**EuroNet-PHL-Study Group**

**EuroNet-Paediatric Hodgkin’s Lymphoma Group**

Recommendations for the Diagnostics and Treatment of children and adolescents with a classical Hodgkin’s Lymphoma during the Interimphase between the end of the EuroNet-PHL-C1 Study and the start of the EuroNet-PHL-C2 Study

2013-1-30
CONTENTS

1. GENERAL INFORMATION 5

1.1. RESPONSIBILITIES WITHIN THE EURONET-PHL-STUDY GROUP 5

1.2. REFERENCE FACILITIES 8

1.3. SYNOPSIS 11

2. RATIONALE OF THE DIAGNOSTIC AND TREATMENT RECOMMENDATIONS 12

2.1. INTRODUCTION OF COPDAC AS NEW STANDARD CONSOLIDATION TREATMENT 15

2.2. RADIOTHERAPY IN PATIENTS WITH ADEQUATE RESPONSE 16

2.3. IDENTIFICATION OF A HIGH RISK GROUP IN TG1 17

3. PATIENTS TO WHOM THESE RECOMMENDATIONS MAY APPLY 19

4 RECOMMENDED DIAGNOSTICS 20

4.1. CONFIRMATION OF DIAGNOSIS 20

4.2. RECOMMENDED CLINICAL AND LABORATORY DIAGNOSTICS BEFORE / DURING THERAPY 20

4.3. RECOMMENDED IMAGING DIAGNOSTICS 21
4.4. RECOMMENDED ASSESSMENT OF INVOLVED REGIONS 24

4.5. INDICATIONS FOR INVASIVE DIAGNOSTICS 27

4.6. OPTIONAL PROCEDURES 27

4.7. RESTAGING 28

5. STAGE CLASSIFICATION AND DEFINITION OF THERAPY OUTCOME 29

5.1. STAGE CLASSIFICATION 29

5.2. RECOMMENDED DEFINITION OF TREATMENT RESPONSE 31
1. GENERAL INFORMATION

On 30 January 2013 the enrolment into the EuroNet-PHL-C1 Study stopped. For the Interim between EuroNet-PHL-C1 and EuroNet-PHL-C2 the clinical board of the EuroNet-PHL Study Group decided on Interim Diagnostic and treatment guidelines which are based on the experiences of the EuroNet-PHL-C1 study.
1.1. RESPONSIBILITIES WITHIN THE EURONET-PHL-STUDY GROUP

<table>
<thead>
<tr>
<th>Role</th>
<th>Name</th>
<th>Contact Information</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inter-group chairperson GPOH-HD</td>
<td>Prof. Dr. Dieter Körholz</td>
<td>Zentrum für Kinderheilkunde&lt;br&gt;Universitätsklinik und Poliklinik für Kinder- und Jugendmedizin&lt;br&gt;Ernst-Grube-Straße 40, 06120 Halle (Saale)&lt;br&gt;Tel +49-345-5572387, Fax +49-345-5572389&lt;br&gt;Email: <a href="mailto:dieter.koerholz@medizin.uni-halle.de">dieter.koerholz@medizin.uni-halle.de</a></td>
</tr>
<tr>
<td>Study chairperson GPOH-HD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Permanent member of EuroNet-PHL clinical board</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inter-group chairperson and National chairperson NCRI</td>
<td>Prof. Dr. W. Hamish Wallace</td>
<td>Consultant Paediatric Oncologist&lt;br&gt;Royal Hospital for Sick Children, Sciennes Road, Edinburgh EH9 1LF, Scotland, UK.&lt;br&gt;Tel +44-131 536 0426, Fax +44-131 536 0430&lt;br&gt;Email: <a href="mailto:hamish.wallace@luht.scot.nhs.uk">hamish.wallace@luht.scot.nhs.uk</a></td>
</tr>
<tr>
<td>National chairperson NCRI</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Permanent member of EuroNet-PHL clinical board</td>
<td>Dr Stephen Daw</td>
<td>University College London Hospitals&lt;br&gt;6th Floor, 250 Euston Road, London, NW1&lt;br&gt;Tel +44 203 447 9950, Fax +44 203 447 9064&lt;br&gt;<a href="mailto:stephen.daw@uclh.nhs.uk">stephen.daw@uclh.nhs.uk</a></td>
</tr>
<tr>
<td>Inter-group chairperson GPOH-HD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study chairperson SFCE</td>
<td>Prof. Dr. Judith Landman-Parker</td>
<td>Hospital d’Enfants Armand Trousseau&lt;br&gt;26, Avenue du Dr Arnold Netter&lt;br&gt;75571 Paris Cedex 12, France&lt;br&gt;Tel +33-1-44737475, Fax +33-1-44736573&lt;br&gt;Email: <a href="mailto:judith.landman-parker@trs.ap-hop-paris.fr">judith.landman-parker@trs.ap-hop-paris.fr</a></td>
</tr>
<tr>
<td>Permanent member of EuroNet-PHL clinical board</td>
<td>Dr. Thierry LEBLANC</td>
<td>Service d’Hématologie Pédiatrique&lt;br&gt;Hôpital Robert DEBRE&lt;br&gt;48, boulevard Sérurier&lt;br&gt;75935 Paris Cedex 19&lt;br&gt;Tel : +33-1-40034185, Fax : +33-1-40034740&lt;br&gt;<a href="mailto:thierry.leblanc@rdb.aphp.fr">thierry.leblanc@rdb.aphp.fr</a></td>
</tr>
<tr>
<td>Study chairperson Austria</td>
<td>Dr. Georg Mann</td>
<td>St. Anna Kinderspital, Zentrum f. Kinder und Jugendheilkunde&lt;br&gt;Kinderspitalgasse 6A&lt;br&gt;A-1090 Wien, Austria&lt;br&gt;Tel +43-1-401704780, Fax +43-1-401707430&lt;br&gt;Email: <a href="mailto:georg.mann@stanna.at">georg.mann@stanna.at</a></td>
</tr>
<tr>
<td>Study chairperson Belgium BSPHO</td>
<td>Dr Anne Uyttebroeck</td>
<td>Paediatric haematology-oncology&lt;br&gt;University Hospitals of Leuven, Herestraat 49&lt;br&gt;3000 Leuven, Belgium&lt;br&gt;Tel +32 00 343972, Fax +32 16 343842&lt;br&gt;Email: <a href="mailto:Anne.uyttebroeck@uz.kuleuven.be">Anne.uyttebroeck@uz.kuleuven.be</a></td>
</tr>
</tbody>
</table>
| Study chairperson Czech Republic | Dr. Michaela Cepelová  
Dpt. of Pediatric Hematology and Oncology, Faculty Hospital Motol,  
V Úvalu 84, Prague 5, 150 06, Czech Republic  
Tel +420 224 436 454, Fax: + 420 224 436 420  
Email: michaela.cepelova@fnmotol.cz |
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-permanent member of EuroNet-PHL clinical board</td>
<td></td>
</tr>
</tbody>
</table>
Study chairperson Denmark  
Dr. Eckhard Schomerus  
Odense Universitetshospital  
5000 Odense, Denmark  
Tel +45 6541 2086; Fax +45 6312 2703  
Email: Eckhard.Schomerus@ouh.regionsyddanmark.dk |
| Study chairperson Denmark |  
**Study Chairperson Netherlands**  
**Study chairperson Netherlands DCOG**  
Dr. Auke Beishuizen  
Erasmus MC - Sophia Childrens Hospital University Medical Center Rotterdam, Dept of Pediatric Oncology/Hematology, PO-Box 2060, 3000 CB Rotterdam, The Netherlands,  
e-mail: a.beishuizen@erasmusmc.nl |
| Study Chairperson Netherlands |  
Study chairperson Norway | Alexander Fossà, MD  
Department of Medical Oncology and Radiotherapy  
Rikshospitalet - Radiumhospitalet HF  
Montebello, 0310 Oslo, Norway  
Phone: +4722934000, Fax: +4722935599  
E-mail: alexander.fossa@radiumhospitalet.no |
| Study chairperson Norway |  
**Study chairperson Poland**  
**Polish Pediatric Leukemia /Lymphoma Study Group**  
**Permanent member of EuroNet-PHL clinical board**  
Prof. Dr. Walentyna Balwierz  
Head of Department of Pediatric Oncology and Hematology, Polish-American Pediatric Institute, Jagiellonian University Medical Faculty  
Wielicka Str. 265, 30-663 Krakow, Poland  
Tel./Fax +48-12-65802-61,  
Email: balwierz@mp.pl |
| Study chairperson Poland |  
Study chairperson Slovakia | Dr. Andrea Hraskova  
Clinic of Pediatric Oncology  
University Children`s Hospital  
Limbova 1, 83340 Bratislava  
Tel +4212-59371230, Fax +421254788000  
Email: andrea.hraskova@zoznam.sk |
| Study chairperson Slovakia |  
Study chairperson Spain | Dr Ana Fernández-Teijeiro Álvarez  
Jefe de Sección de Onco-Hematología Pediátrica  
Hospital Universitario Virgen Macarena  
Avda. Dr. Fedriani nº 3  
41071-Sevilla  
Tel: +34677903132, Fax: +34954370892  
E-mail: anateijeiro@hotmail.com |
| Study chairperson Spain |  
Study chairperson Sweden | Dr. Jonas Karlén  
Pediatric Cancer Unit, Astrid Lindgrens Childrens Hospital, Karolinska University Hospital,  
S-171 76 Stockholm, Sweden  
Tel +46-8-51773016, Fax +46-8-51774467  
E-mail: jonas.karlen@karolinska.se |
| Study chairperson Sweden |  
Non-permanent member of EuroNet-PHL clinical board |  
**Study chairperson Sweden**  
**Non-permanent member of EuroNet-PHL clinical board**  
Dr. Jonas Karlén  
Pediatric Cancer Unit, Astrid Lindgrens Childrens Hospital, Karolinska University Hospital,  
S-171 76 Stockholm, Sweden  
Tel +46-8-51773016, Fax +46-8-51774467  
E-mail: jonas.karlen@karolinska.se |
| Study chairperson Switzerland | Dr. Eva Bergsträsser  
Abteilung Onkologie, Universitäts-Kinderklinik Zürich  
Steinwiesstr. 75, CH-8032 Zürich, Switzerland  
Tel. +41 44 266 7723, Fax: +41-44-2667171  
Email: eva.bergstraesser@kispi.unizh.ch |
|---|---|
| Study Group Secretary  
Permanent member of EuroNet-PHL clinical board | Prof. Dr. Christine Mauz-Körholz  
Zentrum für Kinderheilkunde  
Universitätsklinik und Poliklinik für Kinder- und Jugendmedizin  
Ernst-Grube-Straße 40, 06120 Halle (Saale)  
Tel +49-345-5572746, Fax +49-345-5572389  
Email: christine.mauz-koerholz@medizin.uni-halle.de  
Email: hodgkin@medizin.uni-halle.de |
| Responsible Biometrician  
EuroNet-PHL-Study Group  
Permanent member of EuroNet-PHL clinical board | Dr. Dirk Hasenclever  
Institut für Medizinische Informatik, Statistik und Epidemiologie, Universität Leipzig  
Härtelstr.16-18, D-04107 Leipzig, Germany  
Tel +49-341-9716121, Fax +49-341-9716109  
Email: dirk.hasenclever@imise.uni-leipzig.de |
# 1.2. REFERENCE FACILITIES

