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ORIGINAL REPORT

Role of Radiotherapy to Bulky Disease in Elderly Patients With Aggressive B-Cell Lymphoma

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ABSTRACT

Purpose
R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone) is standard care for aggressive B-cell lymphoma. A prospective trial was conducted to investigate the role of additive radiotherapy (RT) to bulky and extralymphatic disease.

Patients and Methods
The best arm of the RICOVER-60 trial (6×R-CHOP–14+2R [R-CHOP administered once every 2 weeks plus two additional applications of rituximab] plus involved-field RT [36 Gy] to sites of initial bulky [≥ 7.5 cm] disease and extralymphatic involvement) was compared with a cohort receiving the same immunochemotherapy but without RT in an amendment to the RICOVER-60 trial (RICOVER-noRTh) in a prospective fashion.

Results
After a median observation time of 39 months, 164 of 166 RICOVER-noRTh patients were evaluable. In a multivariable analysis of the intention-to-treat population adjusting for International Prognostic Index risk factors and age (> 70 years), event-free survival (EFS) of patients with bulky disease was inferior without additive RT (hazard ratio [HR], 2.1; 95% CI, 1.3 to 3.5; $P = .005$), with trends for inferior progression-free (PFS; HR, 1.8; 95% CI, 1.0 to 3.3; $P = .058$) and overall survival (OS; HR, 1.6; 95% CI, 0.9 to 3.1; $P = .127$). In a per-protocol analysis with 11 patients in RICOVER-noRTh excluded for receiving unplanned RT, multivariable analysis revealed HRs of 2.7 (95% CI, 1.3 to 5.9; $P = .011$) for EFS, 4.4 (95% CI, 1.8 to 10.6; $P = .001$) for PFS, and 4.3 (95% CI, 1.7 to 11.1; $P = .002$) for OS for patients not receiving RT to bulky disease.

Conclusion
Additive RT to bulky sites abrogates bulky disease as a risk factor and improves outcome of elderly patients with aggressive B-cell lymphoma. Whether RT can be spared in patients with (metabolic) complete remission after immunochemotherapy must be addressed in appropriately designed prospective trials.

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INTRODUCTION

The addition of rituximab to CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy (R-CHOP) has improved the outcome of patients with aggressive B-cell lymphoma,[1-3] and with more effective systemic immunochemotherapy, the question of additive radiotherapy (RT) is of renewed interest. In the prerituximab era, patients with localized stage I or II disease treated in the ECOG (Eastern Cooperative Oncology Group) 1484 trial experienced improved progression-free (PFS) but not overall survival (OS) with involved-field RT (30 Gy) after achieving complete remission (CR) with CHOP.[4] In contrast, the GELA (Groupe d'Etudes des Lymphomes de l'Adulte) 93-4 trial failed to demonstrate a benefit of involved-field RT (40 Gy) after four cycles of CHOP in patients age > 60 years with localized stage I or II disease.[5] Regarding stage III to IV disease, two trials suggested that the addition of RT to bulky disease (> 10 cm) improved both PFS and OS in patients in CR after CHOP-like chemotherapy.[6,7]

In the RICOVER-60 (Six Versus Eight Cycles of Biweekly CHOP-14 With or Without Rituximab in Elderly Patients With Aggressive CD20+ B-Cell Lymphomas) trial, elderly patients were randomly assigned to six or eight cycles of CHOP-14 (CHOP administered once every 2 weeks) with or without eight administrations of rituximab. Additive RT was administered

to sites of initial bulky disease (≥ 7.5 cm) and extralymphatic involvement. Six cycles of R-CHOP–14+2R (R-CHOP–14 plus two additional applications of rituximab) was the best of the four treatment arms and significantly improved event-free survival (EFS), PFS, and OS over six cycles of CHOP-14.[3] To address the role of RT within this concept, an additional cohort of patients, designated as RICOVER-noRTh, was treated with this arm, but without RT, in an amendment to the RICOVER-60 trial, and this cohort was compared with patients who had received the same immunochemotherapy plus RT to bulky disease and extralymphatic involvements in the randomization phase of the same trial.

PATIENTS AND METHODS

Patients

The RICOVER-60 trial was performed in accordance with the Helsinki Declaration. The protocol was approved by the ethics review committee of each participating center. All patients provided written informed consent. The characteristics of patients in the RICOVER-60 trial have been described in detail.[3] Briefly, patients with any disease stage or International Prognostic Index (IPI) risk group were eligible if they had previously untreated aggressive B-cell non-Hodgkin lymphoma and were age 61 to 80 years. Patients were randomly assigned to six or eight cycles of CHOP-14 with or without eight applications of rituximab. The trial was planned in a two × two factorial design. The randomization phase of the RICOVER-60 trial was stopped after a planned interim analysis revealed that the predefined stopping rules were fulfilled, and an amendment was implemented. In this amendment, designated as the RICOVER-noRTh study, patients received 6×R-CHOP–14+2R, but without RT. These patients were compared with the patients treated in the randomization phase of the RICOVER-60 trial receiving identical immunochemotherapy but with additional RT (36 Gy) to bulky disease and sites of extralymphatic involvement.

