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Treatment response assessment in lymphoma (Hodgkin's lymphoma and Non-Hodgkin's lymphoma) with FDG-PET in Palestinian health system

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Thesis Approval

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Declaration

I confirm and declare that the work presented in this thesis is titled " Treatment response assessment in lymphoma (Hodgkin's lymphoma and Non-Hodgkin's lymphoma) with FDG-PET in Palestinian health system." was completed under the supervision of Dr. Mohammad Hjouj and Dr. Muntaser Al-Sayyid Ahmed, in partial fulfillment of the requirements for obtaining a Master's degree in Medical Imaging Technology from Al-Quds University.

It's my own study the content of this thesis has not been submitted to any university or other institution for the award of any other academic degree.

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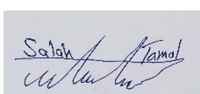
Sign: 

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Abstract

Lymphoma is the most common type of malignant hematological cancer with more than 80 subtypes according to the latest classification of the World Health Organization. Lymphomas come in many forms. Primary subtypes include: Hodgkin's lymphoma (HL), and non-Hodgkin's lymphoma (NHL). Early and accurate diagnosis of these types of cancer helps determine the method of treatment. With the advent of Positron emission tomography/Computed tomography (PET/CT) technology, it helped us detect the location of cancer and determine its stage. In this study, FDG-PET/CT was used to evaluate the response of Hodgkin and non-Hodgkin lymphoma patients to treatment. PET/CT scans were taken for all lymphoma patients from the Patient's Friends Association Al-Ahli Hospital - Hebron, and the Patient's Friends Charitable Society (Al-Rahma Clinic) - Nablus. The study included 310 patients suffering from HL and NHL from Al-Ahli Hospital and Al-Rahma Clinic, where the number of HL patients was (196), number of NHL patients was (114), and the NHL were distributed as follows: (Follicular lymphoma 30, Diffuse large B cell lymphoma (DBCL) 71, T-lymphoblastic lymphoma 8 and Chronic lymphocytic leukemia 5). From the results we obtained, patients' responses to treatment were divided into four categories: stable metabolic response (SMR), partial metabolic response (PMR), complete metabolic response (CMR), and progressive metabolic disease (PMD). These types of responses were divided into Based on comparing patients' reports and monitoring their condition after receiving treatment.

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Abbreviations

Abbreviation	Definition
18F-FDG	Fluorine-18 Fluoro-deoxyglucose
PET	Positron Emission Tomography
CT	Computed Tomography
HL	Hodgkin lymphoma
NHL	Non-Hodgkin lymphoma
KeV	Kiloelectronvolt
MRI	Magnetic Resonance Imaging
HIV	Human immunodeficiency virus
EBV	Epstein-Barr virus
DLBCL	Diffuse large B-cell lymphoma
CLL	Chronic lymphocytic leukemia
SLL	Small lymphocytic lymphoma
DNA	Deoxyribonucleic Acid
3D	Three-dimensional

IPNHLSS	International Pediatric Non-Hodgkin Lymphoma Staging System
AIEOP	Associazione Italiana Ematologia Oncologia Pediatrica
TTP	Time-to-progression
CR	Complete response
PR	Partial response
SUV	Standardized Uptake Value
MCL	Mantle cell lymphoma
CMR	Complete Metabolic Response
PMR	Partial Metabolic Response
CAR	Chimeric antigen receptor
ABVD	Adriamycin, bleomycin sulfate, vinblastine sulfate, and dacarbazine
SPSS	Statistical Package for Social Science

Chapter One

Introduction

1.1 Background

Lymphoma is a type of blood cancer that affects the immune system. It specifically affects lymphocytes, which are white blood cells and a crucial component of the immune system. Lymphatic cancer, or cancer of the lymphatic system, is another name for lymphoma (Jamil et al., 2024). The lymph nodes, spleen, and thymus gland make up the lymphatic system. It is a component of the immune system, which aids in battling illness and infection. Because lymph tissue covers every inch of body, lymphoma can start almost anywhere (Lindsey et al., 2017). There are two main categories of lymphoma: Hodgkin lymphoma and Non-Hodgkin lymphoma (NHL).

Hodgkin's lymphoma is a type of cancer that affects the lymphatic system, which is part of the body's germ-fighting immune system. In Hodgkin's lymphoma, white blood cells called lymphocytes grow out of control, causing swollen lymph nodes and growths throughout the body (Che et al., 2023).

Non-Hodgkin lymphoma is a type of blood cancer that affects white blood cells called lymphocytes, which are an important part of immune system. There are different types of non-Hodgkin lymphoma depending on how the cells are affected and how the cancer behaves (Zanoni et al., 2023).

Both Hodgkin's lymphoma and non-Hodgkin's lymphoma are types of lymphoma. The main difference between Hodgkin's lymphoma and non-Hodgkin's lymphoma is in the specific lymphocyte each involves. The difference between Hodgkin's lymphoma and non-Hodgkin's lymphoma can be seen by looking at the cancer cells under a microscope. If a specific type of cell called a Reed-Sternberg cell is seen, the lymphoma is classified as Hodgkin's. If the Reed-Sternberg cell is not present, the lymphoma is classified as non-Hodgkin's (Allam et al., 2015).

Positron emission tomography (PET) uses small amounts of radioactive materials called radiotracers or radiopharmaceuticals, special detectors, and a computer to evaluate organ and tissue functions. By identifying changes at the cellular level, PET may detect the early onset of disease before other imaging tests can and be used to diagnose and evaluate various diseases. These include cancer, heart disease, gastrointestinal, endocrine, or neurological disorders, and other conditions. Nuclear medicine exams pinpoint molecular activity. This gives them the potential to find disease in its earliest stages. They can also show whether the patients are responding to treatment (Crisan et al., 2022).

Positron emission tomography (PET) with 2-deoxy-2-[fluorine-18] fluoro-D-glucose (18F-FDG), an analog of glucose, provides valuable functional information based on the increased glucose uptake and glycolysis of cancer cells and depicts metabolic abnormalities before morphological alterations occur. 18F-FDG PET/CT acquires PET and CT data in the same imaging session and allows accurate anatomical localization of the lesions detected on the 18F-FDG PET scan (Almuhaideb et al., 2011).

18-fluoro-2-deoxy-D-glucose (FDG) positron emission tomography (PET)/computed tomography, (CT) the most effective imaging method for diagnosis Hodgkin and non-Hodgkin lymphoma. It has been the gold standard for staging and end-of-treatment assessment in patients with this disease since [8]. Fluorine-18-deoxyglucose (FDG), a radiolabeled glucose analog, is the drug that is utilized the most frequently. FDG is transported into cells and phosphorylated similarly to glucose. 60 minutes after the injection of the patient, the positron-emitting 18F isotope to which FDG is linked decays, once the positron is released, and after "bumping" with an electron, it annihilates, emitting two 511-KeV photons that the PET scanner detects (Subocz et al., 2017).

1.2 Problem Statement

Computed Tomography (CT) is one of the most important modern techniques used in imaging the internal organs of the body, bones, and tissues to diagnose many diseases, including tumors. concerning lymph node cancer, the abdomen's prominent visceral involvement can be seen on CT, which also has variable sensitivity for node enlargement above and below the diaphragm. In general, imaging the extent of disease, particularly external extension, is important. Despite advances in CT technology, there are still some applications where the performance of CT imaging is subpar (such as disease in lymph nodes of normal size, infiltration of the spleen, and bone marrow) (Vinnicombe et al., 2003).

Magnetic resonance imaging (MRI) scan helps in detecting the spread of lymph node cancer to the spinal cord or brain. It may also be beneficial for the head and neck region and other parts of the body (Radiology Info 2022). But with regard to assessing the response of patients with lymph node cancer to treatment, the MRI machine does not have the ability to determine it.

In the most advanced management of Hodgkin's disease and aggressive non-Hodgkin's lymphoma, 8F-fludeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT) is now the cornerstone of staging methods. It is crucial for staging, restaging, prognostication, developing effective treatment plans, and tracking therapy (D'souza et al., 2013).

It can detect lymphoma based on morphological information and the skill of the radiologist using CT and MRI devices, but there is a problem in assessing patients response to treatment, so we need to perform PET/CT so that we can assess patients.

1.3 Study Justification

The importance of imaging PET/CT in the staging of patients with Hodgkin's and non-Hodgkin's lymphoma to treatment.

Limited studies on this topic in Palestine.

Availability of the device in the Palestinian health sector in Patients Friends Society (Al-Ahli) Hospital – Hebron, and Patient's Friends Charitable Society (Al-Rahmah Clinic) – Nablus.

1.4 Study Objectives

Assess the value of 18F-FDG PET/CT for monitoring therapeutic progress in patients with Hodgkin's and non-Hodgkin's lymphoma.

Differentiate between the patients with lymphoma who have a residual mass but no residual disease after treatment (ie, complete responders) from those who have a residual mass and residual disease after treatment.

Comparing treatment responses between HL and NHL.

Comparing treatment responses between Ahli and Rahmah.

Comparing treatment efficiency based on gender.

1.5 Study Hypothesis

The PET/CT device will be a great help in assessing the condition of patients with Hodgkin and non-Hodgkin lymphoma before and after treatment.

PET/CT is the best technique for detecting and monitoring cancer cells in their early stages and for staging cancer.

There are differences in treatment responses for patients with HL and NHL

1.6 Study questions

Can a PET/CT scan help in assessing the response of patients with lymphoma to treatment?

Can a PET/CT scan help determine the treatment method for patients with lymphoma?

Are there differences in responses to treatment between HL and NHL patients?

Are there differences in responses to treatment between males and females?

Are there differences in responses to treatment according to location?

Chapter Two

Literature review and similar studies

2.1 Introduction

2.2 lymphoma

The most prevalent hematological malignancy, lymphoma, has more than 80 subtypes according to the most recent World Health Organization (WHO) classification, which was updated in 2016. A cancer of the lymphatic system, which is a component of the body's defense against infection, is lymphoma. The spleen, thymus gland, lymph nodes (lymph glands), and bone marrow are all components of the lymphatic system. All of those locations, as well as other organs throughout the body, can be impacted by lymphoma. Lymphoma comes in numerous forms. Primary subtypes include Hodgkin's lymphoma and non-Hodgkin's lymphoma (Daniel A et al., 2016).

2.2.1 Hodgkin lymphoma

Hodgkin's lymphoma is a type of cancer that affects the lymphatic system that fights infection White blood cells known as lymphocytes overgrow in Hodgkin's lymphoma, resulting in enlarged lymph nodes and growths all over the body. People with Hodgkin's lymphoma now have a better chance of making a complete recovery thanks to developments in the detection and treatment of this illness. The prognosis for those with Hodgkin's lymphoma keeps getting better.

2.2.1.1 Etiology and Risk Factors

Doctors hardly ever understand why one patient gets Hodgkin lymphoma while another does not. However, studies reveal that some risk factors raise a person's likelihood of contracting this illness. It's not a given that someone with one or more risk factors will go on to develop Hodgkin lymphoma. The majority of people with risk factors never get cancer. Risk factors could be certain virus such as Human immunodeficiency virus (HIV) and Epstein-Barr virus (EBV).Weakened immune system due to certain medications used following an organ transplant for a hereditary disease. Most frequently diagnosed with Hodgkin lymphoma are teenagers, individuals between the ages of 15 and 35, and people over the age of 55. Those who are close to someone who has Hodgkin lymphoma or another type of lymphoma may be at higher risk of getting the illness, particularly brothers and sisters (Huang et al., 2022).

2.2.1.2 Epidemiology and Risk Factors

Incidence and age of onset, Hodgkin's lymphoma is an uncommon disorder with an annual incidence of 2-3 per 100,000 in Europe and the USA. Its onset is bimodal, peaking in the third decade and second peak after 50. Men are slightly more affected than women, except for the nodular-sclerosing subtype. The most common subtype is nodular-sclerosing (NS), occurring at a higher frequency in young adults. The WHO classification includes NS, MC, and LD. In developing countries, the disorder predominantly appears during childhood and decreases with age (Thomas RK et al., 2002).

Epstein-Barr virus (EBV) is a viral etiology of (HL), with early birth order, low number of siblings, high maternal education, and single family dwellings in childhood being associated with HL in younger patients. HL is a rare consequence of infection with a common virus at a late age of onset, and patients with a history of EBV-related infectious mononucleosis are at a two- to three-fold higher risk for developing HL. EBV DNA is more frequently present in HL cases in developing countries than in developed countries. In western countries, about 50% of all cases of classical HL are EBV-positive, carrying the virus within tumor cells. EBV is involved in the transformation process in EBV positive HL cases, but evidence of its role in negative cases is scarce (Thomas RK et al., 2002).

2.2.1.3 Staging:

Considers the following to determine the stage of Hodgkin lymphoma: The quantity of afflicted lymph nodes. Whether these lymph nodes are located on the diaphragm's left or right side. Whether the lung, spleen, liver, or bone marrow have been affected by the disease. Depending on whether systemic symptoms are present, each stage is classified as having A or B symptoms (Gini et al., 2020).

Table 2.1 staging of Hodgkin's lymphoma (Gini et al., 2020).

Stage(I)	Involvement of a single lymph node (1) or of a single extra lymphatic site or organ(1).
Stage (II)	Two or more lymph node areas on the same side of the diaphragm are involved (2) or one or more lymph node regions on the same side of the diaphragm are locally involved (2).
Stage (III)	Lymph node regions on both sides of the diaphragm are involved, and the spleen may also be involved, or an extra lymphatic site or organ may be locally involved, or both.
Stage (IV)	Involvement of one or more extra lymphatic organs or tissues, whether or not accompanying lymph nodes are also involved.

2.2.2 Non-Hodgkin lymphomas

Non-Hodgkin lymphoma is a kind of blood cancer that affects lymphocytes, which are vital immune system components known as white blood cells. Non-Hodgkin lymphoma can take on a variety of forms depending on how the cancer affects the cells and manifests itself.

2.2.2.1 Large B-Cell lymphoma

2.2.2.1.a Diffuse large B-cell lymphoma

Diffuse large B-cell lymphoma (DLBCL) is the most prevalent kind of high-grade non-Hodgkin lymphoma (NHL). Children are seldom diagnosed with diffuse large B-cell lymphoma (DLBCL), which is more common in older persons (Padala et al., 2024).

2.2.2.1.b Burkitt lymphoma

Burkitt lymphoma is a type of non-Hodgkin lymphoma (NHL). It may be referred to as high-grade NHL, which indicates that it advances swiftly and requires immediate treatment. B-lymphocytes, a subset of white blood cells, are affected. These are a component of your immune system, which also includes lymphatic system (Padala et al., 2024).

2.2.2.1.c Follicular lymphoma

Follicular lymphoma is the most prevalent form of low-grade non-Hodgkin lymphoma (NHL) White blood cells congregate to create masses in lymph nodes or other organs, which is how it manifests. Follicular lymphoma produces lumps or swellings when aberrant cells collect in organs or lymph nodes (glands) (Kaseb et al., 2024).

2.2.2.1.d Chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL)

Chronic lymphocytic leukemia (CLL) is the most frequent form of leukemia in adults. It's a particular sort of cancer that develops in the bone marrow in cells that eventually become specific lymphocytes, which are white blood cells. Leukemia cancer cells begin in the bone marrow and subsequently go into the blood. Leukemia cells frequently develop slowly in CLL. Many people go years without experiencing any symptoms. The lymph nodes, liver, and spleen are among the body organs where the cells eventually proliferate and disseminate (Mukkamalla et al., 2024).

Small lymphocytic lymphoma (SLL) is a type of blood cancer, similar to chronic lymphocytic leukemia (CLL), when B-cells evolve into an abnormal state (cancer), SLL and CLL occur. White blood cells called B-cells typically aid in the defense against infection. They may also go by the name B-lymphocytes (Ashkan Emadi et al., 2023).

