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ORIGINAL REPORT

Consolidation Radiation After Complete Remission in Hodgkin's Disease Following Six Cycles of Doxorubicin, Bleomycin, Vinblastine, and Dacarbazine Chemotherapy: Is There a Need?

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ABSTRACT

Purpose
Combined modality treatment using multidrug chemotherapy (CTh) and radiotherapy (RT) is currently considered the standard of care in early stage Hodgkin's disease. Its role in advanced stages, however, continues to be debated. This study was aimed at evaluating the role of consolidation radiation in patients achieving a complete remission after six cycles of doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) chemotherapy using event-free survival (EFS) and overall survival (OS) as primary end points.

Patients and Methods
Two hundred and fifty-one patients with Hodgkin's disease attending the lymphoma clinic at the Tata Memorial Hospital (Mumbai, India) from 1993 to 1996 received induction chemotherapy with six cycles of ABVD after initial staging evaluation. A total of 179 of 251 patients (71%) achieved a complete remission after six cycles of ABVD chemotherapy and constituted the randomized population. Patients were randomly assigned to receive either consolidation radiation or no further therapy.

Results
With a median follow-up of 63 months, the 8-year EFS and OS in the CTh-alone arm were 76% and 89%, respectively, as compared with 88% and 100% in the CTh+RT arm ($P = .01$; $P = .002$). Addition of RT improved EFS and OS in patients with age < 15 years ($P = .02$; $P = .04$), B symptoms ($P = .03$; $P = .006$), advanced stage ($P = .03$; $P = .006$), and bulky disease ($P = .04$; $P = .19$).

Conclusion
Our study suggests that the addition of consolidation radiation helps improve the EFS and OS in patients achieving a complete remission after six cycles of ABVD chemotherapy, particularly in the younger age group and in patients with B symptoms and bulky and advanced disease.

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INTRODUCTION

The outcome of Hodgkin's disease (HD) has vastly improved over the last few decades. With the introduction of mechlorethamine, vincristine, prednisone, and procarbazine (MOPP) [1] and doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) [2] polychemotherapy regimens, the long-term survival ranges from 70% to 95% depending on stage, risk factor profile, and adequacy of treatment [3-5]. The optimal treatment for early stage HD is now more or less well-established [6,7] with the use of combined modality treatment (CMT), a combination of chemotherapy (CTh) and radiotherapy (RT). The rationale for this is that while CTh takes care of the disseminated subclinical disease, RT is needed for lasting local tumor control. The combination also allows one to restrict the intensity and duration of CTh and the dose and volume of radiation.

The optimal therapeutic strategy for patients with advanced stage HD continues to be debated. With modern day CTh, more than 75% of such patients would be expected to achieve a complete remission (CR), although up to one-third of them

would eventually relapse [8], mostly in sites of initial involvement. Only 20% to 25% of the relapsed patients achieve a prolonged second remission with standard second-line salvage therapy. With high-dose chemotherapy and stem-cell rescue [9,10], this figure could increase to 30% to 60%. However, more aggressive therapies are associated with more toxicity and an accurate assessment of pretreatment prognostic factors is required to select the appropriate regimen. Not all relapses are innocuous, and prevention of relapse still remains an important issue in HD. Given the fact that it is a radiosensitive tumor, it is logical to use RT in an attempt to eradicate any subclinical disease after remission induction with combination CTh. Several randomized trials [11-18] and one meta-analysis [19] have tried to address the use of adjuvant radiation with a view to minimize risk of relapse with conflicting results. In our trial, we sought to evaluate the role of consolidation radiation after CR induction with six cycles of ABVD chemotherapy. The primary end points were event-free survival (EFS) and overall survival (OS). The primary objective was to detect a 10% difference in the EFS and OS with consolidation radiation versus observation in complete responders assuming a 75% 5-year EFS and 85% 5-year OS in the observation arm (α error = .05; β error = .20).

Secondary end points were assessment of toxicity of the two arms and correlation of EFS and OS with known prognostic factors.

PATIENTS AND METHODS

Eligibility

Patients included in the trial were required to have histologically proven Hodgkin's disease, Ann Arbor stages I to IV, age less than 70 years, WHO performance score 0 to 3, normal hematologic and biochemical profile, no prior history of malignancy or its treatment, and no form of immunosuppression (eg, HIV infection). Only patients in CR clinicoradiologically following six cycles of ABVD were randomly assigned using computer software for randomization. Informed consent was taken from all patients enrolled on the study. Patients with uncontrolled infections, for example, tuberculosis, unstable cardiac disease requiring treatment, pregnancy, and lactation, were also not included in the study.