Treatment

A prephase treatment (vincristine 1 mg on day −7 and prednisone or prednisolone 100 mg orally from day −7 to −1 before first R-CHOP) was

Table 1. Patient Demographic and Clinical Characteristics

Characteristic	RICOVER-60				RICOVER-noRTh				*P*	
	Total (n = 306)		With Bulk (n = 117)		Total (n = 164)		With Bulk (n = 47)			
	No.	%	No.	%	No.	%	No.	%	Total	With Bulk
Sex									.100	.474
Male	168	55	62	53	77	47	22	47		
Female	138	45	55	47	87	53	25	53		
Age, years									.018	.064
Median	69		68		71		70			
Range	61-80		61-80		61-80		61-79			
> 60	306	100	117	100	164	100	47	100		
LDH > normal	152	50	76	65	91	56	37	79	.229	.085
ECOG PS > 1	43	17	27	23	23	14	11	23	.993	.964
Extralymphatic involvement > one	52	14	24	21	38	23	16	34	.105	.068
Stage III to IV disease	152	50	69	59	98	60	36	77	.037	.003
IPI score									.202	.074
1	94	31	20	17	39	24	4	9		
2	89	29	36	31	43	26	8	17		
3	78	26	34	29	50	31	19	40		
4	45	15	27	23	32	20	16	34		
Extralymphatic involvement	161	53	66	56	104	63	34	72	.024	.059
Extralymphatic involvement surgically removed	35*	12	7†	6	31‡	20	7§	15	.020	.118
Liver‖	15	5	11	9	10	6	5	11	.582	.778
Lung‖	16	5	5	4	11	7	4	9	.511	.279
Bulky disease	117	38	117	100	47	29	47	100	.038	—
Bulky sites surgically removed	—		11¶	10	—		6#	13	—	.572
B symptoms	98	32	54	46	62	38	29	62	.208	.072
BM involvement	14	5	5	4	15	9	5	11	.050	.152
Reference histology available	297	97	113	97	159	97	45	96	.817	.488
DLBCL	237	80	84	74	130	82	39	87		
B cell, other subtypes	37	13	14	12	17	11	3	7		
B cell, unspecified	14	5	8	7	9	6	2	4		
Other	9	3	7	6	3	2	1	2		

Abbreviations: BM, bone marrow; DLBCL, diffuse large B-cell lymphoma; ECOG PS, Eastern Cooperative Oncology Group performance status; IPI, International Prognostic Index; LDH, lactate dehydrogenase; noRTh, no radiotherapy; RICOVER-60, six *v* eight cycles of biweekly CHOP-14 with or without rituximab in elderly patients with aggressive CD20+ B-cell lymphomas.

*Information missing in five patients.
†Information missing in four patients.
‡Information missing in six patients.
§Information missing in one patient.
‖No radiotherapy planned.
¶Information missing in four patients. In one patient, only one of two bulky sites removed. Five extralymphatic and six lymphatic bulky sites surgically removed.
#Information missing in two patients. Four extralymphatic and two lymphatic bulky sites removed.

mandatory. CHOP has been described before.[3] CHOP-14 with granulocyte colony-stimulating factor support was repeated every 2 weeks.[3] Rituximab (375 mg/m^2) was administered every 2 weeks together with CHOP-14 plus two additional administrations at 2 and 4 weeks, respectively, after the last chemotherapy cycle.

Patients with initial bulky disease (defined as lymphoma masses or conglomerates with diameter ≥ 7.5 cm) or extralymphatic involvement were to receive RT to these areas if complete remission (CR), unconfirmed CR (CRu), or partial remission (PR) was achieved after chemotherapy except when these lymphoma manifestations were completely removed by surgery. Start of RT was planned to be 3 to 6 weeks after the last chemotherapy cycle. A central RT reference panel developed an individual RT plan for each patient. RT to bulky disease was applied as involved-field RT. If a residual tumor remained after chemotherapy, target volume was adapted. If CR was achieved after chemotherapy, the target volume included the lymph node region of the initial bulk. Lymph node regions were defined according Ann Arbor. Target volume of extralymphatic disease included the complete initially involved extralymphatic area. Patients received RT 36 Gy, at 1.8 to 2 Gy per fraction, administered 5× per week. No RT was to be administered in the RICOVER-noRTh cohort.

Statistical Analysis

EFS, the primary end point, was defined as time from random assignment to disease progression, start of salvage treatment, additional (unplanned) treatments, relapse, or death resulting from any cause. PFS was defined as time from random assignment to disease progression, relapse, or death resulting from any cause, and OS was defined as time from random assignment to death resulting from any cause. EFS, PFS, and OS were estimated according to the Kaplan-Meier method.[8] In univariable outcome analyses, log-rank tests were performed, and the 3-year rates are presented with 95% CIs. Proportional hazards models were adjusted for IPI factors (ie, age > 60 years, lactate dehydrogenase > normal, ECOG performance status > 1, stages III and IV, and extralymphatic involvement > one). In addition, we adjusted for age > 70 years, which was a stratification variable during random assignment in the RICOVER-60 trial. Hazard ratios (HRs) with 95% CIs and *P* values are presented. Preplanned subgroup analyses were performed for patients with bulky disease. In addition, a per-protocol analysis was performed excluding patients with protocol violations (ie, patients who received RT in RICOVER-noRTh and patients with bulky disease who did not receive RT [despite presence of bulky disease] in RICOVER-60). In this per-protocol analysis, patients who did not receive RT because the bulk had been surgically removed or because RT was not feasible (eg, liver or diffuse lung involvement) were included. Patients with an RT indication who did not receive RT although RT was technically feasible were excluded. In the toxicity analysis, patients with bulky disease who received RT in the RICOVER-60 cohort and no RT in the RICOVER-noRTh cohort were included. For differences regarding patient characteristics and responses and therapy-associated deaths, χ^2 and, if necessary, Fisher's exact tests were used. Significance level was $P = .05$ (two sided). For response variables and therapy-associated deaths, 95% CIs according to the Clopper-Pearson method were calculated. For better comparability, the already-published data set of the RICOVER-60 cohort was used to ensure follow-up similar to that of the RICOVER-noRTh cohort.[3] Statistical analyses were performed with SPSS PASW 18 and IBM SPSS Statistics 20 software (SPSS, Chicago, IL) and Cytel Studio 8.0.0 (Cytel, Cambridge, MA).

