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Continuing education

^{18}F-FDG-PET/CT in lymphoma: Two decades of experience☆

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ABSTRACT

The use of ^{18}F-FDG-PET/CT has changed the management of patients with lymphoma for the last two decades. This technique improves initial staging of the disease, making a prognostic approach and appropriate treatment planning, as well as monitoring therapy response of lymphoma. However, there are still controversial issues in medical literature that impact on daily clinical practice. This comprehensive literature review summarizes the current information regarding the potential use of ^{18}F-FDG-PET/CT in patients with lymphoma, highlighting the main applications and the current dilemmas for the nuclear medicine physicians at the time of the evaluation of these studies, trying to standardize criteria for its assessment, particularly in restaging and therapy monitoring.

^{18}F-FDG-PET/TC en linfoma: dos décadas de experiencia

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RESUMEN

El uso del ^{18}F-FDG-PET/TC ha introducido cambios relevantes en el manejo de los pacientes con linfoma en las últimas dos décadas. Esta técnica de imagen funcional permite mejorar la estadificación inicial de la enfermedad, realizar una aproximación pronóstica y planificar un tratamiento adecuado, monitorizar la respuesta a las terapias instauradas y hacer un seguimiento para el diagnóstico de recidiva y reestadificación del linfoma. Sin embargo, aún existen controversias sobre el tema en la literatura médica que repercuten en la práctica diaria. Esta profunda revisión bibliográfica resume la información actual sobre el uso potencial de ^{18}F-FDG-PET/TC en pacientes con linfoma, destacando sus principales aplicaciones y los dilemas que se presentan al evaluar este tipo de estudios, intentando estandarizar criterios para su valoración, particularmente en la reestadificación y monitorización de la terapia.

Introduction

Lymphomas make up a heterogeneous group of neoplastic diseases of lymphocytary origin. These malignant lymphoproliferative processes are clonal B-cell, T-cell or natural killer (NK) cells tumors in different stages of differentiation.

Lymphomas represent 6% of all neoplasms and are responsible for 3% of the mortality by oncological processes.[1] The incidence of lymphomas in Spain is up to 4% each year, with around 6000 new cases being diagnosed annually, mostly non-Hodgkin lymphomas (NHL). This growing incidence is attributable to the increase in situations of immunosuppression [human immunodeficiency virus (HIV), organ transplantation], an oncogenic effect associated with different viral infections [Epstein–Barr virus (EBV), hepatitis C virus (HCV)], environmental changes (antibiotics, chemical agents, vaccines, radiations), etc. together with a longer life expectancy and subsequent ageing of the population at risk.[2–5] Lymphomas are somewhat more frequent in men than in women and more common in 2 age groups: from 15 to 40 years of age (being more frequent between 25 and 30 years) and after the age of 55 years.

Thomas Hodgkin published the first description of lymphoma in 1832, specifically in the form with his name, Hodgkin's lymphoma (HL).[6] In the following 50 years, Virchow, Cohnheim and Billroth, defined other lymphomas different from HL, originally being called lymphosarcomas. Since then many other forms of lymphoma have been described and different classifications have been proposed based on morphological criteria.[7–11] In 1994, the International Study Group of lymphoma established a consensus in the classification based on morphology and immunological, molecular and genetic techniques in an attempt to obtain an internationally accepted classification: the Real European-American Classification of Lymphoid Neoplasms (REAL). This classification was adapted by the World Health Organization (WHO) in 1997, with modifications and updates being made in 2001 and 2008. The WHO classification of 2008, which was based on the previous REAL classification of 1994, is currently recognized worldwide as having a high grade of precision and consensus in the diagnosis of the different varieties of lymphoma, defining the entities according to their histology, on

Abbreviations: ABVD, adriamycin, bleomycin, vinblastine, dacarbazine; BEACOPP, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine and prednisone; NK cells, natural killer cells; REAL classification, Real European-American Classification of Lymphoid Neoplasms; HD, Hodgkin's disease; MCL, mantle cell lymphoma; FL, follicular lymphoma; NHL, non-Hodgkin lymphoma; DLBCL, diffuse large B-cell lymphoma; MRU, minimal residual uptake; NCCN, National Comprehensive Cancer Network; WHO, World Health Organization; ChT, chemotherapy; R-CHOP, rituximab associated with cyclophosphamide, doxorubicin, vincristine and prednisone; RDT, radiotherapy; CT, computed tomography; EBV, Epstein–Barr virus; HCC, hepatitis C virus; HIV, human immunodeficiency virus.

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Table 1
The WHO classification of lymphomas (Jaffe[11]).

