DUAL POINT ACQUISITION IN THE INTERIM PET SCAN PERFORMED DURING ABVD TREATMENT, IN EARLY-STAGE HODGKIN’S LYMPHOMA PATIENTS WITH BULKY LESIONS (2P-HD-10 STUDY)

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SIGNATURE PAGE FOR STEERING COMMITTEE

PROTOCOL APPROVED BY THE FOLLOWING:

Andrea Gallamini, M.D.                                date  20/10/2010
(Study Chairman)

Corrado Tarella, M.D.                                date  20/10/2010
(Study Co-Chairman)
SIGNATURE PAGE FOR INVESTIGATORS

INVESTIGATOR SUBSCRIPTION

I have read the protocol and I agree that it includes all the requested details for the study conduction. I will ensure that all the members of my Haematology Unit will have a copy of the protocol provided by the Consorzio Mario Negri Sud of Santa Maria Imbaro, the CRO of the study. I will discuss the protocol with all the members of the Haematology Unit to make them all be fully aware of the scientific contents and the practical aspects that are needed for the study conduction. After the protocol is approved by the Ethical Committee I will not modify the contents without having previously received the specific authorization from both the sponsor and the Ethical Committee. I declare that I know all the details of the protocol and I will work in agreement with the principles of the Good Clinical Practice (GCP), the Declaration of Helsinki in its latest version and the current laws of the Italian and European legislation.

Investigator signature       Date
## GLOSSARY

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>ABVD</td>
<td>Chemotherapy containing Doxorubicin, Bleomycin, Vinblastine, and Dacarbazine</td>
</tr>
<tr>
<td>ASCT</td>
<td>Autologous Stem Cell Transplantation</td>
</tr>
<tr>
<td>CECT</td>
<td>Contrast-Enhanced CT scan</td>
</tr>
<tr>
<td>CRP</td>
<td>C-Reactive Protein</td>
</tr>
<tr>
<td>ESR</td>
<td>Erythrocyte Sedimentation Rate</td>
</tr>
<tr>
<td>HDS</td>
<td>High-Dose Chemotherapy</td>
</tr>
<tr>
<td>PET</td>
<td>Positron Emission Tomography</td>
</tr>
<tr>
<td>IWC</td>
<td>International Workshop Criteria for Lymphoma staging and restaging.</td>
</tr>
<tr>
<td>MBPS</td>
<td>Mediastinal Blood Pool Structures</td>
</tr>
<tr>
<td>PI</td>
<td>Principal Investigator</td>
</tr>
<tr>
<td>PET-2</td>
<td>PET scan performed after 2 chemotherapy courses</td>
</tr>
<tr>
<td>2P-PET</td>
<td>Dual point-acquisition FDG-PET scan</td>
</tr>
<tr>
<td>FDG</td>
<td>2-[18F] Fluoro-2-deoxy-D-glucose</td>
</tr>
<tr>
<td>PPV</td>
<td>Positive predictive Value</td>
</tr>
<tr>
<td>NPV</td>
<td>Negative Predictive Value</td>
</tr>
<tr>
<td>CT</td>
<td>Computed Tomography</td>
</tr>
<tr>
<td>DW-MRI</td>
<td>Diffusion weighted Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>HL</td>
<td>Hodgkin lymphoma</td>
</tr>
<tr>
<td>DLCL</td>
<td>Diffuse Large B-Cell Lymphoma</td>
</tr>
<tr>
<td>SUV</td>
<td>Standardized Uptake Value</td>
</tr>
<tr>
<td>SUV(_{\text{MAX}})</td>
<td>Maximal value of SUV measured in a Region of Interest</td>
</tr>
<tr>
<td>ADC</td>
<td>Apparent Diffusion Coefficient</td>
</tr>
<tr>
<td>STIR</td>
<td>Short T1 Inversion Recovery</td>
</tr>
<tr>
<td>T</td>
<td>Tesla</td>
</tr>
<tr>
<td>EPI</td>
<td>Diffusion-weighted single-shot echo-planar imaging</td>
</tr>
<tr>
<td>WMA</td>
<td>World Medical Association</td>
</tr>
<tr>
<td>GCP</td>
<td>Good Clinical Practice</td>
</tr>
<tr>
<td>UPN</td>
<td>Unique Patient Number</td>
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<tr>
<td>IF Radiotherapy</td>
<td>Involved-Field Radiotherapy</td>
</tr>
<tr>
<td>IN Radiotherapy</td>
<td>Involved-Node Radiotherapy</td>
</tr>
<tr>
<td>IWC Criteria</td>
<td>International Workshop For Treatment Response in Lymphoma</td>
</tr>
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**SYNOPSIS**

<table>
<thead>
<tr>
<th>Version number</th>
<th>1</th>
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<tr>
<td>Date</td>
<td>17.11.2010</td>
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<tr>
<td>Study Title</td>
<td>Dual point acquisition in the interim PET scan (2P-PET) performed during ABVD treatment in early-stage Hodgkin Lymphoma (HL) patients presenting bulky nodal lesions.</td>
</tr>
<tr>
<td>Short study title</td>
<td>2P-PET in early bulky HL</td>
</tr>
<tr>
<td>Study duration</td>
<td>Patients will be enrolled during two years and will be followed at least for one year.</td>
</tr>
<tr>
<td>Primary outcome measure</td>
<td>To assess specificity and overall accuracy of interim dual-point acquisition PET (2P-PET) in predicting treatment outcome.</td>
</tr>
<tr>
<td>Secondary endpoint</td>
<td>To assess prognostic value of inflammation markers (ESR, CRP, Ferritin, Transferrin, Fibrinogen, Alpha 2–globulins) in early stage HL and relating their levels with the treatment outcome and in relationship to interim 2P-PET.</td>
</tr>
<tr>
<td>Study Outline</td>
<td>Prospective, Multicenter, Observational Study</td>
</tr>
<tr>
<td>Study design</td>
<td>The study is aimed at assessing the specificity of interim 2P-PET performed after 2 ABVD cycles to predict treatment outcome in early-stage HL patients presenting bulky lesions at baseline.</td>
</tr>
<tr>
<td>DW-MRI sub-study design</td>
<td>The Institutions equipped with a Nuclear Magnetic Resonance scanners in which a diffusion-weighted Imaging analysis (DW-MRI) are possible could be allowed to participate to the ancillary sub-study in which the predictive value of interim 2P-PET will be compared with interim DW-MRI. This sub-study is aimed to assess specificity and overall accuracy of DW-NMR performed after 2 ABVD courses on treatment outcome and the value of whole-body magnetic resonance imaging (MRI) including whole body diffusion weighted imaging (DWI), in the baseline staging.</td>
</tr>
<tr>
<td>Statistical aspects</td>
<td>Because of its purely descriptive objectives no sample size calculation has been performed. It is estimated that in the involved centers, during the two years of recruitment, will be collect the data of about 150 early-stage HL patients. According to the aforementioned, no formal statistical tests will be performed in this study and only descriptive tools will be adopted for the characteristics of the population of patients and their outcome, focusing on three characteristics: the distribution, the central tendency, and the dispersion. If the descriptive analysis suggests association, a secondary correlation/association analysis can be carried out.</td>
</tr>
<tr>
<td>Inclusion criteria</td>
<td>Hodgkin lymphoma diagnosis according all the WHO classification subtype but lymphocyte predominance. Age 18 – 60 stage IA- IIA (by FDG-PET scan) Presence of bulky tumour (either in Mediastinum or other site)</td>
</tr>
</tbody>
</table>
- Treatment with ABVD x 4 (early stage)
- Consolidation Radiotherapy on bulky lesion
- Signed the Informed consent form

Exclusion criteria
- Diabetes mellitus uncompensated
- Lymphocyte predominance histology
- Pregnancy or lactation
- Implanted biomedical devices (for DW-MRI sub study)

Definition of bulky lesion
Bulky tumour is defined as a single mass, or a conglomerate of multiple nodal lesion, with a major transverse diameter ≥ 6 cm. The dimension of the bulky lesion should be assessed on contrast-enhanced CT scan (CECT).

Initial treatment
Patients will be treated according to the standard treatment for early-stage HL with bulky lesions: ABVD x 4 courses, followed by involved-fiel radiotherapy.

Initial therapy consist of 2 ABVD cycles: (re-cycle every 28 days, without any dose reduction or time delay: dose intensity 100%).

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doxorubicin</td>
<td>25 mg/m²</td>
<td>iv</td>
<td>1,15</td>
</tr>
<tr>
<td>Bleomycin</td>
<td>10,000 units/m²</td>
<td>iv</td>
<td>1,15</td>
</tr>
<tr>
<td>Vinblastine</td>
<td>6 mg/m²</td>
<td>iv</td>
<td>1,15</td>
</tr>
<tr>
<td>Dacarbazine</td>
<td>375 mg/m²</td>
<td>iv</td>
<td>1,15</td>
</tr>
</tbody>
</table>

This will be given at full dose and on schedule, regardless of blood count. Growth factors may be used at the discretion of investigators but are not routinely advised.

PET scanning
Both baseline and interim PET will be performed using standard technique. The scans are acquired at 60±10’ (early) and 120 ± 10’ (late) after the injection of the tracer. Late acquisition will be made in baseline PET to all patients enrolled in the study and a second, whole-body scan will be performed. Late acquisition in interim-PET scan will be performed only in patients showing a positive, or minimally positive scan at 60’ acquisition time-point. A minimally positive scan is defined as any scan with any residual FDG uptake outside the physiological areas of the tracer concentration (Deauville scores 2-3). In the late acquisition scan, imaging will be limited to the bulky lesion, or to other positive foci avoiding to repeat a whole body scan. (see Appendix 4)

PET Interpretation at +60’ and +120’ time-points.
Baseline and interim PET will be analysed in two different ways according to the different acquisition time-points: in the standard acquisition time (+60’) the 5-point Deauville score will be used and in the late acquisition (+120’) a quantitative method will be used, with the ΔSUV<sub>MAX</sub> determination (ratio between SUV<sub>MAX</sub> at +60 and SUV<sub>MAX</sub> at +120’). PET scan will be centrally reviewed by an expert review panel. PET scan will be re-interpreted by an expert panel upon uploading of the baseline ad interim scan in a dedicated WEB site at the URL https://magic5.to.infn.it at the National Institute of Nuclear Physics (INFN).
<table>
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<th>DW-MRI whole-body scanning (DW-MRI sub-study)</th>
<th>All subjects will be examined by 1.5-T MRI; different anatomical stations (head/neck, chest abdomen and pelvis) will be imaged using T1-, T2- STIR- and diffusion-weighted sequences. Diffusion-weighted single-shot echo-planar imaging (EPI) will be performed in the transverse plane, using two different b-values: b= 0, b=800. Image in T1, T2, STIR and DWI acquisition should be done in free-breathing with respiratory trigger synchronization for thorax and abdomen and in free breathing for head, neck and pelvis.</th>
</tr>
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<tr>
<td>After 2 cycles, PET <strong>negative</strong> and <strong>positive</strong> patients continue with ABVD (for 2 cycles more, for a total of 4 cycles)</td>
<td>ABVD as above, every 28 days for 2 further cycles</td>
</tr>
</tbody>
</table>
| Contrast-enhanced CT scan and FDG-PET will be performed after 4 ABVD courses. | After 4 courses of ABVD patients should be restaged with contrast-enhanced CT scan (CECT) and FDG-PET scan. Patients in CR or PR at CT, with a **single spot, residual FDG uptake** should undergo to radiotherapy, as planned. Patients symptomatic for disease recurrence, or in less than PR with IWC criteria, will get off of protocol. Patients with **two or more foci or new sites** of FDG uptake will be considered non responders and will get off of protocol. In conclusion, at the end of chemotherapy program patients will be considered non responders and will get off of the protocol if:
1) Less than PR according to IWC criteria
2) Symptomatic for disease recurrence
3) Show a FDG-PET with two or more persisting foci of FDG uptake.
High-dose chemotherapy followed by autologous stem cell transplant (ASCT) could be the suggested treatment but centers will follow their own policy for relapsing resistant lymphoma. Patients not fulfilling the above criteria will be treated with Involved Field (or Involved Nodal) Radiotherapy. |
| Radiotherapy | Rx therapy will be delivered on the bulky lesion with the Involved-field, or involved nodal technique, according to the single center policy. The prescribed dose is 30 Gy with a boost of 6 Gy to areas with initial bulky disease. Dose per fraction 2 Gy; the maximum weekly dose will be 10 Gy and five fractions per week will be given. |
| Inflammation marker | The inflammatory markers assessment will be performed in all patients at baseline, interim staging, second restaging and final restaging. |
BACKGROUND

The early evaluation of treatment outcome in HL has gained much interest in recent years. As known, HL is a quite sensitive disease, with more than 75% of patients achieving durable disease control with standard ABVD treatment. Primary treatment failure however, either for progression or early relapsing disease is characterized by a very dismal prognosis, with no more than half of the patients being rescued with high-dose chemotherapy followed by autologous stem cell transplantation (ASCT). For these reasons very early evaluation of treatment response seems very important to single out the patients in which a standard treatment could be insufficient for disease control. However, only a functional imaging technique could be able to detect the presence of few persisting, chemoresistant viable tumour cell within a tumour mass, while conventional, morphologic and static techniques such as CT scan are proved inadequate. And this very early treatment reappraisal is just what has been done with FDG PET scan after 2 or 3 cycles of chemotherapy in the pioneer experience of Hutchings and Mikhaeel. ¹

