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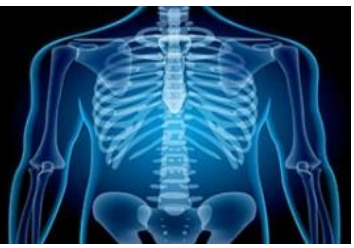

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Role of novel PET-CT Metabolic Measures Total Lesion Glycolysis (TLG) and Total Metabolic Tumour Volume (TMTV) in prediction of treatment response in lymphoma patients

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Abstract
FDG-PET/CT is the current state-of-the-art imaging in lymphoma and plays a central role in treatment decisions. FDG-PET/CT can identify areas of lymphoma missed by CT alone and avoid under-treatment of patients with advanced disease stage who would have been misclassified as having limited stage disease by CT. Particularly in Hodgkin lymphoma, positive interim FDG-PET/CT scans are adversely prognostic for clinical outcomes and can inform PET-adapted treatment strategies, but such data are less consistent in diffuse large B-cell lymphoma. The use of quantitative FDG-PET/CT metrics using metabolic tumour volume, possibly in combination with other biomarkers, may better define prognostic subgroups and thus facilitate better treatment selection. After chemotherapy, FDG-PET/CT response is predictive of outcome and may identify a subgroup who benefit from consolidative radiotherapy. Novel therapies, in particular immunotherapies, exhibit different response patterns than conventional chemotherapy, which has led to modified response criteria that take into account the risk of transient pseudo-progression. In relapsed lymphoma, FDG-PET/CT after second-line therapy and prior to high-dose therapy is also strongly associated with outcome and may be used to guide intensity of salvage therapy in relapsed Hodgkin lymphoma. Currently, FDG-PET/CT has no role in the routine follow-up after complete metabolic response to therapy, but it remains a powerful tool for excluding relapse if patients develop clinical features suggestive of disease relapse.
This review article aims to determine the role of novel PET-CT metabolic measures total lesion glycolysis and total metabolic tumour volume in prediction of management response in lymphoma patients.

Keywords: TLG, TMTV, lymphoma patients, treatment response, disease relapse

Introduction

PET/CT

Fluorine-18-fluorodeoxyglucose (FDG) positron emission tomography (PET) is a functional molecular imaging technique which employs increased glycolysis of cancer cells to visualise both structural and metabolic data. Integrating 18F-FDG-PET with computed tomography (CT) provides precise anatomical site and structural details for the lesion [1].

Principles of FDG production

PET imaging is based on detecting annihilation photons that result from the interaction between positrons, emitted by radionuclides such as 18F, and electrons in tissue. This interaction generates two photons, each with energy of 511 keV, which are captured by the PET scanner. The energy value of 511 keV corresponds to the electron's mass-energy equivalence, as described by the conservation of energy law (Figure 1) [2].

Tumor physiology and FDG uptake

Malignant tumors are characterized by rapid growth, local invasion, and metastasis, which are facilitated by growth factors and angiogenesis promoters. Tumor cells take up glucose through facilitated transport, which undergoes glycolysis to meet their high energy demands.

FDG, an analogue of glucose, is taken up by active tumor cells and becomes trapped due to its inability to undergo further metabolism. This uptake can be quantified using the standardized uptake value (SUV), which reflects the degree of FDG accumulation within a region of interest [4].

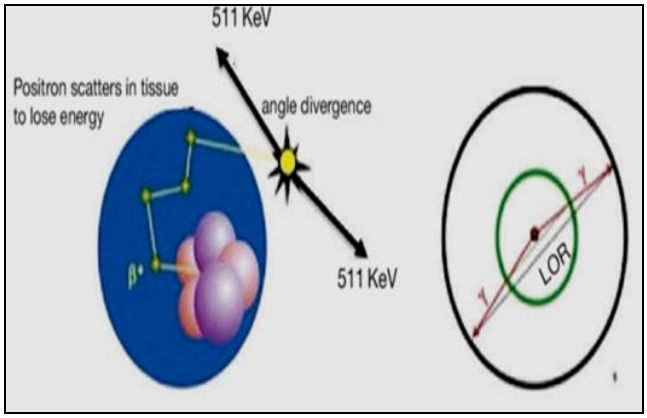

Fig 1: Annihilation coincidence detection (ACD). When a positron is emitted by a nuclear transformation, it scatters via matter, losing energy before annihilating with an electron, producing two 511-keV photons emitted in nearly opposite directions (left). When two interactions are detected concurrently within a ring of detectors encompassing the patient (right), it is assumed that annihilation occurred on the line connecting the interactions (line of response, LOR). ACD serves as a collimator for the positron emission tomography (PET) scanner (electronic collimation) by assessing the path of identified photons [3].