2.2.2.1.e Mantle cell lymphoma

Mantle cell lymphoma is a rare type of non-Hodgkin lymphoma of the B-cell. NHL is a lymphatic system cancer. The B cells are impacted by mantle cell lymphoma. The mantle zone, a region of the lymph node, is where it develops. The bodily organs or lymph nodes begin to accumulate with aberrant B cells. The lymphatic system or the organ where they are forming could later have issues when they develop into tumors (von Hohenstaufen et al., 2013).

2.2.2.2 The etiology of non-Hodgkin lymphoma

Although the precise reason why this disease is unknown, non-Hodgkin lymphoma is caused by a change (mutation) in the DNA of a type of white blood cell called lymphocyte receives basic instructions from DNA, such as when to grow and reproduce. These instructions are altered by the DNA mutation, causing the cells to continue to multiply. They start to grow out of control as a result (Jiajun Lou et al., 2022).

2.2.2.3 Non-Hodgkin lymphoma Staging

The method of staging non-Hodgkin lymphoma involves determining the cancer's location, the number of lymph nodes it has infected, and if the disease has migrated from the initial site to other parts of the body. Stage (1) lymph nodes include those in your neck, armpit, or groin, either above or below diaphragm (the muscle sheet beneath the lungs). Stage (2) at least two lymph node groups on one side of the diaphragm, either above or below, are affected. Stage (3) the cancer has spread to groups of lymph nodes above and below the diaphragm and on both sides of it. Stage (4) the lymphoma has spread past the lymphatic system and is now found in the bone marrow, organs, and lymph nodes (The American Cancer Society medical., 2024).

2.2.3. Lymphoma Diagnosis

Hodgkin lymphoma and non-Hodgkin lymphoma are common malignancies with highly treatable treatments. Imaging plays a significant role in diagnosis, staging, and response using CT, MRI, and metabolic imaging with PET/CT and PET/MRI. Cross-sectional imaging has replaced laparotomy and splenectomy for staging, demonstrating abdominal nodal groups and organ involvement. FDG PET provides information on bone marrow involvement, while MRI elucidates cortical bone details (Kathleen M et al., 2019).

The diagnosis of lymphoma is made using an open lymph node biopsy, based off morphology, immunohistochemistry, and flow cytometry. Although fine-needle aspiration and core needle biopsy are often part of the initial evaluation of any adenopathy, neither will provide adequate tissue for the diagnosis of lymphoma because of the need to verify Hodgkin lymphoma via the presence of Reed-Sternberg cells (William D et al., 2020).

One of the most significant modern imaging methods for diagnosing a variety of illnesses, including tumors, is computed tomography (CT), which images the body's internal organs, bones, and tissues. CT has variable sensitivity for node enlargement above and below the diaphragm, and the prominent visceral involvement of the abdomen can be observed in lymph node cancer cases. Imaging the extent of the disease is generally important, especially if it extends externally. Although CT technology has advanced, there are still certain applications (such as disease in lymph nodes of normal size, splenic infiltration, and bone marrow infiltration) where CT imaging performance is not up to par (Vinnicombe et al., 2003).

A magnetic resonance imaging (MRI) scan aids in the identification of lymph node cancer metastases to the brain or spinal cord. It might also be advantageous for other body parts as well as the head and neck area. However, the MRI machine is unable to evaluate how well patients with lymph node cancer are responding to their treatments (Radiology Info 2022).

The foundation of staging techniques for the most advanced management of Hodgkin's disease and aggressive non-Hodgkin's lymphoma is now 8F-fludeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT). It is essential for prognostication, staging, restaging, creating successful treatment plans, and monitoring therapy (D'souza et al., 2013).

2.2.4. Treatment HL and NHL

Chemotherapy is a treatment option for lymphoma, either alone or in combination with radiation therapy. However, radiation therapy alone is not recommended due to potential long-term side effects and the risk of developing recurrent cancers. Patients over 60 have less favorable outcomes, and the National Comprehensive Cancer Network (NCCN) advises against using specific chemotherapy drugs for them. Doctors should emphasize shared decision-making when discussing treatment options with patients, especially those over 60, regarding whether to pursue treatment (William D et al., 2020).

ABVD (doxorubicin [Adriamycin], bleomycin, vinblastine [Velban], and dacarbazine) is the standard treatment for Hodgkin lymphoma; however, other regimens, such as the Stanford V (doxorubicin, vinblastine, mechlorethamine, etoposide [Toposar], vincristine, bleomycin, and prednisone) and escalated-BEACOPP (bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine [Matulane], and prednisone), can also be utilized. Depending on the histology, non-Hodgkin lymphoma is treated differently, but monoclonal antibodies specific for CD20-positive B cells are often used in combination with rituximab (Rituxan; R-CHOP), or in addition to CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone). Many non-Hodgkin lymphoma treatments also involve the use of additional drugs like lenalidomide (Revlimid), an alkylating agent, and bendamustine (Bendeka) (William D et al., 2020).

2.3 Pervious studies

- **Hutchings et al. (2009)** For the majority of lymphoma subtypes, staging with PET and 18F-FDG is standard practice. It is carried out both during and following treatment for aggressive non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL). The 18F-FDG PET results are highly predictive and positively correlated with survival. The response criteria for aggressive lymphomas have been updated to include this imaging technique, and a number of ongoing trials are examining the usefulness of modifying treatment based on early 18F-FDG PET results for aggressive NHL and HL. The routine use of 18F-FDG PET in the surveillance setting and for monitoring the treatment of indolent lymphomas are not well supported by the available data. In order to facilitate the comparison and easy translation of trial results into clinical practice, consistent, evidence-based protocols for the reporting and interpretation of scans for response monitoring are necessary. We advise looking into the use of interim 18F-FDG PET for response monitoring in carefully planned clinical trials, as it is still unclear whether this technique can enhance patient outcomes (Martin Hutchings et al., 2019).

- **Mester et al. (2016)** The mediastinal blood pool serves as the reference for the visual evaluation of the PET response to therapy for residual nodal masses in lymphoma patients, based on the International Harmonization Project (IHP) criteria. This study's main goal was to identify the best reference for evaluating PET response. This institutional review board-approved retrospective study included 137 patients with either Hodgkin's lymphoma (n = 43) or non-Hodgkin's lymphoma (n = 94), assessed for residual masses (n = 180) after the completion of therapy. The secondary aim was to determine if morphological criteria on computed tomography (CT) could improve the performance of PET. The standard of reference was pathology and clinical and imaging surveillance data (mean follow-up, 19 months). IHP and Deauville criteria were used by two readers to independently evaluate the responses. Based on the standard of reference, the addition of morphological parameters on CT was assessed in relation to therapy response, and 36 patients (26.3%) had lymphoma that persisted. The sensitivity, specificity, and accuracy for the IHP and Deauville criteria were, respectively, 97.2%, 97.2% ($p = 1$); 79.2%, 92.1% ($p < 0.001$); and 83.9%, 93.4% ($p < 0.001$). Only the size change during therapy was significant ($p < 0.003$) and increased the specificity for IHP-based interpretation to 90.4% ($p = 0.008$) among the morphological parameters evaluated (Mester et al., 2016).

- **Sally et al. (2017)** Clinical uses of PET with 18F-FDG for therapy monitoring in lymphoma patients are among the most advanced. These days, response-adapted therapy is administered to adults and children with Hodgkin lymphoma based on "interim" PET scan results. PET/CT is utilized to evaluate chemosensitivity during treatment. Prior to transplantation, PET is also used to evaluate remission and forecast prognosis. Its application in aggressive B-cell lymphomas is well-supported by evidence, and more recent research has demonstrated its efficacy in T-cell lymphomas as well. International guidelines propose using the Deauville five-point scale for response assessment, which applies the Deauville criterion (DC). The reference regions of the normal mediastinum and liver are used to measure FDG uptake. The majority of lymphoma subtypes have been validated for the DC, which enables the threshold for a satisfactory or inadequate response to be changed depending on the clinical setting or research question. In order to ensure accurate interpretation and efficient communication with the multidisciplinary team, it is imperative that PET readers comprehend how the DC is applied in response-adapted trials. To improve response assessment, quantitative methods for standardized PET performance, such as a quantitative extension to the DC (qPET), have been developed. A continuous scale provided by (qPET) can be used to improve treatment in trials or to fine-tune the response threshold in particular therapeutic scenarios. This method lowers the possibility of background activity leading to misunderstanding and is less reliant on the observer (Sally et al., 2017).

- **Elshafey et al. (2018)** The purpose of the study In order to evaluate the clinical utility of [18F]-FDG PET/CT scans for the purpose of restaging non-Hodgkin lymphoma (NHL) patients in Egypt, 45 patients and methods with NHL were employed. Following the conclusion of the treatment program, PET/CT and CECT scans were evaluated, with a 12-month follow-up serving as the standard of reference. The outcomes Significant differences were observed between CT and PET/CT staging in patients with NHL throughout a 12-month follow-up (P = 0.0001). Only 2% of patients had their disease downstaged by PET/CT, while 36% of patients had their disease upstaged (mainly in stages I and II). In phases III and IV, PET/CT and CECT were frequently in accord. The analysis revealed a sensitivity of 95% for FDG-PET/CT and 77% for CT alone.FDG PET/CT should be routinely employed in the follow-up of patients with lymphoma since it greatly increased the sensitivity and specificity of NHL restaging (Elshafey et al., 2018).

- **Galaly et al. (2018)** Currently the most advanced imaging method for lymphoma, FDG-PET/CT is essential for treating the disease. Precise staging at the time of diagnosis is crucial for choosing the right treatment. FDG-PET/CT can identify lymphoma regions that CT alone might miss, avoiding patients with advanced disease stages from receiving inadequate treatment because CT might mistakenly identify them as having limited stage disease. Positive interim FDG-PET/CT scans are associated with a poor prognosis for clinical outcomes in Hodgkin lymphoma and can inform treatment regimens that are tailored to PET. These findings, however, are less reliable in diffuse large B-cell lymphoma. When paired with additional indicators, the use of quantitative FDG-PET/CT measures, such as metabolic tumor volume, may help define prognostic subgroups more precisely and make therapy selection more precise. Following chemotherapy, a subset of patients who may benefit from consolidative radiotherapy can be identified based on the FDG-PET/CT response, which is predictive of outcomes. Distinct response patterns are observed with novel medicines, namely immunotherapies, in contrast to traditional chemotherapy. As a result, response criteria for relapsed lymphomas have been adjusted to take into consideration the possibility of temporary pseudo-progression. FDG-PET/CT, which is done following second-line therapy but prior to high-dose therapy, has been shown to be highly predictive of outcomes and can help determine the extent of salvage therapy for relapsed Hodgkin lymphoma. FDG-PET/CT is currently not used for routine follow-up following a complete metabolic response to therapy; however, if patients show clinical signs suggestive of a recurrence of the disease, it is still a useful tool for ruling out relapse. In summary, FDG-PET/CT is important for managing lymphomas at different stages and is a step toward personalized treatment (Galaly et al., 2018).

- **Younes et al. (2017)** The number of licensed and experimental drugs for the long-term treatment of individuals with lymphoma has grown dramatically in the last few years. In early-stage clinical trials, individuals with a range of malignancies, such as solid tumors and lymphomas, are assessed for these drugs. New "basket" clinical trial designs, which choose patients based on particular genetic abnormalities across many solid tumor types and lymphomas, have been made possible by advances in genome sequencing. The Lugano Criteria, which employ bidimensional tumor measurements on computed tomography scans, and the RECIST criteria, which use unidimensional measurements in solid tumors, are the standard response criteria for lymphoma. In order to evaluate this theory, the RECIL group examined 47,828 imaging measures from 2983 distinct adult and pediatric lymphoma patients who were included in ten multicenter clinical studies. The study clarified response assessment in patients receiving novel immune therapy and targeted drugs that produce unusual imaging scenarios, and also proposed a new provisional category of a small response (Younes et al., 2017).

- **Kobe et al. (2018)** found a high predictive value of F-18-FDG-PET in response assessment has been noted since the introduction of FDG-PET for the staging and restaging of lymphoma patients. There are already a number of established PET response-guided therapy regimens, and numerous PET-adapted study designs are currently being tested in sizable study groups. Following chemotherapy with effective chemotherapy regimens like bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone in advanced stages, radiotherapy can be safely forgone in PET-negative patients with HL. Similar to HL, diffuse large B-cell lymphoma has a prognostic predictive value of FDG-PET after induction therapy that is higher than that of CT alone, allowing us to obtain pertinent prognostic information not available through anatomical imaging. If FDG-PET is negative following conventional chemoimmunotherapy, recent findings from studies in aggressive non-HL with a de-escalating strategy suggest that radiotherapy may be safely forgone. Since 2007, FDG-PET at the conclusion of therapy has been incorporated into the International Working Group criteria and has taken the lead as the preferred imaging method for gauging patient response in aggressive lymphoma. Both the ongoing clinical trials and daily life use sound and repeatable interpretation criteria. With the caveat that the outcome of a PET scan may be affected by forgoing and following treatments, the recommended five-point scale has become the industry standard in assessing PET response (Kobe et al., 2018).

- **McCarten et al. (2019)** Children commonly develop Hodgkin and non-Hodgkin lymphomas, which are now very treatable. Using conventional CT and MRI as well as metabolic imaging with positron emission tomography (PET)/CT and PET/MRI, imaging plays a significant role in diagnosis, staging, and response. Laparotomy and splenectomy for staging have been replaced by cross-sectional imaging which can show abdominal nodal groups and organ involvement. [F-18]FDG or 2-fluoro-2-deoxyglucose bone marrow involvement is revealed by PET, and bone marrow involvement is confirmed by MRI as well as cortical bone details. The St. Jude Classification by Murphy or the more recent revised International Pediatric Non-Hodgkin Lymphoma Staging System (IPNHLSS) are the staging systems for non-Hodgkin lymphoma. The Ann Arbor system with cotswold modifications is the staging system for Hodgkin lymphoma and is based on imaging. Since all pediatric lymphomas are metabolically FDG-avid and detect all nodal, solid organ, cortical bone, and bone marrow disease, staging evaluations for both Hodgkin and non-Hodgkin lymphomas require FDG PET as PET/CT or PET/MRI. Issues of airway compromise at presentation, as seen by imaging, are present in both diseases. Hodgkin lymphoma differs in that it has several separate, poor prognostic factors that can be detected on imaging, including a large mediastinal adenopathy, stage IV disease, systemic symptoms, pleural effusion, and pericardial effusion. Non-Hodgkin lymphoma affects more organs, including the skin, ovary, kidney, and central nervous system. Imaging may not be able to foretell who will relapse, but early or interim PET-negative scans are a reliable indicator of improved clinical outcomes optimize risk-adapted therapy and patient management. According to a recent multicenter trial, PET imaging of children from the base of the skull to mid-thigh is typically sufficient for pediatric lymphoma staging and interim assessment (McCarten et al., 2019).

