

Intergroup Study (EORTC 20051)

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The H10 EORTC/GELA randomized Intergroup trial on early FDG-PET scan guided treatment adaptation versus standard combined modality treatment in patients with supradiaphragmatic stage I/II Hodgkin's lymphoma

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Warning:

This is an Intergroup study coordinated by the EORTC. The present protocol is written according to the EORTC template and is fully applicable to all **collaborative groups** (with the exception of EORTC specific chapters or other collaborative group(s) specific appendix and unless otherwise specified).

The chapters 16 to 19 and the PIS/IC (Appendix E) are fully applicable to **EORTC investigators** only.

Corresponding items and contact addresses for non EORTC investigators are provided in their **Group specific appendix** that supersedes the contents of chapters 16-19 (unless otherwise specified).

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Table of contents:

Protocol summary	8
Trial organization	11
1 Background and introduction	12
2 Objectives of the trial	14
2.1 General objectives	14
2.2 Endpoints	15
3 Patient selection criteria	15
3.1 Treatment group: favorable (F) and unfavorable (U)	16
4 Trial Design	16
5 Therapeutic regimens, expected toxicity, dose modifications	19
5.1 Chemotherapy regimens	19
5.1.1 ABVD	19
5.1.2 BEACOPP escalated	19
5.2 Expected toxicity	20
5.3 Guidelines for dose modification	20
5.3.1 ABVD	20
5.3.2 Escalated BEACOPP	21
5.3.3 Non haematological toxicity (both ABVD and escalated BEACOPP)	23
5.4 Radiotherapy (<i>detailed guidelines in Appendix F</i>)	24
5.4.1 Target volumes	24
5.4.2 Dose specification	24
5.4.3 Dose fractionation	24
5.5 Reasons for stopping protocol treatment	24
6 Clinical evaluation, laboratory tests and follow-up	25
6.1 Before treatment start	25
6.2 During treatment	26
6.2.1 Before & during each cycle	26
6.2.2 After two cycles of ABVD: major evaluation point	26
6.2.3 After completion of chemotherapy	26
6.3 At the end of treatment (final response evaluation)	27
6.4 During follow-up (from end of treatment until disease relapse/progression)	28
6.4.1 Timing of follow-up visits after last administration of protocol therapy (<i>final response evaluation has already taken place at 6-8 weeks after end of treatment</i>)	28
6.4.2 Investigations at follow-up after the end of treatment	28
6.4.2.1 First year: 4, 6 and 9 months	28
6.4.2.2 At 12 months	29

6.4.2.3	Second year every 3 months	29
6.4.2.4	Third and fourth year every 6 months	29
6.4.2.5	At five years	30
6.4.2.6	After five years lifelong	30
6.4.2.7	At the time of relapse or progression	30
6.4.2.8	At the time of death	31
6.5	During follow-up (after disease relapse/progression)	31
6.6	Summary table of required investigations	32
6.6.1	From inclusion to end of treatment	32
6.6.2	Follow-up (from end of treatment until disease relapse/PD)	33
7	Criteria of evaluation	33
7.1	Progression-free survival	33
7.2	Event-free survival	34
7.3	Overall survival	34
7.4	Response criteria	34
7.4.1	Complete remission (CR)	35
7.4.2	Complete Remission unconfirmed (CRu)	35
7.4.3	Partial remission	36
7.4.4	No change or Stable disease	36
7.4.5	Progressive disease	36
7.4.6	Relapsed disease	36
7.5	Toxicity end-points	36
8	Statistical considerations	37
8.1	Statistical design	37
8.1.1	Sample size	37
8.1.1.1	PET negative patients	37
8.1.1.2	PET positive patients	38
8.1.2	Randomization and stratifications	38
8.2	Statistical analysis plan	38
8.2.1	Primary and secondary endpoints	39
8.2.2	Analysis populations	39
8.2.3	Statistical methods	39
8.2.3.1	Progression free survival	40
8.2.3.2	Event free survival	40
8.2.3.3	Overall survival	40
8.2.3.4	Response to protocol therapy	40
8.2.3.5	Adverse events recorded during protocol therapy	40

8.2.3.6	Late adverse events	41
8.2.4	Interim analyses	41
8.2.5	Pre-planned sensitivity, exploratory and prognostic factors analyses	41
8.2.6	Data recoding and display	41
8.3	End of study	42
9	Data monitoring	42
10	Publication policy	43
11	Investigator authorization procedure	43
12	Patient randomization and registration procedures	44
12.1	Initial randomization	44
12.2	Second registration	45
13	Forms and procedures for collecting data	46
13.1	Case report forms and schedule for completion	46
13.2	Data flow	47
13.2.1	Using the paper CRF	47
13.2.2	Using the electronic forms system	48
14	Reporting of Serious Adverse Events	48
14.1	Definitions	48
14.2	Reporting procedure	49
14.2.1	Non- serious adverse events and/or non-serious adverse drug reactions	49
14.2.2	Serious adverse events or serious adverse drug reactions	49
15	Quality assurance	51
15.1	Control of data consistency	51
15.2	Audits	52
15.3	Central review of pathology	52
16	Ethical considerations	54
16.1	Patient protection	54
16.2	Subject identification	54
16.3	Informed consent	54
17	Administrative responsibilities	55
17.1	The study coordinator	55
17.2	The EORTC Data Center	55
17.3	The EORTC group	56
18	Trial sponsorship and financing	57
19	Trial insurance	57

Table of appendices:

Appendix A: References	58
Appendix B: WHO performance status scale	61
Appendix C: Common Terminology Criteria for Adverse Events	62
Appendix D: World Medical Association Declaration of Helsinki	63
Appendix E: Patient Information Sheet and Informed consent document for clinical trials	67
Appendix F: Radiotherapy guidelines	76
Appendix G: FDG-PET Scan guidelines	81
Appendix H: ANN ARBOR STAGING * - COTSWOLDS RECOMMENDATIONS **	83
Appendix I: MEDIASTINUM MEASUREMENT (MT ratio evaluation *)	85

Protocol summary

Title of the Study	The H10 EORTC/GELA randomized Intergroup trial on early FDG-PET scan guided treatment adaptation versus standard combined modality treatment in patients with supradiaphragmatic stage I/II Hodgkin's lymphoma
Objective(s)	<p>Primary objective: To evaluate whether chemotherapy alone is as effective, but less toxic, as combined modality treatment, in patients with stage I/II Hodgkin's lymphoma who are FDG-PET scan negative after two cycles of ABVD. This question will be addressed in the group of patients with favorable stages I/II disease (F) as well as in those with unfavorable stage I/II disease (U).</p> <p>Secondary objective: To evaluate whether chemotherapy with escalated BEACOPP improves the outcome of PET positive patients – after 2 cycles of chemotherapy - when compared with standard therapy</p>
Methodology	<p>Phase III non inferiority (primary objective in PET- pts)</p> <p>Phase III superiority (secondary objective in PET+ pts)</p>
Number of patients	<p>At least 1576 pts, to be simultaneously accrued in all groups</p> <p>608 to 750 pts in group A (F/PET-)</p> <p>720 to 850 pts in group B (U/PET-)</p> <p>248 pts expected in group C (PET+)</p>
Diagnosis and main criteria for inclusion	<ul style="list-style-type: none"> ◆ Histologically confirmed Hodgkin's lymphoma (HL), except for nodular lymphocyte predominant subtype (nodular paragranuloma) ◆ Supradiaphragmatic Ann Arbor clinical stage I or II ◆ Previously untreated ◆ Clinical stages I/II ◆ Age 15-70 years ◆ WHO performance 0-3 ◆ FDG-PET scan prospectively planned after two cycles of ABVD in all patients ◆ Informed consent
Treatment	<p>All eligible patients will be stratified according to the classic EORTC clinical prognostic factors into the favourable (F) and unfavourable (U) subsets as follows:</p> <p><i>Unfavourable (U) subset</i> includes patients with: CSII \geq 4 nodal areas or age \geq 50 yrs or MT ratio \geq 0.35 or ESR \geq 50 (without B-symptoms) or ESR \geq 30 (with B-symptoms).</p> <p><i>Favourable (F) subset:</i> All other patients belong to the F group.</p> <p><i>It is mandatory to perform an FDG-PET scan after two cycles of ABVD in all patients.</i></p>

The F group will be randomized between:

1. *Standard arm:* ABVDx3 cycles + Involved node RT (IN-RT) 30 Gy (+boost of 6Gy to residual lesions); FDG-PET after two cycles of ABVD for comparison with the experimental arm will be performed but no treatment adaptation will take place.

2. *Experimental arm:* ABVDx2 cycles; then FDG-PET evaluation:

PET negative: ABVDx2 without further RT (total of 4 cycles!)

PET positive: presumed poor-risk: switch to escalated BEACOPPx2 + INRT30Gy (+boost 6Gy to residual lesions).

The U group will be randomized between:

1. *Standard arm:* ABVDx4 cycles + IN-RT 30Gy (+boost 6Gy to residual lesions). FDG-PET after two cycles of ABVD for comparison with the experimental arm will be performed but no treatment adaptation will take place.

2. *Experimental arm:* ABVDx2 cycles; then FDG-PET evaluation:

PET negative: ABVDx 4 cycles, without RT (total of 6 cycles)

PET positive: presumed poor-risk: switch to escalated BEACOPPx2 + INRT 30Gy (+boost 6Gy to residual lesions).

ABVD q4 weeks

Doxorubicin	25 mg/m ² i.v.	day 1 and 15
Bleomycin	10 mg/m ² i.v./i.m.	day 1 and 15
Vinblastine	6 mg/m ² i.v.	day 1 and 15
Dacarbazine	375 mg/m ² i.v.	day 1 and 15

BEACOPP escalated q3 weeks

Cyclophosphamide	1250 mg/m ² i.v.	day 1
Doxorubicin	35 mg/m ² i.v.	day 1
Vincristine	1.4 mg/m ² i.v.(max.2mg)	day 8
Bleomycin	10 mg/m ² i.v./i.m.	day 8
Etoposide	200 mg/m ² / i.v.	day 1 to 3
Procarbazine	100 mg/m ² orally	day 1 to 7
Prednisone	40 mg/m ² orally	day 1 to 14
G-CSF	5 mcg/kg s.c.	day 9 to recovery
leukocytes>1.0x10 ⁹ /l		

<p>Duration of treatment</p>	<p>The following are criteria for protocol treatment discontinuation</p> <ul style="list-style-type: none"> ◆ Normal completion of protocol treatment (see above) ◆ Progressive disease during protocol treatment ◆ Excessive toxicity that does not allow to give the protocol treatment e.g. reasons to stop because of excessive hematologic toxicity, or to stop doxorubicin or cyclophosphamide (for details see chapter 5.3.1-5.3.3) ◆ No FDG-PET scan performed after two cycles of ABVD. In this case, patient is considered major protocol violation. ◆ Refusal of patient to further cooperate (at any time and because of any reason) ◆ Investigator's decision
<p>Criteria for evaluation</p> <p><i>Efficacy</i></p> <p><i>Safety</i></p>	<p><i>Primary endpoints:</i> progression-free survival (PFS). PFS is defined as time interval from the date of randomization until documentation of first progression or death whichever comes first</p> <p><i>Secondary endpoint:</i> event free survival (EFS), overall survival (OS)</p> <p><i>Secondary endpoints:</i></p> <p>long-term toxicity (according to CTCAE v 3.0 criteria)</p> <ul style="list-style-type: none"> ◆ secondary malignancies ◆ cardiovascular events ◆ pulmonary events
<p>Statistical methods</p>	<p>Final analysis (group A: ≥ 26 events / group B: ≥ 63 events)</p> <p>Group A : 1 sided logrank test (overall alpha=0.025)</p> <p>Group B : 1 sided logrank test (overall alpha=0.025)</p> <p>Group C : 2 sided logrank test (overall alpha=0.05)</p> <p>Interim futility analysis (group A: ≥ 12 events / group B: ≥ 22 events)</p>

Trial organization

This trial is an Intergroup Trial, jointly conducted by several national/international cancer clinical research groups in different European countries.

The EORTC is the coordinating group in this trial and will be the Sponsor in all countries unless otherwise specified for legal or logistical reasons.

This protocol is to be followed by all participating groups. Chapters 1 to 15 are fully applicable to all groups. Chapters 16-19 are specific to the EORTC participants. All particularities of participation of each individual group are to be included in the Group Specific Appendices to be annexed at the end of the protocol.

The participation to this trial is only possible through one of the participating clinical cancer research groups. For contacts and addresses please refer to the Group Specific Appendix of the group of your membership or of your national group (should you have any difficulty in identifying such a group, please contact the EORTC Data Center).

Investigators members of several groups participating to the trial will receive guidelines through which of these groups they shall participate within the framework of this trial (this because of the national legal framework). For EORTC members all patients will be accounted for the membership independently from the group they choose to participate through (see EORTC Policy 10).

1 Background and introduction

Hodgkin's lymphoma (HL) occurs at an incidence of 2-4/10⁵/year in the Western world. Treatment results have dramatically improved over the last decades resulting in cure rates of >70%. (Ref. 1, Ref. 2) The EORTC Lymphoma Group has a longstanding track record of performing randomized trials in patients with HL. (Ref. 3) In the previous H1, H2, H5, H6, H7, H8 and H9 EORTC Lymphoma Group trials on patients with early stages HL (the H8 and H9 in close collaboration with the Groupe d'Etude de Lymphome Adulte, GELA), we established combined modality as the gold standard treatment which is supported by many other cooperative groups. (Ref. 1, Ref. 2) We identified clinical prognostic factors to separate a favorable prognostic subset of patients (F) that can be treated less aggressively and an unfavorable group (U) that is in need for more intensive treatment. (Ref. 4, Ref. 5, Ref. 6, Ref. 7, Ref. 8, Ref. 9, Ref. 10, Ref. 11, Ref. 12, Ref. 13, Ref. 14) The unfavorable group of patients comprises those who have Ann Arbor CS II with ≥ 4 nodal areas or age ≥ 50 yrs or mediastinum-thorax (MT) - ratio ≥ 0.35 or ESR ≥ 50 , without B-symptoms or ESR ≥ 30 , with B-symptoms. All others belong to the F group. Based on these prognostic factors and the results of previous trials, at present our standard treatment for the F group consists of 3 cycles of chemotherapy followed by involved field RT and for the U group of 4 cycles of chemotherapy followed by the same RT.

The new EORTC/GELA Intergroup H10 trial for patients with early stages HL includes again both favorable (F) and unfavorable (U) prognostic subgroups, using the same upfront clinical prognostic factors as in the H9 trial. (Ref. 14) With the standard combined modality treatment a progression-free survival of 90-95% in the F group and of 85-90% in the U group can be reached (data from H8+H9) (Ref. 12, Ref. 13, Ref. 14) We aim in this new trial at reducing treatment related toxicity - especially long-term- in selected groups of patients who are "overtreated" with the current treatment standard. Patients who are cured of HL have a life-long increased risk of premature death as compared to the general population. About 10-15% of the patients will develop serious late secondary events including secondary malignancies and (lethal) non-malignant diseases e.g. cardiovascular diseases. (Ref. 15, Ref. 16, Ref. 17, Ref. 18, Ref. 19, Ref. 20, Ref. 21, Ref. 22, Ref. 23, Ref. 24) The 10-15% incidence of late adverse effects of treatment are mainly attributed to RT whether or not combined with chemotherapy. Though most of the data concern patients who were treated in the sixties to eighties of the past century with wide field irradiation fields, the incidence of these, often fatal, events is unacceptably high for a disease that can be cured so frequently. The frequencies of these untoward events can probably be reduced by adapting primary treatment e.g. reducing RT. We hypothesize that early response to treatment can guide us in modifying the burden of treatment. Earlier observations from our group indicate that in advanced stages 6 cycles of chemotherapy might be sufficient treatment when an early CR is reached after 4 cycles, whereas the worldwide gold standard is 8 cycles for these patients with stages III/IV. (Ref. 25) In line with these observations we propose, as hypothesis for the H10 trial, that evaluation of tumor response early in the course of treatment (e.g. after 2 cycles of the combination of adriamycine, bleomycine, vinblastine, and dacarbazine -ABVD), (Ref. 26) and preferably by sensitive and specific imaging methods, will predict which patients have a very good prognosis and can be treated less intensively. To conclude from these considerations, we aim primarily at reducing toxicity while maintaining efficacy, considering in our statistical assumptions a decrease of progression-free survival of 10% (roughly the percentage of undesirable, secondary events) as acceptable and compatible with non-inferiority of the experimental arm compared to the standard arm. Even in case of relapse or progression in some of these patients adequate salvage treatment is available (with or without high-dose treatment), that results in salvage of 40-50% of these patients. (Ref. 1, Ref. 2)

After completion of treatment, restaging by physical examination and CT-scan is not very predictive for ultimate outcome. Using F-18 fluorodeoxyglucose positron emission tomography (FDG-PET) scan in the evaluation of treatment response in HL, the negative predictive value is high (81-100%) showing the ability of FDG-PET to identify patients with excellent prognosis. The positive predictive value is more variable (25-100%). When results of FDG-PET are interpreted in combination with clinical history and CT-scan, the positive predictive value increases to >85%, residual activity being strongly suggestive of active Hodgkin remnants. (Ref. 27, Ref. 28, Ref. 29, Ref. 30) Treatment-induced tumor cell death or growth arrest reduce the FDG uptake in non-Hodgkin's lymphoma as early as 7 days after start of therapy. In HL data are less abundant (Ref. 31). Three studies merit special attention with regard to the predictive value of early response evaluation:

i. In a retrospective study by Hutchings et al FDG-PET was performed after 2-3 cycles of chemotherapy in 85 HL patients. The interim PET scans were negative in 63 patients, showed minimal residual uptake in 9 patients and were positive in 13 patients. The 5-year progression free survival was 92%, 88% and 42%, respectively. (Ref. 32)

ii. These findings were confirmed in a prospective study in 77 HL patients. PET scans were performed after 2 cycles of chemotherapy. Two out of the 61 PET-negative patients experienced treatment failure, in comparison with 10 out of 16 PET-positive patients. With a median follow-up of 20 months highly significant associations were reported between early interim FDG-PET and progression free survival ($p < 0.0001$) and overall survival ($p < 0.01$) (Ref. 33)

iii. Gallamini et al showed in a series of HL patients that the degree of decrease in the standardized uptake after two cycles of chemotherapy is of importance for the FDG-PET positive patients implicating that those with >50% decrease will have a good prognosis and those with <50% decrease will fail. (Ref. 34)

From these data it can be concluded that early assessment of response to chemotherapy with FDG-PET is an accurate predictor of progression free survival and overall survival in Hodgkin lymphoma. Therefore, in the H10 trial we use the early response to treatment analyzed by FDG-PET scan, as a guidance to early treatment adaptation. Patients with a negative FDG-PET after 2 cycles of ABVD constitute the good-risk group for whom we can reduce treatment burden. By testing the same hypothesis in the favorable and the unfavorable subsets, we can demonstrate whether this early FDG-PET-based response is an early predictor of outcome, independent of our classical prognostic factors.

