

## Combined modality treatment improves tumor control and overall survival in patients with early stage Hodgkin's lymphoma: a systematic review

Christine Herbst,<sup>1</sup> Fared A. Rehan,<sup>1</sup> Corinne Brillant,<sup>1</sup> Julia Bohlius,<sup>2</sup> Nicole Skoetz,<sup>1</sup> Holger Schulz,<sup>1</sup> Ina Monsef,<sup>1</sup> Lena Specht,<sup>3</sup> and Andreas Engert<sup>1</sup>

<sup>1</sup>Department I of Internal Medicine, Cochrane Haematological Malignancies Group (CHMG), University Hospital Cologne, Germany; <sup>2</sup>Institute of Social and Preventive Medicine, University of Bern, Bern, Switzerland, and <sup>3</sup>Department of Oncology and Hematology, Rigshospitalet, University of Copenhagen, Copenhagen, Denmark

### ABSTRACT

Combined modality treatment (CMT) of chemotherapy followed by localized radiotherapy is standard treatment for patients with early stage Hodgkin's lymphoma. However, the role of radiotherapy has been questioned recently and some clinical study groups advocate chemotherapy only for this indication. We thus performed a systematic review with meta-analysis of randomized controlled trials comparing chemotherapy alone with CMT in patients with early stage Hodgkin's lymphoma with respect to response rate, tumor control and overall survival (OS). We searched Medline, EMBASE and the Cochrane Library as well as conference proceedings from January 1980 to February 2009 for randomized controlled trials comparing chemotherapy alone versus the same chemotherapy regimen plus radiotherapy. Progression free survival and similar outcomes were analyzed together as tumor control. Effect measures used were hazard ratios for OS and tumor control as well as relative risks for complete response (CR). Meta-analyses were performed using RevMan5. Five randomized controlled trials involving 1,245 patients were included. The hazard ratio (HR) was 0.41 (95% confidence interval (CI) 0.25 to 0.66) for tumor control and 0.40 (95% CI 0.27 to 0.59) for OS for patients receiving CMT compared to chemotherapy alone. CR rates were similar between treatment groups. In sensitivity analyses another 6 trials were included that did not fulfill the inclusion criteria of our protocol but were considered relevant to the topic. These trials underlined the results of the main analysis. In conclusion, adding radiotherapy to chemotherapy improves tumor control and OS in patients with early stage Hodgkin's lymphoma.

Key words: combined modality treatment, chemotherapy, Hodgkin's lymphoma.

Citation: Herbst C, Rehan FA, Brillant C, Bohlius J, Skoetz N, Schulz H, Monsef I, Specht L, and Engert A. Combined modality treatment improves tumor control and overall survival in patients with early stage Hodgkin's lymphoma: a systematic review. *Haematologica*. 2010;95:494-500. doi:10.3324/haematol.2009.015644

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### Introduction

Hodgkin's lymphoma (HL) is one of the most common malignancies in young adults.<sup>1,2</sup> The cure rate of patients with early stage disease is high when treated with two to six cycles of ABVD (doxorubicin, bleomycin, vinblastine, dacarbazine) chemotherapy followed by involved field radiotherapy.<sup>3,5</sup> While consolidation radiotherapy is part of treatment for patients with early stage Hodgkin's lymphoma in the ESMO clinical recommendations,<sup>6</sup> the NCCN guidelines<sup>7</sup> consider chemotherapy alone an alternative treatment option.

Depending on intensity and dose of treatment, long-term complications such as secondary malignancies,<sup>8</sup> cardiac disease<sup>9</sup> and infertility<sup>10</sup> are common in Hodgkin's survivors. For

patients with early stage disease, the 20-year cumulative secondary malignancy rate is estimated between 4% and 20%.<sup>8,11</sup> Risk factors for secondary malignancies and cardiac disease are the choice and dose of chemotherapy and radiotherapy.<sup>8,11-17</sup> Unfortunately, long-term comparisons of combined modality treatment with chemotherapy alone (CT-alone) are difficult in cohorts of Hodgkin's survivors. Nonetheless, to avoid additional radiation-induced toxicity, chemotherapy-only treatment for patients with early stage HL has been advocated.<sup>18,19</sup> This notion was supported by two clinical trials comparing CMT with chemotherapy alone in which no significant survival disadvantage was observed in patients receiving chemotherapy alone.<sup>20,21</sup> In both trials, 5-year progression-free survival was better in the group receiving consolidation radio-

Funding: the review was funded by the German Ministry for Education and Research (BMBF) under grant number 01KG0815. The agency had no influence on the design, conduct, analysis, writing the paper nor on the decision to submit the paper for publication.