- **Lopci et al. (2018)** In this study, the researchers used FDG PET to assess response to large blocks in children with Hodgkin's lymphoma (HL) enrolled in the Italian AIEOP-LH2004 trial. They analyzed data from 703 patients (388 male, 315 female; mean age 13 years) with HL and enrolled in 41 different Italian centers from March 2004 to September 2012, all treated with the AIEOP- LH2004 protocol. The cohort included 309 patients with a large mass, 263 of whom underwent FDG PET testing before and after undergoing four cycles of chemotherapy. Responses were determined using a combination of morphological and functional criteria. For each child, time-to-progression (TTP) and relapse rates were calculated using clinical monitoring, instrumental data, and histological data as the standard reference. Patients were followed up for an average of 43 months. For morphological responses with TTP and FDG PET, statistical analyzes were carried out. Using multivariate analysis, independent predictive factors were identified. The result response analysis identified 25 PET-positive patients (9.5%) and 238 PET-negative patients (90.5%), with a significant difference in TTP between these groups (mean TTP: 32.67 months for negative scans, 23.8 months for positive scans; p- value 0.0001, log-rank test). Computed tomography results in the same cohort revealed a complete response (CR) in 85 patients (32.3%), progressive disease (PD) in 6 patients (2.3%), and a partial response (PR) in 165 patients (62.7%). There was a significant difference in TTP between patients with a CR and patients with PD (31.1 months and 7.9 months, respectively; p-value = 0.0001, log-rank test). The difference in relapse rates between PET-positive and PET-negative patients was also statistically significant (p = 0000). Between PET-positive and PET-negative patients, there was also a statistically significant difference in TTP in patients with PR (24.6 months and 34.9 months, respectively; p-value 0.0001). Only the PET result was an independent predictive factor in the multivariate analysis with correction for multiple testing in both the entire cohort of patients and the subgroup showing PR on CT (p-value = 0.01). It was determined that in pediatric HL patients with a bulky mass after four cycles of chemotherapy, FDG PET response assessment is a good indicator of TTP and prognosis. Furthermore, PET was able to distinguish patients with a longer TTP from those who had a PR on CT. Response on FDG PET was an independent predictive factor in paediatric HL patients with a bulky mass and in patients with a PR on CT (Lopci et al., 2018).

Chapter Three

Methods and Procedures

3.1 Definition related to PET scan and treatment response

Response to treatment 1 means the treatment duration between the PET1 and PET2 that patients received chemotherapy sessions. Response to treatment 2 means the treatment duration between the PET2 and PET3 that patients received chemotherapy sessions. Response to treatment 3 means the treatment duration between the PET3 and PET4 that patients received chemotherapy sessions.

Stable metabolic response means there is no difference between PET 1 and follow-up in patients whether they have any lesions or not. Partial metabolic response means that there is a partial recovery of the patient's condition, regardless of the lesions present in him that are evaluated after follow-up of the patient. Progressive metabolic disease means that the patient's disease has progressed and new things have appeared, which are evaluated by following up the patient with PET scans. Complete metabolic response It means that the patient responded completely to treatment and the disappearance of his lesions, and it is evaluated through PET scans.

3.2 Definition the SUV1, SUV2 and SUV3

SUV1 mean the difference in the absorption of radioactive material into the affected organ or area between PET1 and PET2. SUV2 mean the difference in the absorption of radioactive material into the affected organ or area between PET2 and PET3. SUV3 mean the difference in the absorption of radioactive material into the affected organ or area between PET3 and PET4. The value of the SUV is calculated through the following equation (Behera, 2018).

$$SUV = \frac{radioactive\ concentration}{injected\ activity\ /\ body\ weight}$$

3.3 Location of lesions in HL and NHL

Definition of each lesion in the human according to anatomy in Table 3.1

A.3.1

1. Cervical lymph node	(retropharyngeal, submandibular, submental, superior deep cervical, jugulodigastric, mid deep jugular, prelaryngeal, jugulo-omohyoid, inferior deep cervical (jugular), supraclavicular, paratracheal, and pretracheal.)
2. Axillary lymph nodes	(central axillary node, lateral axillary node, anterior axillary node, posterior axillary node, apical axillary node, pectoral axillary node.)

B.3.1	
3. Mediastinal and hilar lymph node	(superior mediastinal node (upper paratreceal , prevascular, retrotreceal lower paratreceal) , inferior mediastinal node (subcarinal) , aortic node (sub aortic, para-aortic), hilar lymph node.)
4. Diaphragm lymph node	(Anterior group, Lateral group, Posterior group.)
5. Pulmonary lymph node	
6. Abdominal lymph node	(Periaortic lymph nodes, Preaortic lymph nodes, Celiac lymph nodes, Hepatic lymph nodes, Gastric lymph nodes, Splenic lymph nodes, Superior mesenteric lymph nodes, Inferior mesenteric lymph nodes, Retroaortic lymph nodes, Common iliac lymph nodes, Internal iliac lymph nodes, External iliac lymph nodes, Sacral lymph nodes, Retroperitoneal lymph nodes.)
7. Liver	
8. Spleen	
9. Bone	
10. Pelvis lymph node	(inguinal lymph node, iliac lymph node (external iliac lymph node, internal iliac lymph node, common iliac lymph node))
11. Other	(Means any lesion location in the human body except the mention in HL and NHL)

3.4 Study design

The study is retrospective and includes patients with Hodgkin's and non-Hodgkin's lymphoma collected from PET/CT systems available at Patients Friends Society (Al-Ahli Hospital) – Hebron, and Patient's Friends Charitable Society (Al-Rahmah Clinic) – Nablus.

3.5 Study sample

The study included 310 patients suffering from Hodgkin and non-Hodgkin lymphoma from Al-Ahli Hospital and Al-Rahmah Clinic, where the number of HL patients was (196), and NHL patients was (114). The NHL were distributed as follows: (Follicular 30, DBCL 71, T-lymphoblastic lymphoma 8, and Chronic lymphocytic leukemia 5).

3.5.1 Sampling method

We randomly collected PET/CT scans of patients with Hodgkin's and non-Hodgkin's lymphoma from Al-Rahmah Clinic and Al- Ahli hospital before and after treatment in order to assess response patients' to treatment without regard to age or gender.

3.5.2 Sample size

In this study, we included all positron emission tomography (PET) scans performed for Hodgkin and non-Hodgkin lymphoma patients available at the mentioned centers from 2019 to 2023. The sample size was 310 patients.

3.5.3 Inclusion criteria

The study will include patients with Hodgkin's lymphoma and non-Hodgkin's lymphoma who received any type of treatment and underwent PET/CT scans before and after treatment in all age groups and genders.

3.5.4 Exclusion criteria

We exclude patients who did not receive any kind of treatment and were only monitored. Patients who received treatment but were not followed up and had a PET/CT scan after treatment and patients with cancers other than lymphoma.

3.6 Ethical consideration

- The researcher has an ethical approval from Al-Quds University – medical imaging department review board to obtain approval and permission to conduct the study.
- The researcher also has ethical approval from the Palestinian Ministry of Health and approval from Al-Ahli Hospital and Al-Rahmah Clinic to collect data information.
- No need for patient consent form because its retrospective study and the patient name unknown
- The collected data's confidentiality was protected. There were no distinguishing features, such as codes, names, or even numbers that may link personal data to a particular patient.

3.7 Data collection

3.7.1 Tools of data collection

143 patients collected from Al-Ahli hospital and the rest 167 patients from Al-Rahmah Clinic in the period from 2019 to 2023 and PET scans for all patients with Hodgkin's lymphoma and non-Hodgkin's lymphoma, taking into account the method of treatment, gender and age of each patient.

3.7.2 Study procedures

The study is a retrospective that includes patients with Hodgkin's lymphoma and non-Hodgkin's lymphoma, PET scans has been taken previously for the patients before and after treatment to assess the patients' response to treatment. The work will include visiting Palestinian hospitals that have a PET/CT device in their content, which is Patients Friends Society (Al-Ahli) Hospital – Hebron, and Patient's Friends Charitable Society (Al-Rahmah Clinic) –Nablus only due to the cost of the device and the difficulty in obtaining the radioactive materials needed to perform the tests. We took all PET/CT scans for HL and NHL patients from both sites and filled out the data for each patient on Excel Sheet, which is (Hospital, Gender, Date Of Birth / Age, Examination Date, Patient History, Lesion Location, SUV max and Measurement).

3.7.3 Statistical analysis

The data was collected and arranged in Excel sheet to fit the community statistical package Science (SPSS) version 20. Tables were used for descriptive analysis of results. It was a bar chart it is used to represent the percentages of the four treatment responses (stable metabolic, response partial metabolic response, progressive metabolic disease and complete metabolic response) and it was also used to describe the percentages of treatment responses compared to the site (Ahli and Rahmah). The Kolmogorov-Smirnov test and Shapiro-Wilk statistics were used to examine the normality of the results. When the p value is less than 0.05 it will be taken into account Statistically significant.

Chapter Four

4.1 Result

4.1 PET prediction chemotherapy responses in Lymphoma cancer patients

4.1.1 Demographic Data

310 participants with an average age of 40.7±17.240. Table 4.1 provides an overview of the demographic distribution of participants across treatment centers, including frequency, percentage, and age. The highest frequency is observed in Rahmah Center (167 participants), and the majority of participants are female (53.2%). Participants from Ahli Center tend to have a slightly higher average age (43.68 years) compared to Rahmah Center (38.15 years).

Hodgkin Lymphoma (HL) is the most prevalent cancer type (63.2%) with age 35.71 ± 16.046, followed by B-cell Lymphoma (22.9%), and Follicular Lymphoma (9.7%). T-lymphoblastic lymphoma and chronic lymphocytic leukemia have the lowest frequencies among the cancer types, with 8 (2.6%) and 5 (1.6%) participants, respectively. All of the last four types of cancer are considered as part of non-Hodgkin lymphoma (NHL) with a slightly higher average age of 49.28 ± 15.83.

Table 4. 1. Demographic Characteristics of Participants in Different Treatment Centers.

		Frequency	Percent	Age
Center	Ahli	143	46.1	43.68± 16.956
	Rahmah	167	53.9	38.15 ± 17.121
Gender	Male	145	46.8	
	Female	165	53.2	
Cancer type	HL	196	63.2	35.71 ± 16.046
	Follicular	30	9.7	49.28 ± 15.83
	DBCL	71	22.9	
	T-lymphoblastic lymphoma	8	2.6	
	Chronic lymphocytic leukemia	5	1.6	
	Total	310	100.0	

4.1.2 Comparing treatment responses between HL and NHL

The study found different patient and lesion numbers for HL and NHL. For patient distribution as seen in Table 4.2, HL was 63.22% (196 patients) and NHL 36.78% (114 patients). However, HL had 58.1% prevalence with 1007 lesions and NHL 41.9% with 727 lesions.

In the study, HL had the most patients (196) and lesions (1007). This suggests that HL is more common in the examined population. The dataset's lowest values were for NHL, with 114 patients and 727 lesions, confirming its lower prevalence.

Table 4.2 shows that HL is more common than NHL, implying a higher risk of HL in the examined group. The prevalence of lesions in HL emphasizes the differences between the two lymphomas in the study. These findings shed light on the epidemiology of HL and NHL in the cohort, helping us understand their occurrence and distribution.

Table 4. 2. Distribution of the patients in term of type of cancer

According to the patients' number	HL	196	63.22
	NHL	114	36.78
According to the Lesions number	HL	1007	58.1
	NHL	727	41.9

Table 4.3 presents the results of normality tests, including Kolmogorov-Smirnov and Shapiro-Wilk statistics, for the response of treatment 1 across various types of cancer. The tests aim to assess the distributional characteristics of the data and evaluate the assumption of normality.

The analysis of normality tests for different types of cancer and their corresponding responses to first treatment 1 yielded significant findings. The results indicate that for each type of cancer response category, the p-values associated with both Kolmogorov-Smirnov and Shapiro-Wilk tests are extremely low ($p < 0.05$), rejecting the null hypothesis of normal distribution. This suggests that the data for the response of treatment 1 in different types of cancer do not follow a normal distribution.

The highest and lowest values for each test statistic provide insights into the variability across cancer types. Notably, the consistently low values of the test statistics indicate a departure from normality, emphasizing the non-normal distribution of the response data. The Lilliefors Significance Correction was also considered in the analysis, further supporting the conclusion that the assumption of normality is not met. These findings are crucial for understanding the nature of the response data and guiding appropriate statistical analyses in subsequent investigations.

Table 4. 3. Tests of Normality for the Response of Treatment in Different Types of Cancer.

Tests of Normality							
		Kolmogorov-Smirnova			Shapiro-Wilk		
		Statistic	Df	Sig.	Statistic	df	Sig.
Type of cancer	Stable metabolic response	.365	342	.000	.633	342	.000
	Partial metabolic response	.398	273	.000	.618	273	.000
	Progressive metabolic disease	.403	374	.000	.615	374	.000
	Complete metabolic response	.375	745	.000	.630	745	.000
a. Lilliefors Significance Correction							

Table 4.4 presents the distribution of metabolic responses, categorized into stable, partial, progressive metabolic disease, and complete metabolic response, for three different treatments in HL and NHL patients. Additionally, the P-values obtained from Mann-Whitney U tests are provided for each treatment, indicating the statistical differences in responses between HL and NHL.

For Treatment 1, the Mann-Whitney U test yielded a non-significant p-value of 0.843, suggesting no significant difference in metabolic responses between HL and NHL patients. In contrast, for Treatment 2, a significant difference was observed with a p-value of 0.004, indicating that the metabolic responses significantly differed between HL and NHL patients. However, for Treatment 3, the Mann-Whitney U test resulted in a non-significant p-value of 0.814, suggesting no significant difference in metabolic responses between the two lymphoma types.

These findings underscore the importance of considering treatment-specific variations in metabolic responses and highlight potential differences in the efficacy of treatments for

HL and NHL patients. The statistical analyses provide valuable insights into the comparative effectiveness of different treatments in the context of metabolic response in the studied population.

Table 4. 4. Comparison of Metabolic Responses to Different Treatments in Hodgkin's Lymphoma (HL) and Non-Hodgkin's Lymphoma (NHL) Patients.

		Stable metabolic response	Partial metabolic response	Progressive metabolic disease	Complete metabolic response	P-value (Mann-Whitney U)
Response of treatment 1	HL	187	167	232	421	0.843
	NHL	155	106	142	324	
Total		342	273	374	745	
Response of treatment 2	HL	561	81	125	240	0.004
	NHL	448	69	74	136	
Total		1009	150	199	376	
Response of treatment 3	HL	779	43	62	123	0.814
	NHL	558	24	63	82	
Total		1337	67	125	205	

Table 4.5 illustrates the percentage distribution of metabolic responses, categorized as stable, partial, progressive metabolic disease, and complete metabolic response, for three different treatments in HL and NHL patients.

For Treatment 1, the highest percentage of stable metabolic response was observed in HL (21.3%), while the lowest was in partial metabolic response for both HL (16.6%) and NHL (14.6%). Additionally, HL had the highest complete metabolic response percentage (41.8%), compared to NHL (44.6%). However, the progressive metabolic disease (%) was found in HL is more than in NHL with 23% compared with 19.5%.

In Treatment 2, the highest stable metabolic response percentages were seen in both HL (55.7%) and NHL (61.6%). The lowest values were recorded in partial metabolic response for both HL (8.0%) and NHL (9.5%). HL also exhibited a higher percentage of complete metabolic response (23.8%) compared to NHL (18.7%). However, the disease progression in HL more than NHL with 12.4% compared with 10%, respectively.

For Treatment 3, HL demonstrated higher percentages across all response categories, with the highest stable metabolic response (77.4%) and the lowest partial metabolic response (4.3%). While differences exist, the variations in response percentages between HL and NHL for Treatment 3 are relatively subtle compared to the other treatments.
These findings highlight the treatment-specific variations in metabolic response rates and provide valuable information for clinicians and researchers studying the efficacy of different treatments in HL and NHL patients.

Table 4. 5. Percentage Distribution of Metabolic Responses to Different Treatments in Hodgkin's Lymphoma (HL) and Non-Hodgkin's Lymphoma (NHL) Patients.

		Stable metabolic response (%)	Partial metabolic response (%)	Progressive metabolic disease (%)	Complete metabolic response (%)
Response of treatment 1	HL	18.6	16.6	23	41.8
	NHL	21.3	14.6	19.5	44.6
Response of treatment 2	HL	55.7	8	12.4	23.8
	NHL	61.6	9.5	10.2	18.7
Response of treatment 3	HL	77.4	4.3	6.2	12.2
	NHL	76.8	3.3	8.7	11.3

During the initial evaluation session, only 41.8% and 44.6% of patients with HL and NHL, respectively, received treatment. Additionally, 23% and 19.5% of patients developed worsening metabolic disease. During the second treatment session, the rate increased by 23.8% and 18.7%, respectively, compared to the initial rate. The second therapy session yielded superior outcomes, with the prevalence of patients afflicted by the condition decreasing to 12.4% and 10.2% in consecutive sessions. The disease's rate of worsening fell to 6.2% and 8.7% respectively after undergoing treatment during the third follow-up. HL patients exhibited a decelerated disease development after undergoing multiple therapy sessions, but NHL patients showed superior initial treatment efficacy. All these findings are shown in Figure 4.1.

