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ИЗУЧЕНИЕ РОЛИ ПЭТ-КТ С ФДГ В ВЫЯВЛЕНИИ ВЫСОКОЗЛОКАЧЕСТВЕННОЙ ДИФФУЗНОЙ В-КРУПНОКЛЕТОЧНОЙ ЛИМФОМЫ

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Exploring the Role of FDG PET CT Scan in Detecting High Grade Diffuse Large B-Cell Lymphoma

Резюме

Введение. Диффузная В-крупноклеточная лимфома (ДВККЛ) является наиболее распространенным типом неходжкинской лимфомы. В настоящее время стандартным методом оценки пациентов на ранних стадиях диагностики рака в онкологических центрах г. Мешхед является компьютерная томография (КТ), гистопатологическое исследование образцов ткани, взятие образца костного мозга и цитологические исследования. Все эти исследования требуют времени и значительных финансовых затрат. Следует отметить, что на данный момент наиболее рекомендуемым подходом к определению стадии лимфомы является ПЭТ-КТ с ФДГ, который сочетает в себе использование меченой глюкозы и КТ-сканирования и является более точной альтернативой. Цель настоящего исследования заключается в изучении возможностей ПЭТ-КТ с ФДГ как инструмента диагностики высокозлокачественной лимфомы. **Методы.** В настоящем исследовании оценивали пациентов с различными типами ДВККЛ, которые прошли ПЭТ-КТ-сканирование с ФДГ для определения стадии заболевания в больнице Разави (г. Мешхед, Иран) в период с 2017 по 2021 годы. Собирали необходимую клиническую и параклиническую информацию, включая информацию о стадии заболевания, локализации опухоли на момент постановки диагноза, результатах иммуногистохимического исследования и ответе на лечение. Кроме того, оценивали результаты ПЭТ-сканирования с ФДГ, включая распространенность процесса и метаболическую активность опухоли до начала лечения, патологические характеристики опухоли, клиническое поведение и ответ на лечение: частоту ответа (ЧО), выживаемость без признаков заболевания (ВБЗ) и общую выживаемость (ОВ) пациентов. Степень агрессивности в настоящем исследовании классифицировали по морфологическим характеристикам и результатам иммуногистохимического окрашивания, прогностическим факторам, клинической картине и ответу на лечение. Для анализа данных использовали пакет программ SPSS, а уровень значимости составлял p <0,05. **Результаты.** Результаты сравнения двух групп пациентов с гистологически подтвержденной высокозлокачественной опухолью (n = 12) и неуточненной опухолью (n = 14) показали, что максимальные значения стандартизированного уровня накопления (SUVmax) у пациентов с агрессивной лимфомой составили 27,5 ± 15,6 (медиана: 25,6), а у пациентов с неуточненной лимфомой — 15,4 ± 9,8 (медиана: 14,4) (p = 0,01). Общая выживаемость пациентов с агрессивной формой составила 10 месяцев, а пациентов с неагрессивной формой — 24 месяца (p = 0,002). Кроме того,

значение SUVmax, равное 21,1, имело чувствительность и специфичность 66 % и 72 % соответственно для дифференциации агрессивных и неагрессивных форм опухоли. **Заключение.** Результаты показали, что ПЭТ-КТ и ФДГ может в значительной степени способствовать дифференциации агрессивных и неагрессивных форм лимфомы, поскольку повышение метаболической активности (SUVmax) зачастую свидетельствует об агрессивном процессе.

Ключевые слова: *ДВККЛ, высокозлокачественная В-крупноклеточная лимфома, ПЭТ-КТ-сканирование, агрессивная лимфома, исход*

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Конфликт интересов

Авторы заявляют, что данная работа, её тема, предмет и содержание не затрагивают конкурирующих интересов

Информация о финансировании

Настоящее исследование «Изучение роли ПЭТ-КТ с ФДГ в выявлении высокозлокачественной диффузной В-крупноклеточной лимфомы» основано на докторской диссертации в Университете медицинских наук г. Мешхед и получило финансовую поддержку проректора по исследовательской и технологической работе Университета медицинских наук г. Мешхед. Однако университет не принимал участие в разработке, проведении или написании этой статьи.