Manuscript received August 14, 2009. Revised version arrived September 17, 2009. Manuscript accepted September 17, 2009.

Correspondence: Andreas Engert, Department I of Internal Medicine, Cochrane Haematological Malignancies Group (CHMG), University Hospital Cologne, Kerperner Strasse 62, 50924 Cologne, Germany. E-mail: a.engert@uni-koeln.de  
The online version of this article has a supplementary appendix.

therapy.

The main objective of this systematic review was to compare chemotherapy alone with identical chemotherapy plus radiotherapy in patients with early stage HL with respect to overall survival, tumor control and complete response rates.

## Design and Methods

### Search methods and literature search

A protocol with a detailed analysis plan was published in the Cochrane Library.<sup>20</sup> We searched the Cochrane Central Register of Controlled Trials, MEDLINE and EMBASE from January 1980 to February 2009. Proceedings of the American Society of Hematology and abstracts of the American Society of Clinical Oncology were hand-searched for the years 1980 to 2008. Proceedings of the International Symposium on Hodgkin Lymphoma were searched from 2004 on. No language restriction was applied.

Randomized controlled trials comparing chemotherapy alone with identical chemotherapy regimens combined with radiotherapy in newly diagnosed HL patients of all ages in clinical stage (CS) I and CS II were included. Trials with less than 80% of patients in CS I or II were excluded according to our review protocol<sup>22</sup> but included in sensitivity analysis. Similarly, trials where the number of cycles varied between treatment arms were only included in sensitivity analyses. Two reviewers screened the abstracts retrieved. Duplicate reports were identified. All included trials were assessed for quality parameters such as randomization, concealment of allocation, masking of patients, care givers and outcome assessors, similarity of baseline patients' characteristics, documentation of dropouts, withdrawals and intention-to-treat analysis. Data on patients' baseline characteristics, chemotherapy regimens, radiation procedures, outcomes, and definitions were extracted independently by two reviewers. Discrepancies were solved through a third reviewer. We contacted authors of the respective publications to obtain missing information.

### Statistical methods

Treatment effect measures for complete remission (CR) were calculated as relative risks. Treatment effect measures for time to event data (OS, tumor control) of each trial were estimated as hazard ratios, using methods described by Tierney and colleagues.<sup>23</sup> Meta-analysis was performed using the fixed effects model. For analyses with unexplained statistical heterogeneity ( $I^2$  statistics value of 50% or more), a random effects model was used. A linear regression test<sup>24</sup> for small trial bias was not performed as the number of included trials was less than ten.<sup>25</sup> Subgroup analysis with respect to different chemotherapy regimens (CVPP, EBVP, ABVD), radiation fields (extended field or involved field), different sequences of chemotherapy and radiotherapy, bulky disease, early favorable or early unfavorable disease were performed. Sensitivity analyses included quality aspects that differed among trials and included intention-to-treat analysis, drop-outs, allocation concealment, length of follow-up and date of recruitment, as well as the effect of single large trials on overall result. In addition, trials that did not fulfill the inclusion criteria of our review protocol, i.e. the number of chemotherapy cycles varied between treatment arms or too many patients in advanced stages, were included in sensitivity analyses. If possible, subgroup information for patients with early stages was used. Tests for interaction between subgroups were performed. Analyses were performed using Review

Manager, version 5. Number needed to treat were calculated for time to event outcomes as described by Altman and colleagues.<sup>26</sup>

### Results of the literature search

We screened 2,742 abstracts and 51 relevant publications were retrieved as full text. Of these, 41 were excluded (Figure 1) and finally five trials<sup>21,27-30</sup> with 1,245 patients from 10 publications were included in the main analysis. All publications except for the EORTC-GELA H9-F trial<sup>29</sup> with three abstract publications<sup>5,29,31</sup> and two presentations<sup>32,33</sup> were full text publications.

