoma

Lymphadenopathies can be diagnosed using standard clinical imaging methods. Several imaging techniques, such as magnetic resonance imaging (MRI), CT scanning, and ultrasonography, can be utilized to establish whether the condition is tumor-related or inflammatory-related. While CT and MRI are used to assess cavitary lymphadenopathies, ultrasound is useful for identifying peripheral lymphadenopathies. However, considering the enhancement mode, size, and location, distinguishing benign lymph nodes from malignant lymph nodes remains difficult [18, 19].

Integrated ^{18}F-FDG PET/CT provides functional and morphological information in a single, noninvasive examination, making it a valuable instrument for malignancy detection, staging, and therapy monitoring. Additionally, this technology is extensively employed in the treatment of HIV-positive individuals who have lymphoma or are suspected of having the virus. In patients with AIDS, CT or MRI are unable to differentiate between primary cerebral lymphoma and toxoplasmosis, whereas ^{18}F-FDG PET/CT can make this distinction. According to a preliminary investigation by Mhlanga et al. [20], patients with HIV it may distinguish between reactive adenopathy and lymphoma using quantitative PET metabolic indicators like MTV and TLG.

Chen et al. [21] conducted a quantitative examination of ^{18}F-FDG PET/CT to identify a novel approach for identifying malignant lymphoma from inflammatory lymphadenopathy in HIV-infected people. The investigation focused on two parameters: the maximum standardized uptake value (SUVmax) of lymph nodes (referred to as SUV_{LN}) and the ratio of the greatest SUVmax of an FDG-avid lesion to the SUVmax of the liver (referred to as SURmax). This study evaluated 59 HIV-positive individuals, of whom 22 had inflammatory lymphadenopathy and 37 had lymphoma associated with HIV. Compared to inflammatory lymphadenopathy, malignant lymphoma colonized extralymphatic lesions more frequently (83.8% vs. 54.5%, P = 0.000). In particular, there was an obvious distinction between the two groups in terms of Waldeyer's ring and the implicated digestive tract lesions (P = 0.033 and 0.004, respectively). Additionally, compared to inflammatory lymphadenopathy, the SURmax, SUV_{LN}, SUV_{Marrow}, and SUV_{Liver} in malignant lymphoma were considerably greater (P = 0.000, 0.000, 0.002, and 0.017, respectively). The optimal balance of sensitivity (68.2%) and specificity (91.9%) was demonstrated by the SURmax cut-off point of 3.1, while the SUV_{LN} cut-off point of 8.0 also demonstrated strong specificity (89.2%) and quite acceptable sensitivity (63.6%). The maximum lymph node diameter of 3.6 centimeters and the number of affected areas cutoff point of 5 exhibited comparatively low specificity (72.7%, 86.4%, respectively) and sensitivity (62.2% and 64.9%, respectively).

In a second retrospective investigation, the ability of the quantitative PET indicators (MTV, TLG, SULmax, and SULpeak) to differentiate HIV-related lymphoma from reactive lymphadenopathy was investigated. Lymphoma patients demonstrated significantly higher quantitative PET measures than inflammatory lymphadenopathy patients (*p*-values = 0.001). The lymphoma could be distinguished from reactive lymphadenopathy with high specificity (100%, 100%) and sensitivity (89%, 84%, respectively) at the TLG and MTV cut-off values of 173 and 53.8, respectively. A SULpeak cutoff of 23.8 had an 84% sensitivity and a 95% specificity, whereas a SULmax cutoff of 28.5 had those values at 84% and 82%, respectively. Viral load and PET measurements showed a favorable

correlation in the group with reactive lymphadenopathy. Nevertheless, no PET parameter in the HIV-related lymphoma group exhibited a statistically significant association with the viral load. Asymmetrical FDG uptake demonstrated a 90.4% accuracy rate in the qualitative MIP symmetry score analysis of the lymph node involvement pattern in distinguishing lymphoma from reactive adenopathy in individuals with HIV [20].