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Abstract

Introduction. Diffuse B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin's lymphoma. Currently, the standard method for evaluating patients at the initial stages of cancer diagnosis in Mashhad oncology centers involves computed tomography scans (CT scans), histopathological evaluation of tissue, bone marrow sampling, and cytogenetic studies, all of which are time-consuming and costly. It is worth mentioning that at present, the most recommended approach for determining lymphoma staging is the FDG-PET/CT scan, which combines labeled glucose with CT scan and offers a more accurate alternative. The objective of this study is to explore the potential of FDG-PET/CT scan as a tool for detecting high-grade lymphoma. **Methods.** In this study, patients with different types of DLBCL who underwent FDG-PET Scan for staging at Razavi Hospital, Mashhad, Iran between 2017 and 2021 were examined. The necessary clinical and paraclinical information, including the stage of the disease, the involved site at the time of diagnosis, the result of immunohistochemical examination, and the response to treatment were collected. FDG-PET Scan information including the extent of involvement and metabolic activity of the tumor before the start of treatment, pathological characteristics of the tumor, clinical behavior, and response to treatment in the form of response rate (RR), disease-free survival (DFS) and overall survival (OS) of the patients. Was also investigated. Aggressive histology in the present study was classified based on morphological characteristics and immunohistochemical staining, prognostic indicators, clinical behavior and response to treatment. Data were analyzed using SPSS software at a significance level of $p<0.05$. **Results.** Comparing the two groups of patients with high grade histology (n=12) and NOS (n=14), the results showed that SUV max values in patients with aggressive lymphoma were 27.5 ± 15.6 (median 25.6) and in patients with NOS lymphoma was 15.4 ± 9.8 (median 14.4) ($p=0.01$). The overall survival of patients in the aggressive group was 10 months and in the non-aggressive group was 24 months ($p=0.002$). Also, the cut — off -point of 21.1 for SUV max has a sensitivity of 66 % and a specificity of 72 % in differentiating aggressive from non-aggressive types. **Conclusion.** The results revealed that FDG PET CT Scan can provide valuable insights into differentiating lymphomas with a more aggressive type from their usual types, as those with heightened metabolic activity (SUVmax) are often indicative of aggressive behaviors.

Key words: *DLBCL, High-Grade B-Cell Lymphoma, PETCT SCAN, Aggressive Lymphoma, outcome*

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Conflict of interests

The authors declare no conflict of interests

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Conformity with the principles of ethics

This research has been approved by the Regional Organizational Ethics Committee of Mashhad University of Medical Sciences with code IR.MUMS.MEDICAL.REC.1401.523. Given that only the health data of the patients was utilized in this study and no interventions were administered, the ethics committee exempted the need for written informed consent.

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What is new?

Due to the remarkable superiority of fluorodeoxyglucose (FDG)-positron emission tomography (PET) for its superior sensitivity in diagnosing lymphatic and extra-lymphatic involvements, Lymphoma plays a significant role in staging patients with DLBCL. Histopathological evaluation of the involved tissue and bone marrow as well as cytogenetic evaluations are the conventional approaches in the examination of patients in their early diagnosis. The diagnosis and staging of this disease require a significant amount of time and resources. Moreover, the aggressive nature of these of these methods and the situation in Iran may impose restrictions on their use. Therefore, this study was carried out to examine the potential impact of FDG PET CT Scan in identifying the types of diffuse B-cell lymphoma with a high level of malignancy and differentiating it from less aggressive types. It needs to be kept in mind that the reliability of visual and quantitative response assessment can be impaired by inconsistent PET scanning protocols and image reconstruction methods. Even though standardization is still lacking, quantitative FDG-PET has the potential to substantially improve prognostication in lymphoma. Over recent years, PET using FDG has brought many advances in the diagnosis and treatment of lymphoma patients.

