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Impact on survival through consolidation radiotherapy for diffuse large B-cell lymphoma: a comprehensive meta-analysis

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ABSTRACT

Rituximab has improved response rates and overall survival in diffuse large B-cell lymphoma. Radiotherapy is an effective treatment modality for lymphomas, but there is uncertainty on its use as consolidation after chemo-immunotherapy mainly in advanced stages. We evaluated its efficacy with a comprehensive meta-analysis and a systematic search of Pubmed, Embase, Cochrane, and abstracts from the American Society of Clinical Oncology, American Society of Hematology, European Society for Medical Oncology and American Society of Radiation Oncology published from June 1966 and December 2018. We identified 11 trials that evaluated consolidation radiotherapy following chemotherapy in a randomized fashion in 4,584 patients. The primary endpoint of this meta-analysis was progression-free survival (PFS). As three of the 11 trials were retracted, this data is based on 2,414 patients. For the primary endpoint, PFS, we found a hazard ratio (HR) 0.77 (95% Confidence Interval [CI]: 0.51-1.17), pooled (tau^2: 0.25; I^2: 85%), and a HR 0.80 (95% CI: 0.53-1.21), pooled in a bivariate meta-analysis and for the secondary endpoint, overall survival, a HR 0.93 (range, 0.61-1.40), pooled (tau^2: 0.25; I^2: 74%) and a HR 0.86 (95% CI: 0.58-1.27) in a bivariate meta-analysis. The lack of benefit did not change over time (P=0.95 (tau^2: 0.32; I^2: 88%), and was also absent for PFS when stratifying for i) chemotherapy, ii) the use of rituximab, iii) age, iv) the dose of radiotherapy and v) application to patients in complete remission with bulky disease. None of the trials used a positron emission tomography-guided approach. This meta-analysis revealed no survival benefit when consolidation radiotherapy is given to unselected diffuse large B-cell lymphoma patients following chemotherapy. These results need to be considered in future trials in the positron emission tomography-computed tomography era.

Introduction

Comprising 35% of all non-Hodgkin lymphomas (NHL), diffuse large B-cell lymphoma (DLBCL) is the most common aggressive lymphoma in adults. The current standard therapy rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) cures two-thirds of patients.[1,2] Several attempts with a variety of approaches including the addition of new drugs have so far failed to improve these results.[3,4] Radiotherapy is an effective treatment option for patients with aggressive lymphomas. It was initially used as a primary modality for various lymphomas and was later used as consolidation when anthracycline-containing regimens became available in the 1980s. Radiotherapy is now commonly used in localized disease.[5] As such, consolidation radiotherapy is part of the first line treat-

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ment of DLBCL in the European Society for Medical Oncology (ESMO)[6] and National Comprehensive Cancer Network (NCCN) guidelines (*https://www.nccn.org/professionals/physician_gls/pdf/b-cell.pdf* (last access: Nov 28, 2019; for details see *Online Supplementary Table S1*). However, significant conceptual issues on its current use outside a clinical trial remain. They include different definitions of bulky disease, the use in advanced stages, and the recent implementation of positron emission tomography-computed tomography (PET-CT) in the clinical management. Albeit not limited to consolidation radiotherapy in DLBCL, treatment recommendations are often built on experience, clinical judgment and guidelines, but ideally should be based on data, preferably from randomized trials. Here we present a comprehensive meta-analysis to assess the impact of radiotherapy in addition to and after first-line chemo-immunotherapy of DLBCL based on the best currently available data by randomized controlled trials. With this large meta-analysis, we aim to provide the rational basis for a future randomized trial on the use of consolidation radiotherapy in DLBCL.

