The evaluation of PET response patterns in the treatment of malignant lymphoma

By

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Summary:

Aim:
The aim is to evaluate the response (including limitations) of PET/CT, Deauville scale and prevalence of extranodal disease in patients undergoing treatment for 3 types of malignant lymphomas (diffuse large B-cell lymphoma, Hodgkin’s lymphoma and Mantle cell lymphoma), as well as the stages of lymphoma before and after PET/CT.

Objectives:
To evaluate PET/CT-findings in patients treated for HL, DLBCL and MCL, to identify:

1. The response rate for every lymphoma type by Deauville scale
2. The limitations of this modality
3. Prevalence of extranodal disease
4. The staging before and after PET/CT was performed

Methods:
A retrospective analysis of the medical documentation of 42 patients (diagnosed with Hodgkin’s lymphoma, DLBCL and MCL) at the Oncology and Haematology department (Kaunoklinikos), between 2014 and 2015 was performed.

Results:
Regarding the evaluation of response of PET/CT in patients treated for the 3 investigated malignant lymphomas, we could see that the type of response was dependent on the type of lymphoma. Looking into complete response, it was found in 55.6 % of HL patients, 60 % of DLBCL patients and 75 % of MCL patients. Since this response is determined by evaluating the Deauville scale, we can conclude that the results of this scale are directly correlating to the Deauville scale. The PET/CT was limited in 6 out of the 42 investigated patients (14.3 %), meaning that this modality was not sufficient enough to detect if there was any response at all. As for the prevalence of extra-nodal disease, it was found to be 33.4 % in HL patients, 48 % in DLBCL patients, and 25 % in MCL patients.

Conclusion:
We can conclude that by looking into the response of each lymphoma type, MCL had the highest prevalence of complete response (75 %), followed by DLBCL (60 %) and finally HL (55.6 %). We can simultaneously conclude that the results of this scale are directly correlating to the Deauville scale. This meaning that the patients whom showed 1-3 points on the Deauville scale (complete response) were 75 % in MCL, 60 % of DLBCL and 55.6 % in HL. There was limitation of PET/CT was in 6 out of the 42 investigated patients (14.3 %). As for the prevalence of extra-nodal disease, it was found to be highest in DLBCL patients (48 %),
followed by HL (33.4 %) and lastly MCL (25 %). Finally, for the staging before and after PET/CT was performed, we have established that the clinical stage was the same as PET/CT stage in 52.4 %, where as it was down-staged in 38 % and up-staged in 9.5 % (for all lymphomas combined).

**Acknowledgement:**

I would like to thank my family and friends in both Sweden and Lithuania, for I am very appreciative for the support that they have given me throughout this journey. Special thanks to my supervisor, Prof. Rolandas Gerbutavicius, who helped me come up with amazing ideas and was always able to get the best out of me. I would also like to thank Dr. Martyna Apinyte for helping me gather the data needed for my research.

**Conflict of Interest:**
The author reports no conflict of interest.

**Ethics Committee Clearance:**

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**Abbreviations list**

DLBCL = Diffuse Large B-cell lymphoma

HL = Hodgkin’s lymphoma

18F-FDG = 18F-fluorodeoxyglucose

PTLD = Post-transplant lymphoproliferative disorders

GIT = Gastrointestinal tract

R-CHOP = Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone

CVP = Cyclophosphamide, vincristine and prednisolone

BMB = Bone marrow biopsy

BMI = Bone marrow involvement

IHD = Ischemic heart disease

AP = Angina Pectoris

AAA = Abdominal Aortic Aneurism
**Introduction:**

Today there are numerous different classification schemes of malignancies of the lymphoid tissues based on their morphological features as well as immunophenotypic, cytogenetic and molecular characteristics. The newest of which was published by the World Health Organization (WHO) in 2008, but was later revised and refined in 2016. [1] However, in this dissertation the patients were separated into 3 groups depending on their lymphoma type; *Hodgkin’s lymphoma*, Diffuse Large B-Cell Lymphoma and Mantle cell lymphoma.

*Hodgkin lymphoma* originates from the B-lymphocytes and accounts for approximately 11% of all lymphomas. [2] For the diagnosis, imaging modalities are of immense significance, not only *during* the diagnostic process, but also throughout the therapeutic process as well. Computed tomography (CT) still remains as the standard imaging modality in HL due to that it is easily performed, available and there exist dependable evidence of its diagnostic significance. Nevertheless there are a few *restrictions* in the CT utilization, including that minor lesions (<1.5 cm diameter) are prone to be missed and that it is exceedingly problematic to determine the characters of any residual masses during and after treatment. [3] Hence, the usage of *PET/CT* is indicated, since by detecting the cells metabolic activity, it makes it feasible to address the restrictions of the CT scans. This modality enhances the uptake of a certain radiotracer, termed 18F-FDG, and this makes it possible not only to visualize slight neoplastic masses that are undetectable by CT scans, but also investigate the characters of any residual masses. [4] Interim PET-CT is utilized to assist in the evaluation of the response to the ongoing therapy, and allows for adjustment of the treatment regimen in individual cases if deemed necessary. Interim refers to that this modality is performed *during* the treatment process and is usually carried out after 2-3 cycles of chemotherapy.