What is important?

The study suggests using FDG PET CT Scan alongside morphological investigations and pathological immunophenotyping during standard staging to identify patients who may benefit from cytogenetic testing. This is particularly important in our country where access to such testing is limited.

FDG — Fluorodeoxyglucose, PET — Positron emission, CT scan — Computed tomography scans, DLBCL — Diffuse large B cell lymphoma, RR — Response rate, DFS — Disease-free survival, OS — Overall survival, CHOP — Chemotherapy regimen used in the treatment of non-Hodgkin lymphoma, IPI — International Prognostic Index, CNS — Central nervous system, SUV — Standardized Uptake Values, DFS — Disease-free survival, BCL2 — B-cell lymphoma 2, BCL6 — B-cell lymphoma 6, BNHL — B-cell non-Hodgkin lymphoma, NCSS — Number Cruncher Statistical Systems, ROC — Receiver operating characteristic, AUC — Area Under the Curve

Introduction

Diffuse large B cell lymphoma (DLBCL) is the most common histological subtype of non-Hodgkin's lymphoma; it accounts for 30-40 % of all newly diagnosed cases [1]. The standard frontline treatment for patients with DLBCL is to use six cycles of chemotherapy regimen that includes cyclophosphamide, doxorubicin, vincristine and prednisone along with the monoclonal antibody rituximab (R-CHOP) [2]. However, unlike the early stages of the disease where treatment could be limited to fewer sessions of chemoimmunotherapy with or without radiotherapy, based on the International Prognostic Index (IPI) definition, high-risk advanced DLBCL, may require intensified treatment including prophylactic treatment of the central nervous system (CNS) [3, 4]. Despite significant advances in the management of this malignancy, the rate of complete recovery is still lower than in Hodgkin's lymphoma, and about one-third of all patients relapse after the first-line treatment [5]. Due to the remarkable superiority of fluorodeoxyglucose (FDG)-positron emission tomography (PET) for its superior sensitivity in diagnosing lymphatic and extra-lymphatic involvements, Lymphoma plays a significant role in staging patients with DLBCL [6]. In addition, several international clinical trials have investigated the role of FDG-PET CT in the early stages of treatment for differentiating patients needing therapy intensification from good responders, i.e., candidates for de-escalation of therapy [7-11]. Histopathological evaluation of the involved tissue and bone marrow as well as cytogenetic evaluations are the conventional approaches in the examination of patients in their early diagnosis.

According to the aforementioned measures, the diagnosis and staging of this disease requires a significant amount of time and resources. Moreover, the aggressive nature of these of these methods and the situation in Iran may impose restrictions on their use. Therefore, this study was carried out to examine the potential impact of FDG PET CT Scan in identifying the types of diffuse B-cell lymphoma with a high level of malignancy and differentiating it from less aggressive types.

Material and Method

This pilot study retrospectively analyzed the files from 2017 to 2021 in the nuclear medicine department of Razavi Hospital in Mashhad, Iran. It was approved by the Regional Ethics Committee of Mashhad University of Medical Sciences with code IR.MUMS.MEDICAL.REC.1401.523. Based on information from the hematology and oncology departments of Qaem and Imam Reza hospitals, as well as private clinics, The files of patients aged 15 to 65 diagnosed with diffuse B cell lymphoma through morphological and immunohistochemical testing were included in the study, all of whom were scheduled to undergo an FDG-PET/CT scan prior to receiving treatment.

Really, in a retrospective study, a sample is selected and the researcher looks back at the history of the members of this sample. Furthermore, in a retrospective study, data is readily available for collection and analysis, requiring a smaller research team and fewer resources. However, this was a limitation of this study mentioned in and future studies are recommended to use prospective approaches.