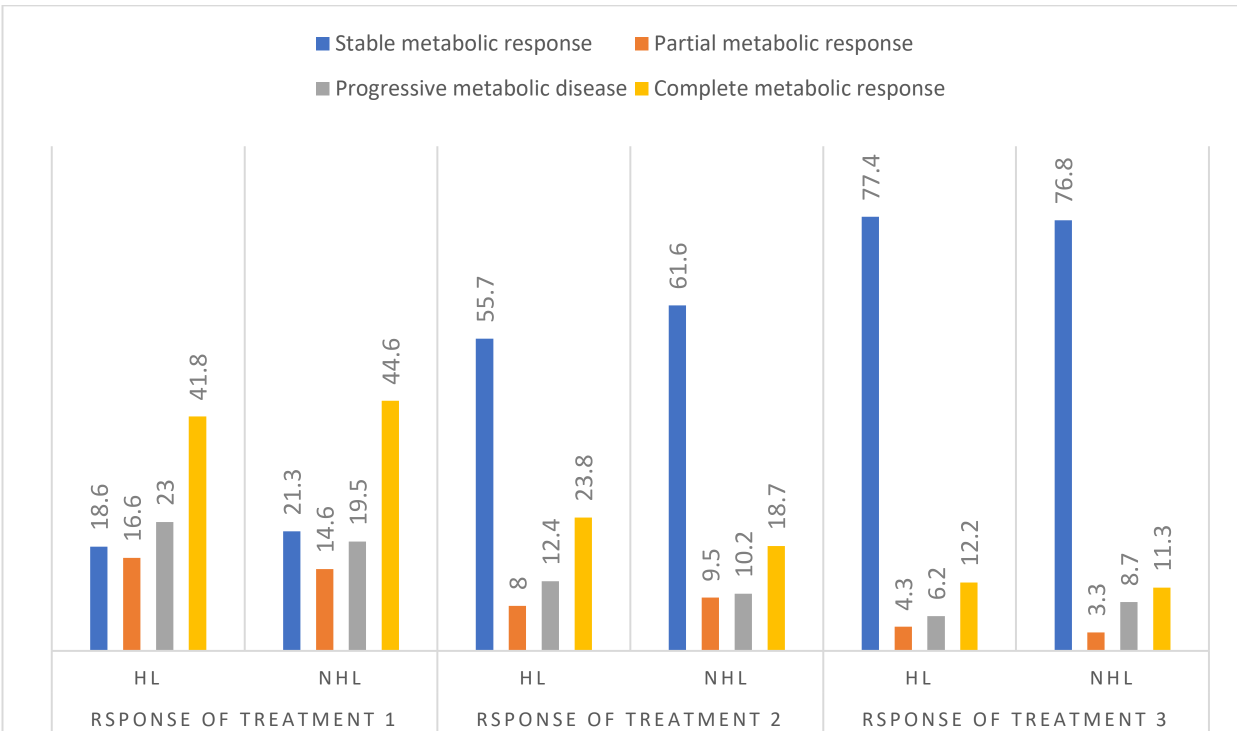

Figure 4. 1. Comparison between treatment responses in three treatment sessions between HL and NHL.

Table 4.6 provides a comprehensive overview of the distribution of metabolic responses, categorized as stable, partial, progressive metabolic disease, and complete metabolic response, for both diseases across three distinct treatment sessions. The "Total treatment response in all sessions" row summarizes the aggregated responses from all sessions.

Analyzing each treatment session individually, Treatment 3 consistently exhibits the highest stable metabolic response (77.1%) and the lowest partial metabolic response

(3.86%). In contrast, Treatment 2 has the highest stable metabolic response (58.18%) and the lowest progressive metabolic disease (11.47%). Treatment 1 falls in between these extremes, with moderate values for each response category.

The aggregated data in the "Total Treatment Response in All Sessions" row shows that stable metabolic response has the highest overall percentage (51.677%), followed by complete metabolic response (25.49177%). The lowest percentage is observed in the partial metabolic response category (9.41855%), indicating that a significant proportion of responses across sessions fall into the stable and complete metabolic response categories.

Table 4. 6. Metabolic Response Distribution for Both Diseases Across Different Treatment Sessions.

For both diseases	Stable metabolic response	Partial metabolic response	Progressive metabolic disease	Complete metabolic response	
Response of treatment 1	19.72	15.74	21.56	42.96	100
Response of treatment 2	58.18	8.65	11.47	21.68	100
Response of treatment 3	77.1	3.86	7.2	11.82	100
Total treatment response in all sessions	51.677	9.41855	13.41268	25.49177	100

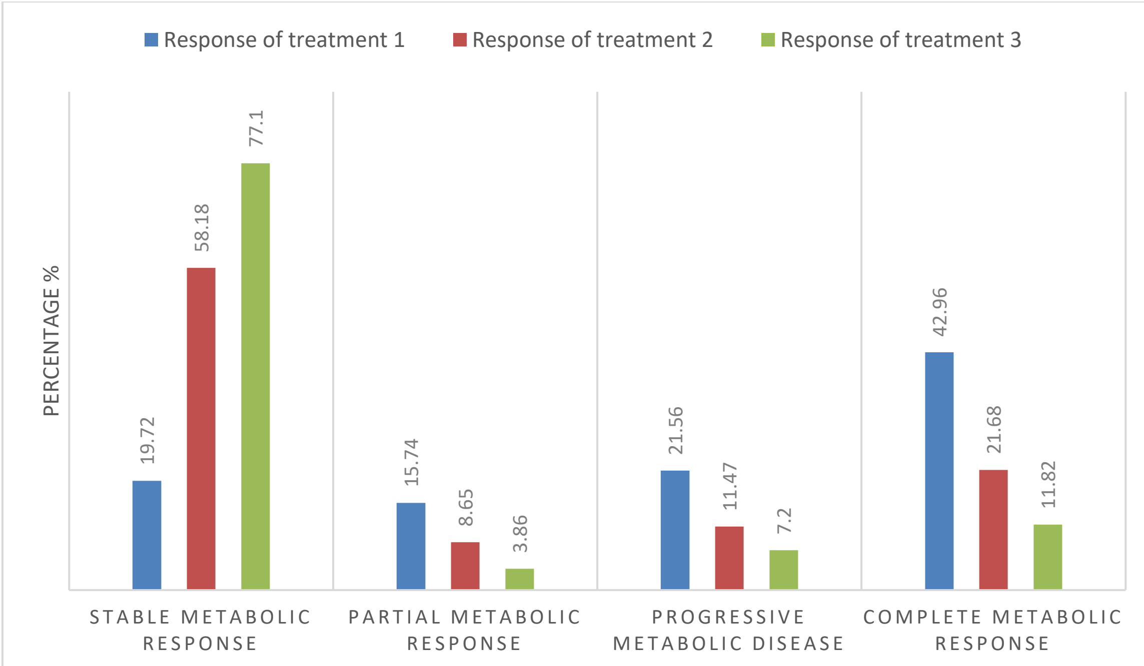

Figure 4. 2. Metabolic Response Distribution for Both Diseases Across Different Treatment Sessions.

4.1.3 Comparing treatment responses between Ahli and Rahmah

According to the Table 4.7, Rahmah Medical Center has a higher number of patients (167) compared to Ahli Medical Center (143), constituting 53.9% and 46.1% of the total, respectively. This indicates a higher patient load at Rahmah Medical Center.
In terms of lesions, Rahmah Medical Center also exhibits a higher number with 947 lesions, accounting for 54.6% of the total, while Ahli Medical Center has 787 lesions, representing 45.4%. The difference in lesion numbers between the two medical centers suggests variations in disease prevalence or diagnostic criteria.

Examining the patient distribution, Rahmah Medical Center has both the highest number of patients and lesions, indicating a potentially larger and more diverse patient population. Ahli Medical Center, while having a smaller patient number, still contributes significantly to the overall distribution.

Table 4. 7. Patient and Lesion Distribution in Ahli and Rahmah Medical Centers.

According to the patients' number	Ahli	143	46.1
	Rahmah	167	53.9
According to the Lesions number	Ahli	787	45.4
	Rahmah	947	54.6

Table 4.8 provides a comprehensive breakdown of the distribution of cancer types, specifically HL and NHL, based on both patient numbers and lesion counts at Ahli and Rahmah Medical Centers. The analysis of patient distribution reveals that Rahmah Medical Center has a higher percentage of both HL (59.7%) and NHL (43.9%) patients compared to Ahli Medical Center. The cumulative percentages emphasize that Rahmah Medical Center contributes more significantly to the overall distribution of both cancer types based on patients' numbers. Examining lesion distribution, Rahmah Medical Center again demonstrates a higher percentage of both HL (64.6%) and NHL (40.7%) lesions compared to Ahli Medical Center. The cumulative percentages underscore the considerable contribution of Rahmah Medical Center to the overall lesion distribution.

Table 4.9 presents the results of normality tests for metabolic responses to Treatment 1 across different hospitals. The statistically significant p-values ($p < 0.05$) indicate a departure from normal distribution for each metabolic response category in all hospitals.
The highest and lowest values of the Kolmogorov-Smirnov and Shapiro-Wilk statistics provide insights into the variability in distribution characteristics among hospitals. Notably, the consistently low values of the test statistics indicate a non-normal distribution for each metabolic response category across hospitals.

Table 4. 8. Distribution of Cancer Types According to Patients and Lesions at Ahli and Rahmah Medical Centers.

	Type of cancer		Frequency	Percent
According to patients' number	HL	Ahli	79	40.3
		Rahmah	117	59.7
		Total	196	100.0
	NHL	Ahli	64	56.1
		Rahmah	50	43.9
		Total	114	100.0
According to Lesions number	HL	Ahli	356	35.4
		Rahmah	651	64.6
		Total	1007	100.0
	NHL	Ahli	431	59.3
		Rahmah	296	40.7
		Total	727	100.0

The Lilliefors Significance Correction was applied to account for potential violations of normality assumptions. The correction did not alter the overall conclusion, emphasizing the robustness of the findings.

These results are crucial for researchers and practitioners as they guide the choice of appropriate statistical analyses that account for the non-normal distribution of metabolic responses to Treatment 1 across different hospitals. The observed differences in normality among hospitals may prompt further investigation into potential factors influencing the distribution of treatment outcomes.

Table 4. 9. Tests of Normality for Metabolic Responses to Treatment Across Different Hospitals.

Tests of Normality							
		Kolmogorov-Smirnova			Shapiro-Wilk		
	Response of treatment	Statistic	df	Sig.	Statistic	df	Sig.
Hospitals	Stable metabolic response	.342	342	.000	.636	342	.000
	Partial metabolic response	.376	273	.000	.630	273	.000
	Progressive metabolic disease	.384	374	.000	.626	374	.000
	Complete metabolic response	.363	745	.000	.634	745	.000
a. Lilliefors Significance Correction							

Table 4.10 provides a detailed comparison of metabolic responses, categorized as stable, partial, progressive metabolic disease, and complete metabolic response, for three different treatments between Ahli and Rahmah Medical Centers. Additionally, the P-values from Mann-Whitney U tests are included, indicating statistical differences in responses between the two medical centers.

The analysis reveals subtle differences in metabolic responses between Ahli and Rahmah Medical Centers across different treatments. Notably, the P-values from the Mann-Whitney U tests are consistently higher than the conventional significance level of 0.05, indicating no significant differences in metabolic responses between the two medical centers for all treatments.

These findings suggest that, statistically, the metabolic responses to the various treatments are comparable between Ahli and Rahmah Medical Centers. While there may be numerical differences in response counts, these differences are not deemed statistically significant based on the Mann-Whitney U tests. Clinically, this information may guide healthcare professionals in understanding the similarity of treatment outcomes between the two medical centers for the specified metabolic responses.

Table 4. 10. Comparison of Metabolic Responses to Different Treatments Between Ahli and Rahmah Medical Centers.

		Stable metabolic response	Partial metabolic response	Progressive metabolic disease	Complete metabolic response	P-value (Mann-Whitney U)
Response of treatment 1	Ahli	172	118	156	341	0.472
	Rahmah	170	155	218	404	
Total		342	273	374	745	
Response of treatment 2	Ahli	474	68	84	161	0.107
	Rahmah	535	82	115	215	
Total		1009	150	199	376	
Response of treatment 3	Ahli	608	21	62	96	0.953
	Rahmah	729	46	63	109	
Total		1337	67	125	205	

Figure 4.3 illustrates the percentage distribution of metabolic responses, categorized as stable, partial, progressive metabolic disease, and complete metabolic response, for three different treatments at Ahli and Rahmah Medical Centers.

The highest and lowest values in each category reveal nuanced differences in the percentage distribution of metabolic responses between Ahli and Rahmah Medical Centers for each treatment. For instance, in Treatment 1, Ahli has a higher percentage of stable metabolic response (21.9%) compared to Rahmah (18.0%), while Rahmah has a slightly higher percentage of partial metabolic response (16.4%) compared to Ahli (15.0%).

In Treatment 2, Ahli consistently exhibits higher percentages across all response categories compared to Rahmah. Notably, the highest difference is observed in the stable metabolic response category, where Ahli has 60.2%, while Rahmah has 56.5%.
Treatment 3 shows minimal differences in the percentage distribution of metabolic responses between Ahli and Rahmah Medical Centers. The subtle variations suggest similar treatment outcomes in terms of metabolic responses between the two medical centers.

These findings are valuable for clinicians and researchers in understanding the variations in treatment outcomes and may guide further investigations into factors influencing the observed differences in the distribution of metabolic responses at Ahli and Rahmah Medical Centers.

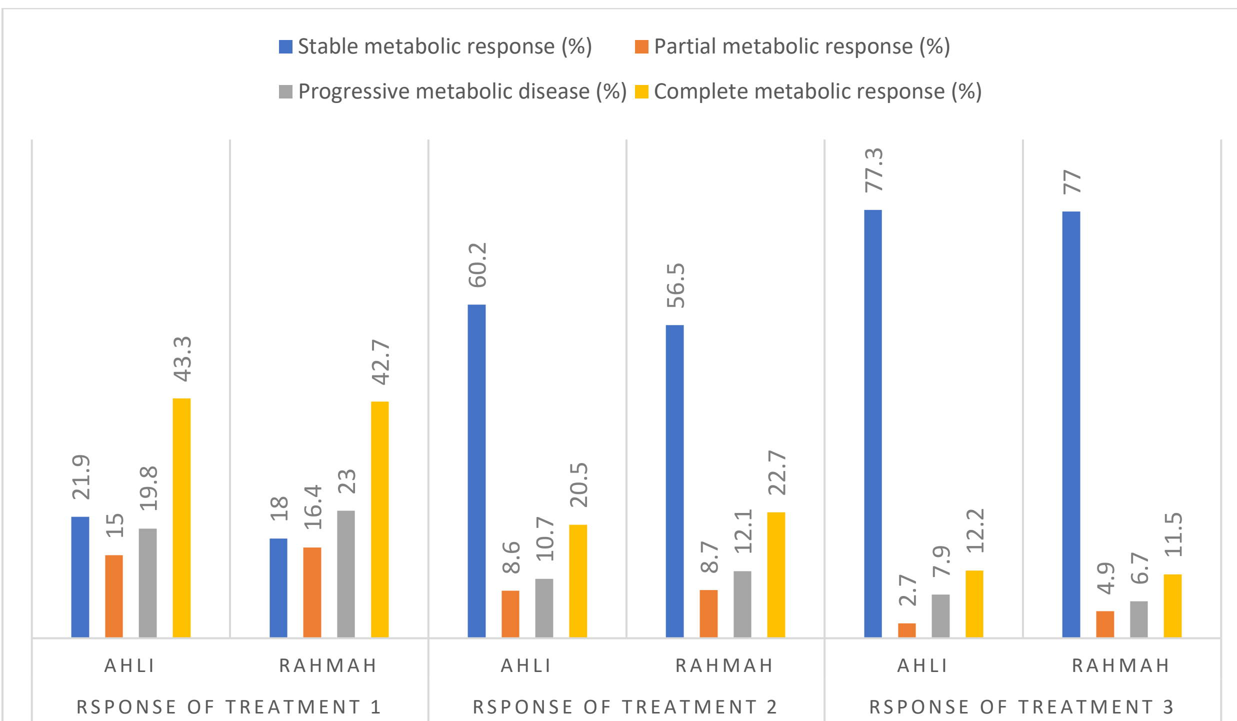

Figure 4. 3. Percentage Distribution of Metabolic Responses to Different Treatments at Ahli and Rahmah Medical Centers.

