Role of radiotherapy to bulky sites of advanced Hodgkin lymphoma treated with ABVD: final results of FIL HD0801 trial

Abstract:

The role of consolidation radiotherapy (RT) to bulky lesions is controversial for advanced stage Hodgkin lymphoma (HL). The primary endpoint of randomized trial was to investigate the potential benefit of RT in advanced-stage HL with a bulky lesion at the onset of treatment. In this phase III randomized study, patients with a bulky lesion at baseline (mass with the largest diameter >5 cm) achieving CMR after 2 and 6 ABVD cycles were randomly assigned 1:1 to RT vs observation with a 20% EFS improvement for RT of 20% (from 60% to 80%). The secondary endpoint was progression-free survival (PFS) at two years. The sample size was calculated estimating an ES of 0.87, with a 95% CI of 0.75-0.95, and the power to detect a difference of 10% with 80% power was 88%. The trial was registered at www.clinicaltrials.gov as #NCT00784537. A total of 1015 patients were enrolled, of whom 507 were randomized (253 to RT and 254 to observation). The ITT PFS was 91.3% vs. 85.8% (HR:1.2, CI:0.5-3, p=0.52) for RT vs observation, respectively (HR:1.19, CI:0.47-3.02, p=0.71). At 2 years, ITT PFS was 91.3% vs. 85.8% (HR:1.2, CI:0.5-3, p=0.52) for RT vs observation, respectively. Our study showed that patients in CMR randomized to observation have a very good outcome and the primary endpoint of a 20% benefit in EFS for RT was not met. However, the sample size was underpowered to detect a benefit of 10% or less, keeping open the question on potential, more limited, role of RT in this setting.

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Role of radiotherapy to bulky sites of advanced Hodgkin lymphoma treated with ABVD: final results of FIL HD0801 trial

RUNNING HEAD: Role of consolidation RT in advanced stage HL

PRIMARY CATEGORY: Clinical trials and observations
SECONDARY CATEGORY: Lymphoid neoplasia

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ABSTRACT

The role of consolidation radiotherapy (RT) to bulky lesions is controversial for advanced-stage Hodgkin's lymphoma (HL) patients achieving complete metabolic response (CMR) after ABVD-based chemotherapy. Herein we present the final results of the Fondazione Italiana Linfomi HD0801 trial, investigating the potential benefit of RT in that particular setting. In this phase III randomized study, patients with a bulky lesion at baseline (mass with the largest diameter ≥ 5 cm) achieving CMR after 2 and 6 ABVD cycles were randomly assigned 1:1 to RT vs observation with a primary endpoint of event-free survival (EFS) at two years. The sample size was calculated estimating an EFS improvement for RT of 20% (from 60% to 80%). The secondary endpoint was progression-free survival (PFS). One-hundred and sixteen (116) patients met the inclusion criteria and were randomized. Intention-to-treat (ITT) analysis showed a 2-year EFS of 87.8% vs. 85.8% for RT vs. observation, respectively (HR:1.5, CI:0.6-3.5, p=0.34). Per-protocol (PP) analysis showed a 2-year EFS of 89.6% vs. 85.8%, respectively (HR:1.19, CI:0.47-3.02, p=0.71). At 2 years, ITT PFS was 91.3% vs. 85.8% (HR:1.2, CI:0.5-3, p=0.7), while PP PFS was 93.8% vs. 85.8% (HR:0.7, CI:0.2-2.1, p=0.52) for RT vs observation, respectively. Our study showed that patients in CMR randomized to observation have a very good outcome and the primary endpoint of a 20% benefit in EFS for RT was not met. However, the sample size was under-powered to detect a benefit of 10% or less, keeping open the question on potential, more limited, role of RT in this setting. This trial was registered at www.clinicaltrials.gov as # NCT00784537.
KEY POINTS

