

Application of the PET-CT method in the diagnosis and staging of chronic lymphocytic leukemia

Uso do método PET-CT no diagnóstico e estadiamento da Leucemia linfocítica crônica

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ABSTRACT

Positron Emission Tomography (PET) combined with anatomical structural images from Computed Tomography (CT) is a technique belonging to nuclear medicine that consists of the morphofunctional evaluation, through the quantification of the cellular uptake of glucose analog molecules linked to radioactive compounds (18F-fluorodeoxyglucose), which represents the avidity glycolytic metabolism by the, tissues including neoplastic processes. In turn, the method can offer a great contribution in the differential diagnosis and staging of chronic lymphocytic leukemia (CLL), whose disease is characterized by the proliferation of type B lymphocytes in lymphoid tissues, bone marrow and peripheral blood. The objective of the study is to indicate the benefits of the PET-CT technique in the early detection of CLL and its respective staging, through a systematic literature review of a qualitative nature, using the databases SciELO e PubMed, whose triage of the articles was carried out using of the PRISMA protocol. PET-CT plays an essential role in the diagnosis of CLL and assessment of the potential for transforming the disease into Richer Syndrome, with a poor prognosis and the need to apply aggressive therapies.

Keywords: Chronic Lymphocytic Leukemia; PET-CT; 18F-FDG

RESUMO

A Tomografia por Emissão de Pósitrons (PET) combinada com imagens estruturais anatômicas de Tomografia Computadorizada (TC) é uma técnica pertencente à medicina nuclear que consiste na avaliação morfofuncional, através da quantificação da captação celular de moléculas análogas à glicose ligadas a compostos radioativos (18F-fluorodesoxiglicose), que representa o metabolismo glicolítico de avidez pelos tecidos, incluindo processos neoplásicos. Por sua vez, o método pode oferecer contribuição no diagnóstico diferencial e estadiamento da leucemia linfocítica crônica (LLC), cuja doença caracteriza-se pela proliferação de linfócitos do tipo B nos tecidos linfóides, medula óssea e sangue periférico. O objetivo do estudo é apontar os benefícios da técnica de PET-CT na detecção precoce da LLC e seu respectivo estadiamento, por meio de revisão da literatura sistemática de natureza qualitativa, utilizando as bases de dados SciELO e PubMed, cuja triagem dos artigos foi realizada pelo protocolo PRISMA. A PET-CT desempenha um papel essencial no diagnóstico da LLC e avaliação do potencial de transformação da doença em Síndrome de Richer, com mau prognóstico e necessidade de aplicação de terapias agressivas.

Palavras-chave: Chronic Lymphocytic Leukemia; PET-CT; 18F-FDG.

INTRODUCTION

Positron Emission Tomography (PET) combined with anatomical structural images Computed tomography (CT) comprise a technique belonging to nuclear medicine and both diagnostic modalities, when fused, present greater accuracy and precision called PET-CT. It consists of morphofunctional evaluation, by quantifying the cellular uptake of similar glucose molecular radioactive compounds (18F-fluorodeoxyglucose), which represents glycolytic metabolic activity by tissues, including neoplastic processes. Therefore, PET-CT has favorable characteristics for application in the diagnosis, staging and treatment of leukemias, including Chronic Lymphocytic Leukemia (CLL) (COUNT et al., 2014).

Whereas malignant tumors have high glucose intake and accelerated metabolism at 18F-fluorodeoxyglucose (18F-FDG), PET radiotracer essential in the diagnosis and staging of pathologies, has been widely used. By PET and a noninvasive molecular imaging technique, through PET-CT technology it is possible to observe regions with significantly increased levels of uptake of 18F-FDG. In general, the uptake of this analogue under benign conditions is very low, however, in some cases there may be physiological accumulation promoting a false-positive interpretation (ZHAO et al., 2020).

