Evolution of Radiation Therapy Within the German Hodgkin Study Group Trials

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Abstract
Since its beginning, more than 16,000 patients have been enrolled in the multicentric randomized trials of the German Hodgkin Study Group (GHSG) for adult patients. Within 6 study generations, the treatment of Hodgkin lymphoma has been developed stepwise by using the results of the completed protocols. Now the sixth generation is active. According to the role of radiotherapy, the study group successfully evaluated different dose–effect relationships and could also prove the efficacy of involved-field radiotherapy in early stages in combination with effective chemotherapy. Currently, a radiation dose of 20 Gy to the involved field after a mildly aggressive chemotherapy (2 cycles of adriamycin, bleomycin, vincristine, and dacarbazine [ABVD]) should be the standard for early-favorable stages according to the GHSG classification. In early-unfavorable or intermediate-risk stages, involved-field radiation therapy with 30 Gy is sufficient; the optimal chemotherapy has to be fixed. For the advanced stages, the question of radiotherapy is still unclear. Preliminary results of the GHSG and others show that additive radiotherapy after intensive chemotherapy might be useful for elective subgroups of patients. The extensive radiotherapy quality assurance program, performed by the GHSG and its radiation therapy reference center, has proven to be successful and necessary to ensure that, with reduced radiation doses and reduced radiation volumes, precise radiotherapy, as defined by the protocol, will be performed by the participating radiotherapy departments.

Radiotherapy (RT) is a key modality in the treatment of Hodgkin lymphoma (HL), and clinical trials are increasing the understanding of its role in the management of this disease. The German Hodgkin Study Group (GHSG), based at the University of Cologne, is the largest international study group on HL. Pivotal studies that have influenced international standards of care include the combined modality approach of a short course of ABVD chemotherapy (adriamycin, bleomycin, vincristine, and dacarbazine) and involved-field RT (IF-RT) in the early stages of HL, and the development of the BEACOPP chemotherapy regimen (bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, and prednisone) in advanced stages.

The development of RT within the consecutive study generations is remarkable. Over the years, field design and radiation techniques changed dramatically from extended field RT to IF-RT (Table 1). In view of high cure rates, the major goal today is to minimize radiation fields and dose to reduce consecutive treatment-related side effects. In the ongoing study generation (HD17), a new target volume definition—the “involved node (IN)” concept—is being compared with standard IF-RT.

These achievements were supported by the RT reference center of the GHSG within the Department of Radiation Oncology at the University of Cologne, which performed quality assurance (QA) programs of the group’s clinical studies. The HD4 study showed the importance of this. Major protocol violations with particular reference to the design of the radiation fields were associated with a statistically significant reduction in freedom from treatment failure (FFTF).

The possibility of more accurate staging through using new imaging techniques, such as CT, MRI, and PET, in recent years has resulted in advances such as the definition of early-favorable, early-unfavorable, and advanced stages, and more specific, risk-adapted treatment strategies.
Early-Favorable HL

Extension of disease is still the most important risk factor. As reported by the Stanford group in the 1980s, RT alone resulted in complete remission rates of 100% and recurrent-free survival of 80% in pathologic stages (PS) IA, IIA, and IIB without mediastinal bulky disease. Polychemotherapy was able to treat most of the recurrences successfully. However,

Table 1 Five Generations of Randomized Clinical Trials in the Treatment of Primary Early-Favorable, Intermediate (Early-Unfavorable), and Advanced-Stage Hodgkin Lymphoma