In general, medical professionals who utilise ^{18}F-FDG PET/CT for the first screening of HIV-related lymphoma should take into full consideration the possibility of false positives resulting from benign lymphadenopathy. To make a reliable diagnosis, a combination of clinical characteristics, PET metabolic parameters, symmetry, and SUVs should be used. **Table 2** provides investigations that evaluated the diagnostic efficacy of ^{18}F-FDG PET/CT in differentiating between benign lymphadenopathy and HIV-related lymphoma. A summary of the differentiation of benign lymphadenopathy from HIV-related lymphoma is provided in **Table 3**.

Distinguishing primary central nervous system lymphoma from cerebral toxoplasmosis using ^{18}F-FDG PET/CT

The most prevalent diagnosis for an intracranial mass in HIV cases is primary central nervous system (CNS) lymphoma, followed closely by cerebral toxoplasmosis. An uncommon kind of extranodal NHL, primary CNS lymphoma affects 4-5 out of 1000 HIV-positive people. Approximately 35.8% of HIV-positive patients have a pooled prevalence of cerebral toxoplasmosis. Clinical differentiation between cerebral toxoplasmosis and primary CNS lymphoma is notoriously challenging due to their frequently overlapping symptoms and signs. It is essential to diagnose accurately and quickly due to the dire prognosis and potentially deadly consequences of misdiagnosis or delayed therapy. Cerebrospinal fluid (CSF) samples showing Epstein-Barr virus DNA and a negative toxoplasmosis serologic test are two laboratory markers that can help identify CNS lymphoma, although they cannot rule it out completely. In addition, conventional cross-sectional imaging methods sometimes fail to differentiate cerebral toxoplasmosis from CNS lymphoma. Recent research has shown that ^{18}F-FDG PET/CT may be useful in using imaging to distinguish between these two conditions. Nonetheless, a biopsy may be necessary for confirmation in 20% of HIV-positive individuals whose imaging and clinical signs are unclear. However, if the diagnosis is confirmed by imaging, clinical, and serologic data, histopathologic confirmation might not be required.

In an investigation of HIV cases, Westwood et al. [22] compared MRI findings of contrast-enhancing lesions to those of ^{18}F-FDG PET/CT brain scans. After administering the radiotracer, the FDG PET/CT were done one hour later. The researchers suspected primary CNS lymphoma based on elevated metabolic activity in locations correlating to enhanced lesions on MRI. Six of the ten HIV-positive individuals who also had contrast-enhancing lesions were diagnosed with cerebral toxoplasmosis because their metabolic activity did not significantly increase. CNS lymphoma was confirmed in two patients with elevated metabolic activity. A patient with hemorrhagic brain metastases and normal metabolic activity was among the two remaining patients; the other patient had ambiguous metabolic activity and was diagnosed with progressive multifocal leukoencephalopathy.

Further research by Hoffman et al. [23] demonstrated that primary CNS lymphoma had higher metabolic activity than nonmalignant disorders. In order to perform a qualitative measurement, the researchers devised the following criteria as a scoring system: a score of 1 stated metabolic activity inferior to that of the contralateral grey matter; a score of 2 indicated activity equivalent to that of the contralateral white matter; a score of 3 indicated activity intermediate between the contralateral white matter and grey matter; a score of 4 signified activity equivalent to that of the contralateral grey matter; and a score of 5 signified activity superior to that of the contralateral grey matter. For semiquantitative analysis, a region of interest (ROI) was delineated on the lesion as well as the corresponding homologous brain region on the contralateral side. A count ratio was then calculated by comparing the metabolic activity of the lesion to that of the contralateral homologous brain region. The results of both qualitative analysis (score 1 or 5 in lymphoma) and semiquantitative analysis (1.8 compared to 0.65, 0.70, and 1.3) revealed higher scores and values in cases of lymphoma compared to toxoplasmosis, syphilis, and progressive multifocal leukoencephalopathy ($P = 0.006$).

These results were corroborated by another semiquantitative analysis, which revealed that the SUV ratio of the contralateral lesion of the brain was lower in cases of cerebral toxoplasmosis or tuberculoma compared to primary CNS lymphoma ($P < 0.04$; SUV ratio, 0.3-0.7 vs. 1.7-3.1) [24]. Similarly, a semiquantitative assessment demonstrated a decrease in lesional uptake in cerebral toxoplasmosis when compared to the normal brain cortex (mean SUVmax: 3.5; range: 1.9-5.8). Conversely, individuals diagnosed with primary CNS lymphoma demonstrated greater uptake of radiotracers in the lesion as opposed to the healthy cerebral cortex (mean SUVmax: 18.8; range: 12.4-29.9) [25].