4.1.4 Find the most lesion treated and most recurrent lesion

The data illustrates in Figure 4.4 that HL has a higher impact on the cervical lymph nodes, spleen, and pelvis in comparison to NHL. Conversely, in the axillary and liver regions, the opposite pattern is observed. The injuries exhibit significant similarity in the regions around the mediastinal lymph nodes, diaphragm, bilateral chest, abdomen, bony dissemination, and other bodily regions.

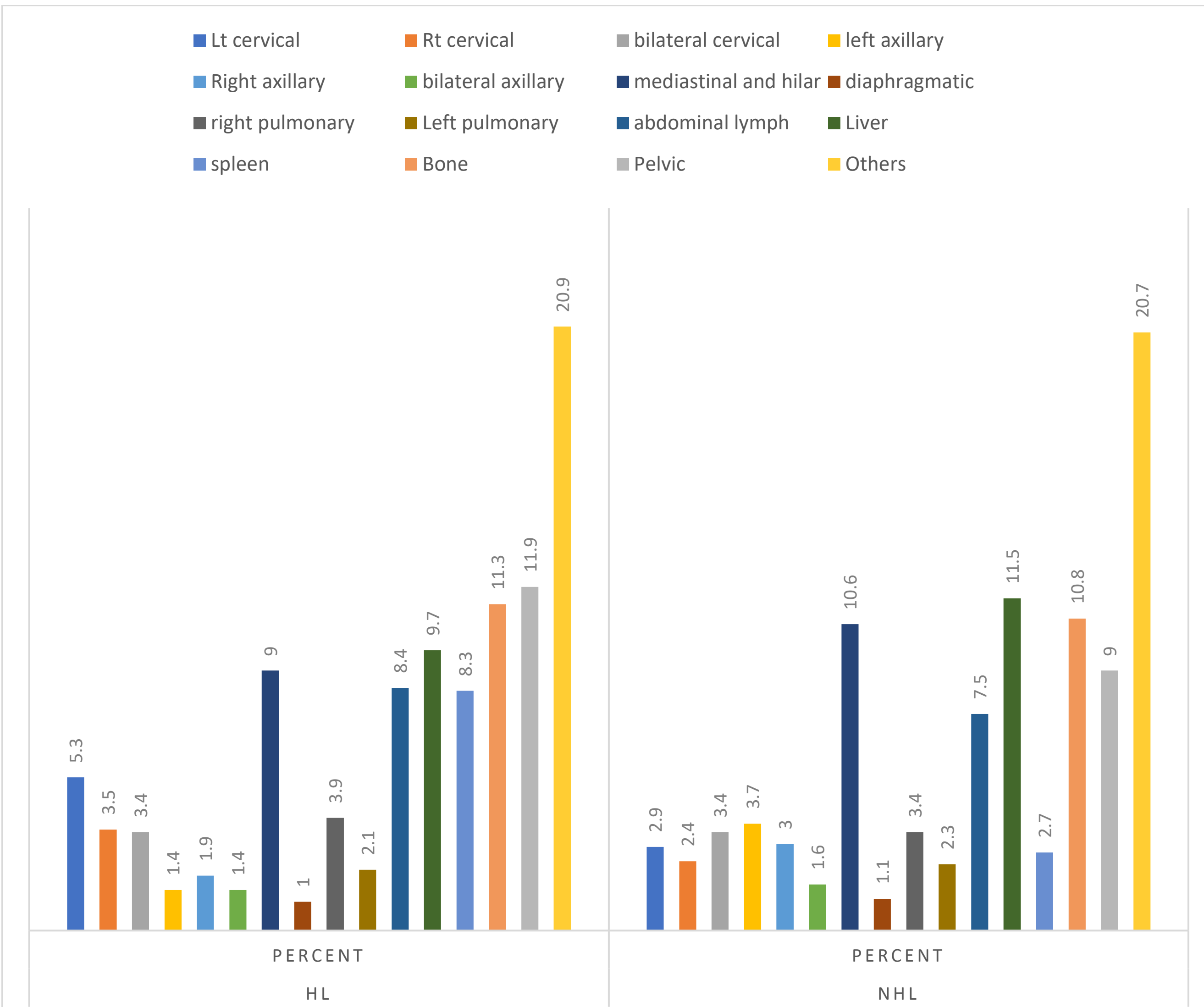

Figure 4. 4. Distribution Location cancer in both HL and NHL.

Based on the data provided, it appears to involve a comparison of Standardized Uptake Value (SUV) measurements between HL and NHL across three different regions of interest. The analysis indicates that there are no notable discrepancies in SUV measurements between HL and NHL across most regions of interest. However, significant differences in SUV measurements between HL and NHL are observed in SUV2 Bilateral Cervical, SUV3 Rt Pulmonary (lung), and SUV3 in bone, as evidenced by the p-values of 0.039, 0.035, and 0.037, respectively. In the case of Bilateral Cervical, the SUV2 measurement indicates that HL exhibits a higher value compared to NHL. Conversely, in the regions of Rt Pulmonary (lung) and Bone, NHL demonstrates a higher SUV3 measurement compared to HL.

These findings summarized in Table 4.11 underscore the intricate variations in metabolic parameters across different anatomical regions in HL and NHL. While some regions show significant differences in mean SUV, others maintain similarities between the two lymphoma types. This nuanced understanding contributes to a more comprehensive assessment of metabolic heterogeneity associated with different lymphomas, aiding in clinical decision-making and prognosis evaluations.

Table 4. 11. Comparison of Standardized Uptake Values (SUV) across different anatomical locations and cancer types.

A.4.11

		SUV1			SUV2			SUV3		
		HL	NHL	P-value	HL	NHL	P-value	HL	NHL	P-value
Lt cervical	N	54	22	.798	54(5.3%)	54	0.22	54	22	.237
	Mean	4.24	3.96		2.31	2.11		1.64	2.07	
	Std. Deviation	5.971	5.623		3.602	3.864		3.964	3.186	
Rt cervical	N	35	18	.840	54	22	.790	54	22	.345
	Mean	4.78	5.04		1.66	2.04		1.14	1.55	
	Std. Deviation	5.575	6.442		2.368	2.879		2.844	2.501	
Bilateral Cervical	N	35	24	.767	35	24	.039	35	24	.832
	Mean	3.9	3.33		3.15	0.98		0.91	0.74	
	Std. Deviation	3.973	3.148		5.052	2.043		1.909	1.592	
Lt Axillary	N	38	10	.469	38	10	.580	38	10	.364
	Mean	6.96	4.74		3.05	2.25		2.03	0.97	
	Std. Deviation	7.759	6.457		3.487	2.791		3.289	2.037	
Rt Axillary	N	31	13	.918	31	13	.146	31	13	.657
	Mean	5.61	5.22		1.35	1.64		0.49	0.31	
	Std. Deviation	6.302	5.16		4.841	2.775		1.311	1.123	
Bilateral Axillary	N	15	11	.238	15	11	.727	15	11	.869
	Mean	5.96	3.64		1.92	1.32		1.05	0.49	
	Std. Deviation	4.833	3.43		4.148	2.787		3.018	1.11	
Mediastinum and hilar	N	107	66	.287	107	66	.317	107	66	.399
	Mean	5.31	4.68		1.85	2.69		0.86	0.92	
	Std. Deviation	5.098	5.191		2.654	4.538		2.219	1.859	
Diaphragmatic LN	N	10	8	.927	10	8	.079	10	8	.266
	Mean	3.9	4.65		4.45	0.99		2.79	0.88	
	Std. Deviation	4.383	6.154		5.681	1.835		3.564	1.634	
Rt Pulmonary (lung)	N	35	27	.490	35	27	.303	35	27	.035
	Mean	3.79	4.43		1.47	1.9		0.7	1.75	
	Std. Deviation	4.047	4.171		2.914	2.665		1.929	2.773	
Lt Pulmonary (lung)	N	24	15	.122	24	15	.027	24	15	.927
	Mean	5.53	2.7		1.58	0.23		0.9	0.86	
	Std. Deviation	5.633	3.357		2.147	0.904		2.034	1.835	

B.4.11										
Abdominal lymph	N	75	61	.795	75	61	.877	75	61	.831
	Mean	5.52	5.08		2.25	2.14		0.9	0.96	
	Std. Deviation	6.269	5.241		3.394	3.435		1.997	1.989	
Liver	N	116	71	.981	116	71	.402	116	71	.722
	Mean	4.9	4.86		2.25	1.94		0.76	0.87	
	Std. Deviation	5.637	4.732		3.816	3.533		1.804	2.036	
Spleen	N	27	59	.080	27	59	.717	27	59	.216
	Mean	5.34	4.11		2.02	1.74		0.48	0.21	
	Std. Deviation	4.296	4.373		4.174	2.972		1.205	0.869	
Bone	N	104	86	.062	104	86	.725	104	86	.037
	Mean	4.51	6.16		1.81	1.78		0.75	1.53	
	Std. Deviation	4.868	6.67		3.203	3.8		1.902	3.171	
Pelvic LN	N	92	84	.269	92	84	.558	92	84	.217
	Mean	5.12	4.55		2.04	1.82		0.8	1.14	
	Std. Deviation	5.291	5.046		2.999	2.843		1.875	2.118	
Others	N	209	152	.000	209	152	.000	209	152	.000
	Mean	5.66	8.01		2.73	5.17		0.99	5.19	
	Std. Deviation	5.822	6.766		5.339	6.898		2.642	10.17	

Table 4.12 provides a detailed examination of the distribution of lesions across various metabolic response categories in HL and NHL for different treatment sessions. The analysis includes the number of lesions and the Pearson Chi-Square test statistics to assess the association between response categories and cancer type. The Chi-Square test assesses the association between the distribution of lesions and cancer type in each response category. A low Chi-Square value suggests a weak association, while a high value indicates a strong association.

In terms of achieving complete metabolic response (CMR), there is a noteworthy correlation between HL and NHL in treatment sessions 1 and 2, as indicated by Chi-Square values of 0.029 and 0.025, respectively. However, in treatment session 3, the association is not significant, with a Chi-Square value of 0.360, exceeding 0.05, suggesting a weaker relationship. Notably, HL demonstrates a higher rate of CMR compared to NHL.

For Stable Metabolic Response, treatment sessions 2 and 3 demonstrate a strong association between HL and a stable metabolic response (Chi-Square: 0.000), suggesting a consistent pattern. While in Partial Metabolic Response, the three treatment sessions show a weak association (Chi-Square: >0.5) between HL and NHL.

Moreover, progressive metabolic disease, no strong association is observed in any treatment session, as indicated by relatively higher Chi-Square values (0.359, 0.473, and 0.491).

These findings provide insights into the distribution of lesions across different metabolic response categories in HL and NHL, aiding in understanding the effectiveness of various treatments.

Table 4. 12. Comparative Analysis of Metabolic Response Categories and Lesion Distribution between Hodgkin's Lymphoma (HL) and Non-Hodgkin's Lymphoma (NHL) in Different Treatment Sessions.

	Response categories with cancer type		Number of lesions	Pearson Chi-Square
Response of treatment 1	Complete metabolic response	HL	421	
		NHL	324	0.029
	Stable metabolic response	HL	187	
		NHL	155	0.163
	Partial metabolic response	HL	167	
		NHL	106	0.057
	Progressive metabolic disease	HL	232	
		NHL	142	0.359
Response of treatment 2	Complete metabolic response	HL	240	
		NHL	136	0.025
	Stable metabolic response	HL	561	
		NHL	448	0
	Partial metabolic response	HL	81	
		NHL	69	0.14
	Progressive metabolic disease	HL	125	
		NHL	74	0.473
Response of treatment 3	Complete metabolic response	HL	123	
		NHL	82	0.36
	Stable metabolic response	HL	779	
		NHL	558	0
	Partial metabolic response	HL	43	
		NHL	24	0.529
	Progressive metabolic disease	HL	62	
		NHL	63	0.491

Table 4.13 presents the mean and standard deviation of the response to treatment for three different treatment stages (Response of Treatment 1, Response of Treatment 2, and Response of Treatment 3) among participants with HL and NHL. Levene's test for equality of variances is also provided for each category.

Following treatment 1, Levene's Test for left cervical lesions indicates no substantial difference in variances between HL and NHL across all regions of interest in the human body, except for mediastinal and hilar, and diaphragmatic lymph nodes, with p-values of 0.005 and 0.003, respectively. In the mediastinal and hilar region, HL exhibits a higher mean of 44.92 compared to NHL's mean of 34.55. Conversely, in the diaphragmatic lymph nodes region, NHL shows a higher mean than HL, with means of 50.75 and 11.3, respectively.

After treatment 2, Levene's Test for left cervical lesions indicates no significant difference in variances between HL and NHL across most regions of interest in the human body. However, there are exceptions in the cervical lymph nodes, right axillary lymph nodes, and diaphragmatic lymph nodes, with p-values of 0.000 and 0.003, respectively. In the cervical lymph nodes region, HL exhibits higher means compared to NHL. Similarly, in the diaphragmatic lymph nodes region, HL shows a higher mean than NHL, with means of 21.4 and 0.5, respectively.

After treatment 3, Levene's Test for left cervical lesions indicates no significant difference in variances between HL and NHL across most regions of interest in the human body. However, there are exceptions in several regions, including mediastinal and hilar lymph nodes, diaphragmatic lymph nodes, right pulmonary lymph nodes, liver lesions, and splenic lesions, with p-values of 0.000, 0.003, 0.000, 0.025, and 0.002, respectively. In the mediastinal and hilar lymph nodes, diaphragmatic lymph nodes, and right pulmonary lymph nodes regions, NHL exhibits higher means compared to HL. Conversely, in the liver lesions and splenic lesions regions, HL shows higher means than NHL.

Table 4. 13. Comparative Analysis of Standardized Uptake Values (SUV) Between Hodgkin's Lymphoma (HL) and Non-Hodgkin's Lymphoma (NHL) Across Anatomical Locations.