<table>
<thead>
<tr>
<th>Trial</th>
<th>Year</th>
<th>Stage</th>
<th>Trial Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>HD1</td>
<td>1978–1988</td>
<td>CS/PS IA/B, IIA/B, and IIIA with risk factors</td>
<td>2 x COPP/ABVD + EF 40 Gy vs. 2 x COPP/ABVD + EF 20 Gy</td>
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<tr>
<td>HD3</td>
<td>1978–1988</td>
<td>CS/PS IIIb, CS/PS IV</td>
<td>3 x COPP/ABVD + 1 x COPP/ABVD vs. 3 x COPP/ABVD + IF 20 Gy</td>
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<tr>
<td>HD4</td>
<td>1988–1994</td>
<td>PS I/II without risk factors</td>
<td>EF-RT 40 Gy vs. EF-RT 30 Gy + IF 10 Gy</td>
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<tr>
<td>HD5</td>
<td>1988–1993</td>
<td>CS/PS I, II with risk factors</td>
<td>2 x COPP/ABVD + EF 30 Gy (bulk 10 Gy) vs. 2 x COPP/ABV/IMEP + EF 30 Gy (bulk 10 Gy)</td>
</tr>
<tr>
<td>HD6</td>
<td>1988–1993</td>
<td>CS/PS IIIb, IV</td>
<td>4 x COPP/ABVD + IF bulk/residual mass vs. 4 x COPP/ABV/IMEP + IF bulk/residual mass</td>
</tr>
<tr>
<td>HD7</td>
<td>1994–1998</td>
<td>CS/PS I, II without risk factors</td>
<td>EF-RT 40 Gy vs. 2 x ABVD + EF-RT 40 Gy</td>
</tr>
<tr>
<td>HD8</td>
<td>1993–1998</td>
<td>CS IA/B, IIA with risk factors, IIB with elevated ESR and/or involvement of &gt; 2 lymph nodes, and CS/PS IIIA without risk factors</td>
<td>2 x COPP/ABVD + EF 30 Gy (bulk 10 Gy) vs. 2 x COPP/ABVD + IF 30 Gy (bulk 10 Gy)</td>
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<tr>
<td>HD9</td>
<td>1993–1998</td>
<td>CS IIB, IIIA with risk factors, PS IIIA + splenic involvement, CS/PS IIIb, and CS/PS IV</td>
<td>4 x COPP/ABVD + RT bulk/residual mass vs. 8 x BEACOPP baseline + RT bulk/residual mass vs. 8 x BEACOPP escalated + RT bulk/residual mass</td>
</tr>
<tr>
<td>HD10</td>
<td>1998–2002</td>
<td>CS I, II without risk factors</td>
<td>4 x ABVD + IF-RT 30 Gy vs. 4 x ABVD + IF-RT 30 Gy vs. 2 x ABVD + IF-RT 30 Gy vs. IF-RT 20 Gy</td>
</tr>
<tr>
<td>HD11</td>
<td>1998–2002</td>
<td>CS I, II with risk factors, IIB with elevated ESR and/or involvement of &gt; 2 lymph nodes</td>
<td>4 x ABVD + IF-RT 30 Gy vs. 4 x ABVD + IF-RT 20 Gy vs. 4 x BEACOPP baseline + 30 Gy IF-RT vs. 4 x BEACOPP baseline + 20 Gy IF-RT</td>
</tr>
<tr>
<td>HD12</td>
<td>1998–2002</td>
<td>CS IIB with large mediastinal mass +/- extranodal involvement, CS III, IV</td>
<td>8 x BEACOPP escalated + 30 Gy bulk/residual mass vs. 8 x BEACOPP escalated vs. 4 x BEACOPP baseline + 30 Gy bulk/residual mass vs. 4 x BEACOPP escalated + 4 x BEACOPP baseline</td>
</tr>
<tr>
<td>LPHD (only stage IA without risk factors)</td>
<td>Since 2000</td>
<td>CS IA without risk factors</td>
<td>30 Gy IF-RT</td>
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<tr>
<td>HD13</td>
<td>2003–2009</td>
<td>CS I, II without risk factors</td>
<td>2 x ABVD + 30 Gy IF-RT vs. 2 x ABVD + 30 Gy IF-RT vs. 2 x AVD + 30 Gy IF-RT vs. 2 x AV + 30 Gy IF-RT</td>
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<tr>
<td>HD14</td>
<td>2003–2009</td>
<td>CS I, II with risk factors, IIB with elevated ESR and/or involvement of &gt; 2 lymph node areas</td>
<td>4 x ABVD + 30 Gy IF-RT vs. 2 x BEACOPP escalated + 2 x ABVD + 30 Gy IF-RT</td>
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<tr>
<td>HD15</td>
<td>2003–2008</td>
<td>CS IIB with large mediastinal mass +/- extranodal involvement, CS III, IV</td>
<td>8 x BEACOPP escalated + RT only to PET-positive residual disease (≥ 2.5 cm) vs. 6 x BEACOPP escalated + RT only to PET-positive residual disease (≥ 2.5 cm) vs. 8 x BEACOPP-14 + RT only to PET-positive residual disease (≥ 2.5 cm)</td>
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Abbreviations: ABV, adriamycin, bleomycin, and vinblastine; ABVD, adriamycin, bleomycin, vinblastine, and dacarbazine; AV, adriamycin and vinblastine; AVD, adriamycin, vinblastine, and dacarbazine; BEACOPP, bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, and prednisone; COPP, cyclophosphamide, vincristine, procarbazine, and prednisone; CS, clinical stage; EF, extended-field; ESR, erythrocyte sedimentation rate; IF, involved-field; IMEP, ifosfamide, methotrexate, etoposide, and prednisone; LPHD, lymphocyte-predominant Hodgkin lymphoma; PS, pathologic stage; RT, radiotherapy.
other well-recommended study groups could not confirm these excellent results.\(^2\)\(^-\)\(^10\)