Reducing treatment burden can be achieved in several ways: less chemotherapy or less radiotherapy or reduction of the combination of both. The question whether patients with early stages HL can be treated with chemotherapy alone is a key question, worldwide. In patients with advanced disease we have shown that additional radiotherapy is no longer needed when a good CR is reached with adequate chemotherapy (EORTC trial #20884) (Ref. 35). However, in patients with early stages the combined modality treatment approach is still standard. Chemotherapy alone appeared to be less effective in several trials (Ref. 14, Ref. 36, Ref. 37). Apparently, one has not selected the most appropriate group in early stages to omit RT. If our present hypothesis is correct, patients who can be treated safely with chemotherapy alone, belong to the group with an early CR as established by FDG-PET. Data from literature indicate that about 85-90% of early stage patients are already FDG-PET negative after two cycles. So, only a small minority of about 10-15% will constitute the group with a less good-risk profile according to our hypothesis. Remarkably, that percentage of 10-15% roughly reflects the percentage of failures to standard treatment. The advantage in progression-free survival for patients who are treated with combined modality as compared to those with chemotherapy alone also reaches about 10% in the recent study of the National Cancer Institute of Canada. (Ref. 36)

Is the group of patients with PET-positivity after two cycles of chemotherapy indeed the poor-risk group and should they be treated more intensively? The escalated BEACOPP schedule, developed

by the German Hodgkin Study Group and already in clinical use by the participants in EORTC and GELA studies, will be used for the intensification of chemotherapy in the investigational arm (Ref. 37).

This is the first randomized intergroup trial on early treatment adaptation guided by the result of FDG-PET scan and aiming at a reduction of treatment burden. The unique design of the H10 trial has already drawn great interest from other cooperative lymphoma groups. The British Lymphoma group will undertake a randomized trial in which FDG-PET response is scheduled after three cycles of ABVD. In their design with FDG-PET being the evaluation after completion of chemotherapy, patients with a negative PET will be randomized between RT and no further treatment. In our study already an early FDG-PET response is taken into account for treatment adaptation.

The H10-trial aims at reducing toxicity while maintaining efficacy in patients with early stage HL who experience an excellent tumor-free outcome with standard combined modality treatment. However, the long-term serious adverse events of treatment ask for modification of primary treatment burden. This randomized phase III trial aims at identifying the group of patients that will enjoy long-term tumor free survival with less intensive treatment and thus -according to our hypothesis- less serious long-term adverse events. The identification of the “good-risk”-group will be based upon the early response to ABVD (after two cycles) analyzed by FDG-PET scan. When according to FDG-PET scanning no viable tumor is left after two cycles of ABVD (both in the *ab initio* favorable (F) as well as unfavorable subgroup (U)), we will withhold RT for these patients and complete the treatment with chemotherapy alone whereas the patients in the standard combined modality arm will receive additional cycles of ABVD + involved node RT (IN-RT) irrespective of the result of the FDG-PET scan. Notably, in the standard arm FDG-PET scan after 2 cycles of ABVD is mandatory as well, but the result will be used for documentation purposes only. When according to FDG-PET scanning viable tumor is still present after two cycles of ABVD (both in the *ab initio* favorable (F) as well as unfavorable subgroup (U)), we will change chemotherapy from ABVD to a more intense schedule e.g. escalated BEACOPP for two cycles followed by IN-RT. By doing this we are aiming at improving the PFS for this subgroup of patients whereas the patients in the standard combined modality arm will receive additional cycles of ABVD + IN-RT.

2 Objectives of the trial

The aim in this trial is to find out whether the outcome of patients with stages I/II Hodgkin's lymphoma can be improved by early treatment adaptation, based on the results of a FDG-PET scan performed after two cycles of chemotherapy.

2.1 General objectives

The primary objective is to evaluate whether chemotherapy alone is as effective -but less toxic-, as combined modality treatment in terms of progression-free survival (PFS), in patients with stages I/II Hodgkin's lymphoma who are FDG-PET scan negative after two cycles of ABVD. This question will be addressed in the group of patients with favorable stages I/II disease as well as in those with unfavorable stages I/II disease.

A secondary objective is to evaluate whether early change of chemotherapy from ABVD to escalated BEACOPP improves the progression-free survival of patients who are FDG-PET-positive after two cycles of ABVD, as compared with those who continue on standard ABVD in both favorable as well as unfavorable subsets of patients.

Another secondary objective is to confirm that early response to FDG-PET scan can predict the outcome of patients with stage I/II Hodgkin's lymphoma. This will be evaluated in the patients randomized in the standard arm.

2.2 Endpoints

Primary endpoint

The primary end-point for all objectives is progression free survival. Progression is defined as progressive disease during protocol treatment, or relapse of HL after previous complete remission/complete remission unconfirmed (CRu), partial remission (PR) or disease stabilization (no change, NC) at the end of protocol treatment.

Secondary endpoints include

- ◆ Event-free survival (see definition of events in chapter 6)
- ◆ Overall survival
- ◆ Long-term toxicity in terms of
 - ◆ secondary malignancies
 - ◆ cardiovascular events
 - ◆ pulmonary events

3 Patient selection criteria

- ◆ Histologically proven Hodgkin's lymphoma, except for the nodular lymphocyte predominant subtype (nodular paragranuloma)
- ◆ Supradiaphragmatic Ann Arbor clinical stage I or II, both favorable and unfavorable prognostic subsets (for definition of favorable (F) and unfavorable (U), see at the end of this section)
- ◆ Previously untreated
- ◆ Age 15 through 70 years
- ◆ FDG-PET scan already prospectively planned after two cycles of ABVD for all patients (see Appendix G).
- ◆ WHO performance status grades 0, 1, 2 or 3 (see Appendix B)
- ◆ Pregnant or breast-feeding women are excluded.
- ◆ Patients of childbearing/reproductive potential should use adequate birth control measures during the whole duration of study treatment.
- ◆ Absence of severe cardiac, pulmonary, neurologic psychiatric or metabolic disease. Patients with unstable diabetes mellitus are excluded (to avoid uninterpretable FDG-PET scan).
- ◆ Adequate liver and renal function (total serum bilirubin ≤ 2.5 x ULN, serum creatinine ≤ 2.5 x ULN)
- ◆ No concomitant or previous malignancies with the exception of basal cell skin tumors, adequately treated carcinoma in situ of the cervix and any cancer that has been in complete remission for >5 years
- ◆ No known HIV infection
- ◆ Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial

- ◆ Written informed consent or confirmed informed consent according to ICH/EU Good Clinical Practice, and national/local regulations. Parent's consent is required for patients under 18 years of age.

Patients can only be randomized in this trial once.

3.1 Treatment group: favorable (F) and unfavorable (U)

The definition of the two subgroups –e.g.favorable (=F) and unfavorable (=U)- according to the *ab initio* prognostic characteristics is similar to that used in the previous EORTC-GELA H9 trial.

Group	Prognostic factors
Favorable	CS I and II (max. 3 involved areas) <i>and</i> <50 years <i>and</i> ESR<50 (no B symptoms) or ESR <30 (B symptoms present) <i>and</i> MT ratio <0.35
Unfavorable	CS II ≥4 nodal areas* involved <i>or</i> age ≥50 years <i>or</i> ESR ≥50 (no B symptoms) <i>or</i> ESR ≥30 (B symptoms present) <i>or</i> MT ratio ≥0.35

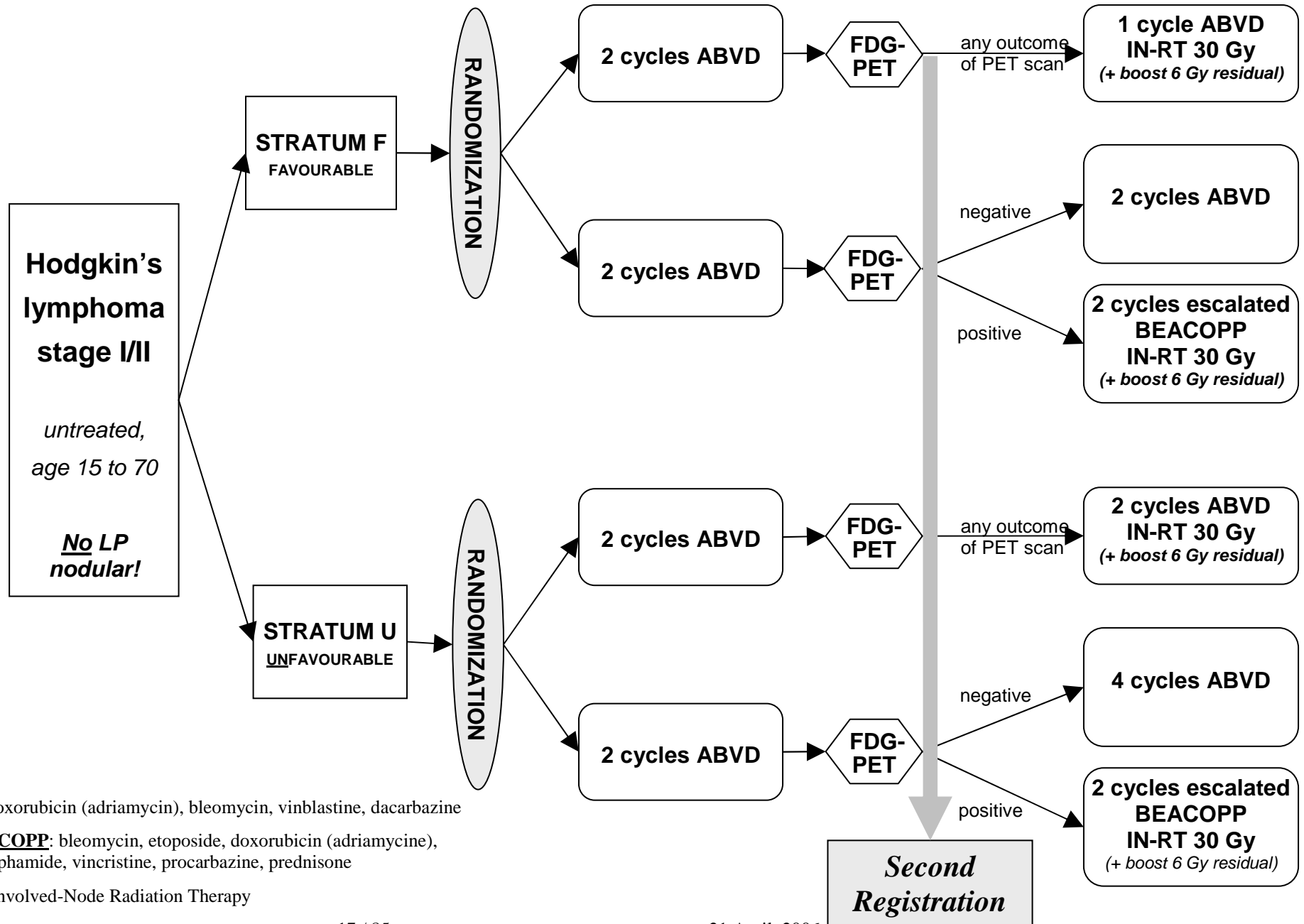
N.B. Mediastinum and hili are considered as one nodal area for this subdivision of prognostic subsets (see also Appendix H and Appendix I for detailed description of Ann-Arbor staging criteria modified according to the Cotswolds adaptations, and the measurement of MT-ratio.)

4 Trial Design

For the primary objective, we perform a phase III randomized non-inferiority trial for early FDG-PET scan negative patients.

For the secondary objective, we perform a phase III randomized superiority trial for early FDG-PET scan positive patients.

Schematically the design of the trial is as follows:



ABVD: doxorubicin (adriamycin), bleomycin, vinblastine, dacarbazine

Esc. BEACOPP: bleomycin, etoposide, doxorubicin (adriamycin), cyclophosphamide, vincristine, procarbazine, prednisone

IN-RT - Involved-Node Radiation Therapy

Eligible patients will be invited to participate in the trial.

After they have given their informed consent for the trial, a FDG-PET-scan will be planned 53 to 55 days after the planned date of treatment start.

Patients will be subsequently randomized to the standard or experimental arm of the trial, before the start of treatment. Randomization will be performed separately for the favorable and unfavorable group, according to the prognostic factors as defined in section 3 (F and U subset).

All patients, in both trial subsets (F and U), will have their FDG-PET scan done after two cycles of ABVD, together with a conventional restaging (chest X-ray and CT-thorax). The FDG-PET scan will be required not only in the experimental arm but in the standard arm as well, and – importantly!- the planning of FDG-PET scan will take some time ! The planned date of the restaging FDG-PET scan has to be known already at the time of randomization and will be documented (see Appendix G on FDG-PET scan timing and performance).

Before the start of the 3rd cycle of therapy, the inclusion of the patient into the trial must be confirmed by a second central registration. Discontinuation of protocol therapy before the end of the 2nd cycle should also be notified by a second registration. Patients will be allocated to groups A, B or C or excluded from the study population (see “analysis populations” in the chapter “Statistical considerations”) according to their prognostic group (F or U), and the results of the FDG-PET scan. The second registration is mandatory for all randomized patients, even if the PDG-PET has not been performed according to the protocol.

In the **standard** arm response evaluation will be done after two cycles of ABVD, after completion of chemotherapy to define the dose of IN-RT and after IN-RT.

In the **experimental** arm response evaluation will be done after two cycles of ABVD, and after completion of chemotherapy for the FDG-PET negative patients. For FDG-PET positive patients an additional response evaluation takes place after the two cycles of escalated BEACOPP to define the dose of IN-RT.

- ◆ In the groups of patients with a negative FDG-PET scan after two cycles, no further RT will be given, even if, on conventional CT scans, residual abnormalities exist/persist. These patients will be closely followed after completion of chemotherapy according to the follow-up guidelines specified in the protocol. Progressive disease should be documented as objectively as possible, preferably by histological examination of suspicious lesions. ***Giving additional treatment whether this is RT or second-line chemotherapy, will be considered treatment failure!***
- ◆ Patients with a positive FDG-PET scan after two cycles will receive additional IN-RT after completion of their chemotherapy. Response evaluation will be carried out after the BEACOPP and after the additional RT.

One interim analysis is planned after observation of approximately 12 events in the non-inferiority part of the trial for the FDG-PET negative patients and 22 events in the superiority part of the trial for the FDG-PET positive patients; at that time 2/3 of the requested number of patients are expected to be accrued.

5 Therapeutic regimens, expected toxicity, dose modifications

5.1 Chemotherapy regimens

5.1.1 ABVD

Doxorubicin	25 mg/m ² i.v.	day 1 and 15
Bleomycin	10 mg/m ² i.v./i.m.	day 1 and 15
Vinblastine	6 mg/m ² i.v.	day 1 and 15
Dacarbazine	375 mg/m ² i.v.	day 1 and 15

(next cycle day 29)

5.1.2 BEACOPP escalated

Cyclophosphamide*	1250	mg/m ² i.v.	day 1
Doxorubicin	35	mg/m ² i.v.	day 1
Vincristine	1.4	mg/m ² i.v.(max.2mg)	day 8
Bleomycin	10	mg/m ² i.v./i.m.	day 8
Etoposide**	200	mg/m ² / i.v.	day 1 to 3
Procarbazine	100	mg/m ² orally	day 1 to 7
Prednisone	40	mg/m ² orally	day 1 to 14
G-CSF ***	5	microgram/kg s.c.	day 9 – recovery leukocytes>1.0x10 ⁹ /l

(next cycle day 22)

*Cyclophosphamide to be given plus Uromitexan (Mesna i.v., on hours 0, 4 and 8 (20% of cyclophosphamide dose, last dose may be given orally) to prevent hemorrhagic cystitis. Patient should also drink 2.5 l of fluid on this treatment day

**113mg Etoposide phosphate is equivalent to 100 mg Etoposide.

***after discontinuing G-CSF, wait at least 48h before recycling chemotherapy.

Additional supportive measures are recommended:

- ◆ Pneumocystis carinii prophylaxis with Sulfamethoxazole/Trimethoprim (Cotrimoxazole)

5.2 Expected toxicity

Toxicities will be assessed according to the CTCAE v 3.0 criteria (see Appendix C).

Acute toxicity:

- ◆ hematological toxicity (blood cell count) can be significant especially for patients who will receive two cycles of escalated BEACOPP. For these patients G-CSF is required to avoid vital complications. The CTCAE grade 4 leukopenia ($\leq 1.0 \times 10^9/l$) and CTCAE grade 4 thrombocytopenia ($\leq 25 \times 10^9/l$) have been observed with escalated BEACOPP. As the nadir may be expected near days 11-12 (mean duration 4 days), daily or 2-daily blood sampling should be done as soon as the CTCAE grade 4 hematological toxicity is observed and until improvement.
- ◆ bleomycine interstitial pneumonitis has been frequently reported and requires immediate stop of further bleomycine administration.
- ◆ rarely, procarbazine allergy and intolerance has been reported.
- ◆ nausea & vomiting due to cyclophosphamide, doxorubicin, dacarbazine and procarbazine may be significant.
- ◆ total reversible alopecia occurs in most cases.
- ◆ escalated BEACOPP-related toxic deaths have been reported not to exceed those observed with standard ABVD, 2-3%.

Late effects:

- ◆ cardiac e.g. cardiomyopathy due to doxorubicin has been reported infrequently.
- ◆ early arteriosclerosis after RT to the mediastinum whether or not combined with chemotherapy is increasingly recognized as a treatment complication.
- ◆ pulmonary sequelae (pneumonitis due to bleomycin and or RT-induced) have been reported frequently
- ◆ gonadal toxicity may be irreversible in a significant number of cases
- ◆ MDS & leukemia (mostly etoposide-related, but also procarbazine related) have been reported infrequently but consistently. The risk is considered to be lower after ABVD than after escalated BEACOPP.
- ◆ Second solid tumors have been reported consistently, certainly in patients treated with additional wide field RT.

5.3 Guidelines for dose modification

5.3.1 ABVD

Complete blood counts should be obtained before each intravenous drug administration, day 1 and day 15.

First cycle

The treatment of the first cycle should be given at a 100% dosage regardless of blood cell counts (patient inclusion into the trial guarantees that patients are able to receive the first cycle at full dosage). Unless a life-threatening CTCAE grade 4 toxicity including infection, occurs before day 15, full doses of ABVD will also be given at day 15 of the first cycle. If a life-threatening CTCAE grade 4 toxicity has occurred, treatment should be postponed for a maximum of two weeks and

treatment should be resumed after decrease of the toxicity to grade 0, 1 or 2 with the day 15 schedule at full dose. When life-threatening CTCAE grade 4 toxicity persists or only decreases to grade 3 beyond two weeks, treatment is stopped and patient goes off protocol.

Subsequent cycles

When full dose cannot be given on day 1 or 15 of subsequent cycles, a 1-week delay is recommended. At that time, treatment must be given according to the guidelines given in the table below. When after one week postponement, blood cell counts do not allow for at least a 50% dose reduction according to the table, treatment is postponed again for one week. If after the second week of postponement blood cell counts did not recover to at least the threshold for giving 50% dose (see table) or life-threatening CTCAE grade 4 toxicity including infection persists, chemotherapy shall be stopped and this will be considered a treatment failure.

