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ORIGINAL PAPER

Relapse patterns in early-PET negative, limited-stage Hodgkin lymphoma (HL) after ABVD with or without radiotherapy–a joint analysis of EORTC/LYSA/FIL H10 and NCRI RAPID trials

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Summary

In the H10 and RAPID randomised trials, chemotherapy+radiotherapy (combined modalities treatment, CMT) was compared with chemotherapy (C) in limited-stage Hodgkin lymphoma (HL), with negative early positron emission tomography (ePET-neg). We analysed patterns of relapses in the H10 trial, validated findings in the RAPID trial and performed a combined analysis stratified by trial. The impact of radiotherapy (RT) on risk of relapse was studied using adjusted Cox models, with time-varying effects. In H10, 1,059 ePETneg patients were included (465 European Organisation for Research and Treatment of Cancer (EORTC) favourable [F], 594 unfavourable [U]). Among the F patients, 2/227 (1%) relapsed after CMT, 30/238 (13%) after C: of these relapses, 21/30 (70%) occurred in less than 2 years and 25/30 (83%) affected originally involved areas. Among the U group, 16/292 (5%) relapsed after CMT: 8/16 (50%) in less than 2 years, 11/16 (69%) in originally involved areas. After C 30/302 (10%) relapsed: 27/30 (90%) in less than 2 years, and 26/30 (87%) in originally involved areas. Similar results were observed in 419 ePETneg RAPID patients (241 F, 128 U, 50 unclassified): among F patients, 6/118 (5%) relapsed after CMT; 13/123 (11%) after C: 11/13 (85%) in less than 2 years and 11/13 (85%) affecting originally involved areas. In U patients, 3/65 (5%) relapsed after CMT and 5/63 (8%) after C. In both trials, omitting RT in ePETneg HL resulted in more early relapses,

mainly affecting originally involved areas. RT significantly reduced risk of early relapses in the combined stratified analysis.

KEYWORDS
chemotherapy, early PET, Hodgkin lymphoma, radiotherapy, relapse

INTRODUCTION

Rates of long-term cure for limited-stage classic Hodgkin lymphoma (HL) currently exceed 90%, with the use of multiagent chemotherapy followed by radiotherapy (combined modalities treatment, [CMT]),[1–3] albeit at the cost of long-term side effects, such as second malignancies and cardiovascular events due to radiotherapy (RT).[4–6] Optimised baseline prognostic factors and early predictors of relapse would be of great clinical importance for balancing early cure rates with the risk of long-term sequelae.

Assessment with early positron emission tomography (ePET) has been shown to be an important predictor of outcomes in both limited and advanced stage HL[7–11]and response-adapted treatments have been the focus of several trials.[12–16]

The randomised-controlled European Organisation for Research and Treatment of Cancer Lymphoma Study Association, and Fondazione Italiana Linfomi (EORTC-LYSA-FIL) H10 and National Cancer Research Institute (NCRI) RAPID trials were designed to establish whether RT could be safely omitted in newly diagnosed, limited-stage HL patients who were early PET-negative (ePETneg) after two (H10) or three (RAPID) cycles of adriamycin, bleomycin, vinblastine and dacarbazine (ABVD).[17,18] Both studies could not demonstrate the non-inferiority of a chemotherapy-only (C) approach. Relapses occurred more frequently in patients treated with C, even when ePET was negative.

The aim of this project was to explore the relapses in ePETneg patients, describing their timing and sites and impact of baseline clinical factors on the risk of relapse. Such information could help tailor the follow-up of patients treated for limited-stage HL and identify those who are at higher risk of relapse, despite being ePETneg. We first conducted the analysis in the H10 cohort, then we sought to validate our findings in the comparable and independent RAPID dataset. Lastly, we performed a combined analysis stratifying by trial.

PATIENTS AND METHODS

Eligibility criteria

The EORTC-LYSA-FIL 20051 H10 trial included patients aged 15–70 with untreated stage I/II HL. Patients were stratified as favourable (F) and unfavourable (U), according to EORTC criteria (U patients had at least one of the following criteria: age ≥50 years, >3 nodal areas or mediastinal-thoracic (MT) ratio ≥0.35, no B symptoms and erythrocyte sedimentation rate [ESR] of ≥50 or B symptoms and ESR of ≥30. F was defined as not fitting the U criteria).