One of the findings in images resulting from the use of PET-CT is CLL, a disease considered rare and more prevalent in the Brazilian male population, usually affecting older adults over 50 years of age. This neoplasm is characterized by increased type B lymphocytes in lymphoid tissues, bone marrow and peripheral blood, usually asymptomatic in its initial phase, in addition to cytopenias (SANTOS et al., 2018).

Another modality of imaging that encompasses hybrid technologies with several advantages is a Positron Emission Tomography combined with Magnetic Resonance Imaging (PET-MRI). Among its benefits include the lower use of ionizing radiation, low rate of adverse reactions to the use of contrast media, in addition to the offering of electrical and anatomical information with excellent resolution, mainly of brain, cervical, hepatic structures, among other tissues and organs including the blood and lymphatic systems. The method is capable of achieving similar or higher efficiency, in some cases, when compared to PET-CT, especially in the case of pathologies of oncological origin (VITOR et al., 2017).

Although the diagnostic and prognostic role of PET-CT is well established by monitoring the Standard Uptake Value - SUVmax, an index that expresses metabolic activity, the method is not unique in character for confirmation of CLL. There is a need to evaluate the clinical characteristics of the patient tied to histological analysis of lesions through biopsies, in addition to three-monthly follow-up of the lymphocytometry of line B in peripheral blood (HALLEK et al., 2018). Thus, how can the PET-CT method contribute to the diagnosis, monitoring and prognosis of patients with Chronic Lymphocytic Leukemia?

A milestone in the advancement of nuclear medicine is the incorporation of computed tomography (CT) with positron emission tomography (PET). However, it is necessary to expand knowledge about the technique for the efficient diagnosis of hematological cancers, including CLL (MONTEIRO, FERREIRA & DUARTE, 2017). Taking into account the expectation of the annual statistical profile of Brazil for 2020-2022 it is expected that approximately 1480 new cases of the disease will be diagnosed. Therefore, by demonstrating great detail of the disease, this method offers reliability and increases the chances of an early diagnosis, further reducing therapeutic costs (BOSCH & DALLA-FAVERA, 2019).

This study aims to identify the benefits of using the PET-CT technique in the early detection of Chronic Lymphoid Leukemia, demonstrating evidence of the presence of the disease through the correlation of the findings during the analysis of the images, enabling the staging of the pathology.

METHODOLOGY

The study is characterized by a qualitative approach of basic research nature, carried out through a systematic review of the literature, using of the PRISMA protocol, which consists of a minimal set of evidence-based items to report studies, dividing in search, analysis and description of some objects and pre-existing study (GALVÃO, PANSANI & HARRAD, 2015). Thus, a complete abstract on the theme was constructed, associating it with a specific context of scientific interest, following the protocols of selection of the articles and their inclusion and exclusion criteria, contemplating the descriptive objective of research.

For the search for scientific articles, a systematic review was used in the databases; Scientific Electronic Library Online - SciELO, PubMed from the bibliographic database of the National Library of Medicine (National Library of Medicine) for search of books, articles and documentation of the National Cancer Institute (INCA).

For the selection of materials, the inclusion criteria were respected, using scientific articles, books and national and international datasources in Spanish and English, published between 2014 and 2021. The descriptors used in the study were based on the reading of the titles of themes studied in the research, using keywords PET - CT, PET - MRI, Leukemia Lymphocytics, Chronic, B Cells, Chronic B Cell Leukemia and hybrid imaging. Abstracts of the selected works were read, for later confirmation of their choice for the study composition.

Regarding the screening process of the selected articles, the Boolean research method was used, which consists of the combination of keywords such as: PET/CT, Chronic Lymphocytic Leukemia, 18F-fluodeoxyglucose and Differential Diagnosis, using the AND, NOT and OR operators to delimit, hide or define articles of interest that involve only topics considered necessary for the preparation of the review. Articles that had more than eight years of publication, which did not contain the chosen keywords, articles related to clinical history of the CLL or on the treatment of the pathology were excluded.