Table 5.3a. Dose modifications ABVD

Leukocytes x10 ⁹ /l	Platelets x10 ⁹ /l	Doxorubicin	Bleomycin	Vinblastin	Dacarbazine
≥ 2.5 and	≥ 80	100%	100%	100%	100%
≥ 1.0 but <2.5 or	≥ 50 but <80	50%	100%	50%	50%
<1.0 or	<50	0%	0%	0%	0%

In general, to avoid delay and dose reduction the application of hematopoietic growth factors (G-CSF) may be considered according to the local guidelines of each participating center or country.

CAUTION

1. Do not give hematopoietic growth factors concomitantly with cytostatic drugs, even if they are not myelosuppressive (Bleomycin), as severe toxicity may ensue.
2. Stop treatment with hematopoietic growth factors at least 48 hours before performing the FDG-PET scan. Treatment with hematopoietic growth factors may severely impair PET interpretation and results.

5.3.2 Escalated BEACOPP

Patients will only receive 2 cycles of escalated BEACOPP. The dosing schedule of the 2nd cycle is highly dependent of the hematological toxicity encountered during the 1st cycle. Especially, nadir values of leukocytes and platelets are leading parameters in adapting doses in the 2nd cycle. As the nadir may be expected near days 11-12 (with a median duration of 4 days), daily or 2-daily blood sampling should be done as soon as the CTCAE grade 4 hematological toxicity is observed and until improvement. This is of paramount importance and specifically holds for the escalated BEACOPP schedule. (*Monitoring of the nadir during ABVD is not common practice and does not guide treatment adaptation*).

Criteria for starting the first cycle (Ref. 39)

The first cycle of escalated BEACOPP (after two previous ABVD cycles) will preferably start at the 100% dosage level. The start will take place on day 29 counting from day 1 of the 2nd cycle of ABVD. When 100% dosage is not allowed because of blood cell counts, being leukocyte count <2.5 x 10⁹/l or platelets <80 x 10⁹/l or due to a not completely resolved life-threatening CTCAE grade 4 toxicity including infection, the start of the first escalated BEACOPP cycle should be postponed for one or maximum two weeks. When after one to two weeks postponement blood cell counts have not recovered to at least leukocytes ≥ 1.0 x 10⁹/l and platelets ≥ 50 x 10⁹/l, treatment with chemotherapy should be stopped (e.g. escalated BEACOPP cannot start) and the patient is considered failure to treatment.

The drug dosing schedule is presented in the table 5.3b:

Table 5.3b: Dose schedule for the 1st escalated BEACOPP course

Cell counts Drug	If at start of cycle leukocytes $\geq 2.5 \times 10^9/l$ and platelets $\geq 80 \times 10^9/l$ administer full dose	If at start of cycle leukocytes >1.0 and $<2.5 \times 10^9/l$ and platelets ≥ 50 and $<80 \times 10^9/l$ implement dose reduction
Bleomycin (day 8)	10 mg/ m ²	10 mg/ m ²
Etoposide (days 1 to 3)	200 mg/m ² /day	175 mg/m ² /day
Doxorubicin (day 1)	35 mg/ m ²	35 mg/ m ²
Cyclophosphamide (day 1)	1250 mg/m ²	1100 mg/ m ²
Oncovin/Vincristine (day 8)	1.4 mg/m ² (max 2mg)	1.4 mg/m ² (max 2mg)
Procarbazine (days 1 to 7)	100 mg/m ² /day	100 mg/m ² /day
Prednisone (days 1 to 14)	40 mg/ m ² /day	40 mg/ m ² /day

Criteria for starting the second escalated BEACOPP cycle

At the start of the 2nd cycle of escalated BEACOPP the same guidelines as for the first cycle of escalated BEACOPP are to be followed. Preferably 100% dosage is given, therefore treatment is postponed for one to maximally two weeks to allow leukocytes to recover $\geq 2.5 \times 10^9/l$ and platelets $\geq 80 \times 10^9/l$. When after two weeks postponement blood cell counts have not recovered to at least leukocytes $\geq 1.0 \times 10^9/l$ and platelets $\geq 50 \times 10^9/l$, treatment with chemotherapy should be stopped and patient is considered failure to treatment.

The doses of chemotherapy in the 2nd cycle of escalated BEACOPP should be adjusted dependent of observed toxicity events during the 1st cycle:

- ◆ **leukocytes:** $<1.0 \times 10^9/l$ for more than 4 days during the previous cycle or
- ◆ **granulocytes:** $<0.5 \times 10^9/l$ for more than 4 days during the previous cycle or
- ◆ **platelets:** $<25 \times 10^9/l$ during the previous cycle or
- ◆ **infection:** CTCAE grade 4 during the previous cycle or
- ◆ **any life-threatening toxicity:** CTCAE grade 4 during the previous cycle

When one or more of these events have occurred during the first cycle of escalated BEACOPP, the doses of chemotherapy in the 2nd cycle will be adapted with one reduction step as outlined in table 5.3c.

Table 5.3c: Dose schedule for the 2nd escalated BEACOPP course

Cell counts or reduction step Drug	If leukocytes $\geq 2.5 \times 10^9/l$ and platelets $\geq 80 \times 10^9/l$ and no grade 4 infection or life threatening event in the previous cycle give full dose	If leukocytes ≥ 1.0 and $< 2.5 \times 10^9/l$ and platelets ≥ 50 and $< 80 \times 10^9/l$ or at least one grade 4 infection or life threatening event in the previous cycle implement dose reduction
Bleomycin (day 8)	10 mg/ m ²	10 mg/ m ²
Etoposide (days 1 to 3)	200 mg/m ² /day	175 mg/m ² /day
Doxorubicin (day 1)	35 mg/ m ²	35 mg/ m ²
Cyclophosphamide (day 1)	1250 mg/m ²	1100 mg/ m ²
Oncovin/Vincristine (day 8)	1.4 mg/m ² (max 2mg)	1.4 mg/m ² (max 2mg)
Procarbazine (days 1 to 7)	100 mg/m ² /day	100 mg/m ² /day
Prednisone (days 1 to 14)	40 mg/ m ² /day	40 mg/ m ² /day

CAUTION:

Do not give hematopoietic growth factors concomitantly with cytostatic drugs, even if they are not myelosuppressive (Bleomycin) as severe toxicity may ensue.

5.3.3 Non haematological toxicity (both ABVD and escalated BEACOPP)

- ◆ In case of **heart failure** whether or not responsive to treatment (cardiac left ventricular function CTCAE grade ≥ 3), doxorubicin should be stopped. In this case, the patient should be treated at the discretion of the investigator out of the protocol and any further treatment will no longer be considered as protocol treatment.
- ◆ In case of gross **hematuria** (CTCAE grade ≥ 3) with clots requiring catheterisation or instrumentation or transfusion, cyclophosphamide (escalated BEACOPP schedule only) should be stopped. In this case, the patient should be treated at the discretion of the investigator out of the protocol and any further treatment will no longer be considered as protocol treatment.
- ◆ In case of **interstitial pneumonitis** (CTCAE grade ≥ 2) bleomycin should be stopped without substitute. However, treatment without bleomycin is still considered as protocol treatment.
- ◆ In case of **neuropathy** (CTCAE grade ≥ 3) **and/or constipation** (CTCAE grade ≥ 3), vincristine has to be replaced by vinblastine 4 mg/m². If besides this replacement, the neuropathy and/or constipation persist, vinblastine has to be stopped without any replacement. However, treatment without vincristine or without vinblastine is still considered as protocol treatment.

- ◆ If case of **procarbazine allergy**, it has to be replaced by chlorambucil 6mg/m²/d (max 10 mg total dose per day). If despite this replacement, the allergy persists, the chlorambucil has to be stopped without any replacement. However, treatment without procarbazine (with or without replacement by chlorambucil) is still considered as protocol treatment.

5.4 Radiotherapy (*detailed guidelines in Appendix F*)

Radiotherapy concerns initially involved nodal areas only (IN-RT). Therefore, a meticulous recording of initially involved nodal areas is an absolute requirement for adequate IN-RT afterwards. Before start of protocol treatment, CT-scans of neck and thorax are mandatory. The radiotherapist should have seen the patient, preferably before the start of chemotherapy and should carefully document the involved areas, preferably together with the radiologist.

Radiotherapy should start within 3-4 weeks after the end of the last chemotherapy course e.g. approximately 6 weeks after the start of the last chemotherapy cycle.

For a detailed description of the involved node radiotherapy protocol see Appendix F.

Here we give a short summary of some specific aspects of the IN-RT.

5.4.1 Target volumes

Instead of the more conventional involved-field principle in which the whole lymph node area is the target volume for RT, in the IN-RT principle only the initial volume of the lymph node(s) before chemotherapy is the target for RT. In other words, it incorporates the initial location and the extent of the disease and takes into account the displacement of normal structures. In case of a complete remission unconfirmed (CRu) with a visible lymph node remnant on CT-scan, the lymph node remnant should be included in the radiation field. For nodal areas in partial remission (PR) after the previous chemotherapy, detailed guidelines are given in the Appendix F.

5.4.2 Dose specification

The prescribed dose is 30 Gy with a boost of 6 Gy to areas with residual disease.

5.4.3 Dose fractionation

Dose per fraction 2 Gy

Maximum weekly dose 10 Gy

5 fractions per week will be given.

In case of digestive or hematological toxicity, lowering of the fraction dose to 1.75 Gy is allowed. Anterior and posterior beams should be used with each fraction each treatment day.

5.5 Reasons for stopping protocol treatment

- ◆ Normal completion of protocol treatment
- ◆ Progressive disease during protocol treatment
- ◆ Excessive toxicity that does not allow administration of the protocol treatment e.g. reasons to stop because of excessive hematologic toxicity, or to stop doxorubicin or cyclophosphamide (for details see chapter 5.3.1-5.3.3)
- ◆ No FDG-PET scan performed after two cycles of ABVD. In this case, the patient is considered major protocol violation.

- ◆ Refusal of the patient to further cooperate (at any time and for any reason)
- ◆ Investigator's decision.

6 Clinical evaluation, laboratory tests and follow-up

6.1 Before treatment start

All the following examinations, tests or imaging studies are mandatory before the start of treatment unless otherwise stated.

- 6.1.1. *History*: B-symptoms, WHO performance status (see Appendix B), menstrual status, method of contraception and smoking history.
- 6.1.2. *Physical examination* including measurement of the maximum dimension of all involved lymph node areas, height, body weight (Ear, Nose, Throat consultation on indication).
- 6.1.3. *Blood tests*: ESR, hemoglobin, platelets, leukocyte count including differential,
- 6.1.4. *Serum chemistry* (total bilirubin, creatinine, alkaline phosphatase, ALAT, ASAT, γ GT, LDH, serum albumin). CRP and β 2-microglobulin are optional.
- 6.1.5. *Hormonal tests*: Thyroid function (T4, TSH), fertility tests (FSH, LH, 17-beta-oestradiol, progesterone, testosterone). In males spermogram, and if indicated sperm preservation.
- 6.1.6. *ECG*
- 6.1.7. *Imaging*: chest X-ray (PA and lateral) and measurement of the MT ratio (see Appendix I), CT-scan of the neck, thorax and abdomen with intravenous contrast, with images at 1 cm intervals.
- 6.1.8. *Imaging*: FDG-PET scan **after 2 cycles of ABVD** is mandatory for all patients and should be planned before the start of treatment: the date of FDG-PET will be asked for at the time of randomization!! **If FDG-PET scan after 2 cycles of ABVD is not performed, the patient will be considered as a major protocol violation.** A baseline FDG-PET scan is highly recommended for reference.
- 6.1.9. *Imaging*: Ultrasound in apparently uninvolved cervical \pm axillary areas and node measurements: MRI and bone scintigraphy are allowed but optional.
- 6.1.10. *Histologic studies*: Initial tumor biopsy specimen should be available for central review.
- 6.1.11. *Bone marrow studies*: Bone marrow biopsy from the iliac crest (with a recommended length of 2 cm) is mandatory except for patients with favorable stages I/II without B-symptoms.
- 6.1.12. *Adverse events assessment according to CTCAE v 3.0 (see Appendix C for reference) with specific attention to cardiac and pulmonary function*: pulmonary function tests and cardiac ejection fraction evaluation are mandatory before the start of treatment since reduction of these toxicities is one of the main objectives of the study.
- 6.1.13. *Quality control*: The assessment of the involved areas should be as rigorous as possible. A mapping chart must be completed, with a check list of all nodal areas, by the radiotherapist the hemato/medical oncologist and preferably in close cooperation with the radiologist.

6.2 During treatment

6.2.1 Before & during each cycle

All investigations are mandatory unless otherwise stated

- ◆ *History*: B-symptoms, WHO performance status (see Appendix B)
- ◆ *Physical examination* including measurement of the maximum dimension of all involved lymph node areas, body weight
- ◆ *Adverse events* assessment according to CTCAE v.3.0 (see Appendix C for reference)
- ◆ *Serum chemistry* (total bilirubin, creatinine, alkaline phosphatase, ALAT, ASAT, γ GT, LDH, serum albumin) *if clinically indicated*
- ◆ *Blood tests*: hemoglobin, platelets, leukocyte count including differential prior to start of chemotherapy:
 - ◆ day 1 and 15 for ABVD
 - ◆ day 1, 8 and 11 (and dependent of the results on day 11 additionally on consecutive days) for escalated BEACOPP

6.2.2 After two cycles of ABVD: major evaluation point

All investigations are mandatory unless otherwise stated

- ◆ *History*: B-symptoms, WHO performance status (see Appendix B)
- ◆ *Physical examination* including measurement of the maximum dimension of all involved lymph node areas,
- ◆ *Blood tests*: hemoglobin, platelets, leukocyte count including differential, ESR
- ◆ *Serum chemistry* (total bilirubin, creatinine, alkaline phosphatase, ALAT, ASAT, γ GT, LDH, serum albumin) if clinically indicated
- ◆ *Imaging*: CT scan of the neck and chest
- ◆ ***Imaging: FDG-PET scan approximately at day 23-27 of the 2nd cycle of ABVD so immediately prior to the start of the next cycle of chemotherapy.*** Guidelines for FDG-PET scan are provided in Appendix G.

Note that patients will be considered major protocol violation in case FDG-PET scan is not performed. Pay special attention to the timing of the FDG-PET scan since scanning prior to day 23 of the 2nd cycle of ABVD may seriously impair a correct interpretation of the result!!

6.2.3 After completion of chemotherapy

Time points of evaluation:

- ◆ For the standard treatment arm after three cycles of ABVD (F group) and after four cycles of ABVD (U group)
- ◆ For those in the standard treatment arm who are already in CR after two cycles of ABVD as established by the CT-scan after two cycles, no repeat CT scan has to be performed after three cycles (F) or four cycles (U) but restaging will take place after the IN-RT.

- ◆ In the experimental arm in FDG-PET negative patients after four cycles of ABVD (F group) and after six cycles of ABVD (U group). This corresponds to the final response evaluation for these subsets of patients!
- ◆ In the experimental arm in FDG-PET positive patients after the second cycle of escalated BEACOPP

Investigations:

All investigations are mandatory. The restaging evaluations are mandatory and required for adequate definition of IN-RT dose since residual disease areas will receive an additional boost of 6 Gy. (only applicable to standard arm and FDG-PET positive patients in experimental arm)

- ◆ *History*: B-symptoms, WHO performance status (see Appendix B)
- ◆ *Physical examination* including measurement of the maximum dimension of all involved lymph node areas,
- ◆ *Blood tests*: hemoglobin, platelets, leukocyte count including differential, ESR
- ◆ *Serum chemistry* (total bilirubin, creatinine, alkaline phosphatase, ALAT, ASAT, γ GT, LDH, serum albumin) if clinically indicated
- ◆ *Adverse events* assessment according to the CTCAE v.3.0 (see Appendix C for reference)
- ◆ *Imaging*: CT scan of the neck and chest

6.3 At the end of treatment (final response evaluation)

The final response evaluation point will take place at the following time points:

For patients in the F group:

- ◆ Patients in the standard arm
 - ◆ 6-8 weeks after end of IN-RT
- ◆ Patients in the experimental arm with FDG-PET negative scan after 2 cycles of ABVD
 - ◆ 4-6 weeks after the start of the 4th cycle of ABVD
- ◆ Patients in the experimental arm with FDG-PET positive scan after 2 cycles of ABVD
 - ◆ 6-8 weeks after end of IN-RT

For patients in the U group:

- ◆ Patients in the standard arm
 - ◆ 6-8 weeks after end of IN-RT
- ◆ Patients in the experimental arm with FDG-PET negative scan after 2 cycles of ABVD
 - ◆ 4-6 weeks after the start of the 6th cycle of ABVD
- ◆ Patients in the experimental arm with FDG-PET positive scan after 2 cycles of ABVD
 - ◆ 6-8 weeks after end of IN-RT

All investigations are mandatory unless otherwise stated.

- ◆ *History*: B-symptoms, WHO performance status (see Appendix B), menstrual status, smoking habits
- ◆ *Physical examination* including measurement of the maximum dimension of all involved lymph node areas,

- ◆ *Blood tests*: hemoglobin, platelets, leukocyte count including differential, ESR,
- ◆ *Serum chemistry* (total bilirubin, creatinine, alkaline phosphatase, ALAT, ASAT, γ GT, LDH, serum albumin) if clinically indicated
- ◆ *Imaging*: CT scan of the neck and chest
 - ◆ FDG-PET scan is optional at the end of treatment.
- ◆ *Hormonal tests*: Thyroid function (T4, TSH), fertility tests (FSH, LH, 17-beta-oestradiol, progesterone, testosterone).
- ◆ *Adverse events assessment according to CTCAE v 3.0 (see Appendix C for reference) with specific attention to secondary tumors, cardiac and pulmonary function. Pulmonary function tests and cardiac ejection fraction evaluation are mandatory since reduction of these toxicities is one of the main objectives of the study.*

6.4 During follow-up (from end of treatment until disease relapse/progression)

After completion of final response evaluation as defined in section 6.3 which is performed at approximately 2 months after end of treatment, patients will be closely monitored for relapse/progression or toxicity of treatment.

The following follow-up schedules apply therefore to all patients until disease relapse/progression.

6.4.1 Timing of follow-up visits after last administration of protocol therapy (*final response evaluation has already taken place at 6-8 weeks after end of treatment*)

- | | |
|--|--------------------------|
| ◆ during the first year: | at 4, 6, 9 and 12 months |
| ◆ during the second year | every 3 months |
| ◆ during the third, fourth and fifth years | every 6 months |
| ◆ beyond the fifth year | yearly |
| ◆ beyond the 10 th year | once every two years |

6.4.2 Investigations at follow-up after the end of treatment

6.4.2.1 First year: 4, 6 and 9 months

All investigations are mandatory at all time points unless otherwise stated.

- ◆ *History*: B-symptoms, cardiopulmonary complaints, menstrual status, smoking habits, WHO performance status (see Appendix B)
- ◆ *Physical examination*: lymph node areas, liver, spleen, cardio-pulmonary status.
- ◆ *Blood tests*: hemoglobin, platelets, leukocyte count including differential, ESR,
- ◆ *Imaging*: CT scan of the neck and chest (only at 4 and 6 months)
- ◆ *Adverse events* assessment according to CTCAE v 3.0

6.4.2.2 At 12 months

All investigations are mandatory at all time points unless otherwise stated.