It is crucial to note that semiquantitative analysis equivalent to the methods mentioned above becomes difficult when the matching contralateral brain has naturally higher FDG uptake. However, it has been demonstrated that delayed ^{18}F-FDG PET/CT can effectively differentiate malignancy from inflammation or infection. In contrast to benign lesions or healthy tissues, malignant tumors exhibit a gradual increase in metabolic activity. This characteristic enhances background contrast and can achieve

Table 2. The diagnostic efficacies of ^{18}F-FDG PET/CT in differentiating HIV-related lymphoma from benign lymphadenopathy

Study	Year	Study type	Study population	Study groups		Parameters					
						SURmax	SUV_{LN}	SUV_{Marrow}	SUV_{Liver}	Number of lymph node involved areas	Maximum diameter of lymph nodes
Chen et al.	2022	Retrospective cross-sectional study	59	37 HIV-related lymphoma (35 B-cell lymphoma; 1 Hodgkin lymphoma; 1T-cell lymphoma)	22 HIV-infected patients with biopsy-proven inflammatory lymphadenopathy	AUC: 0.888 Cut-off: 3.1 Sensitivity: 68.2% Specificity: 91.9% *P*-value: 0.000*	AUC: 0.815 Cut-off: 8 Sensitivity: 63.6% Specificity: 89.2% *P*-value: 0.000*	AUC: 0.611 Cut-off: - Sensitivity: - Specificity: - *P*-value: 0.156	AUC: 0.567 Cut-off: - Sensitivity: - Specificity: - *P*-value: 0.393	AUC: 0.692 Cut-off: 5 Sensitivity: 62.2% Specificity: 72.7% *P*-value: 0.014*	AUC: 0.768 Cut-off: 3.6 Sensitivity: 64.9% Specificity: 86.4% *P*-value: 0.001*
						Single SULmax	TLG	Single SULpeak	MTV	Sum SULpeak	Sum SULmax
Mhlanga et al.	2014	Retrospective study	41	19 had biopsy-proven untreated lymphoma (16 DLBCL, 3 HL)	22 with reactive adenopathy without malignancy	AUC: 0.971 Cut-off: 7.8 Sensitivity: 89% Specificity: 100% PPV: 100% NPV: 92%	AUC: 0.964 Cut-off: 173 Sensitivity: 89% Specificity: 100% PPV: 100% NPV: 92%	AUC: 0.964 Cut-off: 6.6 Sensitivity: 84% Specificity: 100% PPV: 100% NPV: 88%	AUC: 0.957 Cut-off: 53.8 Sensitivity: 84% Specificity: 100% PPV: 100% NPV: 88%	AUC: 0.935 Cut-off: 23.8 Sensitivity: 84% Specificity: 95% PPV: 94% NPV: 88%	AUC: 0.904 Cut-off: 28.4 Sensitivity: 84% Specificity: 82% PPV: 80% NPV: 86%

*Data with statistically significant value (P < 0.05). PPV, positive predictive value; NPV, negative predictive value; AUC, area under the curve; DLBCL, diffuse large B-cell lymphoma; HL, Hodgkin's lymphoma; SUVmax, the maximum of standard uptake value; SURmax, liver SUVmax ratio; SUV_{LN}, SUVmax of only lymph nodes; SUL, SUV at lean body mass; SULmax, the maximum of SUL; SULpeak, the peak of SUL; TLG, total lesion glycolysis; MTV, metabolic tumor volume.

Table 3. Key points about the differentiation of benign lymphadenopathy from HIV-related lymphoma

Key points
● Conventional clinical imaging modalities such as MRI, ultrasound, and CT scans are used to diagnose lymphadenopathies.
● Ultrasound is a highly effective modality for the detection of peripheral lymphadenopathies, whereas cavitary lymphadenopathies are assessed using CT and MRI.
● Distinguishing benign lymph nodes from malignant ones solely based on feature enhancement mode, location, and size poses a significant challenge.
● Functional and morphological information are both acquired during an invasive ^{18}F-FDG PET/CT examination, which is a crucial instrument for monitoring treatment, diagnosing, staging, restaging, and assessing the progress of malignancies, especially in HIV cases with lymphoma and probable infection.
● Quantitative PET metabolic parameters, such as MTV and TLG, have been shown to be valuable in differentiating lymphoma from reactive adenopathy in HIV-infected patients.
● Specific clinical features and PET measurements (such as SUV_{LN} and SUVmax) can help differentiate between malignant lymphoma and inflammatory lymphadenopathy in HIV-positive individuals.

sensitivity measurements of up to 98% based on the specific lesion [26, 27].