FDG-PET Scan

Nearly 80% of the HL patients show a complete normalization of the PET scan after two courses of ABVD. ², ³ However, very similar findings have been reported as early as after one single cycle or seven days after chemotherapy administration. ⁴, ⁵ This impressive sensitivity to antineoplastic therapy, characteristic for HL, can be explained by the peculiar architecture and organization of the neoplastic tissue, where the tumour cells, namely Reed Sternberg and Hodgkin cells (H-RSc), accounting for less than 1% of the total cellular population, are surrounded by a microenvironment non-neoplastic mononuclear elements that contribute to the immortalization of H-RSc via chemokine production. ⁶ Non-neoplastic cells show an impressive FDG avidity, as shown a baseline scan positivity in 100% of the HL cases, but their metabolic activity and chemokine production are shut down after two courses of chemotherapy. This phenomenon occurs in normal-size but also bulky nodes, in spite of a persisting mass, because tumour shrinkage takes time and depends on several factors in the host. This paradoxical phenomenon, that has been called “metabolic CR”, accounts for the high performance of FDG-PET as prognostic tool in predicting treatment outcome. ⁷, ⁸ The early evaluation of the metabolic viability of the microenvironment cells, in fact, works as an amplifier tool for the detection power of FDG-PET and predicts in a “black & white fashion” the treatment outcome. ⁹ This situation is quite different in Diffuse Large-B cell non Hodgkin lymphoma (DLBCL). In DLBCL neoplastic cells range between 85% and 99% of the nucleate cells present in the tumour tissue. The growth fraction is very high, sometimes up to 90%. The persisting FGD uptake could be the balance between cell kill by chemotherapy and cell regrowth. Non-neoplastic cells do not seem to play a role in FDG uptake in DLCL lymphoma subtype. ¹⁰ Interim FDG-PET scan performed very early during treatment has shown an high overall accuracy in predicting treatment outcome in more than 90% of the patients. Quite recently, Terasawa has systematically reviewed all the studies so far published on this issue and reported a sensitivity for HL patients ranging between 43% and 100% and a specificity ranging between 67% and 100%. ¹¹ In all the reviewed studies the authors have confirmed the prognostic role of early PET in predicting treatment outcome and concluded that it is useful and reliable for assessment of the treatment response. In the joint Italian and Danish study, the 2-y progression free survival for interim PET negative and positive patients was 95% and 12%, respectively. Interim-PET emerged as the only
prognostic factor able to predict treatment outcome, whatever the class risk or IPS (International Prognostic Score) the patient belonged to. In 8-10% of the HL patients treated with standard chemotherapy, undergoing early restaging during treatment with an interim PET scan, a persisting, faint FDG uptake is still detectable, most often in a site where a bulky tumour was recorded at baseline. This area of persisting FDG uptake was first described in its pioneer paper by Hutchings et al as Minimal Residual Uptake (MRU). MRU was defined as low grade uptake of FDG (just above background) in a focus within an area of previously noted disease reported by the nuclear medicine physicians as not likely to represent malignancy. The significance of this finding is unknown, and probably is a consequence of the inflammatory tissue reaction to the cytolytic effect of the chemotherapy, with an unspecific FDG uptake by inflammatory cells; the prognosis of MRU+ patients is quite similar to that of patients with a interim-negative scan, and for these reasons it has been proposed that MRU+ patients should be considered as interim-PET negative. Two years later, in 2007, MRU, was defined by Gallamini and Juweid [personal communication] as a weak persisting FDG uptake with an intensity equal or slightly superior to the Mediastinal Blood Pool Structures (MBPS). Finally, in 2008 the Nuclear Medicine team of the St. Thomas Hospital in London, proposed a definition of SUV as a residual FDG uptake with an intensity lower or equal to the one recorded in the liver. This evolution of the MRU concept in the years immediately following its definition consisted in a broadening of the boundaries of the area of the MRU itself, with the aim to increase the specificity and reduce the false positive results of interim PET scan in predicting treatment outcome. These different MRU definitions, however, have been incorporated in the criteria for interim PET interpretation adopted in different clinical trials with a PET-response adapted therapeutic strategy that are running at the moment worldwide for HL.

Nodal FDG uptake after two cycle of chemotherapy is related not only to the presence of residual disease but also to a variable amount of inflammatory tissue. In experimental cultures dual point acquisition is able to differentiate inflammatory from neoplastic...
tissue. Also in clinical studies, this technique has proven to be able to differentiate benign from malignant pulmonary nodules and others benign from malignant conditions. In general inflammatory tissue is expected to reduce the FDG uptake as the time goes by, while the uptake in the neoplastic tissue is supposed to be constant/increasing, see figure here below:

Chemotherapy per se is able to induce inflammation secondary to tissue damage that peaks between 10 and 15 days after therapy administration, exactly in the moment when interim PET is performed, in general 11-12 days after the end of second ABVD course. The interpretation criteria used in interim PET are mainly based on the comparison between the uptake in the residual node and in a reference target organ, generally the mediastinal blood pool structure (MBPS) and the liver.

**Interim-PET scan in early-stage HL patients with bulky lesions**

Since 2001, the presence of bulky lesion was shown to affect the specificity and positive predictive value on treatment outcome of PET scan performed at the end of the chemotherapy. In a preliminary study with 19 HL patients presenting with bulky mediastinal lesions, the positive predictive value of PET scan after chemotherapy alone or combined radio-and chemotherapy was only 60%. In the pioneer Hutching’s experience the positive predictive value of interim-PET was 20% in early stage and 91% in advanced-stage HL. In the ongoing EORTC H10 study, exploring the prognostic role of interim-PET in early-stage HL, the percentage of interim-positive patients was 13% in early favourable and 23% in early unfavourable patients. In the unfavourable stratum most patients presented a bulky mediastinal Tumour. Again, in the ongoing IIL prospective study HD 0801 in a cohort of advanced-stage HL patients presenting at diagnosis a bulky mediastinal tumour, using the IHP criteria for PET interpretation, the percentage of patients with a positive interim PET was 40%. For these reasons, in order to increase the specificity on interim-PET two hypotheses could be done: a) to change the interpretation rules for interim-PET with a higher threshold for PET positivity; b) to introduce a new scanning protocol, based on a dynamic determination of the FDG acquisition, in order to discriminate inflammatory changes from persistent viable tumour tissue. Inflammatory tissue, in fact, is expected to decrease the FDG uptake as the times goes by, while in neoplastic tissue the FDG uptake increases with time. In the proposed study, both purposes have been accepted: the threshold for PET scan positivity has been
increased to a level corresponding to the liver FDG intensity of uptake, and a scan with two acquisition in different time-points will be made: after 60’ and 120’ after FDG injection.

**Inflammation Markers**

Inflammation dominates both the histological and the clinical pictures of HL and there are several clues that accessory cells (neutrophils, macrophages, and so on) have an important role in the development and progression of disease. In fact, the clinical features at diagnosis, including some IPS factors (serum albumin <4 g/dl, Hb <10.5 g/dl, 000/mm white blood cell count ≥153 lymphocyte count <600/mm3 and/or <8% of total white blood cell count) are related with the production of il-6 by Reed-Sternberg cells. Since IPS has shown modest predictive ability in unfavourable early stage patients, modification of the IPS for use with early stages may improve its prognostic power. Moreover, the interim-pet assessment has overcome the IPS evaluation and seems to reflect the tumour chemosensitivity more than the real tumour eradication, related to the ability of chemotherapy to reduce the inflammatory microenvironment (ibidem).

For these reasons, we propose to evaluate the general inflammation status in early-stage HL patients through biochemical parameters (ESR), acute-phase proteins (CRP), iron regulatory proteins (Ferritin, Transferrin), soluble plasma glycoproteins (fibrinogen, alpha 2–globulins) at diagnosis, interim evaluation, end of the treatment and final re-evaluation.

Increased amounts of serum Ferritin in HL have been observed by several investigators in the past, either in children and adults, suggested as a possible tumour marker and associated to poor survival. 24, 25 ESR values at diagnosis are of incontrovertible importance in establishing the prognostic assessment in early-stage HL. 26 Preliminary data show a significant correlation between Ferritin and ESR values at diagnosis and interim-pet positivity (performed after 2 cycles of chemotherapy) in males at early stages. The further evaluation of commonly used inflammatory marker (ESR, CRP, Ferritin, Transferrin, Fibrinogen, alpha 2–globulins) will be useful to better define the prognostic importance of the general inflammation in HL.
STUDY OVERVIEW

Rationale
The proposed study is an non-interventional survey of a cohort of patients in whom interim PET scan is performed only for prognostic aims. PET with $^{18}$F-FDG is a standard staging procedure for most lymphoma subtypes. Performed early during the therapy for HL its results have a high prognostic value and is the main predictor of treatment outcome. [1, 3, 9, 12]. From 2006 onward, interim-PET after 2 ABVD courses has been increasingly performed in the daily clinical practice as a routine test for disease prognosis, and now it can be considered as a standard prognostic tool.

The novelty of the study relies on a new method for interim-PET scan execution: a dynamic study, with 2 different time points of image acquisition. This could potentially enable us to discriminate between unspecific, inflammatory DG uptake, from a “true” uptake form persisting viable neoplastic cells. Therefore, the main aim of the study is reducing false positive results in the interim-PET scan interpretation. Since dynamic changes of FDG uptake in Hodgkin’s lymphoma are still unknown we propose, in the present study, to assess the by the same acquisition technique the pattern of FDG uptake at baseline in untreated patients affected by this neoplasm.

The Institutions equipped with a Magnetic Resonance scanners and a diffusion weighted imaging analysis technique (DW-MRI), could participate to the DW-MRI sub-study.

Inflammation Markers
Inflammatory markers assessment will be performed at baseline staging and during all re-staging. The rationale is to define the importance of commonly used inflammatory markers, evaluable at every laboratory, in the prognosis and management of early stage HL.
STUDY DESIGN

END POINTS

Primary End Point

To assess specificity and overall accuracy of dual-point acquisition PET performed after 2 ABVD courses in predicting treatment outcome.

Secondary End Point

To assess prognostic value of inflammation markers (ESR, CRP, Ferritin, Transferrin, Fibrinogen, Alpha 2–globulins) in early stage HL, and their relationship with the treatment outcome and correlate the values of inflammation markers (ESR, CRP, Ferritin, Transferrin, Fibrinogen, Alpha 2–globulins) with the functional imaging: 2P-PET and DW-MRI performed very early during treatment outcome (after 2 ABVD courses).

ON STUDY PATIENTS

Enrollment

All the patients referred to the participating Institutions fulfilling the enrollment criteria will be the object of the study. The proposed sample size is 150 consecutive untreated patients. The 20-25% of them are expected to be interim-PET positive using the MBPS as reference cut-off value as previously proposed. However the number of patients with a “minimally positive” interim-PET (see below) will be at least double.

Inclusion criteria

All the following criteria should be met.

- Hodgkin lymphoma diagnosis according all the WHO classification subtype but lymphocyte predominance.
- Untreated disease
- Stage I-IIA
- Age 18-60
- Presence of bulky tumour (either in Mediastinum or other site); bulky tumour is defined as a single mass, or a conglomerate of multiple nodal lesion with a major transverse diameter ≥ 6 cm.
- Signed informed consent form

Exclusion criteria

Any of the following

- Steroid treatment during baseline staging
- Diabetes mellitus uncompensated
- Lymphocyte predominance histology
- Pregnancy or lactation

Bulky definition
Bulky tumour is defined as a single mass, or a conglomerate of multiple nodal lesion, with a major transverse diameter ≥ 6 cm. The dimension of the bulky lesion should be assessed on contrast-enhanced CT scan.

**Inflammatory markers evaluation**

In every patient enrolled will be evaluated the general inflammatory assessment and the cytokine detection. Basically, each marker will be considered of pathological interest when at levels greater than 1.5 UNLs (Upper Normal Levels), except for Transferrin, as shown in the table below.

<table>
<thead>
<tr>
<th>ENDPOINT</th>
<th>NORMAL VALUES</th>
<th>LEVELS OF PATHOLOGICAL INTEREST</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESR</td>
<td>&lt;20 mm/h</td>
<td>&gt;30 mm/h</td>
</tr>
<tr>
<td>CRP</td>
<td>5-6 mg/L</td>
<td>&gt;9 mg/dL</td>
</tr>
<tr>
<td></td>
<td>200-240 nmol/L</td>
<td>360 nmol/L</td>
</tr>
<tr>
<td>Ferritin</td>
<td>Male</td>
<td></td>
</tr>
<tr>
<td></td>
<td>15-250 ng/mL</td>
<td>375 ng/mL</td>
</tr>
<tr>
<td></td>
<td>27-670 pmol/mL</td>
<td>1000 pmol/mL</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td></td>
</tr>
<tr>
<td></td>
<td>15-150 ng/mL</td>
<td>225 ng/mL</td>
</tr>
<tr>
<td></td>
<td>27-330 pmol/L</td>
<td>495 pmol/L</td>
</tr>
<tr>
<td>Transferrin</td>
<td>204-360 mg/dL</td>
<td>250 mg/dl</td>
</tr>
<tr>
<td></td>
<td>25-45 μmol/L</td>
<td>30 μmol/L</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>2-4.2 g/L</td>
<td>6.3 g/L</td>
</tr>
</tbody>
</table>
DW-MRI SUB-STUDY

BACKGROUND

Diffusion Weighted Magnetic Resonance (DW-MRI)

The diffusion of water molecules is a biophysical parameter which correlates with the structural characteristics of tissues both in physiological and pathological conditions. Water molecules in the tissues are subject to two types of motion: “orderly” (e.g. the motion of blood within a vessel) and “random”. The latter regards the process of diffusion and is linked to the thermal energy of the tissue. During its motion each particle collides with those nearby and moves following an erratic course. This random motion, also known as Brownian motion, lies at the basis of diffusion phenomena.

Knowing how water molecules move within tissues can provide extremely useful information regarding the microscopic structure of the tissues themselves and the processes taking place within them.

Diffusion weighted imaging (DWI) is a non invasive technique which is able to probe the structure of biological tissue at a microscopic level and may therefore be used for “in vivo” tissue characterization. The principle of DWI evaluates the random translation motion of water protons in biological tissue.

The majority of DW-MRI has focused on the measurement of extracellular water diffusion. In tissue, the random paths extracellular water molecules can be otherwise hindered by structural interfaces. In a highly cellular tissue, extracellular water would not be able to diffuse far during the MR observation period without being blocked by cell membranes; this would lead to a short diffusional path and a reduce ADC (apparent diffusion coefficient).

Conversely, in cystic or necrotic portions of tumours with fewer structural barriers present, the diffusional path-length would be associated with a high ADC value. ADC maps, derived from diffusion-weighted imaging, can therefore provide a non-invasive measure of cellularity. This has obvious potential for diagnosis and treatment monitoring in oncology. In a recent literature report [18], high sensitivity (100%) and negative predictive value (100%), moderate accuracy (71%), low specificity (30,8%) and positive predictive value (66,7%) were reported at whole body DWI scans in detecting nodal lesions during baseline staging for lymphoma. However mapping of the water fraction in each compartment can make DW-MRI more specific to changes during tumour chemotheraphy response.