## 1.2.1. Reference Pathology

| Reference pathology | Association of German Lymphoma reference pathologists  
|---------------------|-----------------------------------------------------------  
| GPOH-HD             | Coordinating reference pathologist: Prof. Dr. Feller  
|                     | Universitätssklinikum Schleswig-Holstein  
|                     | Campus Lübeck, Institut für Pathologie  
|                     | Ratzeburger Allee 160  
|                     | 23538 Lübeck  
|                     | Tel: +49 451 500 2705  
|                     | Fax: +49 451 500 3328  
|                     | Email: ac.feller@uksh.de  
|                     | NCRI  
|                     | Dr Alan Ramsay  
|                     | Consultant Histopathologist  
|                     | Department of Pathology  
|                     | Rockefeller Building  
|                     | University College London Hospitals NHS Foundation Trust  
|                     | 235 Euston Road, London, NW1 2BU  
|                     | Email: alan.ramsay@uclh.nhs.uk  
|                     | SFCE  
|                     | Dr Josette Brière  
|                     | Laboratoire d’anatomie pathologique  
|                     | GELA comité Hodgkin pédia trique  
|                     | Hôpital Saint Louis 1 av Claude Vellefaux  
|                     | 75010 Paris  
|                     | Email: josette.briere@sls.aphp.fr  
|                     | PPLLSG, Poland  
|                     | Jadwiga Małdyk, MD, PhD  
|                     | Department of Pediatric Pathology  
|                     | Medical College  
|                     | ul. Marszałkowska 24, 00-828 Warszawa, Poland  
|                     | Tel.: +4822 6291040  
|                     | Email: jagusiamaldyk@wp.pl  
|                     | Czech Republic  
|                     | Prof. Dr. Roman Kodet  
|                     | Dpt. of pathology and molecular biology  
|                     | Faculty Hospital Motol,  
|                     | V Úvalu 84, Prague 5, 150 06, Czech Republic  
|                     | Tel +420 224 435 601, Fax: + 420 224 435 620  
|                     | Email: roman.kodet@ifmotol.cuni.cz |

## 1.2.2. Central staging and response assessment (for central review only)

| Central review coordinator | Prof.Dr. Christine Mauz-Körholz  
|----------------------------|----------------------------------  
|                            | Zentrum für Kinderheilkunde  
|                            | Universitätsklinik und Poliklinik für Kinder- und |
### Radiology

**Prof. Dr. med. Rolf Peter Spielmann**  
Universitätsklinikum der  
Martin-Luther-Universität Halle-Wittenberg  
Universitätsklinik und Poliklinik für Diagnostische  
Radiologie  
Ernst-Grube-Straße 40  
06120 Halle (Saale) Germany  
Tel +49-345-5572441, Fax +49-345-5572157  
Email: rolf.spielmann@medizin.uni-halle.de

### Nuclear medicine  
**Permanent member of EuroNet-PHL clinical board**

**Prof. Dr. Regine Kluge, Prof. Dr. Osama Sabri**  
Klinik und Poliklinik für Nuklearmedizin  
Universitätsklinikum Leipzig  
Stephanstr. 11, D-04103 Leipzig, Germany  
Tel. +49-341- 97 18 031 or 97 18 000,  
Fax +49-341- 97 18 009  
Email: klur@medizin.uni-leipzig.de,  
sabri@medizin.uni-leipzig.de

### 1.2.3. Reference radiotherapy group

| Reference radiotherapy | Prof. Dr. D. Vordermark  
Universitätsklinikum der Martin-Luther-Universität Halle-Wittenberg  
Universitätsklinik und Poliklinik für Strahlentherapie und Radioonkologie  
Ernst-Grube-Str. 40, D-06120 Halle (Saale), Germany  
Tel.: +49 345- 5573422,  
Fax: +49 345- 5577207  
Email: thomas.kuhnt@medizin.uni-halle.de |
| Reference radiotherapy | Prof. Dr. Karin Dieckmann  
Universitätsklinik für Strahlentherapie und Strahlenbiologie  
Medizinische Universität Wien, Allgemeines Krankenhaus der Stadt Wien  
A-1090 Wien, Währingergürtel 18 - 21  
Tel 0043-1-40400-2692  
Email: Karin.dieckmann@meduniwien.ac.at |
| Reference radiotherapy | Dr. Eve Gallop-Evans  
Velindre Cancer Centre  
Velindre Road, Whitchurch,  
Cardiff, CF14 2TL, Wales, UK  
Email: eve.gallop-evans@wales.nhs.uk |
| Reference radiotherapy | Dr. Christian Carrie  
Centre Léon Berard  
28 rue Laennec |
<table>
<thead>
<tr>
<th>Reference Radiotherapy PPLS G</th>
<th>Krzysztof Paprota, MD, PhD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Department of Radiotherapy</td>
</tr>
<tr>
<td></td>
<td>Children’s Hospital</td>
</tr>
<tr>
<td></td>
<td>tel.: +4881 7185520, fax: +4881 7477220</td>
</tr>
<tr>
<td></td>
<td>Email: <a href="mailto:lekkp@gazeta.pl">lekkp@gazeta.pl</a></td>
</tr>
</tbody>
</table>
### 1.3. SYNOPSIS OF RECOMMENDATIONS

<table>
<thead>
<tr>
<th>Indication for treatment Guidelines</th>
<th>Classic Hodgkin’s lymphoma in childhood and adolescence – first line treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>Patients with untreated classical Hodgkin’s lymphoma under 18 years of age.</td>
</tr>
<tr>
<td>Recommended Therapy</td>
<td>All first line patients get two cycles of OEPA and then undergo response assessment including FDG-PET. Patients in TG-1 do not receive further chemotherapy. Patients in TG-2 and -3 receive additional two or four cycles of COPDAC respectively. If an adequate response was documented treatment stops after chemotherapy. In case of inadequate response to 2 OEPA modified involved field radiotherapy follows for all treatment groups.</td>
</tr>
</tbody>
</table>
2. RATIONALE OF THE DIAGNOSTIC AND TREATMENT RECOMMENDATIONS

The EuroNet-PHL-C1 protocol has been derived from the experiences of the GPOH-HD (Schellong et al., Dörffel et al., Mauz-Körholz HD-2002, Körholz et al.,2003) and the French HL Study group (Oberlin et al, J Clin Oncol, 1992, 10, 1602-1610; Landman-Parker J et al, J Clin. Oncol 2000, 18, 1500-07). The rational for these recommendiations is based on the results of the 3rd Interim analysis of the EuroNet-PHL-C1 trial, the clinical board approved the treatment and diagnostic recommendations. Within the next paragraphs a brief summary of the results of the 3rd interim analysis is depicted.

Fig. 1 Data set of the 3rd interim analysis of the EuroNet-PHL-C1 study

At 25.10.2012 2033 patients have been registered into the EuroNet-PHL-C1 trial. For the 3rd interim analysis 403 patients were excluded for various reasons (details see Fig. 1.).
Within the EuroNet-PHL-C1 trial patients did not receive radiotherapy if they showed an adequate response (AR) to two cycles of OEPA. Out of 1630 patient 1593 were eligible for the analysis of the radiotherapy question (for details on excluded patients see Fig. 2), i.e. whether it is possible to safely drop radiotherapy in patients with AR. In total about 50% of all patients did not receive RT.

In 267/856=31.2% radiotherapy documentation is overdue. In these cases it is unclear whether radiotherapy has been delivered as indicated.

Fig. 2 Data set of patients eligible for the RT question in the 3rd interim analysis of EuroNet-PHL-C1
In order to answer the question whether a procabacine–free chemotherapy combination is as effective as a Procabacine-containing chemotherapy regimen and if at the same time a Procarbacien-free regimen can prevent male infertility in patients with intermediate and advanced stages COPDAC was randomized against COPP chemotherapy. 891 patients have been randomized in the EuroNet-PHL-C1 trial (Fig. 3).
2.1. Introduction of COPDAC as new standard for consolidation treatment

In February 2012 the EuroNet-PHL study group decided to stop the randomization in the EuroNet-PHL-C1 study and to implement COPDAC as new standard consolidation treatment. This decision was made on the basis of the results of the second interim data analysis which showed emerging evidence that COPP and COPDAC are similarly efficacious. These results further stabilized in the 3rd interim analysis (Fig.4)

Fig. 4 EFS survival of patients with intermediate and advanced stage HL randomized to COPP vs COPDAC

Prior to the start of EuroNet-PHL-C1, it was known that chemotherapy regimens containing Procarbazine tended to reduce semen concentration and quality in a dose dependent manner which may lead to azoospermia (Brämswig et al., 1990 Wallace et al., 1997, Hassel et al., 1991). Data on FSH in EuroNet-PHL-C1 confirms this expectation, showing that FSH (which is negatively correlated to sperm count/concentration) is elevated, compared to normal values after treatment with COPP.