Because secondary cancers were reported in up to 10% of patients after high-dose extended field (EF)-RT, the GHSG created the HD4 study, which tested in a randomized setting a dose reduction of 10 Gy in the EF (EF-RT 40 Gy vs. EF-RT 30 Gy/IF-RT 40 Gy) for patients with PS I A, I B, IIA, IIB with no risk factors (large mediastinal mass, extranodal extension, massive spleen involvement, ≥ 3 lymph node areas, high erythrocyte sedimentation rate [ESR]). Staging laparotomy was obligatory in this protocol. The goal of this study was to reduce treatment-related side effects (especially secondary treatment–induced solid tumors) without compromising results. Results in 376 evaluable patients showed no statistically significant differences in recurrence-free and overall survivals between the treatment arms,\(^5\) but the overall recurrence rate approached 20%. Because of a very sufficient salvage therapy, recurrence-free survival after 7 years increased to 80% and the overall survival was 93%.

A careful analysis of the recurrences could show that most of these recurrences occurred outside the radiation fields and could be rated as a diagnostic miss of the initial staging.

In the HD4 protocol of the GHSG, a widespread QA program was initiated for the first time. An RT treatment plan was created for every randomized patient by the RT reference center based on the documented extent of disease on standardized case report forms. After completion of RT, the simulation and verification films of every patient were sent to the RT reference center and analyzed by an expert panel. Results of this analysis showed that major deviations from the RT prescription resulted in a reduced FFTF and proved to be a statistically univariate prognostic factor.\(^1\)\(^5\)

The primary goal of the initial treatment of early-stage HL without risk factors should be the lowest possible recurrence rate, and therefore considerations of further protocols resulted in combining radiotherapy with not-too-toxic chemotherapy for control of subclinical microscopic Hodgkin involvement.

The HD7 protocol randomized patients into 2 treatment arms. Arm A consisted of RT alone (30 Gy EF 40 Gy IF), whereas arm B consisted of the combined modality approach: 2 cycles of ABVD followed by RT (30 Gy EF 40 Gy IF) for early-favorable stages (PS I A, IIA, IIB without risk factors) as in HD4. The spleen was irradiated with 36 Gy in both treatment arms because staging laparotomy was not obligatory. ABVD chemotherapy was chosen because of the well-known toxicity profile (no extensive cardiac or pulmonary side effects) and the relatively low infertility rate. At a median observation time of 87 months, no difference was seen between treatment arms in terms of complete response rate (arm A, 95%; arm B, 94%) and overall survival (at 7 years: arm A, 92%; arm B, 94%; P = .43). However, FFTF was significantly different, with 7-year rates of 67% in arm A and 88% in arm B. This was mainly because of significantly more relapses after EF-RT only (arm A, 22%; arm B, 3%). No patient treated with combined modality treatment experienced relapse before year 3.\(^1\)\(^1\)

These results compare favorably with a meta-analysis about multimodal combined treatment of RT and chemotherapy versus RT alone in early-stage HL,\(^1\)\(^2\) and also with results from the groups from Stanford (with vinblastine, bleomycin, and methotrexate [VAPEC-B]), Manchester (with vinblastine, doxorubicin, prednisolone, etoposide, cyclophosphamide, and bleomycin [VBM]), and the EORTC (with epirubicin, bleomycin, vinblastine, and prednisone [EBVP]), which reported a better outcome for early-stage or favorable disease after radiochemotherapy.\(^1\)\(^3\)\(^-\)\(^1\)\(^5\)