As for *DLBCL*, it is the most common histological subtype of non-Hodgkin lymphomas accounting for approximately 25 percent of all NHL cases. Similarly to most other NHLs, there is a male predominance (~ 55 percent in men) and the median age at presentation is 64 years. As for the imaging modalities, CT scans help us identify the level of lymphadenopathy as well as the presence of any extranodal disease. Moreover, CT-scan findings aid in assessing the degree of response to therapy. PET scans are increasingly being utilized to stage the disease as well as determining whether residual masses represent scars or persistent lymphoma (same as for Hodgkin Lymphoma). [5]

In regards to the treatment, the patients are generally classified as having either *limited* or *advanced* stage disease (based on whether or not the tumour can be contained within one irradiation field). Limited stage disease is treated primarily with systemic chemotherapy, Rituximab, and radiation therapy. The advanced stage disease is treated with systemic chemotherapy plus Rituximab (without radiotherapy). This category includes patients with stage III or IV according to Ann Arbour classification. [6]

Mantle cell lymphoma comprises approximately 7% of adult non-Hodgkin lymphomas in Europe. The median age of patients is 68 years old and males are affected in three-quarters of cases. [7] Frequent involvement sites include bone marrow, spleen, lymph nodes and extranodal sites (GIT, pleura and breast). Full-body CT scanning is important for initial
staging and for assessing response to treatment. The treatment regimens of this type of lymphoma can be similar to other types of NHL, with the options being chemotherapy (R-CHOP or CVP), stem cell/bone marrow transplant, and radiotherapy. [8,9]

I am planning to investigate the value of PET in evaluation of the treatment response in patients suffering these 3 types of lymphomas.

**Aim and Objective**

**Aim:**
The aim is to evaluate the response (including limitations) of PET/CT, Deauville scale and prevalence of extranodal disease in patients undergoing treatment for 3 the types of malignant lymphomas (diffuse large B-cell lymphoma, Hodgkin’s lymphoma and Mantle cell lymphoma), as well as the stages of lymphoma before and after PET/CT.

**Objectives:**
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1. The response rate for every lymphoma type by Deauville scale
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3. Prevalence of extranodal disease
4. The staging before and after PET/CT was performed

**Literature Review:**
Multiple previous articles have been published that address the peculiarities of PET/CT in patients with different types of lymphoma. It is important to emphasize that the study of PET/CT findings in non-Hodgkin’s lymphoma mostly is centered on *B-cell lymphomas*, and very seldom has there been any published articles that investigate the role of PET/CT in peripheral T-cell lymphoma. This is predominantly due to the fact that the prevalence of B-cell lymphomas is significantly higher than T-cell lymphoma, as it is explained in the introduction under the epidemiology/prevalence of each type of lymphoma.

What is furthermore noteworthy is that the different types of lymphomas have significantly diverse clinical presentations, diagnostics (including imaging findings), treatment regimens and prognosis. This is essential to comprehend in order to properly evaluate each patient individually in relation to their type and severity of lymphoma.

Hodgkin’s lymphoma originates from the B-lymphocytes (as we have mentioned above), but what is also worth mentioning is that according to the guidelines given by the WHO, Hodgkin’s lymphoma is to be further classified into five sub-types. [10] These include lymphocyte-rich nodular-sclerosing, lymphocyte-depleted, mixed-cellularity, and nodular lymphocyte-predominant (NLP). The 4 first types are referred to as the *classical* Hodgkin’s lymphomas, whereas the fifth type (NLP) is a separate entity with unique clinical manifestations and a dissimilar treatment paradigm. However, this classification is neither utilized nor mentioned in the articles relating to HL that I have used, and I will therefore not be sub-dividing my patients into these sub-groups.
In Hodgkin’s lymphoma, the particular neoplastic cells are referred to as the Reed-Sternberg cells, and these cells comprise approximately 1-2% of the entirety of the tumor cell mass. The remainder is composed of a mixture of inflammatory cells consisting of neutrophils, histiocytes, lymphocytes, plasma cells and eosinophils.[11]

Most of the patients with HL present with painless cervical adenopathy, but other manifestations may also be present, including early pruritus (early means at the time of first presentation) and constitutional symptoms which include night sweats, fever (>38ºC) and unintentional weight loss (> 10% of the body weight in last 6 months). Although occurring in fewer than 10% of patients with HL, pain at sites of nodal disease which is precipitated by drinking alcohol is a specific (pathognomic) finding for Hodgkin lymphoma. [2,3]

As for the Non-Hodgkin lymphoma, it includes more than 60 types; however Diffuse Large B-cell lymphoma (DLBCL) is the most common type making up about 25-30% of all non-Hodgkin’s lymphomas. Clinically, the initial sign of DLBCL is often a rapidly growing, non-painful mass that is classically an enlarged lymph node in the neck, groin, or abdomen with or without B-symptoms (constitutional symptoms). In about 40% of cases however, the malignancy does not commence in the lymph nodes, but instead develops in a different place, and then travels to the lymph nodes. This is defined as an extranodal disease, and the most common site is the stomach or GIT, although the disease can arise in virtually any organ. Also worth mentioning is that most patients (approximately 60%) are not diagnosed with DLBCL until the disease is already advanced (Ann Arborstage III or IV). In the remaining 40% of patients, the disease is confined to only one side of the diaphragm, which is referred to as localized disease.[5]

Mantle Cell Lymphoma (MCL) is a rare but aggressive type of NHL and the majority (approximately 70%) of patients have advanced-stage disease at time of diagnosis. As mentioned above, frequent sites of involvement include bone marrow, lymph nodes, blood, and extranodal sites. Referring to the prevalence of such presentations, 75 percent of patients initially present with lymphadenopathy, and the remaining 25 percent present with extranodal disease. In relation to the clinical picture of this malignancy, generalized lymphadenopathy is present in 90 percent of patients, splenomegaly in 60 percent and finally hepatomegaly in about 30 percent. Also noteworthy is that approximately one-third of patients simultaneously have systemic B symptoms at presentation. [8,9]

The first article that was considered to be essential was published in The Oncologist in 2014 under the title “Prognostic Value of Interim Positron Emission Tomography in Patients with Peripheral T-Cell Lymphoma”.[12] This article states that it has already been established that interim PET/CT is a reliable prognostic factor for most types of lymphomas, although the role of PET/CT in T-cell lymphomas is still under investigation, since the most recent findings suggest that the FDG-avidity is less predictable in PTCL (post-transplant lymphoproliferative disorders) in contrast to other lymphomas.

