Clinical trials registration number: NCT02389101

Status: Patient enrolment ongoing

1 SUMMARY

Lymphomas are malignant tumours of the immune system. Lymphomas are classified as Hodgkin or non-Hodgkin lymphomas with several subtypes. In Finland the amount of newly diagnosed Hodgkin lymphomas is 120-150 new cases per year and it accounts for 12 % of all lymphomas. Non-Hodgkin lymphoma is the sixth most common cancer in men and the eight most common cancer in women in Finland. There are approximately 1200 new cases per year and the incidence has been increasing during the last decade (1, 2).

Etiology of lymphomas is mostly unknown but many risk factors have been identified. Diagnostics and classification to different subgroups is based on clinical, pathological, molecular, and radiological studies. Some of lymphomas subtypes can be cured with current treatment methods, however, many of them remain still incurable (1). Clearly, more accurate diagnostic tools with subsequent targeted therapies against lymphomas are needed.

Somatostatin receptors (SSTs) are expressed by a wide variety of different tumour cell types, including malignant lymphomas (3-6). Somatostatin receptor imaging by octreotide scintigraphy has showed a sensitivity of 95-100 % in Hodgkin lymphoma and 80 % in non-Hodgkin lymphoma. However, somatostatin receptor scintigraphy does not appear to have a significant role in diagnostic process because of the relatively low uptake of the used somatostatin analogue (oktreotide) and limited sensitivity of the single photon emission computed tomography (SPECT) acquisition to detect and localise small involved nodes (6, 7). Hence, somatostatin receptor imaging has been further developed with the advent of hybrid SPECT and positron emission tomography (PET) and computed tomography (CT) scanners. Several other radioligands have been studied to improve the binding affinity(8) . This has also offered a new target for tumor cell-specific therapy using different somatostatin analogs labelled with therapeutic radionuclides such as ^{90}Y-DOTATOC, a somatostatin receptor subtype 2 (SST_2) -specific ligand. Clinical studies of peptide receptor radionuclide therapy (PRRT) have extensively focused on neuroendocrine tumors as a palliative treatment modality (9-11). Another new candidate for SST based imaging and treatment is ^{68}Ga-DOTANOC, a high-affinity ligand of somatostatin receptor subtypes 2, 3 and 5 (SST_2, SST_3, SST_5) (12). Neuroendocrine tumors are known to express SST_2 and they show high uptake of radiolabeled

somatostatin analogs on PET. However, lymphomas may mimick NETs on DOTANOC PET/CT as was shown in a recent case report (13). Therefore, further studies on SST_2 status and DOTANOC uptake are in order to establish the role of peptide based imaging in diagnosis and possible PRRT in lymphomas.

The aim of the study is to determine tumor uptake of ^{68}Ga-DOTANOC in patients with non-Hodgkin and Hodgkin lymphoma to characterize the SST_2, SST_3 and SST_5 receptor status of the tumour in vivo with ^{68}Ga-DOTANOC PET/CT. In addition, immunohistochemical analysis of SST_2, SST_3 and SST_5 subtype status will be made of the tumor specimens obtained in routine diagnostic biopsy resection. Furthermore, we will correlate PET findings with advanced MRI techniques, such as diffusion weighted imaging (DWI) in an attempt to find methods which limit radiation exposure especially in young patients. Hence, PET/CT will be performed with ^{68}Ga-DOTANOC and ^{18}F-FDG and compared with whole-body MRI (including DWI) to define the most sensitive and specific imaging method appropriate for routine diagnosis and follow-up of patients with lymphoma.