Predictive Parameter for Treatment Outcome with DW-MRI

Diffusion-weighted MRI has been shown to have the potential to prospectively predict the success of some treatments in a number of different tumours. For example, strong negative correlations between pre-treatment tumour Apparent Diffusion Coefficient (ADC) in patients with rectal cancer and size changes after chemotherapy and chemoradiation have been found. This and other similar observations have led to the hypothesis that tumours with higher ADC levels are more likely to have areas of necrosis, which in turn predicts poor outcomes related to hypoxia-mediated radioresistance. This relationship between poor outcomes and high pretherapy ADC may not apply to all tumours and to all therapy types. For example, in an animal tumour model treated with a vascular disruptive agent, low tumour ADC values still had viable tumour cells on histological diagnosis after...
therapy, whereas tumours with higher ADC values had a greater degree of cell kill. DW-MRI has been used in early assessment of tumour response in several tumours with promising results. The aim of the study is to compare the overall accuracy and Predictive Value of this new functional imaging technique in predicting treatment outcome as compared to interim-PET scan (considered, at the moment, the standard test to predict treatment outcome) when performed at the same time-point as interim-PET, very early during ABVD treatment. The secondary endpoint is assessing overall accuracy of DW-MRI in HL baseline staging, as compared to CT scan or CT-PET scan.

**END POINTS**

1) To assess specificity and overall accuracy of interim of DW-NMR on treatment outcome, as compared to interim PET scan.

2) To assess the value of whole-body magnetic resonance imaging (MRI) including whole body diffusion weighted imaging (DWI), for the initial diagnosis and staging.

**SUBSTUDY DESIGN AND CONDUCTION**

The Institutions equipped with a Magnetic Resonance scanners and a diffusion weighted imaging analysis technique (DW-MRI), could participate to the DW-MRI sub-study. All patients whose signed the “ad hoc” informed consent form, and satisfying all the inclusion criteria of principal study can be enrolled into this ancillary sub-study.

**Inclusion Criteria**
- Hodgkin lymphoma diagnosis according all the WHO classification subtype but lymphocyte predominance.
- Untreated disease
- Stage I-IIA
- Age 18-60
- Presence of bulky tumour (either in Mediastinum or other site); bulky tumour is defined as a single mass, or a conglomerate of multiple nodal lesion with a major transverse diameter ≥ 6 cm.
- Signed informed consent form

**Exclusion Criteria**
- Diabetes mellitus uncompensated
- Lymphocyte predominance histology
- Pregnancy or lactation
- Implanted biomedical devices

DW-MRI is performed along with baseline CT-PET and interim PET (PET-2), at the same time points during ABVD treatment.

**MRI of lymph nodes**

All subjects will be examined by 1.5-T MRI (Achieva, Philips Healthcare, Best, The Netherlands); different anatomical stations (head/neck, chest abdomen and pelvis) will be imaged using T1-, T2- STIR- and diffusion-weighted sequences.
It has been used a sixteen element phased-array surface coil on thorax and abdomen (SENSE body, Philips Healthcare, Best, The Netherlands).

T1-weighted gradient-echo imaging will be performed with the following sequence parameters per station: image acquisition in the coronal plane; slice thickness/gap, 6.0/1.0 mm; acquisition matrix, 208 x 280; image acquisition under (end-inspiration) breath-holding for thorax and abdomen and in free breathing for head/neck and pelvis.

T2-weighted turbo spin-echo imaging will be performed with the following sequence parameters per station: image acquisition in the coronal plane; slice thickness/gap, 6.0/1.0 mm; acquisition matrix for head/neck is 416 x 165, for thorax, abdomen 360 x 125 and for pelvis 424 x 165; image acquisition under (end-inspiration) breath-holding for thorax and abdomen and in free breathing for head/neck and pelvis.

STIR imaging will be performed with the following sequence parameters per station: image acquisition in the coronal plane; slice thickness/gap, 6.0/1.0 mm; acquisition matrix, 328 x 120; image acquisition in free breathing with respiratory trigger synchronization for thorax and abdomen and in free breathing for head/neck and pelvis.

Diffusion-weighted single-shot echo-planar imaging (EPI) will be performed in the transverse plane, using two different b-values: b0=, b=800. Slice thickness/gap, 5.0/0.0 mm; acquisition matrix, 104 x 67; image acquisition in free breathing with respiratory trigger synchronization for thorax and abdomen and in free breathing for head/neck and pelvis.

**Lymph nodes evaluation**
Lymphadenopathy will be evaluated on the base of Signal Intensity (SI) at DWI, on the base of ADC value and on the base of nodal dimension at MRI. In particular lymph nodes will be considered pathological if they will show high SI on DWI and low ADC value, regardless nodal dimension. Enlarged lymph nodes at MRI with low SI and high ADC value will be considered expression of pathological nodes with necrotic degeneration.
The DWI and ADC values will be evaluated also during and at the end of treatment. These data will be compared with the starting ones.
STUDY CONDUCTION

Staging at baseline
The following blood tests are required at baseline: Complete haemogram, serum glucose, creatinine, BUN, total protein, Protidogram with albumin and globulin percentages, ESR (Erythrocyte sedimentation rate), CRP, Ferritin, Transferrin, Fibrinogen, Alpha 2–globulins AST, ALT γ-GT, LDH.

Patients will be staged with contrast-enhanced CT scan, dual-point FDG PET scan, bone marrow trephine biopsy.

Whole body DW-MRI scan will be performed in patients enrolled in DW-MRI sub-study. For staging purposes FDG-PET scan will be considered the “gold” standard procedure: in case of stage discrepancy among different techniques, the stage defined by CT-PET will be chosen. Baseline and interim 2P-PET scan should be booked together at the same PET center. Patients will be treated with standard ABVD chemotherapy, and 100% dose intensity will be mandatory. G-CSF could be administered during first cycle and first part of the second cycle. If possible, G-CSF should be omitted after the second part of the second ABVD course.

Interim restaging
After 2 ABVD courses the same blood tests will be required as the Baseline-staging.

A PET/CT scan is performed after 2 ABVD courses.

In case of positive, or minimally positive scan a second acquisition will be made 120’ after FDG injection. A minimally positive scan is defined as any scan with any residual FDG uptake outside the physiological areas of the tracer concentration (Deauville scores 2-3). In this case a new whole body scan is not required and late acquisition will be limited to the site of positive interim PET scan (usually the bulky lesion). For patients enrolled in DW-MRI sub-study, an interim DW-MRI will be performed afterwards. Both functional imaging techniques are non-decisional: no treatment change will be allowed on the basis of interim PET or Interim DW-MRI.

Patients will be then treated with two further ABVD courses with a 100% dose intensity.

Second Interim restaging
At the end of the chemotherapy a final contrast-enhance CT (CECT) and a FDG-PET scan will be performed:

(1) Patients with a single spot, residual FDG uptake and in CR or PR according to IWC criteria should undergo radiotherapy, as planned.

(2) Patients with a frankly positive scan, with two or more foci of FDG uptake will be considered non-responders and will get off of the protocol.

(3) Whatever the result of FDG-PET scan, patients in less than PR according to IWC criteria, will get off of the protocol.

(4) Whatever the results of FDG PET and CECT, patients symptomatic for recurrent disease will get off of the protocol.

(5) Asymptomatic patients with negative FDG PET and in CR or PR according to IWC criteria, will be treated with Involved-Field Radiotherapy.
Every center could treat patients needing an aggressive rescue chemotherapy for primary refractory HL patients according their own policy. High-dose chemotherapy followed by autologous stem cell transplant (ASCT) could be the suggested treatment. In case of treatment switch to a more aggressive therapy a confirmatory biopsy, whenever possible, should be planned.

6. Radiotherapy
Radiotherapy is part of the standard, first-line treatment for early stage HL, according to the concept of combined modality treatment. There is not a suggested or preferred Radiotherapy technique. Centers could be choose either traditional Involved field (IF) schema or involved nodal areas only (IN-RT) radiation field, according to the policy of the reference Radiotherapy center.

*Dose specification*
The prescribed dose is 30 Gy with a boost of 6 Gy to areas with initial bulky disease.

*Dose fractionation*
Dose per fraction 2 Gy; the maximum weekly dose will be 10 Gy and five fractions per week will be given.

*Final restaging*
At the end of treatment the following blood tests will be required complete haemogram, serum glucose, creatinine, BUN, total protein, Protidogram with albumin and globulin percentages, ESR, AST, ALT γ-GT, LDH, Ferritin, PCR, Fibrinogen, P.T., aPTT. A CT-PET scan will be performed at the end of the entire therapeutic program, not earlier than 6 weeks after the end of radiotherapy.
DIAGNOSTIC PROCEDURES AND DATA FORMS

Registration
Patients satisfying all the recruitment criteria will be enrolled; the clinicians of participating centers will fill an accrual form and will register the patients on-line directly on web-site of the Central Data Center.
To register the patients the electronic “registration form” should be used. Once filled, confirmation of enrollment will be sent back to the proposing center within 24 hours together with the Unique Patient Number (UPN).

Staging at baseline
Staging at baseline should be done with physical examination, complete blood count, biochemistry tests [Glucose, BUN, Creatinine, protein electrophoresis, total protein and albumin assay, LDH, AST, ALT, GGT, alkaline phosphatise, ESR (Erythrocyte sedimentation rate),], trephine bone marrow biopsy and contrast-enhanced CT scan, according to IWC criteria, plus FDG-PET scan. In case of discordance between CT and FDG-PET, stage is defined by PET scan. FDG-PET scan should be done with dual point acquisition technique with acquisition times at 60’ and 120’. In both times a whole body scan should be done. For patients enrolled in the DW-MRI sub-study a DW-MRI examination should be done with a whole-body scan, after FDG-PET scan. The dimension of the bulky lesion (in centimetres) should be calculated using the largest diameter measured on contrast-enhanced CT scan. The electronic “baseline form” should be filled and sent.

Interim restaging (after 2 ABVD courses).
Complete blood counts, biochemistry tests [Glucose, BUN, Creatinine, protein electrophoresis, total protein and albumin assay, LDH, AST, ALT, GGT, alkaline phosphatise, ESR] should be done after the 2\textsuperscript{nd} ABVD course. FDG-PET scan should be done with the dual point technique, with the same acquisition protocol than in baseline scan. However, a second whole body scan is not needed and images should limited to the bulky lesion. For patients enrolled in DW-MRI sub-study, an interim DW-MRI scan is performed after the 2P-PET scan. The electronic “Interim-staging form” should be filled and sent.

Second restaging (after 4 ABVD courses).
The restaging should be done with physical examination, complete blood count, biochemistry tests [Glucose, BUN, Creatinine, protein electrophoresis, total protein and albumin assay, LDH, AST, ALT, GGT, alkaline phosphatise, ESR], contrast-enhanced CT scan, and standard FDG-PET scan. The treatment response at the end of ABVD chemotherapy should be assessed with IWC criteria. Patients with less than PR get off of the study. Patients in CR or PR proceed to IF radiotherapy. The electronic “Second restaging form” should be filled and sent.

Final restaging
The final restaging should be done with physical examination, complete blood count, biochemistry tests [Glucose, BUN, Creatinine, protein electrophoresis, total protein and albumin assay, LDH, AST, ALT, GGT, alkaline phosphatise, ESR], standard FDG-PET scan. The criteria used for treatment assessment in the final are those of IHP (Cheson 2007) and therefore a standard FDG PET scan should be done. The electronic “final restaging form” should be filled and sent.
Follow-up
Patient follow-up will be made according to the policy of each center. However, the minimum required follow-up for enrolled patients consist in a complete clinical evaluation, complete blood test, biochemistry every six months for the first three years after the end of treatment and a contrast-enhanced CT scan every 12 months. The electronic “Follow-Up form” should be filled and sent.

DATA COLLECTION
Investigators must enter the information required by the protocol into the electronic-Case Report Forms (e-CRFs). The e-CRFs will be forwarded electronically to the study data management center. (See Chapter “Data Management” page 27).
METHODS

DIAGNOSTIC METHODS

a) PET scanning

Both baseline and interim PET will be performed using standard technique (5). The scans are acquired at 60±10' (early) and 120 ± 10’ (late) after the injection of the tracer. Late acquisition will be made in baseline PET to all patients enrolled in the study, and a second whole-body CT-PET scan will be performed. Late acquisition in interim-PET scan will be performed only in patients showing a positive, or minimally positive scan at 60’ acquisition time-point. A minimally positive scan is defined as any scan with any residual FDG uptake outside the physiological areas of the tracer concentration. (Deauville score 2-3). In the late acquisition scan, imaging will be limited to the bulky lesion or to other positive foci, sparing the patient from performing a second whole body scan. Patients will be kept fasting throughout both the 2P-PET scan up to the end of late acquisition scan. (see the Appendix 4)

Imaging interpretation

Baseline and interim PET will be analysed in two different ways according to different acquisition time-points: in the first we will use a five-point semi quantitative score to visually compare the nodal and MBPS uptake and in the second we will measure simply the SUV\text{Max} in all the nodes. Both methods will be used either in early and late scan interpretation. The change of SUV\text{Max} in the nodes in between the dual point scans will be calculated with the relationship (SUV\text{Max late} – SUV\text{Max early})/SUV\text{Max late}.

The afore mentioned relationship is expected to differ among different patients and therefore all the baseline and interim-PET measurements will be performed on the same patients. PET scan will be centrally reviewed by an expert review panel. PET scan will be re-interpreted by an expert panel upon uploading of the baseline ad interim scan in a dedicated WEB site at the URL [https://magic5.to.infn.it](https://magic5.to.infn.it) at the National Institute of Nuclear Physics (INFN).

Five-point semi quantitative score

The PET-CT response scans are scored with reference to sites of physiological FDG uptake in the following way:

Negative

1. no uptake
2. uptake ≤ Mediastinum
3. uptake > Mediastinum but ≤ liver

Positive

4. uptake moderately increased in respect to liver
5. uptake markedly increased in respect to the liver
PARTICIPATING CENTERS

Several Italian and European centers are expected to participate to the study. The list of participating centers is contained in Appendix III.

STATISTICAL CONSIDERATIONS

This is a pilot study aimed at assessing feasibility of using a novel diagnostic procedure in the real world of clinical practice as well as at describing the outcome of early-stage HL patients. In particular, this study will be focused on the possibility of adopting this new diagnostic procedure in those patients and describe the rate of true positive or false positive results, along with positive and negative predictive value of the diagnostic procedure.