- ◆ *History*: B-symptoms, cardiopulmonary complaints, menstrual status, smoking habits, WHO performance status (see Appendix B)
- ◆ *Physical examination*: lymph node areas, liver, spleen, cardio-pulmonary status.
- ◆ *Blood tests*: hemoglobin, platelets, leukocyte count including differential, ESR
- ◆ *Imaging*: CT scan of the neck and chest
- ◆ *Hormonal tests*: Thyroid function (T4, TSH), fertility tests (FSH, LH, 17-beta-oestradiol, progesterone, testosterone).
- ◆ ***Adverse events assessment according to CTCAE v 3.0 with specific attention to secondary tumors, cardiac and pulmonary function. Pulmonary function tests and cardiac ejection fraction evaluation are mandatory since reduction of these toxicities is one of the main objective of the study.***

6.4.2.3 Second year every 3 months

All investigations are mandatory at all time points unless otherwise stated.

- ◆ *History*: B-symptoms, cardiopulmonary complaints, menstrual status, smoking habits, WHO performance status (see Appendix B)
- ◆ *Physical examination*: lymph node areas, liver, spleen, cardio-pulmonary status.
- ◆ *Blood tests*: hemoglobin, platelets, leukocyte count including differential, ESR
- ◆ *Imaging*: CT scan of the neck and chest: only at 18 and 24 months.
- ◆ *Hormonal tests* (only once, after 24 months) : Thyroid function (T4, TSH), fertility tests (FSH, LH, 17-beta-oestradiol, progesterone, testosterone). In males spermogram.
- ◆ *Adverse events* assessment according to the CTCAE v.3.0

6.4.2.4 Third and fourth year every 6 months

All investigations are mandatory at all time points unless otherwise stated.

- ◆ *History*: B-symptoms, cardiopulmonary complaints, menstrual status, smoking habits, WHO performance status (see Appendix B)
- ◆ *Physical examination*: lymph node areas, liver, spleen, cardio-pulmonary status.
- ◆ *Blood tests*: hemoglobin, platelets, leukocyte count including differential, ESR
- ◆ *Imaging*: CT scan of the neck and chest
- ◆ *Hormonal tests*(only once yearly): Thyroid function (T4, TSH), fertility tests (FSH, LH, 17-beta-oestradiol, progesterone, testosterone)
- ◆ *Adverse events* assessment according to the CTCAE v.3.0.

6.4.2.5 At five years

All investigations are mandatory at all time points unless otherwise stated.

- ◆ *History*: B-symptoms, cardiopulmonary complaints, menstrual status, smoking habits, WHO performance status (see Appendix B)
- ◆ *Physical examination*: lymph node areas, liver, spleen, cardio-pulmonary status.
- ◆ *Blood tests*: hemoglobin, platelets, leukocyte count including differential, ESR
- ◆ *Imaging*: CT scan of the neck and chest
- ◆ *Hormonal tests*: Thyroid function (T4, TSH), fertility tests (FSH, LH, 17-beta-oestradiol, progesterone, testosterone). In males spermogram
- ◆ ***Adverse events assessment according to CTCAE v 3.0 with specific attention to secondary tumors, cardiac and pulmonary function. Pulmonary function tests and cardiac ejection fraction evaluation are mandatory since reduction of these toxicities is one of the main objective of the study.***

6.4.2.6 After five years lifelong

Patients are followed annually and after 10 years once every two years.. The following tests are mandatory unless otherwise stated

- ◆ *History*: B-symptoms, cardiopulmonary complaints, menstrual status, smoking habits, WHO performance status (see Appendix B)
- ◆ *Physical examination*: lymph node areas, liver, spleen, cardio-pulmonary status.
- ◆ *Blood tests*: hemoglobin, platelets, leukocyte count including differential, ESR
- ◆ *Imaging*: chest X-ray, CT scan of the neck and chest: only on clinical suspicion of relapse
- ◆ *Imaging*: mammography in female patients who have been irradiated on mediastinal/axillary fields to start 10 years after end of treatment, and yearly thereafter.
- ◆ *Hormonal tests*: Thyroid function (T4, TSH), fertility tests (FSH, LH, 17-beta-oestradiol, progesterone, testosterone). In males spermogram only after 10 years.
- ◆ ***Adverse events assessment according to CTCAE v 3.0 with specific attention to secondary tumors, cardiac and pulmonary function., Pulmonary function tests and cardiac ejection fraction evaluation after 10 and 20 years are mandatory since reduction of these toxicities is one of the main objective of the study.***

6.4.2.7 At the time of relapse or progression

At the time of relapse or progression, full reevaluation of disease activity should be performed including chest X-ray and CT scans of neck, thorax and abdomen as well as bone marrow histology. A tumor biopsy should be taken to confirm relapse or progressive Hodgkin's lymphoma.

The characteristics of the relapse or progression should be documented as accurately as possible, including:

- ◆ date of relapse / progression
- ◆ type of relapse / progression
 - ◆ site of relapse / progression
 - ◆ nodal areas (previously involved or uninvolved, previously irradiated or not)
 - ◆ extranodal areas (previously involved or uninvolved)
 - ◆ histological type of relapse.

6.4.2.8 At the time of death

- ◆ Causes of death will be recorded in the CRFs

6.5 During follow-up (after disease relapse/progression)

After disease relapse/progression, patients will be followed yearly for survival and assessment of adverse events with specific attention to secondary malignancies, cardiovascular and pulmonary function status.

6.6 Summary table of required investigations

6.6.1 From inclusion to end of treatment

Examinations	Before treatment start			after 3 rd (F) or 4 th (U) ABVD in <u>standard arm</u> and after 2 nd escalated BEACOPP in <u>experimental arm</u>	End of treatment (after RT in combined modality and after chemo in chemo only arm)
		before each cycle	after 2 nd ABVD		
History	×	×	×	×	×
Menstrual status/contraceptives	×				×
Smoking history	×				×
B symptoms	×	×	×	×	×
WHO PS	×	×	×	×	×
Weight & height	×				
Weight only		×			
Measurement of all palpable nodes	×	×	×	×	×
CBC +differential	×	×	×	×	×
ESR	×	×	×	×	×
Serum chemistry (total bilirubin, creatinine, LDH, AF, ALAT, ASAT, etc)	×	If indicated	If indicated	If indicated	×
Chest X-ray	×				
CT-scan neck, thorax	×		×	×	×
				in standard arm not required when in CR after two cycles	
CT-scan abdomen	×				
FDG-PET scan	×		×		×
	(optional)				(optional)
Bone marrow biopsy (unless F without B-symptoms)	×				
Secondary tumors					×
Ventricular ejection fraction	×				×
Respiratory function (RF)	×				×
Adverse events assessment	×	×		×	×
LH, FSH, oestradiol, testosterone, T4, TSH	×				×
Spermogram/Cryopreservation of sperm	×				
Tumor biopsy	×				

6.6.2 Follow-up (from end of treatment until disease relapse/PD)

Examinations	First year after end of treatment		2 nd year	3 rd and 4 th year	5 th year	After 5 th year
	Month 4, 6,9	Month 12	Every 3 months	Every 6 months		Every year until 10 years and every two years thereafter
History	×	×	×	×	×	×
Menstrual status/contraceptives	×	×	×	×	×	×
Smoking history	×	×	×	×	×	×
B symptoms	×	×	×	×	×	×
WHO PS	×	×	×	×	×	×
Measurement of palpable nodes	×	×	×	×	×	×
CBC +differential, ESR	×	×	×	×	×	×
Chest X-ray						×*
CT-scan neck and/or thorax, and /or abdomen	×	×	×	×	×	×*
	only month 4 and 6		only month 18+24			
Secondary tumors	×	×	×	×	×	×
Ventricular ejection fraction		×			×	×**
Respiratory function (RF)		×			×	×**
Adverse events assessment	×	×	×	×	×	×
LH, FSH, oestradiol, testosterone, T4, TSH		×	×	×	×	×**
			Once yearly	Once yearly		
spermogram			×		×	×
			at 24 months			at 10 yrs
mammography						×***

* only on clinical indication; ** after 10 years and 20 years; *** start after 10 years in females, yearly examination.

7 Criteria of evaluation

7.1 Progression-free survival

The primary end-point is progression-free survival (PFS).

Progression is defined as

- ◆ progressive disease during protocol treatment or
- ◆ relapse after reaching CR or CRu on protocol treatment or
- ◆ progression after reaching PR or NC on protocol treatment

7.2 Event-free survival

One of the secondary end-points is event-free survival (EFS). The following events will be considered:

- ◆ progression of disease (see above)
- ◆ premature discontinuation of protocol treatment for any reason (before completion of all chemotherapy cycles, and administration of at least 80% of the prescribed radiotherapy dose, if applicable)
- ◆ start of any off protocol anticancer therapy (including radiotherapy in PET negative patients allocated to the investigational arms)
- ◆ death (from any cause)

7.3 Overall survival

One of the secondary end-points is overall survival. Death from any cause will be considered.

7.4 Response criteria

The criteria for response evaluation according to the recommendations of the Cotswolds Meeting updated in the NCI International Workshop will be used and **adapted to Hodgkin's Lymphoma**. Therefore, the modified criteria will be in bold italic.

Importantly and specifically applicable to this trial, we perform a FDG-PET scan after two cycles of ABVD. In the experimental arm the result of this FDG-PET scan is used to guide further treatment. In fact, it replaces the conventional response evaluation through CT scan but only at this particular time point e.g. after two cycles of ABVD in the experimental arm. In all other response evaluations for the patients in the trial, as specified below, the FDG-PET scan is not used for defining response to treatment but rather as documentation only. In these circumstances conventional restaging through physical examination, chest X-ray and CT scan will be used.

During the initial measurement, a maximum of 6 target lesions will be identified. These lesions (*nodes, nodal mass or measurable extranodal lesion*) should be selected according to the following features:

- ◆ they should be clearly measurable in at least two perpendicular dimensions
- ◆ they should be from as disparate regions in the supradiaphragmatic part of the body as possible
- ◆ they should include mediastinal areas of disease whenever involved

Response to treatment will be evaluated:

- ◆ after the 2nd cycle of ABVD for all patients including FDG-PET scan
- ◆ after the 3rd (F) or 4th (U) cycle of ABVD for patients in the standard combined modality arm to define the dose of subsequent IN-RT unless already in CR after two cycles of ABVD.
- ◆ after the 4th cycle of ABVD (F) or 6th cycle of ABVD (U) in the experimental chemotherapy treatment arm in FDG-PET scan negative group of patients
- ◆ after the 2nd escalated BEACOPP cycle in the experimental treatment arm for FDG-PET scan positive group of patients
- ◆ after IN-RT in all respective groups

Response will be evaluated at around 4 weeks after the first day of the respective chemotherapy cycle and/or within 6-8 weeks after IN-RT.

The response criteria for Hodgkin's Lymphoma are summarized in the following table (*SPD = sum of the product of greatest diameters*):

Response	Physical examination	Lymph nodes, lymph node masses, measurable extranodal masses		Bone marrow
		Initially	At the evaluation	
CR	Normal, no radiological abnormality	>1.5 cm 1.1-1.5 cm	≤1.5 cm < 1 cm or >75% SPD decrease	Normal
CRu (PR≥75%)	Normal	>1.5 cm	>75% SPD decrease	Normal
PR	Normal, decrease in liver/spleen	6 target lesions other nodes	≥50% SPD decrease no increase	Normal
NC	no	▲ ▼	▲ ▼	▲ ▼
Relapse	New sites, enlarged liver/spleen	involved	≥50% SPD increase of >1 node	appearance
Progression	New lesion(s)	involved	≥50% SPD increase from nadir	appearance

7.4.1 Complete remission (CR)

Complete remission requires all of the following

1. Complete disappearance of all detectable clinical and radiographic evidence of disease and disappearance of all disease-related symptoms if present before therapy, and normalization of those biochemical abnormalities definitely assignable to HL.
2. All *lesions (node, nodal mass or measurable extranodal lesion)* must have regressed to normal size (≤1.5 cm in their greatest transverse diameter for nodes > 1.5 cm before therapy). Previously involved nodes that were 1.1 to 1.5 cm in their greatest transverse diameter before treatment must have decreased to ≤1 cm in their greatest transverse diameter after treatment, or by more than 75% in the sum of the products of the greatest diameters (SPD).

7.4.2 Complete Remission unconfirmed (CRu)

1. Criterion #1 same as listed above for CR: no clinical or biological evidence of HL, but some radiological abnormality persists at the site of previous disease.
2. Criterion #2: a residual lymph node mass greater than 1.5 cm in greatest transverse diameter that has regressed by more than 75% in the SPD. Individual nodes that were previously confluent must have regressed by more than 75% in their SPD compared with the size of the original mass.

7.4.3 Partial remission

Partial remission requires all of the following:

1. At least 50% decrease in SPD of the six largest dominant lesions.
2. No increase in the size of the other nodes.
3. No new sites of disease.
4. Resolution of B-symptoms.

7.4.4 No change or Stable disease

No change or Stable disease is defined as less than a PR (see above) but is not progressive disease (see below).

7.4.5 Progressive disease

Progressive disease (PD) requires any of the following:

1. 50% increase from nadir in the SPD of any previously identified abnormal node for PRs or non-responders.
2. Appearance of any new lesion during or at the end of therapy. A biopsy is recommended to confirm active HL and to exclude other type of lymphoma or other disease.

7.4.6 Relapsed disease

Relapsed disease in patients, who achieved CR, or CRu, requires the following:

1. Appearance of any new lesion or increase by 50% in the size of previously involved sites.
2. 50% increase in greatest diameter of any previously identified node greater than 1 cm in its short axis or in the SPD of more than one node.

7.5 Toxicity end-points

One of the important secondary end-points is the occurrence of irreversible toxic events during, shortly after and at prolonged interval after treatment. Special attention will be given to:

- ◆ Second malignancies
 - ◆ Detailed documentation of date of occurrence, type of malignancy, special features (cytogenetics), localization, infield or outfield. Examples are:
 - ◆ Hematologic such as secondary acute leukemia, myelodysplasia, non-Hodgkin types of lymphoma, and other
 - ◆ Solid tumors
- ◆ Cardiovascular events
 - ◆ Detailed documentation of date of occurrence, special features, localization, infield or outfield. Examples are:
 - ◆ Arteriosclerosis, angina, myocardial infarction
- ◆ Pulmonary events
 - ◆ Detailed documentation of date of occurrence, special features, localization, infield or outfield. Examples are:
 - ◆ Pneumonitis, fibrosis

8 Statistical considerations

8.1 Statistical design

8.1.1 Sample size

This study aims at answering different questions in 3 groups of patients:

- ◆ Group A : favorable prognosis, negative PET scan after 2 cycles of ABVD
- ◆ Group B: unfavorable prognosis, negative PET scan after 2 cycles of ABVD
- ◆ Group C: positive PET scan after 2 cycles of ABVD (favorable and unfavorable prognosis).

The expected yearly accrual in the whole trial is 350 patients, distributed as follows:

	Favorable	Unfavorable	Total
PET -	135 (A)	160 (B)	295
PET +	15	40	55 (C)
TOTAL	150	200	350

8.1.1.1 PET negative patients

The principal objective of the study is to find out whether investigational treatments (without radiotherapy) are non inferior to the standard treatments in patients with a negative PET scan after 2 cycles of ABVD. This will be separately evaluated in patients with an initially favorable prognosis (Group A), and in patients with an initially unfavorable prognosis (Group B). The primary end-point is progression free survival. In each group, a 1-sided logrank test will be used, and 1 interim analysis will be performed (see details hereunder).

The event rates and parameters of the statistical design are defined in the following table:

Group of patients	A (favorable)	B (unfavorable)
Standard arm: 5 yrs PFS	95%	90%
Experimental arm: 5 yrs PFS	> 85%	> 80%
Hazard ratio	3.2	2.1
Logrank test	1 sided	1 sided
Alpha	0.025	0.025
Beta	0.2	0.2
Interim analysis	1	1
Nr events required for the final analysis	26	63

The study will be open to recruitment until at least 608 patients are available in group A and 720 patients in group B. This is expected to happen simultaneously, after 4.5 years of recruitment. Under all above assumptions, the final analysis will be performed after an additional follow-up of 2 years.

Potential recruitment / yr	135	160
Nr patients	608	720
End of recruitment	4.5 yrs	4.5 yrs
Time of final analysis	6.5 yrs	6.5 yrs

If the proportion of patients randomized in the different groups is largely different from what is expected, the recruitment will be closed to favorable patients after inclusion of 750 cases in group A, and to unfavorable patients after inclusion of 850 cases in group B.

8.1.1.2 PET positive patients

In PET positive patients, the objective is to find out whether progression free survival can be improved by treatment intensification (investigational treatment) as compared to standard therapy.

This is a secondary objective of the trial. The favorable and unfavorable patients will be grouped for this analysis (group C). The duration of recruitment and the timing of the interim and final analysis will be based only on the accrual and event rates in groups A and B.

According to the above hypotheses a total of 248 will be simultaneously accrued in group C (55/year). At the time of the final analysis, 77 events will be recorded in those patients. The final analysis will provide a 77% power to detect a 20% improvement (from 50% to 70%) in 5 years progression free survival rate with the investigational arm (2-sided logrank test, alpha=0.05, 1 interim analysis).

8.1.2 Randomization and stratifications

Patients will be centrally randomized (for practical details, see chapter on registration / randomization procedure).

A minimization technique will be used for random treatment allocation in each prognostic group (favorable / unfavorable), stratifying by institution, Ann Arbor stage (I vs II) and availability of a baseline FDG-PET to improve the accuracy of the radiation fields (see Appendix F). Patients will be randomized to receive either the standard or the investigational treatment arm.

Patients will all receive 2 cycles of ABVD, followed by a PET scan evaluation. They will be classified in groups A, B or C when the results of the PET scan is available. This means that patients for whom the PET scan results would not be available will not contribute to any part of the study, and, more importantly, can introduce a bias that will invalidate all study results.

It is therefore of utmost importance that the PET scan is performed in all patients, especially those randomized to the standard treatment arms.

8.2 Statistical analysis plan

The primary objective of the trial is to find out whether the investigational treatments are non inferior to standard therapies in groups A and B. Therefore, the principal analysis should take place approximately 6.5 years after start of the recruitment (see above). Parameters of efficacy and safety during therapy will be analyses, as well as overall survival.

Two long term analyses will be carried out, after a median follow-up of 10 and 20 years. Those analyses will focus on late adverse events and overall survival.

8.2.1 Primary and secondary endpoints

The primary end-point in all 3 groups is progression free survival, counted from the date of randomization to the date of documentation of objective progression (see chapter 7) or death (from any cause), whichever occurs first. Patients alive and free of progression will be censored at the date of last follow-up.

Overall survival will be counted from the date of randomization to the date of death (from any cause). Alive patients will be censored at the date of last follow-up.

Event free survival will be counted from the date of randomization to the date of occurrence of death, objective progression, premature discontinuation of protocol therapy, or start of off protocol anti-cancer therapy (see chapter 7). Patients without documented event at the time of the analysis will be censored at the date of last follow-up.

