COLLEGE OF HEALTH SCIENCES, DEPARTMENT OF INTERNAL MEDICINE, NUCLEAR MEDICINE UNIT

ROLE OF ^{18}F-FLUORODEOXYGLUCOSE–POSITRON EMISSION TOMOGRAPHY BEFORE, DURING AND AFTER TREATMENT IN NK-CELL AND T CELL LYMPHOMAS: A RETROSPECTIVE STUDY FROM PASCALE HOSPITAL, NAPOLI, ITALY 2022 G.C

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STATEMENT OF THE AUTHOR

By my signature below, I declare and affirm that this thesis is my own work. I have followed all ethical principles of scholarship in the preparation, data collection, data analysis and completion of this thesis. All scholarly matter that is included in the thesis has been given recognition through citation. I affirm that I have cited and referenced all sources used in this document. Every serious effort has been made to avoid any plagiarism in the preparation of this thesis. This thesis is submitted in partial fulfillment of the requirement for the degree of specialty in Clinical Nuclear Medicine to AAU. I would like to declare that this thesis has not been submitted to any other institution anywhere for the award of any academic degree, diploma or certificate.

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This thesis by Dr. Amanuel Chimdesa Enkosa is accepted in its present form by the board of examiners satisfying thesis requirement for the specialty certificate in Clinical Nuclear Medicine.

Title of project: Role of 18F-Fluorodeoxyglucose–Positron Emission Tomography Before, During and After Treatment in T cell and Nk-Cell Lymphomas: A Retrospective Study from Pascale Hospital, Napoli, Italy 2022 G.C.

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ACRONYMS

ABMT: Autologous bone marrow transplantation

ALCL: Anaplastic lymphoma kinase positive anaplastic large cell lymphoma

AUC: Area under the curve

CHOP: Cyclophosphamide, doxorubicin, vincristine and prednisone

DLBCL: Diffuse large B cell lymphoma

DS: Deauville score

EBV: Epstein–Barr virus (Human gamma herpes virus 4)

ECOG- Eastern Cooperative Oncology Group

FDG-PET: ^{18}F-fluorodeoxyglucose–positron emission tomography

HL: Hodgkin's Lymphoma

IPI: International prognostic index

KPI: Korean prognostic index

MTV: Metabolic tumor volume

NKTL: Natural killer cell and T cell Lymphoma

PACS- Picture archiving and communication system

PET-CT: Positron emission tomography Computer tomography

SUV max: Maximum standardized uptake value

TLG: Total lesion glycolysis

WBMTV: whole-body metabolic tumor volume

WBTLG: whole-body level of total lesion glycolysis

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Abstract

Background: Over the past years, ^{18}F- FDG PET has emerged as an efficient tool to assess Hodgkin's lymphoma and diffuse large B-cell lymphoma's response to treatment. ^{18}F- FDG PET is both sensitive and specific for initial staging in T cell /Natural killer cell lymphomas. However, the predictive value of early or post-therapy ^{18}F- FDG PET remains unknown.

Objective: Therefore, the objective of this study was to assess the role of ^{18}F- FDG PET before, during and after Treatment in T cell and Natural killer cell lymphomas.

Method: A facility-based descriptive retrospective cohort study design was employed. A total of 57 sample populations was selected using purposive sampling technique among patients visiting the nuclear medicine department of the hospital. A quantitative method of data collection was deployed using a data abstraction tool. Data was entered and analyzed using statistical software SPSS for windows V 26.0. The verbal ethical clearance was obtained from National Cancer Institute of Napoli.

Result: The result showed that 25 (61%) were males. About 17 (41.5%) of index cases were in the age group "61-75", and the mean (+SD) age of respondents was 57.8 (±15.4). All 100% of the index cases have been diagnosed with biopsy proven disease and PET/CT also showed positivity on all the index cases.

Discussion: Findings of this study revealed that metabolic parameters like SUVmax and whole-body metabolic tumor volume at the time of the diagnostic, interim and post treatment 18F- FDG PET scans does not predict disease progression of T cell /Natural killer cell lymphomas in the index cases. In addition, Sociodemographic variables such as sex and age on top of clinical parameters such as Ann Arbor staging at the time of diagnosis, primary lesion location, ECOG and international prognostic index (IPI) does not seem to have statistical correlation with that of disease progression.

Recommendation: It is recommended to conduct the study in other centers as well as amending the limitation of our study challenges.

Key words: ^{18}F-fluorodeoxyglucose, positron emission tomography, T-cell lymphoma, T/NK neoplasm.

Chapter 1: Introduction

1.1 Background

Natural killer/T-cell lymphoma (NKTL) is an uncommon subtype of non-Hodgkin's lymphoma which is typically associated with Epstein–Barr virus (EBV) infection (Cai et al., 2014). Patients with NKTL are mainly located at East Asia, Southeast Asia, and Latin America; in contrary, NKTL is relatively unusual in Europe and North America (Gill et al., 2010; William and Armitage, 2013). Clinically, NKTL is divided into two types: extra nodal nasal type NKTL (ENKTL) and extra nasal NKTL. ENKTL is characterized by frequent angiocentric growth, necrosis, and a cytotoxic phenotype and usually affects the nasal cavity, nasopharynx, and upper aerodigestive tract (Tse and Kwong, 2012). Extra nasal NKTL frequently involves multiple areas including the skin, gastrointestinal tract, testis, and soft tissue (Chan et al., 1997). ENKTL is classically associated with a poorer treatment response and prognosis than other types of lymphomas (Yamaguchi et al., 2011). Chemotherapy in combination with radiotherapy is usually needed to achieve superior outcomes (Pokrovsky and Vinnikov, 2017). The cumulative probability of 5-year survival ranges from 37.9% to 49.5% (Lee et al., 2006). Accurate diagnosis and staging are essential in the treatment strategy and prognosis of NKTL. However, neither a paradigmatic treatment nor useful prognostic factors have been determined.

Recent advances in imaging, use of prognostic indices, and molecular profiling techniques have the capability to improve disease characterization and outcomes in lymphoma (Barrington *et al.*, 2014). PET-CT is increasingly used for staging and response assessment in lymphoma, (Cheson, 2011) both for early assessment during treatment, (Cerci et al., 2010) commonly referred to as interim PET-CT (iPET), (Meignan et al., 2009) and for remission assessment at the end of treatment. Almost all lymphomas are FDG avid, but most published data are related to the use of PET in HL, DLBCL, and follicular lymphoma (FL) (Barrington *et al.*, 2014). Over the past years, ^{18}F-fluorodeoxyglucose–positron emission tomography (FDG–PET) has made an appearance as an efficient tool to assess Hodgkin's lymphoma (HL) and DLBCL response to treatment. Furthermore, it has been demonstrated that results of interim FDG–PET predict HL patients' outcome (Terasawa et al., 2010).

Mature T-cell and natural killer (NK) neoplasms are rare and heterogeneous. Except for ALK+ anaplastic large cell lymphoma (ALCL), their outcome is abysmal (Vose et al., 2008). Because of the poorer treatment response and prognosis of ENKTL, accurate diagnosis, staging and prognostication of NKTL is urgently needed. Strategies such as combination chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP)-based chemotherapy regimen, immunochemotherapy (Gallamini et al., 2004), autologous bone marrow transplantation (ABMT) (Rodríguez et al., 2007) or allogeneic stem cell transplantation (allo-SCT) (Le Gouill et al., 2008) have been proposed. However, no consensual strategy has emerged and the CHOP regimen can still be considered as the gold standard. Using conventional chemotherapy regimens, the 5-year overall survival (OS) of non-cutaneous ALK2 T/NK lymphomas ranges between 7% and 64% (Vose et al., 2008).

Recent studies suggest that FDG–PET is both sensitive and specific for initial staging in T/NK lymphomas (Suh et al., 2008). However, the predictive value of early (so called interim) or post-therapy FDG–PET remains unknown. In the present analysis we have examined the impact of FDG-PET on the initial staging of NKTL, we have also investigated the role of interim and post-therapy FDG–PET in predicting the prognosis of T/NK lymphomas in terms of PFS and OS in a retrospective and unicentric study.

1.2 Statement of the Problem

Natural killer/T-cell lymphoma (NKTL) is a highly aggressive type of lymphoma with a median survival time of less than 12 months and with a remarkable geographical prevalence in Asia and South America (Au et al., 2005). There is a clear geographic deviation in NNKTL prevalence. In Asia and South America, NNKTL consists of 3-10% of non-Hodgkin lymphoma, whereas less than 1% in Western countries. Previous studies estimated that the incidence rate of NNKTL is higher in Asia by 10-fold compared to Europe (Harabuchi et al., 2019). No standard effective treatment currently exists, as NKTL is refractory to chemotherapy and is associated with a high rate of therapeutic failure and poor prognosis (Avilés et al., 2000).