To our knowledge, no prospective studies comparing octreodite analogue based PET/CT imaging with standard diagnostic procedures have been published until now. PET/CT offers a clear advantage over scintigraphy in terms of sensitivity and resolution which should be helpful in determining the SST status of various histologic forms of lymphomas We hypothesize that a positive ^{68}Ga-DOTANOC PET/CT scan correlates with the overexpression of all or some SST subtypes in lymphomas, which is possibly linked to a more indolent behavior of the disease. Furthermore, we hypothesize that ^{68}Ga-DOTANOC PET/CT imaging provides a valid method to select patients with lymphoma for radionuclide therapy with ^{177}Lu-DOTATATE. Third, differential diagnosis with NETs may also improve after receiving information on SST status in lymphomas. Thus findings in our study may be useful not only for biologic characterization but also for diagnosis and management of these heterogenous diseases originating in the lymphatic system

2 INTRODUCTION

2.1 EPIDEMIOLOGY AND SURVIVAL

Lymphomas are divided in two main groups: Hodgkin (HL) and non-Hodgkin (NHL) lymphoma, which are two completely different disease entities. In Finland, there are 120-150 newly diagnosed Hodgkin lymphomas per year and the incidence has stayed constant for many years. Correspondingly, there are approximately 1200 new non-Hodgkin lymphomas per year. Incidence of non-Hodgkin lymphoma has increased during the last decade. 5-year relative survival rate is 91-92 % in Hodgkin and 64 % in non-Hodgkin lymphoma. Survival of lymphomas has increased during the last years due to improved treatment protocols (1, 2, 14).

2.2 DIAGNOSIS

Diagnosis of both non-Hodgkin's and Hodgkin's lymphoma is based on radiological imaging and histological findings (biopsies) of the affected organ or tissue. Standard protocol for staging is a CT study from the base of the scull to the upper parts of the thighs. Additional chest x-ray, ultrasound or bone marrow biopsy and PET can be used. To evaluate the morphology and immunologic and genetic profile a biopsy is needed. If the disease is nodal a whole lymph node is removed for biopsy. In approximately 55 % of non-Hodgkin cases lymphoma is extranodal (location outside the lymphatic organs) when a thick needle biopsy can be used. Classification to the different subtypes is based on the histopatological analysis of the biopsy and the staging of the cancer on the CT or PET /CT scans. It is well established that PET/CT imaging is more accurate in finding lymphomatous lesions than standard CT (1). Most commonly used radiotracer [^{18}F]fluorodeoxyglucose (FDG) shows avidity to sites of accelerated glucose metabolism such as cancer cells. Unfortunately ^{18}F-FDG is not highly specific for lymphomas and other cancers because it also accumulates in some non-malignant tissues and inflammatory processes, which can cause false positive results. Also, some lymphoma subtypes such as extranodal marginal zone lymphoma (MALT) and small lymphocytic lymphoma, do not have high avidity for ^{18}F-FDG (15). Therefore, novel radiotracers having high sensitivity and specificity for imaging of lymphomas with low uptake of ^{18}F-FDG would be valuable. Tu illustrate this diversity it has been recently shown that in patients with ^{18}F-FDG -avid lymphoma, DWI-MRI appears to be slightly inferior to ^{18}F-FDG-PET/CT, with regard to pre-therapeutic regional assessment and staging. By contrast, in lymphoma subtypes that show a

low or variable FDG-avidity such as MALT DWI seems to be superior to both ^{18}F-FDG-PET/CT and contrast-enhanced CT (16).

2.3 TREATMENT

With aggressive forms of non-Hodgkin's lymphoma treatment goal is curative. Histological feature, CD20-positivity, age of the patient, physical condition, other diseases and the International Prognostic Index (IPI) all have an influence on the treatment option. Standard treatment option is multiagent chemotherapy (CHOP or CHOEP -combination), and in CD20-positive diseases rituximab is combined to the regimen. In some patients with non-Hodgkin's lymphoma radiation therapy (RT) up to 30-40 Gy given after chemotherapy can improve outcome. In cases of confined Hodgkin's lymphoma (Ann Arbor I-II) standard treatment is combination chemotherapy (2-4 cycles of ABVD) followed by low dose (20-30 Gy) radiation. In cases of more advanced disease (Ann Arbor III-IV) treatment is multiagent chemotherapy, but even then the outcome is excellent if the cancer shows early response to therapy (1).