Among the excluded trials (according to our review protocol) a number of trials were included in sensitivity analyses *post hoc*, as they yielded relevant information to the underlying clinical question. Three trials (566 patients) included patients of all stages and reported some subgroup information for early stage patients.<sup>34-36</sup> One of these trials examined patients with bulky disease and residual masses after VEBEP chemotherapy (etoposide, epirubicin, bleomycin, cyclophosphamide, prednisone) who were PET negative.<sup>36</sup> One trial included patients in stages I through IIIa.<sup>37</sup> Finally, two trials were identified in which the patients in the chemotherapy alone group received more cycles of chemotherapy than the patients in the chemotherapy plus radiotherapy group.<sup>20,38</sup> Characteristics and main results of these trials are described in the *Online Supplementary Table S1*.

For certain risk factors, such as bulky disease, definitions varied between trials (Table 1). Inclusion criteria regarding risk factors also differed. While three trials in the main analysis included both patients with early favorable and early unfavorable stages,<sup>21,28,30</sup> the EORTC H9-F trial<sup>29</sup> included only patients with early favorable disease. In contrast, the Mexico B2H031 trial<sup>27</sup> had only patients with bulky disease. Similar differences were observed in the trials included only in sensitivity analysis (Table 1 and *Online Supplementary Table S1*).

Most patients included in the main analyses were treated with either ABVD chemotherapy (353/1,245)<sup>21,27</sup> or EBVP (epirubicin, bleomycin, vinblastine, prednisone)<sup>29</sup> (578/1,245). Two older trials used CVPP (cyclophosphamide, vinblastine, procarbazine, prednisone).<sup>28,30</sup> Recruitment ranged from the 1970s<sup>28</sup> to 2004,<sup>29</sup> and

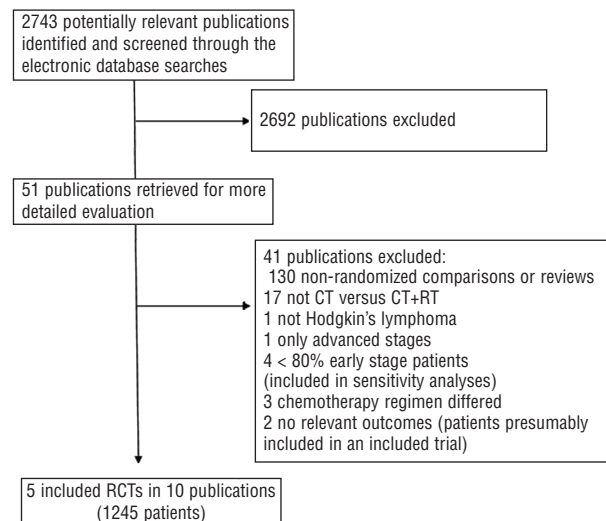


Figure 1. QUORUM diagram.

median follow-up was two to 12 years. Four trials randomized patients at diagnosis, while the EORTC-GELA H9-F trial<sup>29</sup> randomized patients after achieving CR after chemotherapy.

Among the trials included only in sensitivity analyses, chemotherapies used were ABVD,<sup>20,35</sup> COPP/ABV,<sup>34</sup> VEBEP,<sup>36</sup> MOPP (mechlorethamine, vincristine, procarbazine, prednisone)<sup>37</sup> and MOPP/ABVD.<sup>38</sup>

The quality of the trials in the main analysis was acceptable. Randomization procedures were not reported in four of the five trials;<sup>27-30</sup> the randomization procedure was adequate in the MSCKK trial #90-44.<sup>21</sup> An intention-to-treat analysis was performed in two trials.<sup>21,29</sup> Only one trial had more than 10% drop-outs or non-evaluable patients<sup>28</sup> (Table 1). None of the trials

reported blinding of the assessor. The quality of the additional trials for the sensitivity analyses was similar.

**Complete response rate**

Four trials including 653 patients reported the CR rate and were meta-analyzed.<sup>21,27,29,30</sup> The relative risk of reaching CR was 1.07 (95% confidence interval (CI) =0.98 to 1.17). Due to the small number of trials, subgroup and sensitivity analyses were not performed.