Developing optimal approaches for the early identification of patients at high risk of progression or relapse is important in clinical management. The most common approaches include histopathological subtyping and use of the IPI (Au et al., 2005) and the Korean Prognostic Index (KPI) (Suh et al., 2008). Additionally, the immunophenotype and gene expression pattern can be prognostic factors. However, previous prognostic indicators based on the presented parameters have several drawbacks, including lack of consideration of the lymphoma response to treatment and insufficiency for accurately identifying patients with immunochemotherapy-refractory disease (Tse and Kwong, 2017).

Although previous studies have evaluated the prognostic value of these PET/CT parameters for various types of lymphoma, similar studies of NKTL have been limited by sample size. Moreover, previous findings remain controversial due to heterogenous patient enrollment, various imaging conditions, different cut-off values for survival predictions, and undefined treatment protocols. Therefore, the purpose of this research was to evaluate the prognostic role of multiple PET/CT in NK/T-cell lymphoma at three different time points: baseline, interim and end of treatment.

Chapter 2: Literature Review

2.1. Diagnostic utility of PET/CT in patients with NKTL

PET/CT is a valuable tool for assessing extra-nodal involvement in patients with NKTL (Fujiwara et al., 2011; Harisankar, 2015). In one study, the mean ^{18}F-FDG uptake measured by the maximum standardized uptake value (SUVmax) was found to be significantly higher in NKTL (Wu et al., 2010). In 2010, Wu et al. (Wu *et al.*, 2010) retrospectively analyzed 15 patients with NKTL and assessed the role of ^{18}F-FDG PET/CT in staging. ^{18}F-FDG PET/CT detected nasal or extra-nasal lymphoma lesions in at least one site in all 15 patients. Of 11 patients with ENKTL, high levels of ^{18}F-FDG uptake were observed in the nasal cavities in 8 patients and in the nasopharynx in 2 patients, and extranasal lesions were found in 7 patients with nasal type NKTL. In four patients with ENKTL, no obvious ^{18}F-FDG uptake was seen in either the nasal cavity or nasopharynx; however, multiple extranasal lesions were identified. These results suggest that NKTL exhibits high ^{18}F-FDG uptake and that PET/CT is a useful tool in the staging of this disease.

In 2011, Fujiwara et al. compared the utility of PET/CT with conventional methods (including CT, biopsy, and bone marrow examination) in the staging of ENKTL. Nineteen untreated patients with ENKTL were analyzed, and 116 lesions were detected by conventional methods and PET/CT. In total, 108 lesions (93%) were discovered by PET/CT and only 80 lesions were detected using conventional methods. The number of extra-nodal lesions detected by conventional methods and PET/CT was 89; 84 (94%) and 51 (61%) lesions were positive as detected by PET/CT and conventional methods, respectively (Fujiwara et al., 2011). In a similar study, Zhou et al. evaluated the utility of ^{18}F-FDG PET/CT in the diagnosis of cutaneous ENKTL. In total, 39 patients with newly diagnosed ENKTL were included. PET/CT and conventional methods detected 139 lesions, among which 50 were cutaneous and 89 were extracutaneous-positive lesions. ^{18}F-FDG PET/CT detected 48 cutaneous and 88 extracutaneous lesions, while conventional methods detected only 34 cutaneous lesions and 61 extracutaneous lesions that were positive for malignancy (Zhou et al., 2016).

A similar study was performed in a larger group of patients with ENKTL (Moon et al., 2013). In total, 1300 anatomic lesions were assessed with an ^{18}F-FDG PET/CT scan and with conventional methods (Moon et al., 2013). Only 59 nodal and 71 extra-nodal anatomic lesions were truly

positive for malignancy. PET/ CT detected 58 nodal and 69 extra-nodal anatomic lesions that were malignant, whereas conventional methods detected only 44 nodal and 61 extra-nodal anatomic lesions that were malignant (Moon et al., 2013). Thus, PET/CT exhibited a significantly better sensitivity and specificity than conventional methods for the detection of malignant lesions. Moreover, PET/CT findings altered the original staging category for 12 patients (21.2%) and affected treatment planning in 23 patients (44.2%) (Moon et al., 2013). These studies demonstrated that PET/CT is superior to conventional methods in detecting cutaneous and extracutaneous lesions. Zhou et al. (Zhou et al., 2016) assessed the role of FDG-PET/CT in bone marrow involvement in patients with ENKTL and found that the sensitivity and specificity of FDG-PET/CT for identifying bone marrow involvement was 100% and 86%, respectively. They suggested that FDG-PET/CT may be used as a complementary tool in patients with bone marrow involvement not detected by bone marrow biopsy. Thus, PET/CT is a useful tool for staging and treatment planning in patients with NKTL. PET/CT also has limitations, including false-positive results. Liu et al.(Cai et al., 2014) reported 2 false-positive lesions of 429 lesions in 39 patients with ENKTL detected by PET/CT. One lesion with high FDG uptake was found in the right abdominal wall skin, but the biopsy revealed herpes zoster. The other lesion was found on the left lower limb, and the biopsy confirmed inflammatory cell infiltration; this lesion disappeared after 1 month. Cheson et al. reported that the false-positive rate of interim PET was 87% and that the positive predictive value was only 32% in patients with DLBCL (Cheson et al., 2007). They suggested that PET/CT scans should not be performed for at least 3 weeks, preferably 6 to 8 weeks, after completion of therapy because this false-positive result may persist for up to 2 weeks after chemotherapy alone or for 2 to 3 months after radiation therapy or chemoradiotherapy.

2.2. Staging and restaging roles of PET/CT in patients with NKTL

Recent studies have suggested that PET/CT may be more advantageous than a routine work-up in NKTL staging. ^{18}F-FDG PET/CT may be more effective than conventional methods for detecting nodal and extra-nodal malignant lesions and for correctly identifying primary sites missed by conventional methods (Cai et al., 2014; Fujiwara et al., 2011; Moon et al., 2013; Wu et al., 2010). Moreover, the original staging may be modified and the treatment strategies may be influenced by PET/CT data (Cai et al., 2014; Fujiwara et al., 2011; Moon et al., 2013; Wu et al., 2010). However, because limited numbers of patients were included in previous studies, it is difficult to conclude

that ^{18}F-FDG PET/CT should serve as the standard staging method (Cai et al., 2014; Fujiwara et al., 2011; Moon et al., 2013; Wu et al., 2010).

Wu et al. found that ^{18}F-FDG PET/ CT detected more lesions than did conventional methods (biopsies, regional CT or magnetic resonance imaging, B-ultrasound, chest radiography, and medical examination). ^{18}F-FDG PET/CT imaging of patients with ENKTL changed the stage of disease in six patients: four were upstaged and two were down staged (Wu et al., 2010). Fujiwara et al. compared the utility of PET/CT and that of conventional methods in the staging of ENKTL (Fujiwara et al., 2011). The results showed that PET/CT findings altered the stage and treatment strategy in two cases (11%). MacDonald et al. reported that PET/CT improved target volume delineation and aided the staging of and radiotherapy planning in the treatment of ENKTL (MacDonald et al., 2011). Moon et al. reported that PET/CT findings altered the original staging category in 12 patients with ENKTL (21.2%) and affected treatment planning in 23 patients (44.2%). Moreover, PET/CT exhibited significantly better sensitivity than conventional methods for the detection of malignant lesions (Moon et al., 2013). Liu et al. found that ^{18}F-FDG PET/CT provided more accurate staging than did conventional methods in patients with cutaneous NKTL. In total, 39 patients with cutaneous NKTL were assessed using an ^{18}F-FDG PET/CT scan and conventional methods, and the results showed that ^{18}F-FDG PET/CT staging was consistent with the final stage determination (biopsy and clinical follow-up) in 94.9% (37/39) of patients, whereas staging by conventional methods was correct in the final stage determination in 74.4% (29/39) of patients (Cai et al., 2014). These results indicate that ^{18}F-FDG PET/CT is a valuable modality for staging and treatment planning in patients with ENKTL.

2.3. Evaluation of NKTL treatment response with PET/CT

Recent studies have confirmed the beneficial role of PET/CT in monitoring treatment responses in patients with non-Hodgkin's lymphoma, including NKTL, which is FDG-avid. Bai et al showed that the SUVmax predicted the responses to primary treatment in 81 patients with ENKL. A higher SUVmax (31.3) predicted treatment failure and was associated with bulky disease, local invasion, and a high KPI score (Bai et al., 2013). The Deauville score (DS) can also be used to assess treatment responses. The DS is both accurate and reproducible, affording good interobserver agreement (Biggi et al., 2013). Khong et al. used mid-treatment ^{18}F-FDG PET/CT to prospectively evaluate the responses of patients with ENKTL to the standardized SMILE chemotherapy regimen

(prednisolone, methotrexate, ifosfamide, L-asparaginase, and etoposide). ^{18}F-FDG PET/CT was useful for assessing responses during the early to middle phases of treatment. The study findings suggested that the 5-point DS allows continuous evaluation of treatment responses (Khong et al., 2014). Kim et al. found that the post-treatment DS and EBV-DNA status allowed patients with NKTL to be stratified by the risk associated with treatment. All patients were classified into a low- or high-risk group. The low-risk group comprised EBV-DNA negative patients with a post-treatment DS of 1 or 2, and the high-risk group comprised EBV-DNA-positive patients with a DS of 1 or 2 and EBV-DNA-negative patients with a DS of 3 or 4 at the end of treatment. Continuous treatment was recommended for the high-risk patients, while the low risk patients underwent follow-up only (Kim et al., 2015). A similar study also provided evidence by showing that sophisticated patient selection using PET/CT scanning and whole-blood EBV-DNA might provide additional information in the treatment of ENKTL (Suh et al., 2008).