A.4.13

			Response of treatment 1			Response of treatment 2			Response of treatment 3		
		N	Mean	Std. Deviation	Levene's Test for Equality of Variances	Mean	Std. Deviation	Levene's Test for Equality of Variances	Mean	Std. Deviation	Levene's Test for Equality of Variances
Left Cervical	HL	54	32.69	46.070	0.186	24.6667	42.83183	0.001	16.9074	37.516	0.252
	NHL	22	41.91	49.484		10.0455	29.14410		23.3182	42.579	
Right cervical	HL	35	32.49	46.389	0.151	23.4857	42.27249	0.00	14.5143	35.417	0.514
	NHL	18	45.39	50.274		6.3889	23.39467		11.6667	32.154	
bilateral cervical	HL	35	44.20	49.036	0.266	26.3429	43.98124	0.00	17.3714	38.140	0.919
	NHL	24	50.54	50.531		8.8750	28.08731		17.0417	37.911	
left axillary	HL	38	25.18	42.249	0.122	29.8947	45.36208	0.87	16.3421	36.727	0.544
	NHL	10	41.40	50.443		30.5000	47.97048		20.3000	42.016	
Right axillary	HL	31	61.74	48.942	0.541	6.8710	24.88070	0.000	6.7097	24.917	0.773
	NHL	13	47.08	51.006		31.0000	47.88528		7.9231	27.678	
bilateral axillary	HL	15	60.87	49.615	0.578	20.2667	41.27169	0.128	13.3333	35.186	0.512
	NHL	11	55.27	51.397		9.5455	30.01787		9.6364	29.994	
mediastinal and hilar	HL	107	44.92	48.991	0.005	26.5327	43.95309	0.786	7.7383	26.362	0.00
	NHL	66	34.55	46.649		27.8939	44.50588		16.8030	37.495	
Diaphragmatic	HL	10	11.30	31.195	0.003	21.4000	41.44662	0.003	30.7000	47.833	0.003
	NHL	8	50.75	52.663		.5000	.92582		.7500	1.388	

B.4.13											
right	HL	35	43.57	49.592		20.4286	40.38002		3.285	16.862	
pulmonary	NHL	27	38.19	48.323	0.312	23.3333	41.77964	0.714	22.851	42.039	0.00
Left	HL	24	50.92	50.146		17.2083	37.83716		4.583	20.346	
pulmonary	NHL	15	34.00	48.319	0.129	7.4000	25.64817	0.062	1.000	1.309	0.172
abdominal	HL	75	46.15	49.380		19.1467	39.00821		10.853	31.018	
lymph	NHL	61	46.62	49.585	0.821	11.9344	31.98430	0.019	10.196	29.922	0.746
Liver	HL	116	39.93	48.039		25.5517	43.18159		14.086	34.523	
	NHL	71	54.38	49.310	0.094	21.4225	40.96468	0.235	8.676	27.953	0.025
Spleen	HL	27	41.93	49.079	.332	30.2593	46.12991	.458	26.037	44.594	.002
	NHL	59	46.76	49.329		25.7797	43.71541		12.067	32.548	
Bone	HL	104	46.12	49.177		28.2500	44.84076		9.807	29.568	
	NHL	86	40.42	48.473	0.159	22.4767	41.53432	0.066	10.767	30.698	0.704
Pelvic	HL	92	45.43	49.201	.448	15.9565	35.82004	.176	11.293	31.161	.560
	NHL	84	48.42	49.486		19.6071	39.24591		9.916	29.418	
Others	HL	209	43.21	48.560	.066	28.7273	44.81809	.000	14.086	34.575	.006
	NHL	152	47.49	49.337		17.5132	37.60601		9.453	28.945	

4.1.5 Comparing treatment based on genders

The examination of mean ranks and sum of ranks in Table 4.14 for each parameter based on gender provides valuable insights into potential variations between male and female participants. In each parameter (SUV1, SUV2, and SUV3) and the response of treatments (1, 2, and 3), the highest mean rank is observed in the male participants, suggesting a potential dominance or higher values in these parameters among males. The sum of ranks is generally higher for female participants across all three parameters. Differences in mean ranks and the sum of ranks highlight potential gender-based variations in the studied parameters. These variations can be indicative of underlying differences in the response to treatments or characteristics related to the parameters measured. Interpretation should be done considering the specific context and nature of the parameters under investigation.

Table 4.15 provides the results of various statistical tests, including Mann-Whitney U, Wilcoxon W, Z, and the corresponding asymptotic significance (2-tailed) values for SUV1, SUV2, SUV3, and the response to treatments. In the Mann-Whitney U and Wilcoxon W tests, the highest values are generally associated with the response of treatment 3, suggesting potential significant differences in this treatment compared to others. The lowest values are observed in the response of treatment 1 and 2, indicating potential similarities or lower differences in this treatment. The Z values in the Mann-Whitney U test reflect the standardized differences between groups. Negative Z values indicate that the corresponding groups (SUV2, SUV3, and response of treatment 2) have lower ranks compared to the other group. The asymptotic significance (2-tailed) values indicate the probability of obtaining the observed results by chance. A significance value less than 0.05 is commonly considered as evidence to reject the null hypothesis. In this context, the response of treatment 1 and 2 stands out with the lowest p-value 0.037 and 0.000 respectively, suggesting statistically significant differences compared to the other responses.

Table 4. 14 Gender-Based Comparison of Mean Ranks and Sum of Ranks in Different SUV's and treatment responses.

Gender		N	Mean Rank	Sum of Ranks
SUV1	Male	776	859.28	666801.50
	Female	920	839.41	772254.50
	Total	1696		
SUV2	Male	749	807.06	604491.00
	Female	897	837.22	750990.00
	Total	1646		
SUV3	Male	745	818.09	609474.00
	Female	888	816.09	724687.00
	Total	1633		
Response of treatment 1	Male	792	893.43	707598.50
	Female	942	845.70	796646.50
	Total	1734		
Response of treatment 2	Male	792	825.99	654182.50
	Female	942	902.40	850062.50
	Total	1734		
Response of treatment 3	Male	792	866.02	685887.00
	Female	942	868.75	818358.00
	Total	1734		

Table 4. 15. Test Statistics for SUV1, SUV2, SUV3, and Responses to Treatments in both of genders.

	SUV1	SUV2	SUV3	Response of treatment 1	Response of treatment 2	Response of treatment 3
Mann-Whitney U	348594.500	323616.000	329971.000	352493.500	340154.500	371859.000
Wilcoxon W	772254.500	604491.000	724687.000	796646.500	654182.500	685887.000
Z	-.842	-1.443	-.118	-2.086	-3.560	-.154
Asymp. Sig. (2-tailed)	.400	.149	.906	.037	.000	.878

Table 4.16 and 4.17 presents the mean ranks and test statistics, including Mann-Whitney U, Wilcoxon W, Z, and the corresponding asymptotic significance (2-tailed) values, for SUV1, SUV2, SUV3, and the response to treatments in male participants with different types of cancer. Generally, the Z values are close to zero, indicating that the mean ranks of the compared groups are relatively similar. For Response of Treatment 2, the p-value is 0.011, which is below the common significance threshold of 0.05, suggesting a statistically significant difference between the groups.

The mean ranks provide an understanding of the central tendency of each group. Higher mean ranks indicate higher ranks within the sample. The Mann-Whitney U and Wilcoxon W tests, along with Z and significance values, help assess the differences between the mean ranks of different types of cancer for each SUV and treatment response. The p-value of 0.011 for Response of Treatment 2 suggests a significant difference between types of cancer in the male participants in terms of their response to this specific treatment.

Table 4. 16. Comparison of Mean Ranks and Test Statistics for SUVs and Responses to Treatments in Male Participants with Different Types of Cancer.

Type of cancer in male participants		N	Mean Rank	Sum of Ranks
SUV1	HL	430	393.12	169042.5
	NHL	362	382.76	132433.5
	Total	792		
SUV2	HL	432	380	164159.5
	NHL	360	368.19	116715.5
	Total	792		
SUV3	HL	432	366.36	158268
	NHL	360	382.16	119617
	Total	792		
Response of treatment 1	HL	432	389.85	168414
	NHL	360	404.48	145614
	Total	792		
Response of treatment 2	HL	432	412.8	178328.5
	NHL	360	376.94	135699.5
	Total	792		
Response of treatment 3	HL	432	394.9	170596
	NHL	360	398.42	143432
	Total	792		

Table 4. 17. Test Statistics for SUV1, SUV2, SUV3, and Responses to Treatments in male's participant.

	SUV1	SUV2	SUV3	Response of treatment 1	Response of treatment 2	Response of treatment 3
Mann-Whitney U	72402.5	66312.5	64740	74886	70719.5	77068
Wilcoxon W	132433.5	116715.5	158268	168414	135699.5	170596
Z	-0.647	-0.84	-1.364	-0.959	-2.545	-0.293
Asymp. Sig. (2-tailed)	0.517	0.401	0.172	0.338	0.011	0.77
a. Grouping Variable: Type of cancer						

Tables 4.18 and 4.19 illustrate the mean ranks and test statistics, including Mann-Whitney U, Wilcoxon W, Z, and the corresponding asymptotic significance (2-tailed) values, for SUV1, SUV2, SUV3, and the response to treatments in female participants with different types of cancer. Most Z values are close to zero, indicating that the mean ranks of the compared groups are relatively similar. For SUV3, the p-values are 0.004. SUV3 shows a statistically significant difference between types of cancer in female participants.

Table 4. 18.Comparison of Mean Ranks for SUVs and Responses to Treatments in Female Participants with Different Types of Cancer

Type of cancer in female participants		N	Mean Rank	Sum of Ranks
SUV1	HL	574	451.4	259104.5
	NHL	368	475.59	164555.5
	Total	942		
SUV2	HL	572	442.94	253360.5
	NHL	370	459.67	149392.5
	Total	942		
SUV3	HL	575	431.19	247933
	NHL	367	468.96	146783
	Total	942		
Response of treatment 1	HL	575	477.24	274411.5
	NHL	367	462.51	169741.5
	Total	942		
Response of treatment 2	HL	575	479.7	275827
	NHL	367	458.65	168326
	Total	942		
Response of treatment 3	HL	575	471.13	270899.5
	NHL	367	472.08	173253.5
	Total	942		

Table 4. 19. Comparison of Test Statistics for SUVs and Responses to Treatments in Female Participants with Different Types of Cancer.

	SUV1	SUV2	SUV3	Response of treatment 1	Response of treatment 2	Response of treatment 3
Mann-Whitney U	94079.5	89482.5	82333	102213.5	100798	105299.5
Wilcoxon W	259104.5	253360.5	247933	169741.5	168326	270899.5
Z	-1.354	-1.038	-2.917	-0.848	-1.276	-0.071
Asymp. Sig. (2-tailed)	0.176	0.299	0.004	0.396	0.202	0.943
a. Grouping Variable: Type of cancer						

4.2 Discussion

Lymphoma is a type of cancer that originates in the lymphatic system, which is a part of the body's immune system. The average age of onset for lymphoma is reported as 40.7 years with a standard deviation of ±17.240 years. This means that while the average age at which lymphoma occurs is around 40.7 years, there is variability around this average, with some individuals developing lymphoma at younger or older ages. Several factors may contribute to the occurrence of lymphoma around this age range. One possible explanation is that as individuals age, their immune system may become less efficient, making them more susceptible to conditions like lymphoma. Additionally, environmental factors, genetic predisposition, and exposure to certain viruses or chemicals may also play a role in the development of lymphoma (Swerdlow et al., 2016).

The study involves 310 participants with a mean age of 40.7 ± 17.24 years. The participants are distributed across two treatment centers: Rahmah Center and Ahli Center, with Rahmah Center having a slightly higher number of participants and a lower average age.

The higher number of participants at Rahmah Center, coupled with a younger average age, may suggest a demographic shift or differences in patient recruitment practices between the two centers. This could be attributed to various factors such as local population demographics, outreach programs, or differing referral patterns. The lower average age at Rahmah Center might indicate a higher prevalence of lymphoma in a younger demographic within that region, or it could reflect differences in the types of lymphomas being treated at each center.

These demographic variations are crucial for interpreting the study's findings. They may influence treatment response rates and outcomes, which should be considered when generalizing results. The distribution of participants across different age groups and centers highlights the need for a nuanced analysis of treatment efficacy and management strategies, ensuring that findings are applicable to diverse patient populations.

Hodgkin lymphoma (HL) being the most prevalent cancer type with an average age of 35.71 years and a standard deviation of ±16.046 suggests that it disproportionately affects individuals in this age range compared to other cancers. HL is characterized by the presence of Reed-Sternberg cells, which are a type of abnormal immune cell found in the lymph nodes. These cells are more commonly associated with younger individuals, and this may contribute to the higher prevalence of HL in younger age groups (Kaseb et al., 2024). Certain risk factors such as infectious agents (like Epstein-Barr virus), genetic predisposition, and immune system disorders may play a role in the development of Hodgkin lymphoma. Exposure to certain environmental factors or chemicals may also contribute (Moubadder et al., 2020).

HL arises from abnormalities in the immune system. The immune system is generally more active in younger individuals, and dysregulation or abnormalities in its function may lead to the development of HL in this age group (Kolijn et al., 2023). It's also possible that diagnostic and screening practices contribute to the observed prevalence. Younger individuals may be more likely to undergo medical evaluations for various reasons, increasing the likelihood of detecting HL in this age group. Understanding these factors helps to explain why Hodgkin lymphoma is the most prevalent cancer type in individuals with an average age of 35.71 years. However, further research is needed to fully elucidate the underlying mechanisms driving this pattern.

The distribution of various subtypes of lymphoma, such as B-cell lymphoma, follicular lymphoma, T-lymphoblastic lymphoma, and chronic lymphocytic leukemia (CLL), with lower frequencies and slightly higher average age within the non-Hodgkin lymphoma (NHL) category can be attributed to several factors.

Different subtypes of lymphoma arise from distinct genetic and biological mechanisms. B-cell lymphoma and follicular lymphoma, being more prevalent, might have distinct genetic predispositions or environmental triggers compared to rarer subtypes like T-lymphoblastic lymphoma and CLL. These differences could contribute to variations in their occurrence rates and the ages at which they typically manifest (Kolijn et al., 2023).

B-cell lymphoma and follicular lymphoma, being B-cell malignancies, might have different underlying immunological factors compared to T-lymphoblastic lymphoma, which arises from T-cells, or CLL, which is characterized by the accumulation of abnormal B-lymphocytes. Variations in immune system function and immune surveillance mechanisms could influence the development and progression of these lymphoma subtypes (Nassef Kadry et al., 2015).

Differences in genetic susceptibility and environmental exposures may contribute to the heterogeneous distribution of lymphoma subtypes. Certain genetic mutations or environmental factors might predispose individuals to specific subtypes of NHL, influencing their prevalence and age of onset (Morton et al., 2008).

Some subtypes of NHL, such as T-lymphoblastic lymphoma and CLL, might be less frequently diagnosed or more challenging to detect due to overlapping clinical features with other conditions or limitations in diagnostic techniques. This could result in underrepresentation in studies and clinical settings (Howlader et al., 2016).

Hodgkin lymphoma and non-Hodgkin lymphoma are distinct entities with different pathophysiological characteristics. Hodgkin lymphoma is characterized by the presence of Reed-Sternberg cells, whereas non-Hodgkin lymphoma encompasses a heterogeneous group of lymphoid malignancies arising from B-cells, T-cells, or natural killer cells. Variations in disease biology and tumor behavior may contribute to differences in prevalence and lesion counts between HL and NHL (Munir et al., 2023).

Differences in diagnostic criteria and practices for HL and NHL may influence their respective prevalence rates. For instance, HL is typically diagnosed through the identification of Reed-Sternberg cells in lymph node biopsies, whereas NHL encompasses a broader spectrum of lymphoid malignancies diagnosed based on histopathological, immunophenotypic, and genetic features. Variations in diagnostic accuracy and accessibility could impact the reported prevalence and lesion counts for each lymphoma type (Laurent et al., 2015).

The prevalence of HL and NHL may vary across different populations and geographic regions due to differences in genetic predisposition, environmental exposures, and demographic characteristics. Certain populations may have a higher prevalence of HL or NHL based on factors such as age, ethnicity, or socioeconomic status (Abdel Sater et al., 2020).

The Mann-Whitney U test is a non-parametric test used to compare two independent groups when the assumption of normality is violated or when the data are ordinal. This test does not assume that the data follow a normal distribution, making it robust to non-normality and suitable for skewed or non-normally distributed data (Na, D.E.C et al. ,2024). In the context of this study, a non-significant p-value of 0.843 indicates that there is insufficient evidence to reject the null hypothesis, which states that there is no difference in metabolic responses between HL and NHL patients. In other words, the observed difference in metabolic responses between the two groups is not statistically significant at the conventional significance level (e.g., $\alpha = 0.05$).