CHARACTERIZATION

Chronic Lymphocytic Leukemia (CLL) is a type of blood neoplasia characterized by a proliferative and disorganized character of B-line lymphocytes, phenotypically mature in places such as peripheral blood, spleen, bone marrow, and lymph nodes (HUS & ROLIŃSKI, 2015). It is a disease marked by a clinical picture, molecular aspects and heterogeneous prognosis, that is, its staging is related to a group of specific variables for each patient. Among the variables are chromosomal, proteomic and epigenetic abnormalities (VALDESPINO-GÓMEZ, 2014).

CD5+ B lymphocytes are often required by the acquisition and/or manifestations of gene mutations that cause lymphocytosis in the monoclonal B cell line, triggering subsequent transformations in leucemogenesis. Initially lymphocytes are accumulated in

the bone marrow spreading later to lymph nodes and other lymphoid tissues, providing a path for the appearance of signs and symptoms in moderate and severe cases (KIKUSHIGE, 2020).

A striking feature observed in CLL is its discretion, evidenced by the observation of leukemic cells that even exhibiting a malignancy character, multiply and die demonstrating completely measurable rates and with relatively low proliferation when compared to other hematological neoplasms. In this scenario, the accumulation of CD5+ B cells comes from survival rather than multiplying uncontrolled actions (CUESTA-MATEOS, 2021). However, in more severe cases usually caused by chromosomal dissections, CLL may progress to a Prolymphocytic Leukemia with the possibility of transforming into Non-Hodgkin Lymphoma, if there is no early and effective treatment (LIRA & PEREIRA, 2019).

CLL is a disease that in most cases is asymptomatic and has a variable clinical course, according to the level of staging of the disease. Some of the predominant signs and symptoms in the initial phase of the disease are significant fatigue, fever for more than two weeks without evidence, night sweats, reduced appetite and consequent weight loss. In the moderate and advanced phases, it is possible to observe the increase in manifestations, with the prevalence of bleeding and recurrent viral or bacterial infections (SHARMA et al., 2020). Commonly, the predominance of pneumonia, anemia caused by bone marrow infiltration, exaggerated reactions to insect bite is commonly observed, besides the presence of lymphadenomegaly and hypogammaglobulinemia (impaired immune response), which directly interferes with the insatisfactory of the response to treatment, which may lead to death (HTET et al., 2019).

STAGING SYSTEMS FOR CHRONIC LYMPHOCYTIC LEUKEMIA

Currently, there are two accepted staging systems for chronic lymphocytic leukemia, Rai and Binet. The Rai system is part of the stages of the low-risk disease, referring to patients with lymphocytosis with neoplastic cells in the blood and / or bone marrow (lymphoid cells > 30%), formerly called stage Rai 0. The occurrence of the disease in any part of the body associated with hepatomegaly and/or splenomegaly are considered intermediate grade, formerly known as stage Rai I or II. The highest level of severity of the described pathology is reserved to anemic patients related to CLL, with