Response to treatment, assessed at the end of protocol therapy (including radiotherapy, if applicable) will be classified as CR, CRu, PR, NC, PD (modified Costwold criteria, see chapter on evaluation criteria). Premature discontinuation of protocol therapy for progression and for other reasons will be separately classified.

The worst level of adverse events recorded during therapy will be reported according to the CTC-AE, version 3.0. For patients randomized to an arm including radiotherapy, all events will be considered up to 6 weeks after completion of radiotherapy.

The cumulative incidence of late adverse events will be counted from the date of randomization to the date of occurrence of any late severe (grade 3 or more) adverse event. In the primary analysis, only death (from other causes than late AE) will be considered as a competing risk. In a sensitivity analysis, the following events will be also considered as competing risks: disease progression, premature discontinuation of protocol therapy, start of any off-protocol anti-cancer treatment.

8.2.2 Analysis populations

- ◆ Intention-to-treat population: all patients randomized in the trial, irrespective of their eligibility status. All randomized patients will be analyzed in the arm they were allocated by randomization.
- ◆ Study population: intent to treat population, excluding patients who have not completed the 2 first ABVD cycles, or for whom no subsequent PET scan has been performed.
- ◆ “Best” and “worst scenario” populations: intent to treat population, excluding patients who have not completed the 2 first ABDV cycles; patients who have completed those 2 cycles but for whom no PET scan were performed will be respectively classified as PET negative (best scenario) and PET positive (worst scenario)
- ◆ Per protocol population: all “study” patients who were eligible for the trial
- ◆ Safety population: all “study” patients who have started the 3rd cycle of therapy (at least one dose of the study drugs)

A patient will be considered to be eligible if he/she did not have any major deviations from the patient entry criteria listed in chapter 3 of the protocol. Eligibility will be assessed by the Study Coordinator based on the review of each patient file.

8.2.3 Statistical methods

All primary analyses will be separately performed in each of the 3 groups of patients. Therefore, no strict “intent to treat” analysis will be performed, as patients will be classified in groups after the two first cycles of treatment and the subsequent PET scan.

One long term analysis of overall survival may be performed in the intent to treat population (see hereunder).

8.2.3.1 Progression free survival

The primary analysis will be based on the study population. Progression free survival will be estimated by the Kaplan-Meier method, and the hazard ratio will be estimated with its 95% confidence interval.

Randomized arms will be compared using the logrank test stratified by Ann Arbor stage and availability of a baseline FDG-PET scan. In groups A and B, this will be a one-sided non inferiority test, with an overall significance level of 0.025. In group C, this will be a two-sided superiority test, with an overall significance level of 0.05.

A sensitivity analysis of this end-point will be performed in the “best scenario” and “worst scenario” population, and also in the “per protocol” population.

8.2.3.2 Event free survival

This analysis will be performed on the same populations as the primary end-point, using the same tests and significance levels.

If relevant, the cumulative incidence of the different events contributing to this end-point may be estimated by a competing risk method, with an illustrative purpose. No formal tests will be performed on cumulative incidence.

8.2.3.3 Overall survival

The primary analysis will be performed on the same populations as the primary end-point, using the same tests and significance levels.

The long term survival analyses will be performed in the intent to treat population, comparing all patients allocated to a standard therapy to all patients allocated to a PET adapted therapy. In case of significant differences, the analysis will be repeated in the subgroup of patients with an ab initio favorable and unfavorable prognosis. The Hommel step-up procedure for repetitive testing will be applied.

8.2.3.4 Response to protocol therapy

Response to protocol therapy will be reported in the study population, by treatment arm. Results will be tabulated; unevaluable patients will be included as an additional category. The complete response rate (CR + CRu) will be provided with its 95% confidence interval. No other statistical inference will be provided.

8.2.3.5 Adverse events recorded during protocol therapy

The percentage of patients undergoing grade 3 and 4 adverse events during the two first cycles of therapy will be estimated in all “favorable” and “unfavorable” patients who have started the first cycle of therapy. No statistical inference will be provided.

The percentage of patients undergoing grade 3 and 4 adverse events during subsequent protocol therapy will be tabulated in the safety population, by treatment arm. No statistical inference will be provided.

8.2.3.6 Late adverse events

The cumulative incidence of late adverse events will be analyzed in the safety population by competing risk methods. The cumulative incidences will be tabulated, and illustrated by a graph when relevant. The overall incidence of severe late adverse events and the individual incidence of secondary malignancies, cardiovascular events and pulmonary events will be compared between treatment arms using the Gray test. The Hommel step-up procedure for repetitive testing will be applied.

8.2.4 Interim analyses

One formal interim analysis will be performed, after documentation of approximately 12 events (deaths or progression) in group A and 22 events in group B. This will represent between 1/3 and 1/2 of the events to be documented before the final analysis. It is estimated that 2/3 of the patients will already be accrued at that time.

A Lan-DeMets sequential design with Pocock like boundaries will be used for the analysis of progression free survival (the principal end-point). The data will be separately analyzed in group A and in group B. Only the alternative hypothesis will be tested. The recruitment of favorable patients will be stopped in case of futility (rejection of the alternative hypothesis) in group A, i.e. in case of inferiority of the investigational arm; the recruitment of unfavorable patients will be stopped in case of futility in group B. Data will be analyzed using the EAST software.

An interim analysis of the group C cohort will be simultaneously issued; a total of 23 events are expected to be documented at that time. A Lan-DeMets sequential design with Pocock like boundaries will be used for the analysis of progression free survival. Only the null hypothesis will be tested. Results of this analysis may lead to modification of treatments for the PET+ patients, but not to discontinuation of patient recruitment.

Analysis of other efficacy end-points will also be performed as supportive analyses in all 3 groups, but the decision to (partially) close the trial or to modify treatments should not be taken on the basis of these analyses.

A safety analysis will also be performed at that time.

8.2.5 Pre-planned sensitivity, exploratory and prognostic factors analyses

Planned sensitivity and subgroup analyses are addressed hereabove. No other exploratory or prognostic factors analyses are foreseen at this time. However, long term data of a large cohort of patients consistently treated will be generated in this study, and this database will be available for such projects.

8.2.6 Data recoding and display

Frequency tables will be tabulated (overall, by group and by treatment arm) for all categorical variables by the levels of the variables as they appear on the CRF (with %). Categories with a text field specification will be tabulated as categories and then supplemented by a listing with the following information for the patients fulfilling the condition for the specification (patient id, institution, treatment group, value of the item and text field contents).

Dates relating to events prior to entry will be presented as the delay in days (or weeks, months, or years) between the past event and the date of entry (date of randomization – date of past event + 1) and presented using the median and range. For example, on the randomization checklist, the date of first diagnosis of the cancer will be presented as the time elapsed (in days, weeks, months or years,

as appropriate) since the day of the first diagnosis and the date of entry on study (date of randomization – date of diagnosis +1).

Other delays (eg. re-treatment delays) are presented as continuous variables using the median and range.

Continuous variables for which a coding system exists (such as for laboratory data) will be recoded into categories (for adverse events, the grading scale specified in the protocol will be used).

Whenever no specific scale exists, lab data will be categorized based on the normal range: for example, below the lower normal limit (when appropriate), within the normal range, above the upper normal limit (UNL) and the degree to which it is above the UNL (for example $> 2.5 \times \text{UNL}$, $> 5 \times \text{UNL}$, $> 10 \times \text{UNL}$). For laboratory data, the nadir is generally displayed. The nadir in a given cycle is the lowest laboratory value in that cycle; the overall nadir for a patient is the lowest laboratory value among all cycles.

Other continuous variables (for example age, dose ...) are presented using the median and range (minimum, maximum) or presented in categories.

8.3 End of study

End of study occurs when all of the following criteria have been satisfied:

1. Thirty days after all patients have stopped protocol treatment
2. The trial is mature for the analysis of the primary endpoint as defined in the protocol
3. The database has been fully cleaned and frozen for this analysis

9 Data monitoring

A Data and Safety Monitoring Board (DSMB) will monitor the recruitment, the reported adverse events and the data quality at least twice a year. Problems which are identified will be discussed with the Study Coordinator who will take appropriate measures. Relevant information (including relevant safety data) will be included in the study status reports which serve as a basis of discussion during EORTC Group meetings. These reports will be made available to investigators participating in the study and to the EORTC Independent Data Monitoring Committee (IDMC) if interim analyses (planned or not planned) are carried out.

If interim analyses are carried out, the interim monitoring of efficacy and safety data will be performed according to the Statistical Considerations chapter and the EORTC policy on “Independent Data Monitoring Committees and Interim Analyses”.

The results of the interim analyses are confidential and are discussed by the EORTC IDMC. The IDMC will subsequently recommend to the EORTC Group whether any changes should be made to the study.

No efficacy results will be presented at EORTC Group meetings or elsewhere before the trial is closed to recruitment and the data are mature for the analysis of the primary endpoint, unless recommended otherwise by the EORTC IDMC.

10 Publication policy

The final publication of the trial results will be written by the Study Chairman and co-Chairman on the basis of the final analysis performed at the EORTC Data Center. The study chairman will submit a draft manuscript to the Data Center for review no later than six months after receiving the Data Center report. The steering committee is entitled to appoint another main author in case this deadline is not respected. After revision by the Data Center and other co-authors the manuscript will be sent to a major scientific journal.

Authors of the manuscript will include at least the Study Chairman and co-Chairman, the substudy coordinators, investigators who have included significant numbers of eligible patients in the trial (as agreed by the steering committee), the Data Center personnel in charge of the trial. Other coauthors can be considered by the steering committee based on the proposals of the scientific boards of the participating groups. In a note participating centers with the responsible physicians, committee members and board of the groups must be mentioned.

If the group wishes to publish or present study data before this final publication, those will never include comparisons between randomized treatment arms before the number of events required by the protocol for the primary end-point of interest have been observed.

All publications, abstracts or presentations including data from the present trial will be submitted for review to the EORTC Data Center prior to submission.

The title of all manuscripts will include the name of all participating groups, and all manuscripts will include an appropriate acknowledgment section, mentioning all investigators who have contributed to the trial, as well as supporting bodies (NCI, cancer leagues, sponsors...).

The Steering committee must approve all publications, abstracts and presentations based on patients included in this study, after notification of the scientific boards of the EORTC Lymphoma Group and GELA. This is applicable to any individual patient registered/randomized in the trial, or any subgroup of the trial patients. Such a publication cannot include any comparisons between randomized treatment arms or an analysis of any of the study end-points unless the final results of the trial have already been published.

11 Investigator authorization procedure

Investigators will be authorized to register or randomize patients in this trial only when they have returned to their Data Center (for the EORTC investigators see chapter 17: Administrative responsibilities, for non-EORTC investigators: see your group specific appendix):

- ◆ The updated signed and dated Curriculum Vitae of the Principle Investigator
- ◆ The (updated) list of the normal ranges, in their own institution, of all laboratory data required by the protocol, preferably signed and dated by the head of the laboratory.
- ◆ A commitment statement / study acknowledgment form, indicating that they will fully comply with the protocol, to include an estimate of their yearly accrual and if any conflict of interest may arise due to their participation in the trial,
 - ◆ A signed conflict of interest disclosure form: this document will be required only if a possible conflict is declared on the commitment form.
- ◆ A copy of the favorable opinion of their local or national (whichever is applicable) ethics committee mentioning the documents that have been reviewed (incl. version number and date of documents) and indicating the list of the ethics committee members.

- ◆ A copy of the translated, and adapted (according to all national requirements), Patient Information / Informed Consent sheet, clearly mentioning the version number and the date.
- ◆ The signature log-list of the staff members with a sample of each authorized signature and the indication of the level or delegations.
- ◆ The coordinates of the pharmacist who will be responsible for the trial medication (for any trial where the drug will be provided).
- ◆ The accreditation letter for the laboratory. (if available for your center and/or applicable by your national law)

The center specific applicable list of required documents will be included in the protocol activation package, with proper instructions as required by this protocol, your group and / or the applicable national law

The new investigator will be added to the “authorization list”, and will be allowed to register/randomize patients in the trial as soon as

- ◆ All the above mentioned documents are available at their Data Center
- ◆ All applicable national legal and regulatory requirements are being fulfilled

Patient registration/randomization from centers not (yet) included on the authorization list will not be accepted.

12 Patient randomization and registration procedures

12.1 Initial randomization

Patient randomization will only be accepted from authorized investigators (see "Authorization procedure").

A patient can be randomized only after verification of eligibility. This must be done **before the start of the protocol treatment**.

An exhaustive list of questions to be answered during the randomization procedure is included in the registration check-list, which is part of the case report forms. This check-list should be completed by the responsible investigator before the patient is randomized.

Standard questions

- ◆ institution number ?
- ◆ protocol number ?
- ◆ step number: 1
- ◆ name of the responsible investigator ?
- ◆ patient's code (maximum 4 letters) ?
- ◆ patient's chart number (if available) ?
- ◆ patient's birth date (day/month/year) ?

Group affiliation:

- ◆ primary group affiliation (name of the group to which belongs the investigator; investigators belonging to several groups should complete the name of the group with which they deal for all administrative procedures for this trial) ?
- ◆ secondary group affiliation (name of the other group to which belongs the investigator) ?

Protocol specific questions

- ◆ eligibility criteria ?
 - all eligibility criteria will be checked;
 - actual values of the eligibility parameters will be requested when applicable
- ◆ stratification factors ?
- ◆ date of written informed consent ?

At the end of the procedure, the treatment will be randomly allocated to the patients, as well as a patient sequential identification number. This number and the allocated treatment have to be recorded on the randomization check-list, along with the date of randomization. The completed check-list must be signed by the responsible investigator and returned to the data center with the initial data of the patient. The sequential identification number attributed to the patient at the end of the randomization procedure identifies the patient and must be reported on all case report forms.

All participants from non-EORTC groups should contact the Data Center mentioned in their Group Specific Appendix.

All EORTC participants can randomize patients directly on the EORTC Data Center computer, 24 hours a day, 7 days a week, through the INTERNET network. To access the interactive randomization program, the investigator needs a username and a password (that can be interactively requested: <http://www.eortc.be/random>).

Alternatively, EORTC participants can telephone to the EORTC Data Center from 9.00 am to 5.00 pm (Belgian local time) from Monday through Friday to randomize patients. As from January 01, 2003 the phone randomization will not be available on the official bank holiday of Belgium. A list of these dates will be available on our web site and updated yearly.

Telephone: +32 2 77416 00

Internet: <http://www.eortc.be/random>

12.2 Second registration

The inclusion of the patient into the trial must be confirmed by a second central registration **for all randomized patients**. At the time of the second registration, patients will be allocated to groups A, B or C or excluded from the study population (see “analysis populations” in the chapter “Statistical considerations”).

This second registration should be performed after completion of the two first cycles of protocol therapy and performance of the PDG-PET scan, and before the start of the 3rd cycle of therapy.

For patients taken off protocol therapy before the end of the second cycle, this second registration should occur as soon as the decision to remove the patient from the protocol is taken. If the PDG-PET scan is omitted (major protocol violation), the second registration should anyway occur before the start of the 3rd cycle of therapy.

The second registration should be done with the same Data Center as the initial randomization. For patients directly randomized with EORTC, the second registration may be performed either via internet, or by phone, independently of the system used for the initial randomization.

The list of questions to be answered during the second registration procedure is included in the EORTC Second Registration checklist and Coordinating Group's second registration form that are part of the case report forms.

Standard questions:

- ◆ institution number ?
- ◆ protocol number ?
- ◆ step number: 2
- ◆ select the patient from the list menu (all patient's information will automatically be filled out)
- ◆ name of the responsible investigator ?

Group affiliation

- ◆ primary group affiliation (same as for initial randomization) ?

Protocol specific questions

- ◆ date and results of the PDG-PET scan
- ◆ eventually, reason for not performing the PDG-PET scan

13 Forms and procedures for collecting data

13.1 Case report forms and schedule for completion

Data will be reported on the **forms specifically designed by the EORTC Data Center for this study. Those forms will be used by all cooperative groups. Each group can eventually customize the heading frame but not the contents of the forms. Appropriate forms will be distributed to each investigator by their own Data Center.**

All participants from non-EORTC groups should send forms to the Data center mentioned in their Group Specific Appendix.

All EORTC participants should send forms directly to the EORTC Data Center:

Lymphoma Group Data Manager
EORTC Data Center
Avenue Emmanuel Mounier, 83, bte 11
B-1200 Brussels, Belgium

A. Before the treatment starts:

- ◆ the patient must be registered/randomized through your Data Center
- ◆ the registration check-list should be returned to your Data Center

The optimal way to work is to complete the registration check-list first and to register/randomize the patient as soon as it is completed. The date of registration and patient sequential identification number are then completed on the check-list, and this form can be sent to the Data Center.

B. The list of forms to be completed for this study and their submission schedule is appended to the set of case report forms

C. Upon occurrence of a Serious Adverse Event (SAE)

- ◆ SAEs occurring from the time a subject is registered until 30 days after last protocol treatment must be promptly reported.
- ◆ Any SAE occurring after the 30-days period and considered to be reasonably related to the investigational product or study participation, also have to be promptly notified
- ◆ All these events must be reported **by fax** to the **EORTC Pharmacovigilance Unit** on a Serious Adverse Event Form **within 24 hours** of the initial observation.
- ◆ A completed SAE-form must be sent back within 10 calendar days of the initial observation of the Serious Adverse Event.

**ALL Forms must be dated and signed by the responsible investigator
or one of his/her authorized staff members**

13.2 Data flow

Procedures for data collection

Centers will have the option to use the paper version of the CRF or the EORTC Remote Data Capture (RDC) CRF.

Data reported on the paper CRF prepared for this study should be sent to:

(Group) Data Manager

EORTC Data Center

83, avenue Emmanuel Mounier, Bte 11
B-1200 Brussels, Belgium

Centers that choose the option of the EORTC RDC will have to ensure that they have internet connection available and have to request the “username” and “password” to access the system. This “username” and “password” is the same as the one used to access the on-line ORTA system for randomization / registration of patients to the study.

The choice between paper CRF and RDC is linked to the center and thus by default is to be applied for all patients entered into the study. Once an option is chosen any change during the study can only be accepted after clear agreement with the EORTC responsible data manager.

Randomization/ Registration checklist, the SAE form and the Quality of Life form can NOT be filled out electronically. Paper copies will be provided for these forms to all centers.

13.2.1 Using the paper CRF

The case report forms must be completed, dated and signed by the investigator or one of his/her authorized staff members as soon as the requested information is available.

The list of staff members authorized to sign case report forms (with a sample of their signature) must be sent to their respective Data Center by the responsible investigators before the start of the study.

In all cases, it remains the responsibility of the investigator to check that original case report forms are sent to their respective Data Center and that they are completely and correctly filled out.

The original copy must be immediately returned to the respective Data Center and the investigator must keep a copy.

The EORTC Data Center will perform extensive consistency checks on the CRFs and issue Query Forms in case of inconsistent data. Those Query Forms must be immediately answered and signed by the investigator (or an authorized staff member). The original must be returned to the respective Data Center and a copy must be appended to the investigator's copy of the CRFs.

If an investigator (or an authorized staff member) needs to modify a CRF after the original copy has been returned to the respective Data Center, he/she should notify the Data Center using the Data Correction form, sign the notification and append a copy of the notification to his own copy of the CRFs.