We conducted the present study to track the survival of patients with diffuse large B-cell lymphoma. For the follow up, the aftercare protocol involved referencing the disease details documented in medical records from clinics and hospitals, along with input from the attending physician which included a period of 4 months to 3 years, they were only contacted solely to ascertain whether they were alive or dead.

Patients were excluded if they had incomplete information, heart failure, poor performance status (ECOG PS >= 2), or a history of other hematological or solid organ malignancies. The response rate was determined by the patient's state of complete response, partial response, stable disease, or progressive disease.

A complete response indicates that treatment has fully resolved the disease and there is no evidence of disease in any of the primary sites on imaging. A partial response is when the affected areas have decreased by over 20 % compared to their original size with the same initial imaging modality. Progressive disease is when new lesions appear or previous lesions increase in size by over 20 %. Stable disease refers to any other condition. If a patient with lymphoma does not achieve a complete response at the end of treatment, it is considered treatment failure and disease resistance, and the next line of treatment should be pursued. PET information, including SUV, is used to evaluate the pathological characteristics of the tumor and treatment responses in terms of primary response, DFS, and OS.

Patients who exhibit early resistance to chemotherapy, experience relapse within six months, or have an advanced and widespread disease that affects non-lymphatic organs such as the central nervous system, liver, or bone marrow, are classified as high-grade B-cell lymphoma. This includes those who were in stage 4 of the disease from the start, had a high proliferation index (Ki67), or had previously expressed *MYC*, *BCL2*, or *BCL6* genes (i.e. double/triple expressors). Their SUV levels were compared to those of other types of DLBCL without aggressive features. High-grade B-cell lymphomas are traditionally composed of Double HIT, Double Expressor, Burkitt, and Burkitt-like lymphomas.

These cases all had similar characteristics, such as a high mitosis rate (Ki67 cell proliferation index above 80-90 %), advanced stage at diagnosis, initial involvement of the central nervous system, rapid progression, numerous clinical symptoms, poor treatment response, quick relapse, and a high mortality rate. These traits distinguish DLBCL-NOS types from high-grade B-cell lymphoma cases in this study.

Recent evidence indicates that double hit and double expressor classifications, along with the previously mentioned pathological and genetic traits, share similar clinical characteristics, including resistance to standard treatment, early recurrence, high mortality, initial 4th stage disease, high risk of central nervous system involvement, and a high proliferation index [12].

In this study, clinical criteria and morphological characteristics in microscopic examination and immunohistochemical staining were used in pathology evaluation as screening criteria for high grade lymphoma. Due to the high costs of gene rearrangement tests, which are not standard practice even for hospitalized patients in our current economic state, they were not included in this study.

The sample size was estimated based on research by Ngeow et al [13], where SUV max measurements from PET scans were used to distinguish between normal B-NHL types and aggressive B-cell lymphoma types. In that study, the area under the curve (AUC) was reported to be 0.81. With alpha at 0.05 and beta at 0.2, and using NCSS (PASS11) software, the minimum sample size was calculated to be 12 people in each group (aggressive and normal).

As this was a pilot study, only a limited number of patients were included. It is north Worthing that the present study is the first step of the entire research protocol and is often a smaller-sized study assisting in planning and modification of the main study. More specifically, in large-scale clinical studies, the pilot or small-scale study often precedes the main trial to analyze its validity. Researchers had a strong desire to include the data collected from the pilot study into the main study because this allows the researchers to reduce both the number of participants required for the study and the duration of the study. However, this is only allowed in an internal pilot study. Finally, this was one of the main limitations of this study that was discussed in the discussion section. Furthermore, another limitation was that Since the number of events in this study did not reach the level required for Cox regression analysis, we did not perform this analysis [14].