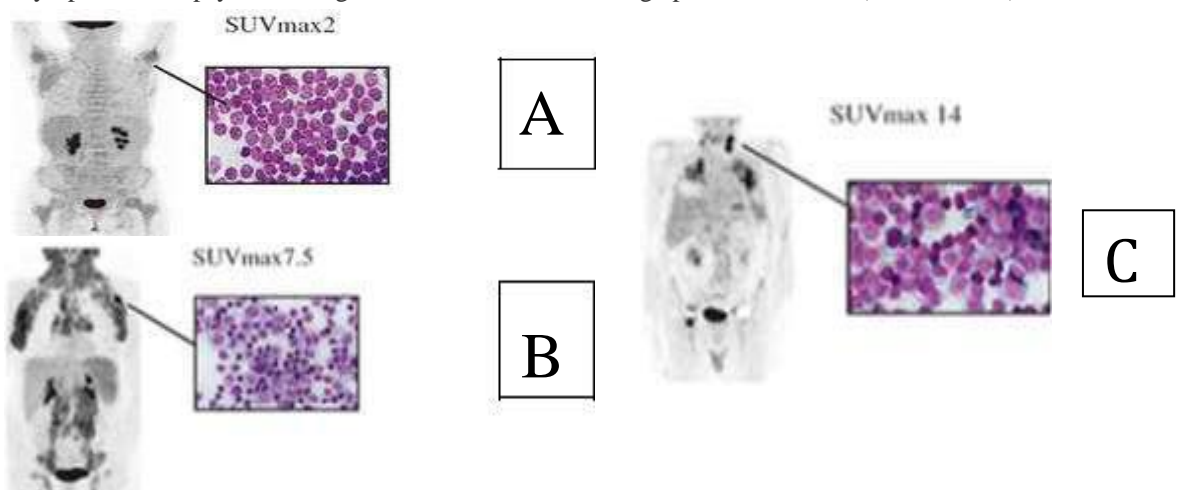
hemoglobin less than 11 g / L or thrombocytopenia with platelet count less than $100 \times 10^9 / L$ - Grade Rai III and IV (HALLEK et al., 2018).

As for the Binet staging system, the severity of the disease is related to the number of affected areas. Considered an affected region when there is increased lymph nodes with a diameter greater than 1 cm or organomegaly. The regions considered to characterize CLL are head and neck; both armpits; both groins, including superficial femoral, palpable spleen and palpable liver (ZHANG & THOMAS, 2014). Therefore, stage Binet A is classified with Hb ≥ 10 g/dL and platelets $\geq 100 \times 10^9/L$ (with up to two of the affected regions). The Stage Binet B with Hb ≥ 10 g / dL and platelets $\geq 100 \times 10^9 / L$, presence of organomegaly and more than three affected regions. Completing the staging levels we have the Binet classification of type C, with Hb less than 10 g / dl and / or platelet count less than $100 \times 10^9 / L$ (TREGLIA, 2019).

RESULTS AND DISCUSSION

CD5+ B lymphocytes are often associated with the manifestation of gene mutations that cause lymphocytosis in the monoclonal B clone, triggering subsequent transformations in leucemogenesis. These lymphocytes are accumulated in the bone marrow and disseminated to lymph nodes and other lymphoid tissues, as shown in Figure 1. This process offers a trigger for the appearance of signs and symptoms in moderate and severe pathological cases (KIKUSHIGE, 2020).

Figure 1 – PET/CT demonstrating recurrence of CLL (A) Patient with stable CLL (SUVmax: 2); (B) Patient with rapid disease progression (SUVmax: 7.5); (C) Patient with recurrence confirmed by lymph node biopsy, and a large number of B cells with high proliferation rate (SUVmax: 14).



Fonte: Zhao et. al., 2020

The development of CLL is discrete and can be evidenced by the observation of leukemic cells that even exist, multiply and suffer apoptosis demonstrating measurable rates, with relatively low proliferation when compared with other hematological neoplasms. Therefore, the accumulation of CD5+ B cells occurs due to prolonged cellular survival and not due to multi-plicuncontrolled actions (CUESTA-MATEOS, 2021). In the most severe cases caused by chromosomal dissections, the disease may progress to a prolycytic leukaemia with possibility of becoming non-Hodgkin lymphoma (LIRA & PEREIRA, 2019).

The basic criterion for the diagnosis of CLL is absolute analysis of B cells of peripheral blood greater than 5.0 g / l, lasting more than three months. The possibility of cell cloning should be confirmed by flow cytometry. One of the main research formats of CLL is immunophotyping, which allows the establishment of a specific diagnosis, where 95% of confirmed patients present cd5 cell surface antigen within typical B lymphocyte markers (CD19, CD20, CD23), which allows differentiation of CLL from other B-cell lymphomas (CONDOLUCI et al., 2020).