Methods

Literature search

We performed a comprehensive search in electronic databases (Pubmed, Embase, Cochrane) in any language between June 1966 and December 2018 for randomized controlled trials. As the data presented on meetings may differ from the peer-reviewed publications,[7] a manual search was done of abstracts from ASCO, ASH, ESMO, and ASTRO proceedings between 2009 and 2018. We used the following search strategy: (radiation therap*[Title] OR radiotherapy*[Title] OR radio-therap*[Title]) AND (non-hodgkin*[Title] OR non Hodgkin*[Title] OR nonhodgkin[Title] OR no Hodgkin*[Title] OR nhl[Title]) OR (lymphoma*[Title]) AND

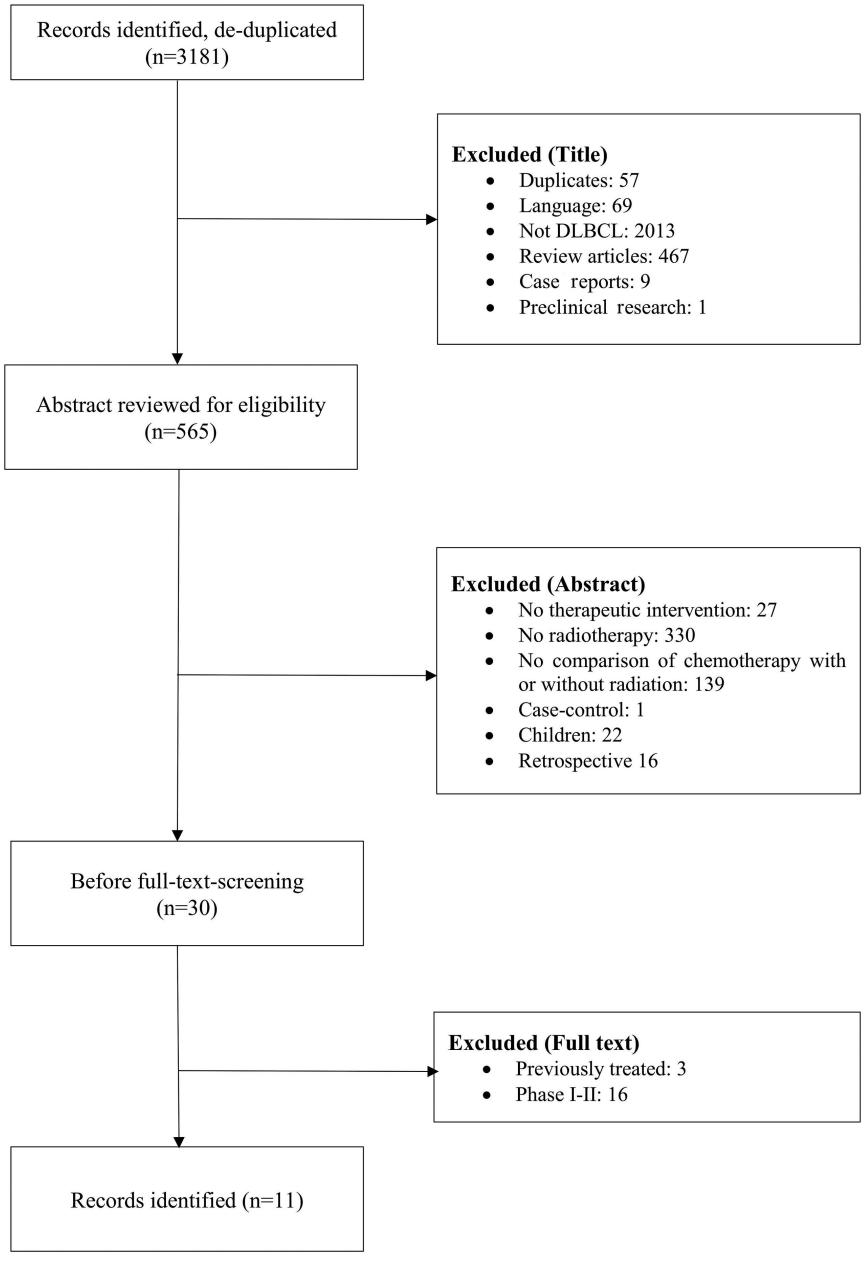

Figure 1. Study selection. Flow diagram according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement to illustrate the search and selection process. DLBCL: diffuse large B-cell lymphoma.

(aggressive[Title] OR malignant[Title] OR advanced[Title] OR histiocytic[Title] OR diffuse[Title] OR undifferentiated[Title] OR mixed[Title] OR high grade[Title] OR centroblastic [Title] OR immunoblastic[Title]).