- The prognosis of advanced HL patients achieving CMR after both 2 and 6 ABVD cycles is excellent without the addition of consolidation RT.
- Additional benefit of consolidation RT to sites >5cm is likely to be small and could not be proven in this study for the small sample size.
INTRODUCTION

The role of consolidation radiation therapy (RT) in advanced Hodgkin’s lymphoma (HL) is controversial, primarily because of conflicting results in randomized studies (1-3). Before the advent of functional imaging, the efficacy of consolidation RT was proved only in patient with bulky disease at baseline (4-6) or achieving a partial remission after chemotherapy (5, 7). The uncertainty has increased in the modern era, in which response to chemotherapy is assessed with positron emission tomography (PET)-computed tomography (CT). Concerns for the increase of late effects, particularly secondary malignancies and cardiac diseases (8-10), have also led to a progressive decline in RT utilization. In fact, despite significant technological advances allowing a meaningful reduction of the dose received by the healthy organs, the RT-related risk of long term complications may not be completely abolished (11-17). Thus, an end-of-treatment PET-driven strategy has been proposed for advanced-stage HL by many research groups.

In the phase III German Hodgkin Study Group (GHSG) HD15 study (18), consolidation RT was delivered only to patients with a positive PET-CT scan (Deauville Score ≥3) and a residual mass >2.5 cm at CT, having the previous HD12 trial showed no inferior outcomes omitting consolidation RT to bulky lesions achieving a complete response after 6-8 cycles of BEACOPP (Bleomycin, Etoposide, Doxorubicin, Cyclophosphamide, Vincristine, Procarbazine, Prednisone) escalated (19).

Two Italian collaborative research groups (Gruppo Italiano Terapie Innovative Linfomi-GITIL and Fondazione Italiana Linfomi-FIL) designed in the mid 2000’s two randomized trials investigating a response-adapted strategy in advanced HL treated with ABVD (Doxorubicin, Bleomycin, Vinblastin, Dacarbazine) regimen. Both trials included an early intensification phase II part for PET-positive patients after two ABVD cycles, and a second phase III part, randomizing patients with bulky disease at baseline (defined as the presence of a nodal mass >5 cm) and both interim (PET2) and end-of-chemotherapy PET negativity to RT vs. observation. Results of the early intensification strategy of these two parallel studies were previously reported, showing excellent
results in terms of progression-free survival (PFS) for early PET-positive patients undergoing either a BEACOPP-based intensification, as per GITIL HD0607 strategy (20), or autologous stem cell transplantation, as per FIL HD0801 strategy (21).

The final results of the HD0607 study on the role of RT have been recently published. After the randomization of 296 PET-negative patients to RT (148) vs. observation (148), 6-years PFS was 92% (CI: 88-97%) for RT vs. 90% (CI: 85-95%) for observation, respectively, showing no benefit for consolidation RT ($p =0.48$) (22).

Here we report the final results of the randomized phase III part of the FIL HD0801 study.

MATERIALS AND METHODS

**Study design and Procedure**

HD0801 was a multicenter study involving patients with newly diagnosed advanced-stage HL, all receiving first-line ABVD treatment and undergoing an interim PET2 evaluation. This trial was designed to address two specific questions: whether an early PET-guided salvage treatment consisting of high-dose chemotherapy with a subsequent autologous bone marrow transplant (ABMT) could be considered safe and effective compared with data in the literature (phase II part) and whether PET2-negative patients could benefit from radiotherapy consolidation for areas of bulky disease, provided they maintained PET negativity upon completion of the planned six ABVD courses (phase III part; *Figure 1*). The phase II part of the study was previously published (21).