In reference to the role of radiation in the treatment of HL, the HD10 trial represents a very decisive step, because irradiation was performed as IF-RT in all treatment arms. Radiation dose–effect relationships for HL are only reported as retrospective analyses, never as prospective randomized trials, and mostly for radiation therapy only. No substantial data exist for the combined modality treatment of radiotherapy and chemotherapy. Therefore, the HD10 trial was initiated to answer 2 questions for early-favorable HL: which radiation dose is necessary after effective chemotheraphy and how much chemotherapy is needed to control subclinical disease. Therefore, patients with PS I A, IIA and IIB without risk factors were randomized in a 4-arm study between an IF-RT dose of 30 versus 20 Gy, and between 2 versus 4 cycles of ABVD.\(^3\)

To ensure that RT was performed as exactly as possible according to the RT prescriptions in the protocol, an extensive QA program was initiated.
that consisted of prospective RT planning by the RT reference center in Cologne based on clinical and laboratory data and all pretreatment diagnostic imaging.\textsuperscript{16}

Because involvement of the mediastinum is a special problem in the treatment of HL,\textsuperscript{17} the GHSG developed a special guideline for RT of the mediastinum to minimize cardiac toxicity after chemotherapy with adriamycin and RT. The upper mediastinum was irradiated selectively in cases of suprabifurcal involvement only. In case of involvement of the lower mediastinum only or involvement of the upper and lower mediastinum, the whole mediastinum was irradiated.\textsuperscript{18}

Final analysis of the HD10 trial showed no significant difference between the chemotherapy regimens with respect to FFTF ($P = .39$) and overall survival ($P = .61$). After 5 years, the FFTF was 93\% with the 4-cycle ABVD regimen and 91.1\% with the 2-cycle ABVD regimen. Regarding the RT doses, no significant difference was seen in FFTF ($P = 1.00$) or overall survival ($P = .61$). The FFTF at 5 years was 93.4\% in the 30-Gy group and 92.9\% in the 20-Gy group. Thus, 2 cycles of ABVD followed by 20 Gy of IF-RT is regarded as the new standard of care in the treatment of early-favorable HL.\textsuperscript{3}

The goal of the following study (HD13) was to further decrease of early and late toxicities. In a 4-arm randomized fashion, 4 different chemotherapy regimens were tested, consisting of 2 cycles of ABVD (arm A), ABV (arm B), AVD (arm C), or AV (arm D), keeping the IF-RT on the level of 30 Gy in all treatment arms. An interim analysis showed more relapses in the treatment arms without dacarbazine (arm B and D), and therefore these were closed earlier.\textsuperscript{19}

The ongoing HD16 trial (Figure 1) is using fluorodeoxyglucose (FDG)-PET for treatment guidance after 2 cycles ABVD chemotherapy. In the standard treatment arm, all patients receive 20 Gy of IF-RT regardless of the PET result. In the experimental arm, FDG-PET–positive patients are irradiated with 20 Gy of IF-RT. Patients with a negative FDG-PET undergo no further treatment. Unless no final results are available, the use of PET for treatment guidance is not advised outside of clinical trials.

### Early-Unfavorable HL

Combined modality therapy consisting of chemotherapy and radiotherapy is the standard treatment approach to the early-unfavorable or intermediate stages of HL, according to the definition of the GHSG (PS I, IIA, and IIB with risk factors such as large mediastinal mass, extranodal involvement, high ESR, $\geq 3$ lymph nodes).

In a 2-arm randomized setting, the HD8 trial tested the question of EF-RT versus IF-RT (plus 10 Gy to bulky areas in each treatment arm) after 2 cycles of cyclophosphamide, vincristine, procarbazine, prednisone (COPP) and ABVD. The final analysis of 1136 patients showed no statistical significant difference between the arms in complete remissions after treatment (98\% vs. 97\%), FFTF

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**Figure 1** HD16 trial for patients with early-favorable stage Hodgkin lymphoma. Abbreviations: ABVD, adriamycin, bleomycin, vinblastine, and dacarbazine; CS, clinical stage; ESR, erythrocyte sedimentation rate; IF, involved-field; RF, risk factors.