2.4 Use of PET/CT to evaluate prognosis of patients with NKTL

Many factors affect the prognosis of patients with NKTL, (Bai et al., 2013; Khong et al., 2014; Kim et al., 2015; Ko et al., 2016a) including advanced-stage disease (stage III or IV), an unfavorable IPI score, a poor KPI score, bone or skin invasion, an elevated level of circulating EBV-DNA, an elevated lactate dehydrogenase level, a higher body mass index at the time of diagnosis, and the presence of EBV-positive cells in the bone marrow (Türker et al., 2012). However, reliable prognostic factors for NKTL remain controversial. New prognostic models continue to be developed; these include the prognostic index of natural killer lymphoma (PINK) and the PINK plus EBV-DNA models (Kim et al., 2016), featuring PET/CT data including the SUVmax, (Bai et al., 2013; Cai et al., 2014; Suh et al., 2008) and models such as the whole-body metabolic tumor volume (WBMTV) and the whole-body level of total lesional glycolysis (WBTLG) (Kim et al., 2013).

Several studies have shown that the SUV and textural features may also predict the prognosis of NKTL (Ko et al., 2016a; Song et al., 2013). However, the SUVmax reflects only the most obvious metabolic activity of a tumor in a region of interest and therefore depicts only the maximum metabolic rates of small regions of certain tumors, not the total tumor metabolism. Thus, use of

the SUVmax alone to predict the prognosis may be quantitatively misleading because FDG uptake may vary according to the individual patient with NKTL, the reference background, and the PET/CT system employed. New models for assessment of the prognosis of NKTL continue to be developed. MTV and total lesional glycolysis (TLG) are easily calculated by new software and reflect the whole metabolic tumor burden. TLG is an ideal metabolic parameter that combines the SUVmean and MTV to combine assessments of tumor volume and metabolism (Kim et al., 2016; Song et al., 2013). However, several limitations exist: some studies include few patients with ENKTL; measurement of MTV is not reliable, and reproducibility is low, especially for multiple disseminated lesions; and a standard MTV threshold has not been established (Bai et al., 2013; Kim et al., 2015).

As early as 2008, Suh et al evaluated whether the pretreatment ^{18}F-FDG uptake was a predictor of survival in patients with ENKTL (Suh et al., 2008). Multivariate analysis revealed that only the SUVmax of the primary site independently predicted disease-specific survival (Suh et al., 2008). However, their study had certain limitations, including a short follow-up time, a retrospective design, and a small number of patients. Bai et al also found that the pretreatment SUVmax is predictive of the prognosis in patients with newly diagnosed ENKTL (Bai et al., 2013). Jiang et al prospectively investigated the prognostic utility of pretreatment ^{18}F-FDG uptake and interim and post-therapy PET/CT data in 33 patients with ENKTL. The multivariate analysis revealed that the SUVmax of the primary tumor and post-therapy PET/CT data were prognostic in terms of both progression-free survival (PFS) and overall survival (OS). However, the interim PET/ CT data were not significantly predictive of survival (Jiang et al., 2016).

Kim et al. were the first to explore whether the SUVmax, WBMTV, and WBTLG of pretreatment FDG PET/CT images were predictive of the prognosis of patients with ENKTL (Kim et al., 2013). The WBMTV and WBTLG were higher in patients with than without progressive disease. The WBMTV and WBTLG of patients who died were higher than those of survivors. The multivariate analysis revealed that an SUVmax of >8.1, WBMTV of >14.4 cm^3, and WBTLG of >52.7 cm^3 were significantly prognostic in terms of PFS. Of these factors, a WBMTV of >14.4 cm^3 was the best prognostic factor in terms of OS (Kim et al., 2013).

Song et al. explored whether the MTV as determined by PET/CT (a measure of the lymphoma burden) was prognostic in 80 patients with IE/IIE stage NKTL (Song et al., 2013). The 3-year PFS

and OS of patients with high MTVs were lower than those of patients with low MTVs when a value of 35.2 cm^3 was used as the MTV cut-off. The multivariate analysis revealed that a good disease status and upfront radiotherapy were independently predictive of both PFS and OS (Song et al., 2013). The addition of radiotherapy to chemotherapy was suggested to benefit patients with high tumor burdens (Song et al., 2013). Liang et al. suggested that the SUVmax reflects the highest metabolic rate at only a single lymphoma site and was thus not representative of the metabolic rates at all lymphoma sites (Liang et al., 2016). Although the WBMTV and WBTLG may better reflect the metabolic status of all lymphoma sites, this is still disputed. Therefore, the cited authors introduced three new models using the SUVs of different sites. The WB1SUVmax model gives the sum of the whole-body SUVmax values of 11 nodal and 10 extra-nodal lesions. The WB2SUVmax model gives the sum of the whole-body SUVmax values of 3 nodal (neck, axillary, and inguinal and spleen) and 10 extra-nodal lesions. The WB3SUVmax model gives the sum of the whole-body SUVmax values of 3 nodal (superior diaphragm, inferior diaphragm, and spleen) and 10 extra-nodal lesions. Receiver operating characteristic curves revealed that the optimal cut-off values for the WB1SUVmax, WB2SUVmax, and WB3SUVmax models were 15.8 (sensitivity, 92%; specificity, 67%; area under the curve [AUC], 0.811; $p < 0.001$), 12.7 (sensitivity, 96%; specificity, 57%; AUC, 0.785; $p < 0.001$), and 15.8 (sensitivity, 88%; specificity, 70%; AUC, 0.793; $p < 0.001$), respectively. The WB1SUVmax, WB2SUVmax, and WB3SUVmax models were all significantly better than the SUVmax model. The WB3SUVmax model was selected for further prognostic investigation. The multivariate analysis showed that the WB3SUVmax value was an independent prognostic factor (Jiang et al., 2017).

Some authors have found that the DS may be prognostic of NKTL. Khong et al. used mid-treatment DS cut-offs of 1 to 3 (compared with 4 to 5) when performing receiver operating characteristic analysis of OS. The DS was the only predictor of both OS and PFS and was thus more powerful than other measures (Khong et al., 2014). Kim et al. used the following 5-point DS scale to assess 102 patients with NKTL after completion of planned treatment: 1 (absence of lesion uptake), 2 (low lesion uptake or uptake equivalent to that of the mediastinum), 3 (high lesion uptake by the mediastinum but low or equivalent uptake by the liver), 4 (moderately high liver uptake), and 5 (markedly high uptake in the liver with development of new lesions). A post-treatment DS of 3 or 4 and EBV DNA positivity were independently prognostic. The results suggested that the DS is

easily calculated, reproducible, and associated with good interobserver agreement when used to assess the prognosis of NKTL (Kim et al., 2015).

The prospective study by Jiang et al. yielded similar results. The cited authors explored the prognostic utility of 3 different models in 60 patients with ENKTL: the International Harmonization Project (IHP) model, the Deauville 5-point scale, and SUV-based assessment. The IHP model was not predictive of either PFS or OS. It was suggested that FDG is not a specific tracer and can be absorbed by inflammatory cells and yield false-positive results on interim PET/CT. All FDG uptake ranges (very low uptake, significant residual uptake but less than pretreatment uptake, no change in uptake, and uptake progression) were associated with high false-positive rates. Univariate analyses revealed that the interim PET/CT outcomes based on the DS and change in SUVmax were predictors of survival. The multivariate analysis showed that the DS was prognostic of PFS and OS and that the change in SUVmax was the only significant predictor of OS (Jiang et al., 2015).

In another study, the authors assessed the ability to predict prognosis using the IHP criteria, Deauville 5-point scale, and change in SUVmax in 59 patients with ENKTL. They found that the Deauville 5-point scale was more valuable for predicting prognosis than was the IHP or change in SUVmax in patients with ENKTL (Jiang et al., 2017). However, Khong et al. found that the change in SUVmax was not significantly prognostic of PFS or OS. Differences in the therapies employed in the two studies may partly explain the conflicting results (Khong et al., 2014).