In this study, the positivity of PET/CT varied from 50% (cutaneous anaplastic large-cell lymphoma) to 78% (angioimmunoblastic T-cell lymphoma), and 100% (adult T-cell leukemia/lymphoma). This could partially be explained by the “aggressivity” of the lymphomas, considering that the more aggressive the tumor spread is, the higher percentage of PET/CT positivity there is. In other words, cutaneous anaplastic large-cell lymphoma is less aggressive and therefore the percentage of its positivity on PET is lower.
In addition, in 29% of the patients the full-body computed tomography (CT) scans were not able to pick up certain sites of the disease, which included cutaneous, subcutaneous, and muscular masses, as well as and lymphadenopathies in the epitrochlear and popliteal regions. Luckily the utilization of PET/CT-scans was very useful in identifying any disease involvement in such sites that are not detectable by CT alone. That also indicates an advantage of PET/CT-scan in identifying lymphomas, since it permits us to visualize and analyze such neoplastic masses in sites that are not possible to perceive with other imaging modalities (including CT alone).

This article also concluded that the overall survival rate is much higher for patients whom were interim PET/CT negative than PET/CT positive (4 year survival was 76% for PET/CT negative and 47% for PET/CT positive). This also strengthens my previous point that PET serves as a strong reliable prognostic factor for the assessment of lymphomas, both before the treatment has initiated as well as during the treatment process (and even after).

It has also been suggested by another article that CT remains the standard imaging modality for initial staging of malignant lymphoma, while PET has an essential role in re-staging after treatment, and early results suggest that PET/CT fusion outperforms both CT alone and PET alone.[13] Basically this article investigated 17 studies, 9 of which investigated Hodgkin’s lymphoma patients and the remaining 8 studies investigated Non-Hodgkin’s Lymphoma patients. It showed that only 1 study (out of the 9 that investigated HL) had investigated the efficacy of PET-scanning before treatment, meaning that only one study investigated PET for initial staging, whereas the remaining 8 HL-studies investigated PET for follow-up of treatment. The sensitivity for restaging the HL ranged between 57.1% (patient-based) and 85% (lesion-based).

This article also included five studies which investigated non-Hodgkin’s lymphoma (NHL) cases. And again, only one study investigated PET for the initial staging of NHL (both high-grade and low-grade), with sensitivity of 83.3% (lesion-based). Sensitivities for restaging NHL ranged between 60% (patient-based) and 80% (lesion-based). Taking all this information into account, we can conclude that based on this article, the sensitivity of PET for initial staging (lesion-based) is slightly higher in Hodgkin’s lymphoma than non-Hodgkin’s lymphoma (85% in contrast to 83.3%).

Moreover, the sensitivity of restaging after treatment (patient-based) was 57.1% for HL and 60% for NHL, making the NHL slightly more sensitive than HL after the treatment. However, looking into the lesion-based sensitivity of PET for restaging, we can see that the sensitivity is slightly higher for HL than NHL (85% and 80%). Four studies investigated fusion of PET with CT (PET/CT), but only 1 onestudy investigated patients with HL exclusively. This study showed a sensitivity of 100% (patient-based) for restaging. The remaining 3 studies that investigated PET/CT fusion were performed in a mixture of patients with HL and NHL. Sensitivity for initial staging approached 100% in one study, and sensitivities for restaging exceeded 90% (region-based and patient-based).

Therefore, PET/CT for initial staging reached 100% (hence all patients) and for restaging the sensitivity exceeded 90% (100% in the exclusive HL study).

Thus as a final conclusion of this article, we can establish that the sensitivity of PET for initial staging is slightly higher for patients with HL in contrast to NHL, but for restaging we need to
look into whether the study is patient-based or lesion-based. This is due to that patient-based studies indicate that the sensitivity of PET for restaging was slightly higher in NHL patients in comparison to HL patients, although lesion-based studies showed the contrary. As for the PET/CT fusion, the sensitivity of initial staging was 100% and for restaging above 90%, meaning that this fusion of both imaging modalities resulted in an exceedingly more accurate modality than if they were done separately.

Another article that was utilized was published in the Polish medical journal *Original Papers* in 2016 under the title “Positron Emission Tomography Scanning in the Management of Hodgkin Lymphoma Patients: A Single-Institution Experience“. [14]

This article stated that CT was the modality of choice for *early* HL staging, and that PET/CT was *under-utilized* in the initial staging process, only having been used in 2 out of 47 patients according to the records of their local hospital/clinic. This article further stated that PET/CT was performed after chemotherapy and before radiotherapy in 23 patients (48.9 % of patients), and for 15 of these patients, the PET/CT findings were *decisive* in whether the radiotherapy was indicated. This was based on whether there was *complete* metabolic response (in which radiotherapy is not indicated) or *incomplete* metabolic response (radiotherapy is indicated). This concludes that PET/CT is used to *assess the efficacy* of the therapy, as well as determine whether the given treatment regimen needs to be *modified* or not. This point was strongly emphasized according to this article, since it indicated that by performing PET/CT we could avoid giving *unnecessary* radiotherapy for patients whom did not require it, due to the fact that if there was complete metabolic response, then we know that radiotherapy should not be given. Likewise does this modality allow us to clearly identify which patients that are indicated for radiotherapy, and thus we could give them such treatments early on and avoid giving the radiotherapy too late in the disease.