Inclusion criteria and trial selection

Three investigators independently screened the studies. The flow diagram according to the PRISMA statement[8,9] depicted in Figure 1 illustrates the search and selection process. We aimed at identifying randomized trials that had enrolled at least 50 adult patients (≥18 years of age) per arm with newly diagnosed DLBCL (or aggressive lymphomas) at any stage according to the Ann Arbor classification. Patients had to be treated with a CHOP based chemotherapy (+/- rituximab), and randomized to subsequent consolidation radiotherapy or no radiotherapy. The 50-patients cut-off was chosen to exclude therapeutic exploratory trials. Although the cut-off is arbitrary, it is safe to assume that no confirmatory trials were excluded given the high (progression-free) survival rates observed in this population. Patients with previously treated or relapsed DLBCL were excluded. The full text report of identified trials was independently checked by the three investigators. Disagreements regarding trial selection were discussed until consensus was found. Each report was scrutinized to eliminate duplicates and to ensure that it was published as an original article.

Outcome measures

Progression-free survival (PFS) and overall survival (OS) were the outcomes of interest. PFS was considered as tumor progression *i.e.*, growth of the tumor during treatment, relapse *i.e.*, growth after previous shrinkage or stabilization, or death. For trials that did not report outcome data that fit this definition, we used data of an outcome that was as close as possible to this definition *e.g.*, event-free survival.

Data extraction

Data was extracted in duplicate and disagreements were resolved by consensus. We used the Cochrane 'Risk of Bias' approach to assess methodological quality of trials.[10] We used the data from the original publications, from intention-to-treat analyses, and from randomized patients only, and for the longest follow-up available for a particular outcome. The hazard ratio (HR) was used as effect measure for both outcomes. If HR and a measure of precision (standard error, variance, or 95% Confidence Interval [CI]) was not available, we digitized Kaplan-Meier curves, reconstructed the underlying time-to-event data, and calculated (log) HR and standard errors using a Cox regression model. Details on the outcome data of the 11 trials are shown in Table 2.

Statistical analysis

Outcome data were pooled with a random-effects model using restricted maximum likelihood. We also did bivariate meta-analysis considering both outcomes in one analysis. Correlation between OS and PFS was estimated from two of the identified trials.[11,12] We performed random-effects meta-regression for PFS over time using the mid of enrolment period as an independent covariate. Stratified analyses to explore possible reasons for heterogeneity were also done using meta-regression. Analyses were done using Stata (StataCorp. 2017. Stata Statistical Software: Release 16. College Station, TX, USA). Taking into account criticisms of meta-analysis,[8,9] the *Online Supplementary Appendix* provides additional details on the analysis methods used and all outcome data. The latter, used in the meta-analysis, is provided in Table 2.

Results

After deduplication, our search strategy generated 3,181 references (Figure 1). With the aim to identify clinical trials that assessed the role of consolidation radiotherapy in a randomized manner as part of the first-line therapy, our search revealed 11 trials amenable for this meta-analysis (details are listed in Table 1). Three of the four trials published by Aviles[13-16] on this topic were later retracted.[14-16] As of September 2019, these retracted papers have together received a total of 39 citations. Their data are provided in the respective figures, but were excluded from the meta-analyses. One trial was stopped early when the benefit of rituximab became evident,[12] or as a result of a planned interim analysis.[17] Older trials included lymphomas classified by the Kiel classification[18] or included DLBCL according to the Working Formulation.[19] Six of the trials included patients with localized disease only, but five of the 11 trials included also advanced stages. With the exception of the GELA LNH 93-1[11] where doxorubicin, cyclophosphamide, vindesine, bleomycin and prednisone (ACVBP) instead of CHOP was given in the comparator arm or SWOG,[20] where the non-irradiated patients received eight cycles of CHOP (instead of three), the same chemotherapy was given to the randomized patients. The current standard R-CHOP was used in four of the 11 trials.[15-17,21,22] Only the recent Lysa/GOELAMS 02 03 trial[21] used PET, although not for guided treatment. Radiotherapy was given to both localized stages 1 and 2, but also advanced disease, and either to all or only patients in complete remission or bulky disease. GOELAMS 02 03[21] was a non-inferiority trial whereas all other trials used for this meta-analysis used a superiority design.