The NCRI RAPID trial enrolled patients aged 16–75 with untreated stage I/IIA HL. Patients with B-symptoms and/or mediastinal bulk (defined as maximum mediastinal diameter ≥33%) were excluded.

Treatment

In H10, patients were randomised upfront to standard or experimental arms. Early PET was performed after two cycles of ABVD. Standard CMT consisted of three cycles (F) or four cycles (U) of ABVD and involved-node RT, irrespective of the ePET result. In the experimental arm, ePETneg patients after two cycles of ABVD received chemotherapy (C) with two (F) or four (U) further cycles of ABVD.

In the RAPID trial, all patients received three cycles of ABVD, followed by ePET. Patients with ePETneg were randomised to 30-Gy involved-field RT or no further treatment. Figure 1 shows the treatment schema in the two trials.

Early PET scans

In the H10 trial, ePET scans were scored according to International Harmonization Project (IHP) criteria (the standard at the start of the trial): lesions of 2 cm or less in diameter were considered positive if uptake was higher than the mediastinal blood pool; lesions of less than 2 cm were considered positive if uptake was higher than the surrounding background.[19]

The RAPID trial used the Deauville 5-point scale and a score of 1 (no uptake) or 2 (uptake ≤ mediastinal blood pool) was considered negative; a score of 3–5 was considered positive.[20]

Statistical analysis

The analysis is mainly descriptive. We first investigated the pattern of relapses in the H10 trial. Time to relapse was defined as the interval between randomisation and relapse. Patients who died without evidence of relapse were censored at the time of death but were not treated as competing risk events. Early relapses are generally defined as occurring within either 1 or 2 years after completion of treatment; we used a cut-off of 2 years from randomisation. Site of relapse

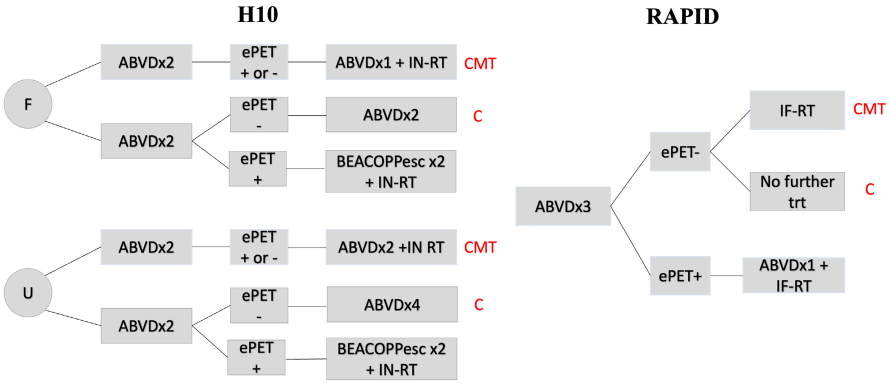


FIGURE 1 Trial schema for H10 (left) and RAPID (right). Left: in the H10 trial, patients with stage I and II classic Hodgkin Lymphoma were stratified as favourable (F) and unfavourable (U), according to the EORTC criteria (age ≥50, erythrocyte sedimentation rate [ESR] ≥30 with B symptoms, ESR ≥50 without B symptoms, >3 nodal areas involved, mediastinal-thoracic (MT) ratio ≥0.35) and randomised upfront between a standard combined modality treatment (CMT), irrespective of early positron emission tomography (ePET) results versus an experimental approach where radio therapy (RT) was omitted when ePET was negative (C). Right: in the RAPID trial, only patients with stage IA and IIA disease were eligible. All patients received three cycles of doxorubicin, bleomycin, vinblastine, dacarbazine (ABVD), followed by ePET. If ePET was negative, patients were randomised between the addition of involved-field radiotherapy (IF-RT), (CMT) and no further treatment (C). BEACOPPesc, bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisolone; IN-RT, involved-node radiotherapy. Of note: For both trials, only data on patients who achieved ePET negativity is presented.

was defined as affecting "originally involved areas", irradiated or not, "originally uninvolved areas" or "originally involved and originally uninvolved areas". Data are presented in frequency tables.