Pretreatment and Follow-Up Evaluations

The initial staging work-up included a detailed physical examination, complete blood count along with a manual differential count, blood biochemistry, lactate dehydrogenase, bone marrow aspiration and biopsy, chest x-ray, and an ultrasonography of the abdomen and pelvis. A computed tomography scan of the abdomen and pelvis was asked for only if the ultrasongraphy was abnormal. The performance status was rated on the WHO scale. Disease was staged using the Ann Arbor Staging System. Bulky disease was defined as any lymph nodal mass more than 7 cm in greatest dimension or a Mediastinal Tumor Ratio greater than 0.35 as seen on a standard postero-anterior chest x-ray for the mediastinum. Institutional pathology review was done for all patients by an experienced hematopathologist, and immunophenotyping was performed wherever possible, using a panel of monoclonal antibodies such as CD15, CD30, CD45, epithelial membrane antigen, leucocyte common antigen, CD20, CD3, and CD45Ro. All patients were jointly evaluated by a radiation oncologist and a medical oncologist in the clinic before the start of any therapy, and once again after six cycles of CTh. All sites of disease were carefully mapped and recorded. Eighty-four patients (47%) received CTh alone and 95 patients (53%) received CMT.

Chemotherapy

The ABVD regimen consisted of standard doses of drugs along with routine antiemetic and steroid prophylaxis. The regimen consisted of doxorubicin 25 mg/m^2 intravenously (IV) day 1 and 15, bleomycin 10 mg/m^2 IV day 1 and 15, vinblastine 6 mg/m^2 IV day 1 and 15, and dacarbazine 375 mg/m^2 IV day 1 and 15. Each cycle was repeated every 4 weeks for a total of six such cycles. Patients on CTh were clinically assessed every week for toxicity. A complete blood count was done before every dose of ABVD (ie, every 2 weeks), or earlier if clinically indicated. After six cycles of ABVD, patients were evaluated for response both clinically as well as radiologically. Response was defined as per the WHO response criterion (Table 1) [20]. The complete responders were then randomly assigned to either observation or consolidation radiation.

Radiotherapy

RT was started at least after 3 weeks from end of CTh and preferably within 6 weeks. External beam radiation was delivered with megavoltage equipment—either a telecobalt or a linear accelerator. Radiation was mostly in the form of involved field radiotherapy (IFRT), either clinically planned (neck) or on simulation (mediastinum, para-aortic, and so on) with standard anteroposterior portals. Eighty patients (84%) received IFRT. Ten patients (11%) received radiation with an inverted-Y technique as a result of extensive prechemotherapy infradiaphragmatic disease, whereas four patients (4%) received mantle field radiation for extensive prechemotherapy supradiaphragmatic disease. Only one patient (1%) received total nodal irradiation (TNI). The planned dose of IFRT was 30 Gy with a 10 Gy boost to site of bulky disease. The planned dose for extended field radiotherapy (EFRT) was 25 Gy with a boost of 10 Gy to bulky disease. The planned dose for TNI was 21 Gy. However, the final total dose of radiation was left to the discretion of the treating radiation oncologist. The dose delivered ranged from 20 Gy to 44 Gy at midplane using anterior and posterior portals (median dose of 30 Gy) with a daily fraction size of 1.5 Gy to 1.8 Gy per fraction. During radiotherapy patients were reviewed every week for acute side effects of radiation. After completion of the planned treatment, patients were followed up

Table 1. WHO Response Assessment Criteria

Complete response	Disappearance of all measurable disease
Partial response	50% or more reduction of all measurable disease
Stable disease	< 50% reduction in total tumor size or < 25% increase in size of 1 or more measurable lesion
Progressive disease	25% or more increase in the size of one or more measurable lesion or appearance of new lesions confirmed by biopsy

every 3 months for the first 2 years, followed by every 6 months for the next 2 years, and yearly thereafter.