The reason behind why this modality is so under-utilized is most likely due to the higher costs of PET scans compared to CT, the small number of PET/CT centers in the region, and the lack of well-defined recommendations concerning PET/CT implementation in routine practice. This is somewhat unfortunate, since according to this article, the usage of PET/CT in the early diagnosis was shown to *upstage* the disease among patients initially diagnosed as stage I or II. This meaning that patient whom were classified as stage I or II by CT, were in reality found to be stage III or IV when PET/CT was performed early in the diagnosis. Therefore, if PET/CT scans were performed early in the diagnostic process, then there would be a more correct diagnosis for these patients, and the treatment would be more specific and aggressive. And by treating these patients aggressively in the *beginning* of their disease, there would be a higher likelihood of eradicating the disease altogether and the prognosis would more likely be better.

As for the *interim* PET-CT, although the evidence from the randomized clinical trials is still being collected, it has been concluded to be advantageous since it usually makes the treatment of HL patients more *individualized*. This meaning that this modality permits us to *predict* treatment failure in patients suffering from HL, and therefore can help us change the treatment regimen to another regimen more fit for the patient before it too late (i.e. this modality permits us to suspect treatment failure before it has actually occurred). However, according to an article published in January 2017 in the medical journal *Cancer Network: Oncology*, the results of interim PET/CT has not been as encouraging in diffuse large B-cell lymphoma (DLBCL) in contrast to HL, with the exception of germinal center B-cell (GCB) lymphoma.[15]
As for Diffuse Large B-Cell Lymphoma, the sensitivity of PET/CT scans in the diagnosis depends on the subtype (based on the cell-of-origin), i.e. germinal center B-cell (GCB) lymphoma, non-germinal center lymphoma, and primary mediastinal B-cell lymphoma. An article published in the journal *The Korean Society of Radiology* in 2017 stated that FDG PET/CT modality has now become the cornerstone for diagnosing, staging and managing patients with lymphoma (including DLBCL).[15] However, when dealing with patients suffering from *mediastinal* DLBCL, then chest radiography is classically the initial modality performed, since it may provide the first indication of any involvement in the mediastinum and lung parenchyma. This makes sense since radiography is sensitive in the detection of any mediastinal as well as lung parenchymal abnormalities, and there is no extravagant use of PET/CT in these conditions.[16,17]

Certain recently published articles have not only evaluated the peculiarities of PET/CT in the diagnosis of lymphoma, but also the sensitivity of this modality in evaluating the *spread* of the disease. One article that was published in January 2017 based on a research done in Beirut (Lebanon) compared the sensitivity of PET/CT scans in contrast to Bone marrow biopsy (BMB) for the evaluation of *bone marrow involvement* (BMI) in patients with DLBCL. [18] The results manifested that out of the 54 patient used in the research, the PET/CT scans detected bone marrow involvement in 12 patients (22%), but the BMB only detected bone marrow involvement in 5 patients (9%). This is a rather reliable indicator that PET/CT is more useful for detecting bone marrow involvement than BMB in patients with DLBCL.

What further strengthens this argument is that we did not only have patients from one gender or age group, but instead we had a diversity of patients in this research; 29 were male and 25 were female, and the age interval was between 16-87 years old, with the mean age being 50 years old. Thus it was concluded by the authors of this research that PET/CT is in fact more sensitive for the detection of bone marrow involvement than BMB in patients with DLBCL.

Finally, looking into Mantle Cell Lymphoma (MCL), it was suggested by an article published in *Internal Medicine Journal RACP* (on September 2016) that even though this type of lymphoma is almost always FDG-avid at the *presentation*, pre-treatment PET/CT has not been shown to contribute significantly to the management of MCL patients, although it has been suggested that a negative post-treatment PET/CT is associated with improved survival.[19] This means that the findings on PET/CT are rather insignificant in determining the *management* of MCL, whereas after the treatment regimen has been completed, the patient’s prognosis could possibly be *predictable* by looking into the PET/CT results.

To further analyze the PET/CT findings in MCL patients, we can look into another article which was published in July 2016, in the medical journal *JNM* (Journal of Nuclear Medicine). This particular article stated that out of 45 patients being treated for MCL with bendamustine-rituximab (BR), 24 had negative PET/CT findings after 6 cycles of BR therapy, and thus manifested *complete response* to the regimen.[20] Out of these patients whom had a complete metabolic response, 91.5% had a greater 1-year progression free survival. This means that PET/CT could be utilized to *predict* (to a certain degree) the prognosis of the disease, by evaluating if the response is complete or partial. Hence, this article has the same conclusion as the aforementioned article about Mantle cell lymphoma, as it also confirmed that PET/CT more reliable for identifying the *outcome* rather than determining what the treatment regimen should be.
Furthermore, according to an article published in 2003 under the title “Utility of FDG-PET scanning in lymphoma by WHO classification”, 172 patients with lymphoma underwent FDG-PET scans, which detected metabolically active lesions in 161 patients (94% of patients) and failed to detect any lesions in 11 patients (6% of patients).[21] Thus it was false-negative in 6% of cases. The most frequent lymphoma diagnoses were DLBCL (n=51), HL (n=47), follicular lymphoma (n=42), marginal zone lymphoma (n=12), MCL (n=7), and peripheral T-cell lymphoma (n=5). FDG-PET detected disease in 100% of patients with DLBCL and MCL, and in 98% of patients with HL and Follicular lymphoma. However, FDG-PET detected disease in only 67% of Mantle Zone lymphoma and 40% of PTCL. Moreover, by comparing the findings of FDG-PET with bone marrow biopsies (from the iliac crest), we could see that FDG-PET was not reliable for detection of bone marrow involvement in any of the lymphoma types. Therefore FDG-PET may be dependable when investigating most types of lymphomas (initial staging and restaging), but is not at all dependable for detecting BM involvement.