Seven trials with a total of 2,488 patients contributed to the analysis of the primary endpoint PFS (Figure 2). Data were extracted from the original publications. The UNFOLDER trial was presented in part at the 12th International Congress on Malignant Lymphomas,[17] and again at the American Society of Clinical Oncology (ASCO) 2018,[22] albeit with different endpoints. The latter have been used for this meta-analysis. Data from Engelhard[18] was not available for the PFS analysis (Table 2). For PFS, the pooled HR was 0.77 (95% CI: 0.51-1.17), and in the pooled bivariate meta-analysis HR was 0.80 (95% CI: 0.53-1.21) (Figure 2). For OS, eight trials with a total of 2,744 patients were included. The pooled HR was 0.93 (95% CI: 0.61-1.40) and 0.86 (95% CI: 0.58-1.27) in the bivariate meta-analysis (Figure 3). Between-trial heterogeneity was high for both outcomes (PFS, tau^2: 0.25, I^2: 85%; OS, tau^2: 0.25, I^2: 74%). The total of 4,584 patients included in this meta-analysis were recruited between 1983 and 2013. However, the lack of benefit of the combined treatment modality remained stable over time, and time alone cannot explain the observed heterogeneity in the meta-analysis (*P*-value for time trend =0.95; tau^2: 0.32; I^2: 88%; Figure 4).

Given the significant heterogeneity (see also Table 1), we analyzed the data by using the following stratifications: i) the applied chemotherapy was similar in both arms, ii) whether rituximab was used, iii) the dose of radiotherapy, and iv) whether the radiotherapy dose was given only in complete morphologic remission. In addition, we stratified according to the following trial population characteristics: v) mean age of the treated patients,

vi) whether the majority had advanced stage, and vii) whether the majority had bulky disease. As shown in Figure 5, we failed to explain between-trial heterogeneity by stratifying on any of these subgroups.

Discussion

We here provide a large and comprehensive meta-analysis with the best currently available data from randomized trials on consolidation radiotherapy in the first-line treatment of aggressive lymphomas. In summary, we find no evidence for a survival benefit of an unselected consolidation radiotherapy for these patients, but uncertainty remains high.

Our analysis extends the data from both retrospective and uncontrolled series in favor[2,23-25] or against[26] the use of consolidation radiotherapy in the first line setting. Our state-of-the art and updated meta-analysis that takes into account general concerns on the reproducibility of meta-analysis[8,9] and significantly corroborates a previous meta-analysis on a limited number of trials.[27] It also goes beyond extrapolations from data on particular extranodal sites,[28] the common use of consolidation radiotherapy for limited clinical stages only,[23] pretreatment with different chemotherapy,[29] or to treat bulky disease only.[2] Collectively, the latter data are the basis for the current recommendations on the combined treatment modality also for patients with advanced stages. They have created an unsatisfactory uncertainty and rely on experts' opinions on the use of radiotherapy when facing an individual patient. However, DLBCL is a disease in which cure, but also treatment-related toxicities and economic factors have to be considered. Unfortunately, our meta-analysis cannot provide data on costs, safety and long term risks of secondary malignancies related to radiation therapy.

Overall, the data that could be used for this meta-analysis is of mixed quality (Tables 1 and 2). As an extreme, three of the four randomized trials by the same group all clearly supporting the added value of radiotherapy have later been retracted, the last one in early 2019.[14-16] We display their results in our figures as they might have influenced the use of consolidation radiotherapy in routine practice or clinical trials before their retraction. The results of the important UNFOLDER trial is still not fully published.[17,22] The trials used for this meta-analysis also harbor considerable conceptual heterogeneity: radiotherapy was given to shorten chemotherapy and its toxicity,

Table 1. Summary on the randomized trials used for the meta-analysis. The number of patients in the respective column indicates the actual number of patients for the individual trials that received consolidation radiotherapy in a randomized fashion. The retracted trials are highlighted in grey. The superscript number in the study column refers to the number of the references in the manuscript.