2.3 RADIONUCLIDE THERAPY

Peptide receptor radionuclide therapy (PRRT) has been studied extensively in inoperable neuroendocrine tumours (NETs) having progressed after treatment with long-acting somatostatin analogues, and the results have been encouraging . The studies have reported variable amounts of tumor regression, increased quality of life, elongated progression-free survival time and overall survival. The most commonly used radionuclide is ^{117}Lu-DOTATATE, owing to its favourable side-effect profile in comparison to ^{90}Y-DOTATOC and the amount cycles which can be given safely (10, 11, 17, 18). In lymphomas only few studies of PRRT have been published, most of which denote the possibility of using radionuclide-labelled somatostatin analogue therapy as a new treatment (19). On the other hand, one in vitro study concluded that lymphomas may not be suitable for RT using radionuclide-labeled somatostatin analogues because of relatively low number of SSTs and low uptake of the used analogue. However, the same study concluded that lymphomas are highly radiosensitive tumors and further research of PRRT is still needed (20). Since tumor SST expression is the prerequisite for an efficient radionuclide therapy, it is emphasized that radionuclide therapy with radiolabeled somatostatin analogues, such as ^{117}Lu-DOTATATE, is a promising treatment modality for patients with SST_2 positive tumours (18). It is essential to determine the individual somatostatin receptor status in vivo by radiological and immunohistochemical methods to avoid groundless and potentially harmful radiation. PET/CT is

the preferred method for determining biodistribution of the radioligand owing to its capacity to quantitatively measure tracer uptake and thus assist in dosimetry

2.4 SOMATOSTATIN RECEPTOR EXPRESSION OF LYMPHOMAS

Somatostatin receptors (SSTs) are expressed by a wide variety of different tumour cell types including Hodgkin and non-Hodgkin lymphomas (3-6). A controversial result has also been published indicating relatively low amount of somatostatin receptor subtypes SST_2 and SST_3 in lymphomas measured by mRNA expression levels in quantitative RT-PCR (20). The SST expression of lymphomas is lower than in neuroendocrine tumors (6), which have been the main target of diagnostic and therapeutic studies regarding somatostatin receptors.

2.5 MOLECULAR IMAGING OF SOMATOSTATIN RECEPTOR

Tumor cells expressing somatostatin receptor enable PET imaging with ^{68}Ga-DOTANOC for tumor delineation. Labeling somatostatin analogue with generator-derived positron emitter ^{67}Ga or ^{68}Ga leads to an enhanced affinity especially for the SST_2 receptors in vitro and in animal models (21). ^{67}Ga has been used in somatostatin receptor scintigraphy in lymphoma patients, and the combination of somatostatin analog (depreotide) with ^{67}Ga seems to potentially enhance specificity and sensitivity (22). So far, somatostatin receptor scintigraphy studies have mostly concluded that it does not have a significant role in the diagnostics or staging of lymphomas with clinically available analogues (octreotide, depreotide, pentetreotide). Most common challenges have been relatively low uptake of used somatostatin analogues compared to NETs, variability and low number of somatostatin receptors in lymphomas compared to neuroendocrine cells, poor usefulness in advanced lymphomas and false positive results due to somatostatin receptor analogue aggregation in inflammatory processes (6, 22-24). Few advantages have also occurred, for example in staging of MALT lymphomas, detecting supradiaphragmatic lesions and differentiating malignant from benign lesions (6, 25, 25, 26).

Imaging with ^{68}Ga-DOTATOC (SST_2-spesific ligand) PET/CT has been widely studied in NETs substituting conventional scintigraphy. Of all ^{68}Ga-DOTA-peptides (DOTATATE, DOTATOC, DOTANOC), only ^{68}Ga-DOTANOC is able to bind with good affinity to SST_2, SST_3 and SST_5 subtypes, hence being increasingly studied in NETs as well. Immunohistochemically SST_2 (subtype A) and SST_5 receptor status appear to have high correlation with tumor uptake of ^{68}Ga-DOTANOC in patients with NETs (27). Several studies have reported the superiority of ^{68}Ga-DOTANOC compared to conventional imaging in neuroendocrine tumors (28, 29). So far, only one case study

has been published on the use of ^{68}Ga-DOTANOC PET in patient with lymphoma where it was found as a second malignancy that mimicked NET in PET scan) (13). Furthermore, we have recently discovered a similar case in Turku University Hospital where a pancreatic tumor initially diagnosed as NET was re-diagnosed as diffuse large B-cell lymphoma after biopsy. Routine diagnostic CT scan or ^{18}F-FDG-PET/CT were not able to raise suspicion of lymphoma and biopsy was considered only after lack of response to somatostatin analogue therapy.