COPDAC was a regimen specifically designed to avoid gonadal damage in boys by replacing Procarbazine with Dacarbazine. Emerging data from EuroNet-PHL-C1 indicates that the FSH distribution after treatment with COPDAC remains in the normal range. FSH after COPP is clearly higher than after COPDAC (p<0.001).
In addition, there is early evidence of a recovery in FSH values after COPDAC, but this is not the case after treatment with COPP. Data on semen analyses post chemotherapy are still sparse, but azoospermia was observed in 2/3 Patients who had COPP and in 0/4 Patients who had COPDAC.

### 2.2. Omission of Radiotherapy in patients with adequate response

Considering the radiotherapy question, the 3rd interim analysis showed that the EFS of all patients did not differ whether they received RT or not. The EFS rate in patients not receiving RT is still slightly below 90% (Fig. 5). However, at the 3rd interim analysis the stopping rule considering the RT questions was not fulfilled. Recently the COG group published their long term results of the study. (Wolden et al., JCO 2012) In this trial patients with good response after the end of chemotherapy were randomized for further radiotherapy or stop of treatment. The 10yr EFS and OS rates were 91.2% and 97.1% for IFRT and 82.9% and 95.9% for patients with no further therapy. Thus, although the EFS rates dropped in the no RT group by about 10%, the overall survival rates were comparable. In addition the results of the 3rd interim analysis may still be underestimated due to the “bad news travel first effect”. Taken together these arguments lead to the decision of the EuroNet-PHL Clinical board that it is still justified to recommend omission of radiotherapy in patients with AR. However, this recommendation will be reevaluated after the 4th interim analysis in October 2013.
Fig. 5 EFS rates in patients with/without RT – data from the 3rd interim analysis of EuroNet-PHL-C1

2.3. Identification of a High risk group in TG1
EFS in TG-1 by ESR $\geq 30\text{mm/h}$ or BULK $\geq 200\text{ml}$

![Graph showing EFS proportion over time](image-url)

**EFS time [months]**

**Proportion event free**
3. PATIENTS TO WHOM THESE RECOMMENDATIONS MAY APPLY

These recommendations may apply to patients fulfilling these criteria:

diagnosis of classic Hodgkin’s lymphoma
aged under 18 years at time of diagnosis
written informed consent of the patient and/or the patient’s parents or guardian according to national laws
No pre-treatment of Hodgkin’s lymphoma differing from these recommendations (except recommended pre-phase therapy of a large mediastinal tumour)
No known hypersensitivity or contraindication to study drugs
No diagnosis of lymphocyte predominant Hodgkin’s lymphoma
No prior chemotherapy or radiotherapy
No other (simultaneous) malignancies
No pregnancy and / or lactation
females who are sexually active and who are not refusing to use effective contraception (oral contraception, intrauterine devices, barrier method of contraception in conjunction with spermicidal jelly or surgical sterile)
No severe concomitant diseases (e.g. immune deficiency syndrome)
No known HIV positivity
4 RECOMMENDED DIAGNOSTICS

If Hodgkin’s lymphoma is suspected, an open biopsy should be obtained as soon as possible (exception large mediastinal tumour). After confirmation of the diagnosis by the local pathologist FDG-PET scanning should be performed before starting treatment (exception oncologic emergency).

4.1. CONFIRMATION OF DIAGNOSIS

The histopathological diagnosis is based on a biopsy of a lymph node or as the case may be of a biopsy of another primarily involved organ. Biopsies using a fine needle are not appropriate.

Reference pathology is strongly recommended and is organized country specific as detailed in the pathology manual of the EuroNet-PHL-C1 protocol.

In case of CD20+ positivity do not start treatment until the differential diagnosis of classic Hodgkin’s lymphoma versus lymphocyte predominant HL is confirmed by reference pathology. Patients with LP-HL qualify for the EuroNet-PHL-LP1 study.

4.2. RECOMMENDED CLINICAL AND LABORATORY DIAGNOSTICS BEFORE / DURING THERAPY

4.2.1. Diagnostics prior to chemotherapy

Exact clinical history including:

- previous and concomitant diseases (e.g. paraneoplastic phenomena such as nephrotic syndromes and other autoimmune diseases),
- systemic symptoms and prior treatment.

Clinical examination

- detailed documentation of all palpable lymph nodes and their localisation.
- examination and inspection of Waldeyer’s ring preferably by ENT-physician.
- Palpation of spleen and liver

Laboratory examinations:
Complete blood count, erythrocyte sedimentation rate, ALAT (GPT), ASAT (GOT), GGT, LDH, AP, creatinine and albumin in the serum, fibrinogen, Immunoglobulin A, G, M
Protein electrophoresis: gamma-globuline and alpha-2-globuline
Baseline virology recommended to include serologic examinations for antibodies against VZV, EBV, CMV, HSV, HIV, toxoplasmosis, hepatitis A, B, C (HCV-PCR).

Functional examinations
ECG
Echocardiography
EEG (optional)

4.2.2. Recommended diagnostic assessment before each course of chemotherapy

Before start of each chemotherapy cycle:
- presence of infections
- detailed clinical examination
- Lansky/Karnofsky score depending on age
- blood counts including differential blood count
- ALAT, ASAT, GGT, bilirubin, creatinine

Further diagnostic measures (such as ECG, lung function etc.) are carried out according to the individual circumstances of the patient.

4.3. RECOMMENDED IMAGING DIAGNOSTICS

4.3.1. Initial staging

For every patient a FDG-PET examination before starting any therapy (exception vital emergencies) is strongly recommended

Cross sectional imaging is also strongly recommended. It should preferably be performed according to options A and B, see below.
Low dose chest CT should be performed with weight-dependent dosage if possible.
A) CT chest with mediastinum, MRI neck / abdomen / pelvis

CT examination:
CT examination of thorax is mandatory, since lung foci can be best diagnosed with CT. (Recommendations for CT examination performance see B).

MRI examinations should include the following sequences:
  o neck: transversal and coronal T2 fat saturated T2 (T2-TIRM, T2-STIR)
  o thorax: If performed in addition to chest CT an MRI examination of lung and mediastinum should provide ECG triggered transversal sequences to avoid pulsation artefacts.
  o abdomen: transversal T2 fat saturated and T1-FLASH 2d dynamic in arterial, portal venous and venous phase
  o pelvis: T1-SE transversal, T2- fat saturated transversal and coronal, T1-SE-transversal after contrast agent with fat saturation

B) CT neck / thorax / abdomen / pelvis

Recommendation for examination performance:
examination region: epipharynx to lower edge of symphysis
layer thickness: reconstructed 5 mm layers
oral contrasting: Yes
i.v. contrasting: depending on KG 1.5 – 2.0 ml/kg KG
(recommended up to 10 kg KG 2 ml/kg, up to 40 kg KG 1.5 ml/kg, from 40 kg 60 ml; choose delay according to device so that a parenchymal phase of liver and spleen is achieved)
reconstruction: lung: sharp kernel and pulmonary window, mediastinum with involvement of axillae, supra- and infraclavicular region: soft kernel and mediastinal window, abdomen and pelvis involving inguinal region: abdominal window (e.g. W 400/C 60)

C) CT in combination with PET:
If only a PET-CT is performed, the CT-images have to be “state of the art” quality. This includes: oral and i.v.contrasting (as described in B), the choice of an adequate mAs dose (not low dose) and a slice thickness not higher than 5 mm. The imaging quality of the PET-CT-images has to be comparable to normal diagnostic CT.
4.3.2. Additional imaging procedures

Sonography of spleen and liver are strongly recommended.
Bone scan: This examination is only performed in patients with suspected skeletal involvement based on FDG-PET or clinical symptoms

4.3.3. Central review – second physician`s opinion

If the patient gives informed consent to a second physicians opinion a central review is offered. Therefore digital transmission of cross sectional imaging and bone scans via Hodgkin network (Hermes server) is appreciated. Alternatively a CD with automatically opening (DICOM) viewer if necessary as teleradiology link) can be send to the central review office in Halle or Vienna (for Austria only). The original report of the local radiologist should be included for orientation.

In non-central review associated centres, the tumour volume is determined at the local hospital.

4.3.4. Additional considerations

Please note, that after lymph node biopsy the respective region should to be re-examined with imaging methods before starting chemotherapy as a prerequisite for accurate response assessment.

PET positive regions not investigated by cross-sectional imaging (e.g. extremities) should be examined using conventional imaging (CT or MRI) before starting therapy.

4.3.5. FDG-PET examination

For detailed instructions please confer to the FDG-PET procedural manual of the EuroNet-PHL-C1 study.
4.4. RECOMMENDED ASSESSMENT OF INVOLVED REGIONS

4.4.1. Assessment of nodal involvement

4.4.1.1. Assessment of lymph node involvement

1. If the largest diameter of a lymph node or a lymph node conglomerate is smaller than 1 cm the region is considered not involved – independent of the PET result. Unidentified micro-findings do not impair therapy results according to previous experience. If however small FDG-PET positive lymph nodes accumulate this region is considered involved.

2. If the largest diameter of a lymph node or a lymph node conglomerate exceeds 2.0 cm the region is considered involved. If such an involved region is FDG-PET-negative this discordancy must be documented, since this is relevant for the decision on radiotherapy because response in such a region cannot be reliably assessed by FDG-PET.