Similarly, the outcome of patients in terms of CR, PR and NR will be described. The study results will allow to have a reliable picture of up to date clinical practice adopting cutting-edge diagnostic and therapeutic approaches and of their outcome. Because of its purely descriptive objectives no sample size calculation has been performed. It is estimated that in the 10 centers involved, during the two years of recruitment, will be collect the data of about 150 early-stage HL patients. According to the aforementioned, no formal statistical tests will be performed in this study and only descriptive tools will be adopted for the characteristics of the population of patients and their outcome focusing on three characteristics: the distribution; the central tendency; and the dispersion. If the descriptive analysis suggests association, a secondary correlation/association analysis can be carried out.

ADMINISTRATIVE CONSIDERATIONS

The study is promoted by the S.C. of Hematology of Azienda Ospedaliera S. Croce e Carle, and will be conducted in the framework of FIL (Fondazione Italiana Linfomi), only for descriptive aims. This study is a non-intervention survey of a cohort of patients in whom interim PET scan is performed with prognostic aims and DW-MRI is performed in order to evaluate the overall accuracy and predictive power of this new functional imaging technique. Currently, interim-PET scan is considered the standard test to predict treatment outcome (as recommended by the NCCN Guidelines). DW-MRI is an innovative technique of functional imaging and will be paid with a dedicate fund expressly arisen for the study. However, not all the centers participating to the 2P-PET study have the opportunity of participate to the DW-MRI study. For this reason centers will be free to adhere or not to the DWQ-MRI sub-study.

Overall, the 2P-HD-10 study aims to improve the clinical practice as integrating part of the standard health care. The study is multicenter because it involves Italian and European Haematological Centers. Because of the observational outside of the study the insurance policy is not necessary (according to D.M. 14 Luglio 2009 and Guideline for the observational studies of 20 Marzo 2008).
ADVERSE EVENTS

SERIOUS ADVERSE EVENT (SAE) REPORTING
A serious adverse event is one that:

• Results in death
• Is life-threatening\(^1\)
• Requires inpatient hospitalization or prolongation of existing hospitalization
• Results in persistent or significant disability or incapacity\(^2\)
• Is a congenital anomaly or birth defect
• Is an important medical event\(^3\)
• Suspected positive Pregnancy

\(^1\) Life-threatening” means that the subject was at immediate risk of death at the time of the serious adverse event; it does not refer to a serious adverse event that hypothetically might have caused death if it were more severe.
\(^2\) Persistent or significant disability or incapacity” means that there is a substantial disruption of a person’s ability to carry out normal life functions.
\(^3\) Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in situations where none of the outcomes listed above occurred. Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also usually be considered serious. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. A new diagnosis of cancer during the course of a treatment should be considered as medically important.

IMMEDIATE REPORTING OF SAES
All SAEs are monitored through the data collected in the CRF. To better monitor patient safety, every SAE explicitly suspected by the Investigator to be related to study medications must be reported to the study Coordinating Center within 24 hours of learning of its occurrence, which will transfer immediately the information to the Ministry of Health and the competent health authorities.

ADVERSE EVENT, LABORATORY ABNORMALITIES, CLINICAL ADVERSE EVENTS
The NCI Common Toxicity Criteria (CTCAE) Version 3.0 will be used for grading of events. Relationship between the adverse event and treatment should be assessed and indicated as related, unrelated or unknown.
In case of allogeneic transplantation, clinical and laboratory abnormalities related to the occurrence of GVHD will not be reported in the Toxicity Evaluation Form, but in the appropriate GVHD form and graded according to the criteria described below.
DATA MANAGEMENT

DATA COLLECTION
Investigators must enter the information required by the protocol into the electronic-Case Report Forms (e-CRFs). The e-CRFs will be forwarded electronically to the study data management center. One print-out version of the e-CRF will be retained at the investigational site. Once the CRFs are received by the data management center, their receipt will be recorded and processed.

DATABASE MANAGEMENT AND QUALITY CONTROL
Database management and quality control for this study are under the responsibility of the Coordinating Center.
At the Coordinating Center, an expert personnel will review the e-CRFs for completeness and accuracy. Errors, omissions or questions will be entered on data query forms, which will be returned to the investigational site for resolution. After the investigator response is received at the data management center, the resolutions will be entered into the database. A copy of the signed data query form will be kept with the print-out of the CRFs. Quality control audits of all key safety and efficacy data in the database will be made at designated times during the study.
When the database has been declared to be complete and accurate, the database will be locked and unblinded.

DATA TRANSMISSION AND PROTECTION
The study will use remote data-entry (RDE) on electronic case report forms (e-CRFs) that will be entered, transmitted and stored electronically. A print-out of the compiled e-CRFs will be stored at the investigational center and at the Coordinating Center, to be used as a backup copy. Electronic signatures are required together with combined identification codes/passwords before access is granted to the computerized system and at the start of a data entry session.
To guarantee the secrecy of the data, but also to avoid manipulation and loss of data, precautionary action (hardware and software) are taken.
In particular:
At the Coordinating Center:
1. Access to data collected from the participating centres is reserved only to authorized members of the Coordinating Center
2. The data-collection network is protected by a firewall
3. The internet connection is encrypted with a digital certificate (SSL technology)
4. The database is located on a server that is protected with a password, that is changed periodically
5. Access to the database is protected with a password and is only accessible by responsible persons of Coordinating Center
6. Periodical back-ups will guarantee secure copies, to allow retrieval of both stored data and the data-collection system
7. The patient is registered and identifiable with a code, to guarantee anonymity

At the participating center:
1. Each center will receive a digital certificate and a “username” and a “password” for each one of the investigators appointed by the PI of the center. Only these investigators will be authorized to enter data on the e-CRFs
2. The investigators or research nurse can only enter and view data concerning their own patients

PROPERTY OF DATA AND PUBLICATION POLICY
All data generated from this study are the property of the Investigators. Analysis and publication of these data will be the responsibility of the Steering Committee in conjunction with the Scientific Coordinating Center. The parties agree to submit all manuscripts and abstracts to all other involved parties 30 days prior to submission.

SCIENTIFIC COORDINATING CENTER
Roberto Marchioli (Coordinator), Maria Rosaria Mennitto, Lorenzo Marfisi, Rosa Maria Marfisi, Anna Polidoro.
ETHIC AND GOOD CLINICAL PRACTICE

The last revision of the Helsinki Declaration as well as the previsions of the Oviedo Declaration provide the general framework for the ethical conduct of the study. The study protocol is designed and will be conducted according to ensure adherence to Good Clinical Practice (GPC) principles and procedures and Italian legislation requirements, as described in the following documents and accepted, with their signature, by the Investigators:


The investigator will be thoroughly familiar with the appropriate use of the study drug as described in the protocol. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

INDEPENDENT ETHIC COMMITTEE

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. Before implementing this study, the protocol, the proposed informed consent form and other information to subjects, must be reviewed by a properly constituted Independent Ethics Committee (IEC) in order to safeguard the rights, safety and well-being of the patients. A signed and dated statement that the protocol and informed consent have been approved by the IEC must be given to the Coordinating Center before study initiation. Safety updates and annual progress reports will be provided to the IEC by the investigator, as well as any revisions to the protocol. Any amendment to the protocol, other than administrative ones, must be approved by this Committee, according to D.M. 21 Dicembre 2007.

INFORMED CONSENT AND PATIENT INFORMATION

The Coordinating Center will supply a proposed informed consent forms (for Registry and Enrollment), which are part of the protocol and comply to regulatory requirements which must be approved by the IEC together with the protocol. Modified versions of the informed consent forms proposed by individual Investigators and approved by their IEC must be forwarded (together with the documentation of protocol approval) to the Coordinating Center.

After the study has been fully explained, written informed consent will be obtained from either the patient or his/her guardian or legal representative prior to study participation as appropriate. The method of obtaining and documenting the informed consent and the contents of the consent will comply with ICH-GCP and Italian legislation which in turn complies with and implements European Union regulations.

PRIVACY RULES AND PROTECTED HEALTH INFORMATION

According to the Italian legislation (which complies with and implements European Union regulations), participating patients must be duly informed, and give their explicit signed
agreement, on the way their rights to the confidentiality of personal data are duly respected. After participating patients have been duly informed and have given their explicit signed agreement, their rights to the confidentiality of personal data are duly respected. In order to maintain patient privacy, all data capture records, study drug accountability records, study reports and communications will be treated anonymously by coordinating center, where no personal data to identify patient will be recorded. Patients will be identified in the study by progressive numeric code.

PROTOCOL COMPLIANCE
The investigator will conduct the study in compliance with the protocol given approval/favorable opinion by the IEC and the Italian regulatory authority(ies). Changes to the protocol will require written IEC approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients. The IEC may provide, if pertinent regulatory authority(ies) allows, expedited review and approval/favorable opinion for minor change(s) in ongoing studies that have already received the approval/favorable opinion of the IEC. The investigator will submit all protocol modifications to AIFA and the regulatory authority(ies) in accordance with the governing regulations. Any departure from the protocol must be fully documented in the source documents.
MONITORING PROCEDURES

The Steering Committee of the study has delegated the GCP monitoring aspects of the study to the Consorzio Mario Negri Sud that will act as Contract Research Organization (CRO).

RECORDING OF DATA AND RETENTION OF DOCUMENTS

Essential documents, as listed below, must be retained by the investigator for as long as needed to comply with national (D. L.vo n.200, 6 Novembre 2007) and international regulations (according to ICH-GCP), generally 7 years after study closure. The Investigator agrees to adhere to the document retention procedures by signing the protocol. Essential documents include:
- IEC approval for the study protocol and all amendments
- Source documents and laboratory records
- Print - out of e – CRFs
- Patient’s consent form
- Any other pertinent study document

AUDITING PROCEDURE

Inspections by Regulatory Authorities during the study, and/or after its completion, could be expected and are welcome.
REFERENCES


Appendice I. – Foglio informativo per il paziente

Codice dello studio: 2P-HD-10

Titolo dello studio:
Studio della interim-PET con acquisizione a due tempi, effettuata durante il trattamento con ABVD in pazienti affetti da linfoma di Hodgkin in stadio limitato e con lesioni linfoghiandolari “bulky”.

Titolo del sotto-studio:
Studio della risonanza magnetica nucleare con tecnica di diffusione, associata alla interim-PET effettuata durante il trattamento con ABVD in pazienti affetti da linfoma di Hodgkin in stadio limitato e con lesioni linfoghiandolari “bulky”.

Perché chiediamo la Sua attenzione per leggere questo breve testo?

Gentile Signore/Signora,
Le chiediamo di leggere attentamente il testo che segue perché vi sono riportate informazioni importanti su una ricerca medico-scientifica che si sta conducendo, anche presso questo centro, e che riguarda i pazienti affetti da Linfoma di tipo Hodgkin, di età compresa tra i 18 e 60 anni.
I medici del centro a cui Lei si è rivolto insieme ad altri colleghi italiani e francesi fanno parte di una rete internazionale di ricerca sulle malattie onco-ematologiche che
• ha ritenuto che questa ricerca fosse particolarmente utile;
• ha sviluppato un protocollo di studio;
• propone anche a Lei di entrare a far parte dello studio.
Vorremmo che quanto qui proponiamo fosse a Lei molto chiaro e soprattutto che si senta del tutto libero di porre domande e richieste di chiarimenti, sia direttamente che indirettamente attraverso il suo medico di fiducia, al medico che La segue in questa struttura.
Le facciamo presente però che la Sua eventuale decisione di partecipare a questa ricerca deve essere comunicata non oltre il giorno prima della data in cui è stato programmat o l’inizio della Sua terapia. Successivamente a questo termine, non potrà comunque essere incluso nella ricerca.
Le diciamo fin da ora che la Sua partecipazione dipende semplicemente dalla Sua volontà e che se deciderà di partecipare dovrà fornire il Suo consenso per iscritto. Ad ogni modo, qualora Lei decidesse di non partecipare, la Sua decisione non influenzerà in alcun modo le cure e le terapie che Le verranno prestate e quindi riceverà in ogni caso le migliori terapie oggi disponibili per la cura della Sua malattia.

Qual è l’obiettivo di questo studio?
Lo scopo di questa ricerca, chiamata 2P-HD-10, è quello di valutare se una nuova procedura diagnostica, può predire con maggiore efficacia l’esito della terapia. La nuova tecnica si chiama “PET dual point”: è l’equivalente del normale esame PET che Lei sarà comunque chiamato ad eseguire, con l’unica differenza che, dopo l’iniezione del tracciante, le immagini saranno raccolte in due tempi, dopo un’ora (come già avviene) ed anche dopo due ore.
Per aumentare le conoscenze sulle tecniche diagnostiche a disposizione per i pazienti affetti da Linfoma Hodgkin, nell’ambito di questo studio è previsto anche un sottoprogetto di ricerca con lo specifico obiettivo di aiutare a capire se invece della PET, che espone il paziente a radiazioni, sia possibile utilizzare un particolare tipo di risonanza magnetica (chiamata “Risonanza Magnetica a Diffusione” o DW-NRM), ottenendo risultati ugualmente validi e precisi per la valutazione precoce della risposta alla terapia, ma con minore impatto sui pazienti.

Questa nostra ricerca è volta ad offrire in futuro a pazienti come Lei cure sempre più valide e metodi diagnostici sempre più accurati.

**Qual è lo stato attuale per la diagnosi e la terapia per il Linfoma Hodgkin in stadio precoce con la presenza di masse Bulky?**

Lo schema di terapia convenzionale, al quale lei aderirà a prescindere dalla Sua partecipazione allo studio, prevede 4 cicli di chemioterapia con Doxorubicina, Bleomicina, Vincristina e Desossimetasone (ABVD), somministrati per via endovenosa, il giorno 1° e il giorno 15° di ciascun ciclo, della durata complessiva di 28 giorni. A seguire, effettuerà un ciclo di Radioterapia, sulle masse Bulky evidenziate all’esordio. Gli esami ai quali si deve sottoporre di routine sono la TAC e la PET-TAC. Più volte nel corso di questo schema terapeutico ripeterà questi esami, che le sono stati effettuati anche per la diagnosi. I tempi delle stadiazioni sono infatti : esordio, secondo ciclo di ABVD, termine dei 4 cicli, termine della Radioterapia.