The nuclear medicine department at Razavi Hospital being the exclusive provider of FDG-PET/CT scans in the eastern region of Iran, enabled us to attain a sufficient sample size. Consequently, all patients were examined through a census method during the specified time period.

After assessing the normality distribution of the data using the Kolmogorov Smirnov test, we applied the student's t-test (or Mann-Whitney) to compare continuous data, and the Chi-square test (or Fisher's exact test) to analyze qualitative data. Additionally, we examined the survival of patients using the Log Rank Test and Kaplan-Meier estimator.

Using the ROC curve, the cut point for SUV max (obtained from PET scan) was established after segregating patients into two groups based on their pathology data — aggressive and normal. SPSS software was employed to conduct statistical analysis, with a significance level of $p < 0.05$ set for all analyses. It is accepted as a rule of thumb that a minimum of 10 events per variable is needed for Cox regression analysis. As in current research the number of events (mortality) did not reach

the desired level (10 events), we did not perform the Cox regression model.

The interpretation of the ROC curve results is as follows [15]:

AUC equal to 0.5: The approach used cannot distinguish between two groups (i.e., ability to diagnose patients with and without the disease or condition based on the test).

AUC Between 0.7 and 0.8: The approach used demonstrates acceptable validity in distinguishing between two conditions.

AUC Between 0.8 and 0.9: The approach used demonstrates excellent validity in distinguishing between two conditions.

AUC more than 0.9: The approach used demonstrates outstanding validity in distinguishing between two conditions.

Results

Out of 59 patients examined, 26 were eligible for the study. The mean age of the subjects was 55.6 ± 13.6 years, with the youngest aged 26 and the oldest 75. The majority of subjects were male, comprising 19 individuals (73.1 %). Additionally, 34.6 % (9 people) had a history of comorbidity upon diagnosis. The distribution of patients by disease stage was as follows: stage three (10 individuals, 38.5 %), stage two (7 individuals, 26.9 %), stage four (5 individuals, 19.2 %), and stage one (4 individuals, 15.4 %). According to the International Prognostic Index, a significant number of individuals fell into subgroups Low-intermediate risk (10 individuals, 38.5 %), High-intermediate risk (7 individuals, 26.9 %), and stage four (5 individuals, 19.2 %). A non-aggressive disease subgroup was reported in 14 patients (53.8 %), while 12 patients (46.2 %) exhibited aggressive behavior and histology. Recurrence was observed in 1 patient (3.8 %) and 7 patients (26.9 %) experienced death. It is worth noting that all cases of death and recurrence were recorded in the group of patients with aggressive disease (Table 1).

In Figure 1, the SUV_{max} variable with AUC=0.79 (95 % CI 0.61-0.96) demonstrated acceptable validity in distinguishing patients with aggressive lymphoma from NOS subtype (p=0.012). Additionally, the cut point of 21.1 for SUV_{max} yielded a sensitivity of 66 % and a specificity of 72 % in distinguishing aggressive from non-aggressive types.

Comparing patients with the aggressive and NOS subtypes, the results indicated that the mean age of the patients was 60.3 ± 11.1 years (median 60.5 years) and 51.6 ± 14.6 years (median 54 years), respectively. The observed difference was not found to be significant (p=0.1).

The values of SUV_{max} in patients with invasive histology were 27.5 ± 15.6 (mean 25.6) and in patients with NOS histology were 15.4 ± 9.8 (mean 14.4), the observed difference It was statistically significant (p=0.01). (Figure 2).

Based on the data in Figure3, patients in the aggressive group had a median overall survival of 10 months, which was significantly lower than the NOS group's overall survival of 24 months (p=0.002, log-rank test).