**Patients**

Patients aged 18 to 70 years were considered eligible if they had previously untreated and histologically documented classical HL (with the exception of nodular lymphocyte–predominant subtype) in clinical stage IIB to IV according to Ann Arbor staging and at least one measurable
target lesion (even if extranodal only). Patients were excluded from the study if they had a severe disease that impaired normal life, presented an active infection, or had an inadequate liver or renal function, unless this was a result of the lymphoma. Those with a history of previous malignancy (except basal cell skin carcinoma and in situ carcinoma of the cervix) were considered ineligible. Responses were primarily evaluated by centrally reviewed PET-scan after two cycles of ABVD and at the end of the scheduled treatment plan, provided that all patients had undergone a complete staging workup, including PET examination, before the start of treatment. The depth of response was graded according to the revised response criteria for malignant lymphomas (23). Details on PET central evaluation in FIL HD0801 trial have been previously described (21).

All local ethic committees at each participating center approved the study protocol and its amendments, in accordance with the Italian law and in compliance with the Declaration of Helsinki. Patients provided written informed consent before being included in the study.

**Randomization and treatment Plan**

In the phase III part of the study, patients achieving complete metabolic response both at PET2 and at the end of chemotherapy (6 ABVD cycles) according with the Juweid’s criteria (24) and with at least one site of bulky disease at baseline (measured on CT scan, largest diameter ≥5 cm) were stratified according to baseline International Prognostic Score IPS (≤2 or ≥3) and then randomized 1:1, using permuted blocks (length 2 and 4), to either consolidation radiotherapy with the dose of 30 Gy in 2 Gy fractions or observation within each strata.

**End Points**

Primary endpoint was the event free survival (EFS), calculated from random allocation after PET response at the end of 6 ABVD cycles, until the date of disease progression, late serious treatment-related events, secondary cancers or death from any cause. Secondary endpoints were PFS
(measured until the date of lymphoma progression or death from any cause) and Overall Survival (OS) (measured until the date of death from any cause).

Statistical methods

The sample size of this phase III study was estimated on an EFS difference favoring RT (primary endpoint). With a two-sided alpha error of 0.05, 120 patients (60 in the RT and 60 in the observation arm) were required to have a statistical power of 80% to detect a 20% improvement in 2-year EFS (from 60% to 80%) in the group receiving RT compared with those who did not receive RT, assuming an accrual of 4 years and a minimum follow-up of 2 years from the enrollment of the last patient. Assuming that 40% of the total enrolled patients could have a bulky lesion at baseline and achieve a complete metabolic response after 2 and 6 ABVD, we initially planned the inclusion of 300 patients. However, after the first 300 enrolled patients, the proportion of bulky lesions achieving a complete metabolic response after 6 ABVD was only 23%. Following a protocol amendment done on January 2013, the total enrollment was increased to 520 total cases to achieve 120 cases randomized to consolidation radiotherapy or observation.

Time-to-event endpoints (EFS, PFS, OS) were estimated with the Kaplan-Meier product-limit method. The main analysis was performed in the intention-to-treat population (ITT), which included all randomized patients. Differences between randomized groups were assessed by stratified log-rank test and hazard ratios (HRs) were estimated with stratified Cox models. A per-protocol analysis (PP) was carried out by excluding patients who did not receive the allocated treatment. Pre-planned subgroup analyses according to age, disease stage, extranodal involvement, (IPS) and Eastern Cooperative Oncology Group (ECOG) performance status were performed using Cox models, adjusting for the stratification variable. The presence of any interaction was tested by including an interaction term between the randomized group and the subgroup covariate. Size of
bulky lesion was then stratified in three subgroups (5-to-7 cm, 7-to-10 cm and >10 cm) to explore any modification for the effect of RT. All reported p-values were two-sided. Statistical analyses were done with STATA software, version 13.0.