Statistical Methods

All analyses were performed on an intent-to-treat basis. Patient characteristics and toxicities were compared using the χ^2 tests. Relapse or death from any cause was considered as a failure (event). EFS was calculated from the date of randomization till the date of relapse, death, or last follow-up. OS was calculated from the date of randomization to the date of death or last follow-up. Failure-free interval was defined as interval from date of randomization to relapse or death. EFS and OS were estimated using the Kaplan and Meier method and were compared according to treatment group by the log-rank tests at $P = .05$ significance level. The failure-free interval was compared using the student's *t*-test. Univariate analysis was done to assess for prognostic factors. Multivariate analysis based on Cox proportional hazards regression model was performed to select disease characteristics that contributed significantly to prognosis. Binary disease characteristics were entered into the model: age (<15 *v* ≥ 15 years); sex (male *v* female); stage (early *v* advanced); histology (mixed cellularity *v* others); B symptoms (present *v* absent); bulk of disease (bulky *v* nonbulky); and mediastinal involvement (involved *v* uninvolved). SPSS statistical software version 10.0 (SPSS Inc, Chicago, IL) was used for the analysis.

RESULTS

Of the 251 patients who were started on induction chemotherapy with six cycles of ABVD from 1993 to 1996, a total of 179 patients achieved a CR clinicoradiologically, giving a CR rate of 71%. This cohort of 179 patients constituted the randomized population. The range of follow-up was 2 months to 121 months with a median of 63 months. The age range of the randomized population was 4 to 70 years with a median age of 18 years. Eighty percent of the patients were male (n = 144) with females constituting only 20% (n = 35) of the randomized population. Among the 179 patients achieving a CR, the Ann Arbor Stage wise distribution was: stage I = 56 (31%); stage II = 43 (24%); stage III = 68 (38%); and stage IV = 12 (7%). Eighty-four patients (47%) were randomly assigned to the observation arm (ie, CTh alone), whereas 95 patients (53%) received consolidation radiation (ie, CTh + RT). The known prognostic factors were well-balanced between the two arms (Table 2).

Table 2. Distribution of Patients in the Randomized Arms As per Prognostic Factors

Factor	Chemotherapy Only (n = 84)		CTh + RT (n = 95)	
	No. of Patients	%	No. of Patients	%
Age				
< 15 years	41	49	42	44
≥ 15 years	43	51	53	56
Sex				
Male	69	82	75	79
Female	15	18	20	21
Histology				
LP	8	10	11	12
NS	10	12	14	15
MC	60	71	63	66
Not specified	6	7	7	7
Stage				
I	26	31	30	32
II	18	22	25	26
III	33	39	35	37
IV	7	8	5	5
Non-bulky	74	88	78	82
Bulky disease	10	12	17	18
Mediastinum involved	17	20	33	35
Mediastinum uninvolved	67	80	62	65
No B symptoms	41	49	42	44
B symptoms	43	51	53	56

Abbreviations: CTh, chemotherapy; RT, radiotherapy; LP, lymphocyte predominant; NS, nodular sclerosis; MC, mixed cellularity.

Efficacy

For the entire randomized population, the 8-year EFS and OS were 82% and 95%, respectively. Various prognostic factors such as stage, age, B symptoms, bulk of disease, mediastinal involvement, sex, and histologic subtype were assessed for both the outcome measures. On univariate analysis, advanced stage ($P = .001$) and presence of B symptoms ($P = .04$) were significant predictors of EFS, whereas stage ($P = .01$) was the only factor associated with OS. On multivariate analysis, stage ($P = .02$) was the only predictor of EFS. No factor was associated with an improved OS on multivariate analysis, although stage ($P = .067$) came closest to predicting outcome.

The 8-year EFS of 88% for the consolidation radiation arm was significantly better than 76% in the CTh-only arm ($P = .01$; Fig 1). Subset analysis for EFS was done with the above prognostic factors to identify any subgroup that would benefit more with the addition of radiation (Table 3). The EFS was significantly better in the CTh + RT arm in

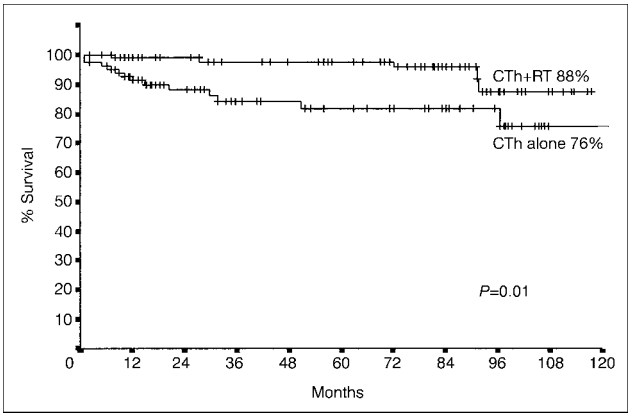

Fig 1. Event-free survival. CTh, chemotherapy; RT, radiotherapy.