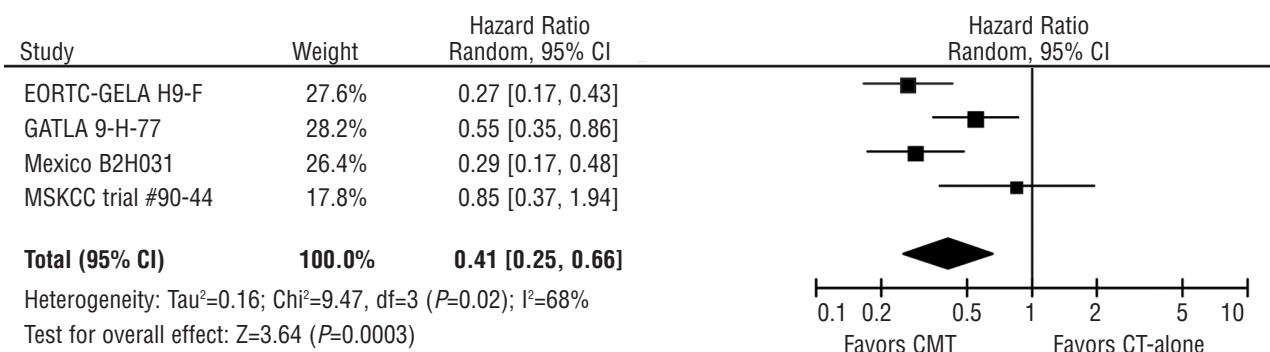
**Tumor control**

In the main analysis, four trials reported endpoints for tumor control, such as event-free survival, time to treatment failure, pro-

**Table 1. Characteristics of included trials.**

Trial	Inclusion criteria	Number of patients	Treatment	Median follow-up in years (range)	ITT-analysis	Not evaluated (%)
Mexico B2H031 <sup>27</sup>	CS I – II	99	6xABVD	11.4 (6.3-16.5)	No	6
	Supra-diaphragmatic disease					
	Bulky disease	102	6xABVD+MF-RT			
CALGB 7751	“poor prognosis”	18	6xCVPP	2 (0 - not reported)	No	32
Interim results <sup>28</sup>	PS I – II	19	6xCVPP+IF-RT			
EORTC-GELA H9-F	CS I – II	130				
Interim results <sup>29</sup>	Supra-diaphragmatic disease					
	All of the favorable features: (age <50 years, ESR <50 mm/h or B symptoms and ESR <30 mm/h, mediastinal-thoracic ratio <0.35)	448	6xEBVP 6xEBVP+36 Gy IF RT or 20 Gy IF-RT	4.3 (1.2-6.8)	Yes	0
GATLA 9-H-77 <sup>30</sup>	CS I – II	142	6xCVPP	4 (not reported)	No	6
	173 patients with favorable and 104 patients with unfavorable characteristics (age >45, sites >2, bulky tumor)	135	6xCVPP+IF-RT			
MSCKK trial #90-44 <sup>21</sup>	CS I – IIIA without bulky disease, 13% with CS IIIA	76	6xABVD	5.6 (0.1-10.4)	Yes (OS)	0 (OS)
#90-44 <sup>21</sup>	~ 30 to 50% unfavorable disease	76	6xABVD + IF-RT or EF-RT		(OS)	9 (CR, tumor control)

\*CS: clinical stage; PS: pathological stage; NR: not reported; CVPP: cyclophosphamide, vinblastine, procarbazine, prednisone; ABVD: adriamycin, bleomycin, vinblastine, dacarbazine; EBVP: epirubicin, bleomycin, vinblastine, prednisone; IF-RT: involved-field radiotherapy; EF-RT: extended-field radiotherapy; MF-RT: mantle-field radiotherapy; SN-RT: subtotal-nodal radiotherapy; CT: chemotherapy; ITT: intention-to-treat; CR: complete response rate; OS: overall survival.