RESULTS

Overall, 520 patients were enrolled onto the study and started ABVD treatment between September 2008 and April 2013 in 50 Italian centers. Of those patients, 512 (99%) underwent a PET2 scan, one patient withdrew consent before therapy, and seven patients interrupted the treatment before the end of the second ABVD cycle. Among the 512 patients with an interim PET2 scan evaluated by central review, 409 (80%) were PET negative and 103 (20%) were PET positive. As stated by the protocol, all 409 PET2-negative patients received four more ABVD cycles. Among them, 16 patients interrupted therapy and 393 were assessed for final response after 6 ABVD cycles. Out of 393, 38 were judged positive at end-of-therapy PET scan and initiated a salvage therapy (25); 355 were screened for entering the phase III part of the study; 230 were non-bulky and 125 had bulky disease at baseline (Figure 2); 9 bulky patients were not randomized (details in Supplemental Data, Table 1). Finally, 116 patients were randomized to either consolidation (RT arm: 58 patients) or observation (OBS arm: 58 patients). The demographic and baseline disease characteristics of the randomized patients are listed in Table 1. Nine patients allocated to RT did not receive consolidation (details in Supplemental Data, Table 2) and were excluded from the PP analysis. None of the patients allocated to OBS received consolidation RT. The median size of initial bulky lesions was 8.15 cm in RT arm and 8.25 cm in OBS arm (range 5-20 cm). Median RT dose was 30 Gy (range 25-40 Gy). Overall, a protocol deviation in RT dose was recorded in 6 patients (one patient treated with 25 Gy, one treated with 34 Gy, two treated with 36 Gy and two treated with 40 Gy). The majority of patients had a single bulky site (overall, 86%;
83% in RT arm and 90% in OBS arm, respectively), mediastinum was the most frequent site of the bulky lesions (overall, 69%; 67% in RT arm and 71% in OBS arm).

**Survival Analysis**

Overall, for EFS, at least one event was recorded in 23 patients, 14 in RT Arm and 9 in OBS Arm. Seventeen patients experienced disease progression, 9 in RT Arm and 8 in OBS Arm, respectively. *Table 2* describes in detail the recorded events according to randomization arm. Notably, 5 out of 9 disease progressions in RT Arm were recorded among the 9 patients not receiving the allocated RT treatment.

Overall, after a median follow-up of 71 months from end-of-chemotherapy PET scan, only one death was recorded (a patient randomized in RT Arm who did not receive consolidation RT).

On an ITT analysis, 2-year Event-free survival (EFS) was 87.8% (95% CI from 76.0% to 94.0%) for RT Arm vs. 85.8% (95% CI from 73.6% to 92.6%) for OBS Arm, respectively. Hazard ratio was 1.5 (95% CI:0.6-3.5), stratified logrank-test p value=0.34 (*Figure 3A*).

The PP analysis showed a 2-year EFS of 89.6% (95% CI: from 76.8% to 95.6%) for RT Arm vs. 85.8% (95% CI from 73.6% to 92.6%) for OBS Arm, respectively. Hazard ratio was 1.1 (CI:0.4-2.8), stratified logrank-test p value=0.7 (*Figure 3B*).

On an ITT analysis, Progression-free survival (PFS) at 2 years was 91.3% (95% CI from 80.3% to 96.3%) for RT Arm vs. 85.8% (95% CI from 73.6% to 92.6%) for OBS arm, respectively. Hazard ratio was 1.2 (95% CI: 0.5-3), stratified logrank-test p value=0.7 (*Figure 4A*).

The PP analysis showed a 2-year PFS of 93.8% (95% CI: 81.9% to 98.0%) for RT Arm vs. 85.8% (95% CI from 73.6% to 92.6%) for OBS Arm, respectively. Hazard ratio was 0.7 (CI:0.2-2.1), stratified logrank-test p value=0.5 (*Figure 4B*).

On an ITT analysis, also the unplanned 6-year estimates were similar for RT Arm and OBS Arm, both in term of EFS (76.4% vs 83.9%) and PFS (83.8% vs 85.8%).
The subgroup analysis showed no modification of effects on EFS and PFS for any of the pre-planned factors (Figure 5). The stratified analysis for the bulky size showed no significant differences in the effect of RT related to different tumor burden. (Supplemental Data, Figure 1).