Trial (with reference)	Diagnosis	Patients (#)	Recruitment period	Mean age (y)	Same chemotherapy in both arms	Rituximab used	Radiation dose >30 Gy
Aviles *et al.*[13]	DLCL	218	1983-1988	59-61	yes	no	yes
Engelhard *et al.*[18]	high grade NHL	110 (of 548)	1986-1989	56	yes	no	yes
ECOG 1484[19]	diffuse aggressive NHL	172 (of 399)	1984-1992	59	yes	no	no
Aviles*et al.*[14]	DLCL	341	1989-1995	53-57	yes	no	yes
SWOG 8736[20]	intermediate & high grade NHL	401 (of 442)	1988-1995	59	no	no	yes
GELA 93-1[11]	aggressive NHL	318 (of 647)	1993-2000	46-47	no	no	yes
GELA 93-4[12]	aggressive NHL	576	1993-2002	68-69	yes	no	yes
Aviles *et al.*[15]	PMBL	124 (of 182)	2001-2004	32-35	yes	yes	no
Aviles *et al.*[16]	DLBCL	258 (of 612)	2006-2010	53	yes	yes	no
UNFOLDER[17,22]	Largely DLBCL	285	2005-2012	44	no	yes	yes
GOELAMS 02 03[21]	DLBCL	334	2005-2013	56	yes	yes	yes

Trial	Publication	Stages	Bulky disease	Randomized
Aviles *et al.*[13]	Int J Radiat Biol 1994	advanced	all	only CR and bulky disease
Engelhard *et al.*[18]	Ann Oncol 1991	localized & advanced	19% initially; bulky not randomized	only CR pts
ECOG 1484[19]	J Clin Oncol 2004	localized	31% initially (tumor > 10cm)	only CR pts
Aviles *et al.*[14]	Leuk Lymphoma 2004	advanced	all	only CR and bulky disease
SWOG 8736[20]	New Engl J Med 1998	localized	number unknown, some initially	all
GELA 93-1[11]	New Engl J Med 2005	localized	12% of RT pts.; 10% of non-RT pts	all
GELA 93-4[12]	J Clin Oncol 2007	localized	9% of RT pts; 8% of non-RT pts.	all
Aviles *et al.*[15]	Int J Radiat Biol 2012	localized	94% of RT pts.	only CR pts
Aviles *et al.*[16]	Hematology 2018	advanced	30 % of RT pts.	only CR and bulky disease
UNFOLDER[17,22]	(12-ICML;a122); ASCO 2018;a7574	localized & advanced	76 % initially	initially 4 arms; random for RT only in CR pts.
GOELAMS 02 03[21]	Blood 2018	localized	for non-bulky disease only	random at start, some PR pts. received RT

NHL: non-Hodgkin lymphoma; DLBCL: diffuse large B-cell lymphoma; CR: complete response; pts: points; RT: radiotherapy; y: years.

to improve the outcome of the first-line treatment[11,12,17,22] or as a salvage option for patients who achieved only a partial remission after chemotherapy.[14,21] As the Korean "ASPIRE" trial was unfortunately later withdrawn (clinicaltrials gov. Indentifier: NCT02054559; three times R-CHOP + radiotherapy *vs.* six times R-CHOP for stage 1 and 2 DLBCL), there is currently no randomized trial supporting the widely used, recently updated and safe approach to give less chemotherapy and PET-guided radiotherapy to patients with localized DLBCL.[5,23,30-33] Also the data on limited stage DLBCL which accounts for 30 % of the cases, harbor significant variability as different definitions for limited stage, bulky disease as well as risk stratification and extrapolations were used.[2,34] This renders the integration of all available results difficult. Furthermore, a detailed view goes beyond the possibilities of a meta-analysis analyzing population level data. Although we do not have information on the stage-modified-IPI20,[35] for all trials included in our analysis, we assume that many patients with localized disease of this meta-analysis had a low risk disease. They have an excellent prognosis, regardless of radiotherapy.[36] The FLYER trial established four cycles of R-CHOP to be sufficient for patients with favorable risk (and non-bulky) DLBCL.[37] Radiotherapy in this trial was limited to the contralateral testis in case of testicular involvement. In the yet unpublished OPTIMAL>60 trial (clinicaltrials gov. Identifier: NCT014778542), radiotherapy (and two additional cycles