*Large mediastinal mass, extranodal disease, high ESR, or 3 or more areas*
Radiotherapy in Hodgkin’s lymphoma

(86% in both arms), or overall survival (91% vs.
94%). Patients who received IF-RT reported a sig-
nificantly lower acute toxicity compared with those
treated with EF-RT.4,20

Because prognosis and treatment results of pa-
tients in early-unfavorable stages of HL were compa-
rable to those in advanced stages, the goal of future
studies is to intensify chemotherapy and fix the dose
of radiation to the IF.

In a randomized 4-arm study, the HD11 trial
tested the ABVD regimen versus an intensified che-
motherapy, consisting of treatment with the BEA-
COPP regimen, followed by IF-RT of 30 or 20 Gy.21
This study randomly assigned 1395 patients to either
arm A (4 cycles of ABVD + 30 Gy IF-RT), arm B (4
cycles of ABVD + 20 Gy IF-RT), arm C (4 cycles
BEACOPP baseline + 30 Gy IF-RT), or arm D (4
cycles of BEACOPP baseline + 20 Gy IF-RT).
The FFTF at 5 years was 85%, overall survival
was 94.5%, and progression-free survival was 86%. BEACOPP baseline was more effective than ABVD when followed by 20 Gy of IF-RT (5-year FFTF dif-
ference, 5.7%). No difference was seen between
BEACOPP baseline and ABVD when followed by
30 Gy of IF-RT (5-year FFTF difference, 1.6%).
Similar results were observed for the RT question:
after 4 cycles of BEACOPP baseline, outcomes with
20 Gy were not inferior to 30 Gy (5-year FFTF differ-
ce, -0.8%; 95% CI, -5.8%–4.2%), whereas after
4 cycles of ABVD, a relevant inferiority of 20 Gy
cannot be excluded (5-year FFTF difference, -4.7;
95% CI, -10.3–0.8). A reduction of RT dose from 30
to 20 Gy IF-RT seems justified only in combina-
tion with BEACOPP baseline, but not with a less effec-
tive chemotherapy, such as 4 cycles of ABVD.21

In a 2-arm randomized study, the following
HD14 trial for patients with early-unfavorable stages
compared 2 different intensified chemotherapy regi-
mens (4 cycles of ABVD vs. 2 cycles of BEACOPP
escalated/2 cycles of ABVD) by keeping the IF-RT
dose of 30 Gy in both treatment arms.22

The third
preplanned interim analysis of this trial showed a
significantly better progression-free survival for the
more intensive “2 + 2” arm at 3 years (“2 + 2”: 97%;
ABVD: 91%; P < .0017). Upfront intensification
with only 2 cycles of escalated BEACOPP improves
outcome in this group of patients; however, one can
argue about the clinical relevance of a 6% absolute
improvement in progression-free survival in the pres-
ence of the putative increased toxicity (e.g., gonadal
damage and secondary malignancies).

The ongoing HD17 trial (Figure 2) also intro-
duces FDG-PET after completion of chemotherapy,
which consists of 2 cycles of BEACOPP escalated fol-
lowed by 2 cycles of ABVD to stratify between PET-
positive and PET-negative patients. Patients with a
negative PET scan are randomized between 30 Gy IF-
RT versus no further treatment. Patients with a posi-
tive PET scan are randomized between 30 Gy IF-RT
versus 30 Gy IN-RT. The IN-RT concept for patients

![Figure 2](HD17 trial for patients with early-unfavorable stage Hodgkin lymphoma. Abbreviations: ABVD, adriamycin, bleomycin, vinblastine, and dacarbazine; BEACOPP, bleomycin, etoposide, adriamycin, cyclo-
phosphamide, vincristine, procarbazine, and prednisone; CS, clinical stage; esc, escalated; ESR, erythrocyte sedimentation rate; IF, involved-field; IN, involved node; RF, risk factors; RT, radiotherapy.
*High ESR, or 3 or more areas
with early-stage HL was recently introduced by the EORTC/GELA Lymphoma Group within the Intergroup study H10. In this study, radiation fields are designed to irradiate the initially involved lymph nodes exclusively and to encompass their initial volume as a consolidation after ABVD chemotherapy. The rationale for this approach is based on the observation that after chemotherapy alone, most relapses of HL occur in previously involved nodes. Because this concept has never been tested in a randomized trial, the GHSG is comparing it with standard IF-RT in the HD17 trial.13