2.5. Significance of the Study

Several recent studies have shown that quantitative metrics including metabolic tumor volume (MTV) and total lesion glycolysis (TLG) are reliable prognostic indicators with high sensitivity and reliability in DLBCL (Khong et al., 2014; Kim et al., 2013; Moon et al., 2013). Additionally, the five-point Deauville score (DS) has been recommended as a qualitative method for evaluating interim and end-of-treatment PET/CT results with good reproducibility and flexibility. Although previous studies have evaluated the prognostic value of these PET/CT parameters for various types of lymphoma, similar studies of NKTL have been limited by sample size. Moreover, previous findings remain controversial due to heterogenous patient enrollment, various imaging conditions, different cut-off values for survival predictions, and undefined treatment protocols. The role of ^{18}F-FDG PET/CT in natural killer/T-cell lymphoma (NKTL) is currently controversial. Furthermore, whether the maximum standardized uptake value (SUVmax), metabolic tumor volume (MTV), total lesion glycolysis (TLG) and Deauville 5-point scale (DS) acquired from PET/CT are predictors of prognosis in ENKTL remains unclear. The aim of this study was to explore the relationship between baseline, interim and end-of-treatment PET/CT (B-PET/CT, I-PET/CT and E-PET/CT) parameters and ENKTL prognosis. In addition, the purpose of this research was to evaluate the role of multiple PET/CT parameters including SUVmax, MTV and DS in ENKTL at three different time points: baseline, interim and end of treatment. The results from the study will improve the understanding in subject matter, will be used as necessary input for health care providers, administrators, educators and policymakers to use it as baseline information for further development and possible intervention in the treatment for NKTL.

2.6. Conceptual Framework

This conceptual framework is adapted and modified after reviewing different literatures (Barrington et al., 2014; Cahu et al., 2011; Wang et al., 2018; Zhou et al., 2016). This shows the effect of independent variables on dependent variable.

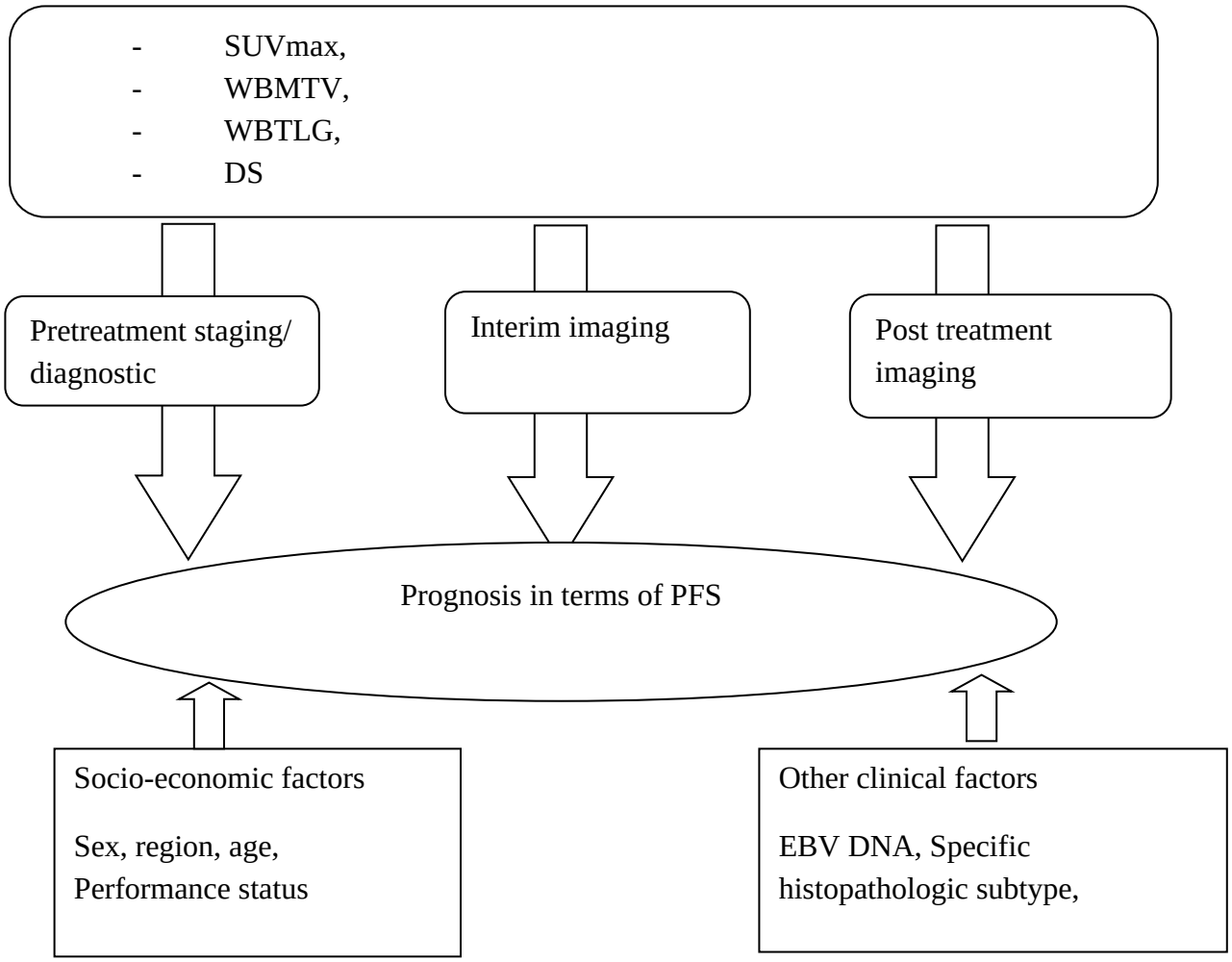


Fig 1. A conceptual framework for ^{18}f-Fluorodeoxyglucose–Positron Emission Tomography before, during and after Treatment in T cell and Nk-Cell Lymphomas: A Study from Pascale Hospital, Napoli, Italy 2022 G.C.

Chapter 3: Objective of The Study

3.1. General Objective

To assess the role of ^{18}F-FDG–PET/CT before, during and after treatment in T-cell and NK-Cell Lymphomas.

3.2. Specific Objectives

The specific objectives of this study are to:

1. To determine the disease staging/re-staging ability of ^{18}F-FDG–PET/CT in T cell and NK-Cell Lymphomas.
2. To identify the role of ^{18}F-FDG–PET/CT for the staging in T cell and NK-Cell Lymphomas.
3. To establish the prognostic ability of ^{18}F-FDG–PET/CT in T cell and NK-Cell Lymphomas in terms of OS and PFS.
4. To identify the correlation between the dependent variable i.e the treatment outcome of NKTL patients in terms of OS and PFS with that of the independent variables.

Chapter 4: Methodology

4.1 Study area and Period

The study was conducted at Istituto Nazionale Tumori IRCCS Fondazione G. Pascale, Naples, Italy. Naples is the third largest city in Italy, located in the southern region of Campania serving as its capital. As of 2012, the population of the *comune di Napoli* totals around 960,000. Naples' wider metropolitan area, sometimes known as Greater Naples, has a population of approximately 4.4 million. The institution IRCCS is founded in 1933 by Senator Giovanne Pascale. The National Cancer Institute represents the regional reference center for the diagnosis and treatment of neoplastic diseases, recognized as a Multi-specialty Oncological Reference Center.

The study was conducted in Istituto Nazionale Tumori IRCCS Fondazione G. Pascale from September 01, 2022 until Dec 31, 2022. After collecting the data from Pascale hospital, data analysis and final write up was conducted in AAU.

4.2 Study Design

An institution-based Retrospective cohort study design using routine clinical data from an established Clinical Information Network.

4.3 **Population**

4.3.1 Source Population

All Patients that visit the Nuclear Medicine department of Istituto Nazionale Tumori IRCCS Fondazione G. Pascale hospital from January, 2012-December, 2022 G.C and that fulfill the inclusion criteria.

4.3.2 Study Population

All NKTL Patients that underwent ^{18}F-FDG PET/CT scan in the Istituto Nazionale Tumori IRCCS Fondazione G. Pascale hospital from January, 2012-December, 2022 G.C and that fulfill the inclusion criteria.

4.4. Eligibility Criteria

4.4.1 Inclusion Criteria

- All patients that have a pathological diagnosis of NKTL according to the World Health Organization lymphoma classification criteria, as determined by pathologists.

- All included patients should have undergone at least one of the following three PET/CT scans: Base line-PET, Interim-PET (after 2 to 4 cycles of chemotherapy) and End of cycle-PET (after first-line therapy).

-The lymphoma stage should be evaluated by the Ann Arbor staging system.

- During the diagnosis, mid-treatment and after the completion of the first-line regimen, patients should undergo routine evaluations, including a physical examination, blood routine tests, a blood biochemical examination, bone marrow aspiration and a biopsy, CT or MRI if necessary.