2.6 18F-FDG PET IN LYMPHOMAS

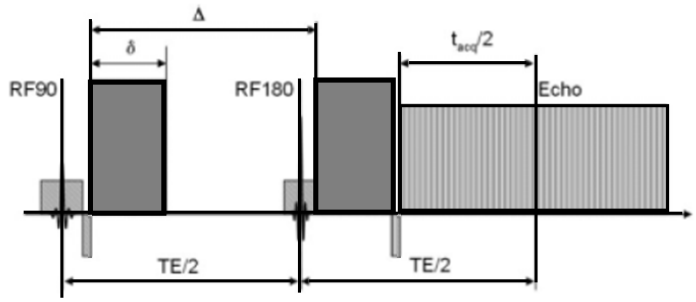
PET/CT imaging with ^{18}F-FDG is currently the most sensitive diagnostic method to detect nodal and extranodal lymphoma but its routine use in staging is not supported by most national guidelines (1). Unfortunately uptake of ^{18}F-FDG is not specific for lymphomas and some benign conditions including inflammatory and infectious processes such as sarcoidosis and aspergillosis can cause false positive results. High uptake is typical in Hodgkin's lymphoma and the majority of common non-Hodgkin's subtypes such as diffuse large B-cell and mantle cell lymphoma. By contrast, many indolent subtypes including extranodal marginal zone lymphoma (MALT) and small lymphocytic lymphoma tend to have a low avidity for ^{18}F-FDG (15). The role of ^{18}F-FDG PET/CT in primary diagnosis is still controversial although in Hodgkin's lymphoma it may abrogate the need for bone marrow biopsy and in planning of post-chemotherapy RT baseline ^{18}F-FDG PET/CT is valuable. Furthermore, ^{18}F-FDG PET/CT may be the most sensitive method for early response monitoring and evaluating the risk for residual disease in patients who are candidates for autologous bone marrow transplant

2.7 WHOLE BODY MRI IN LYMPHOMAS

It has been recently shown that in patients with FDG-avid lymphoma, DWI-MRI appears to be slightly inferior to ^{18}F-FDG-PET/CT, with regard to pre-therapeutic regional assessment and staging. In MALT and other lymphoma subtypes which show variable FDG-avidity DWI seems to be superior to both ^{18}F-FDG-PET/CT and contrast-enhanced CT (16). Currently DWI is not in routine use in evaluation of lymphomas and the repeatability and sequential imaging of DWI during treatment using different sequences remain arenas of further study.

In order to measure diffusion properties of tissue using MRI, the Stejskal–Tanner imaging sequence is used (Stejskal and Tanner, 1965). Information about proton diffusion is acquired by applying

motion-encoding gradients, which cause phase shifts in moving protons. This phase shift depends on the quantity as well as direction of movement.



where γ denotes the gyromagnetic ratio, G the diffusion gradient amplitude, δ the diffusion gradient duration and Δ the time between the leading edges of the diffusion gradient pulses.

Due to sensitivity of DWI to water molecule displacement, DWI holds a great promise for non-invasive detection and characterization of lymphomas. Furthermore, DWI is increasingly being used for cancer therapy monitoring (30).