**Premessa**

Fino a questo momento il modello prognostico (= di previsione del risultato di cura) più usato nel linfoma di Hodgkin è il modello IPS (Indice Prognostico Internazionale), in grado di identificare come ad alto rischio di insuccesso della terapia a 10 anni solo l’11% dei pazienti. Nei fatti si osserva, però, che l’insuccesso della terapia standard, condotta secondo lo schema convenzionale sopracitato, ABVD, riguarda il 30-35% dei pazienti.

**La PET, che cos’è e perché eseguirla precocemente?**

Negli ultimi anni è stata introdotta in oncologia la PET, per valutare la vitalità o meno della massa tumorale al termine della terapia standard.

La PET (Tomografia ad Emissione di Positroni) è un esame tecnologicamente molto avanzato, che consente di dimostrare la presenza, dentro il nostro corpo, di accumuli di tessuto tumorale anche di dimensioni inferiori al mezzo centimetro. L’esame, che somma in sé i vantaggi della più tradizionale TAC (Tomografia Assiale Computerizzata), viene infatti effettuato dopo aver iniettato al paziente una sostanza molto simile al glucosio (FDG), che viene captata selettivamente solo dal tessuto tumorale, molto avido di glucosio. Ma l’FDG, a differenza del normale glucosio, una volta captato dalla cellula non può né uscire né essere scissa in composti più semplici. Perciò, mediante un sofisticatissimo programma informatico (software), è possibile ricostruire al computer l’immagine tridimensionale del tessuto tumorale presente nell’organismo e anche determinarne la vitalità.

Recentemente questo sofisticato e potente strumento tecnologico è stato impiegato precocemente nel corso della malattia come strumento prognostico, per predire cioè con largo anticipo il risultato finale della terapia.

La PET effettuata precocemente si è rivelata uno strumento utile per capire la prognosi del paziente e la sua risposta al trattamento. Nel 90% dei casi è stata infatti in grado di predire l’esito della terapia. Questo ci ha aiutato ad evitare a pazienti che rispondevano bene al trattamento di prima
linea una terapia più aggressiva ed evidentemente dalla maggiore tossicità. Avere a disposizione esami accurati come la PET ed eseguirli precocemente ci aiuta ad adattare la terapia al paziente, caso a caso. Questo esame, effettuato dopo 2 cicli di chemioterapia (PET-2) è stato introdotto nel 2006 nella pratica clinica quotidiana come il principale strumento per predire la risposta finale al trattamento per il linfoma di Hodgkin, e oggi si può considerare una procedura standard nella pratica clinica quotidiana.

Nel 10% dei pazienti però la PET effettuata precocemente nel corso della terapia (interim-PET o PET-2) non è stata in grado di predire l’esito finale del trattamento, per lo più perché alcuni esami PET, che con i criteri tradizionali venivano interpretati come positivi, si sono poi rivelati in realtà negativi, perché in questa piccola frazione di pazienti non si osservava (fortunatamente per il paziente) alcuna ricaduta o progressione della malattia. In altre parole, questi pazienti presentavano esami PET “falsamente positivi”. Molto più raramente si verificava il fenomeno opposto: pazienti con interim-PET negativa dimostravano precocemente una ricaduta o progressione della malattia. In quasi tutti i pazienti con PET falsamente positive, era presente una massa Bulky all’esordio di malattia.

Vi sono rischi aggiuntivi per il paziente che si sottoponga a una PET con acquisizione a due tempi?

Il paziente che si sottopone a una 2P-PET non presenta alcun rischio aggiuntivo rispetto a chi si sottoponga ad una normale PET, sia effettuata durante la stadi azione della malattia, sia durante lo svolgimento della chemioterapia. La dose iniettata di FDG è la stessa e la entità di esposizioni a radiazioni ionizzanti derivanti da un secondo esame PET alla diagnosi è del tutto trascurabile, dal momento che la TAC effettuata contemporaneamente alla PET viene eseguita senza mezzo di contrasto radiografico e a basse energie di irradiazione.

Cosa c’è di innovativo?

Successive osservazioni, effettuate presso la SC di medicina Nucleare dell’Ospedale di Cuneo, permettevano di riconoscere, almeno in alcuni casi, la presenza di PET falsamente positive grazie all’esecuzione di un secondo esame, limitato alle zone dove è presente una massa Bulky, effettuato più tardivamente rispetto allo standard per la PET: anziché un’ora dopo, due ore dopo l’iniezione nel paziente del tracciante PET, il Fluoro-deossi-glucosio (FDG). Questa innovativa tecnica di esecuzione della PET, denominata PET con acquisizione a due punti (Dual point PET scan), in definitiva pare molto più efficace della interim-PET tradizionale nel distinguere le positività false della PET (dovute ad infiammazione dei tessuti) da quelle vere (dovute a persistenza del linfoma).

Negli stessi anni in cui veniva studiata la interim PET, un’altra tecnica radiologica veniva messa a punto: la Risonanza magnetica nucleare pesata per la diffusione (DW-MRI). Anche questa tecnica di immagine, come la PET, si propone di dimostrare la presenza di tessuto tumorale nei linfonodi e negli organi interessati dal linfoma. Il principio sul quale si basa la DW-MRI è diverso da quello della PET: quest’ultima riconosce la presenza di cellule tumorale per la loro tendenza ad accumulare FDG al loro interno, mentre la prima misura la presenza di acqua nei tessuti (grazie ai movimenti spontanei che gli ioni idrogeno hanno all’interno dei tessuti). Il contenuto di acqua è inversamente proporzionale alla quantità di tessuto tumorale presente.
La RMN (Risonanza Magnetico-Nucleare) è una tecnica di immagine che permette di conoscere con estremo dettaglio le strutture anatomiche (in condizioni normali o in caso di malattia) del nostro corpo. Essa si basa sulla possibilità di riconoscere minime onde (frequenze) elettromagnetiche liberate dai protoni da cui è formata la materia vivente, quando questa viene esposta e successivamente esclusa da un campo magnetico generato intorno ad essa. Le forze generate nel campo magnetico fanno sì che i momenti magnetici delle molecole del paziente si allineino alla direzione del campo esterno, inducendo temporanee alterazioni dei nuclei che, quando le onde radio vengono interrotte, ritornano alla normalità dando luogo a segnali che vengono trasmessi a un computer e trasformati in immagini tridimensionali. Questa tecnica fornisce immagini dettagliate non solo del piano trasversale del corpo (cosiddetto "fetta di salame" come la TAC), ma anche dei piani orientati in qualsiasi modo nello spazio (sagittale e frontale), ottimizzando la visualizzazione dell'area corporea in esame. In queste immagini i tessuti si presentano di colore chiaro se ricchi di acqua, a causa dell'abbondante presenza di protoni (elemento basilare dei tessuti biologici) e scuri se ne sono poveri. Essa inoltre ha il vantaggio, rispetto alla TAC di non esporre il paziente ad alcuna radiazione ma solo ad un campo magnetico.

La DW-MRI è stata impiegata con successo come metodica di stadiazione del linfoma. Resta invece da ricercare la possibilità di documentare precoce e precocemente la persistenza di tessuto tumorale nel corso della terapia, come era già stato fatto per la PET. Come precedentemente accennato, la RMN possiede il vantaggio, rispetto alla TAC e alla PET, di non esporre il paziente ad alcuna radiazione. Scopo dello studio è pertanto osservare se la DW-MRI possa fornire le stesse prestazioni della PET per la valutazione precoce della risposta alla terapia, in modo da poter usare, in futuro, questa tecnica al posto della PET, ottenendo i medesimi risultati, con minore impatto sui pazienti.

**A chi viene proposto di partecipare a questo studio?**
Questo studio viene proposto a tutti i pazienti affetti da Linfoma di tipo Hodgkin in stadio precoce, ma con grandi agglomerati di linfonodi interessati dalla malattia (detti masse “Bulky”), che si rivolgono presso questo centro o gli altri centri che fanno parte della rete di ricerca e che rispondono, come Lei, alle caratteristiche richieste dal protocollo dello studio.

**Criteri di inclusione:**
Tutti i seguenti criteri devono essere presenti:
- Diagnosi di linfoma di Hodgkin in accordo con I criteri della classificazione WHO, con l’eccezione del sottotipo a prevalenza linfocitaria.
- Età tra i 18 e i 60 anni
- Stadio I-IIA
- Presenza di grandi masse adenopatiche (bulky), sia nel mediastino che in alter sedi.
- Consenso informato

**Criteri di esclusione:**
- Diabete mellito scompensato (glicemia oltre I 200 mg/dl)
- Sottotipo a prevalenza linfocitaria.
- Gravidanza
- Presenza di pace-maker, protesi o altro materiale metallico impiantato (per il sottostudio DW-MRI).
DONNE IN ETÀ FERTILE E GRAVIDANZA

La gravidanza e l’allattamento figurano tra i criteri di esclusione, in considerazione degli elevati rischi per l’embrione/feto o per il bimbo allattato.

Nel caso Lei sia una donna in età fertile, in accordo con il suo partner e con il suo medico di famiglia deve impegnarsi a prevenire la gravidanza con l’assunzione di estro-progestinici. In caso di gravidanza accertata durante lo svolgimento dello studio, deve impegnarsi ad avvisare immediatamente il medico responsabile della ricerca preso il suo Centro di cura e dovrà interrompere la partecipazione allo studio.

Qual è, in concreto, la proposta che Le viene fatta?

La proposta che Le viene fatta è quella di permetterci di effettuare, in aggiunta alla classica acquisizione delle immagini con l’esame PET classico, un’acquisizione tardiva delle immagini, per approfondire le nostre conoscenze sulla tecnica diagnostica che si sta valutando in questo studio.

Per valutare in maniera scientifica se questa nuova tecnica produce dei reali vantaggi, riducendo la possibilità di risultati che appaiano positivi, nonostante il paziente sia guarito, il metodo più affidabile è quello di osservare, paragonando entrambi gli esami, se c’è una differenza tra i risultati della PET classica e quelli della PET dual point. Per garantire la produzione di risultati affidabili, questo confronto sarà fatto seguendo due regole semplici:

- Lei, così come tutti i/le pazienti che partecipano allo studio, effettuerà tutti gli esami diagnostici attualmente in uso e in più prima di iniziare la terapia ci permetterà di eseguire una seconda “registrazione” delle immagini, dopo due ore dall’iniezione del tracciatore (che le avremo somministrato per la PET classica).
- Nel caso in cui, dopo i primi due cicli di chemioterapia, quando Lei ripeterà tutti gli esami per valutare lo stadio della Su malattia, la PET dovesse risultare ancora positiva, ci permetterà di acquisire nuovamente le immagini “tardive”, per valutare con maggiore precisione se quella “positività” è vera o se è solo un “falso positivo”.

In concreto, se Lei accetta di partecipare alla ricerca:

- riceverà tutte le migliori cure raccomandate e utilizzate nell’attuale pratica clinica per i pazienti con le Sue caratteristiche;
- in più, potrà effettuare un esame aggiuntivo (la PET dual point), massimo due volte (all’inizio dello studio sicuramente e solo in alcune condizioni dopo i primi due cicli di terapia), che può dire con maggiore precisione qual è lo stato della sua malattia.

Le verrà proposto inoltre di sottoporsi a prelievo di sangue, come da regolare procedura, per gli esami di routine per il monitoraggio delle sue condizioni, alla diagnosi, dopo i primi 2 cicli di terapia, alla fine del trattamento e alla visita di controllo dell’anno successivo. In queste occasioni verrà effettuata una valutazione dei maggiori marcatori dell’infiammazione.

Infatti, numerosi studi biologici hanno dimostrato che è importante per la progressione dei tumori l’infiltrazione di cellule infiammatorie. I suoi dati ci aiuteranno a stabilire una relazione tra i mediatori dell’infiammazione e gli aspetti clinici della malattia.

Inoltre, se nel centro a cui afferisce è dotato di una strumentazione tecnologicamente avanzata quale la risonanza magnetico nucleare con tecnica di acquisizione di immagini mediante diffusione, DW-NMR, Le verrà effettuato questo ulteriore esame. Ai tempi descritti di seguito:

2P-HD10

Version 1.0 - November 17th, 2010
- stadiazione iniziale (insieme alla PET)
- Dopo 2 cicli di chemioterapia con schema ABVD (insieme alla PET-2)
- Al termine dell’intero programma (insieme all’ultima PET)

Ad un anno dalla fine della terapia, verrà di nuovo sottoposto a tutti i controlli per verificare il Suo stato di salute e noi raccoglieremo nuovamente i suoi dati.

**Che cosa Le si chiede per partecipare a questo studio?**
Se dovesse decidere di partecipare allo studio, Le chiediamo collaborazione per i seguenti punti:
1) rispetto delle scadenze programmate per gli esami strumentali e per la chemioterapia;
2) segnalazione immediata di qualunque effetto indesiderato;
Le chiediamo inoltre di non partecipare ad altre sperimentazioni, dal momento che potrebbero prevedere percorsi terapeutici e di indagine strumentale diversi e di interpellare il medico responsabile dello studio prima di assumere qualsiasi altro farmaco.
La preghiamo altresì di evitare eccessi alimentari e alcolici.

**Quali sono i suoi diritti?**
La Sua partecipazione a questo studio è volontaria. Lei può rifiutarsi di partecipare allo studio ed avrà in ogni momento il diritto di interrompere la Sua partecipazione senza dover fornire alcuna spiegazione, contattando il medico responsabile dello studio che segue il Suo caso. Se Lei dovesse prendere questa decisione i dati che sono già stati ottenuti non saranno distrutti, ma non verranno raccolti nuovi dati.
Ad ogni modo, il Suo rifiuto a partecipare o la Sua scelta eventuale di ritirarsi dello studio non influenzerà in alcun modo le terapie e le cure di cui necessita.
La sua partecipazione allo studio è completamente gratuita e non comporta alcuna spesa.

**Altre informazioni importanti dello studio**
Gli scopi e le procedure di questa studio sono stati approvati dal Comitato Etico della Struttura Sanitaria a cui fa riferimento il Medico responsabile dello studio, nonché dalle competenti Autorità Sanitarie o dalle Istituzioni da queste delegate.