4.4.2. Exclusion Criteria

- Patients with central nervous system involvement were excluded as ^{18}F-FDG is insensitive to diagnose CNS lesions.

4.5. Sample Size Determination and Procedure

4.5.1 Sample Size Determination

The sample size is calculated using Sample size formula for independent cohort studies (Kasiulevičius et al., 2006).

$$n = \frac{\left[Z_{\alpha}\sqrt{(1+1/m)\bar{p}(1-\bar{p})} + Z_{\beta}\sqrt{p_0(1-p_0)/m + p_1(1-p_1)}\right]^2}{(p_0 - p_1)^2}$$

… Equation 1

This formula gives the minimum number of case subjects required to detect a true relative risk or experimental event rate with power and two-sided type I error probability α (alpha). 5% is the usual choice for α. Usual values for power (probability of detecting a real effect) are 80%, 85% and 90%, (for the purpose of this study a standard 80% is taken). β = 1 – power, n is the sample size, m is the number of control subjects per experimental subject, p0 is the probability of event in controls, p1 is the probability of event in experimental subjects, and Zp is the standard normal deviate for the probability p.

Zalpha=1.96

Zbetta=1.28

M=1

Po=59%

P1=46%

Pbar=52.5%

After calculating the sample size n was 315. The total number of patients diagnosed for NKTL in Pascale hospital in the study period was taken from the department of pathology, which and 69. Therefore sample size correction for <10000 source population was implemented with the following formula.

$$n' = \frac{n}{1 + \frac{n-1}{N}}$$

… Equation 2

Hence the final sample size is **57.**

4.5.2. Sampling Procedure

For this study, all the 57 patients were studied from 2012-2022 G.C. All the patients were selected from the PACS database of the hospital's nuclear medicine unit. A stepwise approach was implemented to select the patients. Initially the pathology department was contacted and patient records with specific histopathologic variant from all the lymphoma patients in the past 10 years were selected (From January 2012-December 2022). A total of 63 cases were reported for the study period. After filtering out the ones with NKTL, 57 were selected with lottery method. All patients fulfilling the inclusion criteria were selected in retrospective manner giving priority to patients diagnosed latest.

4.6 Study Variables

4.6.1 Dependent Variables

- Patient treatment outcome (prognosis) in terms of PFS and OS of NKTL Patients

4.6.2 Independent Variables

Socio-demographic characteristics:

- Age
- Sex
- Functional status
- Region

Diagnostic, interim and post-therapy FDG–PET analysis

- Diagnostic FDG–PET
- Interim FDG–PET
- Post-therapy FDG–PET

Biomedical factors:

- LDH
- Positive bone marrow biopsy
- Therapy
  - First-line therapy, induction therapy
  - First-line therapy, consolidation therapy
  - Salvage therapy

4.7. Operational Definitions

- **SUVmax**: Is quantified as the measure of the greatest amount of FDG uptake in a region of interest normalized to body weight (Wang et al., 2018).
- **MTV**: Is determined from the attenuation-corrected PET data using the software. It refers to the metabolically active volume of the tumor segmented using FDG PET, and has been shown to be useful in predicting patient outcome and in assessing treatment response (Wang et al., 2018).
- **TLG** I: Is calculated as the sum of the individual MTVs multiplied by the SUVmean of every lesion (Wang et al., 2018).

- **DS**: is defined as follows: 1, no uptake; 2, uptake < the mediastinum; 3, uptake > the mediastinum but < the liver; 4, uptake that was moderately greater than the liver; 5, uptake markedly greater than the liver and/or the presence of new lesions; and X, new areas of uptake unlikely to be related to lymphoma (Wang et al., 2018).

- **PFS**: The length of time during and after the treatment of a disease, such as cancer, that a patient lives with the disease but it does not get worse (NCIN).

4.8. Data Collection Tool and Procedure

There was a structured data abstraction chart/ format prepared in English (Annex A). The tool (based on the Cochrane Consumers and Communication Review Group's data extraction template), was pilot-tested it on 5% of the sample size included in the study to maintain data reliability. Patient characteristics, including (age, gender, Ann Arbor stage, IPI score, treatment regimen, and follow-up time), imaging techniques (including the imaging system, interval time between FDG administration and scanning, FDG dose, and imaging interpreters; and survival data) was extracted from patients' records. After standardizing the data abstraction tool data was be collected by the principal investigator.

4.9. Data Quality Management

The data collection tool was pretested before the actual data collection period for its consistency and relevance to answer the question in the study. The principal investigator made necessary supervision throughout the data collection period to guide and correct any problems. Before start of the analysis the consistency of the data and missing information were checked.

4.10. Data Analysis and Presentation

Differences in SUVmax between the progression and progression-free groups, as well as those between the death and the survival groups, were assessed using the Mann-Whitney U-test. The Pearson $\chi 2$ test and Fisher exact tests were used to analyze the relationships between the PET/CT results and clinical variables [gender, age, B symptoms, Eastern Cooperative Oncology Group (ECOG) performance status, serum lactate dehydrogenase (LDH) level, IPI, KPI, Ann Arbor staging and lesion site]. OS and progression-free survival (PFS) are chosen as endpoints to evaluate

the prognostic value of PET/CT. OS is defined as the period from diagnosis to death. PFS is defined as the period from diagnosis to disease relapse, progression or death from any cause. The log-rank test and the Kaplan–Meier method were used for a univariate survival analysis. A multivariate Cox proportional hazards model were used to identify the potential independent effects of clinical variables and PET/ CT results. P -value of ≤ 0.05 with 95% CI will be considered statistically significant. The statistical software package SPSS 26.0 were used for statistical calculations.

4.11. Ethical Consideration

Ethical clearance was obtained from the director of Nuclear medicine department at the Istituto tumori Fondazione G.Pascale in verbal manner. Furthermore, the director ascertained that, Formal ethical paper will be obtained from the institute after completion of the paper and review of the results through the director and the ethical committee of the institute. Confidentiality of the information collected was maintained by omitting patients name and personal identification from the checklist.

4.12. Dissemination Plan

This study's findings will be presented to Addis Ababa University, College health sciences school of Medicine, Nuclear medicine department and the hard copy will be available at the AAU library. It will be published in peer-review journals and presented in seminars.

Chapter 5: Results

5.1 Socio-Demographic Characteristics of Index Cases

A total of 57 Index cases with a pathologic diagnosis of NKTL were included for the purpose of this study, 41 of them were found to fulfil the inclusion criteria as well as complete set of data, making the response rate of 72%. Regarding sex of the index cases, 25 (61%) were males. About 17 (41.5%) of index cases were in the age group "61-75", and the mean (+SD) age of respondents was 57.8 (±15.4). The minimum and maximum age of respondents was 19 and 84 years respectively. Table 1 below summarizes the socio demographic characteristics.

Table 1: Socio-Demographic Characteristics of Index cases In Pascale Hospital, Napoli, Italy 2022 G.C (n = 41).

Characteristics		**Frequency**	**Percentage (%)**
Age	<30	3	7.3
	30-45	6	14.6
	46-60	11	26.8
	61-75	17	41.5
	>75	4	9.8
Sex	Male	25	61
	Female	16	39

5.2 Conformity of PET/CT with prior pathologic diagnosis in patients with NKTL

Regarding the primary location of the lesion of diagnosis, 19 (46.3%) were non-nasal type, 20 (48.8%) were nasal type and the rest 2 (4.9%) were aggressive type of NKTL. All 100% of the index cases have been diagnosed with biopsy proven disease and PET/CT also showed positivity on all 41 index cases.

SUVmax measurements for the lesions of interest were measured in the index cases and the one with the highest value was recorded. Regarding the pre-treatment (Initial) SUVmax measurement, the mean (+SD) SUVmax of diagnostic image of the index cases was 12.16 (±8.8). According to Noy and his team, SUVmax of >10 was found to be 80% lymphomatous, SUVmax > 13 were

found to be 90% lymphomatous and SUVmax >20 was found to be >99% lymphomatous (Noy et al., 2009). And hence, such a classification scheme was used for this study. As summarized in Table 2 below, The majority of our index cases i.e 16 (39%) were having the highest SUV max of their diagnostic FDG PET scan of < 10. Similar classification scheme was also used to classify interim FDG PET results of index cases pertaining to the SUVmax of the largest lesion identified. The mean (+SD) SUVmax of interim image of the index cases was 5.15 (±9.6). The majority of our index cases i.e 28 (68.3%) were having the highest SUV max of their diagnostic FDG PET scan of < 10. The mean (+SD) SUVmax of post treatment image of the index cases was 2.39 (±5.6). In addition, regarding the post treatment SUVmax values of index cases, 30 (73.2%) were having their diagnostic F18- FDG PET scan of < 10.