3 OBJECTIVES AND PURPOSE

3.1 HYPOTHESES

- ✓ Lymphomas express one or several SST receptors which can be imaged with ^{68}Ga-DOTANOC PET/CT
- ✓ Tumor uptake of ^{68}Ga-DOTANOC correlates with immunohistochemically determined SST receptor status
- ✓ Uptake of ^{68}Ga-DOTANOC PET/CT is heterogenous and may not show all sites affected by lymphoma when compared to ^{18}F-FDG PET/CT and whole body MRI
- ✓ ^{68}Ga-DOTANOC PET/CT provides a valid method to select patients with lymphoma for radionuclide therapy with ^{177}Lu-DOTATATE
- ✓ High expression of SST and high tumour uptake of ^{68}Ga-DOTANOC correlates with good prognosis
- ✓ Whole body MRI is most sensitive and specific method for imaging certain lymphoma subtypes when compared to FDG-PET/CT and DOTANOC-PET/CT

3.2 AIMS

- ✓ To characterize tumour cell uptake of intravenously injected somatostatin analog ^{68}Ga-DOTANOC in patients with lymphoma
- ✓ To study the correlation of tumor uptake of ^{68}Ga-DOTANOC and immunohistochemical SST_2, SST_3 and SST_5 receptor status of the tumor specimen in lymphomas
- ✓ To evaluate whether lymphomas are candidates to radionuclide therapy with ^{117}Lu-DOTATATE using ^{68}Ga-DOTANOC PET/CT
- ✓ To evaluate therapy response using whole body MRI, including DWI, and FDG-PET/TT
- ✓ To study which imaging method would be most sensitive and spesific in diagnosing and evaluating treatment outcome in lymphomas

4 STUDY DESIGN

4.1 TYPE AND DESIGN

This is a non-randomized prospective study to obtain information with PET/CT imaging on tumor uptake of somatostatin analogue ^{68}Ga-DOTANOC in patients with newly diagnosed non-Hodgkin and Hodgkin lymphomas. ^{68}Ga-DOTANOC PET/CT images will be compared to whole body MRI and ^{18}F-FDG PET/CT studies.

4.2 GENERAL STUDY OUTLINE

Suitable patients meeting the inclusion criteria will be enrolled to the study after informed consent, radiological, and histological diagnosis of non-Hodgkin or Hodgkin's lymphoma. All eligible patients will receive standard oncological therapy. Before treatment PET/CT scan with intravenously injected ^{18}F-FDG and ^{68}Ga-DOTANOC and whole body MRI will be performed within 2-4 weeks. Tissue samples obtained for diagnostic purposes by tumour biopsy will be utilized to immunohistochemically study expression of molecules that may influence PET tracer uptake. This includes the evaluation of SST2, STT3 and STT5 receptor expression, counting the proliferation index using the Ki-67 marker, and detecting CD68 positive macrophages.

5 PATIENT SELECTION

5.1 SOURCE POPULATION

All new cases of lymphoma are referred for oncological treatment to Turku University Hospital from the Hospital District of South Western Finland. Total population in the hospital district is

approximately 474 000. Number of eligible non-Hodgkin lymphoma patients in one year is approximately 70-90 and that of Hodgkin lymphoma 10-20, respectively.

5.2 NUMBER OF PATIENTS

This study comprises of 10-50 patients with different non-Hodgkin and Hodgkin's lymphoma subtypes receiving ^{68}Ga-DOTANOC PET/CT imaging to study SST_2, STT_3 and STT_5 receptor status. In addition, some of these patients will undergo three repeated MRI examinations (before, during, and after therapy) to monitor and evaluate therapy response.

5.3 INCLUSION CRITERIA

- Age: 18-75 years old
- Language spoken: Finnish or Swedish
- Patients with diagnosed untreated non-Hodgkin or Hodgkin lymphoma with measurable disease (the diagnosis is based on radiological, histological and clinical grounds)
- Before treatment CT and FDG-PET performed
- Mental status: Patients must be able to understand the meaning of the study
- The patient signs the appropriate Ethical Committee (EC) approved informed consent documents in the presence of the designated staff

5.4 EXCLUSION CRITERIA

- Any medical or psychiatric condition that compromises the subject's ability to participate in the study
- Any other significant disease including liver or renal disease
- Pregnant or lactating women
- Contraindications for MR imaging

6 ^{68}Ga-DOTANOC PET/CT IMAGING

6.1 PRE-STUDY EVALUATION

All lymphoma patients are first evaluated by an oncologist. Patients meeting inclusion criteria but not any exclusion criteria will be asked to participate in the study. Patients will be informed orally and in written form about the study and if they are willing to participate in it they will be asked to

sign the informed consent form. Typically they will be allowed 2-4 days to read the patient inform sheet preferably with their close relatives before their consent to participate is requested.

