

RESEARCH ARTICLE

Editorial Process: Submission:08/09/2025 Acceptance:06/07/2026 Published:06/18/2026

Impact of Depiction of Brown Adipose Tissue (BAT) in Baseline FDG PET/CT on Progression-free Survival in Lymphoma Patients

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Abstract

Introduction: Brown adipose tissue (BAT) activity seen on 18F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT) has been increasingly recognized as a potential biomarker in various cancers, including lymphomas. The aim of this study was to investigate the correlation between posttreatment survival outcomes and BAT activity depicted in baseline FDG PET/CT scans in lymphoma patients. **Material and Method:** This retrospective study was conducted at the PET/CT Section of the Department of Radiology, Aga Khan University Hospital, Karachi, Pakistan (2019–2025). The study was granted exemption by the Ethical Review Committee (2024-10630-31016). Patients with lymphoma (Hodgkin's and non-Hodgkin's; HL; NHL) whose baseline FDG PET/CT revealed BAT activation were selected. FDG PET/CT scan was acquired using a standardized protocol adopted from the European Association of Nuclear Medicine Guidelines (2015). These patients were followed for a mean of 03 years (range 15–36 months) for survival outcome (progression-free survival; PFS). **Results:** During the study period, 259 patients with lymphomas (96 HL and 163 HL) who had baseline FDG PET/CT were selected. The cohort included 75% males (n = 194) and 25% females (n = 65), with a median age of 58 years (range: 03-80). BAT activation was identified in 27% of patients (n = 69). A significant association was observed between BAT activation and higher 3-year PFS, with activated BAT patients achieving a survival rate of 78% compared to 58% in those without activation (p < 0.05). **Conclusion:** Lymphoma patients with activated BAT depicted in their baseline FDG PET/CTs showed longer progression-free survival than those without. This study also emphasizes the need for further evaluation of BAT's role in metabolism, tumor microenvironment, and long-term prognosis in patients with lymphomas.

Keywords: Brown adipose tissue- lymphoma- Hodgkin's- Non-Hodgkin's- Progression free survival- BAT

Asian Pac J Cancer Prev, 27 (6), 2061-2064

Introduction

Fat in the human body is classified as white adipose tissue (WAT) and brown adipose tissue (BAT). WAT deposits extra energy into triglycerides, while BAT has the unique ability to convert mitochondrial energy into heat (rather than ATP) via uncoupling protein-1 (UCP-1). WAT distributed in abdomen and subcutaneous is responsible for obesity while BAT is considered to reduce risk of obesity due to thermogenesis [1]. WAT secretes many adipokines which are proinflammatory and among them leptin has been demonstrated to play important role in lymphoma and breast cancers [2, 3]. Leptin is also secreted by BAT in lesser concentration, and few reports favor its role in development and progression of cancers [4]. 18-Fluoro

Deoxy glucose (FDG) PET/CT is considered a standard of care in lymphoma due to its pivotal role in diagnosis, staging and response assessment. Depiction of BAT on FDG PET/CT is more common in female, younger, lower body mass index, lower blood glucose and lower room / outdoor temperature [5]. There are published reports highlighting the role of BAT depicted on FDG PET/CT in reducing tumor growth in animal model and significantly longer overall and progression free survival in patients with lymphomas and breast cancers [5, 4]. The aim of this study was to find the progression free survival (PFS) in lymphoma patients with or without BAT activation on baseline FDG PET/CT studies.

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Materials and Methods

This retrospective study was conducted at PET/CT Section of Department of Radiology, Aga Khan University Hospital Karachi, Pakistan (2019-2025). The study was granted exemption by ethical review committee (2024-10630-31016). Patients with lymphoma (Hodgkin's and Non-Hodgkin's; HL; NHL) who had had baseline FDG PET/CT during study period were selected. FDG PET/CT scan was acquired using standardized protocol adopted from European Association of Nuclear Medicine Guidelines 2015[6]. Based on depiction of brown adipose tissue (BAT) on FDG PET/CT patients were classified into BAT +ve and BAT -ve. These patients were followed for a mean 03 years (range 15- 36 months) for progression free survival (PFS).