**Figure 2.** Meta-analysis of tumor control among patients with early stage Hodgkin’s lymphoma who received chemotherapy (CT) alone or chemotherapy and radiotherapy (CMT). Solid squares represent effect estimates for the single trials, the size of square represents the weight of individual studies in the meta-analysis. Horizontal lines indicate 95% confidence intervals (CIs). The width of diamonds shows the 95% confidence intervals for the pooled hazard ratios.

gression-free survival, and time to progression. Exact definitions are given in Table 2. The combination of chemotherapy and radiotherapy improved tumor control with a hazard ratio (HR) of 0.41 (95% CI 0.25 to 0.66, random effects model; Figure 2). There was clear statistical heterogeneity between trials ( $I^2=68\%$ ) which may in part be due to the different definitions used. For example, some trials examined progression or treatment failure in all randomized patients, while others examined disease free survival which is restricted to patients who reached CR. A subgroup analysis by the type of tumor control definition was statistically significant ( $P=0.01$ ), indicating that the variation in definitions for tumor control may be responsible for the observed heterogeneity. Other subgroup and sensitivity analyses (see *Design and Methods* section) showed neither statistically significant difference between subgroups nor resulted in a relevant reduction of statistical heterogeneity.

All of the trials that did not meet the strict inclusion criteria of our review protocol had an effect estimate in favor of combined modality treatment.<sup>20,34-38</sup> When including all of these trials into a meta-analysis for tumor control, the HR was 0.38 (95% CI 0.28 to 0.51). When restricting the analysis to the trials that kept the number of cycles the same between the group that received radiotherapy and those that did not<sup>34-37</sup> the HR was 0.39 (95% CI 0.27 to 0.55).

**Overall survival**

All five trials in the main analysis (1,245 patients) reported OS. The addition of radiotherapy significantly improved OS

(HR=0.40; 95% CI 0.27 to 0.59) with small heterogeneity between trials ( $I^2=3\%$ ) (Figure 3). In three trials the hazard ratios were extracted from survival curves or reported dates of deaths<sup>27,29,37</sup> assuming constant censoring.<sup>23</sup> While this assumption is problematic for the EORTC-GELA H9-F trial<sup>29</sup> because the no-radiation arm was closed early, different estimates of censoring had little effect on the estimated hazard ratio of the trial. Another uncertainty in the hazard ratio calculation arose from a  $P$  value with only one significant digit.<sup>30</sup> The results of the meta-analysis were dominated by the Mexico B2H031 trial,<sup>27</sup> which had a weight of 50.4% (Figure 3). When excluding the Mexico B2H031 trial<sup>27</sup> from the meta-analysis in a sensitivity analysis, the summary hazard ratio remained statistically significant favoring CMT (0.57; 95% CI 0.33 to 0.98,  $I^2=0\%$ ). None of the subgroup analyses showed statistically significant differences between the subgroups examined (type of chemotherapy, early favorable or unfavorable disease, bulky or no bulky disease, type and timing of radiation therapy, quality measures).

The sensitivity analysis that included trials not fulfilling the inclusion criteria of our review protocol<sup>20,34-38</sup> yields a HR of 0.60 (95% CI 0.35 to 1.03),  $I^2=48\%$ . When excluding the trials where the number of cycles varies, the HR was 0.46 (95% CI 0.27 to 0.78),  $I^2=27\%$  with the remaining heterogeneity due to the O'Dwyer trial. The two trials that examined chemotherapy plus radiotherapy versus more chemotherapy reported conflicting results among the two trials.<sup>20,38</sup> The trial by Meyer and colleagues<sup>20</sup> comparing four cycles of ABVD plus subtotal nodal irradiation with six cycles of ABVD had an (estimated) HR of 1.73

Table 2. Definitions of tumor control.

Trial	Definition of tumor control
Mexico B2H031	Contradictory definitions. In the <i>Design and Methods</i> section: "Disease free survival was calculated for CR patients from the beginning of treatment until clinically or radiologically and biopsy proven relapse." In the <i>Results</i> section percentages of disease free survival were calculated based on the full population.
EORTC-GELA H9-F	Definition of disease free survival not reported. Note: all patients are in CR at the time of randomization.
GATLA 9-H-77	Patients who failed to respond were evaluated as relapsed at first month. Patients in CR were evaluated from date of CR to date of first relapse or death.
MSCKK trial #90-44	Time from enrolment until any progression of disease.