6.2 SYNTHESIS OF ^{68}Ga-DOTANOC

A fully automated synthesis is used for the preparation of ^{68}Ga-DOTANOC. A commercial TiO_2-based ^{68}Ge/^{68}Ga radionuclide generator using 0.1N HCL as eluent is applied. Radiolabelling is performed as described by Zhernosekov et al with slight modifications.

6.3. PET/CT IMAGING

6.2.1 Patient preparation and positioning for imaging

The phycisian gives the patient a thorough explanation of the test. There is no need for fasting before injection. One catheter will be inserted in an antecubital vein for injection of ^{68}Ga-DOTANOC.The patients are placed in a supine position in the PET/CT scanner. The activity of radiopharmaceutical to be administered is determined after taking account of the Directive 97/43/EURATOM. The amount of ^{68}Ga-DOTANOC injected should be below 50µg. This amount is not expected to have any clinically significant pharmacological effect. Before scanning patients should void. Elimination of the extra fluid intake will help to flush out unbound labelled DOTANOC and non-peptide-bound ^{68}Ga by glomerular filtration. This will reduce the background noise as well as the radiation dose to kidneys and bladder. After imaging, the concentration of ^{68}Ga-DOTANOC will be defined from a blood sample taken from the catheder in first 10 patients.

6.2.2 PET imaging

The imaging device is a whole-body PET/CT scanner GE Discovery VCT (General Electric Medical Systems, Milwaukee, WI) operated in three-dimensional mode (11). The scanner is a combined 64-slice CT and PET with 24 rings of bismuth germanate detectors, which acquires 47 imaging planes with an axial field of view of 15.7 cm. The plane thickness of the PET scanner is 4.7 mm, and the axial spatial resolution for 3D mode is 5.12 mm in full width at half maximum in the 1 cm offset from center of the field of view.

Dynamic PET imaging of the largest tumour mass is done over 60 minutes, followed by static PET imaging of the whole body taking about 30 minutes. Only static imaging starting at 60 min after injection will be applied if the condition of the patient does not allow dynamic imaging. Intravenously injected dose of ^{68}Ga-DOTANOC will be approximately 120 MBq.

To obtain the input function, radioactivity in the plasma is measured with automatic gamma counter (1480 Wizard, Wallac, Turku, Finland) cross-calibrated with the dose calibrator (VDC-202; Veenstra Instruments, Joure, the Netherlands) and the PET/CT scanner. For this purpose venous blood samples are collected into heparinized tubes after PET imaging, and analyzed according to MET5001.

7 WHOLE BODY MRI

7.1.1 *Whole body MRI*

Whole body MRI examination will be performed using a 1.5T Siemens system (Magnetom Aera, Erlangen, Germany) or 1.5T/3T Philips system (Philips Ingenia, Best, Netherlands). The body matrix coil in combination with a spinal coil will be used for image acquisition.T1-weighted anatomic imaging, STIR fat suppressed images, and DWI will be performed in axial and coronal directions. DWI will be obtained with single-shot 2D spin-echo echo-planar imaging. No gadolinium-enhanced imaging will be performed. The total scan time will be approximately 40 minutes. Imaging data will be analyzed using the Siemens "Leonardo" dedicated workstation.

8 ADVERSE EVENTS

8.1 DEFINITIONS

An adverse event includes any noxious, pathological or unintended change in anatomical, physiological or metabolic functions as indicated by physical signs, symptoms and/or laboratory changes occurring in any phase of clinical study whether or not considered drug related.

8.2 REPORTING ADVERSE EVENTS

The investigator will report the occurrence of any adverse events and reactions during clinical trials as provided in sections 10e and 10f of the Act on Medical Research (488/1999). All serious unexpected adverse reactions which are fatal or life-threatening will be reported to the National Agency for Medicines as quickly as possible, however no later than within seven days. Any additional relevant information on such an adverse reaction must be reported within eight days of submission of the first notification. Serious unexpected adverse reactions which are not life-threatening or fatal will be reported to the National Agency for Medicines as soon as possible and in any case within 15 days.