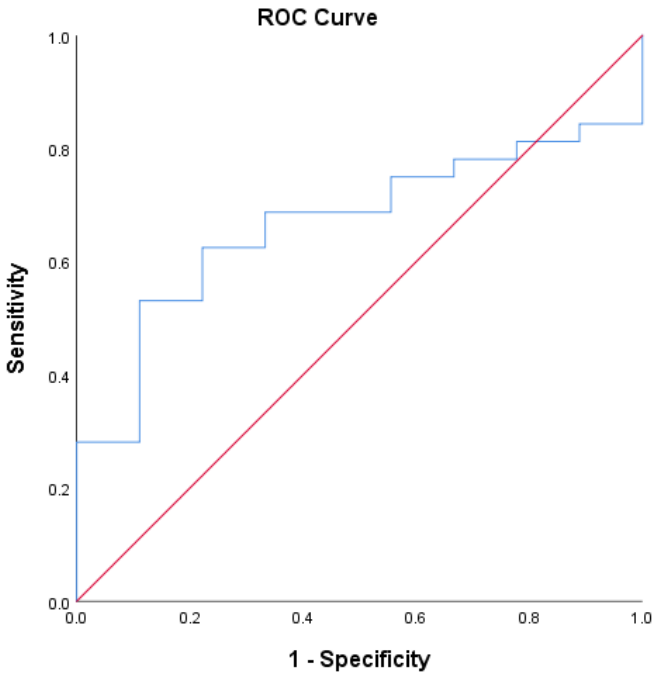
Table 2: Frequency Distribution of Diagnostic utility of ^{18}F- FDG PET scan for NKTL among index patients of Pascale Hospital from 2012-2022 G.C, Napoli, Italy, 2022 (N=41)

Characteristics		**Frequency**	**Percentage (%)**
Anatomic location of the pathology	Nasal	20	48.8
	Extra Nasal	19	46.3
	Aggressive	2	4.9
SUVmax of Diagnostic FDG PET	<10	16	39
	10-13	8	19.5
	13.1-20	11	26.8
	>20	6	14.6
SUVmax of Interim FDG PET	<10	28	68.3
	10-13	3	7.3
	13.1-20	0	0
	>20	4	9.8
SUVmax of Post treatment FDG PET	<10	30	73.2
	10-13	0	0
	13.1-20	1	2.4
	>20	1	2.4

5.3. Metabolic diagnostic parameters of Index cases

MTVX was defined as the volume for which the SUV was over or equal to X (Abelson et al., 2012). In similarity, MTVX% was defined as the volume over or equal to X% of SUVmax. For the purpose of this particular study MTV50% was used. For the initial diagnostic FDG PET Scan, MTV50% ranged from 1.59-852.3 ml. In contrary, it ranged from, 0-939 ml and 0-116.7 ml for the interim and post treatment studies respectively. Meanwhile, the mean MTV50% Remained to be 117.6 ml, 41.85 ml and 11.37 ml for diagnostic, Interim and post treatment PET Scan of the index cases respectively.

In order to find the appropriate cut point values for our data on MTV, we used the ROC curve. We made receiver operating characteristics curves (ROC curves) for PET parameters of OS and MTV values at the baseline (MTV1), interim (MTV2) and post treatment (MTV3) values. The area under the curve (AUC Values) for MTV1 and MTV2 were 0.667 and 0.979 respectively. And hence the cutoff values with good sensitivity and less false positive (1-Specificity) result for MTV 1 and MTV 2 were 122.3 and 78.2 respectively. Appropriate cut-off was defined as the point on the curve nearest to the upper left corner of the ROC graph. Using the cutoff values MTV1 was classified as “lower” and “upper” with a result of 28 (68.3%) and 13 (31.7%) respectively. AUC and ROC Curve could not be generated for MTV3. Table 3 below summarize the WBMTV 1 and 2 in category format.



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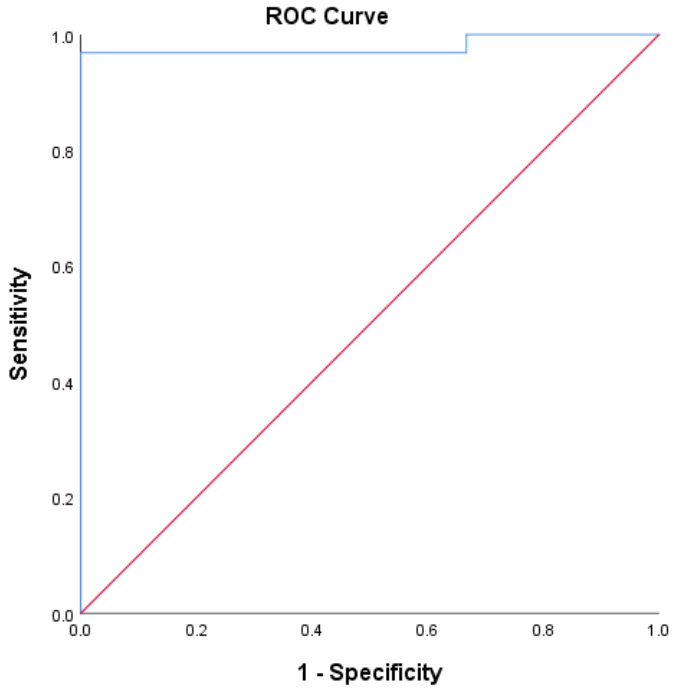


B

Fig 2: ROC curve analysis comparing the prognostic accuracy for disease progression and determining the optimal cut-off values. AUCs of (a), MTV1 (b), and MTV2 were 122.3, and 78.2, respectively. (Sensitivity: 85%, specificity: 82%)

Table 3: Frequency Distribution of Other diagnostic parameter status for NKTL among index patients of Pascale Hospital from 2012-2022 G.C, Napoli, Italy, 2022 (N=41)

Characteristics		Frequency	Percentage (%)
WBMTV1 Categorized	Lower	28	68.3
	Higher	13	31.7
WBMTV2 Categorized	Lower	31	75.6
	Higher	4	9.8

5.4 Evaluated Clinical conditions

Regarding the Ann Arbor staging of the illness upon diagnosis, most patients i.e 12 (29.3%) were found to be stage 3. As presented in Table 4 down below, International prognostic stage was also calculated out of 5 and revealed 11 (26.8%) of index cases revealed an IPI value of 1. In addition, ECOG of index cases revealed significant majority of them have ECOG value of 1. Finally, Death as an outcome was recorded in 9 (22%) of index cases within 5 years, while the rest survived more than five years.

Table 4: Frequency Distribution of Evaluated clinical conditions for NKTL among index patients of Pascale Hospital from 2012-2022 G.C, Napoli, Italy, 2022 (N=41)

Characteristics		Frequency	Percentage (%)
Ann Arbor staging	Stage 1	11	26.8
	Stage 2	7	17.1
	Stage 3	12	29.3
	Stage 4	9	22
	Aggressive	2	4.9
Calculated International	0	9	22
prognostic index	1	11	26.8
	2	9	22
	3	3	7.3

	4	5	12.2
	5	4	9.8
ECOG	ECOG 1	28	68.3
	ECOG 2	11	26.8
	ECOG 3	2	4.9
5 Years Outcome of Patients	Death	9	22
	Survival	32	78

5.5. Survival analysis

In many medical studies, time to death is the event of interest. However, in cancer, another important measure is the time between response to treatment and recurrence or relapse-free survival time (also called progression-free survival time). Hence, for the purpose of this study, we were interested in relapse in the time period between a confirmed response and the first relapse of cancer.