By multivariable analysis (Supplemental Data Table 3), age at diagnosis ≥50 years was significantly associated with a reduced EFS (HR = 5.45, CI 2.00 – 14.90, p < 0.001). No other factors showed a statistically significant association with the clinical outcomes.

Toxicity

Acute chemotherapy-related toxicity was described in details in the previous paper (21). Concerning RT, no acute toxicity events were detected, according to the SAE/SUSAR reporting.

Regarding late toxicity, only 7 events were recorded among the 116 randomized patients. In details, 3 patients (2 in RT Arm and 1 in OBS Arm) had a second cancer (1 breast cancer, 1 follicular lymphoma and 1 not specified), 1 patient (OBS Arm) experienced a myocardial infarction, 1 patient (RT Arm) with an inconclusive diagnosis of myelodysplastic syndrome developed a severe respiratory failure, 1 patient (RT Arm) had a persistent severe neutropenia (inconclusive for myelodysplastic syndrome) and 1 (RT Arm) showed severe neutropenia and thrombocytopenia.

Only 1 patient died for a myocardial infarction (the one who did not receive RT despite being randomized in RT Arm).

DISCUSSION

Survival rates for advanced HL have substantially increased over the last two decades. Early response evaluation with PET-2 proved to be an effective strategy in guiding the intensification of systemic agents in several prospective studies (20, 21, 26) (27, 28). Therefore, we might use a
similar strategy for assessing the need of consolidation RT in advanced HL, based on the metabolic response at the end of chemotherapy.

The phase III parts of two similar (both Italian) studies (20, 21) investigated for the role of consolidation radiotherapy for patients with bulky disease at baseline, achieving complete metabolic response after the end of chemotherapy (6 ABVD cycles). The role of radiotherapy is debated due to concerns on late toxicity, as the majority of bulky sites at diagnosis are in the mediastinum. In fact, the combination of anthracyclines and radiation is a known risk factor for late cardiac toxicity (especially coronary artery disease and chronic heart failure) (29-31) and the risk of developing a secondary cancer (especially breast cancer in younger female patients) (10, 32). Although modern radiotherapy (doses and volumes reduction, conformal treatment delivery) favors a better sparing of healthy tissues located in close proximity of the target volumes (11-16), the risk of long term complications cannot be completely removed. Thus, the rationale for both studies was to investigate for the possible omission of RT, maintaining the same tumor control probability with a reduced therapeutic burden.

The phase III part on consolidation RT of the GITIL HD0607 study (22) was designed with PFS as primary endpoint. Final results showed no differences between RT and observation arms in patients with nodal masses larger than 5 cm at baseline and PET-negative at the end of ABVD chemotherapy, with a PFS at 6 years of 92% for RT vs. 90% for observation, respectively. The phase III part of the FIL HD0801 also failed to demonstrate a meaningful improvement in 2-years PFS, as well as in 2-years EFS, between patients who received RT vs. observation.