One multivariable Cox model adjusted for baseline characteristics was used to estimate the hazard ratio (HR) of RT versus no RT, its 95% confidence interval (CI) and *p*-value. In the H10 trial, baseline characteristics were age, sex, stage, histology, B-symptoms, number of involved areas, ESR and mediastinal bulk. The proportional hazard (PH) assumption was checked and the hazard was plotted over time to understand any potential time-dependency[21](Figure S1). As there was evidence of non-PH for the treatment effect, one model with time-varying HR for treatment effect (<2 years vs. ≥2 years) and adjusted for the same baseline characteristics was used.

To externally validate findings from the H10 trial, we repeated the analysis in the RAPID cohort. Patients were assigned retrospectively to F or U prognostic groups, according to the EORTC criteria. As the RAPID cohort did not include patients with bulk and/or B symptoms, the number of U patients was small, and so were relapses. This prevented a reliable comparison with the H10 U counterparts. Moreover, because of differences in inclusion criteria and smaller numbers, the Cox model in the RAPID trial was only adjusted for age, sex, histology and stage.

Finally, as the results from the two trials showed similar effects of RT on the time to relapse, data were combined in an analysis stratified by trial. In addition to adjusting for age, sex and stage, this Cox model was stratified by trial to account for differences between the two studies.

Additional unplanned analyses to investigate the potential predictive value of the baseline characteristics were conducted, although no formal analysis of interaction was possible because of the lack of statistical power. These exploratory descriptive analyses were conducted by displaying Kaplan–Meier curves of progression-free rates (PFR) by RT and each level of the baseline characteristics. Rates at 5 years were estimated with corresponding 95% CIs.

All statistical tests were conducted at the two-sided 0.05 significance level. All analyses were performed with SAS software, version 9.4 (SAS Institute).

RESULTS

Timing of relapses

Details of early and late relapses and PFR curves are detailed in Table 1 and Figure 2.

In the H10 trial, 1,059 ePETneg patients were included. With a median follow up of 5.1 years, calculated using the reverse Kaplan–Meier curve of overall survival, 78/1059 (7%) patients relapsed: 18/519 (3%) relapsed after CMT and 60/540 (11%) after C. Among the 465F patients, 2/227 (1%) relapsed after CMT, one after less than 2 years; 30/238 (13%) relapsed after C, of which 21/30 (70%) within 2 years. The 5-year PFR was 99% (95% CI 96%–100%) after CMT and 88% (95% CI 83%–91%) after C. Among the 594U patients, 16/292 (5%) relapsed after CMT, 8 (50%) in less than 2 years; 30/302 patients (10%) relapsed after C, 27/30 (90%) within 2 years. The 5-year PFRs were 94% (95% CI 90%–96%) for CMT and 90% (95% CI 86%–93%) for C.

In the RAPID trial, 419 patients were ePETneg. With a median follow up of 5.2 years, 30/419 (7%) relapsed: 9/208 (4%) after CMT and 21/211 (10%) after C. Fifty/419 (12%) patients could not be assigned to F or U, mainly due to lack of ESR values. Among the 241 F patients, 6/118 (5%) relapsed after CMT, 13/123 (11%) after C; of these relapses, 11/13 (85%) occurred within 2 years in C, and 2/6 (33%) in CMT. The 5-year PFR was 94% (95% CI 90%–96%) after CMT and