For staging as well as therapeutic purposes, it is important to perform non-invasive assessment of splenic involvement in patients with lymphoma, especially in HL, since the spleen is the abdominal organ most commonly affected by the disease. [22] Consequently, splenic involvement in HL is responsible for increasing the stage of disease, and by doing so also prompting an alteration in treatment strategies. In NHL however, splenic involvement is of less relevance to the overall staging due to the fact that most patients present with disseminated disease. In a dissertation published in 2009, the diagnostic value of PET-scans, CT-scans and PET/CT-scans for initial staging of splenic involvement in different types of lymphomas was investigated.[22] The results showed that for the 40 patients with DLBCL, splenic involvement was detected in 67% of the cases with PET but in 100% of the cases with PET/CT. This means that the fusion of PET/CT detected all of the DLBCL patients with splenic involvement. Similar results could be found in the 15 patients diagnosed with HL; where PET detected splenic involvement in 70% of cases and PET/CT detected splenic involvement in 100% of cases. This concludes that PET/CT have the ability to detect splenic involvement in all of the patients with HL and DLBCL. This is quite reliable since the patients in this study were miscellaneous, meaning that they were from a variety of different age groups (ages ranging from 17 to 86 years old) and included patients with different stages of disease according to the Ann Arbour scale (patients with stage I, II, III and IV were investigated).

**Research Methodology and Methods**

For this retrospective study, patients that have been diagnosed and treated for Hodgkin’s lymphoma, Diffuse Large B-Cell Lymphoma and Mantle Cell Lymphoma at the Oncology and Haematology department (in Kaunoklinikos), were chosen. By analysing patients that were treated for the 3 aforementioned types of Lymphomas in 2014 and 2015, the final quantity of patients were picked for this dissertation were 42 patients (these patients had PET/CT-scans taken before and after treatment).
Results and Their Discussions

Starting from the basic demographic data of the investigated patients, it can be established that there is a wide variety patients from different age groups, genders, comorbidities and treatments. A table manifesting these basic demographic data is given below (Table 1.1).

Table 1.1 Basic demographic data of patients

<table>
<thead>
<tr>
<th>Type of Lymphoma</th>
<th>Quantity of patients</th>
<th>Age (average/mean)</th>
<th>Patients by gender</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hodgkin’s Lymphoma</td>
<td>9</td>
<td>39.8 years (range 20-75 years)</td>
<td>Males: 5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Females: 4</td>
</tr>
<tr>
<td>Diffuse Large B-Cell</td>
<td>25</td>
<td>67.0 years (range 45-86 years)</td>
<td>Males: 13</td>
</tr>
<tr>
<td>Lymphoma</td>
<td></td>
<td></td>
<td>Females: 12</td>
</tr>
<tr>
<td>Mantle cell Lymphoma</td>
<td>8</td>
<td>70.3 years (range 58-76 years)</td>
<td>Males: 3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Females: 5</td>
</tr>
</tbody>
</table>

As can be seen in the aforementioned table, we have a wide variety (or versatility) of patients, in terms of type of lymphoma, age and number of representatives from each gender. This is somewhat advantageous since it prompts that the results that we will have will most likely be comprehensive. The first thing that might be noticed is that more than half of the patients that were investigated were treated for Diffuse Large B-Cell Lymphoma (DLBCL), and therefore the analysis of these patients will be more profound than the other lymphomas. Secondly, we can see that there is (almost) equal distribution of patients from each gender, and this applies to the patients of all 3 types of lymphomas. This also shows that we will have a result that depicts the PET-findings for patients of both genders equally.

Now we will look deeper into the patients from each type of lymphoma, starting from Hodgkin’s Lymphoma. Most of the patients with this type of lymphoma were diagnosed with stage IV (5 out of 9 patients, thus 55.6 %) and the remaining had lower stages; 2 patients with stage III (22.2 %) and 2 patients with stage II (22.2%). This means that by the time the patients become diagnosed, more than half of them already had late stage disease. But nonetheless, the probability of the treatment being successful for these patients was still high, based on the patients that were investigated in this dissertation. This is based on the fact that 4 out of the 9 patients (hence 44.4 %) had complete response, since the Deauville score which was 1-2 points for these patients(Table 1.2). Furthermore, 3 patients had partial response (3-4 points on Deauville scale) to the given treatment and the final 2 patients had no response (stable or progressive disease) to treatment (5 points on Deauville scale).

Table 1.2 The percentage of Deauville scores from each type of lymphoma

<table>
<thead>
<tr>
<th>Lymphoma type</th>
<th>1-2 points on Deauville scale</th>
<th>3-4 points on Deauville scale</th>
<th>5 points on Deauville scale</th>
<th>Unknown/doubtful response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hodgkin’s lymphoma</td>
<td>44.4 %</td>
<td>33.3 %</td>
<td>22.2 %</td>
<td>-</td>
</tr>
<tr>
<td>Diffuse Large B-Cell</td>
<td>52 %</td>
<td>20 %</td>
<td>12 %</td>
<td>16 %</td>
</tr>
</tbody>
</table>
The probability of complete response is also not specific for the stage of lymphoma, since we could see that out of the 4 patients with complete response, 2 patients had stage IV, 1 patient had stage III and 1 patient had stage II. Moreover, out of the patients whom showed partial response (Deauville score 3-4), 1 patient was diagnosed with stage III and 2 patients with stage IV. Finally, from the patients with no response, 1 was diagnosed with stage II and the other with stage IV, thus concluding that the likelihood of complete response was not dependent on the stage of lymphoma.