A first consideration on the difference between GITIL HD0607 study and the present study is the sample size and the frequency of bulky lesions. GITIL HD0607 investigators randomized 296 bulky patients, out of 580 PET-negative at the end of chemotherapy (51%). In the FIL HD0801 study, we randomized 116 bulky patients out of 355 with PET negativity after the end of chemotherapy (32.6%). Despite having both studies centralized PET imaging review and the same cut-off for the definition of bulky lesions, the proportion of bulky lesions among PET-negative patients was
significantly lower in the FIL HD0801 study. This difference in the prevalence of bulky presentations among PET-negative patients is quite challenging to explain, given the same frontline therapeutic strategy and the proportion of patients achieving a complete metabolic response at the end of chemotherapy, slightly lower in our study (580/783, 74%, in the GITIL HD0607 study and 355/520, 68%, in the FIL HD0801 study, respectively). Secondly, the overall outcome was inferior in patients enrolled in the HD0801 trial, with an ITT 6-year PFS of 83.8% for RT and 85.8% for observation, respectively, in comparison with 92% for RT and 90% for observation, respectively, in the GITIL HD0607 trial (22). This could be partially caused by the higher proportion of stage IIB patients randomized in GITIL HD0607 compared to HD0801 (47% vs 29%, respectively). Lastly, the two studies had a different design; the primary endpoint of FIL HD0801 was EFS (and not PFS as it was in the GITIL trial), with the hypothesis of achieving superior 2-year EFS with consolidation RT (80% vs. 60%). The choice of EFS as primary endpoint was justified by the consideration that all clinically relevant events, including toxicity, should be accounted for when comparing an additional treatment with potential toxicity, such as RT, to observation. Moreover, EFS was the primary endpoint of several studies investigating the role of RT in advanced HL in “pre-PET era” (4, 6, 7). Nevertheless, the assumptions underlying our study had at least three limitations: a) the expected EFS for the observation arm in patients in CMR, even with bulky lesions, was too low compared to previous studies reporting EFS rates always >70% (4); b) in previous studies, the addition of RT provided a benefit in EFS and PFS of maximum 12-15% (4, 6). Therefore, our expectation for an absolute difference between RT vs. no RT of 20% was too high; c) RT-induced toxicity cannot be reliably estimated before 2-3 decades since treatment delivery. These limitations led to a small sample size, and made the study underpowered to detect (or exclude) differences in EFS and PFS below 10%.

Despite these limitations, our trial showed that patients achieving CMR after 2 and 6 ABVD cycles have a good outcome (EFS and PFS at 2 years were 85.8%) without the addition of consolidation RT to bulky sites, confirming two previous studies in which the omission of RT was considered
safe in the context of ABVD-based chemotherapy. (22, 27) Moreover, almost all relapses occurred outside the bulky sites not just in the RT arm, but also in the OBS arm and we did not detect any significant difference in RT impact across different bulky sizes (5-7 cm, 7-10 cm, or more than 10 cm) and in the pattern of relapse between irradiated vs. non-irradiated areas. On the other hand, RT arm had a slightly superior outcome at 2 years, ranging 2% (ITT EFS) to 8% (ITT PFS); however, any potential benefit of adding RT could not be proven by our study for the small numbers that did not confer enough power to detect a difference of such a limited entity. As an example, the randomized controlled trials that proved a significant PFS benefit with the addition of RT in early stage HL included several hundreds of patients to achieve a small superiority, ranging 6-12% (33-35). Therefore, considering the good outcome of patients not receiving RT in our study, approaching the same rates of early stage HL, any potential benefit of adding RT would be probably small and would require a larger amount of patients to be demonstrated. Nevertheless, our study included only patients with a CMR after both 2 and 6 cycles. Therefore, we cannot provide any information on the role of radiotherapy in patients continuing ABVD with a positive finding after either 2 or 6 cycles.

Moreover, it should be noted that nine patients randomized to RT did not really receive consolidation treatment, mostly for medical decision, and five of them relapsed. It is well known that bulky size affects the prognosis of HL patients in both the early and the advanced setting (20, 36). In the first GITIL HD0607 report (20), the authors found bulky lesions larger than 7 cm being predictive for worse PFS at multivariable analysis, regardless of the receipt of consolidation RT. The same cut-off was also identified for early stage HL patients in a collaborative study from American Institutions, showing a mitigation of the prognostic role of bulky masses >7 cm with the addition of RT (PFS at 4 years >90% vs 55% for chemotherapy alone group, p<0.001) (36). In the HD0801 trial, we were not able to demonstrate any beneficial role for RT in patients with bulky lesion >7 cm. Again, the study was considerably underpowered to address this question (overall, only 33 out of 73 patients with a bulky >7 cm received consolidation RT).
A recent study from the collaborative International Lymphoma Radiation Oncology Group (ILROG) (37) further highlighted the complex association between bulk (size and site) and clinical outcomes. The authors showed a better OS in patients with mediastinal bulky lesion compared to patients without bulky lesions. Moreover, bulky location had a significant prognostic role: in fact, OS was higher in patients with a mediastinal (MB) location compared to those with a “non-mediastinal” (NMB) bulk (92% vs 86% at 5 years, p < 0.01). This may be justified, at least partially, by several confounding factors. In fact, advanced non-bulky and NMB patients are generally older and with associated bone involvement.