TABLE 1 Timings and sites of relapses in H10 and RAPID

	H10 trial				RAPID trial			
	Favourable		Unfavourable		Favourable		Unfavourable	
	CMT	C	CMT	C	CMT	C	CMT	C
Number of patients	227	238	292	302	118	123	65	63
Relapse/progression of patients *n*, (%)	2 (1%)	30 (13)	16 (5)	30 (10)	6 (5%)	13 (11)	3 (5)	5 (8)
Timing of relapses *n* (%)								
<2 years	1 (50)	21 (70)	8 (50)	27 (90)	2 (33)	11 (85)	1 (33)	3 (60)
Hazard rate- time unit = year (95% CI)	0.0023 (0.0000–0.0067)	0.0385 (0.0202–0.0567)	0.0145 (0.0045–0.0246)	0.0476 (0.0293–0.0659)	0.0087 (0.0000–0.0207)	0.0482 (0.0198–0.0767)	0.0081 (0–0.0241)	0.0254 (0–0.0542)
≥2 years, *n* (%)	1 (50)	9 (30)	8 (50)	3 (10)	4 (67)	2 (15)	2 (67)	2 (40)
Hazard rate – time unit = year (95% CI)	0.0012 (0.0000–0.0034)	0.0095 (0.0029–0.0160)	0.0075 (0.0023–0.0126)	0.0029 (0.0000–0.0062)	0.0089 (0.0002–0.0176)	0.0048 (0.0000–0.0114)	0.0086 (0–0.0206)	0.0091 (0–0.0217)
Site of relapses, *n* (%)								
Originally involved, *n* (%)	0	22 (73)	5 (31)	20 (67)	1 (17)	6 (46)	1 (33)	3 (60)
Originally uninvolved, *n* (%)	1 (50)	5 (17)	4 (25)	4 (13)	2 (33)	2 (15)	2 (67)	1 (20)
Originally involved + originally uninvolved, *n* (%)	1 (50)	3 (10)	6 (38)	6 (20)	3 (50)	5 (38)	0	1 (20)
Unknown, *n* (%)	0	0	1 (6)	0	0	0	0	0

Abbreviations: C, Chemotherapy; CMT, Combined modalities.

