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PET/CT DISADVANTAGES IN PATIENTS WITH LYMPHOMA: A LITERATURE REVIEW

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ABSTRACT

Relevance: *Positron emission tomography combined with computed tomography (PET/CT) is a young and promising technique for lymphoproliferative diseases' primary detection, staging, and evaluation of the treatment results. However, at this stage of nuclear medicine development, some shortcomings in PET/CT diagnostics of lymphomas using 18Fluorodeoxyglucose (F18-FDG) affect its reliability to a certain extent.*

The study aimed to *evaluate the physical and technical weaknesses of F18-FDG PET/CT in diagnosing lymphomas and review the analytical methods that affect opinion accuracy.*

Methods: *The articles on the use of F18-FDG PET/CT in diagnosing lymphomas, its reliability, and methods for optimizing were searched in the PUBMED database for 2012-2022.*

Results: *One of the main shortcomings of F18-FDG PET/CT in diagnosing lymphomas is the Deauville 5-point scale, which does not fully meet clinical requirements. This scale has some disadvantages, including low inter-reader agreement and an unreliable reference organ for F18-FDG accumulation. Mathematical algorithms for correction to the patient's weight also require optimization.*

Conclusion: *Some of the existing deficiencies can be improved at the software level and through educating staff about the importance of changing the SUV calculation method. However, other deficiencies, such as classifications that do not meet clinical requirements, require more efforts at the level of international experts and much more in-depth study of this issue to avoid such shortcomings of new staging methods. However, even considering all the shortcomings described, at the moment, PET/CT with F18-FDG is one of the most reliable modalities available, both for the initial detection and for evaluating the therapy effectiveness in patients with lymphomas.*

Keywords: *Positron emission tomography (PET/CT), lymphoma, Deauville, SUV, 18 Fluorodeoxyglucose (F18-FDG), tumor staging.*

Introduction: Positron emission tomography with computed tomography (PET/CT) is a hybrid radioisotope method for diagnosing various diseases based on the difference in radiopharmaceutical absorption. A radiopharmaceutical, or a tracer, is a two-component drug consisting of a radioisotope and a biological molecule. The radioisotope emits photons that a PET/CT detector can capture. The detector can recognize the radiopharmaceutical accumulation sites and determine the accumulation level. The biological molecule delivers the radioisotope directly to the pathological tissue and makes the radioisotope as tropic to the tissue as possible.

As an alternative to previously used mono-PET scanners, most countries now use PET/CT to analyze structural changes together with functional conditions. The most common radiopharmaceutical is F18-FDG, which is analogous to glucose. Most malignant tumors have high proliferative activity, and most of their energy comes from glucose. Because of this, malignant tumors consume significantly more glucose than benign tumors and normal tissue. This allows using F18-FDG for initial disease detection, staging, and prognosis [1, 2].

After intravenous administration, the drug is distributed throughout the circulatory system. Further, it accumulates most strongly in organs with a physiologically high capture of radiopharmaceuticals and malignant tumors with high proliferative activity. Physiologically, the brain, myocardium, kidneys, and bladder have high levels of F18-FDG accumulation.

F18-FDG accumulation in tissues is measured by Standardized Uptake Value (SUV) calculated as:

$$SUV = \frac{A}{dose} \times bodyweight$$

Where *A* is the concentration of radioactivity in the area of interest (*MBq/mL), dose* – the administered dose (MBq), and *bodyweight* – the patient's body weight.

PET/CT diagnostics includes several stages: 1 – administration of a radiopharmaceutical dose considering the patient's body weight, 2 – scanning, 3 – post-processing, and 4 – analysis and interpretation. While the dose administration and scanning follow certain pre-set algo-

rithms and depend more on the PET/CT scanner performance and manufacturability, post-processing and interpretation of the results are quite variable. Namely, stages 3 and 4 of the examination have some weaknesses and are subject to improvement and modernization.

Considering the complexity and multicomponent nature of PET/CT examination, each stage allows different execution options with varying degrees of correctness. Such variability of execution options can significantly affect the reliability of the results. Many authors, some mentioned in this review, offer solutions to improve the PET/CT correctness and the reliability of the result interpretation.

The study aimed to evaluate the physical and technical weaknesses of F18-FDG PET/CT in diagnosing lymphomas and review the analytical methods that affect opinion accuracy.

Materials and methods: The articles on the use of F18-FDG PET/CT in diagnosing lymphomas, its reliability, and methods for optimizing were searched in the PUBMED, MEDLINE, and Cochrane databases over the last ten years.