The interim and baseline ^{18}F-FDG PET/CT prognostic values for HIV-related lymphoma

Lymphoma associated with HIV is managed using both baseline and interim ^{18}F-FDG PET/CT scans. Baseline ^{18}F-FDG PET/CT is performed before the start of treatment to assess the extent of the disease and to determine the baseline metabolic activity of the tumor. Interim ^{18}F-FDG PET/CT is performed during treatment, usually after two or three cycles of chemotherapy, to assess the response to therapy and to predict the prognosis of the patient [28].

Early response analysis and dependable staging of lymphoma have been accomplished with ^{18}F FDG-PET/CT imaging, enabling the development of more individualised therapies. Prior multicenter studies have established the effectiveness and feasibility of risk- and stage-adjusted care. In addition, as five-year survival rates for both HL and NHL have increased, attention has switched to decreasing treatment-related problems (such as additional malignant tumors and cardiovascular events). Quickly and reliably stratifying the risk of lymphoma in HIV-infected individuals can enhance the prognosis and reduce treatment complications [21, 29].

In solid tumors, SUV, MTV, and TLG on baseline PET can predict tumor aggressiveness and treatment response [30]. However, there is substantial inconsistency in the existing evidence on HIV-related lymphoma. In univariate analysis, Louarn et al. [31] discovered that all initial PET scan parameters were associated with progression-free survival (PFS). However, only high total metabolic tumor volume (MTV) revealed an independent connection with PFS in multivariate analysis (hazard ratio, 3.62). The researchers determined that a total MTV of 527 cm^3 is the optimal cutoff point for prognostic assessment. Patients with a total MTV of more than 527 cm^3 had a 2-year PFS of 71%, whereas those with a total MTV of 527 cm^3 or less had a 2-year PFS of 91%. With a *p*-value of 0.004, the difference between the two categories was statistically significant.

According to the findings of Lawal and colleagues [32], there were no significant differences in the SUVmax, MTV, or TLG values of lesions between the HIV-negative and HIV-positive groups. However, it should be noted that treatment failure of the ABVD regimen was significantly more prevalent among those with HIV infection in comparison to the non-HIV group (40.4 versus 17.7%, P = 0.0034). In the analysis, the only factor that significantly predicted treatment outcome was the patients' HIV status (P = 0.001). The treatment result was not predicted by the SUVmax, MTV, TLG, or Ann Arbor stages of the lesions. Furthermore, the results of a multiple logistic regression analysis indicated that treatment outcome could be significantly predicted by HIV status alone [overall rate (OR) = 2.930, 95% confidence interval (CI): 1.197-7.122, P = 0.023], when metabolic parameters and Ann Arbor stage were considered.

Another study by the same contributor corroborated these findings. Lawal et al. [33] investigated 160 cases diagnosed with HL, of whom 57 were HIV-infected. Patients infected with HIV exhibited marginally larger median values for SUVmean, SUVmax, TLG, and MTV. Nevertheless, no observable distinction could be made between the two categories. The only things that were significantly different between the two groups were serum albumin (< 4 g/dl) and male (non-HIV-infected group higher, P = 0.005). These were the only two of the seven International Prognostic Score (IPS) factors that are linked to a poor prognosis.

A retrospective investigation conducted on children diagnosed with HIV-related lymphoma found the same findings. According to Reed et al.'s study [34], HIV infection level as well as therapy response on PET were significant independent predictors of PFS (P = 0.036 and P = 0.001, respectively). Conversely, no metabolic characteristic was predictive of overall survival (OS) or PFS. The results of the adult trial showed that the total MTV at baseline was not a significant predictor of therapy response (P = 0.017).