CALGB 7751	5.1%	0.63 [0.11, 3.65]
AORTC-GELA H9-F	4.6%	0.27 [0.04, 1.74]
GATLA 9-H-77	30.7%	0.68 [0.33, 1.40]
Mexico B2H031	50.4%	0.29 [0.17, 0.51]
MSKCC trial #90-44	9.2%	0.31 [0.08, 1.14]
<b>Total (95% CI)</b>	<b>100.0%</b>	<b>0.40 [0.27, 0.59]</b>
Heterogeneity: Tau <sup>2</sup> =0.00; Chi <sup>2</sup> =3.89, df=4 ( $P=0.42$ ); $I^2=0\%$		
Test for overall effect: Z=4.57 ( $P<0.00001$ )		

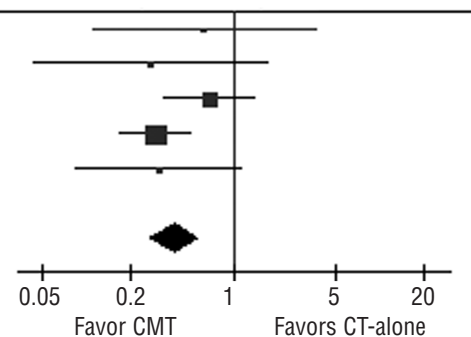


Figure 3. Meta-analysis of OS among patients with early stage Hodgkin's lymphoma, who received chemotherapy (CT) alone or chemotherapy and radiotherapy (CMT). Solid squares represent effect estimates for the single trials, the size of square represents the weight of individual studies in the meta-analysis. Horizontal lines indicate 95% confidence intervals (CIs). The width of diamonds shows the 95% confidence intervals for the pooled hazard ratios.



(95% CI 0.62 to 4.86), while the Kung trial<sup>38</sup> comparing four cycles of MOPP/ABVD + IF-RT with six cycles of MOPP/ABVD had an estimated HR of 0.86 (95% CI 0.29 to 2.54).

## Discussion

The following findings emerge from this meta-analysis: (i) In patients with early stage HL, there is no evidence that the complete response rate is different in patients receiving chemotherapy alone compared to those receiving CMT; (ii) tumor control is better in patients receiving CMT compared to chemotherapy-alone (HR 0.41; 95% CI 0.25 to 0.66). The median observation in this meta-analysis is approximately five years, and (iii) adding radiotherapy to chemotherapy improves the OS in this group of patients (HR 0.40; 95% CI 0.27 to 0.59).

To our knowledge, this is the first comprehensive review focusing on patients with early stage Hodgkin's lymphoma that compares chemotherapy alone with CMT consisting of chemotherapy plus additional radiotherapy. The main analysis according to the strict inclusion criteria of our review protocol included five randomized controlled trials with 1,245 patients of both early favorable and early unfavorable Hodgkin's lymphoma. The literature search revealed a number of trials with more than 20% of patients in advanced stages or with fewer cycles of chemotherapy in patients receiving radiotherapy. Because these trials were considered to be relevant to the underlying clinical question, these trials were included in sensitivity analyses, where subgroup information of early stage patients was used if available. These sensitivity analyses underlined the results of the main analyses.

The effect estimate for tumor control is high with an HR of 0.41 (0.25 to 0.66). This corresponds to 6 patients (95% CI 5 to 11) requiring treatment with CMT to prevent one additional relapse, progression or death in the chemotherapy alone group, assuming a 5-year tumor control of 70% in the CT-alone group. Unfortunately, the meta-analysis had substantial heterogeneity, which may in part be due to the variety of definitions used by the individual trials. However, all trials (even those included only in sensitivity analyses) had an effect estimate favoring CMT. This is not surprising given that radiotherapy is a very effective treatment for Hodgkin's lymphoma.

The hazard ratio for overall survival (0.40; 95% CI 0.27 to 0.59) is similar to that of tumor control. With an assumed OS of 85% at five years as observed in three of the trials included here,<sup>21,27,30</sup> approximately 11 patients (95% CI 9 to 18) would require treatment with CMT for one additional patient to survive during the first five years. With better survival (97.5%) as reported in the EORTC-GELA H9-F trial,<sup>29</sup> approximately 55 patients (95% CI 46 to 86) would be needed. These potentially surprising results were robust when excluding the Mexico B2H031 trial,<sup>27</sup> which had a high weight in the analysis due to the long follow-up and relatively high mortality. The only concern in the overall survival analyses stem from hazard ratios estimated from survival curves<sup>27-29</sup> and the use of preliminary data from the EORTC-GELA H9-F trial.<sup>29</sup> However, these are minor points, as the direction of the effect is clear and only the magnitude may vary slightly. Again, the trials included in the sensitivity analyses<sup>20,34-38</sup>