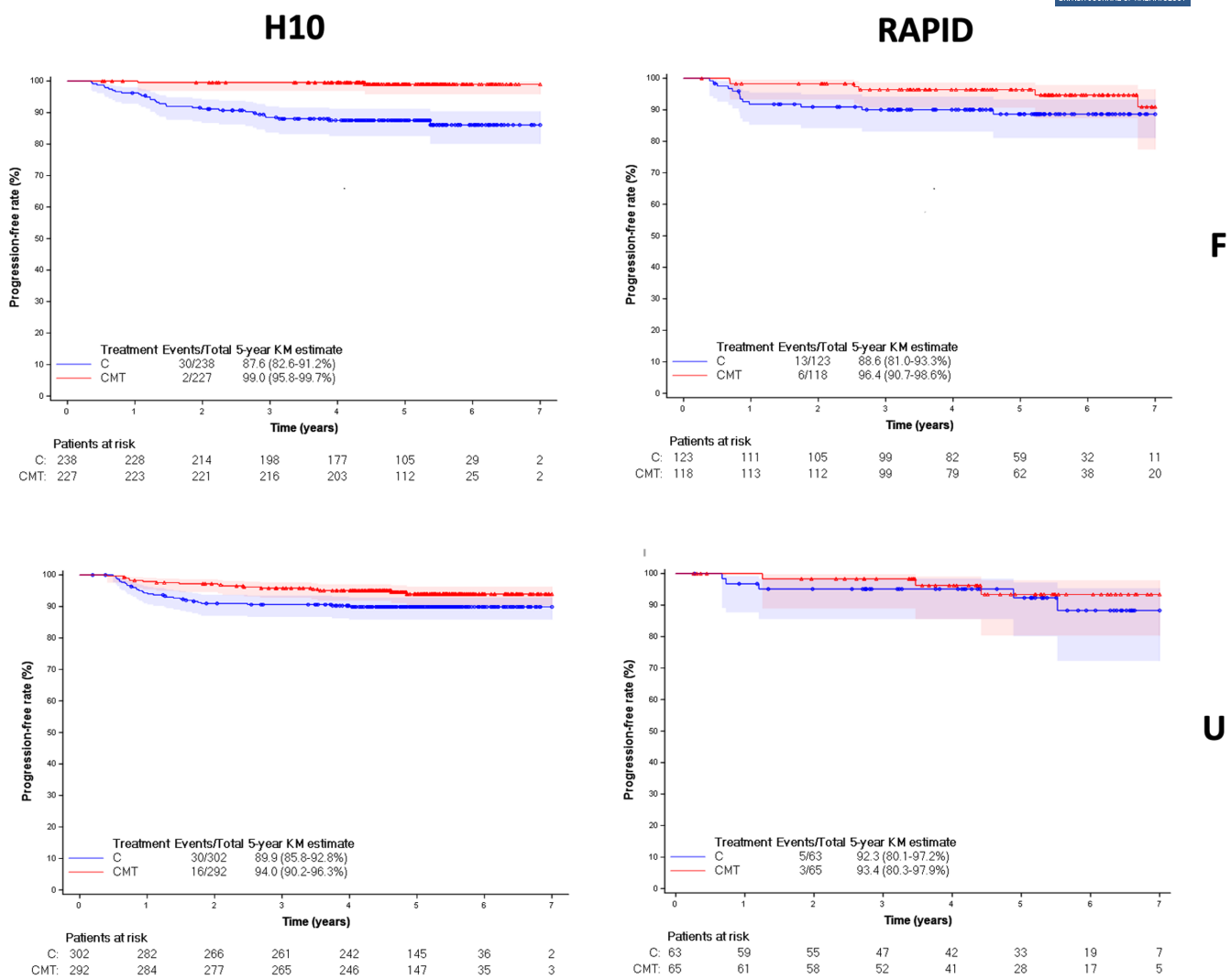


FIGURE 2 Progression-free survival rate and its 5-year estimate in the H10 and RAPID trials. Blue line, patients treated with chemotherapy; red line, patients treated with combined modalities treatment. Top row: (left) H10 F, right RAPID F; Bottom row: left H10 U, right RAPID U (right).

90% (95% CI 86%–93%) after C. Only 128 patients were categorised as U in the RAPID trial: 3/65 (5%) patients relapsed after CMT and 5/63 (8%) after C, with a 5-year PFR of 93% (95% CI 80%–98%) and 92% (95% CI 80%–97%), respectively.

Sites of relapses

Sites of relapses are detailed in Table 1.

In the H10 trial, after CMT, in F patients there were no relapses restricted to originally involved areas, one relapse affecting originally involved and originally uninvolved areas and one affecting originally uninvolved areas only. In U patients, 11/16 relapses (69%) affected originally involved areas, of which 5/16 (31%) were confined to originally involved areas.

Relapses after C mostly affected originally involved areas both in F and U patients: 25/30 (83%) and 26/30 (87%), respectively. Relapses were confined to originally involved areas in 22/30 (73%) F patients and 20/30 (67%) U patients, while 3/30 relapses (10%) in F and 6/30 relapses (20%) in U patients affected originally involved as well as originally uninvolved areas.

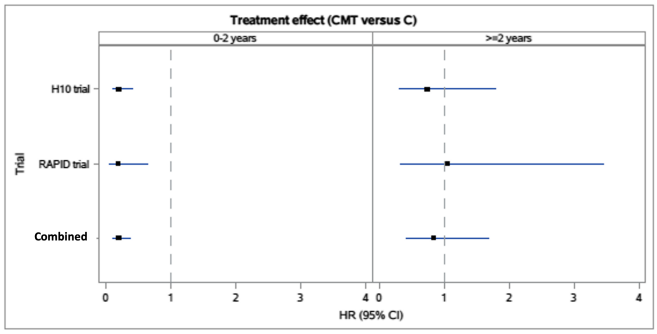
In RAPID F patients, after CMT there were 4/6 (67%) relapses affecting originally involved areas, one of which was confined to originally involved areas.

After C, 11/13 (85%) relapses affected originally involved areas, six of which were confined to originally involved areas.

Effect of RT and baseline characteristics on timing and risk of relapse

Results are summarised in Figure 3 and Table 2.

In the H10 trial, the Cox proportional hazard models adjusted for baseline characteristics included 1,023 ePETneg



		H10 trial		RAPID trial		Combined analysis	
Parameter	Level	Hazard ratio (95% CI)		Hazard ratio (95% CI)		Hazard ratio (95% CI)	
		<2 years	≥2 years	<2 years	≥2 years	<2 years	≥2 years
Treatment	C	1	1	1	1	1	1
	CMT	0.21 (0.10-0.43)	0.76 (0.32-1.84)	0.19 (0.06-0.65)	1.07 (0.32-3.53)	0.20 (0.11-0.37)	0.84 (0.41-1.69)

FIGURE 3 Effect of radiotherapy (combined modalities treatment versus [CMT] versus chemotherapy [C]) on risk of relapse in H10 and RAPID patients and in the combined analysis.