The non-significant result suggests that, based on the metabolic responses measured, there is no apparent distinction in how HL and NHL patients respond to Treatment 1. This finding has implications for clinical practice, indicating that Treatment 1 may have similar efficacy or metabolic effects in both HL and NHL patients. If Treatment 1 demonstrates comparable efficacy or metabolic effects in both HL and NHL patients, clinicians may consider it as a viable treatment option for a broader range of lymphoma patients. This expands the treatment options available and allows for more personalized therapeutic approaches based on individual patient characteristics and preferences.

Identifying a treatment that is effective across different subtypes of lymphoma simplifies treatment protocols and clinical decision-making. Clinicians may be able to use Treatment 1 as a standardized approach for managing lymphoma patients, potentially reducing the complexity and variability in treatment regimens (Lodhi et al., 2020).

The observation that progressive metabolic disease occurs more frequently in HL compared to NHL, despite a higher rate of complete metabolic response in HL. Where the observed difference in metabolic responses between the two groups is statistically significant at the conventional significance level (P-value= 0.004).

Although HL patients may have a higher rate of complete metabolic response to initial treatment compared to NHL patients, the sensitivity of residual disease to subsequent treatments may differ between the two lymphoma types. NHL encompasses various subtypes with different treatment sensitivities and prognoses, which may influence the likelihood of achieving durable remission and preventing disease progression (Pratap et al., 2019).

Treatment approaches for HL and NHL may differ in intensity, duration, and modalities used. The aggressiveness of treatment regimens, including chemotherapy, radiation therapy, and immunotherapy, may influence the risk of disease progression and the development of resistant disease. Differences in treatment strategies between HL and NHL could impact disease control and long-term outcomes.

Variations in patient demographics, disease stage at diagnosis, comorbidities, and treatment adherence may also influence disease progression and treatment outcomes in HL and NHL. Factors such as age, performance status, and treatment-related toxicities may affect the ability to achieve and maintain a complete metabolic response and control disease progression (Stienen et al., 2015).

While both HL and NHL are often treated with chemotherapy, radiation therapy, and targeted therapies, their response rates and patterns may differ. HL, particularly classical HL, generally has a higher response rate to standard chemotherapy regimens such as ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine), with cure rates exceeding 80-90% in many cases. NHL, depending on the subtype and stage, may have varying response rates to different chemotherapy regimens. Some subtypes of NHL may require more aggressive treatment approaches or stem cell transplantation for better outcomes (Shanbhag et al., 2018).

After the initial 6-12 months of treatment, long-term management strategies may also differ between HL and NHL. HL survivors may require long-term monitoring for late effects of treatment such as secondary cancers, cardiovascular complications, and infertility. NHL survivors may also require long-term surveillance for disease recurrence and late effects, with the specific approach depending on the subtype and individual patient characteristics (Ng et al., 2016).

The decision to initiate treatment for lymphoma often depends on various factors, including the stage of the disease, the presence of symptoms, and the overall health status of the patient. Patients with early-stage disease or indolent (slow-growing) lymphomas may initially be managed with a strategy called watch and waiting, where treatment is deferred until there is evidence of disease progression. Therefore, some patients may not have received treatment initially because they were being monitored without active treatment (Jeong et al., 2022).

Diagnosis and staging of lymphoma can be complex and may require multiple tests, including imaging studies, biopsies, and laboratory investigations. It's possible that some patients were still undergoing diagnostic evaluations or awaiting confirmation of the diagnosis before treatment initiation (Paquin et al., 2023).

Patients with underlying health conditions or significant comorbidities may not be suitable candidates for aggressive treatment regimens. In such cases, treatment may be deferred or modified to minimize risks and optimize outcomes. Additionally, patients with poor performance status or compromised organ function may require careful evaluation and supportive care before initiating treatment. Delays in treatment initiation can occur due to various logistical factors, including scheduling issues, availability of treatment facilities, and access to specialized care. Some patients may experience delays in starting treatment due to these practical considerations (Amoozger et al., 2022).

Despite receiving treatment, some patients may experience treatment resistance or inadequate response, resulting in disease progression or incomplete metabolic remission. This could be due to intrinsic characteristics of the tumor cells, such as genetic mutations or alterations in signaling pathways, which render them less responsive to standard therapies (Amoozger et al., 2022).

Treatment-related toxicities and side effects can sometimes exacerbate metabolic dysfunction or impair the body's ability to cope with the disease. For example, certain chemotherapy agents may cause metabolic disturbances or organ dysfunction, which could contribute to worsening metabolic parameters despite treatment (van Leeuwen et al., 2016).

Patients with underlying medical conditions such as diabetes, metabolic syndrome, or hormonal imbalances may be predisposed to metabolic abnormalities. These pre-existing conditions could potentially worsen or be exacerbated by the stress of cancer and its treatment (Jha et al., 2023).

The decrease in complete metabolic response (CMR) over time in patients with HL and NHL can be attributed to several factors: Lymphomas are biologically heterogeneous diseases, and individual tumors may exhibit varying degrees of aggressiveness, sensitivity to treatment, and potential for relapse. Despite achieving initial CMR, residual tumor cells or microscopic disease may persist undetected, leading to disease recurrence or progression over time (Juskevicius et al., 2017).

Moreover, The tumor microenvironment plays a crucial role in the growth and survival of cancer cells. Over time, changes in the tumor microenvironment, such as alterations in immune cell populations, cytokine levels, and angiogenesis, may create a more favorable environment for tumor growth and evasion of treatment-induced cell death. These changes could contribute to disease relapse or progression despite achieving CMR initially (Xian et al., 2021).

Cancer cells are known to evolve over time through the accumulation of genetic mutations and clonal selection. Subpopulations of tumor cells with intrinsic resistance to treatment may emerge and proliferate, leading to disease relapse or resistance to subsequent therapies. Additionally, activation of alternative signaling pathways or up regulation of drug efflux pumps can confer resistance to chemotherapy and targeted agents, diminishing the effectiveness of treatment over time (Zhang et al., 2022).

The choice of treatment regimen, duration of therapy, and intensity of treatment can impact the likelihood of achieving and maintaining CMR. Some patients may receive suboptimal or inadequate treatment initially, leading to incomplete eradication of tumor cells and an increased risk of disease recurrence. Additionally, treatment-related toxicities or side effects may necessitate dose reductions, treatment interruptions, or discontinuation, compromising the efficacy of therapy and increasing the risk of relapse (Rusconi et al., 2020).

Also, the host immune system plays a critical role in recognizing and eliminating cancer cells. However, immune dysfunction or exhaustion, which can occur as a result of chronic antigen exposure, systemic inflammation, or immunosuppressive therapies, may impair immune surveillance and facilitate tumor escape. Consequently, patients may experience disease relapse or progression despite achieving CMR initially (Gonzalez et al., 2018).

Finally, Long-term follow-up studies may reveal disease relapses or progression that were not evident during earlier assessments. Detection bias, stemming from more frequent or intensive surveillance of patients enrolled in clinical trials or long-term observational studies, may lead to the identification of disease recurrence or progression that would otherwise have gone unnoticed (Fitzpatrick et al., 2018).

In 2017, a study by Barrington et al. demonstrated that the overall complete metabolic response (CMR) rate in HL ranges from 30% to 40%, while in NHL, particularly in B-cell lymphoma, it ranges from 40% to 60% (Barrington et al., 2017).

These findings closely resemble our own results. However, (Venkatraman et al., 2023). reported a higher CMR rate with 88% achieving CMR, while 12% achieved partial metabolic response (PMR) in the interim PET/CT scans (Radhakrishnan et al., 2023).

Table 4.3 presents the results of normality tests for treatment responses in different types of cancer, revealing that the data do not follow a normal distribution. This non-normality is important for choosing appropriate statistical tests.

The non-normal distribution of treatment response data highlights a critical aspect of statistical analysis, the selection of appropriate methods. Since parametric tests, such as t-tests and ANOVAs, assume that data follow a normal distribution, their application to non-normal data could lead to inaccurate conclusions.

In this context, non-parametric tests, such as the Mann-Whitney U test or Kruskal-Wallis test, become more appropriate as they do not require the data to meet the assumption of normality. These tests will provide more reliable results for comparing treatment responses among different cancer types.

The p-values from the Mann-Whitney U tests are consistently higher than the conventional significance level of 0.05, indicating no significant differences in metabolic responses between the two medical centers for all treatments for HL and NHL. It's possible that there are genuinely no significant differences in metabolic responses between the two medical centers Al-Ahli and Al-rahmah center for the treatments being studied. This could occur that both centers provide similar quality of care or if the treatments themselves have similar efficacy.

Tables 4.4 and 4.5 detail the metabolic responses to three different treatments, with significant findings from Mann-Whitney U tests indicating differences between HL and NHL responses in some treatments.

The differences in metabolic responses between Hodgkin Lymphoma and Non-Hodgkin Lymphoma observed in Treatment 1 highlight several important aspects:

1. Efficacy of Treatment: The overall treatment efficacy appears comparable for both HL and NHL, as indicated by the similar complete response rates. However, HL shows a slightly higher rate of progressive disease, which could suggest that HL may require more intensive or alternative treatment strategies in some cases.
2. Variations in Response Rates: The variations in stable and partial response rates between HL and NHL suggest that different types of lymphoma may respond differently to the same treatment. This could be due to inherent biological differences between the two lymphoma types or variations in how each type of lymphoma interacts with the treatment.
3. Significance of Findings: The significant differences identified through the Mann-Whitney U tests underline the importance of tailored treatment approaches. While both HL and NHL benefit from Treatment 1, the variations in response rates highlight the need for lymphoma-specific treatment adjustments and ongoing evaluation to optimize outcomes.

Mann-Whitney U p-value: 0.004 (significant) The Mann-Whitney U p-value of 0.004 for Treatment 2 is significant because it indicates a substantial difference in the metabolic responses between HL (Hodgkin Lymphoma) and NHL (Non-Hodgkin Lymphoma) patients. This low p-value suggests that the observed differences are unlikely to be due to random chance, meaning the treatment affects the two groups differently.

Table 4.6 summarizes the metabolic responses across all treatment sessions and provide a comprehensive of the overall treatment effectiveness and patient outcomes:

1. Effectiveness of Treatment: The high percentage of stable metabolic responses (51.68%) and the notable rate of complete metabolic responses (25.49%) suggest that the treatments used in the study are generally effective. They are successful in either stabilizing or fully resolving the disease in a significant portion of patients.

2. Areas for Improvement: The presence of progressive disease in 13.41% of patients highlights that some individuals are not responding adequately to the current treatments. This underscores the need for ongoing research to develop more effective therapies or personalized treatment plans for these patients.

3. Clinical Implications: The distribution of responses suggests that the treatments can be beneficial for a large proportion of patients but may not be uniformly effective across all individuals. Healthcare providers should consider these varying response rates when designing treatment plans and managing patient expectations.

4. Future Directions: The data highlight the importance of further research to optimize treatment strategies. Understanding why some patients achieve only partial or progressive responses could help in tailoring treatments more effectively and improving overall outcomes.

In summary, the aggregate metabolic response data show that the treatments are generally effective, with a majority of patients experiencing stable or complete responses. However, the presence of progressive disease in a subset of patients indicates that improvements are needed in treatment approaches for those who do not respond as well.

The findings provide valuable insights into the treatment and management of Hodgkin Lymphoma (HL) and Non-Hodgkin Lymphoma (NHL):

1. HL vs. NHL Prevalence: The higher prevalence of HL suggests that healthcare providers need to be particularly vigilant in managing this type of lymphoma. The increased number of lesions associated with HL also underscores the need for effective and potentially more aggressive treatment strategies.

2. Tailoring Treatment Approaches: The significant difference observed in Treatment 2's efficacy highlights the importance of tailoring treatment strategies based on lymphoma type. Treatments should be customized to address the specific response patterns of HL and NHL to maximize effectiveness.

3. Effective Treatment Outcomes: The predominance of stable and complete responses across treatments indicates that the current therapies are largely effective. However, continuous evaluation and adaptation of treatment plans are essential to maintain and improve these outcomes.

4. Strategic Management: The observed variation in initial and long-term efficacy between HL and NHL patients suggests that different management strategies might be required. For NHL patients, initial treatment may need to be more robust, while for HL patients, prolonged monitoring and extended therapy sessions might be beneficial.

5. Utilizing Visual Aids: Figures 4.1 and 4.2 are instrumental in visualizing treatment responses and understanding the nuanced differences between HL and NHL. These visual comparisons can guide clinical decision-making and improve patient management strategies.

In conclusion, the findings underscore the need for a nuanced approach to treating Hodgkin and Non-Hodgkin Lymphomas. By recognizing the differences in prevalence, treatment efficacy, and response patterns, healthcare providers can better tailor treatment plans and improve patient outcomes.

Results showing the distribution of lesions across different metabolic response categories (complete metabolic response, stable metabolic response, partial metabolic response, and progressive metabolic disease) provide insight into the effectiveness of treatment. Significant associations were observed between HL and NHL in achieving complete metabolic response in treatment sessions 1 and 2, indicating higher CMR rates in HL compared to NHL.

Levene's test for equality of variances is used Across different treatment stages, this test indicates significant differences in lesion distribution between HL and NHL across different anatomical regions, indicating potential areas where treatment outcomes and responses may differ between the two types of lymphoma.

Overall, these results underscore the complexity and difference in treatment outcomes and metabolic responses between Al-Ahli and Al-Rahma medical centers. Despite some numerical differences, statistical analyzes provide confidence in the similarity of treatment efficacy across these medical centers, guiding clinical decisions and further research into lymphoma treatment strategies.

Overall, these findings emphasize the importance of personalized treatment plans based on lymphoma type and response patterns. Further research may be needed to explore why these differences exist and to refine treatment strategies to enhance effectiveness for both Hodgkin Lymphoma and Non-Hodgkin Lymphoma patients.

In HL and NHL affecting the axillary lymph nodes, the expression of receptors may vary compared to lymph nodes in other parts of the body. In HL, the tumor cells are characterized by the presence of Reed-Sternberg cells, which typically express CD30 and CD15 markers. The expression of other receptors such as CD20 (found on B cells) may be reduced or absent in HL, making it less responsive to certain targeted therapies like rituximab, which targets CD20. The tumor microenvironment in HL often includes a mixture of inflammatory cells, including T cells, macrophages, and eosinophils, which can contribute to the unique histological features of HL.

In NHL comprises a diverse group of lymphoid malignancies, each with its own unique genetic and molecular characteristics. The expression of receptors in NHL can vary depending on the subtype and genetic alterations present in the tumor cells. Some subtypes of NHL, such as diffuse large B-cell lymphoma (DLBCL), may express CD20 and other B-cell markers, making them potential targets for therapies like rituximab. Other subtypes of NHL, such as T-cell lymphomas or indolent lymphomas, may have different patterns of receptor expression, which can influence treatment strategies (Kos et al., 2021).

The expression of receptors in axillary lymph nodes affected by HL or NHL may differ from that in lymph nodes located in other regions of the body, such as the cervical, mediastinal, or inguinal lymph nodes. Differences in receptor expression may impact the choice of targeted therapies and treatment outcomes, as certain receptors may be more or less prevalent in specific lymph node regions (Mohammed et al., 2019). Therefore, while both HL and NHL can affect axillary lymph nodes, the expression of receptors in these lymphomas may vary depending on the subtype and genetic characteristics of the tumor cells. Understanding these differences is essential for developing personalized treatment strategies and optimizing outcomes for patients with lymphoma affecting the axillary region.

Metastasis to pulmonary nodes and bone in NHL can be more challenging to treat compared to HL. NHL comprises a heterogeneous group of lymphoid malignancies with various subtypes, each with distinct biological characteristics and treatment responses. Some NHL subtypes may have a higher propensity for metastasis to specific organs such as the pulmonary nodes and bone, making treatment more challenging (Mahajan et al., 2022).