The investigator's copy of the CRFs may not be modified unless modifications are reported on the Data Correction Form or following a Query raised by the EORTC Data Center.

13.2.2 Using the electronic forms system

The forms must be electronically completed by the investigator or one of his / her authorized staff members as soon as the requested information is available. The schedule for form completion will be provided together with the completion guidelines. Staff members allowed to complete the RDC should be listed (with a sample of their signature) on the signature log sent to the EORTC Data Center before the start of the study.

In all cases it remains the responsibility of the investigator to check that the RDC of case report forms are completely and correctly filled out, and that they are sent to the Data Center as soon as possible. The EORTC data manager will perform extensive consistency checks on the electronic forms, and issue Queries in case of inconsistent data. Queries will be sent by Email in PDF format. The investigator (or authorized staff member) will answer these queries and sign the query forms. The EORTC data manager will subsequently verify the modifications and update the data base at the EORTC Data Center. If an investigator (or authorized staff member) needs to modify a CRF after the electronic form has been sent to the EORTC Data Center, he / she should notify the Data Center using the Data Correction form which will be provided together with the form completion guidelines.

For both the EORTC generated queries and on-site Data Corrections the originals have to be sent to the EORTC Data Center and a copy kept on site.

14 Reporting of Serious Adverse Events

14.1 Definitions

AE: An **Adverse Event** is defined as any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended signs (such as rash or enlarged liver), symptoms (such as nausea or chest pain), an abnormal laboratory finding (including blood tests, x-rays or scans) or a disease temporarily associated with the use of the protocol treatment, whether or not considered related to the investigational medicinal product.

AR: An **Adverse reaction of an investigational medicinal product** is any untoward and unintended responses to an investigational medicinal product related to any dose administered.

All adverse events judged by either the reporting investigator or the sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

UAR: An Unexpected Adverse Reaction is any adverse reaction, the nature, or severity of which is not consistent with the applicable product information (e.g. investigator's brochure for an unapproved investigational product or summary of product characteristics (SmPC) for an authorised product).

When the outcome of the adverse reaction is not consistent with the applicable product information this adverse reaction should be considered as unexpected.

Severity: The term “severe” is often used to describe the intensity (severity) of a specific event. This is not the same as “serious,” which is based on patient/event outcome or action criteria.

SAE: A Serious Adverse Event is defined as any undesirable experience occurring to a patient, whether or not considered related to the protocol treatment.

SAR: A Serious Adverse Event (SAE) which is considered related to the protocol treatment is defined as a **Serious Adverse Reaction**

An **Adverse Event** or **Adverse Reaction** which is considered as **serious**:

- ◆ results in death,
- ◆ is life-threatening (i.e. an event in which the subject was at risk of death at the time of event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- ◆ requires hospitalisation or prolongation of existing inpatients' hospitalisation,
- ◆ results in persistent or significant disability or incapacity,
- ◆ is a congenital anomaly or birth defect.
- ◆ results in any other medically important condition (i.e. important adverse reactions that are not immediately life threatening or do not result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed above).

SUSAR: Suspected Unexpected Serious Adverse Reactions

14.2 Reporting procedure

14.2.1 Non- serious adverse events and/or non-serious adverse drug reactions

Adverse Events (AE) and /or Adverse Reactions (AR) must be recorded as indicated in the protocol.

14.2.2 Serious adverse events or serious adverse drug reactions

All Serious Adverse Events (SAE) occurring from the time a subject is registered until 30 days after last protocol treatment, must be reported to the EORTC Pharmacovigilance Unit within 24 hours. (Ref. <http://ctep.info.nih.gov/reporting/ctc.html>).

All SAEs that are simply signs and symptoms of the disease being studied do NOT need to be collected!

Examples of SAEs that do not need to be reported:

- ◆ Medical or surgical procedure (e.g., endoscopy, appendectomy); the condition that leads to the procedure is an AE
- ◆ Situations where an untoward medical occurrence did not occur (social and/or convenience admission to a hospital)
- ◆ Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen
- ◆ The disease/disorder being studied, or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the subject's condition
- ◆ A hospitalization which was planned before the patient consented for study participation and where admission did not take longer than anticipated.

Any SAE that occurs outside of the SAE detection period (after the 30-days period), considered to be reasonably related to the investigational product or study participation, have to be promptly notified to the EORTC Pharmacovigilance Unit.

This must be done by fax within 24 hours of the initial observation of the event. The principal investigator will decide if these events are related to the protocol treatment (i.e. unrelated, likely related, and not assessable) and the decision will be recorded on the Serious Adverse Event form, if necessary with the reasoning of the principal investigator.

The investigator is obligated to assess the relationship between investigational product and the occurrence of each AE/SAE. A "reasonable possibility" is meant to convey that there are facts/evidence or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out. The investigator will use clinical judgement to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the investigational product will be considered and investigated.

The product reference documents are

For marketed products: Summary Of Product Characteristics which can be found on <http://www.emea.eu.int/hums/human/epar/epar.htm#>

For non-marketed products: Current version of the Investigators Brochure

For the causality assessment, the following definitions must be used:

Relationship to the protocol treatment	Description
UNRELATED	There is no evidence of any causal relationship to the protocol treatment
LIKELY RELATED	There is (some) evidence to suggest a causal relationship to the protocol treatment and influence of other factors is unlikely or absent.
NOT ASSESSABLE	There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship to the protocol treatment.

Details should be documented on the specified Serious Adverse Event Form.

Investigators participating through **non-EORTC groups** should consult their **group specific appendix** for further details on the reporting of Serious Adverse Events.

Investigators participating through **EORTC** should follow recommendations below:

PLEASE FAX THE REPORT TO:

EORTC Pharmacovigilance Unit:
Fax No. +32 2 772 8027

The EORTC Pharmacovigilance Unit will forward all Serious Adverse Event reports within 24 hours of receipt to all appropriate persons (**See Administrative chapter**).

To enable the sponsor to comply with regulatory reporting requirements, completed documentation of any reported serious adverse events or serious adverse reactions must be returned within 10 calendar days of the initial report. If the completed form is not received within this deadline, the Pharmacovigilance Unit will make a written request to the investigator.

It should be recognized that Serious Adverse Reactions (SAR) which have not been previously documented in the Investigators' Brochure, or which occur in a more severe form than anticipated (i.e. they are 'unexpected' by nature or severity), are subject to rapid reporting to the Regulatory Authorities.

ANY QUESTION CONCERNING SAE OR SAR REPORTING CAN BE DIRECTED TO:

EORTC Pharmacovigilance Unit
Phone: +32 2 774 1676
Fax: +32 2 772 8027
e-mail: pharmacovigilance@eortc.be

ALL FORMS MUST BE DATED AND SIGNED BY THE RESPONSIBLE INVESTIGATOR OR ONE OF HIS/HER AUTHORIZED STAFF MEMBERS.

15 Quality assurance

15.1 Control of data consistency

Data forms will be entered into the database of the EORTC Data Center by a double data entry procedure. Computerized and manual consistency checks will be performed on newly entered forms; queries will be issued in case of inconsistencies. Consistent forms will be validated by the data manager and then entered into the master database. Inconsistent forms will be kept "pending" until resolution of inconsistencies.

15.2 Audits

To ensure quality of data, study integrity, and compliance with the protocol and the various applicable regulations and guidelines, the EORTC Quality Assurance Unit regularly conducts site visits to institutions participating to EORTC protocols.

The investigator, by accepting to participate to this protocol, agrees to co-operate fully with any quality assurance visit undertaken by third parties, including representatives from the EORTC, national and/or foreign regulatory authorities or company supplying the product under investigation, as well as to allow direct access to documentation pertaining to the clinical trial (including CRFs, source documents, hospital patient charts and other study files) to these authorized individuals.

The investigator must inform the EORTC immediately in case a regulatory authority inspection would be scheduled.

This procedure does not apply to non-EORTC investigators who should refer to their Group Specific Appendix for the information on eventual audits performed by their group.

15.3 Central review of pathology

The following is applicable for the investigators participating on behalf of the EORTC.

For non-EORTC investigators please see the specific group appendix.

In order to assure the high quality and consistent pathology diagnosis, a centralized pathology review is included in this trial.

Within two weeks from the date of randomization, the local pathologist must send to the Panel Committee the following material:

- ◆ fifteen (15) unstained slides or paraffin block(s)
- ◆ the original pathology form (only the local pathology part should be completed)

Panel Committee address:

J. BOSQ
Pathology Department
INSTITUT GUSTAVE ROUSSY (Number: 225)
39, rue Camille Desmoulins
FR 94805 VILLEJUIF CEDEX
France
Phone: + 33 142114514
Fax: + 33 142115264
e-mail: bosq@igr.fr

The Panel Committee, including J. Bosq, D. de Jong, K. MacLennan, J. Diebold., will review all received slides. Once this pathology review has been performed, the fully completed pathology form will be sent to the EORTC Data Center in Brussels.

The final diagnosis of the Central Pathologists will be considered as definitive for the trial.

The diagnosis made by the local pathologist of the participating center will be accepted for the randomization.

Chapters 16 through 19 pertain specifically to the participation of EORTC investigators. Participants from other organizations should consult the appendix that is specific to their group to determine if the contents of these chapters are superceded by procedures specific to their group.

16 Ethical considerations

16.1 Patient protection

The responsible investigator will ensure that this study is conducted in agreement with either the Declaration of Helsinki (Tokyo, Venice, Hong Kong, Somerset West and Edinburgh amendments) and/or the laws and regulations of the country, whichever provides the greatest protection of the patient.

The protocol has been written, and the study will be conducted according to the ICH Harmonized Tripartite Guideline on Good Clinical Practice (ICH-GCP, available online at <http://www.emea.eu.int/pdfs/human/ich/013595en.pdf>).

The protocol must be approved by the competent ethics committee(s) as required by the applicable national legislation.

16.2 Subject identification

The name of the patient will neither be asked for nor recorded at the EORTC Data Center. A sequential identification number will be automatically allocated to each patient registered in the trial. This number will identify the patient and must be included on all case report forms. In order to avoid identification errors, the patient's code (maximum of 4 letters), date of birth and local chart number (if available) will also be reported on the case report forms.

16.3 Informed consent

All patients will be informed about

- ◆ the aims of the study
- ◆ the possible adverse events
- ◆ the procedures and possible hazards to which the patient will be exposed
- ◆ the mechanism of treatment allocation
- ◆ strict confidentiality of any patient data
- ◆ medical records possibly being reviewed for trial purposes by authorized individuals other than their treating physician.

The template of the patient's informed consent statement is given as an appendix to this protocol.

It is the responsibility of the Coordinating Investigators for this trial (sometimes called National Coordinators) to translate the enclosed informed consent document. The translated version should be dated and version controlled.

The bold sections of the informed consent document must be reflected in any translation. The content of these bold sections can either be translated literally or translated in any way that best captures the information given.

The translated informed consent documents are to be submitted to ethics committees for approval. The competent ethics committee for each institution must approve the informed consent documents before the center can join the study. It is the responsibility of the competent ethics committee to

ensure that the translated informed documents comply with ICH-GCP guidelines and all applicable national legislation.

It is emphasized in the patient information sheet that participation is voluntary and that the patient is free to refuse further participation in the protocol whenever he/she wants to. This will not have any impact on the patient's subsequent care. Documented informed consent must be obtained for all patients included in the study before they are registered and/or randomized at the EORTC Data Center. The written informed consent form must be signed and personally dated by the patient or by the patient's legally acceptable representative".

All of the above must be done in accordance with the applicable national legislation and local regulatory requirements.

17 Administrative responsibilities

17.1 The study coordinator

The Study Coordinator (in cooperation with the Data Center) will be responsible for writing the protocol, reviewing all case report forms and documenting his/her review on evaluation forms, discussing the contents of the reports with the Data Manager and the Statistician, and for publishing the study results. He will also generally be responsible for answering all clinical questions concerning eligibility, treatment, and the evaluation of the patients.

Study coordinator: John Raemaekers

UNIVERSITY MEDICAL CENTRE NIJMEGEN, Dept of Hematology
P.O. Box 9101 - Geert Groteplein 10
NL 6500 HB NIJMEGEN
The Netherlands

Phone: + 31 24 3614762

Fax: + 31 24 3542080

e-mail: J.Raemaekers@HEMAT.umcn.nl

17.2 The EORTC Data Center

The EORTC Data Center will be responsible for reviewing the protocol, collecting case report forms, controlling the quality of the reported data, and generating reports and analyses in cooperation with the Study Coordinator. All methodological questions should be addressed to the EORTC Data Center.

EORTC DATA CENTER

83, avenue Emmanuel Mounier, Bte 11
B-1200 Brussels, Belgium
Fax: +32 2 7723545

Registration of patients:

Phone: +32 2 7741600

or

<http://www.eortc.be/random>

Statistician:**Martine Van Glabbeke**

Phone: +32 2 7741625

e-mail: martine.vanlabbeke@eortc.be**Data Manager:****Bart Meulemans**

Phone: +32 2 7741079

e-mail: bart.meulemans@eortc.be**Coordinating Physician:****Liliana Baila**

Phone: +32 2 7741663

e-mail: liliana.baila@eortc.be**Pharmacovigilance Unit:**

Phone: +32 2 774 1676

Fax: +32 2 772 8027

e-mail: pharmacovigilance@eortc.be

The EORTC Pharmacovigilance Unit will forward all SAE within 24 hours of receipt to the EORTC Study Coordinator and the EORTC Data Manager.

All SUSARs will additionally be notified to all EORTC participating investigators and all central Data Managers of all Cooperating Groups.

The EORTC Pharmacovigilance Unit will take in charge the expedited reporting to the Competent Authorities, whenever applicable, in the countries where EORTC is the sponsor.

The EORTC Pharmacovigilance Unit will prepare the Annual Safety report and distribute it to the central Data Managers of all Cooperating Groups

17.3 The EORTC group

All questions concerning membership in the group should be addressed to the chairman and/or secretary of the group.

Lymphoma EORTC group

Chairman:

Mads HANSEN

RIGSHOSPITALET

Blegdamsvej 9

DK 2100 COPENHAGEN

Denmark

Phone: +45 35451128

Fax: +45 35454448

e-mail: mth@rh.dk

Secretary:

Berthe Aleman

THE NETHERLANDS CANCER INSTITUTE-ANTONI VAN LEEUWENHOEKZIEKENHUIS

Plesmanlaan 121

NL 1066 CX AMSTERDAM

The Netherlands

Phone: +31 205122125

Fax: +31 206691101

e-mail: b.aleman@nki.nl

18 Trial sponsorship and financing

EORTC is the legal European Sponsor unless otherwise specified for legal or logistical reasons.

The Director General of the EORTC is:

Françoise Meunier

EORTC Central Office

Avenue Mounier 83, Bte 11

B-1200 Brussels, Belgium

Phone: +32 2 7741641

Fax: +32 2 7712004

e-mail: francoise.meunier@eortc.be

19 Trial insurance

A clinical trial insurance has been taken out according to the laws of the countries where the study will be conducted. An insurance certificate will be made available to the participating sites at the time of study initiation.

Clinical trial insurance is only valid in centers authorized by the EORTC Data Center. For details please refer to the chapter on investigator authorization.

Patients treated at **satellite institutions** are only covered by clinical trial insurance, if these satellite institutions are properly reported to the EORTC Data Center. For details please refer to the chapter on investigator authorization.

Appendix A: References

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- Ref. 11 Noordijk EM, Carde P, Mandard AM, et al. Preliminary results of the EORTC-GPMC controlled clinical trial H7 in early stage Hodgkin's disease. *Ann Oncol* 1994, 5, S107-12.
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- Ref. 14 Noordijk E, Thomas J, Ferme C, et al. First results of the EORTC-GELA H9 randomized trials: the H9-F trial (comparing 3 radiation dose levels) and H9-U trial (comparing 3 chemotherapy schemes) in patients with favourable or unfavourable early stage Hodgkin's lymphoma. 41st Annual Meeting of the American Society of Clinical Oncology, *J Clin Oncol* 2005;23 (16S):561S (abstract 6505).
- Ref. 15 Henry-Amar M, Somers R. Survival outcome after Hodgkin's disease: a report from the international data base on Hodgkin's disease. *Semin Oncol* 1990, 17, 758-68.

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Appendix B: WHO performance status scale

Grade	Performance scale
0	Able to carry out all normal activity without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out light work.
2	Ambulatory and capable of all self-care but unable to carry out any work; up and about more than 50% of waking hours.
3	Capable of only limited self-care; confined to bed or chair more than 50% of waking hours
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair.

Appendix C: Common Terminology Criteria for Adverse Events

In the present study, adverse events and/or adverse drug reactions will be recorded according to the **Common Terminology Criteria for Adverse Events (CTCAE), version 3.0.**

At the time this protocol was issued, the full CTC document was available on the NCI web site, at the following address: <http://ctep.cancer.gov/reporting/ctc.html>.

The EORTC Data Center web site www.eortc.be provides a link to the appropriate CTC web site. This link will be updated if the CTC address is changed.

Appendix D: World Medical Association Declaration of Helsinki

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th World Medical Assembly
Helsinki, Finland, June 1964
and amended by the
29th World Medical Assembly, Tokyo, Japan, October 1975
35th World Medical Assembly, Venice, Italy, October 1983
41st World Medical Assembly, Hong Kong, September 1989
48th General Assembly, Somerset West, Republic of South Africa, October 1996
and the
52nd WMA General Assembly, Edinburgh, Scotland, October 2000

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 fulfillment 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.
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.
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.

Appendix E: Patient Information Sheet and Informed consent document for clinical trials

INFORMATION FOR INVESTIGATORS:

This document is an English version of the Patient information sheet & informed consent for clinical trials (PIS & IC). The translation and national regulatory submission process of this document is the responsibility of the National Coordinator for this trial. He/she will keep you aware and informed and will send the translated and approved document as soon as available.

INFORMATION FOR THE NATIONAL COORDINATORS:

- this document represents an English version of PIS & IC to be used in the present study

 - it is the responsibility of the national coordinator to:
 - translate the patient information sheet and informed consent in preparation for the submission of the dossier to the ethics committee (the submission may be the responsibility of EORTC or the investigator depending on the local regulations)

 - send a copy of the approved translated document to EORTC Data Center who will then distribute the document to other national participating investigators

 - bold parts, appearing in the English template, **must** appear also in the translated version of the PIS & IC

 - final translated and approved PIS & IC must have a version number and a date
-



AISBL International Non-Profit Association under Belgian law IVZW

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1. Title of the research protocol

The H10 EORTC/GELA randomized Intergroup trial on early FDG-PET scan guided treatment adaptation versus standard combined modality treatment in patients with supradiaphragmatic stage I/II Hodgkin's lymphoma

2. Invitation to participate in the study

The EORTC Lymphoma Group in close collaboration with the GELA group - Groupe d'Etudes des Lymphomes de l'Adulte is initiating a clinical trial on patients that have a disease similar to yours. The study will be conducted at the European level under the supervision of doctors recognized as experts in this field of medicine. You are invited to take part in this clinical research project after having received full information about the study.