3. If a lymph node or a lymph node conglomerate has a diameter of 1.0 – 2.0 cm the region is considered
   involved if it is FDG-PET positive.
   not involved if it is FDG-PET negative
   doubtfully involved if the FDG-PET has not been performed or is not evaluable (e.g. in muscle artefacts). In these cases the decision on involvement of this region is made including further criteria, such as clinical data, ultrasound findings, proximity to larger involved region.

4.4.1.2. Assessment of Waldeyer’s ring

1. Involvement is defined by clinical assessment preferably by ENT physician and is not measurable: involvement yes/ no; localisation left/right;

2. FDG-PET assessment is irrelevant.

3. Biopsy is not required and not appreciated since too invasive
4.4.2. **Assessment of extra-nodal involvement**

4.4.2.1. **Pleura and pericardium**

Involvement of the pleura is assumed if
- the lymphoma is contiguous with the pleura without fat lamella or
- the lymphoma invades the chest wall or
- a pleural effusion occurs which can not be explained by a venous congestion.

Pericardial involvement is assumed if
- the lymphoma has a broad area of close contact towards the heart surface beyond the
  valve level (ventriculus area) or
- a pericardial effusion occurs.

Pleura and/or pericardial involvement are generally considered E-lesions.

4.4.2.2. **Extra-nodal involvement**

Extra-lymphatic structures or organs that are infiltrated per continuum out of a lymphatic mass are termed E-lesion (examples: lung, intestine, bones) and do not automatically qualify for stage IV. **Exceptions:** Liver or bone marrow involvement always implies stage IV.

4.4.3. **Organ involvement**

4.4.3.1. **Lung involvement**

A disseminated lung involvement (implying stage IV) is assumed if
- there are more than three foci or
- an intrapulmonary focus has a diameter of more than 10 mm.

If a smaller than 10 mm involvement is seen (also if FDG-PET positive) or there is only a PET positive finding, stage IV is not assumed since these patients have had a very good prognosis in the past without upstaging.

E-lesion of the lung is restricted to one pulmonary lobe or perihilar extension with homolateral hilar lymphadenopathy.
4.4.3.2. Liver and spleen involvement

Liver involvement implies always stage IV.
Exclusive splenic involvement without other lymphatic disease is classified as stage I.
Mere enlargement of liver / spleen only is not considered as involvement.
Focal changes in the liver / spleen structure that are tumour suspicious in ultrasonography are considered involved – independent of the FDG-PET result.
In case of doubtful involvement of liver or spleen (e.g. structures atypical of tumour in sonography or MRI) the liver / spleen is considered
  o involved if FDG-PET is positive.
  o not involved if FDG-PET is negative.
  o doubtfully involved if the FDG-PET was not performed or if it is not evaluable. In these rare cases the decision on involvement is made taking further criteria into the account.

4.4.3.3. Bone / bone marrow involvement

Bone involvement is assumed if
  A bone biopsy is positive or
  CT bony window is positive with or without further confirmation by other imaging methods in the same region or
  A positive bone scan is confirmed by either FDG-PET or MRI.
  MRI positive in bone and adjacent soft tissue (T2 fat saturated sequences).

In the event of an isolated lesion or relevant history (e.g. trauma) only a positive biopsy indicates bony involvement.

Bone marrow involvement is assumed if
  bone marrow biopsy is positive or
  FDG-PET and MRI are both positive in the same region

A bone marrow biopsy is mandatory unless stage I or IIA. Bone marrow involvement implies stage IV.
4.5. INDICATIONS FOR INVASIVE DIAGNOSTICS

4.5.1. Bone marrow biopsy
All patients with a stage >IIA should get a bone marrow biopsy in one or two regions.

4.5.2. Selective laparoscopy
Selective laparoscopy is indicated only in rare cases where involvement can not be clarified with any available imaging method including FDG-PET.

4.5.3. Ovariopexy
Whenever an iliac lymph node region is to be irradiated in girls lateral movement of the adjacent ovary should be considered.
Ovariopexy is particularly recommended if both ovaries are expected to receive a dose of more than 5 Gy which may lead to significant long-term ovarian impairment. Using opposed fields with 20 Gy, this can be usually be avoided, if the ovary is more than 2 cm from the adjacent field (shield) border.

When performing an ovariopexy sutures should be marked with clips! After consultation with the radiotherapist surgery should be carried out immediately before infra-diaphragmatic irradiation.

4.6. OPTIONAL PROCEDURES
Male patients who are post-pubertal with testicular volumes, as measured using a Prader Orchidometer of >10mls should be offered semen cryopreservation before treatment begins. Techniques to preserve fertility in pre-pubertal males remain entirely experimental. For females the only established method of fertility preservation is embryo freezing which requires a consenting male partner. Harvesting of ovarian cortical tissue or eggs for cryopreservation remains experimental and should only be undertaken in institutions with appropriate ethical consents in place.

4.7. RESTAGING

4.7.1. General information
The following cross-sectional imaging procedure is recommended for restaging:
4.7.2. First restaging after 2 cycles of chemotherapy

All patients should get a FDG-PET examination on day 14 (day 17 as latest) after the last application of chemotherapy. All initially involved regions are checked. CT/MRI/ultrasound examinations have to be performed between day 10 and 14 after the last application of chemotherapy.

Response in initial bone or bone marrow involvement is only assessed by FDG-PET, assuming that it would be still detectable by conventional imaging.

Patients with suspected progression should get a complete staging of all lymph node regions.

4.7.3. Second restaging after full chemotherapy in therapy groups 2 + 3

After 4 or 6 cycles of chemotherapy all initially involved regions of the patients in TG-2 +3 are re-examined. CT / MRI / ultrasound examinations should be performed between day 10 and 14 after the last application of chemotherapy in the fourth or sixth cycle respectively. **FDG-PET is not performed**. Patients with suspected progression should have a complete staging of all lymph node regions.

4.7.4. Follow-up

Follow-up starts six weeks after completion of therapy according to the recommendations (Tab.1)
Table 1 Recommendations for follow-up examinations

<table>
<thead>
<tr>
<th>Procedures</th>
<th>1st year</th>
<th>2nd year</th>
<th>3rd year</th>
<th>4th year</th>
<th>5th year</th>
<th>6th year on</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical history and examination</td>
<td>4 - 8x</td>
<td>4 - 8x</td>
<td>4x</td>
<td>2x</td>
<td>2x</td>
<td>Individually</td>
</tr>
<tr>
<td>Blood counts, ESR</td>
<td>4x</td>
<td>4x</td>
<td>2x</td>
<td>2x</td>
<td>2x</td>
<td>Individually</td>
</tr>
<tr>
<td>After radiation of mediastinum and/or lung: Functional lung evaluation</td>
<td>1x</td>
<td>Individually</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consultation of radiotherapist</td>
<td>1x</td>
<td>1x</td>
<td>1x</td>
<td>1x</td>
<td>1x</td>
<td>Individually</td>
</tr>
<tr>
<td>Assessment of quality of life (Germany only)</td>
<td>1x</td>
<td>1x</td>
<td>1x</td>
<td>1x</td>
<td>1x</td>
<td></td>
</tr>
<tr>
<td>Sonography abdomen</td>
<td>4x</td>
<td>4x</td>
<td>2x</td>
<td>2x</td>
<td>2x</td>
<td>Individually</td>
</tr>
<tr>
<td>MRI in involved region</td>
<td>2-4x</td>
<td>1-2x</td>
<td>1-2x</td>
<td>1-2x</td>
<td>1-2x</td>
<td></td>
</tr>
<tr>
<td>CT thorax in case of lung involvement</td>
<td>2x</td>
<td>1x</td>
<td>Individually</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After neck radiation: thyroidsonography, fT4, TSH, TG</td>
<td>1x</td>
<td>1x</td>
<td>1x</td>
<td>1x</td>
<td>1x</td>
<td></td>
</tr>
<tr>
<td>ECG / echo-CG</td>
<td>1x</td>
<td></td>
<td>Individually</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FDG-PET</td>
<td></td>
<td></td>
<td>Only if relapse confirmed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>After radiation of supra-/infraclavicular region, axillae, mediastinum or lungs: Mammary carcinoma screening (Sono, MRI)</td>
<td></td>
<td></td>
<td></td>
<td>To be considered in women above age 25 annually</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

5. STAGE CLASSIFICATION AND DEFINITION OF THERAPY OUTCOME

5.1. STAGE CLASSIFICATION

Stage classification is performed according to Cotswolds revision of the classical Ann Arbor staging system.
Definition of lymph node regions and extra-nodal sites on which staging is based, stage classifications and definitions of A and B symptoms are described in Tab. 2-4.

Table 2 Independent lymph node regions

<table>
<thead>
<tr>
<th>Independent lymph node regions are:</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Waldeyer’s ring (left and right)</td>
</tr>
<tr>
<td>- cervical (left and right) with sub-regions relevant for irradiation:</td>
</tr>
<tr>
<td>o upper neck: up to upper edge of larynx</td>
</tr>
<tr>
<td>o lower neck: up to supraclavicular fossa</td>
</tr>
<tr>
<td>- supraclavicular (left and right)</td>
</tr>
<tr>
<td>- infraclavicular (left and right): subpectoral on the thoracic wall</td>
</tr>
<tr>
<td>- axillar (left and right)</td>
</tr>
<tr>
<td>- lung hilus (left and right): bronchopulmonary LN</td>
</tr>
<tr>
<td>- mediastinum with sub-regions relevant for irradiation:</td>
</tr>
<tr>
<td>o upper mediastinum: down to bifurcation</td>
</tr>
<tr>
<td>o middle mediastinum: hilus down to subcarinal region</td>
</tr>
<tr>
<td>o lower mediastinum: down to diaphragm</td>
</tr>
<tr>
<td>- supradiaphragmatic: diaphragmatic recessus</td>
</tr>
<tr>
<td>- spleen</td>
</tr>
<tr>
<td>- splenic hilus</td>
</tr>
<tr>
<td>- liver hilus</td>
</tr>
<tr>
<td>- mesenteric: mesentery, mesocolon</td>
</tr>
<tr>
<td>- paraortic: coeliac, paraortocaval, pararenal, paralienal, parapancreatic</td>
</tr>
<tr>
<td>- iliac (left and right): parailiac</td>
</tr>
<tr>
<td>- inguinal (left and right): inguinal, femoral</td>
</tr>
</tbody>
</table>

Table 3 Stage classification Hodgkin’s lymphoma

Stages of Hodgkin’s lymphoma according to the Cotswolds revision of the Ann Arbor staging system

I Involvement of a single independent lymph node region or lymph node structure
II Involvement of 2 or more lymph node regions on the same side of the diaphragm
III Involvement of lymph node regions or lymph node structures on both sides of the diaphragm
IV Involvement of extra-nodal sites beyond “E”-sites
Table 4 Annotations to stage definitions

A. No B symptoms

B. At least one of the following systemic symptoms
   a. Inexplicable weight loss of more than 10% within the last 6 months
   b. Unexplained persisting or recurrent temperature above 38 °C
   c. Drenching night sweats

E. Involvement of a single extra-nodal site contiguous or proximal to known nodal site.
   (For the distinction between stage IV and the E-stages see chapter 4.4.2.)