RESULTS

Between August 2005 and October 2007, 65 centers recruited 166 patients for the RICOVER-noRTh amendment. Two patients withdrew their informed consent, leaving 164 for evaluation. These patients were compared with 306 patients from RICOVER-60 who had been randomly assigned to 6×R-CHOP–14+2R plus RT to bulky disease and extralymphatic sites of involvement, designated as the RICOVER-60 cohort. Median follow-up was 34 months for patients treated in the RICOVER-60 cohort and 39 months for patients treated in the RICOVER-noRTh cohort. Patients in RICOVER-noRTh were older, more often had stage III or IV disease and extralymphatic involvement, and more frequently belonged to the IPI high-intermediate or high-risk group, but they less often had bulky disease (n = 47 [29%] *v* 117 [38%]; $P = .038$; Table 1). Protocol adherence (total dose, duration, relative dose-intensity) was comparable in both cohorts.[3] In the RICOVER-60

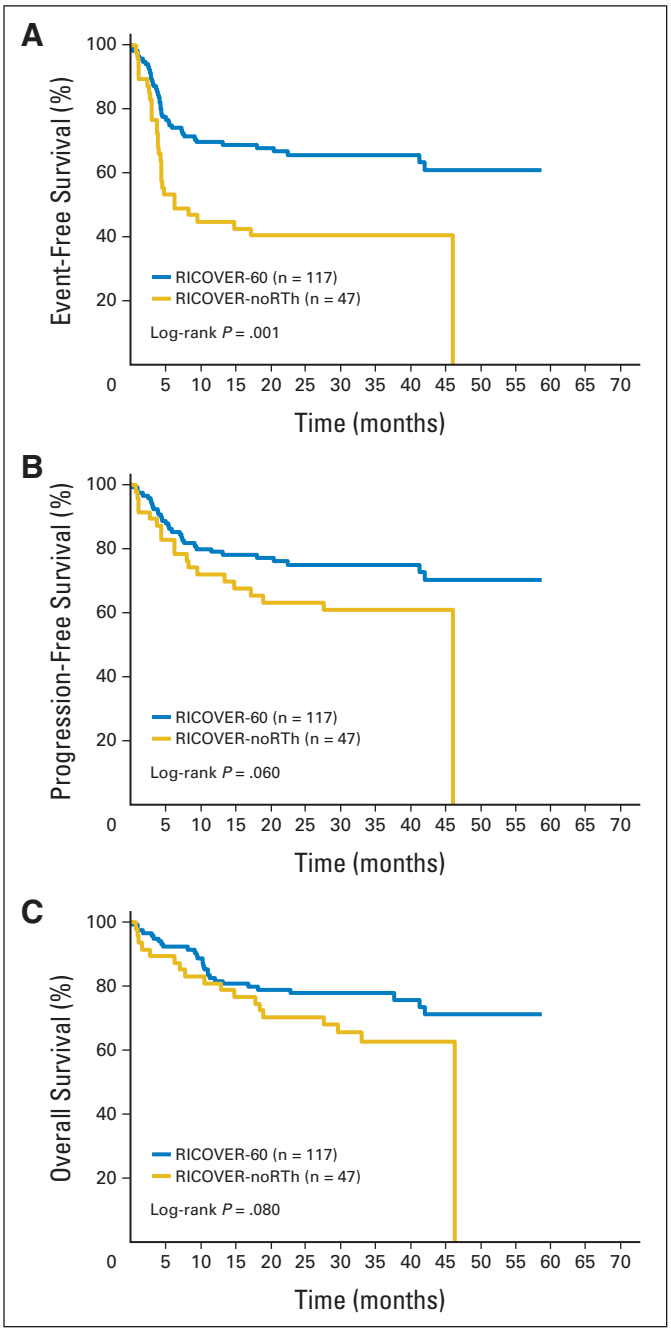

Fig 1. (A) Event-free, (B) progression-free, and (C) overall survival of patients with bulky disease in RICOVER-60 (six *v* eight cycles of biweekly CHOP-14 with or without rituximab in elderly patients with aggressive CD20+ B-cell lymphomas) and RICOVER-noRTh (no radiotherapy) cohorts.

cohort, 111 (36%) of 306 patients received RT, and 117 patients had bulky disease, of whom 67 (57%) underwent irradiation. Reasons for withholding RT to sites of bulky disease were prior surgical resection (n = 7) or medical impracticality (n = 4), insufficient response (< PR after immunochemotherapy; n = 9), excessive toxicity (n = 4) or therapy-associated death during chemotherapy (n = 5), protocol violation (n = 13), patient wishes (n = 1), concomitant disease (n = 1), and other reasons (n = 3). Two patients received salvage RT, and one patient received RT to a site distinct from the bulk. In RICOVER-noRTh, 14 (9%) of 164 patients received RT to extralymphatic or bulky disease as a protocol violation; 47 patients had bulky disease, of whom 11 (23%) underwent unplanned irradiation; and one patient received salvage RT. RT started at a median of 5.1 weeks after the eighth rituximab application (lower quartile, 4.0 weeks; upper quartile, 7.4 weeks with no difference between two cohorts).