Interim ^{18}F-FDG PET/CT has shown predictive value in both NHL and HL in the general population size: interim PET negative correlates with longer PFS, but persisting tumor avidity on PET after two to four cycles correlates with shorter PFS. Patients who are identified early as being at high risk of not responding well to standard treatment may benefit from a more intensive approach, which will ultimately improve survival and prognosis [35].

Nevertheless, research on the predictive usefulness of interim ^{18}F-FDG PET/CT in individuals with HIV-infected lymphoma is limited. Okosun et al. [36] found a negative interim PET was related to a longer PFS. This investigation included the participation of 23 individuals who were diagnosed with severe HIV-related HL. The Deauville criteria were utilised to assess the metabolic activity of lesions; lesions receiving a Deauville score ranging from 1 to 3 were classified as PET-negative. Patients who tested positive on interim PET had a 50% to 100% PFS rate at two years, whereas those who tested negative had a 100% PFS rate. This was determined after an average of 27 months of follow-up (log-rank P = 0.0012).

Minamimoto et al. [37] showed a similar correlation among interim PET data and overall survival. Twenty-four cases with HIV-related lymphoma (11 BL and 13 DLBCL) participated in this study via interim PET/CT. Interim PET findings were classified as "positive" in 10 of 24 cases and "negative" in the other cases. Interim PET-negative cases were associated with a considerably longer overall survival (932 ± 549 days) than positive cases (454 ± 442 days, P = 0.043). In contrast to the 29% (95% CI, 16%-41%) survival rate observed in positive cases, the aggregate two-year survival rate for negative results on interim PET was 80% (95% CI, 69%-91%). Additionally, the Eastern Cooperative Oncology Group performance status (hazard ratio 10.52, 95% CI 1.26-87.82, P = 0.03) and interim PET results (hazard ratio 4.57, 95% CI 0.88-23.73, P = 0.07) were found to be superior predictors of overall survival.

Danilov et al. [38] proved that response-adapted medicine based on interim PET was applicable in HIV-associated HL cases. According to Deauville criteria, 10 of 12 patients attained PET-negative status after two initial cycles of ABVD, whereas 2 of 12 remained PET-positive (Deauville scores 4 or 5). One patient with a positive PET result remained on ABVD treatment, while all other cases tested negative. A BEACOPP regimen consisting of six cycles of bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, and procarbazine was administered to the other patient who received a positive PET scan result. In conclusion, a partial response (PR) was observed in 25% of HIV-HL patients, while a complete response (CR) was observed in 75%. Two-year progression-free survival (PFS) was 83% (95% CI, 46.1%-95.3%) with an average of 39 months of follow-up, which was similar to that of patients without HIV associated HL in the same research (79% at 2 years) [39]. **Tables 4** and **5** summarize the prognostic predictions of baseline and interim ^{18}F-FDG PET/CT for HIV-related lymphoma, respectively.

The benefits and risks of ^{18}F-FDG PET/CT at the end of therapy

FDG-PET is particularly useful in identifying a CT-detected residual mass, which is a critical aspect of HL and NHL response examination at the end of therapy. It has been shown to be a valuable instrument for response assessment and therapy strategy in DLBCL and HL. The use of ^{18}F-FDG PET/CT at the end of therapy has been found to be predictive of outcome in HL, and it can help determine the optimal treatment approach for patients with limited stage HL who are PET-positive after chemotherapy [40, 41]. FDG-PET at the end of the therapy for DLBCL can assist in identifying patients who might gain an advantage from more intensive treatment. Following the end result of the intended treatment, viable tumour cells can be distinguished from fibrosis or necrosis using an ^{18}F-FDG-PET/CT scan [14]. The German Hodgkin Study Group (GHSG) HD15 trial enrolled 2182 HL patients. Only those with a post-chemotherapy residual mass ≥ 2.5 cm in contrast-enhanced CT and focal FDG uptake in end-of-treatment PET received 30 Gy of additional radiotherapy, while those without a residual mass or a negative PET did not [42]. A negative end-of-treatment PET was defined by IHPC criteria as a residual FDG uptake no higher than the surrounding background or a residual mass with a diameter ≥ 2 cm no higher than the mediastinal blood pool [43]. Of 739 cases with a residual mass ≥ 2.5, 191 (26%) had a positive PET scan. Patients receiving consolidation radiotherapy decreased from 71% in the HD 9 trial to 11% due to the high NPV of 94.1% at 12 months (95% CI 92.1-96.1) [42]. Patients who had contrast-enhanced CT partial remission and PET-negative residual mass after treatment had the same 4-year PFS rate of 92.1% as those who did not have residual mass. ^{18}F-FDG PET/CT evaluation additionally demonstrated that patients who received consolidative radiotherapy after receiving a positive end-of-treatment PET had a poorer prognosis than those who received chemotherapy alone without radiotherapy and had a PET-negative residual mass (86.2% versus 92.6% at 48 months). At the end of treatment, the Deauville 5-point scale is utilized to evaluate the various degrees of response that have occurred. Complete metabolic remission is indicated by a Deauville score between 1 and 3, while residual condition is characterized by a score between 4 and 5 [40, 42].