FDG PET/CT Imaging

FDG PET/CT was performed as per institutional protocol adopted from EANM guidelines [6]. All patients had 4-6 hour fasting (only plain water was allowed) and a fasting blood sugar less than 200 mg% before receiving an intravenous FDG dose of 3 MBq/Kg in the uptake room. During uptake period (55 -75 minute) patients were requested to lie comfortably and allowed to take about 500-1000 ml of plain water. Bladder was emptied prior to call the patient for PET/CT imaging suite equipped with Celesteion, Toshiba, Japan. A low dose CT examination (mid brain to mid-thigh) without intravenous contrast from head to toe followed by acquisition of PET imaging using 3 minute/bed position from toe to head in all patients. Both PET and CT images were acquired with patients under normal tidal breathing. PET (both non-attenuation corrected, and attenuation corrected), CT and fusion FDG PET/CT images were examined in axial, coronal and sagittal planes on the manufacturer's review station. All FDG PET/CT images were evaluated by two nuclear physicians having an experience of more than 5 years. On a transaxial, attenuation-corrected PET image, the maximum standardized uptake values (SUVmax) were obtained by placing regions of interest (ROIs) on hypermetabolic lesions that had been identified on visual analysis.

Statistical Analysis: Continuous variables were described by mean \pm standard deviation (SD). Comparisons between patient groups were performed using Student's t test for continuous variables and the χ^2 test for categorical variables. Kaplan–Meier cumulative survival analysis was performed, and survival curves were compared by the Logrank test. Statistical significance was defined as $P < 0.05$. Commercially available packages Microsoft excel 2010, Medcalc® and statistical package for social sciences (SPSS 19®) were used.

Results

During the study period (2019-2025), 259 patients with lymphomas (96 HL and 163 NHL) who had had baseline FDG PET/CT were selected. The cohort included 75% males (n=194) and 25% females (n=65), with a median age of 58 years (range 03–80). Body mass index (BMI)

was high (≥ 27.5 Kg/m²) in 75 (29%) of patients (obese) while 184 (71%) were non-obese. According to Lugano Classification, patients were categorized to have Stage I (n=15; 06%), Stage II (n=29; 11%), Stage III (n=60; 23%) and Stage IV (n=155; 60%). BAT activation was identified in 27% of patients (n=69) while in 73% (n=190) it was not appreciated on FDG PET/CT (Table 1). Kaplan Meier survival curve shows a significant association observed between BAT activation and improved 3-year progression free survival rates, with activated BAT patients achieving a survival rate of 78% compared to 58% in those without activation ($p < 0.05$) (Figure 1).

Discussion

We herein present the results of a study analyzing the relationship between presence of activated BAT and PFS in lymphoma patients. To the best of our knowledge, our study has the highest study population than previously published studies with similar objective [7, 8]. BAT activation seen on FDG PET/CT studies was found to have a positive correlation for significantly longer survival in patients with breast cancers and lymphoma [4, 8].

The frequency of activated BAT depicted on FDG PET/CT has been reported to range from 1.7 to 9.3% [9]. Current study demonstrated a much higher prevalence of active BAT of 27% in lymphoma patients. This is much higher than 12% incidence in a published study aimed to find the determinants of BAT in lymphoma patients [10]. This incidence is surprisingly high because our standard PET/CT protocol includes efforts to prevent BAT activation like maintaining constant ambient temperatures and calling patients early to adapt to indoor temperature. Our protocol does not include pharmacological intervention like propranolol or diazepam. On further analyzing the results, we could not find any significant association with age distribution and season (winter or summer) during which scans were performed. However, our study had 60% of patients with Stage IV disease which could have a contributory role. According to a published smaller study including different cancers, total metabolic activity

Table 1. Study Demographics of Lymphoma Patients with Brown Adipose Tissue on Baseline FDG PET/CT

Variables	N=259
Age (years) Mean \pm SD; Median (range)	43 \pm 18; 58 (03-80 years)
Gender (Male: Female)	194: 65 (75: 25%)*
BMI (Kg/m ²) Mean \pm SD	25.626 \pm 10.751
Obesity (≥ 27.5 Kg/m ²)	75 (29%)*
Hodgkin's ; Non-Hodgkin's	96 (37) ; 163 (63%)
Lugano Stage	
I: II: III: IV	15: 29: 60: 155 (06%: 11%: 23%: 60%*)
BAT on baseline FDG PET/CT	
Positive: Negative	69:190 (27%:73%)*
3 years PFS	
BAT positive: BAT negative	54:110 (78%:58%)

* $p < 0.05$; SD, standard deviation; BMI, Body Mass Index; BAT, Brown Adipose Tissue