Moreover, Certain aggressive NHL subtypes, such as diffuse large B-cell lymphoma (DLBCL) or mantle cell lymphoma (MCL), may have a higher likelihood of metastasizing to distant sites like the pulmonary nodes and bone. These subtypes often require more intensive treatment regimens, including combination chemotherapy, targeted therapy, and sometimes stem cell transplantation, to achieve remission (Lynch et al., 2024).

Also, NHL involvement in bone often leads to diffuse infiltration of the bone marrow, compromising its normal function and posing challenges for treatment. This infiltration can cause bone pain, fractures, and marrow failure, requiring specialized management approaches such as radiation therapy or bone marrow transplantation. NHL-related bone involvement can weaken the bone structure and increase the risk of fractures and skeletal-related events. Treating bone metastases in NHL often requires a multidisciplinary approach involving oncologists, orthopedic surgeons, and radiation oncologists to address pain control, bone stability, and tumor burden (Sultan et al., 2018).

Metastatic NHL lesions in pulmonary nodes and bone may exhibit resistance to standard chemotherapy regimens or targeted therapies, necessitating the exploration of alternative treatment approaches such as immunotherapy, chimeric antigen receptor (CAR) T-cell therapy, or novel agents targeting specific molecular pathways. Aggressive treatment approaches for metastatic NHL, such as high-dose chemotherapy or radiation therapy, can lead to significant treatment-related toxicities, including myelosuppression, infection, and organ dysfunction. Balancing treatment efficacy with minimizing treatment-related complications is essential in managing metastatic NHL (Dizman et al., 2021).

HL may have a higher rate of achieving CMR compared to NHL due to HL is known to be more sensitive to chemotherapy and radiation therapy compared to NHL. The characteristic Reed-Sternberg cells in HL are more susceptible to cytotoxic treatments, resulting in a higher likelihood of achieving CMR. In contrast, NHL subtypes may exhibit variable responses to treatment depending on their genetic and molecular features (Dizman et al., 2021).

Moreover, Advances in targeted therapies, such as monoclonal antibodies and immune checkpoint inhibitors, have improved outcomes for HL patients. Drugs like brentuximab vedotin and checkpoint inhibitors like nivolumab and pembrolizumab have shown efficacy in treating refractory or relapsed HL, potentially contributing to higher CMR rates (Witkowska et al., 2018).

The treatment regimens used for HL often involve combination chemotherapy with or without radiation therapy, which may effectively eradicate tumor cells and achieve CMR. In NHL, treatment approaches vary depending on the subtype and may include chemotherapy, immunotherapy, targeted therapy, or stem cell transplantation, which may have differing efficacy in achieving CMR.

The initial treatment response favoring HL over NHL in mediastinal and hilar lymph nodes may be attributed to the distinctive biological characteristics of HL, including specific cellular targets, increased radiosensitivity, chemotherapy sensitivity, early treatment response, and the tumor microenvironment. However, treatment outcomes can vary depending on individual patient factors, disease stage, and treatment regimen, highlighting the importance of personalized treatment approaches in lymphoma management (Witkowska et al., 2015). However, the differential treatment response favoring NHL over HL in the diaphragmatic lymph nodes region may be attributed to the chemotherapy sensitivity, disease biology, infiltrative nature of NHL, efficacy of immunotherapy, and the tumor microenvironment. These factors underscore the importance of personalized treatment approaches tailored to the specific subtype and biological characteristics of lymphoma in optimizing treatment outcomes (Alvaro et al., 2010).

HL and NHL are distinct types of lymphomas with different biological characteristics. HL is characterized by the presence of Reed-Sternberg cells, which are large, abnormal B cells typically found in the lymph nodes. These cells can contribute to higher metabolic activity and increased uptake of imaging agents such as FDG (fluorodeoxyglucose) on PET scans, resulting in higher mean SUV1 (Standardized Uptake Value) measurements in HL compared to NHL and after SUV2 the differences will be more than that found in NHL (Physicians, F.O.R). Moreover, the extent and pattern of lymph node involvement may differ between HL and NHL. In the cervical lymph nodes region, HL may exhibit more extensive or widespread involvement compared to NHL, leading to higher mean SUV values. Similarly, in the diaphragmatic lymph nodes region, HL may demonstrate greater infiltration or disease burden, resulting in higher mean SUV measurements compared to NHL (Laurent et al., 2015).

The tumor microenvironment, including the presence of inflammatory cells, stromal components, and cytokines, may vary between HL and NHL and influence metabolic activity and SUV measurements on PET scans. The composition of the tumor microenvironment can impact disease progression and treatment response, potentially leading to differences in mean SUV values between the two lymphoma types.

The study reveals gender-based variations in metabolic parameters and treatment responses among lymphoma patients. While males often show higher mean ranks in SUV measurements, females contribute more significantly to cumulative ranks. Treatment responses, particularly in Treatment 3, demonstrate statistically significant differences between genders, highlighting the importance of gender-specific considerations in lymphoma treatment strategies. These findings provide critical insights into potential gender-related differences in lymphoma management, guiding personalized treatment approaches and further research into optimizing therapeutic outcomes based on gender-specific factors.

The observation that treatment in HL and NHL at the initial time is higher in males compared to females may reflect differences in disease incidence, age at diagnosis, clinical presentation, healthcare seeking behavior, biological factors, and access to healthcare. Further research is needed to better understand the underlying reasons for these gender disparities in lymphoma treatment initiation. (Horesh et al., 2014).

showed similar results, they found NHL incidence among males is significantly higher than in females. In addition to gender itself, gravidity has a protective role against NHL occurrence.

Finally, the observation that treatment in HL and NHL after a long-term period is higher in females compared to males may reflect differences in survivorship issues, disease biology, healthcare-seeking behavior, hormonal factors, access to healthcare, and psychosocial factors. Further research is needed to better understand the underlying reasons for these gender disparities in long-term treatment utilization in lymphoma patients.

The observation is that treatment in males with HL is higher than in males with NHL especially in treatment 2. Hodgkin's Lymphoma tends to occur more frequently in males compared to females, and NHL incidence rates also show a male predominance. Therefore, since HL is more common in males, there may be a higher absolute number of male patients receiving treatment for HL compared to NHL (Horesh et al., 2014).

HL often presents in younger age groups compared to NHL, and younger individuals may be more likely to receive aggressive treatment regimens. Additionally, HL may have a higher disease burden or more aggressive clinical features in males compared to NHL, leading to a greater need for intensive treatment approaches (Ocier et al. ,2021). HL is generally considered more curable than NHL, especially in young, otherwise healthy individuals. Males with HL may have a better prognosis and higher likelihood of achieving long-term remission compared to males with NHL, prompting more aggressive treatment strategies to optimize outcomes.

Clinical guidelines and treatment standards for HL often recommend specific treatment regimens based on disease stage, risk factors, and patient characteristics. These guidelines may prioritize aggressive treatment approaches for HL, particularly in males, to achieve optimal outcomes (Kuruvilla et al. ,2009). Overall, the higher treatment rates in males with HL compared to NHL may be attributed to differences in disease incidence, age at diagnosis, disease burden, treatment response, clinical guidelines, access to specialized care, and treatment advances. Further research is needed to better understand the specific factors driving these differences and to optimize treatment strategies for male patients with lymphoma.

Chapter Five

5.1 Conclusion

Through this study, we conclude the importance of PET/CT in monitoring patients' response to treatment in Hodgkin and non-Hodgkin lymphoma. This was done by dividing treatment into three stages, and each treatment stage was a comparison between the PET/CT scans of the same patients. Cases were divided The response is divided into four stages: there was a Stable metabolic response, Partial metabolic response, Complete metabolic response and Progressive metabolic disease.

By comparing the responses of HL and NHL patients to treatment, it was found that there were few differences in treatment compared to the type of cancer present and the stage of treatment, as at one stage of treatment, the response of NHL patients to treatment was higher than that of HL, while HL patients had more infections and multiple lesions.

5.2 Recommendations

From the results we obtained, it was found that there is no significant difference in the patient's condition between PET 1 and PET 2. This means that future studies should focus on the examinations' durations. Through this study, it became clear that the treatment used for patients with HL and NHL is chemotherapy, and I advise researchers to conduct studies on this subject using other methods of treatment and comparing them to chemotherapy.

5.3 References

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Appendices

Appendices A: ethical approval from Al-Quds University to conduct the study.

Al Quds University
Faculty of Health Professions
Jerusalem –Abu Dis

جامعة القدس
كلية المهن الصحية
القدس – أبو ديس

Research Ethics Subcommittee of Faculty of Health Professions
Letter of approval

Sep. 3rd, 2023
Ref. No.: RESC/2024-2

Dear Applicants, (**Dr. Mohammad Hjouj, Mr. Salah Jardat**)

Program: **MSc Medical Imaging Department**

The Research Ethics subcommittee of the Faculty of Health Professions has recently reviewed your proposal entitled (**Treatment response assessment in lymphoma (Hodgkin's lymphoma and Non-Hodgkin's lymphoma) with FDG-PET in Palestinian health system**) submitted by (**Dr. Mohammad Hjouj**). Your proposal is deemed to meet the requirements of research ethics at Al-Quds University, but further assessment is required by the Central Research Ethics Committee of Al-Quds University. We wish you all best for the conduct of the project.

Hussein ALMasri, PhD
Associate Professor of Medical Imaging
Research Ethics Subcommittee Chair
Faculty of Health Professions

Hussein ALMasri

CC: File
CC: Committee members

Tel. Fax: 02 2791243 Email: dean@hpro.alquds.edu تلفاكس: 02 2791243

Appendices B:

Al Quds University
Faculty of Health Professions
Medical Imaging Department
Jerusalem –Abu Dies

جامعة القدس
كلية المهن الصحية
دائرة التصوير الطبي
القدس- أبوديس

التاريخ :10\SEP\2023

السادة ادارة المستشفى الاهلي المحترمين،

تحية طيبة وبعد،

الموضوع : تسهيل مهمة باحث من جامعة القدس – ابو ديس

ايمانا منا بدوركم في خدمة وتطوير المجتمع الفلسطيني واستنادا لمعرفتنا بالدور الهام الذي تقومون به في دعم التعليم والبحث العلمي،

نتوجه لحضرتكم التكرم بالايعاز للمعنيين المساعدة بتسهيل مهمة طالب الدراسات العليا الباحث صلاح جرادرت من برنامج ماجستير تكنولوجيا التصوير الطبي – كلية المهن الصحية \جامعة القدس في جمع المعلومات اللازمة لدراستة الخاصة بتقييم الاستجابة للعلاج في سرطان الغدد الليمفاوية باستخدام ^{18}F-FDG PET/CT في النظام الصحي الفلسطيني.

سيقوم الطالب بعمل بحث بعنوان:

Evaluation of response to treatment of lymphoma (Hodgkin's and non-Hodgkin's) Using 18F-FDG PET/CT in the Palestinian health system.

وعليه اقتضى اعلامكم وطلب مساعدتكم الهامة وسيتم اطلاعكم على نتائج البحث.

وتفضلوا بقبول فائق الاحترام والتقدير،،،

Mohammad Hjouj PhD د.محمد حجوج
Academic Supervisor المشرف الاكاديمي

Associate Professor of Medical Imaging
Faculty of Health Professions
Al-Quds University - Abu Deis - Main Campus
Jerusalem –Palestine

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Appendices C:

Al Quds University
Faculty of Health Professions
Medical Imaging Department
Jerusalem –Abu Dies

بسم الله الرحمن الرحيم

جامعة القدس
كلية المهن الصحية
دائرة التصوير الطبي
القدس- أبوديس

التاريخ :10\SEP\2023

السادة المحترمين ادارة مستوصف الرحمة – جمعية اصدقاء المريض\ نابلس

تحية طيبة وبعد،

<u>الموضوع : تسهيل مهمة باحث من جامعة القدس – ابو ديس</u>

ايمانا منا بدوركم في خدمة وتطوير المجتمع الفلسطيني واستنادا لمعرفتنا بالدور الهام الذي تقومون به في دعم التعليم والبحث العلمي،

نتوجه لحضرتكم التكرم بالايعاز للمعنيين المساعدة بتسهيل مهمة طالب الدراسات العليا الباحث صلاح جرادرت من برنامج ماجستير تكنولوجيا التصوير الطبي – كلية المهن الصحية \جامعة القدس في جمع المعلومات اللازمة لدراستة الخاصة بتقييم الاستجابة للعلاج في سرطان الغدد الليمفاوية باستخدام

^{18}F-FDG PET/CT في النظام الصحي الفلسطيني.

سيقوم الطالب بعمل بحث بعنوان:

Evaluation of response to treatment of lymphoma (Hodgkin's and non-Hodgkin's) Using 18F-FDG PET/CT in the Palestinian health system.

وعليه اقتضى اعلامكم وطلب مساعدتكم الهامة وسيتم اطلاعكم على نتائج البحث.

وتفضلوا بقبول فائق الاحترام والتقدير،،،

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تقييم الاستجابة للعلاج في سرطان الغدد الليمفاوية (سرطان الغدد الليمفاوية هودجكين وسرطان الغدد الليمفاوية في النظام الصحي الفلسطيني FDG-PET غير هودجكين) باستخدام

اعداد: صلاح جمال جرادات

المشرف: د. محمد حجوج

المشرف المشارك: د. منتصر السيد أحمد

الملخص:

سرطان الغدد الليمفاوية هو النوع الأكثر شيوعا من سرطان الدم الخبيث مع أكثر من 80 نوعا فرعيا وفقا لأحدث تصنيف لمنظمة الصحة العالمية. الأورام اللمفاوية تأتي في أشكال عديدة. تشمل الأنواع الفرعية الأساسية: سرطان الغدد الليمفاوية هودجكين (HL)، وسرطان الغدد الليمفاوية غير هودجكين (NHL). ويساعد التشخيص المبكر والدقيق لهذه الأنواع من السرطان في تحديد مرحلة السرطان وطريقة العلاج. مع ظهور تقنية التصوير المقطعي بالإصدار البوزيتروني/التصوير المقطعي المحوسب (PET/CT)، ساعدتنا على اكتشاف موقع السرطان وتحديد مرحلته وطريقة علاجه . في هذه الدراسة، تم استخدام FDG-PET/CT لتقييم استجابة مرضى ليمفوما هودجكين وغير هودجكين للعلاج. تم جمع فحوصات PET/CT لجميع مرضى سرطان الغدد الليمفاوية من جمعية أصدقاء المريض المستشفى الأهلي - الخليل، وجمعية أصدقاء المريض الخيرية (عيادة الرحمة) - نابلس. شملت الدراسة 310 مريضاً مصابين بسرطان العقد اللمفاوية من نوع هودجكين (HL) وغير هودجكين (NHL) من المستشفى الأهلي وعيادة الرحمة، حيث بلغ عدد مرضى HL (196) مريض ، وكان عدد مرضى NHL (114) مريض ، وتوزعت NHL على النحو التالي: (سرطان الغدد الليمفاوية الجريبي (Follicular lymphoma) 30 مريض ، سرطان الغدد الليمفاوية للخلايا البائية الكبيرة المنتشرة (DBCL)71 مريض ، سرطان الغدد الليمفاوية التائية -T) (lymphoblastic lymphoma 8 مرضى وسرطان الدم الليمفاوي المزمن (CLL) 5 مرضى). من النتائج التي حصلنا عليها، تم تقسيم استجابات المرضى للعلاج إلى أربعة أقسام: الاستجابة الأيضية المستقرة (SMR)، والاستجابة الأيضية الجزئية (PMR) ، والاستجابة الأيضية الكاملة (CMR) ، والمرض الأيضي التقدمي (PMD) . وقد تم تقسيم هذه الأنواع من الاستجابات بناء على مقارنة تقارير المرضى ومراقبة حالتهم بعد تلقي العلاج.