In the case of a differential diagnosis, in cases that are still suspected, some useful diagnostic methods are used, including the evaluation of lymph node megalia by PET-CT and bone marrow biopsy, which should be allocated before the beginning of therapy, repeated in cases of persistent cytopenias after treatment and in confirmations of total remission. Lymph node biopsy is indicated only in cases of suspected cellular transformations that occur for an aggressive type of Lymphoma (Richter syndrome), at clinical medical discretion and according to the patient's needs (ZHAO et al., 2020).

The PET-CT technique shows the functional status of the examined structures, in addition to morphological aspects, allowing the measurement of the metabolic activity of the lesions, thus demonstrating the degree of their activity, allowing an earlier diagnosis (MAURO et al., 2015).

PET-CT TECHNIQUE AND 18-FLUORDEOXYGLUCOSE (18F-FDG)

To perform the PET-CT technique, intravenous injection of a glucose analogue linked to radioisotope fluoride, called F18- fluorodeoxyglucose (18F- FDG) is performed. Continuing the process, the compound is distributed by the patient's body via peripheral blood circulation, concentrating on tissues with more intense metabolism due to its greater

requirement for energetic substrate. After approximately one hour of radiopharmaceutical application, the imaging cycle of the examination begins. Computed tomography, which has images of the entire body, is performed initially in the first minutes of the examination. Subsequently, signals emitted by the radioactive compound are picked up by the high-sensitivity detectors of the PET-CT equipment and converted into images in approximately 30 to 40 minutes, according to the model of each equipment. The more intense the capture of the radiopharmaceutical in the images (represented by warm colors or black coloration in black and white images), the greater the metabolic activity verified in the regions of the body demonstrated through the technique (MATO et al., 2019).

The interpretation of images can be performed in several ways, being by factors qualitative, visual or semiquantitative, using standard uptake value (SUV) capture indexes, which is defined by the ratio between the capture of 18F-FDG local regional and the average uptake in the rest of the organism, and this quotient is influenced by factors such as injected dose, distribution of 18F-FDG in the body, patient weight, endogenous glucose levels, and lesion size. The main purpose of the use of this unit of measurement is to facilitate the evaluation of the therapeutic response, besides distinguishing between malignant and benign lesions (ABOUZIED et al., 2020).

In the oncological branch, radiotracers are used that have the function of highlighting the metabolic activity of the tissue with suspected alterations. Among the most widely used radiopharmaceuticals is 18F-fluorodeoxyglucose (18F-FDG), a compound analogous to the glucose molecule that differentiates the metabolism of a normal tissue from a neoplastic tissue, demonstrating a great contrast in relation to the capture of the analogous glucose molecule, due to glycolytic hypermetabolism (SPICK, et. al., 2016).

HYBRID IMAGING

PET-CT has become a reference standard in oncological images when compared to the performance of other techniques, however, a new technique has been highlighted, presenting multiparametric results. This new technology presents the combination of Tomografia by Emission of Pósitrons (PET) and magnetic resonance imaging (MRI), a hybrid technology that incorporates morphological images by MRI and functional images by PET (PET- MRI), promising technique aimed at improving cancer diagnosis. One of the benefits of PET-MRI corresponds to the detection of soft tissue neoplasms, in addition

to the evaluation of the brain, head and neck, liver, pelvis and bone metastases. However, the mode displays disadvantages in the evaluation of pulmonary nodules (HAPKIDO et al., 2016).

PET-RM has other important advantages including excellent high resolution image quality, tissue contrast, and emit less ionizing radiation (compared to PET-CT) making it an excellent modality simultaneously providing anatomical and molecular information. PET-RM is recommended in cases that the investigation requires both advantages of PET in the detection of diseases and the sensitivity of MRI in the identification of spinal cord lesions and residual areas after treatment, offering even greater diagnostic reliability in the distinction between benign and malignant lesions. In the future, the multiparametric potential of MRI should be explored, culminating in the replacement of PET-CT by the PET-RM technique. This transition of technologies will occur, in fact, when PET-RM becomes economically viable (VITOR et al., 2017).