TABLE 2 Effect of baseline characteristics on risk of relapse

		H10 trial		RAPID trial		Combined analysis	
Parameter	Level	Hazard ratio (95% CI)	*p*-value	Hazard ratio (95% CI)	*p*-value	Hazard ratio (95% CI)	*p*-value
Sex	Male	1	<0.001	1	0.378	1	<0.001
	Female	0.42 (0.25–0.69)		0.72 (0.35–1.50)		0.49 (0.33–0.74)	
Age	≤50 years	1	0.900	1	0.600	1	0.639
	>50 years	0.95 (0.42–2.14)		0.77 (0.29–2.05)		0.86 (0.46–1.60)	
Stage	Stage I	1	0.025	1	0.596	1	0.029
	Stage II	2.37 (1.11–5.06)		1.24 (0.56–2.79)		1.78 (1.06–2.98)	
Histology	Nod Scler/Lym Rich Class	1	0.029	1	0.637	–	–
	Mix Cell/Lym Depl	2.01 (1.08–3.75)		–		–	–
	other	–		1.21 (0.55–2.64)		–	–
B-symptoms	No	1	0.352	–	–	–	–
	Yes	1.29 (0.75–2.21)		–	–	–	–
Bulky mediastinum	No	1	0.437	–	–	–	–
	Yes	1.24 (0.72–2.13)		–	–	–	–
Number of involved areas	≤3	1	0.470	–	–	–	–
	>3	1.27 (0.67–2.41)		–	–	–	–
ESR	<30	1	0.229	–	–	–	–
	[30–50]	1.68 (0.90–3.13)		–	–	–	–
	≥50	1.50 (0.81–2.76)		–	–	–	–

Abbreviation: ESR, erythrocyte sedimentation rate.

patients (after excluding 27 patients with unclassifiable HL subtype, five incorrectly enrolled with stage III/V, two with missing values for mediastinal size and two patients with missing ESR values) with a total of 71 events observed. The adjusted risk of relapse was significantly lower in CMT than in C patients during the first 2 years (adjusted HR = 0·21, 95% CI 0·10–0·43, $p < 0·001$), but not afterwards (adjusted HR = 0·76, 95% CI 0·32–1·84, $p = 0·545$).

In the H10 trial, the following were independent prognostic factors: sex (HR [female v. male] = 0·42, 95% CI 0·25–0·69, $p < 0·001$); Ann Arbor stage (HR [stage II vs. I] = 2·37, 95% CI 1·11–5·06, p = 0·025) and histology (HR [mixed cellularity or lymphocyte depleted versus nodular sclerosis or lymphocyte rich] = 2·01, 95% CI 1·08–3·75, $p = 0·029$). The presence of a bulky mediastinal mass or B symptoms, age, number of nodal areas and ESR did not

show a significant prognostic effect on the risk of relapse in the multivariate analysis.

In the RAPID trial, all 419 patients were included in the multivariate model, with 30 events observed. Results in this dataset externally validated the findings of the association with RT from the H10 trial: the effect of RT was statistically significant and of similar magnitude during the first 2 years (adjusted HR = 0·19, 95% CI 0·06–0·65, p = 0·008); after 2 years, the observed adjusted HR was close to 1 (adjusted HR = 1·07, 95% CI 0·32–3·53, p = 0·914).

In the RAPID trial, no strong evidence for prognostic baseline factors was observed. The effects for sex (HR (female versus male) = 0·72, 95% CI 0·35–1·50, p = 0·378) and stage (HR (stage II vs. I) = 1·24, 95% CI 0·56–2·79, p = 0·596) were in the same direction as the H10 trial, but due to the low number of events, the CIs were wide.

As the effect of RT was similar in both studies, data were combined in an adjusted Cox model stratified by trial. In the combined dataset, the observed HR for relapses in the CMT cohort compared to C was 0.20 (95% CI 0.11–0.37, $p < 0.001$) in the first 2 years, and 0.84 (95% CI 0.41–1.69, p = 0.618) after 2 years. As expected, the prognostic effect of sex and stage remained statistically significant in the combined stratified analyses as the results were mainly driven by H10.