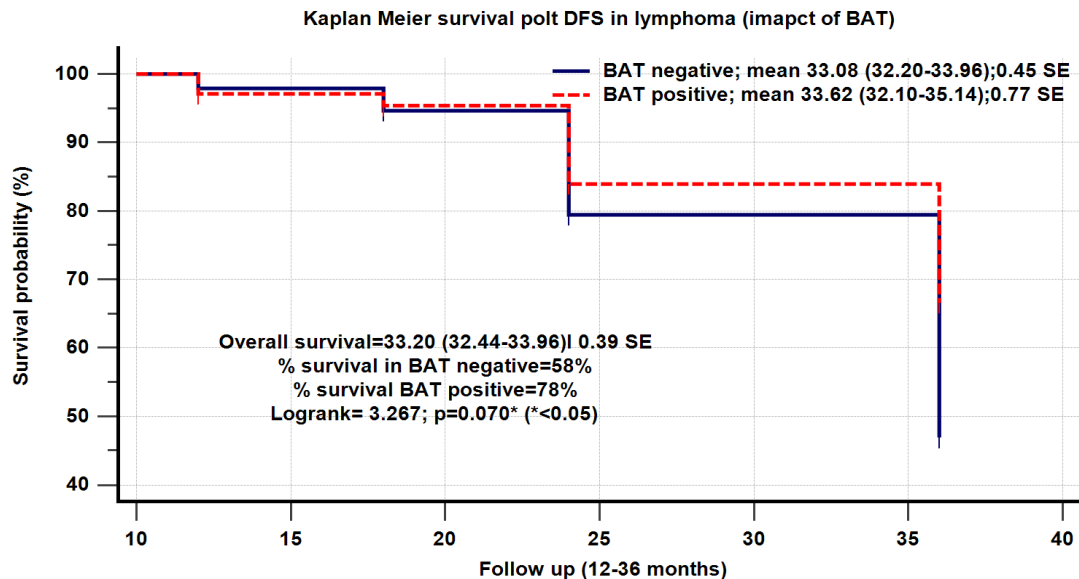


Figure 1. Kaplan Meier Survival Plot for Progression Free Survival in Lymphoma Patients with Presence and Absence of Brown Adipose Tissue in Baseline PET/CT Scan. SE, Standard Error; BAT, Brown Adipose Tissue; * $p < 0.05$

(TMA) of activated BAT had significant association with cancer grade [11]. In-vitro studies have shown that tumor necrosis factor alpha (TNF- α) increases the thermogenic activity of BAT and promotes synthesis of fatty acid from glucose in assayed BAT tissue [12]. TNF- α is produced by germinal center dendritic reticulum cells (DRC) in lymphoid tissue and plays a regulatory role in local immune responses. In lymphoproliferative disorders, expressions of the p75 receptor and TNF- α was found primarily in high-grade non-Hodgkin lymphomas [13]. So, in our study, larger number of patients with advanced stage NHL reasonably explains the unusual higher frequency of activated BAT on FDG PET/CT studies.

Our results suggest that the presence of BAT activation is associated with longer PFS in lymphoma patients. This finding is in accordance with a recently published study on case-controlled patients with active BAT on FDG PET/CT images had significantly longer overall and progression-free survival [8]. Studies in animal models have suggested that activated BAT can suppress tumor growth potentially due to its ability to consume significant amounts of glucose and other nutrients. So, activated BAT deprived the cancer cell of resources required for tumor growth [14]. Fundamentally, activated BAT can act as a “metabolic sink,” limiting the fuel supply for tumor cells [14]. There are some studies which had found no association of BAT and lymphoma’s metabolic activity but found an inhibitory effect of prior radiotherapy and chemotherapy on BAT recruitment [10]. In essence, active BAT appears to be a favorable prognostic factor in lymphoma, potentially through mechanisms that reduce tumor burden and enhance treatment response. However, more research is required to fully understand the implications of BAT for lymphoma management. The primary limitation of our study is its retrospective nature which undeniably may introduce inherent biases. But the most important limitation is that we are not aware of mechanism(s) leading to association between BAT

and longer PFS. This brings our focus towards future prospective studies to assess if increasing BAT mass or activity could be a useful addition to cancer therapy regimens. Equally important will be the identification of the hormones and cytokines that modulate BAT activity and how they are influenced by cancer.

Lymphoma patients with activated BAT depicted in their baseline FDG PET/CTs showed longer progression free survival than those without. This study also emphasizes the need for further evaluation of BAT’s role in metabolism, tumor microenvironment and long-term prognosis in patients with lymphomas.

Author Contribution Statement

Maseeh uz Zaman: Conception, interpretation, critical revision, final approval. Nosheen Fatima: Interpretation, Statistics, drafting, final approval. Sidra Zaman: Literature search, drafting, critical revision. Anwar Ahmad: Literature search, drafting, critical revision. Uzair Ahmed: Data Collection, Literature search. Minhaj Ahmed: Data Collection, Literature search. Areeba Zaman: Conception, Design, Critical revision. Rabiya Fatima Hashmi: Literature search, data collection.

Acknowledgements

The authors acknowledge the editors for their valuable comments to improve the manuscript.

Ethical Approval

This study was approved by ethical review committee of Aga Khan University Hospital via ERC#: 2024-10630-31016

Conflict of Interest

There is no financial or institutional conflict of interest.

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