Table 3. EFS and OS Correlated to Prognostic Factors in the Two Arms

Factor	8-Year EFS			8-Year OS		
	CTh-Only Arm (%)	CTh + RT Arm (%)	*P*	CTh-Only Arm (%)	CTh + RT Arm (%)	*P*
Stage I/II	94	97	.29	98	100	.26
Stage III/IV	59	78	.03	80	100	.006
Age < 15 years	53	97	.02	89	100	.04
Age ≥ 15 years	83	85	.18	90	100	.02
B symptoms	66	86	.03	85	100	.006
No B symptoms	90	89	.20	94	100	.11
Bulky disease	72	100	.04	90	100	.19
Non-bulky disease	76	84	.05	89	100	.004
Mediastinum involved	76	82	.18	86	100	.05
Mediastinum uninvolved	75	89	.03	90	100	.01

Abbreviations: EFS, event-free survival; OS, overall survival; CTh, chemotherapy; RT, radiotherapy.

patients younger than 15 years, patients with B symptoms, patients with bulky disease, and patients in advanced stages. Histologic subtype and sex did not have an impact on EFS. Patients younger than 15 years of age had an 8-year EFS of 53% in the CTh-only arm as compared with 97% in the CTh + RT arm ($P = .02$). In the presence of B symptoms, the addition of consolidation radiation improved EFS, the 8-year estimates being 66% versus 86% in the CTh-only and CTh + RT arm, respectively ($P = .03$). Patients with bulky disease had a 72% EFS in the CTh-only arm as compared with 100% in the CTh + RT arm ($P = .04$). The outcome in stages III and IV combined was better for consolidation RT, the 8-year EFS being 59% *v* 78% in the CTh-only versus CTh + RT arm ($P = .03$). Surprisingly, patients without involvement of mediastinum also fared better with the addition of radiation, the 8-year EFS being 75% and 89% in the CTh-only and CTh + RT arms, respectively ($P = .03$).

As far as OS is concerned, a significantly better outcome was seen with the addition of consolidation radiation. The 8-year OS was 89% in the CTh-only arm versus 100% in the CTh + RT arm ($P = .002$; Fig 2). Once again, a subset analysis for OS was done for prognostication (Table 3). Survival benefit for consolidation radiation was more pronounced for patients with advanced stage disease, presence of B symptoms, and the younger age group. The 8-year OS for patients with stage III/IV disease was 80% in the CTh-only arm versus 100% for the CTh + RT arm ($P = .006$). In patients with B symptoms, the 8-year OS was 85% in the CTh-only arm as compared with 100% in the CTh + RT arm ($P = .006$). Patients younger than 15 years fared better with the addition of radiation, the 8-year OS being 89% in the CTh-only arm versus 100% in the CTh + RT arm ($P = .04$). Once again, patients without mediastinal involvement had a superior 8-year OS for CTh + RT (100%) versus CTh-only (90%; $P = .01$). Sex and histologic subtype did not impact on OS whether or not consolidation radiation was given. Surprisingly, patients with non-bulky disease showed a significantly better 8-year OS with the addition of RT, whereas patients with bulky disease did not show any such benefit. Patients without bulky disease had a 89% 8-year OS in the CTh-only arm as compared with 100% in the CTh + RT arm ($P = .004$), whereas patients with bulky disease had a 90% OS in the CTh-only arm versus 100% in the CTh + RT arm ($P = .19$). Although the magnitude of benefit was similar in bulky as well as non-bulky disease (around 10%), the smaller numbers of patients in the bulky group could explain the statistically nonsignificant benefit of consolidation radiation.