Table 1.3 The percentage of all responses from each type of lymphoma

<table>
<thead>
<tr>
<th>Lymphoma type</th>
<th>Complete response</th>
<th>Partial response</th>
<th>Stable disease</th>
<th>Progressive disease</th>
<th>Unknown, doubtful response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hodgkin’s lymphoma</td>
<td>44.4 %</td>
<td>33.3 %</td>
<td>11.1 %</td>
<td>11.1 %</td>
<td>-</td>
</tr>
<tr>
<td>Diffuse Large B-cell lymphoma</td>
<td>52 %</td>
<td>20 %</td>
<td>8 %</td>
<td>4 %</td>
<td>16 %</td>
</tr>
<tr>
<td>Mantle cell lymphoma</td>
<td>75 %</td>
<td>25 %</td>
<td>-</td>
<td>-</td>
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As Table 1.3 shows, from the Hodgkin’s Lymphoma group of patients we had 4 with complete response (44.4 %), 3 with partial response (33.3 %), 1 with stable disease (11.1 %) and 1 with progressive disease (11.1 %). From the DLBCL group of patients, 13 had complete response (52 %), 5 had partial response (20 %), 2 had Stable disease (8 %), 1 had progressive disease (4 %) and 4 had unknown (16 %). And finally, from the MCL patients, 6 had complete response (75 %) and 2 had partial response (25 %). These patients are all analyzed in depth below.

When analysing the particular PET/CT-findings, one patient (with stage III) whom achieved partial response and 3 points on the Deauville scoring system, had slight metabolic activity below the diaphragm after completion of the chemotherapy that could not be differentiated from an inflammatory reaction. This insinuates that there is a limitation of PET/CT in differentiation between lymphoproliferative disease and inflammatory reactions, since this modality failed to differentiate between these two processes. Although, this patient still was established as having partial response because the likelihood of that process being inflammatory was higher than the likelihood of it being lymphoproliferative disease (according to the radiologist whom investigated this patient).

Furthermore, for one patient (with stage IV) whom had partial response to the given chemotherapy (ABVD regimen), it was mentioned that a secondary follow-up PET/CT scan was necessary to ascertain if complete response eventually would be established. This is due to that even though the PET/CT-scan that was performed was after completion of the chemotherapy, more time would be needed to establish if full response would eventually be
achieved. This is somewhat peculiar considering that usually, after the completion of the chemotherapy regimen, there should be clear manifestations of whether there is complete or partial response. This means that the PET/CT in this particular patient could not determine whether complete response was going to be established or not.

As for the patient with progressive disease, it’s worth mentioning that there were numerous complications that arose, including the development of Pneumonia during the course of the given BEACOPP-regimen, and since there was no response, an additional course of DHAP-regimen was prescribed. After completion of the first chemotherapy regimen (BEACOPP), the PET/CT showed that the patient still had lymphoproliferative processes on both sides of the diaphragm (same locations as before the treatment), but also the PET/CT showed that there was now metabolic activity in the bones. This meant that not only was the chemotherapy not eradicating the lymphoproliferative processes in that patient, but it did not even stop the dissemination. After the second chemotherapy regimen (DHAP), the follow-up PET/CT showed that the dissemination of the lymphoproliferative process had reached the one lung (there was no metabolic activity in the lungs in the previous PET/CT scans), and it was finally concluded that the patient had progressive disease and thus 5 points according to the Deauville scale.

The size of the lesions seen on PET/CT scans plays a significant role in determining if there will be response or not, and that is what was seen for one patient with stage II. For this particular patient, the PET/CT scan that was performed prior to initiating the chemotherapy (the PET/CT at the time of diagnosis) showed that the patient had massive lymphoproliferative processes in the affected regions (up to 6.1x4.2x6.7 cm metabolically active lesion in the costophrenic sinus), and that could be the plausible reason why the patient did not respond to the treatment, and eventually was shown to have 5 points on the Deauville scale.

Moving swiftly on, looking into the patients whom were treated for Diffuse Large B-Cell Lymphoma, there are 11 patients with stage I/II (5 patients with stage I and 6 patients with stage II) and 14 patients with stage III/IV (1 patient with stage III and 13 patients with stage IV). As table 1.2 and 1.3 shows, 52% had complete response (1-2 points on Deauville score) and 20% had partial response (3-4 Deauville score), 8% had stable disease, 4% had progressive disease, and 16% had doubtful/unknown response.

Starting from the patients whom showed complete response which were 13 out of 25 patients (thus 52%), they were from diverse ages, therefore the response cannot be related to their ages. Looking in detail into the precise findings on PET/CT of these patients with complete response, the first aspect we can establish is that the location of the lesions did not play a role in the sensitivity of the PET/CT. This is based on that these patients had lesions on numerous different areas in their bodies (including liver, cervix uteri, spleen, bone etc.), and nonetheless the PET/CT still managed to detect the metabolic activities equally for all of them.