also supported the results in favor of CMT. Three trials had effect estimates favoring CMT, two trials observed no deaths<sup>34,36</sup> and only one trial<sup>20</sup> observed a slight effect favoring chemotherapy alone, which was not statistically significant. The trial by Meyer and colleagues<sup>20</sup> replaced two to four cycles of ABVD chemotherapy with subtotal nodal irradiation. It is, therefore, not directly comparable to the trials which used the same number of cycles in both arms of the trials, nor to trials examining smaller radiation fields. The other trial with a similar trial design had an effect favoring CMT.<sup>38</sup>

In the present analyses we found no evidence for interaction of treatment options or patients' characteristics. Two of the five trials of the main analysis employed ABVD, and the summary hazard ratios in the subgroup analyses by chemotherapy regimen were very similar. No difference in tumor control or OS was observed between trials that examined the addition of involved field or extended field radiotherapy. This is in line with the finding that extended field radiotherapy had little or no advantage over involved field radiotherapy in Hodgkin's patients when used alone or after effective chemotherapy.<sup>3,8</sup> In addition, subgroup analyses gave no hint that the hazard ratios may differ depending on the proportion of patients with early favorable or early unfavorable disease or the inclusion or exclusion of patients with bulky disease. However, due to the small number of trials included, reliable information from subgroup analyses is unlikely.

Long-term adverse effects such as secondary malignancies or cardiac disease are important in HL patients and can occur later than the reported observation times of the discussed trials. Radiotherapy can induce secondary malignancies while the exact increase in the risk is unclear. The absolute risk difference between chemotherapy alone and chemotherapy plus radiotherapy in a recent individual patient data meta-analysis was about 1% in early stage patients at 15 years.<sup>8</sup> Cohorts of Hodgkin's patients of any stage suggest that this difference is much higher.<sup>8,11-17,39</sup> However, patients who relapse have a more pronounced risk of secondary malignancies according to a cohort study by Aleman and colleagues.<sup>16</sup> Therefore, the addition of radiotherapy which reduces the number of patients with relapse (who require more aggressive therapy) may contribute to a smaller overall risk difference than suggested by the cohorts who do not distinguish between relapsed and non-relapsed patients when evaluating the risk of radiotherapy.

Cardiac disease is associated with mediastinal radiation and with the cumulative dose of chemotherapy, in particular doxorubicin. Radiation fields have been reduced substantially from extended field radiotherapy to involved field or even the involved node radiotherapy used today. Replacing consolidation radiotherapy with chemotherapy, as evaluated by Meyer and colleagues,<sup>20</sup> increases the dose of doxorubicin and may thus increase long-term cardiac toxicity. Importantly, there was also a detrimental effect on progression-free survival in the group of patients receiving chemotherapy only.

Identifying patients at low risk of relapse might be considered an alternative to consolidation radiotherapy for all patients. Currently, however, no reliable evidence for such a strategy exists. In this meta-analysis, the presence of

conventional complete response after chemotherapy such as ABVD<sup>21,27</sup> or EBVP<sup>29</sup> does not seem to accurately identify a group of patients who do not benefit from radiotherapy with regard to tumor control. PET may be an alternative. However, in patients with bulky early stage disease having residual masses in CT that are PET negative, the rate of relapse after ABVD chemotherapy was much higher in patients who did not receive consolidation radiotherapy.<sup>36</sup> Two other trials are planned or underway in patients with early stage Hodgkin's lymphoma (*clinicaltrials.gov identifiers: NCT00736320, NCT00433433*).

In conclusion, additional radiotherapy prevents relapse and improves 5-year overall survival in patients with early stage Hodgkin's lymphoma. Combined modality treatment (ABVD and consolidation radiotherapy) is standard of care in this patient group.

## Authorship and disclosures

CH is the principle investigator and takes primary responsibility for the paper. FR, JB, CB, HS, LS and AE wrote the protocol. CH and FR carried out the literature search. IM designed the search strategy. Data extraction was performed by CH, FR, CB and NS. The analysis was performed by CH, CB and FR. CH wrote the paper. All authors commented on and approved the final version of the manuscript.

The authors declare that there are no conflicts of interests.

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