Exploratory predictive analysis for differential treatment effects of baseline characteristics on the risk of relapse

In this additional exploratory part of the project, the prognostic significance of the variables RT and each level of the baseline characteristics were analysed using the Kaplan–Meier method. The PFR curves are shown in Figure S2.

In the H10 trial, Kaplan–Meier curves suggest that age, sex and the number of nodal areas involved may have an influence on treatment effect. Males seem to benefit more from RT (5-year PFR 95% in CMT vs. 84% in C) than females (5-year PFR 97% in CMT vs. 93% in C). Patients over the age of 50 (5-year PFR 95% in CMT vs. 94% in C) seem to benefit less from RT, compared to younger patients (5-year PFR 96% in CMT vs. 88% in C). Finally, patients with three or less nodal areas involved (5-year PFR 97% in CMT vs. 89% in C) appear to benefit from RT, while patients with more than three do not (5-year PFR 87% in CMT vs. 88% in C).

In the RAPID trial, because of smaller patient numbers and fewer events, it is even more difficult to draw reliable conclusions about the predictive value of the baseline characteristics. Nonetheless, as in H10, male patients and younger patients seem to benefit more from RT than female patients or older patients.

The potential predictive value of the baseline characteristics could not be assessed through formal interaction analyses due to lack of power. Overall, these results need to be interpreted with caution as the analyses are exploratory and the number of events is small.

DISCUSSION

This project is the result of an international collaboration between the EORTC/LYSA/FIL and the UK NCRI Groups. This collaboration allowed us to externally validate the findings from the H10 trial, in the comparable independent RAPID dataset.

The overall risk of relapse in patients with limited stage HL achieving an ePETneg status after 2–3 cycles of ABVD was low (7%) in both trials.

Risk of relapse was lower in patients treated with CMT (3% in H10 and 5% RAPID) compared to C (11% in H10, 10% in RAPID) after a median follow-up of more than 5 years. When we separately analysed the EORTC/LYSA/FIL H10 and RAPID cohorts by EORTC prognostic groups (F and U), differences in 5-year PFR in ePETneg patients between the CMT and C only group were as follows: 99% vs. 88% in the H10 F group, 94% vs. 90% in the RAPID F group; 94% vs. 90% in the H10 U group and 93% vs. 92% in the RAPID U group, respectively. Remarkably, very similar results have been reported recently from the HD16 trial in limited-stage, favourable German Hodgkin Study Group (GHSG) patients (similar to EORTC F category) with 93% vs. 86% 5-year PFS respectively for CMT versus C.[11] It is worth noting that in the HD16 trial, ePET negative patients received a shorter treatment, consisting of either two cycles of ABVD + 20Gy IF-RT in the CMT arm, or two cycles of ABVD in the C arm.

In the H10 F cohort, most relapses after C occurred within 2 years (21/30; 70%) and this was also observed in the RAPID cohort (11/13; 85%). Results were similar in the H10 U cohort: 27/30 (90%). Because of the differences in inclusion criteria, the small number of patients classified as U in the RAPID dataset (63 C, 65 CMT) did not allow for any reliable comparison between studies in this subgroup, with very few relapses observed (n = 3 within 2 years and n = 2 after 2 years in C).

In support of these observations, RT significantly reduced the risk of relapse in the first 2 years (HR in the combined stratified analysis 0·20, 95% CI 0·11–0·37), but not after (HR 0·84, 95% CI 0·42–1·69). This finding was consistent in the separate analyses of each trial. The main objective of both trials was to evaluate whether C was non-inferior to CMT in terms of risk of relapse in ePET-negative patients. In the statistical design of both trials, a non-inferiority threshold of difference in relapse risk of 7%–10% was defined. This was based on data in the literature of incidence of late events, so as to compensate a presumed increased risk of relapse after C by the increased risk of late, long-term side effects after CMT. The non-inferiority of C could not be demonstrated, mainly because of the increased relapse risk after C in the first 2 years post-treatment. Whether the increased risk of early relapse after C will translate into improved long-term survival through the presumed lower incidence of long-term side effects has to be determined after prolonged observation periods, which are not yet available.