5.2. RECOMMENDED DEFINITION OF TREATMENT RESPONSE

5.2.1. Local response definitions for nodal involvement with measurable tumour volume

At staging all measurable nodal sites (i.e. all nodal except for the spleen and Waldeyer’s ring) are grouped in separately measurable reference volumes. Reference volumes can include multiple sites if these are contiguous.

The composition of these reference volumes is defined and documented. Initial volumes of reference volumes are measured.

Volumes are approximated as ellipsoids. If a, b, c denote the principal axes of the ellipsoid the volume is calculated as  \( V = \frac{a \times b \times c}{2} \).

In this recommendations overall response to treatment is determined according to a systematic assessment of tumour response in all involved sites.

In those sites where the tumour is measurable from CT/MRI scanning the change in tumour volume is compared the original pre-treatment reference volume and then assigned a treatment response for that local site.

5.2.1.1. Local Complete remission (localCR)

A reference volume is in "local complete remission" (in short: localCR) if:

the residual tumour volume is less or equal 5% of the reference volume (CT/MRI) and
the residual tumour volume is less or equal 2 ml.

### 5.2.1.2. Local complete remission unconfirmed (localCRu)

A reference volume is in "local complete remission unconfirmed" (in short: localCRu) if:

- No localCR and
  - the residual tumour volume is less or equal 25% of the reference volume (CT/MRI) or (!)
  - the residual tumour volume is less or equal to 2 ml

### 5.2.1.3. Local partial remission (localPR)

A reference volume is in "local partial remission" (in short: localPR) if:

- No localCR or localCRu and
  - the residual tumour volume is less or equal 50% of the reference volume (CT/MRI) or the residual tumour volume is less or equal 5 ml (to safeguard against artefacts due to measurement errors).

### 5.2.1.4. Local no change (localNC)

A reference volume is in "local no change" (in short: localNC) if

- no localCR or localCRu or localPR and
- no local Progression

### 5.2.1.5. Local Progression (localPRO)

A reference volume is in "local progression" (in short: localPRO) if

- The residual tumour volume is larger than 125% of the reference volume or significantly increases compared to the best previous response – be aware of possible measurement error in small tumour volume.

### 5.2.2. Local response definitions for extra-nodal involvement or for nodal involvement with non-measurable tumour volume

For all extra-nodal sites or for nodal involvement with non-measurable tumour volume three response categories are distinguished by radiological or clinical criteria:

- Locally undetectable
Locally detectable  
Locally progressive  
Only “Locally undetectable” is consistent with overall CR.

Note: In case of multi-focal bone or bone marrow involvement multiple sites are assessed separately. Initial bone or bone marrow involvement is only assessed by FDG-PET assuming it is still detectable by conventional imaging.

5.2.3. Overall (patient level) response definitions

Overall (patient level) response categories are obtained from the worst local response in reference volumes and the worst local response in non measurable nodal or extra-nodal disease as illustrated in the following figure 7:

**Fig. 7 Definition of overall response**

<table>
<thead>
<tr>
<th></th>
<th>worst local response in nodal reference volumes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>overall CR</td>
</tr>
<tr>
<td>overall CR</td>
<td>overall CRu</td>
</tr>
<tr>
<td>overall CRu</td>
<td>overall CR</td>
</tr>
<tr>
<td>overall PRO</td>
<td>overall PRO</td>
</tr>
</tbody>
</table>

*legend*: overall CR, overall CRu, overall PR, overall NC, overall PRO

5.2.3.1. Complete remission (CR)

"Complete remission" (in short: CR) is achieved if in restaging

all disease symptoms have disappeared and

no new lymphatic or extra-lymphatic lesions have occurred and

all initially involved extra-nodal sites or involved regions with non-measurable tumour volume are locally undetectable and
all reference volumes are in localCR

5.2.3.2. Complete remission unconfirmed (CRu)

"CR unconfirmed" (in short: CRu) is achieved if in restaging

no CR and
all disease symptoms have disappeared and
no new lymphatic or extra-lymphatic lesions have occurred and
all initially involved extra-nodal sites or involved regions with non-measurable tumour volume are not locally progressive and
all reference volumes are at least in localCRu

5.2.3.3. Partial remission (PR)

"Partial remission" (in short: PR) is achieved if in restaging

no CR or CRu and
all disease symptoms have disappeared and
no new lymphatic or extra-lymphatic lesions have occurred and
all initially involved extra-nodal sites or involved regions with non-measurable tumour volume are not locally progressive and
all reference volumes are at least in localPR

5.2.3.4. No change (NC)

"No change" (in short: NC) is achieved if in restaging

no CR or CRu or PR and
no PRO

5.2.3.5. Progression (PRO) / Relapse (R)

Progression / Relapse of the disease occurs if

recurrence or occurrence of new disease symptoms which can not be explained otherwise or
occurrence of new lymphatic or extra-lymphatic lesions or
at least one initially involved extra-nodal site or involved region with non-measurable tumour volume is locally progressive or
at least one reference volume is in localPRO

Biopsy of an enlarging region or new lesion is mandatory according to these recommendations.

A progression / relapse of the disease is called

- **progression** if it occurs until three months after the end of therapy (last day of chemotherapy application (including Prednisone/prednisolone) or last day of radiotherapy respectively).
- **early relapse** if it occurs between three and twelve months after the end of therapy.
- **late relapse** if it occurs later than twelve months after the end of therapy.

5.3. EARLY FDG-PET RESPONSE ASSESSMENT

After two cycles of chemotherapy early response reassessment including FDG-PET is performed. **FDG-PET examinations are assessed only for initially involved regions** (except in case of suspected progression).

5.3.1. Definition local FDG-PET response

For each initially involved reference volume or non-measurable nodal or extra-nodal site a local PET response is defined based on the initial PET and the response assessment PET results as illustrated in:

Fig. 8 Definition local FDG-PET response
<table>
<thead>
<tr>
<th>initial PET – involved regions only</th>
<th>+</th>
<th>-</th>
<th>? / nd</th>
</tr>
</thead>
<tbody>
<tr>
<td>early response assessment PET</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>-</td>
<td>-</td>
<td>?</td>
</tr>
<tr>
<td></td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>

+ = positive FDG-PET  
- = negative FDG-PET  
? / nd = questionable FDG-PET or FDG-PET not done

Definition local FDG-PET response

- **Local PET response positive** if the response assessment PET is positive anywhere in the reference volume or involvement site.
- **Local PET response unclear**, if the response assessment PET is unclear or the response assessment PET is negative, but the initial PET was discordantly negative.
- **Local PET response negative** if the response assessment PET is negative and the initial PET was positive or unclear (i.e. not discordantly negative).

NOTE: A PET examination is locally unclear if

- Not done
- Not evaluable due to technical problems
- After a biopsy the PET is not positive

in rare cases of questionable PET results.

5.3.2. Definition worst local FDG-PET response

In case of **Local PET response unclear** a further distinction is made by local CT/MRI response:

- **Locally PET unclear, but localCR or locally undetectable (by CT/MRI)**
- Locally PET unclear, but not localCR or locally detectable (by CT/MRI)

The **worst local PET response** is defined based on the following order relation:

“Local PET response positive” worse than

“Locally PET unclear, but not localCR or locally detectable” worse than

“Locally PET unclear, but localCR or locally undetectable” worse than

“Local PET response negative”
5.4. RESPONSE GROUP DEFINITION

If no tumour progression is found, response groups are obtained from the overall response and the worst local PET response in reference volumes and in non measurable nodal or extra-nodal disease as illustrated Fig. 9 and Tab 5:

Fig. 9 Response group definition

<table>
<thead>
<tr>
<th>overall response</th>
<th>worst local PET response</th>
</tr>
</thead>
<tbody>
<tr>
<td>CR</td>
<td>AR1</td>
</tr>
<tr>
<td>CRu</td>
<td>AR2</td>
</tr>
<tr>
<td>PR</td>
<td>AR2</td>
</tr>
<tr>
<td>NC</td>
<td>IRu</td>
</tr>
</tbody>
</table>

AR1 = adequate response group 1  no radiotherapy
AR2 = adequate response group 2  no radiotherapy
IRu = inadequate response group unconfirmed  radiotherapy
IR  = inadequate response group  radiotherapy
Table 5 Response groups in non progressing patients

<table>
<thead>
<tr>
<th>Adequate response 1 (AR1)</th>
<th>Patients in overall complete remission irrespective of PET results.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate response 2 (AR2)</td>
<td>Patients in overall CRu or overall PR for whom all initially involved regions are PET-negative or PET-unclear and o in local CR or o undetectable</td>
</tr>
<tr>
<td>Inadequate response (IR)</td>
<td>Patients not in overall complete remission and at least one initially involved region is PET-positive.</td>
</tr>
<tr>
<td>Inadequate response unconfirmed (IRu)</td>
<td>Patients in overall CRu or overall PR and no initially involved region is PET-positive and at least one initially involved region is PET-unclear and o not in local CR or o still detectable or Patients in overall No Change and no initially involved region is PET-positive.</td>
</tr>
</tbody>
</table>

The distinction between AR1 and AR2 is made because in TG-1 AR1 the GPOH 95 study has already shown that omitting radiotherapy is safe, irrespective of PET.
6. RECOMMENDED THERAPY PLAN

In case of **CD20+ positivity do not start treatment** until the differential diagnosis of classical Hodgkin’s lymphoma versus lymphocyte predominant HL is confirmed by reference pathology. Patients with LP-HL qualify for the EuroNet-PHL-LP1 study.