A literature review was conducted on the Pubmed database for 2012-2022 for the following keywords: "PET/CT in the diagnosis of lymphomas," "relevance of PET/CT with P18-FDG in the diagnosis of lymphomas," and "sensitivity and specificity of PET/CT with P18-FDG in the diagnosis of lymphomas". This literature review includes 27 references.

Results: Lugano classification is the most common for staging lymphomas. However, it is quite complicated and focuses more on CT sizes than radiopharmaceutical accumulation during PET. This increases the risk of false positive results with a residual fibrous but metabolically inactive tumor [3].

Lugano classification also includes the five-point Deauville scale (5D) reflecting the metabolic status of a lymphoma lesion. This allows tracking of both structural and metabolic changes in patients with lymphoma. The Deauville classification is based on a 5-point scale that compares the tumor uptake with the physiological levels of uptake in the brain, liver, and mediastinum (Fig. 1).

Thus, Score 1 means no pathological FDG uptake; Score 2 means moderate accumulation in the tumor ≤ mediastinum; Score 3 means that accumulation in the tumor is higher than in mediastinum but lower than in the liver; Score 4 means that accumulation in the tumor is slightly higher than in the liver; and Score 5 means a much higher accumulation compared to the liver (sometimes close to the accumulation in the brain).

Previously it was believed that the mediastinum (blood pool) and the liver have a relatively stable accumulation level. This made it possible to level out differences related to patients, examination protocols, the PET scanner's characteristics, and the knowledge level of the radiologist interpreting this result.

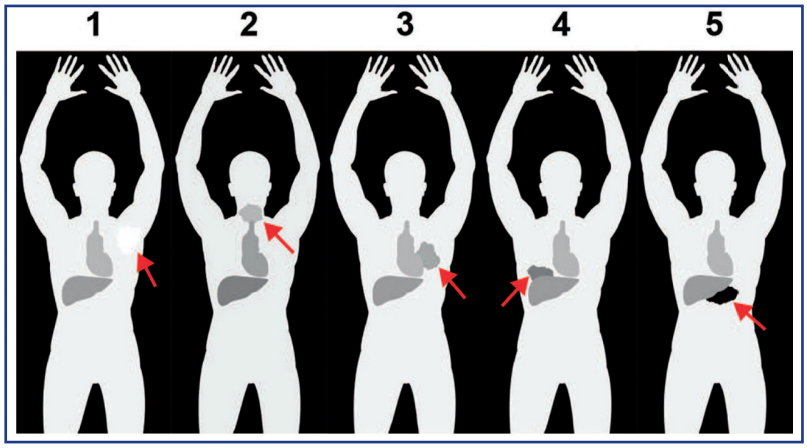

Figure 1 – The five-point Deauville scale [20]

Even if 5D performed better in terms of prognosis than only SUV or the CT part comparison [5-7], this scale has several further problems associated with its clinical use.

Score 5 on the Deauville 5D scale

One disadvantage of the 5D scale is an inefficient ranking of results at high capture rates in two studies compared over time. For example, a patient Scored five at the initial PET/CT. Then, an intermediate PET/CT showed a decrease in the formation volume and maximum metabolic activity, with clear clinical progress. However, SUVmax remained higher than in the liver, and the report will still give 5 points on the 5D scale (Fig. 2). Thus, the treating oncologist who will compare the primary and intermediate Scores may be misled that there is no effect of therapy. This may lead to an unjustified increase in treatment courses or the dose of chemoradiotherapy, a change in the treatment protocol, and a decrease in treatment efficacy.

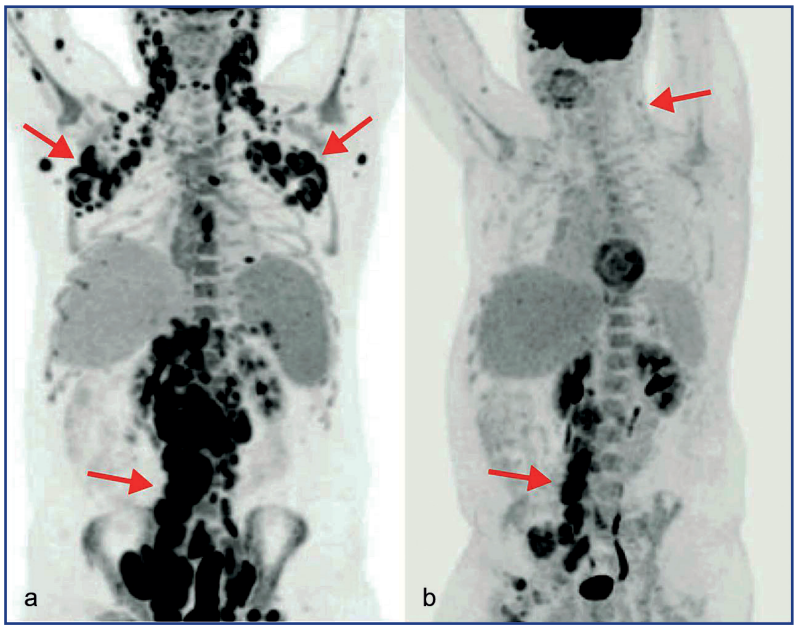

Figure 2 – Score 5 on the 5D scale: a – before treatment, b – intermediate PET/CT. Arrows indicate affected areas [20]