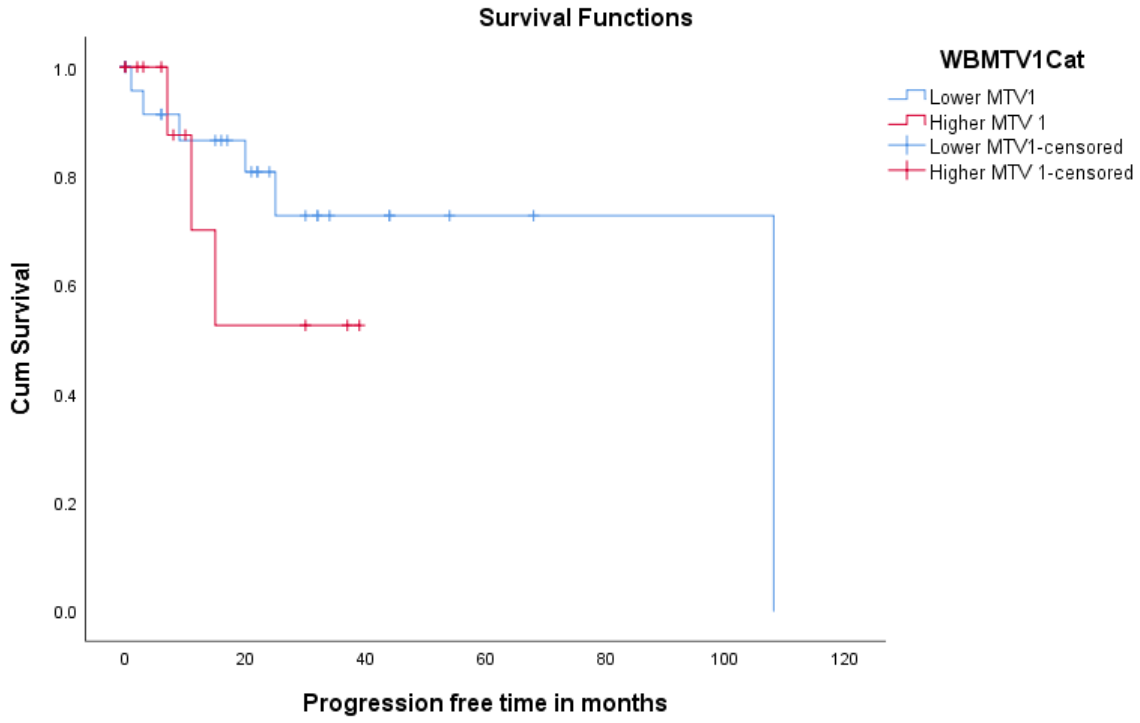
Total follow up months in the department ranges from 0-177 in months, with a mean of 22.8 months ± 30.1. while the total progression free survival period ranges from 0- 108 in months, with a mean of 20.02 months ± 21.8. In addition, a total of 27 (65.9%) from the index cases were found to have no progression.

Total follow up time categorized in terms significant time period was analyzed, significant majority of index cases 18 (43.9%) were having <12 months of total follow up duration. Similarly, total progression free survival categorized in terms of significant time period revealed 19 (46.3%) were having <12 months of total PFS period. Finally, Progression was recorded in 9 (22%) of index cases.

Table 5: Frequency Distribution of survival analysis parameters for NKTL among index patients of Pascale Hospital from 2012-2022 G.C, Napoli, Italy, 2022 (N=41)

Characteristics		**Frequency**	**Percentage (%)**
Disease progression as an outcome	No progression	27	65.9

	Progression	9	22
	Unknown	5	12.2
Follow up period	0-12 months	18	43.9
	12-24 months	9	22
	25-36 months	6	14.6
	37-60 months	6	14.6
	>60 months	2	4.9
Progression free survival period	0-12 months	19	46.3
	12-24 months	9	22
	25-36 months	6	14.6
	37-60 months	5	12.2
	>60 months	2	4.9
Progression as a category	Yes	9	22
	No	32	78



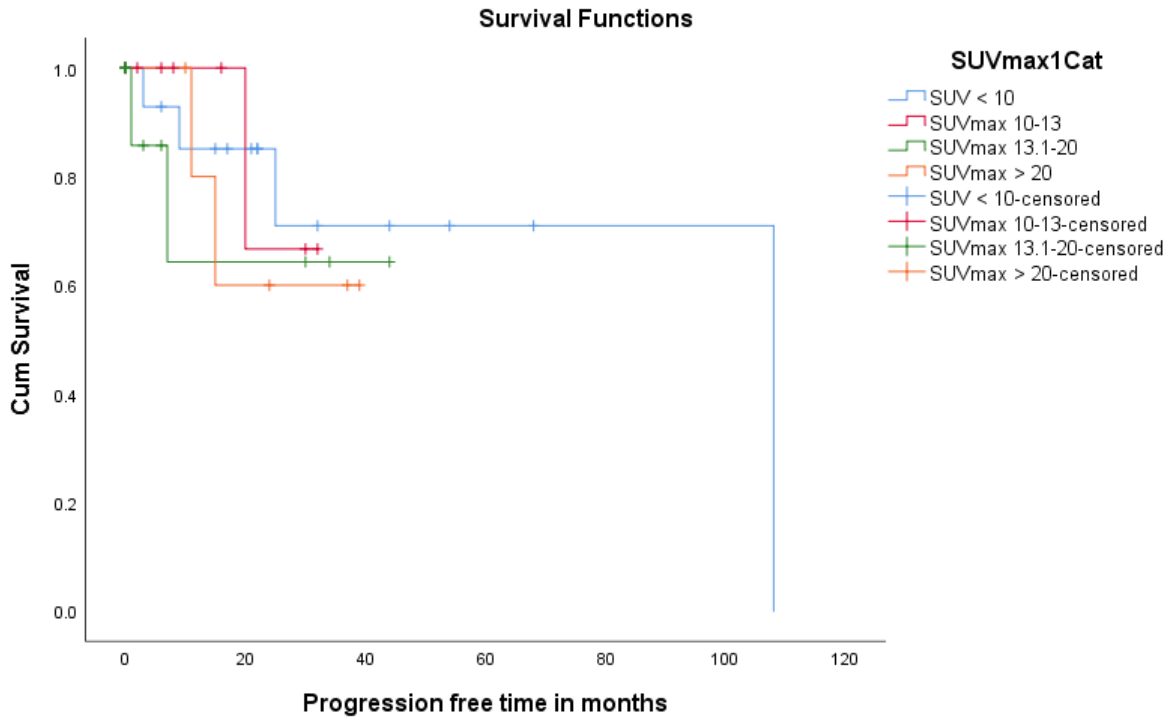


Fig 3: Kaplan-Meier curve analysis comparing the prognostic accuracy of metabolic parameters for disease progression. A) Diagnostic WBMTV and B) Diagnostic SUVmax.

Patients were divided according to the below and above cut-off value for MTV and SUVmax. We found that MTV and SUVmax were not identified as significant prognostic factor for PFS by log-lank test (P>0.05, 0.86).

5.6 Association between Progression free survival as an outcome Vs Independent variables

Regression analysis of progression of malignancy in index cases with related variables

Bivariate and multivariate logistic regression analysis was conducted to identify the factors that are associated with presence or absence of progression. On binary logistic regression analysis all socio-demographic variables (sex and age) of index cases were not significantly associated with progression of malignancy at p-value <0.05 with 95% C.I. In addition, all metabolic variables (Pretreatment, interim and post treatment SUVmax as well as MTV) were not significantly associated with progression of malignancy at p value <0.05 with 95% CI. Similarly. Other assessed variables like Ann arbor staging of malignancy, calculated IPI and ECOG were also found to have no statistical correlation with disease progression. The following table summarized the correlational analysis. Logistic regression is presented in Table 6 below.

Table 6: Association Between Independent and dependent variables (n=41)

Variable	Disease progression		COR (95%CI)	P Value	AOR (95%CI)
	No	Yes			
	Age in years				
<30 years	3	0	1.6(0.00-)	.99	
30-45 years	3	3	6.05(0.00-)	.99	
40-60 years	8	3	1.6(0.00-)	.99	
61-75 years	14	3	1.6(0.00-)	1	
>75 years	4	0	1		
	Sex				
Male	19	6	0.73(0.15-3.46)	.693	
Female	13	3	1		
	Ann Arbor Staging of the pathology				
Stage 1	9	2	0.00(0.00-)	0.99	
Stage 2	5	2	0.78(0.087-6.98)	.82	
Stage 3	9	3	1.4(0.14-13.5)	.77	
Stage 4	7	2	1.16(0.15-9.01)	.88	
Aggressive	2	0	1		
	Calculated international prognostic index				
0	9	0	1.0(0.00-)	1.00	
1	6	5	1.34(0.00-)	0.99	
2	7	2	4.61(0.00-)	0.99	
3	1	2	3.2(0.00-)	0.99	
4	5	0	1(0.00-)	0.99	
5	4	0	1		
	ECOG Performance status				
1	21	7	0.33 (0.018-6.06)	0.458	

2	10	1	.10(.003-3.15)	.191
3	1	1	1	
	SUVmax at diagnosis			
SUVmax<10	12	4	0.667(0.087-5.13)	0.697
SUVmax 10-13	7	1	0.28(0.019-4.2)	0.363
SUVmax 13.1-20	9	2	0.28(0.019-4.2)	.487
SUVmax> 20	4	2	1	
	Interim Imaging SUVmax			
SUVmax<10	21	7	0.33(0.04-2.83)	.314
SUVmax 10-13	3	0	.00(00-)	.99
SUVmax> 20	2	2	1	
	Post Treatment SUVmax			
SUVmax<10	22	8	NA	
SUVmax 10-13	1	0		
SUVmax> 20	1	0		
	Pre-treatment WBMTV			
Lower MTV	22	6	.9 (.18-4.39)	.906
Higher MTV	10	3	1	
	Interim WBMTV			
Lower MTV	24	7	.29(.035-2.46)	,258
Higher MTV	2	2	1	
	Primary location of the lesion			
Aggressive	2	0	0.00(00-)	.999
Nasal type	16	4	0.7(.157-3.1)	.641
Non-Nasal type	14	5	1	

Chapter 6: Discussion

This study is aimed to assess the role of ^{18}F-Fluorodeoxyglucose–positron emission tomography before, during and after treatment in T cell and NK-cell lymphomas, in a retrospective manner in Napoli, Italy.