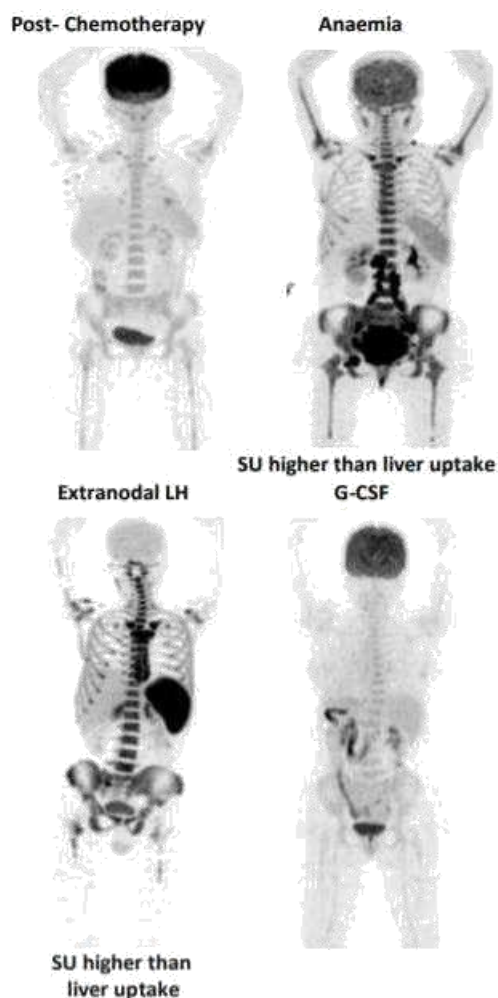
Increased patient safety during the performance of the PET-MRI examination is a primary factor that should be taken into account. The lower exposure to compounds and/or ionizing radiation, the more advantageous its application becomes (ZUCCHETTA, BRANCHINI & ZORZ, 2019).

PET-CT X CHRONIC LYMPHOCYTIC LEUKEMIA

Among the criteria for the evaluation of neoplastic positivity in blood tissue, through PET-CT images, we can consider the observation of ¹⁸F-FDG diopharmaceutical ra capture in a diffuse and homogeneous manner, especially in the region of bone marrow and lymph nodes, and a higher SUV locoregional pattern was verified than in the hepatic region, in addition to negative focal uptake in osteocytes (MAURO et al., 2015).

In cases where chemotherapy has already been initiated (Figure 2) and PET-CT is used to verify the staging and effectiveness of other maneuvers to improve the prognosis of patients affected by CLL, radiopharmaceutical uptake tends to increase even more in bone medula and slightly in splenic region (ARIMOTO, NAKAMOTO & NAKATANI, 2015).

Figure 2 - Findings on PET-CT images using 18F-FDG in several situations involving diffuse and homogeneous uptake in bone marrow.