Table 1. *Demographic characteristics of patients*

Variable		Frequency	Percentage
Sex	Male	19	73.1
	Female	7	26.9
History of comorbidity**	Yes	17	65.4
	No	9	34.6
Disease Stage	1	4	15.4
	2	7	26.9
	3	10	38.5
	4	5	19.2
International Prognostic Index	Low risk	3	11.5
	Low-intermediate risk	10	38.5
	High-intermediate risk	7	26.9
	High risk	6	23.1
Behavior group	Aggressive	12	46.2
	Non-aggressive	14	53.8

Note. **The current study identified aggressive histology as the diagnosis of Burkitt's lymphoma, unclassifiable Burkitt-like lymphoma with a high mitosis rate (Ki67 cell proliferation index above 80-90 %), advanced stage at diagnosis, CNS involvement from the start, rapid progression, numerous clinical symptoms, poor treatment response, and quick relapse.

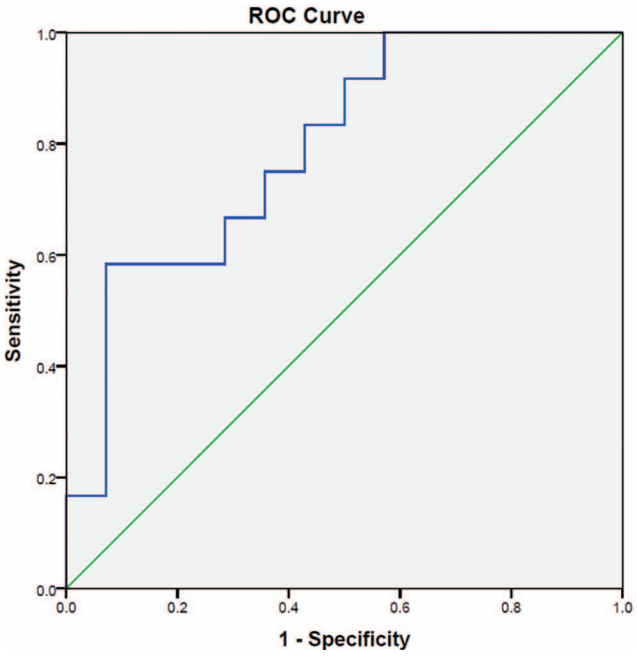

Figure 1. *ROC curve of SUV_{max} value in differentiating aggressive from NOS subtype in DLBCL patients*

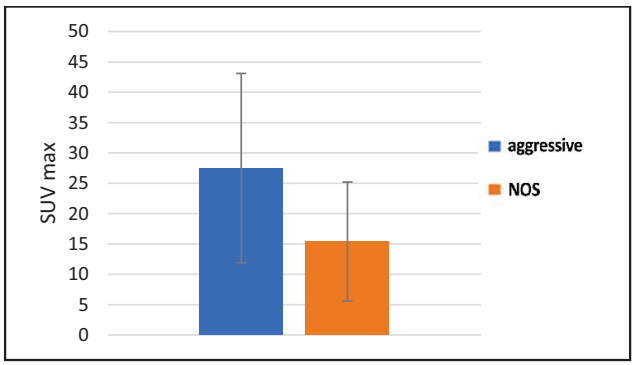

Figure 2. *Comparison of SUV_{max} in DLBCL patients with aggressive and NOS subtype*

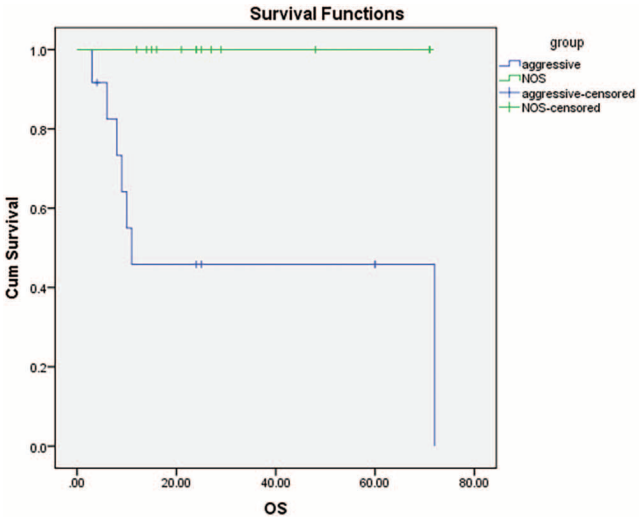

Figure 3. *Comparison of overall survival of DLBCL patients with aggressive and NOS subtype*