**Chi analizzerà i dati raccolti?**
Le informazioni e i dati raccolti nel corso dello studio saranno inviati presso il centro di coordinamento dello studio (Consorzio Mario Negri Sud, Santa Maria Imbaro, Chieti). Il personale responsabile dell’analisi statistica avrà accesso ai dati in maniera anonima e non potrà mai associare i risultati alla Sua identità.

**Come viene garantita la riservatezza dei dati raccolti?**
La Sua partecipazione a questo studio rimarrà strettamente confidenziale. Per garantire la riservatezza, tutti i dati relativi al suo schema di terapia ai suoi esami ed ai relativi risultati saranno raccolti ed archiviati con un apposito codice mentre il Suo nome e le altre informazioni che possono identificarlo saranno conservate in un luogo sicuro e con accesso limitato. Solo il medico responsabile dello studio ed i collaboratori da lui indicati ed autorizzati avranno accesso ai suoi dati anagrafici ed ai risultati delle analisi. Queste persone dovranno comunque mantenere stretto riserbo...
e garantire confidenzialità sulle informazioni e sui risultati della ricerca nel rispetto della vigente normativa sulla privacy “Codice in materia di protezione dei dati personali” (Decreto Legislativo n.196/2003),

Sempre ai fini di garantire la riservatezza dei dati, il Medico responsabile della ricerca non includerà nessuna notizia riguardante la Sua partecipazione a questo studio o i risultati delle analisi di laboratorio o strumentali specifiche dello studio nella Sua cartella clinica.

**Come verranno utilizzati i dati derivanti da questo studio?**

I dati che deriveranno da questo studio saranno elaborati esclusivamente a scopi di ricerca scientifica correlati al presente studio. I risultati ottenuti potranno essere presentati a congressi scientifici o essere pubblicati su riviste scientifiche specializzate. In ogni caso, i dati presentati saranno anonimi e aggregati: non saranno cioè presentati dati riferiti a singoli pazienti e comunque non sarà fatto nessun riferimento all’identità dei pazienti.

I dati ottenuti per questo studio, come pure i dati riguardanti la Sua storia clinica sono strettamente confidenziali e sono soggetti alle stesse regole di confidenzialità di tutti i dati medici. Rimangono di esclusiva proprietà del gruppo di ricercatori dello studio 2P-HD-10 e potranno essere utilizzati (in modo del tutto anonoimo) solo a scopi di divulgazione scientifica.

**Quali sono i possibili rischi e disagi derivanti dalla partecipazione a questo studio?**

Non ci sono effetti collaterali nell’esecuzione dell’esame PET dual point, dal momento che non si prevede l’ulteriore iniezione di tracciatore radioattivo, rispetto al normale esame PET che andrebbe ugualmente ad effettuare.

**Quali sono i possibili benefici derivanti dalla partecipazione a questo studio?**

Lei potrebbe non beneficiare direttamente della partecipazione a questo studio, dal momento che l’esito del nuovo esame in discussione non è discriminante per la terapia che deve seguire (che sarà la medesima in ogni caso). Ad ogni modo, con la Sua partecipazione può aiutare altre persone contribuendo alla Ricerca e all’approfondimento delle conoscenze scientifiche sulle tecniche diagnostiche oggi a disposizione. Questo ci permetterà di fare un passo avanti e garantire un’assistenza sempre più specifica ai pazienti che in futuro si troveranno nella Sua condizione (ma con una malattia in stato più avanzato) e per i quali il risultato di quest’esame può essere discriminante nella scelta della terapia da seguire.

**Il medico di famiglia sarà informato circa la partecipazione allo studio?**

Se Lei è d’accordo, può essere utile informare con apposita lettera il Suo medico di famiglia della partecipazione a questo studio, al fine di evitare interferenze con eventuali altri farmaci che potrebbe prescriverle o con trattamenti a cui potrebbe sottoporla.

**Chi si farà carico di eventuali conseguenze legate alla partecipazione allo studio?**

Secondo quanto previsto dalle regole vigenti per gli studi osservazionali come questo, non è necessaria un’assicurazione per i pazienti che decidano di partecipare, dal momento che nessun aspetto di questa ricerca implica un danno o un rischio a carico dei pazienti.
Nell’ambito di questo studio ci si limita ad osservare le capacità della tecnica diagnostica oggetto di studio, per poter dire se effettivamente (contando sui risultati ottenuti dai Suoi dati e da quelli dei pazienti che come Lei sceglieranno di aderire allo studio) è più specifica e precisa rispetto a quella classica.

**È previsto un finanziamento dello studio?**

Lo studio è condotto dal gruppo di ricercatori 2P-HD-10 in maniera autonoma rispetto all’industria farmaceutica sia nella ideazione che nello svolgimento sia, soprattutto, nell’analisi e nella utilizzazione dei dati e sono garantite le finalità esclusivamente scientifiche e mediche dello studio.

**Che cosa deve fare per partecipare?**

La invitiamo a rivolgere ogni domanda che ritenesse opportuna al Medico responsabile della ricerca, che Le fornirà tutti i chiarimenti richiesti. Il Medico Le chiederà anche di firmare e datare il Modulo di Consenso informato per confermare che Lei ha letto tutte le informazioni qui contenute, che ha compreso gli scopi della ricerca, i benefici futuri che potrebbero derivarne e che infine ha dato liberamente il Suo consenso a parteciparvi.

L'originale dell'atto di Consenso Informato Scritto da Lei firmato verrà conservato presso l'archivio dell'ospedale, mentre a Lei ne rimarrà una copia.
Appendice II

(CARTA INTESTATA DEL CENTRO PARTECIPANTE)

Modulo per il consenso informato
(Studio Principale 2P-HD-10)

Informativa e consenso ai sensi del D. Lgs.196 del 30/06/03

STUDIO DELLA INTERIM-PET CON ACQUISIZIONE A DUE TEMPI, EFFETTUATA DURANTE IL TRATTAMENTO CON ABVD IN PAZIENTI AFFETTI DA LINFOMA DI HODGKIN IN STADIO LIMITATO E CON LESIONI LINFOGHIANDOLARI “BULKY”.

Parte riservata al Paziente
Nome ______________________  Cognome __________________

DICHIARO:
• di essere stato informato/a sugli scopi e le terapie proposte dal presente studio;
• di aver compreso le informazioni contenute nel “Foglio illustrativo per il paziente”;
• di avere avuto l’opportunità di porre domande, a cui mi è stata data una risposta;
• di aver compreso che la mia partecipazione è del tutto volontaria;
• di essere consapevole di poter uscire dal protocollo per mia volontà, in qualsiasi momento e per qualsiasi ragione.

firma __________________________________________

ACCONSENTO a partecipare a questo studio
________________ ______________________     _______________________________________
luogo   data      firma

 ☐ ACCONSENTO   ☐ NON ACCONSENTO

che il mio medico venga informato.

firma __________________________________________

ACCONSENTO alla raccolta, gestione e trattamento dei miei dati personali esclusivamente per fini statistici, alla comunicazione degli stessi dati alle competenti Autorità Regolatorie mediante accesso diretto alla cartella clinica, ed al trasferimento all’estero, ove ciò sia richiesto, essendomi stato assicurato che queste informazioni saranno da considerare riservate e quindi gestite in accordo al Decreto legislativo 30/06/2003 n 196 e Decreto del Ministro della Sanità del 15/7/1997

_________________   ______________________
Parte riservata al Medico

Nome _________________  Cognome _________________

Confermo di aver spiegato il trattamento proposto, i possibili rischi e benefici e le opzioni terapeutiche disponibili in termini, secondo il mio giudizio, comprensibili.

data __________________

firma del medico ______________________________
NOTA INFORMATIVA AL PAZIENTE IN TUTELA DELLA RISERVATEZZA DEI PROPRI DATI PERSONALI

Informativa e manifestazione del consenso al trattamento dei dati personali
(Deliberazione n. 52 del 24 luglio 2008)

Titolari del trattamento e relative finalità
Il Centro di sperimentazione ________________________________________ e il Gruppo di Investigatori 2P-HD-10, rappresentato dalla S.C. di Ematologia dell’Azienda Ospedaliera S.Croce e Carle di Cuneo, che ha commissionato lo studio che Le è stato descritto, ciascuno per gli ambiti di propria competenza e in accordo alle responsabilità previste dalle norme della buona pratica clinica (d.l. 211/2003), tratteranno i Suoi dati personali, in particolare quelli sulla salute e, soltanto nella misura in cui sono indispensabili in relazione all'obiettivo dello studio, altri dati relativi al Suo stato demografico e ai Suoi stili di vita, esclusivamente in funzione della realizzazione dello studio e a fini di farmacovigilanza.
A tal fine i dati indicati saranno raccolti dal Centro di Sperimentazione e trasmessi al Laboratorio di Epidemiologia Clinica delle malattie Cardiovascolari del (CMNS - Consorzio Mario Negri Sud - sito in via Nazionale 8/A 66030 S. Maria Imbaro, Chieti) diretto dal Roberto Marchioli.

Natura dei dati
Il medico che La seguirà nello studio La identificherà con un codice: i dati che La riguardano raccolti nel corso dello studio, ad eccezione del Suo nominativo, saranno trasmessi al CMNS, registrati, elaborati e conservati unitamente a tale codice, alla Su data di nascita, al sesso e a tutte le informazioni indicate in precedenza. Soltanto il medico e i soggetti autorizzati potranno collegare questo codice al Suo nominativo.

Modalità del trattamento
I dati, trattati mediante strumenti anche elettronici, saranno diffusi solo in forma rigorosamente anonima, ad esempio attraverso pubblicazioni scientifiche, statistiche e convegni scientifici. La Su partecipazione allo studio implica che, in conformità alla normativa sulle sperimentazioni cliniche dei medicinali, il personale della S.C. di Ematologia dell’ospedale S.Croce e Carle o del CMNS, il Comitato Etico e le autorità sanitarie italiane e straniere potranno conoscere i dati che La riguardano, contenuti anche nella Su documentazione clinica originale, con modalità tali da garantire la riservatezza della Su identità.

Esercizio dei diritti
Potrà esercitare i diritti di cui all'art. 7 del Codice (es. accedere ai Suoi dati personali, integrarli, aggiornarli, rettificarli, opporsi al loro trattamento per motivi legittimi, ecc.) rivolgendosi direttamente al centro di sperimentazione (Dott ___________ Indirizzo ___________) o, per il suo tramite, al promotore dello studio.
Potrà interrompere in ogni momento e senza fornire alcuna giustificazione la Su partecipazione allo studio: in tal caso non saranno raccolti ulteriori dati che La riguardano, ferma restando l'utilizzazione di quelli eventualmente già raccolti per determinare, senza alterarli, i risultati della ricerca.

Consenso
Sottoscrivendo tale modulo acconsento al trattamento dei miei dati personali per gli scopi della ricerca nei limiti e con le modalità indicate nell'informativa fornitami con il presente documento

Nome e Cognome dell'interessato (in stampatello) ______________________
Firma dell'interessato ______________________
Data ______________________
Appendice III

(CARTA INTESTATA DEL CENTRO PARTECIPANTE)

Modulo per il consenso informato
(sotto-studio DW-MRI del protocollo 2P-HD-10)
Informativa e consenso ai sensi del D. Lgs.196 del 30/06/03

STUDIO DELLA RISONANZA MAGNETICA NUCLEARE CON TECNICA DI DIFFUSIONE, ASSOCIATA ALLA INTERIM-PET EFFETTUATA DURANTE IL TRATTAMENTO CON ABVD IN PAZIENTI AFFETTI DA LINFOMA DI HODGKIN IN STADIO LIMITATO E CON LESIONI LINFOGHIANDOLARI “BULKY”.

Parte riservata al Paziente

Nome ______________________  Cognome __________________

DICHIARO:
- di essere stato informato/a sugli scopi e le terapie proposte dal presente studio;
- di aver compreso le informazioni contenute nel “Foglio illustrativo per il paziente”;
- di avere avuto l’opportunità di porre domande, a cui mi è stata data una risposta;
- di aver compreso che la mia partecipazione è del tutto volontaria;
- di essere consapevole di poter uscire dal protocollo per mia volontà, in qualsiasi momento e per qualsiasi ragione.

firma __________________________________________

ACCONSENTO a partecipare a questo studio

__________________   _____________________     _______________________________________
luogo   data      firma

☐ ACCONSENTO   ☐ NON ACCONSENTO
che il mio medico venga informato.

firma __________________________________________

ACCONSENTO alla raccolta, gestione e trattamento dei miei dati personali esclusivamente per fini statistici, alla comunicazione degli stessi dati alle competenti Autorità Regolatorie mediante accesso diretto alla cartella clinica, ed al trasferimento all’estero, ove ciò sia richiesto, essendomi stato assicurato che queste informazioni saranno da considerare riservate e quindi gestite in accordo al Decreto legislativo 30/06/2003 n 196 e Decreto del Ministro della Sanità del 15/7/1997.

__________________   _____________________
luogo   data
Parte riservata al Medico

Nome _________________  Cognome __________________

Confermo di aver spiegato il trattamento proposto, i possibili rischi e benefici e le opzioni terapeutiche disponibili in termini, secondo il mio giudizio, comprensibili.

data __________________

firma del medico ______________________________
APPENDIX IV:  
LETTERA PER IL MEDICO CURANTE

Caro Collega,

con la presente ti segnalo che il/la tuo/a assistito/a sig./sig.ra ....................................................... È stato/a incluso/a nello studio osservazionale dal titolo “Interim PET con studio di acquisizione a due tempi (2P-PET) effettuata dopo 2 cicli di chemioterapia con ABVD nel Linfoma di Hodgkin in stadio limitato con lesioni linfonodali “bulky” – 2P-HD10”. Desidero quindi informarti su quelle che sono le caratteristiche di tale studio.

Esso è rivolto a raccogliere dati che permettano di fornire una risposta al seguente quesito clinico:

- è possibile migliorare la specificità della PET sulla risposta finale alla terapia nella malattia di Hodgkin in stadio Precoce (I e IIA) e con grosse masse linfonodali (Malattia bulky), mediante una modificazione nella tecnica di esecuzione della PET, (acquisendo le immagini in 2 tempi: tempo standard e tempo tardivo)?