Score 3 on the Deauville 5D scale

Scores 1 & 2 on the Deauville 5D scale are considered a complete or partial metabolic response, that is, a positive effect of treatment, while Scores 4 & 5 are perceived as a lack of response or progress of the disease [8], meaning ineffective therapy. However, Score 3 raises doubts: is there a response to therapy or not? In most cases, Score 3 is perceived as a complete metabolic response, a positive treatment result [9]. Still, some studies on de-escalation of therapy consider Score 3 as a non-adequate response meaning insufficient treatment. [10]. This leads to over-diagnostics and over-treatment to avoid relapse [5].

Congruency among doctors

Using SUV to measure relative accumulation by tissues/organs facilitates comparison between patients and has been proposed as a basis for diagnosis. However, SUV is a semi-quantitative indicator. There are two main reasons why using any threshold to decide on a positive or negative result is wrong. First, primary detection and staging should not depend on the exact SUV level because, for such purposes, it is often sufficient to compare the SUV values in the area of interest and the surrounding tissue. Second, SUV is highly variable due to physical and biological parameters. In particular, studies have shown that using SUV thresholds (like SUV>2.5) to identify a nodule or mass as benign or malignant often gives invalid results. Many benign infectious/inflammatory processes may have a high uptake of F18-FDG with a high SUV value. Conversely, many indolent or slow-growing malignancies may have minimal uptake and low SUV values.

Besides the variability of SUVs, the lack of a unified SUV measurement algorithm produces a high risk of subjective assessment by the describing radiologist. Thus, in several studies, the congruency between the analyzing doctors using 5D was very low [11-13]; that is, different doctors evaluated the same patients differently. Using a binary scoring system increased the congruency between clinicians, allowing them to accept Scores 1, 2 & 3 as negative and Scores 4 & 5 – as positive [11, 14].

The tumor-to-liver SUV ratio (SUVTLR)

As described above, the liver is one of the guides used by nuclear medicine doctors for 5D scoring (Fig. 1). There are several methods for measuring the level of uptake in the liver: a round 2D on one slice [15, 16] and a spherical 3D [17]. 2D measurement considers the isotope capture activity on only one slice, which reduces the reliability of the results. Moreover, the accumulation in the liver does not remain stable. It may be affected by chemotherapy due to reversible changes in the liver parenchyma, such as steatosis and duct obstruction, that CT, MRI, or ultrasound examination can detect. Besides, different chemotherapy protocols can have a different effect on the level of metabolism and, therefore, on the SUV of the liver. For example, the ABVD effect on liver metabolism differs much from the effect of MOPP or BEACOPP schemes. Therefore, the interpretation of the liver SUV at intermediate PET/CT shall consider the duration of chemotherapy and the types of chemotherapy drugs used in the treatment [18].

The patient's body weight

The radiopharmaceutical dose administered to a patient is measured in mega becquerels (MBq) and de-

pends on the patient's body weight. The usual dose is 1.2 MBq of 18F-FDG per 1 kg of body weight. Formula 1 shows that SUV is calculated based on the patient's body weight. However, it has long been known that adipose tissue uptakes much less 18F-FDG than other tissues so SUV can vary greatly depending on the body structure. Therefore, an alternative method for calculating SUV normalized by lean body mass (SUL Lean body mass (LBM) represents the weight of lean connective, muscle, and nervous tissues. The classic formula for calculating LBM considers gender, height, and body weight. Though some studies reported the possibility of obtaining a reliable LBM by scanning a limited part of the body on a CT scanner [19, 20], the most common is the James equation: $\mathrm{LBM} = 1{,}1bw - 123(\frac{bw}{h})^2$ for man and $\mathrm{LBM} = 1{,}07bw - 148(\frac{bw}{h})$ for women. Modern scanners use the James equation to calculate LBM. SUL is calculated as $SUL = \frac{A}{dose} \times \mathrm{LBM}$ [21]. As in a usual SUV equation, it is assumed that F18-FDG is evenly distributed over the body. However, real and calculated SUVs can vary greatly, especially in patients with large body weights [22, 23]. Therefore, SUL is a more stable and reliable value [24]. Studies also support the significant difference between SUV and SUL in the liver [25], which is critical in evaluating treatment outcomes in patients with lymphomas. Unfortunately, in most cases, including PET centers in Kazakhstan, they still use SUVs instead of SUL.