Although functional imaging with ^{18}F-FDG PET/CT is a useful tool for evaluating treatment response and interpreting post-chemotherapy residual masses in HL patients, it has limitations. False positive results, particularly during check point inhibitors treatment, can occur due to post-chemotherapy thymus hyperplasia and persistent FDG uptake in lymph nodes not related to HL. PET-positive residual lymph nodes in the mediastinum after treatment for HL do not always indicate persisting HL, and further

Table 4. The prognostic predictions of baseline ^{18}F-FDG PET/CT for HIV-related lymphoma

Study	Year	Study type	Study population	Lymphoma's subtype	Parameters									
Louarn et al.	2022	Retrospective study	109, HIV (+)	HL		Total MTV		TLG		SUVmax		SUVmean		SUVpeak	
					Cut-off value	≤527	>527	≤230	>230	≤8.7	>8.7	≤5.1	>5.1	≤7.1	>7.1
					AUC	0.60	-	0.59	-	0.55	-	0.53	-	0.55	-
					P-value	0.004*	-	-	-	-	-	-	-	-	-
					Complete remission	87%	-	-	-	-	-	-	-	-	-
					Survival rate (%)	2-year PFS 91 5-year OS 89.1	2-year PFS 71 5-year OS 69.4	5-year OS 96.0	5-year OS 82.9	5-year OS 94.4	5-year OS 81.1	5-year OS 94.3	5-year OS 81.1	5-year OS 94.6	5-year OS 80.8
Lawal et al.	2017	Prospective study	136, 57 with HIV (+)	HL		MTV		TLG		SUVmax					
					P-value	0.589		0.460		0.087					
Lawal	2018	Retrospective study	160, 57 with HIV (+)	HL		MTV		TLG		SUVmax		SUVmean			
					P-value	0.766		0.965		0.401		0.056			
						MTV		TLG		SUVmax		Total MTV			
Reed et al.	2021	Retrospective study	69, 13 with HIV (+)	HL	*P*-value	0.065		0.099		0.379		<0.001*			

*Data with statistically significant value (P < 0.05). AUC, area under the curve; HL, Hodgkin's lymphoma; SUV, standard uptake value; SUVmax, the maximum of SUV; SUVmean, the mean of SUV; MTV, metabolic tumor volume; TLG, total lesion glycolysis; PFS, progression-free survival; OS, overall survival.

Table 5. The prognostic predictions of interim ^{18}F-FDG PET/CT for HIV-related lymphoma

Study	Year	Study type	Study population	Lymphoma's subtype	Parameters		
Okosun et al.	2012	Retrospective study	23, HIV (+)	HL		PET (-)	PET (+)
					P-value	0.0012*	-
					Complete remission	96%	-
					Survival rate (%)	2-year PFS 100	2-year PFS 50
Minamimoto et al.	2013	Retrospective study	24, HIV (+)	13 DLBCL, 11 BL		PET (-)	PET (+)
					P-value	0.043*	-
					Complete remission		
					Survival rate (%)	2-year OS 80	2-year OS 29
Danilov et al.	2017	Phase II trial	12, HIV (+)	HL		PET (-)	PET (+)
					P-value	-	-
					Complete remission	75%	
					Survival rate (%)	2-year PFS 83	