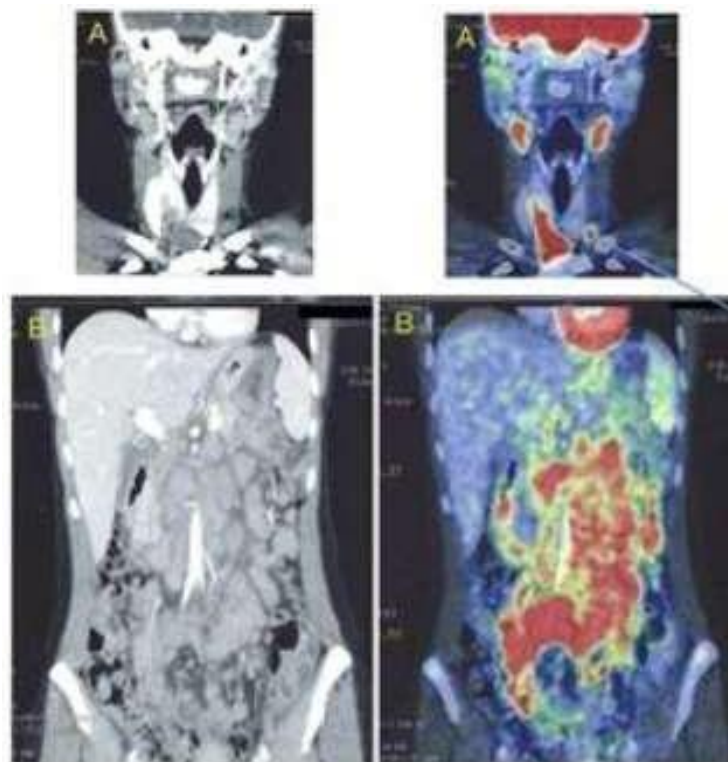
Fonte: Arimoto, Nakamoto e Nakatani, 2015.

Another hematological parameter that is related to SUVmax is the levels of serum cytokines that alter the behavior and organization of leukemic cells. However, it is necessary to verify the neoplastic level in lymph nodes, axillary and inguinal (PORRAZZO, NICOLAI & RIMINUCCI, 2020).

Despite the excellent efficiency of the use of 18F-FDG linked to the PET-CT technique in the diagnosis and staging of CLL, findings can be found in images that designate falsepositives, primarily diffuse patterns in bone marrow associated with splenic uptake, a condition that also occurs in clinical conditions of inflammatory processes with medullary involvement. This situation implies the need for observation and correlation of lymphocyte count and distribution in peripheral blood (RHODES & MATO, 2019).

Standardized capture values (SUV_{max}) ≥ 5 , evidenced in patients already diagnosed with CLL through biopsy, they are often related to the 11q chromosome. Furthermore, it is evident that when the SUV_{max} exhibits \geq values of 10, there is a higher probability of involvement by Richter Syndrome (RS) which is the most severe form of the disease, resulting in a lower survival prognosis and increasing rates of lymph node proliferation (PORRAZZO, NICOLAI & RIMINUCCI, 2020).

Figure 3 – Evolution of the clinical picture of a patient transitioning from stage 0 to stage II of Rai, after 4 years of course of untreated CLL. PET-CT images in coronal plane demonstrating large diffuse uptake of 18F-FDG in abdominal and cervical lymph nodes.



Fonte: Molica, 2014

PET-CT with 18F-FDG has been shown to be very efficient in cases of patients with suspected transform disease, assuming its most severe form, Richter Syndrome (RS), as shown in Figure 3. The method also defines the best region for tissue collection with subsequent biopsy. Therefore, the PET-CT technique should always be aligned with histological analysis and should not be interpreted independently. Although highly efficient for the evidence and staging of the disease, observation of the possibility of transformation of the disease into RS, PET-CT is a still relatively expensive method that exposes (even minimally) the patient to ionizing radiation (MOLICA, 2014).

CONCLUSION

In cases of CL, the observation of the correlations between the uptake of 18F-FDG and neutrophil count in peripheral blood is impressive, which are associated with the clinical tracings cited in the staging classifications of Rai and Binet. As the bone marrow supplies red, white and platelet cells to blood vessels, a reasonable amount of detectable archaic radiomaccumulates on images provided by Positron Emission Tomography.

It is can be concluded that the PET-CT method should never be considered independently and should always be associated with clinical signs and laboratory results from patients, including histological techniques that tissues, mainly lymph nodes and bone marrow. PET-CT plays an essential role in the diagnosis of CLL, staging and evaluation of the potential for disease transformation in Richter Syndrome, with an extremely poor prognosis and the need for aggressive therapeutic maneuvers.

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