Discussion: Lymphoma classification and staging have evolved from 1950, when the three-component Peters classification was first introduced, to 2011, when the Lugano classification was proposed. In 1976, the World Health Organization introduced the concept of a radiological and quantitative assessment of response to cancer therapy using CT and quantitative tumor measurements [4]. Since then, radiology has been tasked both with the initial diagnosis and evaluating the treatment efficacy. Today, this task is becoming increasingly important in light of the emergence of new therapeutic drugs and the growing popularity of personalized therapy. The ability of PET/CT to determine not only tumor anatomy but also its metabolic status provides more reliable information about the effect of therapy much earlier than traditional computer tomography [26, 27].

Lugano classification, approved in 2011 at the congress of leaders in this field in Lugano, Switzerland, has become the first specific system for evaluating the effectiveness of therapy in malignant lymphoma. The first results of studies evaluating response to treatment using this scale were published as early as 2014 [5, 8, 9]. Lugano classification became the standard to assess the response to treatment. This classification was based on CT measurements of up to 6 lesions measuring at least 1.5 cm for nodal lesions and at least 1.0 cm for extranodal lesions. Each formation was measured in 2 projections, then these measurements were multiplied, and the sum of multiplications before treatment was compared with the sum of multiplications after treatment to quantify response to therapy [5].

Such a procedure was very laborious and lengthy. Even more significant in comparing the two surveys was that such procedures were difficult to reproduce. Studies showed a large variation in the assessments of the same formations by different radiologists. Besides, in this case, it remained unclear whether the formation was a fibrous tissue remaining after treatment or a viable tumor [3].

Today, we evidence the rapid development of nuclear medicine. More new radiopharmaceuticals become available for clinical use; new calculation and image analysis methods emerge. However, the classical PET/CT with 18F-FDG and SUV calculation remains the most common research method for a wide variety of pathologies, including cancers.

18F-FDG is suitable for lymphoma visualization due to the high proliferative activity of most lymphomas. PET/CT can be used for primary detection, staging, and evaluating the results of lymphoma treatment. Despite the clear advantages of PET/CT over more traditional CT and MRI methods, including the ability to assess both structural changes and – even more important – the metabolic status, this method has its shortcomings, as described above. Now there is a clear trend towards simplifying these methods due to too complex and difficult to replicate the analysis methods, including algorithms for evaluating PET/CT results [8].

Conclusion: Since nuclear medicine is one of the youngest fields of medicine and due to the general trend of describing only the positive aspects of various methods of diagnosis and treatment, only a few publications reveal the weaknesses of a particular method. However, this review summarizes the most obvious shortcomings of PET/CT in diagnosing lymphomas. Some of the existing deficiencies, such as PET/CT adjustment for LBM, can be improved at the software level and through educating staff about the importance of changing the SUV calculation method. However, other deficiencies, such as classifications that do not meet clinical requirements, require more efforts at the level of international experts and much more in-depth study of this issue to avoid such shortcomings of new staging methods. Therefore, even being the most high-tech and expensive radiological procedure, PET/CT with F18-FDG has shortcomings that should be known to both nuclear medicine physicians and oncologists involved in diagnosing and treating lymphomas.

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АҢДАТПА

ЛИМФОПРОЛИФЕРАТИВТІ АУРУЛАРДЫ ДИАГНОСТИКАЛАУДАҒЫ ПЭТ/КТ ЗЕРТТЕУЛЕРІНІҢ КЕМШІЛІКТЕРІ: ӘДЕБИЕТТЕРГЕ ШОЛУ

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Өзектілігі: *Компьютерлік томографиямен (ПЭТ/КТ) біріктірілген позитронды-эмиоссиялық томография лимфопролиферативті ауруларды емдеу нәтижелерін алғашқы анықтау, стадирлеу және бағалау үшін жас және перспективалы әдіс болып табылады. Алайда,*

ядролық медицинаның дамуының осы кезеңінде 18 фтор-Дезоксиглюкозбен (F18-FDG) лимфомалардың ПЭТ / КТ диагностикасында оның сенімділігіне белгілі бір дәрежеде немесе басқа да бірқатар кемшіліктер бар.