*Data with statistically significant value ($P < 0.05$). AUC, area under the curve; HL, Hodgkin's lymphoma; DLBCL, diffuse large B-cell lymphoma; BL, Burkitt's lymphoma; SUV, standard uptake value; SUVmax, the maximum of SUV; SUVmean, the mean of SUV; MTV, metabolic tumor volume; TLG, total lesion glycolysis; PFS, progression-free survival; OS, overall survival.

follow-up or biopsy may be necessary [44]. Dual-point PET imaging, involving two scans performed at different time intervals after FDG injection, can help differentiate neoplastic tissue from inflammatory tissue in post-chemotherapy residual masses. The integration of imaging studies with emerging methodologies such as radiomics or tumor-associated cell-free DNA has the potential to enhance the understanding of residual mass subsequent to chemotherapy in HL [40, 45].

The role of ^{18}F-FDG PET/CT in surveillance of relapsed/refractory HIV-related lymphoma

Refractory or relapsed HIV lymphomas have been associated with poor outcomes. Almost 10%-20% of individuals with early-stage HL experience relapses following first-line therapy, while 30%-40% of patients with advanced-stage HL experience relapses [46]. A comprehensive retrospective investigation involving 254 patients who obtained a full response with the first treatment found an 11% relapse rate in DLBCL, BL, and PBLs [47]. The released studies on relapsed HIV-related lymphoma are limited. As a result, it is currently unclear whether or not FDG PET is useful for post-treatment observation in the general population.

In a prospective investigation, ^{18}F-FDG PET/CT correctly identified relapsed or refractory disease in 5 individuals while six patients had false-positive findings [48]. Several other studies agreed with these findings. The average positive predictive value (PPV) of PET was 28% in a retrospective research of 161 cases with HL, while the negative predictive value (NPV) was 100% [49]. PET exhibited an 85% PPV in an analysis of 75 DLBCL cases, nevertheless, its utility was confined to high-risk individuals who presented with recurrence symptoms and were aged 60 years or older [13].

Thus, there is a lack of data to support routinely recommending PET for lymphoma patients as a surveillance method. ^{18}F-FDG PET/CT should only be used on individuals who have a high risk of recurrence in order to minimize radiation exposure and related expenses [50].

The pitfalls of ^{18}F-FDG PET in diagnosing and monitoring HIV/AIDS-associated lymphomas

There are benefits and drawbacks to utilising ^{18}F-FDG PET for the detection and monitoring of lymphomas associated with HIV/AIDS. In HIV-positive patients with cerebral lesions, ^{18}F-FDG PET/CT has been shown to be helpful in determining glucose metabolism, assisting in the diagnosis work-up of HIV-related diseases, and distinguishing between infection and malignant causes. Nevertheless, a research investigation also noted a reduction in the absorption of ^{18}F-FDG among patients living with HIV, specifically those who also used cocaine; this suggests possible restrictions in specific conditions. Furthermore, there are certain limitations associated with the use of ^{18}F-FDG PET to diagnose lymphomas related to HIV/AIDS. These include challenges in differentiating benign from malignant lymph nodes, potential confounding variables including elevated viral loads and low CD4 counts, and the influence of HIV-associated reactive changes on the interpretation of FDG-PET outcomes in HIV cases.

These limitations highlight the importance of careful assessment and additional diagnostic techniques when evaluating HIV/AIDS-associated lymphomas with ^{18}F-FDG PET.

Conclusion

In conclusion, ^{18}F-FDG PET/CT has proven to be a useful tool for the management of HIV-related lymphoma. Its

capacity to appropriately stage the disease, measure therapy response, and evaluate long-term follow-up makes it an essential component of the multidisciplinary treatment approach for this complex condition. In individuals with HIV-related lymphoma, ^{18}F-FDG PET/CT improves patient outcomes by guiding treatment decisions, optimizing therapy, and enhancing anatomical localization.

Despite this, the majority of the investigations that were accessible were retrospective studies conducted at a single center and utilized small sample sizes. In addition, the PPV of PET imaging will increase, and additional lesion characteristics will be made available by the accelerated development of radiomics and PET/MR imaging. Prospective, multicenter studies with large sample numbers are needed to evaluate novel PET imaging radiotracers for HIV-related lymphoma, such as 68Ga-FAPI and immuno PET biomarkers.

Disclosure of conflict of interest

None.

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