Outcome

Overall response was similar in both cohorts (CR or CRu: 76%; 95% CI, 68 to 82 *v* 78%; 95% CI, 73 to 82; progression: 6%; 95% CI, 3 to 10 *v* 7%; 95% CI, 4 to 10; relapse after CR or CRu: 15%; 95% CI, 10 to 23 *v* 10%; 95% CI, 7 to 15; therapy-associated deaths: 7%; 95% CI, 4 to 12 *v* 6%; 95% CI, 3 to 9 in RICOVER-noRTh *v* RICOVER-60, respectively). There was no difference with respect to 3-year EFS (61%; 95% CI, 54 to 68 *v* 66%; 95% CI, 61 to 72; $P = .109$), PFS (72%; 95% CI, 65 to 79 *v* 73%; 95% CI, 67 to 78; $P = .593$), and OS (77%; 95% CI, 70 to 83 *v* 78%; 95% CI, 73 to 83; $P = .654$; Appendix Figs A1A to A1C, online only). This was also confirmed in a multivariable analysis adjusting for IPI risk factors and age (data not shown). Outcome of patients with extralymphatic disease was not a subject of this analysis. The intention-to-treat analysis limited to patients with bulky disease revealed more relapses after CR or CRu in RICOVER-noRTh than in RICOVER-60 (n = 6 [22%] of 27; 95% CI, 9 to 42 *v* n = 3 [4%] of 82; 95% CI, 1 to 10; $P = .007$). The percentage of patients with bulky disease achieving CR or CRu was lower (n = 27 [57%] of 47; 95% CI, 42 to 72 *v* n = 82 [70%] of 117; 95% CI, 61 to 78; $P = .121$), and the percentage of patients achieving PR was higher (n = 6 [13%] of 47; 95% CI, 5 to 26 *v* n = 7 [6%] of 117; 95% CI, 2 to 12; $P = .199$), in RICOVER-noRTh. In the intention-to-treat analysis, eight unplanned (protocol-violating) RT administrations in RICOVER-noRTh were counted as events, and 3-year EFS for patients with bulky disease was inferior in RICOVER-noRTh, where RT was not allowed (40%; 95% CI, 26 to 55 *v* 66%; 95% CI, 57 to 75; $P = .001$; Fig 1A). This was confirmed in a multivariable analysis adjusting for IPI risk factors and age (Table 2). There was no statistical difference in PFS for patients with bulky disease (for whom unplanned RT was not counted as event; five of eight patients were censored, and two patients with progression and one non–lymphoma-related death were counted as events), but there was a trend for faring worse in the RICOVER-noRTh cohort (61%; 95% CI, 47 to 75 *v* 75%; 95% CI, 67 to 83; $P = .060$; Fig 1B). Three-year OS of patients with bulky disease showed a trend for worse outcome in RICOVER-noRTh (63%; 95% CI, 48 to 77 v 78%; 95% CI, 70 to 85; $P = .080$; Fig 1C). In RICOVER-60, 28 (24%) of 117 patients with bulky disease died; in RICOVER-noRTh, 18 (38%) of 47 died. Causes of death study treatment related (n = 7 [6%] *v* 4 [9%]), lymphoma related (n = 19 [16%] *v* 12 [26%]), and other (n = 2 [2%] *v* 2 [4%]) in RICOVER-60 versus RICOVER-noRTh, respectively.

A per-protocol analysis restricted to patients with bulky disease who did not receive RT in RICOVER-noRTh, but did receive RT in RICOVER-60 as planned according to the protocol, revealed inferior 3-year EFS (54%; 95% CI, 38 to 71 *v* 80%; 95% CI, 71 to 89; $P = .001$), PFS (62%; 95% CI, 46 to 78 *v* 88%; 95% CI, 80 to 95; $P < .001$) and OS (65%; 95% CI, 49 to 81 *v* 90%; 95% CI, 84 to 97; $P = .001$; Figs 2A to 2C) in RICOVER-noRTh compared with RICOVER-60, which was confirmed in a multivariable analysis (Table 3). HRs for patients not receiving RT to bulky disease were 2.7 (95% CI, 1.3 to 5.9; $P = .011$) for EFS, 4.4 (95% CI, 1.8 to 10.6; $P = .001$) for PFS, and 4.3 (95% CI, 1.7 to 11.1; $P = .002$) for OS. According to the per-protocol analysis, 10 (13%) of 78 patients with bulky disease died in RICOVER-60, whereas 13 (37%) of 35 died in RICOVER-noRTh. Causes of death were study treatment related (n = 2 [3%] *v* 4 [11%]), lymphoma related (n = 6 [8%] *v* 8 [23%], and other (n = 2 [3%] *v* 1 [3%]) in RICOVER-60 and RICOVER-noRTh, respectively. In a multivariable Cox model adjusted for IPI factors and age (> 70 years), bulky disease was a prognostic factor in RICOVER-noRTh but not in RICOVER-60 (Appendix Table A1, online only).

Toxicity

We observed 19 (6%) and eight (5%) secondary neoplasms in RICOVER-60 and RICOVER-noRTh, respectively. Besides solid tumors, two patients with acute myeloid leukemia or myelodysplastic syndrome were observed in the RICOVER-60 cohort. Because long-term toxicity is a special concern, we analyzed toxicities that persisted during follow-up after the end of treatment. Appendix Table A2

Table 2. Multivariable Intention-to-Treat Analysis of Patients With Bulky Disease

	EFS			PFS			OS		
Variable	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
RICOVER-noRTh *v* RICOVER-60	2.1	1.3 to 3.5	.005	1.8	1.0 to 3.3	.058	1.6	0.9 to 3.1	.127
LDH > normal	1.3	0.7 to 2.3	.395	1.7	0.8 to 3.5	.152	1.7	0.8 to 3.6	.172
ECOG PS > 1	1.9	1.1 to 3.4	.024	2.9	1.4 to 5.6	.003	2.5	1.2 to 5.0	.011
Extralymphatic involvement > one	1.0	0.5 to 1.9	.986	0.7	0.3 to 1.6	.407	0.7	0.3 to 1.7	.456
Stage III to IV disease	0.8	0.5 to 1.4	.494	0.7	0.4 to 1.4	.385	0.9	0.4 to 1.7	.679
Age > 70 years	1.4	0.8 to 2.3	.223	1.3	0.7 to 2.3	.407	1.4	0.7 to 2.6	.312

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; EFS, event-free survival; HR, hazard ratio; LDH, lactate dehydrogenase; noRTh, no radiotherapy; OS, overall survival; PFS, progression-free survival; RICOVER-60, six *v* eight cycles of biweekly CHOP-14 with or without rituximab in elderly patients with aggressive CD20+ B-cell lymphomas.