6.1. TREATMENT GROUPS

Patients are divided into treatment groups (TG) according to the reference stage (defined by the central review in the GPOH-HD study office) or the local stage (non-GPOH associated hospitals).

Treatment groups are as follows:

TG-1: patients of stages I A/B and II A **without bulk>=200 ml and without ESR>=30mm/hr**

TG-2: patients of stages IeA/B, IieA, II B or III A

and **patients of stages I A/B and II A with bulk>=200 ml and/or ESR>=30mm/hr**

TG-3: patients of stages IIeB, IIIeA/B, III B or IV A/B

6.2. TREATMENT GROUP 1 (TG-1)

All patients receive two cycles of OEPA. Patients in TG-1 with adequate response (response groups AR1 and AR2) receive no further therapy (Fig. 10). Patients with inadequate response (IR and IRU) will receive involved field radiotherapy (see chapter 7 and radiotherapy manual). Radiation therapy should start by day 35 after the last dose of chemotherapy in the second OEPA-cycle (i.e. day 77 after start of treatment) **at latest**.

![Fig. 10 Treatment overview for TG-1](image-url)
6.3. TREATMENT GROUP 2 AND 3 (TG-2, TG-3)

Following completion of 2 cycles of OEPA and after early response assessment including FDG-PET, patients in TG-2 receive two cycles, patients in TG-3 four cycles of COPDAC.

Patients in TG-2 / TG-3 with adequate response in early response assessment (response groups AR1 and AR2) receive no radiotherapy.

Patients with inadequate response (IR and IRU) will receive involved field radiotherapy after the end of chemotherapy (see chapter 7 and radiotherapy manual). Radiotherapy begins 14 days after last dose of prednisone/prednisolone of the 4th respectively 6th chemotherapy cycle (TG-2: day 112 after start of treatment, TG-3: day 168 after start of treatment).

6.4. CHEMOTHERAPY REGIMEN

The first cycle of OEPA starts immediately after completion of staging. In the rare case of a staging laparoscopy, the first cycle of OEPA should start about 5 days after surgery. Details of chemotherapy administration are available in the chemotherapy drug monographs in the appendix.

The subsequent chemotherapy cycle starts on d29 of each cycle when the following criteria are fulfilled:

---

Fig. 11 Treatment overview for TG-2 and TG-3

---
general condition satisfactory
WBC over 2,000 / mm$^3$
ANC over 500 / mm$^3$
platelets over 80,000 / mm$^3$
no contraindication to any of the prescribed drugs

In case of patients with an expected delay of more than one week, please contact your regional chairperson of the EuroNet-PHL-study group.

Severe side effects are not expected with OEPA or COPDAC. Chemotherapy should only be interrupted in case of severe inter-current infections. In parallel to chemotherapy patients may receive hyperhydration with 2.5-3 l/m$^2$ per day of glucose-saline solution.

For oncological emergencies in patients with initially large tumour mass please see below.

6.4.1. OEPA

Application schedule and dosage of cytotoxic drugs during a cycle are shown in Table 6. After each cycle there is a treatment-free interval between day 16 and 28. The next cycle starts on day 29.
Table 6 OEPA scheme

<table>
<thead>
<tr>
<th>Prednisone/prednisolone</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>60 mg/m²/day p.o. divided into 3 doses</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>day 1 – 15</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Vincristine                   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 1.5 mg/m² i.v., max. SD 2 mg  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| day 1 + 8 + 15                |   |   |   |   |   |   |   |   |   |   |   |   |   |   |

| Doxorubicine                  |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 40 mg/m² as 1-6 hour infusion |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| day 1 + 15                    |   |   |   |   |   |   |   |   |   |   |   |   |   |   |

| Etoposide/Etopophos           |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 125 mg/m² as 1-2 hour infusion|   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| day 1 – 5                     |   |   |   |   |   |   |   |   |   |   |   |   |   |   |

Day 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15

6.4.2. COPDAC

Application scheme and dosage of cytostatic drugs during a cycle are shown in Fehler! Verweisquelle konnte nicht gefunden werden. and 0. After each cycle there is a treatment-free interval between day 16 and 28. The next cycle starts on day 29.

To minimise toxicity to the urinary tract, there is the option to give the uroprotector Mesna along with every application of Cyclophosphamide.

Dacarbazine is highly emetogenic. Therefore 5-HT3-antagonists, possibly supplemented with Dexamethasone (optional) or neuroleptics (e.g. Levomepromazin), are recommended for antiemesis.

Table 7 COPDAC scheme

<table>
<thead>
<tr>
<th>Prednison/Prednisolone</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>40 mg/m²/day p.o. divided into 3 doses</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>day 1 – 15</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Dacarbazine                   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 250 mg/m² as 15 - 30-min. inf. |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| day 1 – 3                     |   |   |   |   |   |   |   |   |   |   |   |   |   |   |

| Vincristine                   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| 1.5 mg/m² i.v. max. SD 2 mg   |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
| day 1 + 8                     |   |   |   |   |   |   |   |   |   |   |   |   |   |   |
**Cyclophosphamide**

500 mg/m², 60-min. inf. day 1 + 8

Intravenous hydration with glucose/saline solution at a rate of 3 l/m²/24 hours commencing with the first cyclophosphamide dose and continuing for at least six hours after last cyclophosphamide dose.

<table>
<thead>
<tr>
<th>Day</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
<th>13</th>
<th>14</th>
<th>15</th>
</tr>
</thead>
</table>

### 6.5. DOSE MODIFICATIONS

Since chemotherapy is well tolerated no detailed provisions for dose modifications are given, even in patients with haematotoxicity CTC grade 4. A short therapy delay may be indicated in a few cases.

In case of drug-specific toxicity (examples: impaired cardiac function after Adriamycin, severe neuropathy during or after Vincristine) or other unexpected severe adverse events the national chairpersons of the EuroNet-PHL study group should be consulted to discuss therapeutic alternatives.

### 6.6. CONTRACEPTION

All patients are advised that during chemo-/radiotherapy and up to one year afterwards procreation of children is not recommended, there is a risk of an adverse effect on the fetus. The treating physician should advise about methods of contraception individually. The occurrence of pregnancy in patients or their partners should be reported to the study office.

### 6.7. SIDE EFFECTS OF CHEMOTHERAPY

General acute side effects of chemotherapy include: nausea, vomiting, weight loss and alopecia. General late side effects of chemotherapy include: increased risk of secondary malignancies, infertility or premature menopause, and increased cardiac event risk.

For additional information on side effects please check chemotherapy drug monographs in the appendix of this protocol.
6.7.1. Etoposide

Acute side effects of Etoposide include: allergic reaction, mucositis, peripheral neuropathies, CNS toxicities, mild bone marrow depression and secondary leukaemia.

6.7.2. Dacarbazine (DTIC)

Dacarbazine is highly emetogenic. Diarrhoea, influenza-like symptoms, allergic skin reactions, fever, photosensitization, local vein irritation as well as flush symptoms can occur during or after injection. Bone marrow toxicity is generally low. Rarely liver, kidney and CNS toxicities (apathy, seizures) occur. A mutagenic, carcinogenic and teratogenic effect for DTIC has been demonstrated in animal experiments. During the GPOH-HD 2002 Pilot study one patient died with rhabdomyolysis after DTIC, which also has been described before (Hauschild et al., 2001).

6.7.3. Vincristine (VCR)

Acute side effects after application of Vincristine are: peripheral neuropathy, constipation, rarely syndrome of inappropriate ADH secretion (= SIAD). In case of severe peripheral neuropathy, especially in motor disturbances or paralysis of hands and/or legs, a replacement of Vincristine by Vinblastine in a dose of 6 mg/m² is recommended.

6.7.4. Cyclophosphamide

Under Cyclophosphamide the following side effects can occur: bone marrow depression, increased infection risk, haemorrhagic cystitis.

6.7.5. Adriamycin (Doxorubicine)

Even at a low cumulative dose Adriamycin can lead to a permanent damage of the heart muscle. However, the extent of the long-term cardiac risk is unknown. Therefore before starting chemotherapy the heart function has to be examined (echocardiography) and documented. In case of initial damage of the heart function a therapeutic alternative should be discussed with the study chairpersons.

6.7.6. Prednisone/Prednisolone

Changes in the bone metabolism have been detected (especially in patients with leukaemia) which can lead to osteonecrosis. In rare cases an artificial joint replacement may be required. In
addition, the Prednisone/Prednisolone therapy can lead to reversible retention of water, increase in weight, increased infection risk and psychosis/mental disorders.

7. RADIOTHERAPY

For patients in all therapy groups (TG-1, TG-2 and TG-3), the decision on radiotherapy is based on early response assessment after 2 cycles of OEPA. Patients with adequate response (response groups AR1 and AR2) will not receive radiotherapy.

A detailed description of the principles of radiotherapy, radiation planning and technical requirements are provided by the radiotherapy manual of the EuroNet-PHL-C1 study.

8. SUPPORTIVE CARE

Management of febrile neutropenia is according to locally agreed guidelines. In the UK, Portacath/IHickman line insertion prior to treatment is recommended to avoid extravasation particularly of adriamycin.