What is notable is that one patient with stage II showed complete response to the given treatment regimen and 1 point on Deauville score, but his PET/CT indicated that he had certain lesions on some of his mediastinal lymph nodes that resembled inflammatory
reactions. That means that the conclusion of that PET/CT stated that the patient had complete response although there were lesions that could not be differentiated from inflammatory processes (and histopathological analysis was needed). Similarly, a histological verification was deemed necessary for 2 other patients, but for these two patients however, we could not conclude that we had complete response. This means that for these 2 patients, the PET/CT-scan showed that there was some response (not complete) to the chemotherapies, but the PET/CT could not differentiate between inflammatory and lymphoproliferative reactions. So far, 3 out of the 11 abovementioned patients needed additional testing (in this case, biopsy samples with histological examination), since PET/CT lacked the ability to differentiate between inflammatory and lymphoproliferative processes.

As for the patients with partial response, most of them had PET/CT-scans which detected metabolic activity in the same areas that were affected prior to treatment (including cervical and axillary lymph nodes and the liver), although the metabolic activity had slightly declined, hence the response was deemed as partial.

For the 3 patients with stable disease however, the PET/CT showed that the metabolic activity was identical to that which was before treatment, meaning that they were not responding to the given chemotherapies at all. This could perhaps be explained by the fact that these patients had rather disseminated disease, since they had involvement of both sides of the diaphragm (including abdominal lymph nodes, liver, spleen, cervical lymph nodes, thyroid and tonsils). However, for one of these patients with stable disease, it was recommended to do additional tests of the thyroid, because the metabolic activity could be of non-oncological origin. This meaning that the PET/CT could not differentiate between lymphoproliferative and non-oncological activity of the thyroid!

Moreover, the PET/CT was not sufficient to detect the level of response to the given therapy for 3 of the investigated patients. For one patient, the PET/CT showed that the metabolic activity had declined and in some areas completely disappeared, but some lymph nodes seemed to have enlarged although they appeared to be metabolically inactive. Hence the PET/CT could not differentiate if these lymph nodes were still lymphoproliferative or not, since the enlargement pointed toward the idea that they still might have some lymphoproliferative component, but the failure to detect metabolic activity pointed toward that it might be of non-oncological origin. For this patient, a histological examination was recommended. Similarly, for the second patient we could see good response (meaning that the metabolic activity was rapidly declining), but there were some lesions in the sigmoid colon that needed to be differentiated from benign polyps. Hence even here, the PET/CT was not able to differentiate between lymphoproliferative and non-oncological lesions. For this patient, it was recommended to perform a colonoscopy (and biopsy sample) to verify the response!

Finally, the PET/CT was unable to detect if there was any response, for a patient whom had lesions in their abdominal lymph nodes, hip region, wrist and caecum, since it was stated that the metabolic activity was “too minimal” for the PET/CT to make a conclusion. For this patient, this imaging modality could not differentiate between partial response and stable
disease. This means that the PET/CT has some sort of *threshold* when it comes to detection of changes in the metabolic activity, meaning that even though it could *detect* the metabolic activity for the diagnosis, it could not establish if whether that activity had declined or remained the same!

As for *interim* PET/CT, one patient with stage II underwent a PET/CT during the chemotherapy (hence interim), which showed that the metabolic activity of the involved areas was declining (in the mediastinal lymph nodes), and the follow-up PET/CT that was done after the termination of the treatment showed complete response. This means that *interim* PET/CT was a reliable prognostic factor for the disease in this patient. However, this interim PET/CT was only performed for 1 patient, and such a conclusion cannot be drawn based on a single patient alone!

Regarding the patients whom were diagnosed and treated for Mantle Cell lymphoma, all had *late stage* disease at the time of diagnosis (4 patients with stage III and 4 patients with stage IV). The number of *complete response* however was quite high, denoting 6 out of the 8 patients, which makes up 75 % (three quarters) of all patients. The two remaining patients whom had *partial response* (25 %) were diagnosed with stage III and IV respectively, and both of them had 4 points on the Deauville scale. This means that, out of all the MCL patients that were used in this investigation, all of them had *late stage* disease, but despite that, most of them had *complete response* to the given treatment, thus the prognosis was quite good for these patients.

Now looking into the prevalence of patients from each type of lymphoma whom had extranodal disease, meaning that there was involvement of other sites than lymph nodes, spleen, thymus and Waldeyers tonsillar ring (Table 1.4).

<table>
<thead>
<tr>
<th>Lymphoma type</th>
<th>Extranodal Disease</th>
<th>No extranodal disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hodgkin’s lymphoma</td>
<td>33.3 %</td>
<td>66.7 %</td>
</tr>
<tr>
<td>Diffuse Large B-cell</td>
<td>48 %</td>
<td>52 %</td>
</tr>
<tr>
<td>lymphoma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mantle cell lymphoma</td>
<td>25%</td>
<td>75%</td>
</tr>
</tbody>
</table>

For the patients which were investigated, the extranodal disease included numerous scattered locations, but most commonly involved were the lungs, liver, pancreas, large intestines, Cervix uteri, and bone marrow. As the aforementioned table shows, the extranodal disease prevalence was highest in patients with DLBCL (about half of the patients had extranodal involvement), and this could be related to that about half of these patients had *early stage* disease (stage I/II) at the time of diagnosis and the other half had *late stage* disease at the time of diagnosis. Mantle cell lymphoma had the lowest prevalence of extranodal disease,
which could perhaps be the reason for the high percentage of complete response to treatment (Table 1.2 and 1.3).

Then directly we can look into the limitation of PET/CT, since a few of the investigated patients had PET/CT-scans which were not clear. This is manifested in Table 2.1, which indicates the number of patients from each type of lymphoma in which PET/CT was insufficient (limited).