8.3 EMERGENCIES

Emergencies may occur during PET/CT or MRI scans. A medical doctor will be present all the times. Vital functions will be monitored, and materials and drugs needed for first aid/resuscitation are readily available.

9 ETHICS

9.1 ETHICAL CONSIDERATIONS

At least one of the medical doctor investigators will be available to patients at all times during their participation in the study. All necessary investigator contact information will be provided along with a description of the study.

The studies will be performed using standard procedures. The duration of the PET/CT imaging will be 30-90 minutes. The effective dose of radiation from one ^{68}Ga-DOTANOC PET/CT is 6,3 mSv. This dose is little more than the annual dose of background radiation (5 mSv). In general, the effective dose of radiation for the patient in PET depends on the injected dose and the radioactive half-life of the tracer and CT resolution requirements.

9.2 ETHICAL REVIEW

This study will be conducted according to Good Clinical Practice, the Declaration of Helsinki, and US 21 CFR Part 50 - Protection of Human Subjects and Part 56 - Institutional Review Boards. Written informed consent for the study will be obtained from all subjects before protocol-specific procedures are carried out. Patients will be informed of their right to withdraw from the study at any time without specifying any reason.

This protocol will be submitted to the appropriate ethics review committee (Ethics Committee of Southwest Finland Hospital District), and the written unconditional approval obtained by Ethics Committee (EC) is required before commencement of the study. Additionally, an approval by the Turku PET Centre scientific review board is needed. EC will be informed by the Investigator of all subsequent protocol amendments and of serious or unexpected adverse events occurring during the study, which are likely to affect the safety of the subjects or the conduct of the study.

9.3 SUBJECT INFORMATION AND INFORMED CONSENT

The study will be performed in the Turku PET Centre, Turku, Finland

The principles of informed consent in the current edition of the Declaration of Helsinki and national regulations will be implemented before protocol-specified procedures are carried out.

Information will be given in both oral and written form. Subjects, their relatives, guardians or, if necessary, legal representatives must be given ample opportunity to inquire about details of the study.

The consent form generated by the investigator, must be approved (along with the protocol) by the EC before its use. Consent forms must be in a language fully comprehensible to the prospective subject. Informed consent process shall be documented on written consent form approved by the EC and signed by the subject and the investigator.

The written informed consent document will embody the elements of informed consent as described in the Declaration of Helsinki and will also comply with local regulations. This form may be read to the subject, but, in any event, the investigator shall give either the subject or the representative adequate opportunity to read it before it is signed.

Consent must be documented by the dated signature of the subject. The signature confirms that the consent is based on information that has been understood. Each subject's signed informed consent form must be kept on file by the investigator for possible inspection by Regulatory Authorities. Copy of the form will be given to subject.

10 DATA COLLECTION AND MANAGEMENT

10.1 SUBJECT MEDICAL INFORMATION

Medical information will be filled out during the initial clinical examination by oncologist in order to collect subject's personal information and their medical status and history relevant to the aims and exclusion criteria of this study.

10.2 ELECTRONIC DATA COLLECTION

Data from the case report forms, clinical observations as well as results from the study (MRI and PET/CT results), and all study results will be gathered in electronic form.

10.3 DATA MANAGEMENT AND STORAGE

All data collected is strictly confidential. It will be archived on paper or electronically for at least twenty years in a designated space in Turku PET Centre, as required by the local Quality System.

11 DATA ANALYSIS

11.1 ANALYSIS OF PET DATA

PET studies are analyzed by using regions of interest (ROI) manually drawn on coregistered magnetic resonance images to obtain absolute values from anatomical structures. Visual analysis is done Carimas 2.8 imaging platform (Carimas 2.8, Turku PET Centre). ROIs are placed in the late acquisition image planes covering the whole tumor volumes. Heterogeneity of ^{68}Ga-DOTANOC uptake within tumor is estimated by calculating maximum and whole-tumor uptake in ROI volumes from adjacent planes using pixel-by-pixel analysis over different time points. Dynamic curves are then obtained by superimposing the tumor ROIs over all dynamic frames and calculating the weighted average radioactivity concentration in each plane showing tumor volume.