Patterns of Relapse

The total number of patients relapsing was 16 (9%) in the entire randomized population. Eleven of 84 patients (13%) relapsed in the CTh-only arm as compared with five of 95 patients (5%) in the CTh + RT arm. Of the 11 patients relapsing in the CTh-only arm, six (55%) had a nodal relapse only, whereas four (36%) had a systemic relapse in addition to a nodal failure. Only one patient (9%) had an

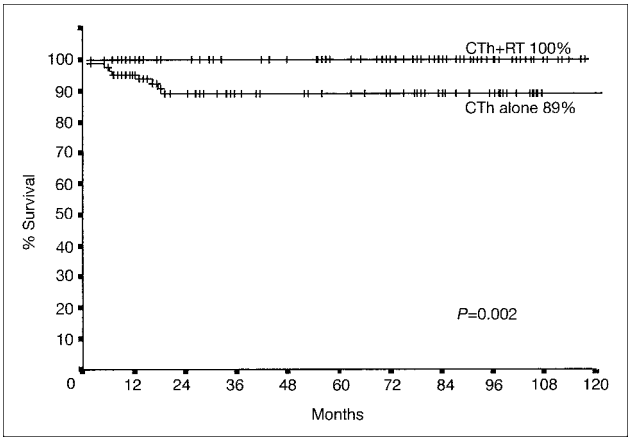

Fig 2. Overall survival. CTh, chemotherapy; RT, radiotherapy.

isolated systemic relapse. In the CTh + RT arm, all five relapses were nodal, none of which was seen in the previously irradiated site. Of the 11 relapses in the CTh-only arm, three patients had successful salvage treatment with further therapy, whereas six patients died with disease. Of these six deaths, five were as a result of disease and one patient died in relapse as a result of cardiotoxicity within 2 months of completion of CTh. The remaining two patients are alive with disease. In the CTh + RT arm, four patients had successful salvage treatment, and one is alive with disease.

In addition to the six deaths, two more toxic deaths were encountered, each as a result of cardiotoxicity and fulminant hepatitis in the CTh-only arm.

Considering all events (relapse or death), the mean and median failure-free intervals were 32 and 17 months, respectively. In the CTh-only arm, these values were 22 and 12 months, which were significantly inferior ($P = .03$) to the 57 and 72 months, respectively, in the CMT arm.

Toxicity

The acute morbidity was similar in both the arms. Twenty-one percent of patients in the CTh-only arm had a grade 2 or worse neutropenia, as compared with 11% in the CTh + RT arm. The incidence of grade 2 or worse peripheral neuropathy was also similar in the two arms at 6% and 5%, respectively. Clinically significant pneumonitis was seen in 2% and 3% patients in the CTh-only and CTh + RT arm, respectively.

DISCUSSION

The peak incidence of HD in India is seen in patients 15 to 20 years of age as compared with the bimodal peak seen in the western world. Mixed cellularity is the most common histologic subtype (55% to 60%) in this part of the world as opposed to nodular sclerosis ($>$ 70%) in the west [21]. These differences may be influencing outcome and could partly explain the variance with the results in most western series.

This is the first large trial showing a survival advantage of consolidation radiation in patients achieving a CR after induction with six cycles of ABVD chemotherapy over observation. The 8-year OS for the CTh-only versus the CTh + RT arm was 89% and 100%, respectively ($P = .002$). This survival advantage was more pronounced for patients with advanced stage disease, with the presence of B symptoms, and in younger patients ($<$ 15 years). This study shows the benefit of consolidation RT in improving the EFS as well. The 8-year EFS of 88% in the CTh + RT arm was significantly better than 76% in the CTh-only arm ($P = .01$). Once again, this advantage was more pronounced in patients with advanced stage disease, bulky disease, presence of B symptoms, and those in the younger age group. The study also shows an improvement in the failure-free interval for the consolidation radiation arm. The duration of remission and stage at relapse are strong prognostic factors [22] for salvage therapy in relapsed HD. The majority of the relapses in the CTh-only arm were early and systemic, whereas in the CTh + RT arm, the relapses were late and localized. This could explain the differences in the salvage rates and ultimate outcome.

Several studies have tried to evaluate the benefit of additional RT following chemotherapy [11-15]. Although a few of these trials have established the role of radiation in improving the relapse-free survival (RFS) or EFS in particular subsets of patients, only one of them could demonstrate a benefit in OS too.