Table 2.1 Summarized data of PET/CT for all patients

<table>
<thead>
<tr>
<th>Type of Lymphoma</th>
<th>Quantity of patients</th>
<th>PET/CT limitation</th>
<th>Percentage of limitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hodgkin’s Lymphoma</td>
<td>9</td>
<td>1</td>
<td>11.1 %</td>
</tr>
<tr>
<td>Diffuse Large B-Cell Lymphoma</td>
<td>25</td>
<td>5</td>
<td>20 %</td>
</tr>
<tr>
<td>Mantle cell Lymphoma</td>
<td>8</td>
<td>0</td>
<td>0 %</td>
</tr>
</tbody>
</table>

The first conclusion that can be seen by looking into Table 2.1 and 2.2 is that the limitation of PET/CT only in 14.3 % of patients, making it a reliable imaging modality. From all three types of lymphoma, the highest prevalence of limited PET/CT was seen in DLBCL (20 % of patients), followed by HL (11.1 %). In MCL, the PET/CT was not limited in any of the investigated patients, since it showed if there was a response of not in all the analysed patients.

Table 2.2 Summarized data of PET/CT limitation for all patients

<table>
<thead>
<tr>
<th>All patients</th>
<th>PET/CT limitation</th>
<th>Percentage of limitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>42</td>
<td>6</td>
<td>14.3 %</td>
</tr>
</tbody>
</table>

Last but not least, we will look into how PET/CT will change the initial staging for each and every type of investigated lymphoma case. This is due to that we initially have a clinical stage of lymphoma based on the objective findings during patient’s physical evaluation and laboratory tests. The clinical stage itself is only predicting the stage, and thus for a more accurate evaluation is it necessary to do radiological examinations (in this case PET/CT).

Table 2.3 Summarized data of PET/CT stage in comparison to clinical stage

<table>
<thead>
<tr>
<th>Lymphoma type</th>
<th>Less advanced stage after PET/CT</th>
<th>Same stage as after PET/CT</th>
<th>More advanced stage after PET/CT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hodgkin lymphoma</td>
<td>44.4 %</td>
<td>44.4 %</td>
<td>11.2 %</td>
</tr>
<tr>
<td>Diffuse large B cell lymphoma</td>
<td>36 %</td>
<td>52 %</td>
<td>12 %</td>
</tr>
<tr>
<td>Mantle cell</td>
<td>37.5 %</td>
<td>62.5 %</td>
<td>0 %</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>38 %</td>
<td>52.4 %</td>
<td>9.5 %</td>
</tr>
<tr>
<td>----------</td>
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<td>------</td>
</tr>
<tr>
<td>Summary</td>
<td></td>
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</tbody>
</table>

As we can see Table 2.4, almost 50 percent of the investigated cases stage changed after performing the PET/CT scans. To analyse the table in depth, we can see that in 52.4 % of cases, the stage remained unchanged before and after PET/CT, whereas in 47.6 % of cases the stage was changed. Furthermore, HL showed the highest prevalence of down-staging (44.4 %) whereas DLBCL showed the lowest prevalence of down-staging (36 %). As for the type of lymphoma where the stage remained the same before and after PET/CT, we can see that the highest prevalence was in MCL (62.5 %) and lowest in HL (44.4 %). Finally, looking into the prevalence of up-staging the lymphoma using PET/CT, we can see that it occurred in 12 % of the DLBCL cases and in 11.2 % in HL cases (not in a single MCL case).
Conclusion
Starting from the first objective which was to identify the number of each type of response for every lymphoma. We can simultaneously analyze the Deauville scale for these patients since this scale is directly related to the type of response.

As for the patients with MCL, 75 % had complete response and the remaining 25 % had partial response. For the patients with HL, 44.4 % showed complete response, 33.3 % showed partial response, 11.1 % showed stable disease and 11.1 % showed progressive disease. From the DLBCL group of patients, 52 % had complete response, 20 % had partial response, 8 % had stable disease, 4 % had progressive disease and 16 % had unknown/limited response. But this limitation is discussed a bit later.

We can also conclude that by looking into the Deauville scale of all the investigated patients, the first noteworthy thing that could be seen is that the percentages are the same as for the response evaluation, which is due to that they depict the same thing only in other words. This meaning that the type of response is determined by the number of points on the Deauville scale (complete response has the same meaning as 1-2 points on Deauville scale etc).

The extranodal disease prevalence was highest in patients with DLBCL (48 %), followed by HL (33.3 %), and finally MCL had the lowest prevalence of extranodal disease (25 %).

Now looking into the limitations of this imaging modality, starting from Hodgkin’s lymphoma. It was already stated that out of the 9 patients with HL, PET/CT was deemed insufficient for 1 of these patients since for one patient a histological examination was necessary to differentiate from inflammatory process. To summarize, for 1 out of the 9 patients with Hodgkin’s lymphoma, the PET/CT was not sufficient (hence 11.1 %).

As for Diffuse Large B-Cell lymphoma, we had 25 patients, and for 5 of these patients the PET/CT was insufficient, making up 20 % of all DLBCL patients. Finally analysing Mantle cell lymphoma, it was established that the PET/CT had no limitations in detecting any metabolic activity, since it was comprehensive in showing detailed metabolic activity in all of the investigated patients (0 % limitation in MCL). Therefore, in regard to the limitation of PET/CT, we can conclude that it was seen only in 14.3 % of all the investigated patients, meaning that in 85.7 % of cases the PET/CT was useful, thus concluding that it is a reliable imaging modality for patients with these types of lymphomas. The limitation was different depending on the type of lymphoma, since the highest prevalence of limitation was seen in DLBCL (20 % of patients), followed by HL (11.1 %).

Finally, addressing the staging before and after PET/CT was performed, we have established that the clinical stage was the same as PET/CT stage in 52.4 %, where as it was down-staged in 38 % and up-staged in 9.5 % (for all lymphomas combined).
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