11.2. ANALYSIS OF MRI DATA

Anatomical MRI data will be evaluated visually while quantitative approach will be used for DWI.

Monoexponential calculation of apparent diffusion coefficient (ADC) can be described by following equation (eq.1):

$$ADC = -\ln\left(\frac{SI(b_2)}{SI(b_1)}\right) \qquad \text{(eq. 1)}$$

where $SI(b_2)$ and $SI(b_1)$ denotes the signal intensity at higher (b_2) and lower b-value (b_1).

12 STATISTICS

11.1 SAMPLE SIZE

The first sub-group of the current study consists of 10 patients with Hodgkin or non-Hodgkin lymphoma. We will then evaluate whether DOTANOC-PET/CT imaging is continued in other patients too. The second sub-group of the current study consists of maximum of 40 patients who will undergo a total of three repeated whole body MRI examinations (before, during and after treatment). Due to the exploratory nature of the study a power analysis was not considered necessary.

12.2 POSSIBLE INTERIM ANALYSES AND STOPPING RULES

If in the first ten patients PET/CT imaging shows no uptake of ^{68}Ga-DOTANOC, it will not be performed to any other patients and the study will continue only with repeated MRI examinations. If any patient wants to stop participating the study they can do it anytime and without any explanations required.

13 QUALITY ASSURANCE

13.1 INFORMATION OF STUDY PERSONNEL AND TRAINING

The technical and other supporting personnel of Turku PET Centre is well experienced in performing PET and MRI studies with various labeled tracers. In the beginning of the study nuclear medicine and radiology technologists will be informed on the practical implementation of the protocol in a separate institutional meeting. They will be informed on the rationale of the study and possible clinical implications as well.

14 STUDY SCHEDULE

Screening of subjects will start in Autumn 2014 but will mainly happen during year 2015. The subjects will undergo normal physical examinations and radiological studies at the department of oncology, and then they will be invited to the PET/CT and MRI studies ideally within 2 weeks of the first visit in oncology. All studies will ideally be completed by the end of 2016. The first results will be reported in Spring 2016 and the final report will be written in 2017.

15 BUDGET AND FINANCING

The study will be financed in part by Finnish Governmental Special Funding (in Finnish 'erityisvaltionosuus, EVO') and by a research grant from Cancer Foundation.

16 INSURANCE

The study patients are insured during the PET procedure by the "Insurance against medicine-related injuries" (in Finnish: "Lääkevahinkovakuutus") under regulations currently in effect in Turku University Central Hospital.

17 STUDY REPORT AND PUBLICATION(S)

Reports of this study will be submitted to peer-reviewed journals.

18 ARCHIVING

The PI retains a list of all patients and their identifying codes for at least 15 years after completion or discontinuation of the study. All patient files, including EC approvals and amendments, all source documents and case report copies, PET raw data, and patient informed consent forms are kept in a locked room at the Turku PET Centre of Turku University Central Hospital for a minimum of 15 years.

All PET studies including raw sinogram data and reconstructed images are stored up on DVD-RAM disks (Unix) and/or CD-R disks (PC/Unix) at the Turku PET Centre of Turku University Central Hospital in a locked room under continuous guard of the Hospital Staff.

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20. **APPENDIX**

SEQUENCE OF EVENTS

Event	*Measures*
Diagnosis of Hodgkin or non-Hodgkin lymphoma.	^{18}F-FDG PET/CT
↓	
Inform consent by patient	
↓	
Referral to PET/CT, MRI examination	
↓	
^{68}Ga-DOTANOC PET/CT and whole body MRI (two examinations) performed on different days	
↓	
Imaging and pathology correlation	
↓	
Physically fit and willing patients continue in the next phase of the study	
↓	
2nd cycle of chemotherapy	
↓	
whole body MRI (one examination)	CT
↓	
Imaging and pathology correlation	
↓	
Last (6th) cycle of chemotherapy	
↓	
whole body MRI (one examination)	^{18}FDG-PET/CT