One of the early trials by the Southwest Oncology Group (SWOG 78-08) [11] used six cycles of nitrogen mustard, vincristine, prednisone, bleomycin, Ooxorubicin, and procarbazine as induction chemotherapy. Complete responders (278 patients) were then randomly assigned to 20 Gy IFRT versus no further therapy. The 5-year RFS was 67% and 74% in the CTh-only and CTh + RT arm, respectively ($P > .2$). On subset analysis, patients with bulky disease and nodular sclerosis histology benefited with the addition of consolidation radiation.

Another trial by the National Cancer Institute of Canada [12] was a three-arm trial with a complex design. Eighty-two patients achieving a CR after six cycles of MOPP were randomly assigned to no further therapy versus EFRT (20 to 30 Gy). Preliminary analysis showed no benefit of EFRT in terms of RFS or OS.

The Pediatric Oncology Group [13] randomly assigned 179 children with advanced HD to eight cycles of alternating MOPP-ABVD with or without low-dose TNI or sub-TNI (21 Gy). The actuarial EFS and OS at 5 years for the CMT arm was 80% and 87%, respectively, which was not significantly different from the corresponding values of 79% and 96% in the CTh-only arm (intention-to-treat analysis). An additional analysis of the 161 patients who were in CR after CTh failed to show an advantage for consolidation radiation (5-year EFS of 82% *v* 87%, respectively; $P = .6$). However, since all patients received eight cycles of CTh, it is likely that the majority of them may have incidentally received some sort of consolidation therapy (those in CR after three to six cycles) in the form of additional chemotherapy, obviating the benefit of radiation.

Only one randomized study by the South Eastern Cancer Study Group (SEG 81-328) [14] involving 30 patients has shown a significant benefit of adding IFRT to six cycles of BCNV, cyclophosphamide, vinblastine, prednisone, and procarbazine. The 5 year OS was 100% for the 15 patients randomly assigned to the CMT group, as compared with 67% for the other 15 patients in the CTh-only arm ($P = .05$).

The Children's Cancer Group [15] tested the role of consolidation radiation in the largest and probably best designed trial to date. Of the 829 patients enrolled onto the

study, 501 patients achieved a CR after risk adapted combination chemotherapy and were randomly assigned to low-dose IFRT or no further therapy. The trial had to stop accrual early because of significantly higher number of relapses on the CTh-only arm. The 3-year EFS in the randomized population was 92% and 87% in the IFRT and no RT arm, respectively ($P = .057$, intention-to-treat analysis). Thirty patients switched to alternate treatment after randomization (23 patients refused RT and seven received RT). Thus, on as-treated analysis, the corresponding 3-year EFS estimates were 93% and 85%, respectively ($P = .0024$, statistically highly significant). There were no differences in the 3-year OS, however. The authors concluded that CMT remains the standard of care for children and adolescents with HD. However, this was a preliminary analysis and more mature data could affect outcome in the long run.

Several randomized trials have shown that there is no difference between addition of further chemotherapy or radiotherapy as consolidation treatment after CR with standard chemotherapy [16-18].

A trial by the German Hodgkin's Study Group [16] consisted of 288 patients who underwent induction chemotherapy. Of the 171 patients achieving CR after six cycles of cyclophosphamide, vincristine, procarbazine, and prednisone/ABVD, 50 refused randomization and 21 patients refused any further treatment, leaving only 100 patients eligible for randomization to 20 Gy IFRT versus two more cycles of consolidation CTh with COPP/ABVD. The 5-year RFS and OS were similar in both the arms at 76% and 79%, and 92% and 96%, respectively. However, because of the increased number of relapses in the no treatment group (patients refusing therapy), the authors concluded that some form of consolidation therapy is needed to reduce the risk of relapse in patients achieving CR with six cycles of chemotherapy.

A recent study by the Groupe d'etudes des Lymphomes de l'Audite (GELA H89) [17] comparing further CTh with consolidation RT in patients achieving either CR or good partial response with six cycles of standard chemotherapy in stage III/IV HD did not demonstrate any benefit of RT over further CTh. The 5-year disease-free survival was 74% and 79%, respectively, in the CTh-only arm, as compared with the CTh + RT arm. The 5-year OS was also similar at 85% and 88% in the two arms, respectively. The authors conclude that it is preferable to consolidate the response with the use of two additional cycles of doxorubicin-based standard CTh for advanced HD if CR or $> 75\%$ response is achieved after six cycles.