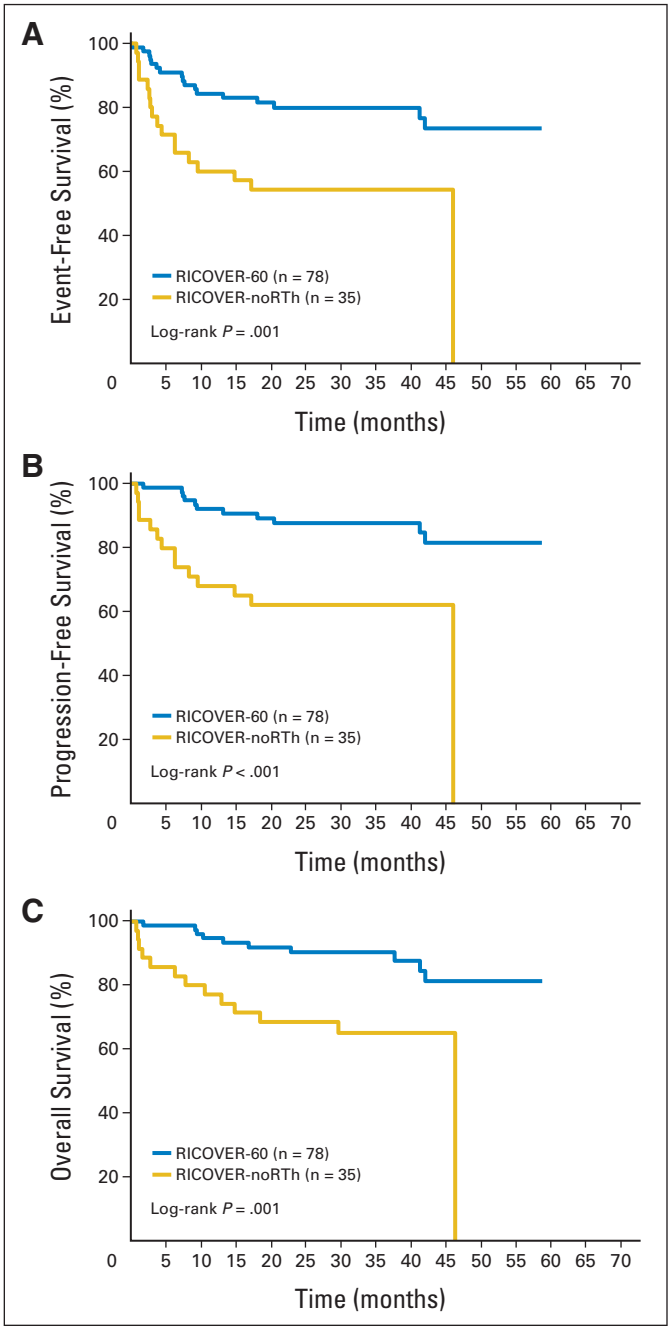

Fig 2. (A) Event-free, (B) progression-free, and (C) overall survival of patients with bulky disease receiving radiotherapy or not according to protocol. Eleven of 78 RICOVER-60 (six *v* eight cycles of biweekly CHOP-14 with or without rituximab in elderly patients with aggressive CD20+ B-cell lymphomas) patients with primary bulky disease did not undergo irradiation (surgical removal of bulk, n = 7; radiotherapy medically contraindicated, n = 4). noRTh, no radiotherapy.

(online only) summarizes the persistent toxicities. In this analysis, only those patients from RICOVER-60 who underwent irradiation and from RICOVER-noRTh who did not were included. Persistent toxicity was mild, with the leading adverse effect being persistent peripheral neuropathy resulting from vincristine administered during chemotherapy but not RT. One additional grade 3 toxicity was heart failure in a woman age 72 years who did not receive RT, most likely as a result of anthracyclin toxicity.

DISCUSSION

Our study is the first to our knowledge to assess the role of RT to bulky disease in patients with aggressive B-cell lymphoma in the rituximab era treated in a prospective fashion. The recruitment pattern underlines the difficulties of such a trial. First, the proportion of patients with bulky disease was significantly lower in the RICOVER-noRTh cohort than in the respective patients from the randomization phase of the RICOVER-60 trial, suggesting that many physicians (or patients) did not want to take the risk of omitting a putatively effective modality. Second, even in the cohort of patients who consented to be treated without RT, 11 (23%) of 47 received unplanned RT to bulky disease even though they had responded well to 6×R-CHOP–14+2R, thus violating the protocol and negatively affecting the EFS end point, because unplanned RT was counted as an event in EFS. Both facts can be interpreted as reflecting great concern among physicians (and patients), being accustomed to RT to bulky disease for decades in Germany.

Outcome in both cohorts was similar with respect to EFS, PFS, and OS (Appendix Fig A1). However, when only patients with bulky disease were analyzed by intention to treat, superior EFS and a strong trend for better PFS and OS were seen in RICOVER-60, where RT was administered to bulky disease (Fig 1). Assuming that RT to bulky disease reduces progression and relapse, unplanned RT might have improved PFS in the RICOVER-noRTh cohort at the same time. This is supported by the analysis restricted to patients who received therapy as per protocol in RICOVER-noRTh without RT to bulky disease. These patients had a significantly (> 20%) worse outcome with respect to the major end points EFS, PFS, and OS compared with the respective cohort in the RICOVER-60 study (Fig 2), strongly suggesting a benefit of RT to bulky disease.