Lymphoma

Lymphomas are a diverse group of malignancies caused by excessive cell proliferation in the lymphatic system. They make an important contribution in the area of oncology. These cancers include a variety of tumours derived from lymphoid cells, such as B-cell, T-cell, and natural killer (NK)-cell lymphomas, as well as Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). The World Health Organisation has classified about ninety subtypes and core types of lymphoma [5].

While both NHL and HL are classified as lymphoma, they differ in surface protein expression, histologic appearance, cell of origin, clinical evolution, response to treatment, and other characteristics. These variations provide significant understanding into lymphoma's natural biology, as well as potential diagnostic and therapeutic markers [6].

Hodgkin Lymphoma (HL)

Biological and clinical research had classified this disease into two types: classical Hodgkin lymphoma and nodular lymphocyte-predominant Hodgkin lymphoma (NLP-HL). The clinical and pathological characteristics of these two diseases differ. Classical Hodgkin lymphoma makes up around 95 percent of all HL and is further classified into four subgroups: nodular sclerosis (NSHL), lymphocyte-rich (LRHL), mixed cellularity (MCHL), and lymphocyte-depleted (LDHL). Hodgkin lymphoma has distinguishing features. They commonly appear in the cervical lymph nodes; the disease is more common in young adults; there are scattered large mononuclear Hodgkin and multinucleated cells (Reed-Sternberg) intermixed in a background of non-neoplastic inflammatory cells; and finally, T lymphocytes are frequently seen surrounding the characteristic neoplastic cells [7].

Non-Hodgkin lymphoma (NHL)

Non-Hodgkin lymphoma (NHL) is a group of malignant lymphoproliferative problems that primarily affect lymph nodes and exhibit a wide range of clinical and histological features [8].

Nodal lymphoma

Cervical lymphadenopathy is the most common head and neck presentation of NHL, characterised by numerous painless nodes. These lesions are not as hard as metastatic nodules and do not adhere to the skin or deep planes. NHL spreads more frequently to non-contiguous nodes. Mediastinal engagement is uncommon, whereas abdominal involvement is more prevalent [9].

Extranodal lymphoma

Extranodal lymphoma develops through an array of mechanisms, such as genetic changes, immune dysregulation, and infections caused by viruses. Extranodal lymphoma is primarily caused by viral infections, such as hepatitis B and C, the Epstein-Bar. Extranodal lymphoma of B-cell, T-cell, and NK-cell origin exhibits a wide range of pathogenesis. The precise mechanism of development of extranodal lymphoma is still being investigated, but it is thought to be an intricate combination of genetic and environmental variables [10].

Current role of FDG-PET/CT in lymphoma management

FDG-PET/CT has demonstrated superior diagnostic performance to CT, particularly for extranodal involvement, because this functional imaging can identify tumour lesions with high glucose metabolism when no significant deviations are detected by CT. This resulted in treatment modifications in several cases where FDG-PET/CT was used to upstage lymphoma patients **[11]**

Positron emission tomography combined with computed tomography using [18F]-fluorodeoxyglucose (18F-FDG PET/CT) is commonly used as a noninvasive three-dimensional imaging technique in the treatment of lymphoma patients. In lymphoma patients, 18F-FDG PET/CT has a variety of clues, involving first staging before treatment, re-staging, assessment after treatment, therapy monitoring of progress, post-therapy follow-up, and disease transformation assessment. However, it is important to recognise that this technology has limitations, involving variances in FDG avidity between multiple lymphoma subtypes, as well as the possibility of false-negative and false-positive results [12].

The evaluation of bone marrow infiltration in lymphomas has a significant impact on prognosis and therapeutic management. Bone marrow biopsy (BMB) has long been considered the gold standard for this assessment. At the same time, 18F-FDG-PET has been recognised as a significant lymphoma staging tool and could potentially be used as a non-invasive BMB substitute or replacement. Permanent research and arguments continue regarding the clinical use of 18F-FDG-PET to assess BMI in lymphomas. To identify BMI in lymphoma patients, radiomic features extracted from 18F-FDG PET/CT images offer a further aid for visual evaluation [13].

Radiomics is a rapidly growing research field that focusses on quantitatively extracting features from medical images and converting them into rich, high-dimensional data. The

artificial intelligence (AI) learning process begins with data collection and preprocessing, and then progresses to feature extraction, model training, and evaluation. The analysis of these data yields novel biological insights, which improve understanding of disease processes and aid in clinical decision-making. In addition, 18F-FDG PET/CT radiomics improves diagnosis, allows for the development of personalised therapies, and refines outcome predictions based on factors such as tumour heterogeneity and lymphoma's biological, pathological, and metabolic characteristics. This non-invasive approach has received a lot of attention in the clinical setting due to its versatility [14].