All patients receive Trimethoprim during chemo- and radiotherapy and up to three months after end of chemo-radiotherapy as per local/national guidelines.

If WBC is below 1000/ mm3, patients may receive, e.g. oral colistin sulfate optional as per local guidelines.

Transfusions of packed red cells or platelets should be leukocyte-depleted and irradiated with 30 Gy to avoid GvHD.

During chemotherapy and radiotherapy patients may receive antifungal prophylaxis according to local recommendations.

9. ONCOLOGICAL EMERGENCIES

9.1. Large mediastinal mass

For patients with large mediastinal tumour the level of respiratory insufficiency should be determined.

level 0: No respiratory insufficiency. No restriction of trachea or bronchi visible in X-ray and/or thorax CT. No venous congestion.
level 1: Clinically no signs of respiratory insufficiency but radiological restriction of trachea or bronchi.
level 2: Stridor and / or upper venous congestion (first sign among others headache).
level 3: Orthopnoea

Only in patients up to level 1 a lymph node biopsy under local anaesthesia or a minithoracotomy in general anaesthesia can be performed. Before surgery it should be discussed with the anaesthetist that the patient may need prolonged mechanical ventilation for 1 – 2 days until the tumour has shrunk during treatment. **In all other cases before biopsy a pre-phase with Prednisone/prednisolone 30 – 60 mg / m² (5 – 10 days) should be initiated.**

A therapeutic pleura puncture should be performed under local anaesthesia in case of respiratory insufficiency caused by a large pleural effusion. The same applies to a clinically relevant pericardial effusion.

**9.2. Tumour lysis syndrome**

In the rare case of tumour lysis syndrome (in patients with hyperuricemia or patients with bulky disease) the following is recommended:

Hyperhydration with a liquid volume of 3000 (up to 5000 ml/m²; maximal 7000 ml) per day.

For forced diuresis the infusion should contain 10 mg Furosemide /1000 ml. Every 6 hours fluid balance should be calculated and if needed Furosemide should be applied additionally.

The initial infusion should not contain KCl (addition of KCl only in patients with hypokalaemia only under strict indication with in short-term electrolyte checks).

Urine alkalinization is not recommended as increasing the pH will reduce the solubility of phosphate.

Prophylactically all patients should receive Allopurinol. In case of hyperuricaemia Rasburicase (Fasturtec® or a comparable drug) may be considered.
10. ORGANISATION OF CENTRAL REVIEW

Since it has been shown that quality assurance by central review can affect staging and response assessment (Dieckmann et al., 2002) and thus may also lead to improved event-free survival (Lüders et al. in prep) the EuroNet-PHL reference centre at Halle/Leipzig will continue to offer the central review service to all centres of the EuroNet-PHL study group which want to participate in the central review process as during interim phase. These centres may consider the following:

10.1. INFORMED CONSENT

Before treatment starts an informed consent must be signed.

If parents and/or patients agree a second physician’s opinion can be offered by the EuroNet-PHL reference centre at Halle/Leipzig. In this case please follow the instructions described below:

10.2. Staging

Once the diagnosis is confirmed and the staging investigations completed, this information is documented on a staging form and sent to the EuroNet-PHL reference centre in Halle/Leipzig (Vienna for Austria). The staging results are checked, and then the investigator receives the information and documentation required for treating according to these recommendations.

10.3. Early response assessment

The dates for imaging diagnostics for early response assessment (first restaging) (sonography, CT/MRI, FDG-PET) are time-critical and therefore should be fixed by the start of the second OEPA cycle at the latest.

Only initially involved regions are examined (except if progression is suspected). It is crucial that the FDG-PET is performed on day 14, at the latest on day 17 after the last application of chemotherapy of the second OEPA cycle.

All required documents (imaging submission form and written reports of radiologic images and PET data) and images concerning the early response assessment (first restaging) have to be sent to the reference centre in Halle/Leipzig (Vienna for Austria) at the latest until day 21 after the last application of chemotherapy in the second OEPA cycle.
Please note: There will be no reminder of the central review team for sending of these documents and images.

As soon as possible after central review, the investigator receives the information whether radiotherapy is indicated and - if so - the final reference radiotherapy plan.

NOTE: It is not necessary to wait for the results of the central review before starting the next chemotherapy cycle (TG-2 and TG-3).

10.4. Late response assessment in TG2+3

Documents and images may be send to the EuroNet-PHL reference centre in case of suspected progression.

11. REFERENCE EVALUATION

Applies only if patients or guardians agree to central review process.

11.1. CENTRAL STAGING AND RESPONSE ASSESSMENT

11.1.1. Determination of reference stage

The reference stage is defined for every patient by the central review panel during tumour conferences taking place regularly (at least weekly) at the EuroNet-PHL reference centre. The following information and material is required for the central staging and response assessment, and has to be provided by the treating investigator:

- Results of clinical examination (including ENT findings)
- Results of sonography
- Results, images (preferably electronically) of all CT / MRI examinations and FDG-PET data sets
11.1.2. Organisation of the tumour conference

11.1.2.1. Preparations before tumour conference

Participating treatment centres send the necessary written results and films or data sets (except: PET images – these are transmitted directly by the local nuclear medicine physician) to the EuroNet-PHL-reference centre via Hermes or on CD after patient or parent gave consent to seconded physicians opinion.

The reference coordinator and her authorised assistant check the documents for completeness. If necessary documents are missing, a reminder telephone call is made immediately. As soon as all necessary documents are available the patient is scheduled by the reference centre assistant in the weekly tumour conference.

Prior to the tumour conference both the reference radiologist and the reference nuclear medicine physician independently evaluate the submitted images or data sets (being aware of the written reports of the local centre).

11.1.2.2. Organisation of FDG-PET examinations

The cooperation of the nuclear medicine centres with the reference centre should be organized as following:

FDG-PET examinations are performed according to PET manual measuring data are sent to the reference nuclear medicine physician in the EuroNet-PHL reference centre preferably within one working day via internet and the report on diagnostic results is transmitted to the investigator at the latest on the following day

For complete and timely data acquisition the following should be ensured:

The nuclear medicine reference centre gets preliminary information on place and time of arranged PET examinations based on the data of patient informations send from the local centre.

The electronic data transmission of measured data from the respective PET facility to the PET reference centre is carried out on the day of examination.

The dispatch of the finding by the local PET centre to the investigator and the reference nuclear physician is also performed electronically or by fax at the latest on the following day.

If necessary the reference nuclear medicine physician reminds the local nuclear medicine physician of missing data.
The nuclear medicine physician and the paediatric oncologist of the treating site are responsible for the investigation and initial assessment of skeletal scintigraphy in case of positive PET results in the skeletal system. In preparation of the tumour conference PET findings are evaluated by the reference nuclear medicine physician or his deputy. If discrepancies with the local report occur they are discussed with the contact persons appointed by the cooperating PET centres.

11.1.2.3. Tumour conference

Participants of the tumour conference are: the pediatric oncologist of the reference centre, the reference radiologist, the reference nuclear medicine physician and the reference radiotherapist or their respective deputies.

In the tumour conference as a first step the clinical findings and the findings collected in sonography are presented by the study secretary. Next the reference radiologist reports and compares the results based on his CT/MRI evaluation. Then these data are related to the PET results by the reference nuclear medicine physician. Finally the reference stage is determined in consultation with pediatric oncologist or his deputy.

11.1.2.4. Transmission of information to the investigators

The result of the tumour conference is noted on a staging / response assessment form – tumour conference. Subsequent to the tumour conference these forms are sent to the investigators by fax and/or letter within maximal two working days with corresponding annotations by the reference coordinator.

The EuroNet-PHL reference centres are responsible for establishing the reference stage after final evaluation of the PET / CT / MRI examination findings in synopsis with clinical findings. Also the assignment to therapy groups as well as the PET oriented therapy stratification in TGs.

11.2. REFERENCE RADIATION PLANNING

For all patients undergoing central review a reference radiation plan is designed by the reference radiotherapist or their deputy. This plan considers the involvement pattern, the response to treatment and also the vicinity to risk organs. The reference radiotherapist or their
deputy are also at the local physician’s disposal for concrete questions regarding the patient’s radiation planning and performance.

The definite radiotherapy plan (with additional information on boost regions and also lung radiation if necessary) is defined within the scope of the first restaging tumour conference (after two cycles of chemotherapy). Also this plan, which is signed by the reference radiotherapist and the head of the reference centre, is transmitted to the treating investigators together with the result of the restaging tumour conference.
REFERENCES


## ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abt.</td>
<td>(Abteilung) Division</td>
</tr>
<tr>
<td>ALAT</td>
<td>Alanine-amino-transferase</td>
</tr>
<tr>
<td>AML</td>
<td>Acute Myeloid Leukemia</td>
</tr>
<tr>
<td>AP</td>
<td>Alkaline Phosphatase</td>
</tr>
<tr>
<td>AR</td>
<td>Adequate response</td>
</tr>
<tr>
<td>ASAT</td>
<td>Aspartate-amino-transferase</td>
</tr>
<tr>
<td>B-symptoms</td>
<td>Systemic symptoms: unexplained fever, weight loss, night sweats</td>
</tr>
<tr>
<td>C</td>
<td>Celsius</td>
</tr>
<tr>
<td>°C</td>
<td>Degree Celsius (temperature dimension unit)</td>
</tr>
<tr>
<td>Ca</td>
<td>Calcium</td>
</tr>
<tr>
<td>CCLG</td>
<td>Children’s Cancer &amp; Leukaemia Group (England, Scotland, Ireland and Wales)</td>
</tr>
<tr>
<td>CCS</td>
<td>Children’s Cancer Study</td>
</tr>
<tr>
<td>CD</td>
<td>Compact Disc</td>
</tr>
<tr>
<td>cf.</td>
<td>Confer</td>
</tr>
<tr>
<td>Cm</td>
<td>Centimeter</td>
</tr>
<tr>
<td>CMV</td>
<td>Cytomegalovirus</td>
</tr>
<tr>
<td>CNS</td>
<td>Central Nervous System</td>
</tr>
<tr>
<td>COPDAC</td>
<td>Chemotherapy cycle: Cyclophosphamide, Vincristine, Prednisone/Prednisolone, Dacarbazine</td>
</tr>
<tr>
<td>COPP</td>
<td>Chemotherapy cycle: Cyclophosphamide, Vincristine, Prednisone/Prednisolone, Procarbazine</td>
</tr>
<tr>
<td>Cp</td>
<td>Compare</td>
</tr>
<tr>
<td>CR</td>
<td>Complete remission</td>
</tr>
<tr>
<td>CRF</td>
<td>Case Report Form</td>
</tr>
<tr>
<td>Cru</td>
<td>Complete remission unconfirmed</td>
</tr>
<tr>
<td>CT</td>
<td>Computed tomography</td>
</tr>
<tr>
<td>Cum.</td>
<td>Cumulative</td>
</tr>
<tr>
<td>D</td>
<td>Dimension</td>
</tr>
<tr>
<td>2D</td>
<td>Two-dimensional</td>
</tr>
<tr>
<td>3D</td>
<td>Three-dimensional</td>
</tr>
<tr>
<td>DAL</td>
<td>Deutsch-Österreichische-Leukämie/Lymphom-Liga</td>
</tr>
<tr>
<td>DAL-HD</td>
<td>Deutsch-Österreichische-Leukämie/Lymphom-Liga-Hodgkin’s Disease</td>
</tr>
<tr>
<td>DD</td>
<td>Differential diagnosis</td>
</tr>
<tr>
<td>DFS</td>
<td>Disease free survival</td>
</tr>
<tr>
<td>DICOM</td>
<td>Digital imaging file format</td>
</tr>
<tr>
<td>DNA</td>
<td>Desoxyribonucleic acid</td>
</tr>
<tr>
<td>DTIC</td>
<td>Dacarbazine</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Definition</td>
</tr>
<tr>
<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>DVH</td>
<td>Dose Volume Histogram</td>
</tr>
<tr>
<td>EBV</td>
<td>Epstein Barr Virus</td>
</tr>
<tr>
<td>ECG</td>
<td>Electrocardiogramme</td>
</tr>
<tr>
<td>Echo</td>
<td>Echocardiogramme</td>
</tr>
<tr>
<td>Echo-CG</td>
<td>Echocardiogramme</td>
</tr>
<tr>
<td>ED</td>
<td>Einzeldosis (single dose)</td>
</tr>
<tr>
<td>EEG</td>
<td>Electroencephalogramme</td>
</tr>
<tr>
<td>EFS</td>
<td>Event free survival</td>
</tr>
<tr>
<td>e.g.</td>
<td>Example given</td>
</tr>
<tr>
<td>E-lesions</td>
<td>Extranodal lesions by contiguous involvement</td>
</tr>
<tr>
<td>ENT</td>
<td>Ear, Nose and Throat</td>
</tr>
<tr>
<td>Et al.</td>
<td>Et altra (and others)</td>
</tr>
<tr>
<td>Euro-Net</td>
<td>European Network</td>
</tr>
<tr>
<td>Euro-Net-PHL-C1</td>
<td>European Network on Pediatric Hodgkin`s Lymphoma-Classical Hodgkin-1</td>
</tr>
<tr>
<td>FAB</td>
<td>French-American British (classification for acute leukemias)</td>
</tr>
<tr>
<td>FDG-Pet</td>
<td>Fluoro-Deoxyglucose-Positron emission tomography</td>
</tr>
<tr>
<td>Fig.</td>
<td>Figure</td>
</tr>
<tr>
<td>FSH</td>
<td>Follicle stimulating hormone</td>
</tr>
<tr>
<td>fT4</td>
<td>Free Tetra-iodineThyionine</td>
</tr>
<tr>
<td>GGT</td>
<td>Gamma Glutamyl transferase</td>
</tr>
<tr>
<td>GOT</td>
<td>Synonyme for ASAT (Aspartate-amino-transferase)</td>
</tr>
<tr>
<td>GPOH</td>
<td>Gesellschaft für Pädiatrische Onkologie und Hämatologie, (German Society for Paediatric Oncology and Haematology)</td>
</tr>
<tr>
<td>GPOH-HD</td>
<td>GPOH-HodgkinStudiengruppe (GPOH-Hodgkin`s study group)</td>
</tr>
<tr>
<td>GPT</td>
<td>Synonyme for ALAT (Alanine-amino-transferase)</td>
</tr>
<tr>
<td>GvHD</td>
<td>Graft versus host diseqase</td>
</tr>
<tr>
<td>Gy</td>
<td>Gray</td>
</tr>
<tr>
<td>H</td>
<td>Hour</td>
</tr>
<tr>
<td>HCV</td>
<td>Hepatitis C Virus</td>
</tr>
<tr>
<td>HIV</td>
<td>Humane Immunodeficiency Virus</td>
</tr>
<tr>
<td>HL</td>
<td>Hodgkin`s Lymphoma</td>
</tr>
<tr>
<td>HLA</td>
<td>Human Leukocyte Antigen</td>
</tr>
<tr>
<td>HSV</td>
<td>Herpes simplex virus</td>
</tr>
<tr>
<td>5-HT-3 antagonist</td>
<td>Serotinine-antagonist</td>
</tr>
<tr>
<td>ID</td>
<td>Identification code</td>
</tr>
<tr>
<td>i.e.</td>
<td>Id est</td>
</tr>
<tr>
<td>IF-RT</td>
<td>Involved field radiotherapy</td>
</tr>
<tr>
<td>Incl.</td>
<td>Including</td>
</tr>
<tr>
<td>IR</td>
<td>Inadequate response</td>
</tr>
<tr>
<td>IRu</td>
<td>Inadequate response unconfirmed</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Form</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>i.v.</td>
<td>Intravenously</td>
</tr>
<tr>
<td>KCL</td>
<td>Potassium chlorine</td>
</tr>
<tr>
<td>Kg</td>
<td>Kilogram</td>
</tr>
<tr>
<td>LDH</td>
<td>Lactate dehydrogenase</td>
</tr>
<tr>
<td>LESP</td>
<td>Late Effect Study Group</td>
</tr>
<tr>
<td>LH</td>
<td>Luteinizing Hormone</td>
</tr>
<tr>
<td>LH-RH</td>
<td>Luteinizing Hormone Releasing Hormone</td>
</tr>
<tr>
<td>LN</td>
<td>Lymph node</td>
</tr>
<tr>
<td>LSRA</td>
<td>Local staging and response assessment</td>
</tr>
<tr>
<td>m²</td>
<td>Square meter</td>
</tr>
<tr>
<td>mAS</td>
<td>milli Ampere seconds</td>
</tr>
<tr>
<td>Mg</td>
<td>Milligram</td>
</tr>
<tr>
<td>MHD</td>
<td>French Hodgkin’s Lymphoma trial name</td>
</tr>
<tr>
<td>Min</td>
<td>Minimum</td>
</tr>
<tr>
<td>MI</td>
<td>Milliliter</td>
</tr>
<tr>
<td>Mm</td>
<td>Millimeter</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>MTX</td>
<td>Methotrexate</td>
</tr>
<tr>
<td>NC</td>
<td>No change</td>
</tr>
<tr>
<td>ND</td>
<td>Not done</td>
</tr>
<tr>
<td>NHL</td>
<td>Non Hodgkin’s lymphoma</td>
</tr>
<tr>
<td>Non-GPOH</td>
<td>Not belonging to GPOH group</td>
</tr>
<tr>
<td>OEPA</td>
<td>Chemotherapy cycle: Vincristine, Etoposide, Prednisone, Adriamycin</td>
</tr>
<tr>
<td>OS</td>
<td>Overall survival</td>
</tr>
<tr>
<td>PCR</td>
<td>Polymerase Chain Reaction</td>
</tr>
<tr>
<td>PD</td>
<td>Progressive disease</td>
</tr>
<tr>
<td>PET</td>
<td>Positron emission tomography</td>
</tr>
<tr>
<td>p.i.</td>
<td>Per injectionem</td>
</tr>
<tr>
<td>p.o.</td>
<td>Per os (by mouth)</td>
</tr>
<tr>
<td>PR</td>
<td>Partial remission</td>
</tr>
<tr>
<td>Prog.</td>
<td>Progression</td>
</tr>
<tr>
<td>PTV</td>
<td>Primary target volume</td>
</tr>
<tr>
<td>11q23</td>
<td>Cytogenetic abnormality; fusion chromosome</td>
</tr>
<tr>
<td>Resid.</td>
<td>Residual, residuum</td>
</tr>
<tr>
<td>Resp.</td>
<td>Respectively</td>
</tr>
<tr>
<td>RNA</td>
<td>Ribonucleic acid</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>SE</td>
<td>Standard error</td>
</tr>
<tr>
<td>SIAD</td>
<td>Syndrome of inadequate</td>
</tr>
<tr>
<td>Sono</td>
<td>Sonography, ultrasound</td>
</tr>
</tbody>
</table>
SRA  Staging and response assessment
SST  Secondary solid tumour
STAR  strategy for treatment adapted to response
T2-STIR  Fat saturated T2-weighted spin echo sequence (MRI)
T1-Flash  T1-weighted gradient echo sequence (MRI)
TG  Therapy group
T2-TIRM  Fat saturated T2-weighted spin echo sequence (MRI)
TOX  Toxicity
T1-SE  T1-weighted spin echo sequence (MRI)
TSH  Thyroid stimulating hormone
UK  United Kingdom
VCR  Vincristine
VP-16  Etoposide
Vs.  Versus
WHO  World Health Organisation
VZV  Varicella zoster Virus
X-ray  Two-dimensional radiogramme