Our analysis has limitations. Patients were not allocated to RT by random assignment, and there was an obvious recruitment bias, with fewer patients with bulky disease enrolled onto the RICOVER-noRTh study. These differences made multivariable analyses indispensable, which showed inferiority of RICOVER-noRTh with respect to all end points (Table 2); this was even more pronounced in the per-protocol analysis (Table 3).

Results from other prospective trials allow only indirect and inconclusive interpretations concerning the role of RT. The MInT (MabThera International Trial) study included young patients with good prognosis age 18 to 60 years with aggressive B-cell lymphoma and randomly assigned patients to six cycles of a CHOP-like chemotherapy with or without rituximab.[2,9] Additive RT to bulky disease was administered to all patients. A Martingale residual analysis of patients treated with rituximab showed a linear adverse prognostic effect of maximal tumor diameter[10] but suggested no major impact of RT on outcome. A phase II trial in younger patients with primary mediastinal B-cell lymphoma and bulky disease treated with dose-adjusted EPOCH-R (etoposide, vincristine, doxorubicin, cyclophosphamide, and prednisone plus rituximab)[11] cannot be compared with our cohort of elderly patients, who did not have primary mediastinal disease. However, a comparison of the results obtained in young patients with an age-adjusted IPI of 1 in the MInT and LNH02-03B trials, respectively, suggested a benefit of additive RT to bulky disease, because patients in MInT receiving six cycles of R-CHOP and RT to bulky disease fared

Table 3. Multivariable Per-Protocol Analysis of Patients With Bulky Disease

Variable	EFS			PFS			OS		
	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
RICOVER-noRTh *v* RICOVER-60	2.7	1.3 to 5.9	.011	4.4	1.8 to 10.6	.001	4.3	1.7 to 11.1	.002
LDH > normal	0.9	0.4 to 2.0	.728	0.6	0.2 to 1.7	.391	0.5	0.2 to 1.3	.161
ECOG PS > 1	1.4	0.6 to 3.4	.465	1.6	0.5 to 4.9	.439	1.0	0.3 to 3.5	.949
Extralymphatic involvement > one	1.3	0.5 to 3.4	.561	0.8	0.3 to 2.4	.664	0.9	0.3 to 2.8	.850
Stage III to IV disease	0.8	0.4 to 2.0	.684	1.2	0.5 to 3.4	.662	1.9	0.7 to 5.6	.230
Age > 70 years	2.2	1.1 to 4.5	.033	1.6	0.7 to 3.9	.271	1.8	0.7 to 4.6	.196

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; EFS, event-free survival; HR, hazard ratio; LDH, lactate dehydrogenase; noRTh, no radiotherapy; OS, overall survival; PFS, progression-free survival; RICOVER-60, six *v* eight cycles of biweekly CHOP-14 with or without rituximab in elderly patients with aggressive CD20+ B-cell lymphomas.

considerably better than patients receiving eight cycles of R-CHOP (without RT to bulky disease) in the LNH02-03B trial and actually did as well as patients who had received the more intensive R-ACVBP (rituximab plus doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone followed by a sequential consolidation with high-dose methotrexate, ifosfamide, etoposide, and cytarabine) program[12] in LNH02-03B. A definitive answer to the question of the role of additive RT to bulky disease in the rituximab era can only be obtained from a randomized trial. Recently, the two arms without RT in the UNFOLDER (Unfavorable Low-Risk Patients Treated With Densification of R-Chemo Regimens) study of the Deutsche Studiengruppe Hochmaligne Non-Hodgkin Lymphome (DSHNHL)—which randomly assigned young patients to R-CHOP–21 or R-CHOP–14 and patients with bulky and extralymphatic disease to additive RT or observation in a two × two factorial design—had to be closed because the predefined stopping rules were met in a planned interim analysis, also suggesting a benefit of additive RT to subpopulations with diffuse large B-cell lymphoma in the rituximab era (ClinicalTrails.gov identifier, NCT00278408).

In our study, response after immunochemotherapy was evaluated according to International Workshop criteria,[13] without [^{18}F]fluorodeoxyglucose–positron emission tomography (PET) scans. Some cooperative groups have totally abandoned RT in their therapeutic armamentarium in the rituximab era or do not administer RT to residual masses of primary bulky disease unless a postchemotherapeutic [^{18}F]fluorodeoxyglucose-PET scan is positive because of the high negative predictive value of such a post-therapy PET.[14] Support for such a strategy of limiting additive RT for patients not in (metabolic) CRT after immunochemotherapy comes from an exploratory analysis in this study, which showed that there were no differences in outcome for patients with bulky disease achieving CR or CRu after complete immunochemotherapy between RICOVER-60 and RICOVER-noRTh with respect to 3-year EFS (75%; 95% CI, 56 to 94 *v* 84%; 95% CI, 70 to 97; $P = .430$), PFS (75%; 95% CI, 56 to 94 *v* 84%; 95% CI, 70 to 97; $P = .430$), and OS (79%; 95% CI, 61 to 97 *v* 87%; 95% CI, 75 to 99; $P = .839$; Appendix Figs A2A to A2C, online only). Because of the low number of patients, this should be interpreted with caution, because the CIs are large, and therefore, this observation must be confirmed in a prospective study. A recent study suggested that RT can be limited to patients with a positive PET after immunochemotherapy, where it results in an outcome similar to that of patients with a negative PET[15]; however, other investigators have reported on the limited prognostic value of a negative PET if the residual mass has a diameter > 2 cm on computed tomography.[16] Whether RT to bulky disease can indeed be omitted in patients with a negative PET after immunochemotherapy should be answered in the ongoing OPTIMAL>60 (Improvement of Outcome and Reduction of Toxicity in Elderly Patients With CD20+ Aggressive B-Cell Lymphoma by an Optimised Schedule of the Monoclonal Antibody Rituximab, Substitution of Conventional by Liposomal Vincristine, and [18F]Fluorodeoxyglucose Positron Emission Tomography Based Reduction of Therapy) trial by the DSHNHL, where this strategy is pursued in a prospective fashion in elderly patients with diffuse large B-cell lymphoma.