Accanto al predetto studio, viene proposto, per i centri dotati di Risonanza Magnetico-Nucleare con ricostruzione delle immagini con tecnica pesata sulla diffusione (DW-MRI), un sotto-studio “ancillare” con DW-MRI effettuata alla diagnosi e dopo 2 cicli di chemioterapia. Dal momento che la seconda tecnica non è basata su immagini ottenute con radiazioni ionizzanti, seppure a basse dosi, ma su immagini generate da un campo magnetico, la seconda tecnica potrebbe avere il vantaggio di non esporre il paziente a radiazioni. Il sotto-studio DW-MRI è volto a raccogliere dati utili a fornire una risposta al seguente quesito:

- È possibile avere lo stesso valore predittivo della PET sulla risposta finale al trattamento con una tecnica di Risonanza Magnetico Nucleare (meno costosa e non basata su somministrazione di radiofarmaci)?

Entrambi i quesiti verranno valutati in uno studio osservazionale prospettico e multicentrico, in cui la PET svolge un ruolo “non decisionale” (la terapia non viene modificata sulla base del risultato della interim PET). I pazienti affetti da linfoma di Hodgkin in stadio precoce (I e IIA) e con voluminosa malattia adenopatica (malattia “bulky”), verranno trattati secondo lo stato dell’arte e con la terapia oggi ritenuta golden standard: 4 cicli di chemioterapia con ABVD, seguiti da irradiazione sulla massa adenopatica bulky. I pazienti verranno sottoposti a stadiazione iniziale con CT, PET (con procedura standard e con doppia acquisizione (dual-point) dopo 60’ e 120’ dalla iniezione di FDG e per i centri che potranno aderire al sotto-studio, con Risonanza Magnetico Nucleare. Dopo 2 cicli di chemioterapia i pazienti verranno “ristudiati” con 2P-PET e Risonanza Magnetico-Nucleare (sotto-studio DW-MRI). Qualunque sia l’esito della PET i
pazienti proseguono con il trattamento standard per gli stadi iniziali con altri 2 ABVD, seguiti dalla radioterapia. Una CT effettuata al termine della chemioterapia insieme ad una PET standard verrà effettuata per sapere se i pazienti stanno rispondendo (se ottengono cioè una remissione completa “CR” o una remissione parziale “PR”), e quindi, al termine della chemioterapia, procedono alla radioterapia. Se, viceversa, i pazienti, valutati con i criteri radiologici/funzionali standard non ottengono una CR o una PR (se cioè sono resistenti alla chemioterapia), escono dallo studio e sono trattati con alte dosi di chemioterapia seguite da autotrasplantato. Al termine dello studio si vedrà il valore predittivo della 2P-PET nei confronti della PET tradizionale. Nel sotto-studio DW-MRI, si valuterà il valore predittivo della DW-MRI nei confronti della PET tradizionale e si vedrà inoltre il contribuito della risonanza magnetico nucleare alla stadiazione. Il numero previsto di pazienti da arruolare nello studio è di 150 soggetti. Tali pazienti saranno arruolati nei diversi centri clinici appartenenti alla Fondazione Italiana Linfomi (FIL) e ad altri gruppi cooperatori Europei.

Ringraziandoti per la tua collaborazione rimango a tua disposizione per ogni chiarimento o problema nella gestione del paziente.

Data, ............

Firma, ............................................................
APPENDIX V: Baseline staging evaluation form for PET, CT and DW-MRI scans

The following anatomical regions will be used to compare baseline staging with FDG-PET scan and DW-MRI scan. Results will be expressed in terms of sensitivity, specificity and overall accuracy of the DW-MRI as compared with FGC-PET/CT scan, considered as the “golden standard” procedure.
Midollo: ........................ ID .................
Milza: ........................ SUVMax ............ sede ......
Scheletro: ...... ...... ...... Bulky cm .......... sede ......
Polmone: ........................ Stadio PET: .................
Fegato: ......................
.......................... Caso interessante ..........
**Legenda sedi nodali:**
1) Laterocervicale dx alto
2) Laterocervicale dx basso
3) Laterocervicale sin alto
4) Laterocervicale sin basso
5) Sovracleare dx (+infraclaveare)
6) Sovracleare sin
7) Ascellare dx
8) Ascellare sin
9) Mediastino sup.dx
10) Mediastino sup.sin.
11) Mediastino anter. sup
12) Ilo polmonare dx.
13) Ilo polmonare sin.
14) Mediastino inf.dx
15) Mediastino anter. Inf.
16) Mediastino inf. sin
17) Addominali sup. dx (+ mesenterici)
18) Addominali sup. sin (+ splenici)
19) Addominali inf. dx
20) Addominali inf. sin
21) Iliaci comuni esterni dx.
22) Iliaci comuni esterni sin.
23) Pelvici (+ presacrali)
24) Inguinali dx
25) Inguinali sin.
26) ..................
27) ..................

**Lesione nodale:** Lesione focale = 2 slice; uptake > background circostante, non attribuibile ad una sede fisiologica di captazione i presenza di un corrispettivo nelle immagini CT

**Massa bulky:** massa = 10 cm su immagine TC in qualsiasi sede (isolata o conglobata)

**Midollo:** No anormalità nella CT associata alla PET
A. Lesione focale = 2 slice; uptake > fegato (SUVMax...)
B. Captazione omogenea diffusa limitata allo scheletro assile e alle porzioni prossimali appendicolari; uptake > fegato
C. Captazione omogenea diffusa a tutto lo scheletro e alla milza; uptake > fegato; milza > fegato
D. Captazione omogena diffusa; uptake < fegato; milza < fegato; no lesioni focali

**Milza:**
A. Lesione focale = 2 slice; SUVMax e Dimensioni milza (asse trasverso)
B. Captazione aumentata in modo diffuso; uptake > fegato; uptake midollo < fegato; SUVMax e dimensioni milza (asse trasverso)
C. Captazione aumentata in modo diffuso; uptake > fegato; uptake midollo = fegato. SUVMax e dimensioni milza (asse trasverso)
D. Captazione diffusa = fegato; dimensioni milza (asse trasverso)

**Schelretro:** anormalità nella CT associata alla PET
A. Lesione focale = 2 slice; uptake > fegato; SUVMax e tipo di lesione (osteolitica – osteo addensante)
B. No lesioni

**Polmone:**
A. Lesione focale = 2 slice; uptake = fegato in corrispondenza di lesione TC; dimensioni.
B. Lesione focale = 2 slice; uptake < fegato; dimensioni
C. No lesioni

**Fegato:**
A. Lesione focale = 2 slice; uptake > fegato
B. No lesioni
APPENDIX VI : PET SCANNING

Preacquisition procedure

- Patients are not allowed to consume any food or sugar for at least 6 h prior to the start of the PET study. Parenteral nutrition and intravenous fluids containing glucose should be discontinued at least 4 h before the PET examination.

- Adequate pre-hydration is mandatory before FDG administration and scanning (1 litre of water in the 2 hours prior the injection; half a litre of water in the hour before the scan begins).

- All patients must avoid (extreme) exercise for at least 6 h before the PET study (for example, they must not cycle to the hospital).

- During the injection of FDG and the subsequent uptake phase the patient should remain seated or recumbent and silent to minimize FDG uptake in muscles. The patient should be kept warm in the 30–60 min before the injection of FDG and throughout the following uptake period and PET examination to minimize FDG accumulation in the brown fat.

- The FDG PET study can be performed only if plasma glucose level is <8 mmol/l ( <140 mg/dl).

- For type II diabetes mellitus patients, the PET study should preferably be performed late in morning; patients continue to take oral medication observing fasting rules as described above. For type 1 diabetes mellitus patients, the PET study should be scheduled for late morning: patients should have a normal breakfast at 7.00 a.m. and then should assume the normal amount of the prescribed insulin. Thereafter the patient should not consume any more food or fluids, apart from the prescribed amount of water.

- The recommended interval between FDG administration and the start of acquisition is 60±10’ min.

- FDG activities to be administered are based on a fixed scan duration of 3 min per bed in 3D or 4 min per bed in 2D assuming an injected activity of 3.7 MBq/kg body weight (±10%).

- All studies of the same patients (baseline, interim, pre-RT and final PETs) will be injected with the same dose ±10%.

- Patients are invited to void bladder or reservoirs 5 minutes prior the beginning of the scan.

acquisition protocol

- A standard ‘whole-body’ scan should cover the part of the body from the skull base to mid-femora. The patient should be positioned with the arm elevated over the head to avoid beam
hardening artifacts as well as artifacts caused by truncation of the field of view. For the
examination of head and neck region, a two step protocol is recommended (head and neck
portion and from the apex of the lung through mid thigh) with the appropriate acquisition
and reconstruction parameters adapted for the protocol. All the studies of the same patients
(baseline, interim, pre-RT and final PETs) will be acquired in the same position as baseline.
- CT acquisition parameter: the same used in clinical routine practice by each participating
centre. In order to reduce the added dose to the patient consequent to the delayed baseline
and interim WB scan (related only to the CT part of both studies) it should be preferable to
reduce the amperage of the delayed CT acquisition (120 min). A dosimetric estimation of
the added effective dose deriving from the dual time acquisition protocol is reported in the
Addendum.
- PET images reconstruction has to be performed with iterative algorithm and attenuation,
scatter and random correction. Other parameters of images reconstruction as number of
iterations, subsets, matrix size (128 or 256) and image filtering will be chosen by each single
centre according its own clinical experience. Each study will be performed with the same
acquisition/processing parameters. PET centre that use reconstruction algorithm using point
spread function recovery for correcting partial volume effects should discuss this issue with
the coordinating PET centre (Cuneo).
- If any of the above parameter will be changed along the time of the study coordinating PET
centre (Cuneo) must be informed as soon as possible before preceding with further patients
enrolment. The same will be done if an upgrade of PET/CT scanner potentially affecting
SUV calculation will be performed.
- All the studies (baseline, interim, pre-RT and final PETs should be performed using the
same PET/CT system

**timing of PET scanning**
- Interim PET/CT after 2 ABVD should be acquired between 10 an 13 days after the end of
treatment;
- Restaging PET/CT after 4 ABVD should be acquired no earlier than 15-20 days after the
end of the 4 ABVD;
- Final restaging should be acquired no earlier than 12 weeks after the end of radiotherapy

**dual point specific protocol**
- In baseline PET/CT a late whole-body scan acquisition should be performed 120±10’ after the injection of the tracer.
- In interim PET/CT, after 2 ABVD cycles, a late partial-body acquisition should be performed 120±10’ after the injection of the tracer. Partial-body acquisition should be performed from the area of positive residual foci showing an uptake equal or higher than mediastinum (Deauville score 2-5) to encompass the liver.
- In both late scan:
  - 1) the patients has to be kept fasting and in rest condition
  - 2) late images should be acquired in the same position as early images
  - 3) the bed acquisition time of the late images will be increased by a factor 1.3 to compensate for the loss in count rate due to the decay

**interpretation protocol by the local centre**
- Baseline PET/CT will be analysed according to standard criteria taking into account all the clinical information available (biopsy, infection, etc.). The generally used definition of a positive (abnormal) PET finding should be made by visual assessment considering focal or diffuse FDG uptake above local background in a location incompatible with normal anatomy/physiology or with unspecific uptake (brown fat, left ventricle and heart structure, stomach and intestinal uptake, muscle, etc.).
- For the purpose of this study bone marrow/bone or spleen involvement were defined in presence:
  a) of a focal skeletal uptake with an activity higher than liver uptake, present in two or more consecutive slides with or without abnormalities on CT. In presence of such an abnormality RM correlation is mandatory in order to confirm bone/bone marrow involvement whatever the CT results.
  b) focal/multifocal spleen uptake with an activity higher than local spleen uptake or enlarged spleen with an homogeneous diffuse uptake higher than the liver uptake in presence of normal bone marrow uptake
- New lesion in interim PET/CT after 2 ABVD, at a different sites from disease in baseline, usually is not related to lymphoma except in cases with a clear evidence of disease progression at other sites.
- Interpretation and reporting of all studies will be done according to the local standard

**interpretation protocol by the reviewer**
- All studies, independently from the local interpretation, will be uploaded in the web site [https://magic5.to.infn.it](https://magic5.to.infn.it) for the reviewing process

- All five reviewers review independently all the studies submitted, without knowledge of clinical status; the main parameters will be evaluated as follows

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Interim after 2 ABVD</th>
<th>Interim after 4 ABVD</th>
<th>End of therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>60’</td>
<td>120’</td>
<td>60’</td>
<td>60’</td>
</tr>
<tr>
<td>Stage Score Dimension</td>
<td>Stage Score</td>
<td>Score Dimension</td>
<td>Score Dimension</td>
<td>Score Dimension</td>
</tr>
<tr>
<td>SUVmax - lesion</td>
<td>SUVMax - lesion</td>
<td>SUVmax - lesion</td>
<td>SUVmax - lesion</td>
<td>SUVmax - lesion</td>
</tr>
<tr>
<td>- liver</td>
<td>- liver</td>
<td>- MBP</td>
<td>- MBP</td>
<td>- MBP</td>
</tr>
</tbody>
</table>

**Qualitative analysis**

1. The score of the lesion was determined according to the Deauville 5 point scale.
2. Score 5 should read uptake >> liver and/or new lesions
3. New focal uptake/new lesions. Two possibilities exists:
   - new lesion at a different sites from disease, probably NOT lymphoma \(\rightarrow\) score 1
   - new lesion at a different sites from disease with a clear evidence of disease progression at other sites \(\rightarrow\) score 5
4. Diffuse uptake in spleen or marrow on the interim scan is most likely due to chemotherapy and should be scored as no disease especially if growth factors have been used (even if focal uptake is present at baseline).
5. Focal uptake in marrow can be scored as no disease if there is reduced uptake at sites where there was disease on baseline (due to marrow ablation) and increased uptake at sites with no disease at baseline (due to chemotherapy effect). This means that uptake on the interim scan may be like a ‘mirror’ of the uptake on the baseline scan
6. Tonsillar uptake on interim scan if it reduces to physiologic levels is regarded as no disease (HL much less likely to have tonsillar involvement than NHL anyway)
**SUV analysis**

1. **baseline**: the five most active lesion who are representative of the whole patient are identified in the early images (the number of lesion to be measured will be decided after consensus between reviewer); SUVMax is calculated in transaxial slices taking into account the higher value of SUVMax of the entire lesions, drawing a large ROI enclosing the entire lesion. The SUVMax after 120’ is measured in the same lesion and in the same way as performed after 60’.