Table 2. *Comparison of Mortality Rates in DLBCL patients based on Aggressive and NOS Histology*

		Aggressive	NOS	p-value
Dead		7(58.3)	0	0.001*
Relapsed		1(8.3)	0	0.4*
Disease Stage	1	2(16.7)	2(14.3)	0.4**
	2	2(16.7)	5(35.7)	
	3	5(41.7)	5(35.7)	
	4	3(25)	3(14.3)	
International Prognostic Index	Low risk	0	3(21.4)	0.3**
	Low-intermediate risk	5(41.7)	5(35.7)	
	High-intermediate risk	4(33.3)	3(21.4)	
	High risk	3(25)	3(21.4)	

Note. *Fisher's exact test
** Mann-Whitney

Unfortunately, due to only one recorded case of recurrence, a disease-free survival analysis could not be performed.

This study found a notable disparity in mortality rates between patients with aggressive and NOS histology. The former had a mortality rate of 58.3 %, while the latter had a rate of 0 % (p=0.001) (Table 2).

Overall survival was compared by grouping patients based on their SUV_{max} values (less than 21 vs. equal to or greater than 21.1). The analysis showed no significant difference in survival between the two groups (24 months versus 15 months; log-rank test (p=0.6)). The study's small sample size may have hindered the recognition of a substantial difference, despite the evident contrast in the survival rates between the two groups.

Discussion

Recent cytogenetic studies have shown that diffuse large B cell lymphoma is not a uniform disease, consisting of different subgroups [16, 17]. Aggressive behavior in specific subgroups can lead to the early involvement of non-lymphatic organs in the diagnosis process. The core principle of the cytogenetic investigations mentioned above involves the examination of *MYC*, *BLC6*, and *BLC6* gene rearrangements. As a result, 90 % of B-cell lymphomas are classified as non-germinal center (NGC) or activated B cell (ABC) subtypes, associated with worse outcomes and are rarely DH, while the remaining 10 % are classified as GCB, with better outcomes and include double expressor (DE) and double hit (DH) cases. Despite the unreliability of IHC results for patient classification, access to cytogenetic evaluations in Mashhad is limited due to expensive costs, leading to most patients receiving monotonous treatment without consideration for specific subgroups. Meanwhile, following the European Society of Medical Oncology (ESMO) guideline and with a focus on resource conservation, patients with B-cell lymphoma are first screened with IHC, then their results are confirmed through FISH and NGS. With the increasing use of PET/CT scans for lymphoma patients, this research explores its effectiveness in identifying diverse forms of diffuse large B-cell lymphoma, with higher aggressive behavior compared to conventional ones. Additionally, as a functional imaging method, PET can also show tumoral cell activity.

The study demonstrates that FDG-PET/CT scans effectively distinguish between aggressive and non-aggressive lymphomas. Aggressive lymphomas exhibit higher metabolic activity and SUV_{max}, with a determined cut-off point of 21.1 MBq/g for differentiating aggressive histology from normal histology. Additionally, research by Kuker et al. (2023)[18] and Zhou et al. (2016)[19] supports the prognostic value of FDG-PET/CT scans, particularly in predicting overall and disease-free survival in patients with DLBCL. These findings highlight

the significance of metabolic activity and SUV_{max} as prognostic indicators in lymphoma patients.

Zhao et al. (2021) studied 87 DLBCL patients who had FDG PET/CT scans before treatment. Their findings indicated that increased metabolic activity is linked to worse outcomes for patients treated with the R-CHOP regimen, and tumor metabolic volume independently predicts prognosis in this patient group [20].