3. Introduction

Hodgkin's lymphoma is nowadays a disease that can be treated effectively with a combination of chemotherapy and radiotherapy (RT). The large majority of patients will be cured after this treatment. However, we know that many years after treatment undesirable toxicities can occur caused by the treatment. Compared to the "general" population, patients who have been treated for Hodgkin's lymphoma with a combination of chemotherapy and RT have a higher risk of developing other types of malignant disease, diseases of the heart and blood vessels such as arteriosclerosis, and pulmonary function impairment. In addition, specific types of chemotherapy and/or RT can induce infertility in males and females and early menopause in females. Therefore, there is a continuing search worldwide to adapt the treatment in order to maintain the high cure rates but to decrease the occurrence of the toxic events. One way to adapt treatment is to omit RT since we know that RT is responsible for toxicity when large areas of the body are being irradiated. Possibly, RT can be omitted in certain groups of patients when chemotherapy is intense and efficacious enough. The standard chemotherapy is the combination of adriamycine, bleomycine, vinblastine and dacarbazine (ABVD). We now try to define the group of patients that can be treated with chemotherapy alone. In identifying that group of patients we need to do a large clinical trial in which patients are randomly assigned to either the standard treatment consisting of the combination of chemotherapy and RT or chemotherapy alone. Only then we can conclude whether chemotherapy alone is as good as combined treatment but associated with less undesirable events.

For the small proportion of patients that will not be cured by our current standard treatment, we try to find new ways to improve the results. By changing the chemotherapy schedule early in the course of treatment, from ABVD to an alternative schedule we hope to increase the cure rate for this small group of patients. This intensification of treatment should be reserved for those who really need it and in this trial we hope to define that particular small group of patients.

One of the recent advances in the imaging of the tumor sites (where is the Hodgkin disease localized in your body?), is the so-called FDG-PET (fluorodeoxyglucose-positron emission tomography) scan. With this FDG-PET scan, lymph node areas involved with Hodgkin Lymphoma are visualized based on their need for energy supplements such as carbohydrates. Such a carbohydrate is glucose. Glucose can be radio-actively labeled, and administered intravenously to patients. It will distribute throughout your body and selectively accumulate in those areas in which

energy supplements are eagerly needed. This process is visualized on a scan with hot spots due to accumulation of radioactive labeled glucose. There is now wide experience with this FDG-PET scan. Recent findings suggest that when a FDG-PET scan is being made early after start of chemotherapy, e.g. already after two cycles, a normal FDG-PET scan result may possibly indicate that the Hodgkin lymphoma has been eradicated rapidly. An abnormal FDG-PET scan result may possibly indicate that the disease is somewhat less sensitive to the treatment given so far. Therefore when the FDG-PET scan is made after two cycles of ABVD chemotherapy and the result is negative, e.g. probably no indication of active Hodgkin's disease, we anticipate that this is the group of patients that can be treated less intensively and so we will omit RT in this group of patients. When the FDG-PET scan is positive after two cycles of ABVD, e.g. probably still active Hodgkin's disease, we anticipate that this is the group patients that should be treated right away more intensively by an alternative chemotherapy schedule combined with RT.

As stated above to meet these goals we have to perform a so-called randomized clinical trial in which 50% of patients will be assigned to the standard treatment (chemotherapy + RT) without taking into account the results of the FDG-PET scan after two cycles of ABVD and the other 50% of patients will receive the new treatment strategy with the FDG-PET scan result as the guidance for adapting the treatment.

The EORTC Lymphoma Group and the GELA group have a longstanding experience in performing this kind of clinical research and have completed several large clinical trials with thousands of patients throughout Europe aiming at improving the results of treatment in patients with Hodgkin's lymphoma.

4. Description of the research

On the basis of characteristics of the Hodgkin's lymphoma in your situation we can identify two groups of patients:

- ◆ Patients with a favorable (F) profile: the F-group
- ◆ Patients with an unfavorable (U) profile: the U-group

Whatever the group you are assigned to you will receive either the experimental treatment or the standard conventional treatment.

- ◆ The **standard** treatment for patients in the F group consists of 3 cycles of chemotherapy being adriamycine, bleomycine, vinblastine and dacarbazine (ABVD) followed by RT directed to the initially involved lymph nodes.
- ◆ The **standard** treatment for patients in the U group consists of 4 cycles of chemotherapy being adriamycine, bleomycine, vinblastine and dacarbazine (ABVD) followed by RT directed to the initially involved lymph nodes.
- ◆ The **experimental** treatment for patients in the F group consists of the following:
 - ◆ Patients receive 2 cycles of ABVD
 - ◆ If the FDG-PET scan after the two cycles of ABVD is negative, patients receive 2 additional cycles of ABVD but without RT.
 - ◆ If the FDG-PET scan after the two cycles of ABVD is positive, patients change from ABVD to escalated BEACOPP (combination of bleomycine, etoposide, adriamycine, cyclophosphamide, vincristine, procarbazine, prednisone) chemotherapy from which patients receive 2 cycles followed by RT.

- ◆ The **experimental** treatment for patients in the U group consists of the following:
 - ◆ Patients receive 2 cycles of ABVD
 - ◆ If the FDG-PET scan after the two cycles of ABVD is negative, patients receive 4 additional cycles of ABVD but without RT.
 - ◆ If the FDG-PET scan after the two cycles of ABVD is positive, patients change from ABVD to escalated BEACOPP (combination of bleomycine, etoposide, adriamycine, cyclophosphamide, vincristine, procarbazine, prednisone) chemotherapy from which patients receive 2 cycles followed by RT.

The treatment you will receive will be decided by chance. This is called randomization. Your doctor will call a central statistical office, which will assign one of the two treatments to you. Your chances of getting either the experimental treatment or the standard chemotherapy are equal (50% either way) neither you nor your doctor can choose the treatment.

A scheme of the study is also available.

4.2. Chemotherapy scheduling

In the ABVD schedule every cycle consists of administration of chemotherapy on day 1 and 15. The next cycle start on day 29.

In the more intense escalated BEACOPP schedule every cycle consists of administration of chemotherapy on day 1 and 8. The next cycle starts on day 22.

Both chemotherapy schedules will be given on an outpatient basis. You will stay several hours at the outpatient ward according to local guidelines.

4.3. Duration of treatment

The chemotherapy will take 3-6 months depending on the number of cycles and type of chemotherapy.

When radiotherapy (RT) is planned as part of the treatment, the RT will start 4-8 weeks after the last chemotherapy cycle and will take 4-6 weeks.

4.4. Required investigations

All patients will undergo so-called staging investigations to evaluate the extent of the disease. These examinations consist of a medical history, physical examination, blood tests and imaging by conventional chest X-ray, and CT-scans of neck, chest and abdomen. In addition a bone marrow biopsy will be taken from your iliac crest (except for some patients in special circumstances). These investigations are always performed whether or not you participate in this clinical trial.

For this trial the FDG-PET scan after two cycles of ABVD is the main decision guidance for further treatment. For patients who are assigned to receive the standard treatment, the results of the FDG-PET scan will not be used to adapt treatment but only for documentation purposes and to facilitate a fair comparison of results between the groups of patients with the standard and the experimental treatment. As stated above, in the experimental treatment group the result of the FDG-PET scan will be used to adapt the treatment.

After two cycles of ABVD, after 3- 4 cycles and after completion of treatment a restaging will be performed with physical examination, blood tests, and CT-scans of neck and chest, to evaluate the result of treatment. Bone marrow biopsy will not be repeated.

The same investigations including CT scan of the abdomen, will be repeated at 4, 6, and 12 months after treatment.

In the second year these investigations will be performed every 3 months, except for the CT-scans that will be performed only every 6 months.

In the third and fourth year these investigations will be performed every 6 months.

At five years once yearly, and thereafter the imaging studies will be performed only on clinical indication when your treating physician considers it necessary.

In addition to these investigations, tests will be done to monitor whether undesirable events take place (for example cardiac and pulmonary disease):

- ◆ A cardiac function test by radionuclides is performed at the start of treatment, at the end of treatment, after one year, after 5 years and after 10 and 20 years.
- ◆ A pulmonary function test is performed at the start of treatment, at the end of treatment, after one year, after 5 years and after 10 and 20 years.
- ◆ Fertility tests will be performed by blood tests at the start of treatment, at the end of treatment, after one year, after 5 years and after 10 and 20 years.
- ◆ For female patients who have received RT on the chest or axillae, a yearly mammographic examination will start 10 years after end of treatment.

4.5. Number of patients in the trial

We will need around 1600 patients included in the study to be able to answer the question whether the new treatment approach is as at least as good as the conventional standard treatment but with less undesirable late adverse events. We expect to include this number of patients within 5 years.

4.6. Pathology review

To verify the initial diagnosis (done by the pathologist in your hospital), glass slides or representative images of tumor material (taken at the time of establishing the diagnosis or during surgical procedure you undergo) will be reviewed by a pathologist(s) expert(s) in this field (generally using the microscope). The expert(s) will not necessarily be working in the hospital where you receive(d) protocol treatment, nor even the same country. In some cases, a sample of your tumor biopsy, removed at the time of establishing the diagnosis or during a surgical procedure that you may undergo, might be used to perform additional examination.

5. Description of foreseeable risks and discomforts

Chemotherapy has well known side effects during treatment. Nausea and vomiting occur frequently but can be greatly prevented by prophylactic use of the so-called serotonin inhibiting drugs.

In most instances a complete but reversible hair loss develops during chemotherapy.

Irritation and inflammation of the veins in which the chemotherapy is injected, resulting in pain, can occur and can be treated according to local guidelines.

Due to low white blood cell counts you can be susceptible to infections. Prompt institution of antibiotics in case of high fever and chills is warranted and will be performed to the guidelines in the hospital where you are treated.

When you are treated with RT, local skin reactions with some desquamation can occur, temporarily and in general manageable with local measures. Irritation of your esophagus can develop resulting in difficulty to swallow and pain. It will recover within 1-2 weeks. Mostly reversible loss of taste and dry mouth can occur in those patients who are treated with RT to the neck.

The late side effects of treatment as mentioned already in the introduction of this information sheet are being closely monitored and whenever possible prevented or ameliorated by appropriate means.

Both female and male patients are advised to take appropriate contraceptive measures during the whole duration of study therapy.

If you need to undergo another medical treatment, we advise you to inform the study doctor to ensure this will not have any effect on your participation to the trial.

Everything has been done and will continue to be done to prevent health problems occurring as a result of your taking part in this trial.

6. Description of the ultimate goal of the clinical research project

The main objective of this clinical trial is to ensure that the high cure rates will be maintained while trying to reduce the amount of treatment and thereby the toxicity of treatment. In a small subset of patients (those with a positive FDG-PET scan after two cycles of ABVD) chemotherapy will be intensified to increase the cure rate.

7. Expected benefits (description of possible expected benefits)

This research will teach us more about cancer. This might enable us to improve the treatment and so help other patients with cancer in the future. However, nobody can predict whether you will directly benefit from participating in this clinical trial.

When you decide not to participate in this trial you will receive the standard treatments outlined above.

8. Voluntary participation

Your participation in this clinical trial is entirely voluntary and you will be given sufficient time to decide whether or not you wish to participate. You are free to decide at any time without giving any reason that you no longer wish to participate in the trial. Such decision will not affect your subsequent treatment or relationship with your treating doctor or the hospital staff in any way. Medical data collected during your participation to the clinical trial as well as follow up data which will still be prospectively collected will be kept for research and analysis unless you specify otherwise.

9. Data protection

Your consent for participation in this protocol also includes your consent to allow the use of the data in your medical/clinical record to be used for research purposes. Your consent also includes allowing this data to be linked to data coming from other sources (such as cancer registries, medical/clinical record).

All data (personal, clinical, economic and data coming from research on biological material) collected on your behalf will be treated in compliance with the European and national applicable laws.

Recorded medical information may be checked by authorized persons under strict confidentiality (health authorities). It is very important that the information collected is accurate therefore, from time to time, this collected information may be checked against your medical records. Duly authorized persons (EORTC research staff, national and/or foreign health authority representatives may have access to your medical records). With the exception of access by the duly authorized persons to your personal data on your medical record, all information will be strictly confidential.

10. Sponsorship

This clinical trial is conducted under the legal framework of EORTC.

The EORTC, which is responsible for the conduct of this trial, has asked your treating doctor to disclose any existing conflict of interest he/she may have as a result of his/her activities related to this trial. The EORTC has set up procedures to ensure the integrity of this process.

11. Insurance

The sponsor of the Study has obtained clinical trial insurance in accordance with the applicable legislation of your country to cover risks related to your participation in this study

12. Ethics Committee

This research protocol has been submitted to the ethics committee whose mission is to verify that all conditions with respect to your safety and rights are respected. Approval to this research has been given by the Ethics Committee of _____ on _____

13. Contact persons

In case of any problem or question, your doctor will be pleased to answer any further questions and may be contacted as follows:

Name of the doctor: _____

Hospital: _____

Telephone: _____

If you consent to join this trial, you will be given a telephone number of the hospital that you can contact at any time if you feel unwell or have further questions. With your agreement, your family doctor will also be informed about your taking part in this trial and what is involved, if you agree.

Please take your time to consider this information and do not hesitate to ask further questions to your doctor if anything is unclear. You are entitled to keep a copy of this document after you and your doctor have signed it.

Informed consent

- I have been properly informed about the clinical trial and have been given sufficient time to consider my participation.*
- I have received a copy of the patient information sheet.*
- All my rights have been clearly explained to me.*
- I agree to participate in the clinical research study entitle: **The H10 EORTC/GELA randomized Intergroup trial on early FDG-PET scan guided treatment adaptation versus standard combined modality treatment in patients with supradiaphragmatic stages I/II Hodgkin's lymphoma and to be registered in EORTC study number #20051. I accept that any data resulting from this clinical research study can be linked with other resources for cancer research purposes. My participation is completely voluntary and I have the possibility to withdraw my consent at any time without explanation. This will not affect my relationship with my treating doctor. The data collected on my behalf will be strictly confidential and treated according to the European and national applicable laws.***
- I have been informed that the data (personal, clinical and biological material) collected may be used in the future for cancer scientific research purposes while confidentiality will be ensured.*

All data (personal, clinical and research on biological material) collected on my behalf will be treated in compliance with the European and national applicable laws.

My consent does not discharge the organizers of the research from their responsibilities and I keep all my rights guaranteed by the law.

Patient's name: _____

Patient's signature: _____ Date: _____

Parent or legal guardian's signature: _____ Date: _____

Person designated by the investigator to participate in the informed consent process:

Name: _____

Signature: _____ Date: _____

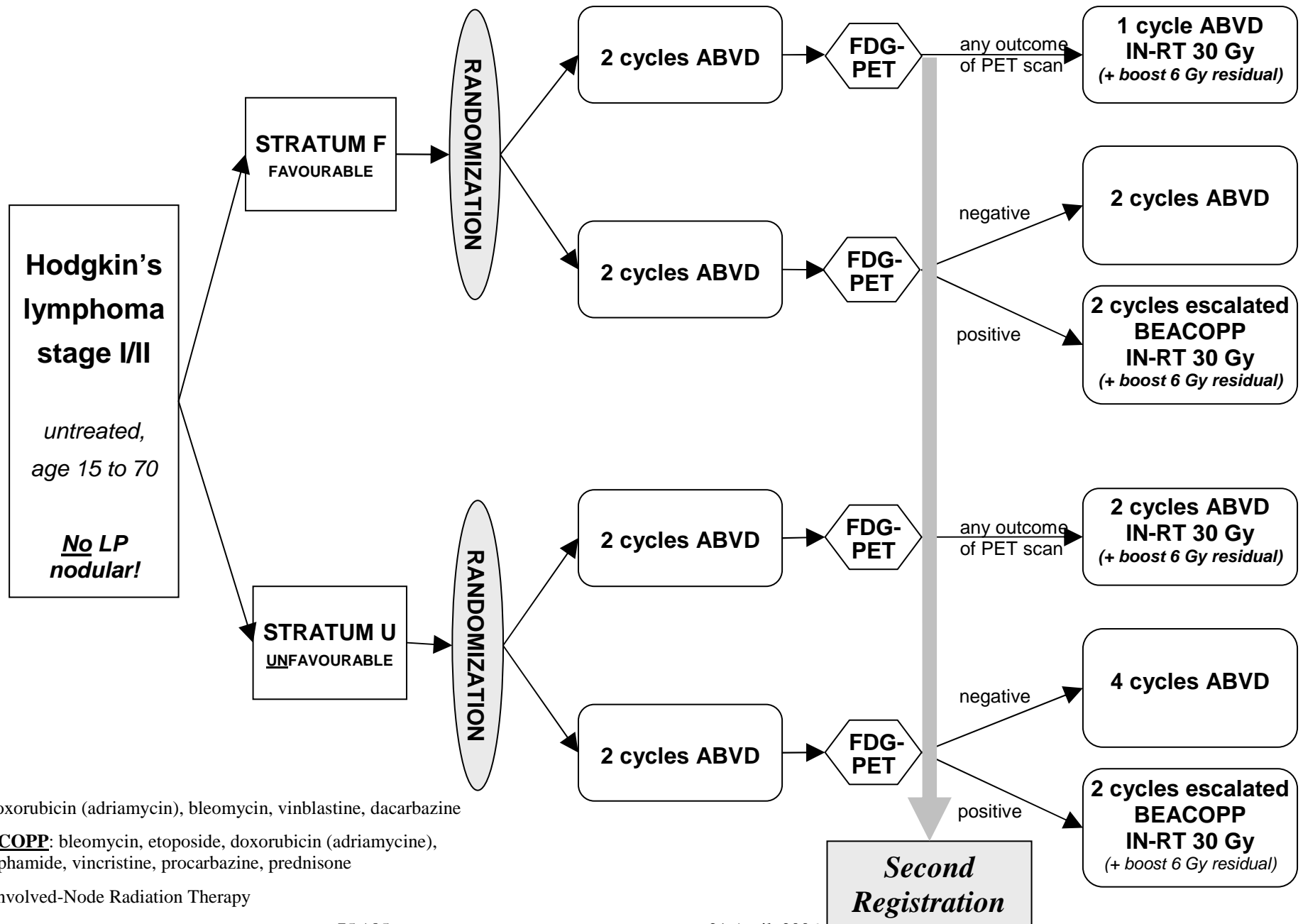
Investigator's name: _____

Title/Position: _____

Investigator's Signature: _____ Date: _____

This document has been prepared taking the following documents into account:

- World Medical Association Declaration of Helsinki, adopted by the 18th World Medical Assembly, Helsinki, Finland June 1964. Revised 1975, 1983, 1989, 1996 and on October 6, 2000 in Edinburgh, Scotland (www.wma.net).
- ICH-GCP Guidelines; Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95), Sept. 1997.
- International Ethical Guidelines for Biomedical Research involving Human Subjects, Council for International Organizations of Medical Sciences (CIOMS), Geneva 1993.
- WHO: Operating Guidelines for Ethics Committee that Review Biomedical Research, Geneva, 2000.
- European Union Directive on the protection of individuals with regard to the processing of personal data (Dir/95/46/EC)



ABVD: doxorubicin (adriamycin), bleomycin, vinblastine, dacarbazine

Esc. BEACOPP: bleomycin, etoposide, doxorubicin (adriamycine), cyclophosphamide, vincristine, procarbazine, prednisone

IN-RT - Involved-Node Radiation Therapy

Appendix F: Radiotherapy guidelines

Involved Node Radiation Therapy (INRT)

T GIRINSKY, R VAN DER MAAZEN, B ALEMAN,
P POORTMANS, C MEERWALDT, Y LIEVENS,
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E NOORDIJK.