2. **interim after 2 ABVD**: SUVMax is calculated taking into account the higher value of SUVMax of the entire lesions, drawing a large ROI enclosing the entire lesion. The SUVMax after 120’ is measured in the same lesion and in the same way as performed after 60’.

3. **after 4 ABVD and end of study**: SUVMax is calculated taking into account the higher value of SUVMax of the entire lesions, drawing a large ROI enclosing the entire lesion.

4. it is necessary to measure SUVMax of the lesion in baseline if residual lesion after 2 ABVD or later studies were not measured.

5. SUVMax of the liver (transaxial slices) will be measured using a large ROI (5 pixel or more) in all the studies (if possible in the same location).

6. SUVMax of the MBPS (aortic ROI in transaxial slice) will be measured using a small 2-3 pixel ROI (pixel with high activity should be excluded).

**Addendum**

**Dosimetric evaluation.**

In this protocol a second delayed PET/CT acquisition is scheduled for all the patients at baseline and for those showing a residual foci uptake higher or equal than mediastinum (score 2 or more, about 35% of patients). Considering the addiction of a second CT scan, an estimation of the dose to the patient has been performed.

**Hypothesis for calculation**

- Effective Internal Dose due to 18F-FDG administration according ICRP publication n° 103 (2007)
- External Dose due to CT according CT-Expo V 1.5 (2005) and ImPACT CT patient dosimetry calculator V 1.0.2 (2009); in table 2 the maximal values obtained according the two calculation systems is reported.
- Scanner PET/CT: GE Discovery 600 (16 slices CT scanner)
Acquisition Protocol

For any phase of the protocol, each component of the studies addicting effective dose to the patient is named “Modality”

Phase: Baseline PET/CT
- Modality 1 = 10 mCi 18F-FDG
- Modality 2 = CT total body at 60 min. after tracer admin.
- Modality 3 = CT total body at 120 min. after tracer admin.

Phase: Interim PET/CT
- Modality 4 = 10 mCi 18F-FDG
- Modality 5 = CT total body at 60 min. after tracer admin.
- Modality 6 = CT including residual mass and liver (2 PET FOV) at 120 min. from after admin.

In table 1 CT acquisition parameters for each CT scan are reported.

Table 1- CT acquisition parameter

<table>
<thead>
<tr>
<th>Modality</th>
<th>Acq. Mode</th>
<th>Bean collimation</th>
<th>Pitch</th>
<th>Voltage (kV)</th>
<th>Amperage (mA)</th>
<th>mAs</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>Helical</td>
<td>10 mm (16x0.625)</td>
<td>1.375:1</td>
<td>120</td>
<td>60</td>
<td>48</td>
</tr>
<tr>
<td>3</td>
<td>Helical</td>
<td>10 mm (16x0.625)</td>
<td>1.375:1</td>
<td>120</td>
<td>30</td>
<td>24</td>
</tr>
<tr>
<td>5</td>
<td>Helical</td>
<td>10 mm (16x0.625)</td>
<td>1.375:1</td>
<td>120</td>
<td>60</td>
<td>48</td>
</tr>
<tr>
<td>6</td>
<td>Helical</td>
<td>10 mm (16x0.625)</td>
<td>1.375:1</td>
<td>120</td>
<td>30</td>
<td>24</td>
</tr>
</tbody>
</table>

Table 2 - Summary of estimated dose to the patient for each modality.

<table>
<thead>
<tr>
<th>Modality</th>
<th>Effective Dose (mSv)</th>
<th>Contribution (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7</td>
<td>23.6</td>
</tr>
<tr>
<td>2</td>
<td>5.9</td>
<td>19.9</td>
</tr>
<tr>
<td>3</td>
<td>3</td>
<td>10.1</td>
</tr>
<tr>
<td>4</td>
<td>7</td>
<td>23.6</td>
</tr>
<tr>
<td>5</td>
<td>5.9</td>
<td>19.9</td>
</tr>
<tr>
<td>6</td>
<td>0.9</td>
<td>3.0</td>
</tr>
<tr>
<td>Total</td>
<td>29.7</td>
<td>100</td>
</tr>
</tbody>
</table>
Modality 3 and 6 are the added low amperage CT scan performed in the delayed PET/CT studies; overall, they account for 3.9 mSv added to the patient, corresponding to 13.1% of the total dose administered to the patient enrolled in the study. In standard clinical condition, performing modality 1+2+4+5, the estimated total dose to the patient is 25.8 mSv. That means an increase of 15.1% of effective dose for the patients enrolled in the protocol in comparison to standard clinical condition. We have to consider that effective dose can change in function of the technical characteristics of the scanner and the acquisition parameter of CT scan.

SUV data and CT parameters
In order to assess the possible variation of SUVMax in function of the different CT amperage (from 20 to 100 mA) used for attenuation correction map, a PET NEMA IQ phantom has been acquired (hot spheres/background ratio = ratio 4:1) with various CT amperage values; PET images have been reconstructed with attenuation correction map of each CT amperage and the SUV of hot sphere has been calculated.

In table 3 the results of the SUVmax test are reported.

<table>
<thead>
<tr>
<th></th>
<th>SUVmax</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>20 mA</td>
</tr>
<tr>
<td>Sphere 1 (37 mm)</td>
<td>4.1</td>
</tr>
<tr>
<td>Sphere 2 (28 mm)</td>
<td>4</td>
</tr>
<tr>
<td>Sphere 3 (22 mm)</td>
<td>3.8</td>
</tr>
<tr>
<td>Sphere 4 (17 mm)</td>
<td>3</td>
</tr>
<tr>
<td>Sphere 5 (13 mm)</td>
<td>2.3</td>
</tr>
<tr>
<td>Sphere 6 (10 mm)</td>
<td>1.6</td>
</tr>
</tbody>
</table>

There was not found significant differences among the SUVMax value obtained in the same sphere with different amperage value.
Appendix VII: ABVD Chemotherapy schedule

Chemotherapy will be given according to the classical ABVD schedule. No dose reduction is planned for cycle 1 and 2. G-CSF (either Lenograstim or Filgrastin) could be given according to the policy of the single clinical center.

<table>
<thead>
<tr>
<th>Farmaco</th>
<th>dose mg/mq</th>
<th>Via</th>
<th>giorni</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Adriamicina</td>
<td>25</td>
<td>Ev</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Bleomicina</td>
<td>10</td>
<td>Ev</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Vinblastina</td>
<td>6</td>
<td>Ev</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>Dacarbazina</td>
<td>375</td>
<td>Ev</td>
<td>*</td>
<td>*</td>
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</tbody>
</table>

Ciclo ripetuto ogni 28 giorni

After the 2nd cycle dose reduction could be allowed according to the following schedule.

<table>
<thead>
<tr>
<th>Neutrofili</th>
<th>Piastrine</th>
<th>%</th>
<th>Farmaci</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 1.500</td>
<td>&gt;100</td>
<td>100 %</td>
<td>Tutti</td>
</tr>
<tr>
<td>1.499-1.000</td>
<td>99-70</td>
<td>100 %</td>
<td>Blm, Adm, Vbl</td>
</tr>
<tr>
<td></td>
<td></td>
<td>75 %</td>
<td></td>
</tr>
<tr>
<td>&lt; 1.000</td>
<td>&lt;70</td>
<td>rinvio 3-4 gg.</td>
<td>Tutti</td>
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</table>

Riduzione delle dosi per tossicità ematologica (esclusi i cicli 1 e 2)
## APPENDIX VIII - Participating centers

<table>
<thead>
<tr>
<th>Centre</th>
<th>Centre Name</th>
</tr>
</thead>
<tbody>
<tr>
<td>1)</td>
<td>AO SS Antonio e Biagio e C. Arrigo</td>
</tr>
<tr>
<td>2)</td>
<td>Azienda Ospedaliera Universitaria - Umberto I</td>
</tr>
<tr>
<td>3)</td>
<td>Centro Riferimento Oncologico - IRCCS</td>
</tr>
<tr>
<td>4)</td>
<td>Azienda Ospedaliera Ospedali Riuniti</td>
</tr>
<tr>
<td>5)</td>
<td>Ospedale Ferrarotto</td>
</tr>
<tr>
<td>6)</td>
<td>Azienda Ospedaliera dell'Annunziata</td>
</tr>
<tr>
<td>7)</td>
<td>ASO &quot;S. Croce e Carle&quot;</td>
</tr>
<tr>
<td>8)</td>
<td>Azienda Ospedaliera Universitaria Ospedali Riuniti</td>
</tr>
<tr>
<td>9)</td>
<td>Azienda Ospedaliera Universitaria S. Martino</td>
</tr>
<tr>
<td>10)</td>
<td>Ospedale &quot;S. M. Goretti&quot;</td>
</tr>
<tr>
<td>11)</td>
<td>Hospital 12 de Octubre</td>
</tr>
<tr>
<td>12)</td>
<td>Azienda Ospedaliera Ospedali Riuniti Papardo</td>
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<tr>
<td>13)</td>
<td>Ospedale dell'Angelo</td>
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<tr>
<td>14)</td>
<td>Istituto San Raffaele</td>
</tr>
<tr>
<td>15)</td>
<td>Azienda Ospedaliera Universitaria</td>
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<tr>
<td>16)</td>
<td>Azienda Ospedaliera San Gerardo</td>
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<tr>
<td>17)</td>
<td>Azienda Ospedaliera Universitaria Federico II</td>
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<tr>
<td>18)</td>
<td>Ospedale Umberto I</td>
</tr>
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<td>19)</td>
<td>Ospedale San Carlo</td>
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<tr>
<td>20)</td>
<td>Azienda Ospedaliera Bianchi-Melacrino-Morelli</td>
</tr>
<tr>
<td>21)</td>
<td>Azienda Ospedaliera Arcispedale S. Maria</td>
</tr>
<tr>
<td>22)</td>
<td>IRCCS/Centro Riferimento Oncologico della Basilicata</td>
</tr>
<tr>
<td>23)</td>
<td>Azienda Ospedaliera &quot;S. Camillo - Forlanini&quot;</td>
</tr>
<tr>
<td>24)</td>
<td>Policlinico Tor Vergata</td>
</tr>
<tr>
<td>25)</td>
<td>Policlinico Universitario Campus Bio-Medico</td>
</tr>
<tr>
<td>26)</td>
<td>Azienda Ospedaliera S. Giovanni - Addolorata</td>
</tr>
<tr>
<td>27)</td>
<td>Centro Poliagnostico</td>
</tr>
<tr>
<td>28)</td>
<td>Ospedale &quot;Casa Sollievo della Sofferenza&quot;</td>
</tr>
<tr>
<td>29)</td>
<td>Azienda Ospedaliera S. Giovanni Battista</td>
</tr>
<tr>
<td>30)</td>
<td>Ospedale &quot;G. Panico&quot;</td>
</tr>
<tr>
<td>31)</td>
<td>Azienda Ospedaliera Universitaria Integrata Verona</td>
</tr>
</tbody>
</table>
APPENDIX IX: Form for Inflammation markers evaluation to be used for each time-point.

<table>
<thead>
<tr>
<th>ENDPOINT</th>
<th>NORMAL VALUES</th>
<th>PATIENT VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESR</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CRP</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ferritin</td>
<td>Male</td>
<td></td>
</tr>
<tr>
<td>Transferrin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fibrinogen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alpha – 2 globulins</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*(timing: baseline, interim staging, second restaging, final restaging)*
APPENDIX X. DECLARATION OF HELSINKI

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI
Ethical Principles for Medical Research Involving Human Subjects
Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by
the
29th WMA General Assembly, Tokyo, Japan, October 1975
35th WMA General Assembly, Venice, Italy, October 1983
41st WMA General Assembly, Hong Kong, September 1989
48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000
Note of Clarification on Paragraph 29 added by the WMA General Assembly, Washington
2002
Note of Clarification on Paragraph 30 added by the WMA General Assembly, Tokyo 2004

A. INTRODUCTION
1. The World Medical Association has developed the Declaration of Helsinki as a statement
of ethical principles to provide guidance to physicians and other participants in medical
research involving human subjects. Medical research involving human subjects includes
research on identifiable human material or identifiable data.

2. It is the duty of the physician to promote and safeguard the health of the people. The
physician's knowledge and conscience are dedicated to the fulfilment of this duty.

3. The Declaration of Geneva of the World Medical Association binds the physician with
the words, "The health of my patient will be my first consideration," and the International
Code of Medical Ethics declares that, "A physician shall act only in the patient's interest
when providing medical care which might have the effect of weakening the physical and
mental condition of the patient."

4. Medical progress is based on research which ultimately must rest in part on
experimentation involving human subjects.

5. In medical research on human subjects, considerations related to the well-being of the
human subject should take precedence over the interests of science and society.

6. The primary purpose of medical research involving human subjects is to improve
prophylactic, diagnostic and therapeutic procedures and the understanding of the
aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and
therapeutic methods must continuously be challenged through research for their
effectiveness, efficiency, accessibility and quality.

7. In current medical practice and in medical research, most prophylactic, diagnostic and
therapeutic procedures involve risks and burdens.
8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.

16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can
be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.

19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

20. The subjects must be volunteers and informed participants in the research project.

21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject’s physical and mental integrity and on the personality of the subject.

22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.

26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.
27. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.

29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.1

30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.2

31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.

32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

1 Note of clarification on paragraph 29 of the WMA Declaration of Helsinki

The WMA hereby reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that in general this methodology should only be used in the absence of existing proven therapy. However, a placebo-controlled trial may be ethically acceptable, even if proven therapy is available, under the following circumstances:

Where for compelling and scientifically sound methodological reasons its use is necessary to determine the efficacy or safety of a prophylactic, diagnostic or therapeutic method; or

Where a prophylactic, diagnostic or therapeutic method is being investigated for a minor condition and the patients who receive placebo will not be subject to any additional risk of serious or irreversible harm.

All other provisions of the Declaration of Helsinki must be adhered to, especially the need for appropriate ethical and scientific review.

2 Note of clarification on paragraph 30 of the WMA Declaration of Helsinki
The WMA hereby reaffirms its position that it is necessary during the study planning process to identify post-trial access by study participants to prophylactic, diagnostic and therapeutic procedures identified as beneficial in the study or access to other appropriate care. Post-trial access arrangements or other care must be described in the study protocol so the ethical review committee may consider such arrangements during its review.