In summary, our analysis of two prospectively treated cohorts from the RICOVER-60 trial provides strong support for adding RT to sites of bulky disease for elderly patients with aggressive B-cell lymphoma. We recommend this additive and (at doses of 36 Gy) relatively low-toxic treatment modality in all patients with bulky disease until a prospective study proves that it can be omitted in patients with a negative PET after immunochemotherapy.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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Appendix

Table A1. Multivariable Analysis of Bulk As Risk Factor*

	RICOVER-60 (n = 306)									RICOVER-noRTh (n = 164)								
	EFS			PFS			OS			EFS			PFS			OS		
Variable	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
Bulk *v* no bulk	0.9	0.6 to 1.4	.776	0.7	0.4 to 1.1	.097	0.8	0.5 to 1.4	.524	2.4	1.4 to 4.2	.001	1.6	0.9 to 3.0	.128	2.1	1.1 to 4.1	.030
LDH > normal	1.7	1.1 to 2.7	.013	2.2	1.3 to 3.6	.003	1.9	1.1 to 3.2	.027	1.3	0.7 to 2.4	.340	1.6	0.8 to 3.2	.152	1.6	0.7 to 3.4	.234
ECOG PS > 1	1.6	0.9 to 2.6	.083	1.6	0.9 to 2.9	.120	1.8	1.0 to 3.3	.061	1.6	0.8 to 3.1	.162	1.8	0.8 to 3.8	.148	1.9	0.8 to 4.2	.130
Extralymphatic involvement > one	1.4	0.8 to 2.3	.262	1.2	0.6 to 2.1	.635	1.2	0.7 to 2.4	.509	1.0	0.5 to 2.0	.972	0.9	0.4 to 2.0	.789	0.5	0.2 to 1.3	.179
Stage III to IV disease	1.3	0.8 to 2.1	.263	1.4	0.9 to 2.4	.163	1.4	0.8 to 2.4	.271	0.8	0.5 to 1.5	.529	1.2	0.6 to 2.3	.676	1.2	0.6 to 2.4	.628
Age > 70 years	1.5	1.0 to 2.2	.065	1.3	0.8 to 2.0	.320	1.8	1.1 to 3.0	.015	1.7	1.0 to 2.8	.044	2.4	1.3 to 4.5	.004	3.0	1.5 to 6.2	.002

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; EFS, event-free survival; HR, hazard ratio; LDH, lactate dehydrogenase; noRTh, no radiotherapy; OS, overall survival; PFS, progression-free survival; RICOVER-60, six *v* eight cycles of biweekly CHOP-14 with or without rituximab in elderly patients with aggressive CD20+ B-cell lymphomas.

*Adjusted for LDH, ECOG PS, extralymphatic involvement, disease stage, and age (> 70 years).

Table A2. Toxicity Documented During Follow-Up

	RICOVER-60 (n = 67)*†				RICOVER-noRTh (n = 35)‡			
	All Grades		Grade III to IV		All Grades		Grade III to IV	
Toxicity	No.	%	No.	%	No.	%	No.	%
Immune system disorders	—		—		1§	3	—	
Peripheral neuropathy	19	29	—		8	28	—	
Dysgeusia	—		—		1	3	—	
Cardiac disorders	—		—		1	3	1	3
Exocrine pancreatic deficiency	1	2	—		—		—	
Pulmonary fibrosis	1‖	2	—		—		—	
Musculoskeletal disorders	2	3	—		—		—	
Pulmonary embolism	1	2	—		—		—	

Abbreviations: noRTh, no radiotherapy; RICOVER-60, six *v* eight cycles of biweekly CHOP-14 with or without rituximab in elderly patients with aggressive CD20+ B-cell lymphomas.

*Patients whose bulk was surgically removed and who did not receive RT as planned in protocol are not included in toxicity analysis (n = 11).

†Follow-up available in 65 (97%) of 67 patients.

‡Follow-up available in 29 (82.9%) of 35 patients.

§Secondary immunoglobulin deficiency; patient experienced repeated urinary tract infections.

‖Radiologic abnormalities at sites of irradiation without functional impairments.