Looking in detail, it cannot be excluded that some patients would benefit from consolidation RT, and the next research step could be merging similar studies with updated follow-up to perform individual patient data meta-analysis, with the scope of achieving more robust evidence on the role of consolidation RT among different risk subgroups.

In conclusion, the phase III part of the FIL HD0801 study did not meet its primary endpoint, failing to show difference in either EFS or PFS for patients receiving or not receiving consolidation RT to bulky sites at baseline. Moreover, the study showed that patients in CMR after 6 cycles of ABVD have a very good prognosis also without the addition of consolidation RT. However, these results are still not definitive and cannot directly demonstrate the non-inferiority of observation. In the future, the combination of clinical, radiological and biological factors could better identify patients at higher risk of relapse: this strategy might refine upfront those to be included in future randomized trials with the aim of clarifying the potential role of consolidation RT, eventually with a dose de-escalation as already tested in early-stage HL (38) and diffuse large B cell lymphoma (39).
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Table 1: Baseline Characteristics of patients randomized to radiotherapy (RT) vs observation (OBS)

| Factors          | N°   | RT (N=58) | OBS (N=58) | Total (N=116) |
|------------------|------|-----------|------------|---------------|
| Age, median IQR  | 116  | 31.50 (26.00;39.75) | 29.50 (25.00;37.00) | 31.00 (25.00;39.00) |
| Sex              | 116  |           |            |               |
| Male             |      | 34 (59%) | 30 (52%)   | 64 (55%)      |
| Female           |      | 24 (41%) | 28 (48%)   | 52 (45%)      |
| IPS              | 116  |           |            |               |
| 0-2              |      | 33 (57%) | 35 (60%)   | 68 (59%)      |
| >=3              |      | 25 (43%) | 22 (40%)   | 48 (41%)      |
| Histology        | 116  |           |            |               |
| NS               |      | 38 (66%) | 39 (67%)   | 77 (66%)      |
| MC               |      | 11 (19%) | 5 (9%)     | 16 (14%)      |
| LD               |      | 1 (2%)   | 3 (5%)     | 4 (3%)        |
| LR               |      | 2 (3%)   | 5 (9%)     | 7 (6%)        |
| NA               |      | 6 (10%)  | 6 (10%)    | 12 (10%)      |
| B symptoms       | 116  |           |            |               |
| No               |      | 14 (24%) | 21 (36%)   | 35 (30%)      |
| Yes              |      | 44 (76%) | 37 (64%)   | 81 (70%)      |
| ECOG PS          | 116  |           |            |               |
| 0                |      | 35 (60%) | 38 (66%)   | 73 (63%)      |
| 1                |      | 16 (28%) | 17 (29%)   | 33 (28%)      |
| Stage | Involved nodal sites, median (IQR) | Number of Bulky sites | Bulky site | Bulky size |
|-------|----------------------------------|-----------------------|------------|-----------|
|       |                                  |                       | Mediastinum | Other sites |
|       |                                  |                       |            |            |
| 1     | 6.00 (4.00; 8.00)                 | 52 (90%)              | 41 (71%)   | 17 (29%)   |
| 2     |                                  | 48 (83%)              | 39 (67%)   | 19 (33%)   |
| 3     |                                  | 100 (86%)             | 80 (69%)   | 36 (31%)   |
| 4     |                                  |                       |            |            |
|       |                                  | 5 (9%)                | 6 (10%)    | 11 (9%)    |
|       |                                  | 1 (2%)                | 3 (5%)     | 4 (3%)     |
|       |                                  | 0 (0%)                | 1 (2%)     | 1 (1%)     |
| Extranal sites | 116                        | 19 (33%)              | 24 (41%)   | 43 (37%)   |
| 0     |                                  | 39 (67%)              | 34 (59%)   | 73 (63%)   |
| >= 1  |                                  |                       | 19 (33%)   | 24 (41%)   |
|       |                                  |                       | 43 (37%)   |            |
| 2     |                                  | 1 (5%)                | 3 (5%)     | 4 (3%)     |
| 3     |                                  | 0 (0%)                | 1 (2%)     | 1 (1%)     |
| 4     |                                  |                       |            |            |
|       |                                  | 19 (33%)              | 18 (31%)   | 37 (32%)   |
| <7    |                                  |                       |            |            |
| 7-10  |                                  | 16 (28%)              | 19 (33%)   | 35 (30%)   |
| ≥10   |                                  | 23 (40%)              | 21 (36%)   | 44 (38%)   |
Abbreviations: IPS, International Prognostic Score; NS, nodular sclerosis; MC, mixed cellularity; LD, lymphocyte depleted; LR, lymphocyte rich; NA, not available; ECOG, Eastern Cooperative Oncology Group; PS, performance status