TLG and MTV in evaluation and risk assessment at diagnosis in Hodgkin lymphoma

Hodgkin lymphoma (HL) is a haematological cancer characterised by malignant cells, known as Reed-Sternberg cells (RSC), which are enclosed by an inflammatory microenvironment of reactive cells. Traditional approaches cure a large number of patients, but about 15-30% relapse or progress. The Ann Arbour (AA) staging system is the standard tool for assessing disease burden. It categorises HL in I to IV stages based on the number of influenced lymph nodes and/or extranodal sites, their position relative to the diaphragm, and the existence or lack of B symptoms. Nevertheless, AA staging does not reliably forecast outcomes. Total lesion glycolysis (TLG) is the most effective single PET/CT-related tumor-load variable that substantially enhances HL risk evaluation if contrasted with AA staging [15]. New ways to assess tumor burden, such as baseline fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT), detect active disease with higher sensitivity in comparison with computed tomography (CT). Standardized uptake value (SUV) is the most frequent semiquantitative PET metric used for measuring tumor glucose metabolism. It is defined as the ratio of the decay-corrected FDG concentration in a volume of interest (VOI) to the injected dose normalized to the patient's body weight. SUVmax is defined as the maximum value of SUV in a VOI representing the highest metabolism in the tumor, and it is commonly used in response criteria in PET scans after treatment in oncology [16]. Metabolic tumor volume (MTV) and total lesion glycolysis (TLG) are volume-based PET parameters, and they reflect tumor biology. MTV represents the volume (mL or cm3) resulting from the sum of the metabolic volume of each tumor tissue with increased threshold FDG uptake. TLG is defined as the product of the average SUV (SUVmean) of the total tumor multiplied by the corresponding MTV; it represents both the tumor size and the extent of FDG uptake and is representative of the metabolic activity throughout the entire tumor (including both RSC and its inflammatory microenvironment) [17].

Until now, many researches had described a prognostic role of these parameters in non-Hodgkin lymphoma (NHL) and HL, some of them comparing PET-based assessment with standard AA staging and the specific prognostic indexes. However, current standard tools to assess HL tumor burden and prognosis at diagnosis are still based only on AA staging [18].

FDG PET/CT in non-Hodgkin's lymphoma (NHL)

FDG PET/CT is critical for outcome prediction and prognosis. The only difference in NHL is that some histological subtypes do not effectively express FDG avidity. Indolent NHL had variable FDG avid NHL, whereas aggressive NHL have moderate to high FDG avidity (Table 1). As a result, the incorporation of FDG PET/CT is most widely recognised in the evaluation of aggressive NHL [19].

Table 1: Status and degree of FDG avidity in each type and subtype of Lymphoma [20]

Category	Subtype of Lymphoma	FDG Avidity	Degree of FDG Avidity
HL [1]	Classical	Avid	High
	Mixed cellularity	Avid	Moderate to high
	Lymphocyte depletion	Avid	Moderate to high
	Lymphocyte predominance	Avid	Moderate
Aggressive NHL [2]	Diffuse large B-cell	Avid	High
	Burkitt	Avid	High
	Anaplastic Large cell	Avid	High
	Mantle Cell	Avid	Moderate
Indolent NHL [2]	Follicular	Variable	Low-high
	Lymphoplasmacytic	Variable	Low-high
	Marginal zone	Variable	None-high
	Small lymphocytic	Variable	None-high
	Cutaneous Anaplastic	Variable	None-moderate

HL1: Hodgkin's Lymphoma; NHL2: Non-Hodgkin's Lymphoma.

Conclusion

FDG-PET/CT stands as the main imaging modality in lymphoma. Compared to computed tomography, FDG-PET/CT improves staging and end of treatment evaluation, including improved residual mass evaluation by discriminating between fibrosis and remaining disease. The identification of pathways or specific receptors in lymphomas has enabled the development of new radiopharmaceuticals providing great opportunities for molecular imaging in treatment evaluation and management. It is unclear whether these radionuclide probes besides FDG will have a part to play in clinical routine diagnostics. However, the tendency for very advanced treatments, which depend on the genetic and phenotypic composition of lymphoma cells, provides exciting opportunities for nuclear medicine in the context of immunotherapy and personalized medicine. Ultimately, molecular imaging could lead to greater cost-effectiveness by allowing candidate selection for expensive targeted therapies, among which CXCR4 is a serious candidate. Other new tracers, such as FAPI, could be used in addition to FDG-PET/CT imaging, specifically in indolent lymphoma patients [1].

Conflict of Interest
Not available

Financial Support
Not available

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