***Зерттеудің мақсаты** – F18-FDG мен ПЭТ/КТ-ның әлсіз жақтарын лимфомаларды диагностикалауда физика-техникалық жағынан да, қорытындының дұрыстығына әсер ететін талдау әдістерін де зерттеу.*

***Әдістері:** Мақалада 2012-2022 жылдарға арналған PABMED дереккорындағы дереккөздерге шолу берілген. лимфомалардың диагностикасында F18-FDG бар PET/CT қолдану, оның сенімділігі және осы зерттеуді оңтайландыру әдістері туралы.*

***Нәтижелері:** Лимфоманы диагностикалаудағы F18-FDG мен ПЭТ/КТ-ның басты кемшіліктерінің бірі-клиникалық талаптарға толық сәйкес келмейтін Deauville емдеу нәтижелерін бағалау шкаласы. Бұл шкала бірқатар әлсіз жақтарға ие, оның ішінде дәрігерлер арасындағы төмен сәйкестік және F18-FDG жинақтаудың сенімді емес органыОлар сондай-ақ пациенттің салмағын түзетудің математикалық алгоритмін оңтайландыруды талап етеді.*

***Қорытынды:** Кейбір кемшіліктерді бағдарламалық жасақтама деңгейінде шешуге болады және қызметкерлерге SUV есептеу әдісін өзгертудің маңыздылығы туралы түсіндіруге болады, бірақ басқа да кемшіліктер, мысалы, жіктеудің клиникалық талаптарына толық сәйкес келмеуі халықаралық сарапшылар деңгейінде айтарлықтай күш салуды және жаңа кезең әдістерінің осындай кемшіліктерін болдырмау үшін осы мәселені тереңірек зерттеуді қажет етеді. Дегенмен, тіпті сипатталған барлық кемшіліктерді ескере отырып, Ф18-ФДГ ПЭТ/КТ қазіргі уақытта лимфоманы бастапқы анықтау үшін де, емдеудің тиімділігін бағалау үшін де қол жетімді ең сенімді әдістердің бірі болып табылады.*

***Түйінді сөздер:** позитронды-эмиссиялық томография (ПЭТ/КТ), лимфома, Deauville, SUV, 18-фтор-дезоксиглюкоза (Ф18-ФДГ), ісік сатысы.*

АННОТАЦИЯ

НЕДОСТАТКИ ПЭТ/КТ ИССЛЕДОВАНИЯ ПРИ ДИАГНОСТИКЕ ЛИМФОПРОЛИФЕРАТИВНЫХ ЗАБОЛЕВАНИЙ: ОБЗОР ЛИТЕРАТУРЫ

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***Актуальность:** Позитронно-эмиссионная томография совмещенная с компьютерной томографией (ПЭТ/КТ) является молодой и перспективной методикой для первичного выявления, стадирования и оценки результатов лечения лимфопролиферативных заболеваний. Однако, на данном этапе развития ядерной медицины, в ПЭТ/КТ диагностике лимфом с 18Фтор-Дезоксиглюкозой (F18-FDG) есть ряд недостатков, в той или иной степени оказывающие на ее достоверность.*

***Цель исследования** – изучить слабые стороны ПЭТ/КТ с F18-FDG в диагностике лимфом с физико-технической стороны и методы анализа, влияющие на достоверность заключения.*

***Методы:** В статье представлен обзор источников из базы PUBMED за 2012-2022 гг. по применению ПЭТ/КТ с F18-FDG в диагностике лимфом, его достоверности, и методов оптимизации данного исследования.*

***Результаты:** Одним из главных недостатков ПЭТ/КТ с F18-FDG в диагностике лимфом является не полностью отвечающая клиническим требованиям шкала оценки результатов лечения Deauville. Данная шкала имеет ряд слабых сторон, включая низкую согласованность между врачами и недостоверный орган-ориентир накопления F18-FDG. Также требуют оптимизации математические алгоритмы коррекции к весу пациента.*

***Заключение:** Некоторые из имеющихся недостатков можно решить на уровне программного обеспечения и разъяснения персоналу о важности изменения метода расчета SUV, но другие недостатки, как например не совсем отвечающие клиническим требованиям классификации требуют более значительных усилий на уровне международных экспертов и значительного более глубокого изучения данного вопроса во избежание подобных изъянов новых методов стадирования. Однако, даже учитывая все описанные недостатки, на данный момент, ПЭТ/КТ с Ф18-ФДГ является одной из самых достоверных модальностей из имеющихся, как для первичного выявления, так и для оценки эффективности лечения лимфом.*

***Ключевые слова:** Позитронно-эмиссионная томография (ПЭТ/КТ), лимфома, Deauville, SUV, 18Фтор-Дезоксиглюкоза (F18-FDG), стадирование опухолей.*

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