**Table 2: List of the events recorded in the two arms**

| Event                          | RT   | OBS |
|-------------------------------|------|-----|
| Progression                   | 9*   | 8   |
| In field/bulky site           | 1    | 0   |
| Out of field                  | 6    | 6   |
| Not specified                 | 2    | 2   |
| Secondary neoplasm            | 2    | 1   |
| Severe cardiac toxicity       | 0    | 1   |
| Severe respiratory toxicity   | 1    | 0   |
| Other Severe toxicity         | 2    | 0   |
| Death                         | 1#   | 0   |
| Patients with at least one event | 14  | 9   |

* Five out of nine relapsing patients did not receive consolidation RT.

# The deceased patient did not receive consolidation RT (cause of death: myocardial infarction).

**Figure Legends**
**Figure 1:** Study outline

**Figure 2:** Patient flow diagram

**Figure 3:** Event-Free survival determined as “intention-to-treat” (A) or “per-protocol” (B) from the time of randomization.

**Figure 4:** Progression-Free survival determined as “intention-to-treat” (A) or “per-protocol” (B) from the time of randomization.

**Figure 5:** Event-Free survival (A) and Progression Free-Survival (B) stratified by subgroups (per-protocol analysis).
Figure 1

Staging: including CT and PET scan

ABVD, two cycles

PET2 evaluation

Negative

ABVD, two cycles

Optional CT scan

End of treatment PET evaluation

Negative

NON bulky

Randomize bulky (> 5 cm)

Consolidation RT

Positive

Early salvage treatment (previously published, Zinzani P.L. et al.)

Positive

Off study (previously published, Rigacci L. et al.)

Observation
Figure 2

Enrolled (N=520)
- Consent Withdrawal N=1
- Treated with ABVD, two cycles (N=519)
  - Treatment interruptions (N=7)
  - PET2 evaluable patients (N=512)
    - PET2 positive patients, candidate to early salvage (N=103)
      - Treatment interruptions (N=16)
    - PET6 evaluable patients (N=393)
      - PET6 positive patients (N=38)
        - Non-bulky patients (N=230)
        - Not randomized patient (N=9)

Randomized patients (N=116)
- Arm A (consolidation RT)
  - Intention-to-treat population (N=58)
    - Treatment interruptions (N=9)
      - Per-protocol population (N=49)
- Arm B (observation)
  - Intention-to-treat population (N=58)
    - Per-protocol population (N=58)
Figure 3

A

B
Figure 4

A

B

At risk:

RT No 58 51 46 44 42 34 24 16 3
RT Yes 58 53 52 49 49 37 22 11 4