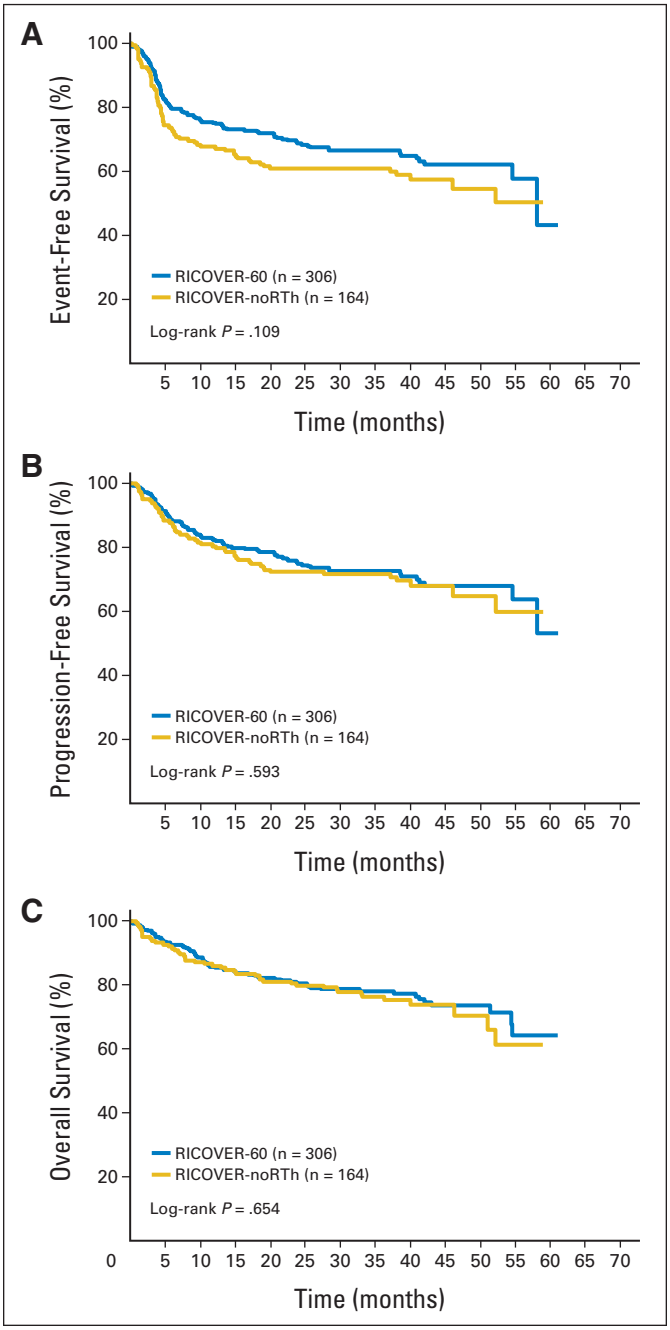

Fig A1. (A) Event-free, (B) progression-free, and (C) overall survival of all patients (including those without bulky disease) in RICOVER-60 (six *v* eight cycles of biweekly CHOP-14 with or without rituximab in elderly patients with aggressive CD20+ B-cell lymphomas) and RICOVER-noRTh (no radiotherapy) cohorts.

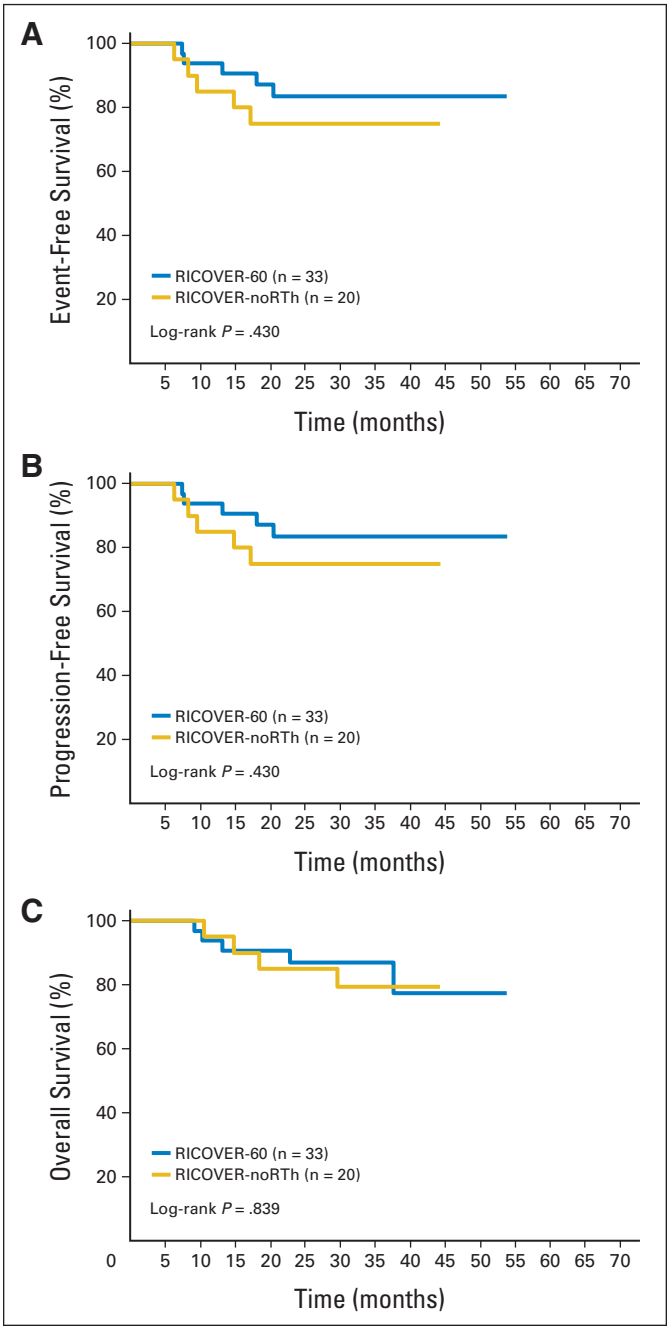

Fig A2. (A) Event-free, (B) progression-free, and (C) overall survival of patients with bulky disease achieving complete remission or unconfirmed complete remission after complete immunochemotherapy and administration (or not) of radiotherapy per protocol. Seven of 33 RICOVER-60 (six *v* eight cycles of biweekly CHOP-14 with or without rituximab in elderly patients with aggressive CD20+ B-cell lymphomas) patients did not undergo irradiation (surgical removal of bulk, n = 4; radiotherapy contraindicated, n = 3). noRTh, no radiotherapy.