Mature B-cell neoplasms	Mature T and NK cell neoplasms	Hodgkin's disease
Chronic lymphocytic leukemia/well differentiated lymphocytic leukemia prolymphocytic leukemia	Prolymphocytic T-cell leukemia	Hodgkin's lymphoma Nodular lymphoma of lymphocytic predominance
Splenic marginal lymphoma (villous lymphocytes)	T-cell leukemia with large granular lymphocytes	Classical Hodgkin's lymphoma Nodular sclerosis
Hairy cell leukemia	Chronic lymphoproliferative NK cell disease	Mixed cellularity
Unclassifiable splenic lymphoma/leukemia	Aggressive NK cell leukemia	Rich in lymphocytes
Lymphoplasmacytic lymphoma	Lymphoproliferative systemic T-cell disease	Lymphoid depletion
Waldenström macroglobulinemia	Vacciniforme-like lymphoma	**Post-transplant lymphoproliferative disease (PTLD)**
Heavy chain disease	Adult T-cell leukemia/lymphoma	Early lesions
Myeloma	Extranodal NK/T-cell lymphoma (nasal)	Plasmacytic hyperplasia
Solitary osseous plasmocytoma	T-cell lymphoma associated with enteropathy	Infectious PTLD mononucleosis-like
Extraosseous plasmocytoma	Hepatosplenic T-cell lymphoma	Polymorphic PTLD
Marginal zone extranodal lymphoma (MALT)	T-cell lymphoma	Monomorphic PTLD
Marginal zone nodal lymphoma	Subcutaneous panniculitis	Classical Hodgkin-type lymphoma
Follicular lymphoma	Fungoid mycosis	
Primary cutaneous centrofollicular lymphoma	Sezary's syndrome	
Mantle cell lymphoma	Primary cutaneous Cd30+ lymphoproliferative	
Diffuse non-specified large B-cell lymphoma	T-cell disease	
Lymphomatoid granulomatosis	Primary cutaneous gamma-delta T-cell lymphoma	
Primary mediastinal (thymic) large B-cell lymphoma	Primary aggressive cytotoxic epidermotropic cutaneous Cd8+ lymphoma	
Large intravascular cell and large B-cell Alk+ lymphoma	Primary cutaneous Cd4+ small/medium T-cell lymphoma	
Plasmablastic lymphoma	Peripheral non-specific angioimmunoblastic T-cell lymphoma	
Large B-cell lymphoma in multicentric Castleman's disease	T-cell lymphoma	
Primary effusion lymphoma (Body cavity lymphoma)	Large cell Alk+ anaplastic lymphoma	
Burkitt's lymphoma	Large cell Alk-anaplastic lymphoma	

the clinical basis, and immunophenotype and genetics into 4 large groups by cell types (Table 1).

There are important differences among the principal types of lymphoma. Hodgkin's disease (HD) is characterized by the presence of a tumor mass formed by inflammatory cells including malignant cells (Reed–Sternberg cells) and presents a pattern of dissemination by continuity, with infrequent extra lymph node involvement. The origin of NHL is in the B- or T-cells. Extra-lymphatic involvement is much more frequent than in HD and the lymph node dissemination is "more disorderly", often compromising peripheral lymph nodes (inguinal, axillary). The definitive diagnosis of malignancy and classification of the different subtypes is based on meticulous interpretation of the preparation obtained of the biopsied tissue.[12]

Positron emission tomography and its application in lymphomas

PET as a diagnostic imaging technique that demonstrates changes in tissular metabolic activity has shown to be a very useful tool in the evaluation of this type of tumors. Since its introduction in the clinical setting to the current use of hybrid PET/CT equipment its use has significantly modified the management of patients with lymphoma. The information provided by this technique allows improvement in the initial staging, determination of the prognosis and the planning of an adequate treatment, monitoring the response to the therapy implemented and carrying out the follow-up to diagnose recurrence and restaging of lymphoma.[13,14] Thus, in 2007, a report by the National Comprehensive Cancer Network (NCCN) already mentioned that ^{18}F-FDG-PET/CT may be used to evaluate lymphomas in up to more than 50% of the total number of studies performed in reference institutions.[15] The radiotracer most commonly used, ^{18}F-FDG, allows evaluation of lymphoproliferative processes, obtaining images and quantifying the glycolytic metabolism within the tumor cell. However, it is known that the "avidity" of FDG by the tumor cells varies due to the different grades of malignancy and proliferative activity of each histological subtype, especially in NHL (Table 2). A direct relationship has been reported between the grade of malignancy and FDG uptake, with the consequent lower diagnostic yield of PET in indolent or low grade lymphomas.[16–18]

Table 2
The uptake of ^{18}F-FDG-PET/CT of the different subtypes of lymphoma.

Type of lymphoma	% Patients with uptake	Uptake intensity
Hodgkin's disease		
Classical HD	100	High
Nodular HD with lymphocytic predominance	100	Moderate–high
Aggressive NHL		
Diffuse large B-cell lyphomas	97	Moderate–high
Burkitt's lymphoma	100	High
Peripheral T-cell lymphoma	90	Low–high
Anaplastic large cell lymphoma	100	High
Mantle cell lymphoma	100	Moderate
Indolent NHL		
Follicular lymphoma [a]	95[a]	Low–high[a]
Lymphoplasmocytic lymphoma	100	Low–moderate
Marginal zone nodal lymphoma	100	Null–high
Marginal zone extranodal lymphoma (MALT)	54	Null–high
Small cell lymphocytic lymphoma	83	Null–high
Cutaneous T-cell lymphoma	40	Null–moderate

Modified from Refs. 16–18.

[a] Take the cytological grade of follicular NHL into account, grade III follicular NHL is considered as aggressive, presenting moderate–high avidity for FDG. However, grades I and II (considered to be indolent) present low–moderate uptake.

Lymphoma staging by PET/CT

The strategy of the initial treatment in patients with lymphoma is based on the determination of the histological subtype, pre-treatment identification of risk factors and precise disease staging. Staging of the lymphoproliferative process has classically been carried out based on bone marrow biopsy and CT with intravenous contrast. However, in the last decade, ^{18}F-FDG-PET/CT has