The most recently published trial by the European Organization for Research and Treatment of Cancer [18] used response adapted induction CTh for advanced stage HD with the MOPP/ABV hybrid regimen. Patients achieving CR after four cycles were given two additional cycles of CTh. Patients in partial remission after four cycles also received two more cycles of the hybrid regimen and were reevaluated for response. Those achieving a CR after six cycles were then given two additional cycles of MOPP/ABV. Complete responders were then randomly assigned to IFRT to a dose of 24 Gy or no further RT. Partial responders, even after six cycles, were given 30 Gy IFRT and patients with progression or no change went off the study. Of the 739 patients enrolled onto the trial, 421 achieved CR, of which 333 were randomly assigned. The 5-year EFS of 79% for the IFRT arm (n = 172 patients) was not significantly different ($P = .35$) from 84% for the no RT arm (n = 161 patients). The 5-year OS of 85% and 91%, respectively, in the two arms was also similar ($P = .07$). This study, however, does not test consolidation radiation in the proper perspective because all patients in CR received consolidation chemotherapy (two additional cycles of CTh) before randomization. Had the authors randomized immediately after CR, the benefit of radiation could have been evident. In the patients achieving partial response after CTh, the addition of radiation was beneficial and their outcome was similar to those achieving a CR after CTh (5-year EFS and OS of 79% and 87%, respectively).

An ongoing study by German Hodgkin's Study Group HD-12 is randomly assigning patients to eight cycles of escalated bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (BEACOPP) or four cycles of escalated BEACOPP plus four cycles of baseline BEACOPP. The patients are then subsequently randomly assigned to radiotherapy for initial bulky and residual disease or no further therapy. The results of this large trial are eagerly awaited.

A pooled analysis [19] of 918 patients from seven trials with additional RT design showed a benefit of RT in the rate of continuous complete remission and the RFS of about 11% at 10 years with a 95% CI of 4% to 18%. A stratified log-rank test was highly significant ($P < .001$). These findings were confirmed on multivariate analysis. The hazard ratio of HD treatment failure was reduced by nearly 35% using additional RT (relative risk, 0.63). The magnitude of this benefit, however, varied substantially within subsets of patients with different prognostic factors. It was most pronounced in patients with mediastinal involvement, less pronounced in patients with mixed cellularity or lymphocyte-depleted histology, and virtually absent in stage IV disease. With respect to OS, the pooled analysis of 1,003 patients from eight trials could not show any benefit of adding RT (stratified log-rank test, $P = .6$).

The same meta-analysis [19] tried to evaluate the role of additional CTh vis-a-vis consolidation radiation. A pooled analysis of 837 patients with parallel design showed no significant difference in the rate of continuous CR and RFS in patients receiving additional RT or further CTh. This was confirmed on multivariate analysis where the relative risk of failure was not reduced by RT as compared with additional CTh. Remarkably, the OS in this pooled analysis

involving 939 patients from eight trials was significantly better in patients receiving chemotherapy alone. Ten years after start of treatment, the OS was 8% better for CTh-only as compared with CMT.

Nevertheless, a closer look at the meta-analysis reveals several flaws which call into question its broad conclusions [23]. Firstly, only six of the 14 trials had ever been published as full manuscripts. Secondly, only 70% of patients accrued in corresponding trials up to that time had been included, leaving a sizeable 30% unaccounted for. Lastly, the trials with additional radiation design were quite heterogeneous in terms of field sizes and doses. A meta-analysis of this sort with such heterogeneity needs to be interpreted cautiously and judiciously [23].

The role of consolidation radiation remains to be defined in the setting of dose intensive chemotherapy. Prospective trials using short course aggressive induction CTh followed by RT in high-risk disease have shown promising results [24,25].

Our study suggests that consolidation radiation helps improve the EFS as well as OS in patients who achieve a CR after six cycles of ABVD, particularly in advanced stages, in the presence of B symptoms and in younger patients. However, this benefit in outcome needs to be weighed against the chances of increased risk of second cancers and cardiopulmonary toxicity. With a view to mitigate these toxicities, future clinical research should focus on the role of low-dose consolidation IFRT using modern radiotherapeutic techniques like three dimensional conformal radiation therapy and intensity modulated radiation therapy, especially in the setting of dose-intensive multi-agent chemotherapy.

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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