Consistent with our findings, other studies, including those by Esfahani et al. (2013) [21], Xie et al. (2016) [22], and Shagera et al. (2019) [23], in various patient populations with lymphoma have reported similar results regarding the relationship between metabolic activity and patient survival. It seems that higher metabolic activity and volume in patients are associated with worse outcomes compared to those with lower levels. Evidence from a meta-analysis of 13 DLBCL studies [24]and a large phase III clinical trial (registration code NCT01287741) in the US Clinical Trials Registry [25] supports this conclusion.

In comparing patients with aggressive and NOS histology, this study found that histology type has no significant relationship with disease stage at diagnosis and IPI. However, patients with aggressive histology experience poorer median survival and higher mortality, consistent with the findings of numerous other studies.

Several investigations have explored the impact of aggressive histologies (double and triple HIT DLBCL) on the prognosis and treatment efficacy of DLBCL patients. Barrans et al. (2010) examined 303 newly diagnosed DLBCL patients, most of whom received R-CHOP therapy. The results revealed that being diagnosed with double-hit or triple-hit DLBCL is associated with a higher likelihood of GCB and a lower survival rate compared to cases without rearrangements but with a higher IPI score [26]. Another study by the British Columbia Cancer Agency (BCCA) followed 135 DLBCL patients treated with R-CHOP, showing poor outcomes in cases with aggressive histologies [27].

Our research supports previous studies and provides strong evidence that DLBCL is not a homogeneous disease, requiring precise cytogenetic and histopathological assessment for accurate diagnosis and treatment. Our study also suggests poorer overall survival in patients with increased metabolic activity, although this was not statistically significant. This study is one of the first to investigate the role of lymphoma metabolic activity in determining the invasion rate of malignant lesions in Iran, with a significant sample size. However, the study had limitations, particularly the retrospective approach. Additionally, the limited availability of complete cytogenetic evaluation, specifically FISH analysis for *MYC*, *BCL2*, and *BCL6* gene rearrangements, was another constraint.

The findings may be less generalizable if there are some double expressors in the less aggressive category, given the clinical criteria used for classification. Moreover, as there was only one recorded case of recurrence, we could not perform DFS analysis.

The population studied in this research was highly heterogeneous, including Burkitt's lymphoma patients and those with double or triple DLBCL, which may lead to varying outcomes. Considering that Diffuse Large B-Cell Lymphoma is a broad subset of non-Hodgkin's lymphoma, here, we made an effort to ensure that every patient belonged to the Diffuse Large B-Cell Lymphoma subgroup, in order for heterogeneity not to negatively impact the interpretation of the results. Really, Heterogeneity can indicate differences within individual samples, between samples, and between experimental results in a meta-analysis.

These patients were diagnosed at a younger age and underwent more intense treatment, potentially skewing the overall results of the study. The SUVmax results were not compared based on cytogenetic evaluation, suggesting that reported SUVmax values may be affected if this evaluation is completed. Future studies should assess the expression levels of MYC proteins, BLC6, and BLC2 in patients to understand their correlation with SUVmax and disease prognosis. Additionally, if financial conditions allow, genetic modifications of these proteins can be assessed using PCR. It is recommended that upcoming research incorporates radiomics into the evaluation of FDG-PET/CT scan images and explores the predictive value of each individual feature.

Conclusion

The study involved 26 patients and found that MBq/g = 21.1 SUV max with (95% CI 0.61 — 0.96) AUC = 0.79 is a valid means of distinguishing between aggressive and less aggressive DLBCL lymphoma (p=0.012). As such, the study suggests using FDG PET CT Scan alongside morphological investigations and pathological immunophenotyping during standard staging to identify patients who may benefit from cytogenetic testing. This is particularly important in our country where access to such testing is limited.

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Марзие Азмун: рецензирование и редактирование

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