In the H10 F cohort, most relapses after C were confined to originally involved areas, while in the RAPID cohort this pattern was less pronounced. Whether the difference in study protocol treatment, in which additional chemotherapy was given in H10 to ePETneg C patients, whereas in RAPID no further treatment was given, is speculative. In U patients the risk of relapse after C was still higher than after CMT, but the difference was not as marked due to rather "delayed" relapses after CMT and a high number of relapses occurring in the irradiated sites in patients receiving CMT. In the H10 trial, U patients assigned to C received six cycles of ABVD chemotherapy, while patients assigned to CMT received four. One possible explanation is that more advanced disease, possibly reflecting a more "widespread" disease, could benefit from more effective systemic therapy rather than local RT. Owing to the smaller numbers of U patients in the RAPID trial, these findings could not be validated in the RAPID cohort.

Taken together, these results show that in ePETneg patients, relapses occur more often after C than after CMT, and they occur early after treatment, particularly in F patients. A high proportion of relapses occur in originally involved areas, strongly suggesting that local residual disease remained, despite the ePETneg status. Salvage treatment was not standardised in either trial and it was left to the discretion of the treating physician. Although data on salvage treatment are being collected, a formal complete analysis has not yet been performed, so it is not possible to comment on the efficacy or the kind of salvage treatment.

The second part of the project explored whether any baseline factors were associated with the observed higher risk of relapse when RT is omitted. This was a post-hoc analysis and, as such, only hypothesis generating. Our data suggest that RT may have a more pronounced effect on reducing the risk of relapse in males compared to females. This difference was less pronounced in the RAPID cohort. Caution should be advised in interpretation of these data, and because of the relatively small numbers of events and patients in the different subgroups, we decided not to perform a statistical significance test. While no definitive conclusions can be drawn, this finding could be of clinical interest and the subject of further investigations.

This project has limitations. it is a retrospective analysis, albeit from two large phase III, randomised-controlled trials. Differences in inclusion criteria prevented a more in-depth comparison of the U groups. The analysis of the impact of treatment and baseline characteristics on the risk of relapse was an exploratory, post-hoc analysis. The small number of relapses resulted in limited power for this analysis, therefore, the predictive value of baseline characteristics could not be reliably evaluated.

Long-term follow-up will reveal whether the increased risk of early relapses after C is balanced by a lower risk of late secondary events.

A key strength of this study is that the analyses initially conducted in the H10 trial were externally validated in the independent and comparable RAPID trial dataset. Even in ePETneg patients, relapses were more frequent after C than after CMT, most occurred after less than 2 years and affected originally involved areas. RT significantly reduced the risk of early relapses.

AUTHOR CONTRIBUTIONS

Valeria Fiaccadori, Catherine Fortpied, Igor Aurer, Anouk Neven, Marc Andre, Massimo Federico, John M. M. Raemaekers designed the research project; Catherine Fortpied, Anouk Neven, Laura Clifton-Hadley, Nicholas Counsell conducted the statistical analysis. All authors reviewed the results and contributed to data interpretation. Valeria Fiaccadori, Anouk Neven, Catherine Fortpied, John M. M. Raemaekers wrote the manuscript. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data will be shared according to each consortium's policy:

For H10, please refer to EORTC data release policy (https://www.eortc.org/data-sharing/).

For RAPID, please refer to http://www.ctc.ucl.ac.uk/DataSampleSharing.aspx

INFORMED CONSENT AND CLINICAL TRIAL REGISTRATIONS

No additional consent was needed for these projects as no additional data were collected. For original consent and ethical approval details please refer to the original publications (Andre et al, JCO 2017; Radford et al, NEJM 2015).

Clinical Trial Registration: NCT00433433; NCT00943423.

PRIOR PRESENTATIONS

Presented in part as oral presentation at the 2018 International Symposium on Hodgkin Lymphoma (ISHL)- Cologne (abstract awarded with young investigator award) and as oral presentation at the 2021 International Conference on Malignant Lymphoma (ICML)- Lugano.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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