On behalf of the EORTC-GELA LYMPHOMA GROUP

Rationale

Chemotherapy is effective notably for microscopic disease; therefore large fields are no longer necessary. On the other hand, consolidating radiation therapy to involved lymph nodes after a limited number of chemotherapy cycles remains a necessity.

It has been demonstrated in numerous studies that radiotherapy-induced complications are dependent on the irradiated volume and the total radiation dose (Ref. 40, Ref. 41, Ref. 24, Ref. 43, Ref. 23, Ref. 44).

It is therefore of utmost necessity to decrease the size of radiation fields and to limit radiation doses. The concept of involved field radiotherapy (IFRT) which included the whole lymph node area is replaced by the concept of a field which includes the initially involved lymph node (s).

Definitions and rules

All patients must have pre- and post- chemotherapy cervical and thoracic CT scans (axillary lymph node areas must be clearly visible on thoracic CT scans). Patients must be examined by the radiation oncologist before chemotherapy. Whenever possible, CT scans should be evaluated with the radiologist.

THE REMISSION STATUS AFTER CHEMOTHERAPY SHOULD BE DETERMINED FOR EACH INITIALLY INVOLVED LYMPH NODE EXCLUSIVELY USING CT SCANS.

Radiation Fields

- 1) CT simulation is strongly advised when designing INRT fields.
- 2) It is strongly recommended that pre- and post-chemotherapy CT scans be performed, whenever possible, with patients in the treatment position.
- 3) As a rule, fusion possibilities, allowing the overlapping of the pre- and post-chemotherapy CT scans are strongly recommended. However, they must be used with caution owing to many assumptions underlying such techniques.

IMPORTANT:

Whenever available, prechemotherapy PET-CT will be used to increase the CT scan contouring accuracy of the GTV.

Delineation of the initially involved lymph nodes using information from both PET and CT is recommended if available. Whenever feasible, patients should have a prechemotherapy PET-CT and a postchemotherapy CT in the same position or even better in treatment position. The prechemotherapy PET-CT should be then fused with the postchemotherapy CT.

The PET scan positive areas will be used to improve the accuracy of the GTV contouring on the CT scan which remains the standard to detect previously undetected involved lymph nodes

I) INITIALLY INVOLVED LYMPH NODES IN CR or CRu

a) Cervical and axillary lymph nodes

As initially involved lymph nodes are either no longer visible or of normal size or are in CRu, only a CTV should be outlined.

- 1) **The CTV is the initial volume of the lymph node(s) before chemotherapy. In other words, the CTV incorporates the initial location and the extent of the disease and takes into account the displacement of normal structures.**

In case of a CRu with a visible lymph node remnant, the lymph node remnant should be included in the CTV

As the CTV is expected to be relatively small, blood vessels can be included in the CTV. However, if initially involved lymph nodes were clearly located at a distance from blood vessels, whenever feasible, those blood vessels can be excluded.

2) **The PTV** is the CTV with a margin to take into account organ movement and set-up variations. In most situations, a 1 cm isotropic margin is considered adequate.

b) Mediastinal area

As the mediastinal area is considered to be in complete remission or CRu, only a CTV should be outlined

1) **The CTV** is the initial volume of the mediastinal mass (in the case of a CRu, the lymph node remnant should be considered as part of the CTV).

Two main rules should be applied:

- 1) Whenever feasible, blood vessels must be avoided
- 2) In order to decrease lung toxicity

A) The length of the CTV is the length of the mediastinal mass or lymph node(s) before chemotherapy

B) The width of the CTV is the width of the mediastinal mass or lymph node(s) after chemotherapy

a) In the case of a CR, the normal mediastinum is contoured and the CTV should not exceed the lateral mediastinal boundaries.

b) In the case of a CRu, the normal mediastinum is contoured and the CTV should not exceed the lateral mediastinal boundaries except where lymph node remnants persist.

2) **The PTV** is the CTV with a margin taking into account organ movement and set-up variations. In most situations, a 1 cm isotropic margin is considered adequate.

II) INITIALLY INVOLVED LYMPH NODES IN PR (partial remission)

a) Cervical and axillary lymph nodes

As initially involved lymph nodes are in partial remission

The GTV is the lymph node remnant(s).

The GTV: as a rule, the GTV should be contoured first and is the lymph node remnant(s).

The CTV is the initial volume of the lymph node(s) before chemotherapy. In other words, the CTV incorporates the initial location and the extent of the disease and takes into account the displacement of normal structures

Therefore 2 PTVs should be outlined

- 1) **The initial PTV (or PTV1)** is the CTV including the GTV (i.e. initial tumor mass and lymph node remnant(s)) with a margin to take into account organ movement and set-up variations. In most situations, a 1 cm isotropic margin is considered adequate.
- 2) **The boost PTV (or PTV2)** is the GTV with a margin to take into account organ movement and set-up variations. In most situations, a 1 cm isotropic margin is considered adequate.

b) mediastinal area

As initially involved lymph node(s) or the tumor mass is (are) in partial remission, a GTV should be contoured.

The GTV: as a rule, the GTV should be contoured first and is the lymph node remnant(s) or the remaining mass alone.

The CTV is the initial volume of the mediastinal mass.

Two main rules should be applied:

Whenever feasible, blood vessels must be avoided

In order to decrease lung toxicity

A) The length of the CTV is the length of the mediastinal mass or lymph node(s) before chemotherapy

B) The width of the CTV is the width of the mediastinal mass or lymph node(s) after chemotherapy

The normal mediastinum is contoured and the CTV should not exceed the lateral mediastinal boundaries except where lymph node or mass remnant(s) persist(s).

Therefore 2 PTVs should be outlined:

- 1) **The initial PTV (or PTV1)** is the CTV including the GTV (i.e. initial tumor mass and the lymph node remnant(s)) with a margin to take into account organ movement and set-up variations. In most situations, a 1 cm isotropic margin is considered adequate.
- 2) **The boost PTV (or PTV2)** is the GTV alone with a margin to take into account organ movement and set-up variations. In most situations, a 1 cm isotropic margin is considered adequate.

Treatment and Dose Prescription

General rules

The dose should be specified according to ICRU 50/62 recommendations (Ref. 42). The PTV must receive a dose comprised between 95% and 107%. In other words, the PTV must be included in the 95% isodose.

If the initially involved lymph nodes are more than 5 cm apart, then separate fields should be devised. Otherwise involved lymph nodes should be included in the same radiation field.

Radiation should be delivered using anterior-posterior fields, 3D-conformal radiotherapy or intensity modulated radiotherapy. The choice of the technique will be left to the discretion of the physician. **Radiation treatments will be delivered using 5 fractions of 2 Gy per week.**

Portal imaging of all fields should be performed consecutively, within the first two days of treatment and once a week thereafter.

An early retrospective quality assurance program should be set up in large cancer centers and should involve all local treating facilities.

Radiation dose for patients in complete remission or cru

The PTV must receive 30 Gy. If a conventional treatment is used with anterior and posterior fields, the size of the field should be at least 5 x 5 cm.

Radiation dose for patients in partial remission

The PTV1 or initial PTV must receive 30 Gy. If a conventional treatment is used with anterior and posterior fields, the size of the field should be at least 5 x 5 cm.

PTV2 or the boost PTV must receive an additional dose of 6 Gy.

Definitions of minor and major deviations

◆ Major deviations

Less than 90% of the prescribed **dose** delivered to the PTV (e.g. 30 Gy x 90% = 27 Gy).

The 90% **isodose** inside the PTV (e.g. 30 Gy x 90% = 27 Gy).

Incorrect assessment of the CTV or GTV resulting in **poor coverage** of the initial tumor mass.

More than 2 incorrect **portals** (which potentially leads to 4 Gy (2 fractions) incorrectly delivered to the PTV (e.g. 30 Gy – 4 Gy = 26 Gy)

Overall treatment time exceeding the normal overall treatment time by more than 10%. (Normal overall treatment times: up to 14 days for 20 Gy; 21 days for 30 Gy and 26 days for 36 Gy.)

◆ Minor deviations

All above items which are between major DEVIATIONS and properly implemented treatment rules.

Quality assurance program

Early retrospective quality assurance meetings should be held in designated cancer centers. These meetings will mostly be conducted through videoconferences using new and relatively inexpensive available videoconferencing software. Local meetings with all involved physicians could also be organized but would be more costly to implement.

Appendix G: FDG-PET Scan guidelines

1. PET working party

P. Lugtenburg, S. Stroobants, W. Oyen, J. Pruim, J. Lumbroso, S. Bardet, T. Vander Borgh, M. Hutchings.

2. Baseline FDG-PET scan

A baseline (pre-treatment) FDG-PET scan is optional, but strongly recommended.

3. Timing of the interim FDG-PET scan

The FDG-PET scan should be carefully planned in advance: at least 7-10 days after day 15 of the second cycle of ABVD. In case of use of G-CSF, the FDG-PET scan should be planned at least 48 hours after stop of G-CSF, to avoid false positive scans. The planned date of the scan is asked for at the time of randomization and is mandatory information at that time point.

4. Patient preparation

Patients should be fasting for at least 4 hours prior to scanning, but have free access to water and normal medication. Intravenously administered fluids should not contain glucose. The height of the patient will be recorded at baseline, the weight will be checked on each scan days. A venous catheter is placed in a vein of the forearm. If a patient has a Port-a-Cath, this access can also be used. Prior to injection of FDG a 1 ml blood sample for serum glucose measurement is obtained and the value is recorded in the case record form. Optional: before tracer injection the blood glucose level is also checked with the glucose meter. Patients with fasting blood glucose levels > 180 mg% (> 9.9 mmol/l) at baseline should be rebooked and performed as the level is < 180 mg% (< 9.9 mmol/l). At follow-up visit it will be left to the investigators discretion whether to scan or delay until a fasting glucose level < 180mg% (< 9.9 mmol/l) is obtained.

5. Technical requirements PET scanner

5.1. PET scanner

FDG-PET scanning must be performed with a modern full-ring dedicated PET camera. Coincidence PET cameras are not allowed, because of lower sensitivity. Combined PET/CT scanners in which the images are fused, allowing for improved data interpretation are permitted. Each patient is preferably scanned on the same camera for baseline and interim study.

5.2. PET acquisition

A dose of approximately 250 MBq - 550 MBq [¹⁸F]FDG (> 3.5 MBq/kg) is administered intravenously as a bolus. The administered activity of FDG and the time of injection is recorded on the case record form. Patients are kept well hydrated (oral or intravenous fluid intake of 500 ml water during FDG uptake phase) to minimize image artefacts due to urinary stasis. Between injection and scanning, patients are asked to lie still (or sit down quietly) to avoid muscular [¹⁸F]FDG uptake. Prior to the scanning the patient is asked to void. A whole-body acquisition with attenuation correction (either with a high energy photons or non-contrast-enhanced CT) and with emission scans of at least 4 min per bed position is started 60-90 minutes after injection of

[¹⁸F]FDG], starting from groin up to the head. The time of the commencement of the scan is recorded in the case record form. For the follow-up visit the interval between FDG administration and scan acquisition should be as similar as possible (difference of < 15 minutes should be achieved).

5.3. PET reconstruction

Scan data will be recorded for decay, body weight and injected dose and reconstructed using an iterative algorithm. The same FDG dose, acquisition protocol and reconstruction algorithm must be used for baseline and follow-up scans.

6. PET analysis

The whole body scans will be displayed in both projection and volume views, the latter using coronal, sagittal and transaxial views.

The interim PET results must be scored according to a three point visual scoring system:^{1,2}

0 = negative/normal/benign

1 = minimal residual uptake

2 = positive/malignant

The PET scans are scored with knowledge of the CT data.

Minimal residual uptake is defined as low-grade uptake of FDG (just above background) in a focus within an area of previously noted disease, regarded by the nuclear medicine physicians as not likely to represent malignancy.

A positive PET is defined as a scan with FDG-uptake in a focus exceeding the normal FDG uptake, in previously diagnosed disease sites, which is considered to represent lymphoma involvement.

In case of a positive PET scan (or with minimal residual uptake) after 2 ABVD cycles, all the PET scans together with the CT scans must be send directly to the reference centre for review.

In the H10 protocol the patients with an interim FDG-PET scan with minimal residual uptake will be regarded as PET negative.

7. Central PET review

A central review of the minimal residual uptake and positive FDG-PET scans is mandatory and is organized.

Appendix H: ANN ARBOR STAGING * - COTSWOLDS RECOMMENDATIONS **

ANATOMICAL STAGING CRITERIA

Lymph node involvement. (a) Clinical enlargement of a node when alternative pathology may reasonably be ruled out (suspicious nodes should always be biopsied if treatment decisions are based on their involvement) ; and (b) enlargement on plain radiograph, CT scan, or Lymphography.

Spleen involvement. Unequivocal palpable splenomegaly alone, or equivocal palpable splenomegaly with radiological confirmation of either enlargement or multiple focal defects which are neither cystic nor vascular (radiological enlargement alone is inadequate).

Liver involvement. Multiple focal defects which are neither cystic nor vascular noted with at least two imaging techniques. Clinical enlargement alone with or without abnormalities of liver function tests is not adequate.

Lung involvement. Radiological evidence of parenchymal involvement in the absence of other likely causes especially infection.

Bone involvement. History of pain or elevation of serum alkaline phosphatase, supported by plain X-ray changes or evidence from other imaging studies (isotope, CT scan or MRI).

CNS involvement. (a) A spinal extradural deposit may be diagnosed on the basis of the clinical history and findings supported by plain X-ray, myelography, CT scan and/or MRI ; and (b) intracranial involvement will rarely be diagnosed clinically at presentation. It should be considered on the basis of a space occupying lesion in the face of disease in additional extranodal sites.

CRITERIA FOR "B" SYMPTOMS

(a) Unexplained weight loss of more than 10% of the body weight during the 6 months before initial staging investigation ;

(b) Unexplained, persistent, or recurrent fever with temperatures above 38°C during the previous month ;

and (c) Recurrent drenching night sweats during the previous months.

CRITERIA FOR BULK DISEASE

The bulk of palpable lymph nodes will be defined by the largest dimension (cm) of the single largest lymph node or conglomerate node mass in each region of involvement. A node or nodal mass must be 10 cm or greater to be recorded as "bulky".

A mediastinal mass will be defined as "bulky" on a postero-anterior chest radiograph, when the maximum width is equal or greater than one-third of the internal transverse diameter of the thorax at the T5-T6 level. The chest radiography should be taken with maximal inspiration in the upright position at a source-skin distance of 2 m. (*see also Appendix I for detailed description*)

CRITERIA FOR EXTRANODAL SPREAD (E)

Involvement of extra lymphatic tissue on one side of the diaphragm by limited direct extension from an adjacent nodal site will be classified as extranodal extension (E) with the implicit expectation of a prognosis equivalent to that for treatment of nodal disease of the same anatomical

extent. The E category may also include an apparently discrete single extranodal deposit consistent with extension from a regionally involved node. Multiple extranodal deposits will not be included. A single extralymphatic site as the only site of disease should be classified as I_E.

STAGING NOTATION

Nodal disease (I-III)

Stage I

Involvement of a single lymph node region (e.g. cervical, axillary, inguinal, mediastinal) or lymphoid structure as spleen, thymus and Waldeyer's ring.

Stage II

Involvement of two or more lymph node regions or lymph node structures on the same side of the diaphragm. Hilar nodes should be considered to be "lateralized" and when involved on both sides, constitute stage II disease. The number of anatomical regions involved should be indicated by a subscript (e.g. II₃). For the purpose of defining the number of anatomical regions, all nodal disease within the mediastinum is considered to be a single lymph node region. Hilar involvement constitutes an additional site of involvement.

Stage III

Involvement of lymph node regions or lymphoid structures on both sides of the diaphragm. This may be subdivided stage III₁ or III₂, stage III₁ being described for patients with spleen or splenic, hilar, coeliac or portal node involvement and stage III₂ for those with paraaortic, iliac or mesenteric node involvement.

Bulky disease

The subscript "X" will be used if bulky disease is present. No subscripts will be used in the absence of bulk.

Extranodal disease

"E" subscript if limited extranodal extension as described above, is documented. More extensive extranodal disease will be designated stage IV.

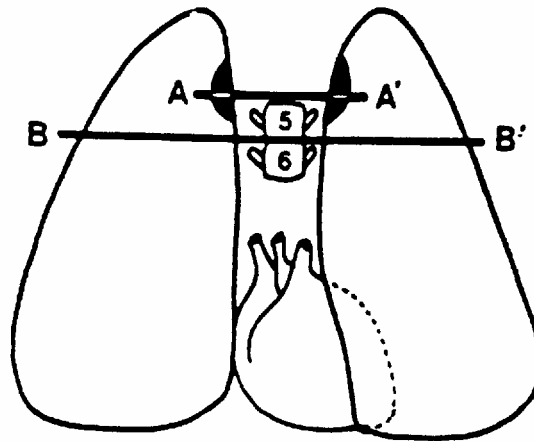
Example

Asymptomatic clinically staged patient with bilateral neck and axillary nodes, bulky mediastinum, enlarged left hilar node and extension into chest wall: CSII₆XEA.

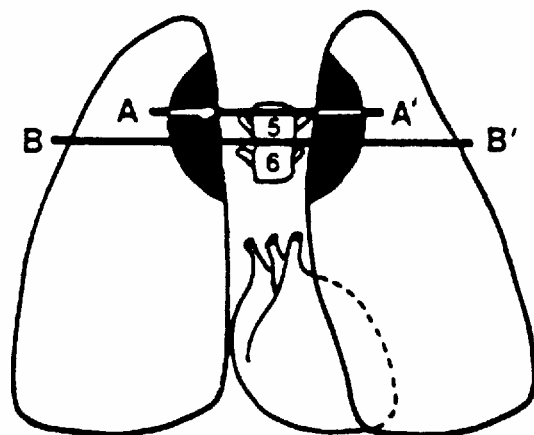
* Carbone PP, Kaplan HS, Musshoff K, et al. Report of the committee on Hodgkin's disease staging classification. *Cancer. Res.* 31:1860-1861, 1971.

** Lister TA, Crowther D, Sutcliffe SB, et al. Staging for Hodgkin's disease. Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting. *J. Clin. Oncol.* 7:1630-1636, 1989 (Erratum *J. Clin. Oncol.* 8:1602, 1990).

Appendix I: MEDIASTINUM MEASUREMENT (MT ratio evaluation *)



$$\frac{A-A'}{B-B'} < 0.35 = \text{NON BULKY}$$



$$\frac{A-A'}{B-B'} > 0.35 = \text{BULKY}$$

Largest diameter of the mediastinum / thoracic diameter at the T5-T6 level, in standing position.

*Lee CKK, Bloomfield CD, Goldman AI, Seymour HI. Prognostic significance of mediastinal involvement in Hodgkin's disease treated with curative radiotherapy. *Cancer* 46:2403-2409, 1980.