**Advanced-Stage HL**

The basis of successful treatment of patients in the advanced stages of HL is intensive polychemotherapy. Since the introduction of MOPP chemotherapy (mechlorethamine, vincristine, procarbazine, prednisone) by de Vita in the sixties,24 prognosis for long-term survival has become markedly better but could not overcome a certain level until BEACOPP and its modifications had been developed by the GHSG. The role of consolidative RT in advanced HL depends on the efficacy of the prior chemotherapy. A randomized EORTC study showed that consolidation with IF-RT did not improve outcomes in patients experiencing complete remission after 6 to 8 courses of alternating MOPP and ABV, but potentially improved the outcomes of those experiencing partial remission.25

The HD9 trial tested the newly developed BEACOPP regimen against the GHSG standard COPP/ABVD chemotherapy regimen. Patients with advanced stages (clinical stage [CS] IIB, IIIA with risk factors; PS IIIA + splenic involvement; CS/PS IIIB; and CS/PS IV) were randomized into 3 treatment arms: 4 cycles of COPP/ABVD, 8 cycles of BEACOPP escalated, or 8 cycles of BEACOPP baseline. Consolidative RT (30 Gy) was applied in patients with initial bulky disease (≥ 5.0 cm) or residual disease (≥ 1.5 cm). Results of 1195 randomized patients showed a clear superiority of BEACOPP escalated over BEACOPP baseline and COPP/ABVD at 5 years and also at 10 years.4,26 At 10 years, the FFTF and overall survival rates were 64% and 75% for COPP/ABVD, 70% and 80% for BEACOPP baseline, and 82% and 86% for BEACOPP escalated, respectively.26 However, toxicity of BEACOPP escalated remains a concern. The subsequent HD12 trial therefore had the goal of deescalating chemotherapy by comparing 4 courses of BEACOPP escalated with 4 courses of BEACOPP baseline (“4 + 4”). The role of RT was tested by a second randomization to either consolidative RT to initial bulky and residual disease or no RT. At 5 years, the overall survival, FFTF, and progression-free survival rates were 91%, 85.5%, and 86.2%, respectively. Statistically, more patients with progressive disease were documented with the “4 + 4” arm. Concerning the RT question, the study was biased because of a central review.27 Almost 10% of patients were irradiated who had originally been randomized to the observation arm. Thus far, unpublished data from the HD12 trial indicate a benefit of RT to residual disease in terms of progression-free survival. Thus, outside of clinical trials, the GHSG still considers 8 cycles BEACOPP escalated followed by RT to residual disease as standard treatment for patients with advanced-stage HL.

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**Figure 3** HD18 trial for patients with advanced-stage Hodgkin lymphoma.

Abbreviations: BEACOPP, bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, and prednisone; esc, escalated; RT, radiotherapy; R, rituximab.
In the GHSG HD15 trial, 311 of 817 patients (38%) showed residual disease (≥ 2.5 cm), as determined by CT after the completion of chemotherapy with BEACOPP. At that time, 79% (n = 245) of these patients had a negative PET scan. These patients did not receive any additional RT. However, PET-positive patients were irradiated in the region of residual tumor. The progression-free survival was 96% for PET-negative patients and 86% for PET-positive patients. Compared with the limited literature, the prognosis of PET-positive patients is still good because of the consolidative RT. The negative predictive value for PET after chemotherapy was defined as 94%.

The ongoing HD18 trial (Figure 3) evaluates early PET-determined response. All patients receive a PET scan after 2 cycles of BEACOPP escalated. Patients who are PET-positive receive 6 further cycles of BEACOPP escalated. PET-negative patients are randomized to either the standard regimen of 6 additional cycles of BEACOPP or only 2 additional cycles. RT is applied in the region of PET-positive residual disease (≥ 2.5 cm) after completion of chemotherapy, similar to the procedure in HD15.

References