Findings of this study revealed that metabolic parameters like SUVmax and WBMTV at the time of the diagnostic, interim and post treatment ^{18}F- FDG PET scans does not predict disease progression of NKTL in the index cases. In addition, Sociodemographic variables such as sex and age on top of clinical parameters such as Ann Arbor staging at the time of diagnosis, primary lesion location, ECOG and IPI does not seem to have statistical correlation with disease progression.

All 100% of the index cases have been diagnosed with biopsy proven disease and PET/CT also showed positivity on all the index cases. ^{18}F- FDG PET was reported to be a valuable tool for assessing extra-nodal and nodal involvement in patients with NKTL (Fujiwara et al., 2011; Harisankar, 2015). The role of FDG PET for the staging as well as the diagnosis of NKTL have also been demonstrated in multiple other studies (Kim et al., 2013; Moon et al., 2013; Zhou et al., 2016). The resemblance in our findings could be secondary to comparable number of sample sizes used on top of similarity in study design. This implies FDG PET/CT is an invaluable tool for staging.

Interim ^{18}F- FDG PET may be of importance on two different levels. In the beginning, it might have prognostic and predictive value. Second, based on the results of the ^{18}F- FDG PET, it might direct the course of treatment. With so many therapeutic options being used without any kind of agreed-upon plan, such as conventional chemotherapy, immunotherapy, ABMT, or alloSCT, picking the best course of treatment for T/NK lymphomas is even more crucial. Some treatments, like ABMT, are debatable, and their precise indication is still unknown (Cahu et al., 2011).

PFS did not differ statistically between our cohort's positive and negative groups. We concur that given a statistical difference might have appeared from larger cohorts, this lack of difference should be interpreted cautiously. Despite the difficulty of defining a clear cut, any statistical difference, if it exists, should be large enough to be clinically important. Furthermore, the present study's histology and treatment approaches vary widely. Given that PFS and recurrence rates differ based on therapy, the heterogeneity of therapies is even more crucial. Consequently, it is important

to examine ^{18}F- FDG PET in the context of a particular therapy (e.g., ABMT, allo-SCT or standard chemotherapy). Our rather small sample in addition to not having adequate data on therapy prevented us from performing a stratification by therapy.

After the course of treatment, there was no discernible difference in PFS between patients who had positive or negative ^{18}F- FDG PET results. As we noted for interim ^{18}F- FDG PET, larger cohorts may reveal a statistical difference. Although not statistically significant, our data suggest that patients with a positive ^{18}F- FDG PET had a greater PFS than patients with a negative ^{18}F-FDG PET.

Prognostic models including PET/CT data including the SUVmax and models such as the whole-body metabolic tumor volume (WBMTV) and the whole-body level of total lesional glycolysis (WBTLG) were previously reported to predict the prognosis of NKTL in terms of PFS and OS (Kim et al., 2013; Ko et al., 2016b; Song et al., 2019). The discrepancy with our finding could be attributed to the differences in sample size, the source population, the study design and methods.

In conclusion, our study shows the sensibility of ^{18}F- FDG PET at diagnosis in NKTL malignancies. However, a significant incidence of relapse occurs in NKTL despite a negative interim or post-therapy ^{18}F- FDG PET. Therefore, complete metabolic response does not necessarily translate into prolonged PFS in NKTL lymphomas.

Chapter 7: Strength and Limitations

The research objectives are thoroughly addressed by the study, which is the main purpose of the investigation. Despite the strength, this study had certain limitations, and thus the results might not represent the prognostic ability of ^{18}F- FDG PET in NKTL. Foremost the sample size is not adequate to generalize the results in addition, the study carried out in a retrospective manner, in addition difficulty to standardize measurements of WBMTV as well as calculating the TLG values from the old PACs system pose a difficulty. In addition, inability to find the outcome of followed patients to assess overall survival pose a difficulty as data is incomplete in the PACs. Absence of treatment history, initial diagnostic history was also a major thrust of its limitations. Another limitation is the mode of data collection at the work setting itself, since data was collected in Italy in face of clinical attachment with time constraints also pose a difficulty.

Chapter 8: Conclusion

Based on the results of this study, it could be concluded that: ^{18}F- FDG PET is an ideal tool both for diagnosis and staging of NKTL. To the contrary, ^{18}F- FDG PET metabolic parameters such as SUVmax and WBMTV early in diagnosis, interim or post treatment setting does not predict the prognosis of NKTL patients in terms of PFS. The study also demonstrated there is no statistical correlation between socio-demographic parameters and clinical parameters suck as Ann arbor staging, ECOG, IPI and lesion location with that of disease progression.

Chapter 9: Recommendation

Based on the findings of this study the following recommendations are made:

It is recommended to Use ^{18}F- FDG PET for diagnostic as well as staging purposes for NKTL.

There is insufficient statistical evidence to use ^{18}F- FDG PET as a prognostic indicator for NKTL and hence it is recommended to further study the matter as well as develop a comprehensive criterion strong enough to be used to predict the prognosis of NKTL early in the course of the illness.

The study could be replicated in other hospitals, and a comparison made with the current study to establish if ^{18}F- FDG PET scan can be used as a prognostic tool for NKTL. Other researchers are also encouraged to further study identified gap of our study by mitigating to the limitations of this report.

The study should be replicated with a larger sample size. It is recommended for the Italian colleagues to design a multicentric, retrospective cohort of a larger size to make up for the statistical limitations. It is also recommended for the Ethiopian researchers to design a prospective, multicentric study on the subject matter.

Chapter 10: References

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ANNEXES

Annex A: English Version Data Abstraction Tool

Addis Ababa University

College of Health Sciences

School of Medicine

This is the data abstraction tool designed to assess Utility of ^{18}F- FDG PET Before, During and After Treatment in T cell and Nk-Cell Lymphomas: A Study from Pascale Hospital, Napoli, Italy 2022 G.C.

SECTION 1: Questions related to patients' socio-demographic characteristics

No.	Socio-demographic Variables	Answer
101	How old is the index patients?	_____Years
102	What is the gender of the index patient?	1.Male 2.Female
103	What region of Italy is the index patient from?	_____

SECTION 2: Questions to assess patients 'clinical status

No.	**Assessed clinical condition**	**Answer**
201	Where is the lesion of the diagnosis?	
202	What is the highest SUV max of the lesion?	
203	What is the Ann Arbor stage of the malignancy?	
204	What is the TNM staging of the malignancy?	
205	Calculated International prognostic index	

206	Calculated Korean Prognostic Index	
207	Was bone marrow aspiration performed	1.Yes 2. No
208	What was the bone marrow aspiration result	
209	What is the ECOG (Functional status) of the index patient?	
210	What is Serum LDH level of the index patient (Mention all results with report time)	
211	Does the patient complain of presence of B-Symptoms? If so, mention them	
212	Chemotherapy Regimen - First-line therapy, induction therapy (Anthracyclin based)	1. Yes 2. No
	First-line therapy, consolidation therapy (Select all that applies)	-Anthracyclin based -Cisplatin based -Pentostatin -Radiotherapy -ABMT -Allo-SCT -Others
	Salvage therapy (Select all that applies)	-Anthracyclin based -Cisplatin based -Pentostatin -Alemtuzumab -ABMT -Allo-SCT -Others
213	Progression report on the disease	

214	Death as an outcome	1. Yes 2. No
215	Progression free time in months	_____Month
216	Survival time in months	_____Month
217	Follow up time in month	_____Month

SECTION 3: Question to assess 18F FDG PET-CT Parameters

No.	**Assessed clinical condition**	**Answer**
301	Pre-Treatment (Diagnostic) PET result	
302	Interim PET result (IHP criteria)	
303	End of treatment PET result (IHP criteria)	
304	WBMTV baseline	

Annex B: Ethical Approval

November 1, 2022

Protocol Title: "Role of ^{18}F-Fluorodeoxyglucose-Positron Emission Tomography Before, during and After Treatment in T cell and Nk-Cell Lymphomas: A Retrospective Study from Pascale Hospital, Napoli, Italy 2022 G.C."

Dr. Amanuel Chimdesa Enkosa

Permission to conduct your research at Pascale Hospital

Istituto Nazionale Tumori IRCCS Fondazione G. Pascale has grant to you a permission to conduct the above mentioned research at Nuclear Medicine Unit, Pascale Hospital. The research proposal has no ethical issue and was approved. The Manuscript/thesis is only intended for academic purpose (Graduation thesis defense at Addis Ababa University).

The final thesis should be submitted to both Addis Ababa University and Istituto Nazionale Tumori IRCCS Fondazione G. Pascale.

Secondo Lastoria, MD

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