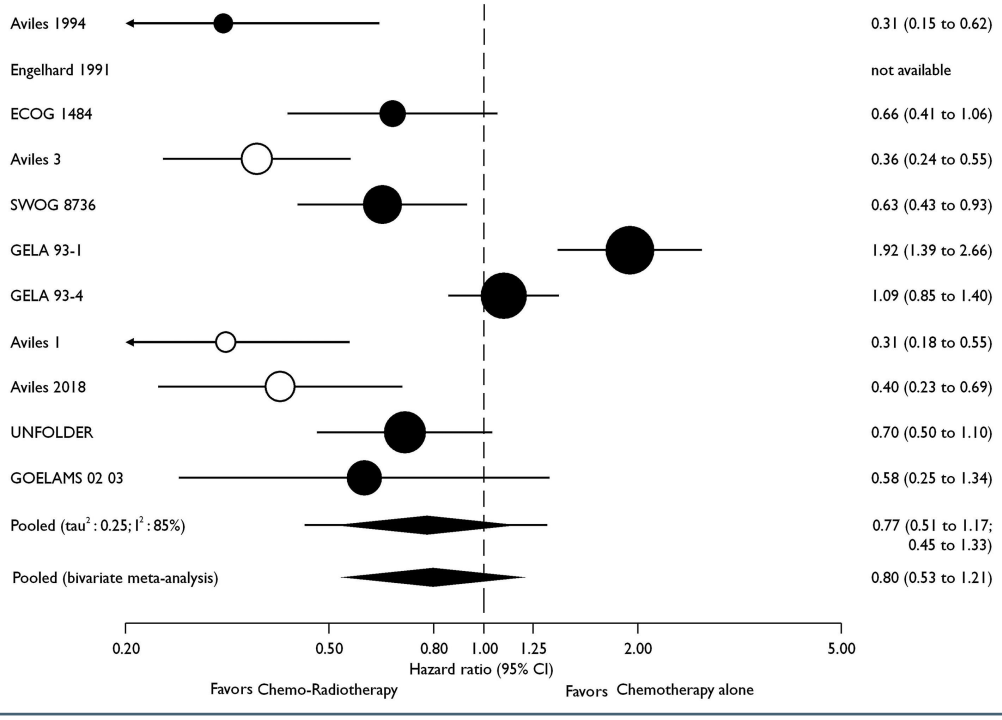

Figure 2. Effect of consolidation radiotherapy on progression-free survival. Circles are proportional to trial size *i.e.*, number of patients; retracted trials are displayed with hollow circles.

Table 2. Outcome data of the individual trials used for the meta-analysis. Correlation between progression-free and overall survival were done for the GELA trial. The superscript number in the study column refers to the number of the references in the manuscript.

Trial (with reference)	Overall survival Hazard ratio	Progression-free survival ln HR (SE)	Hazard ratio	ln HR (SE)
Aviles *et al.*[13]	0.33	-1.11 (0.44)	0.31	?-1.17 (0.36)
Engelhard *et al.*[18]	2.09	0.74 (0.58)	n/a	n/a
ECOG 1484[19]	0.81	-0.21 (0.28)	0.66	?-0.41 (0.24)
Aviles *et al.*[14]	0.35	-1.04 (0.25)	0.36	-1.02 (0.22)
SWOG 8736[20]	0.64	-0.44 (0.23)	0.63	-0.46 (0.19)
GELA 93-1[11]	1.98	0.68 (0.20)	1.92	0.65 (0.16)
GELA 93-4[12]	1.08	0.07 (0.14)	1.09	0.09 (0.13)
Aviles *et al.*[15]	0.21	-1.54 (0.29)	0.31	-1.16 (0.28)
Aviles *et al.*[16]	0.28	-1.27 (0.32)	0.4	-0.92 (0.28)
UNFOLDER[17,22]	1.2	0.18 (0.38)	0.7	-0.36 (0.20)
GOELAMS 02 03[21]	0.52	-0.66 (0.45)	0.58	-0.54 (0.43)

HR: hazard ratio; ln: natural logarithm; SE: standard error.

of chemotherapy) is given just to PET-positive sites after four cycles of chemotherapy. According to an interim analysis, this can compensate the inferior outcome of this population.[37] Furthermore, the authors of this trial communicated that radiotherapy to PET-negative bulky disease is not needed.[38]

In the latest ESMO guidelines, consolidation radiotherapy for DLBCL patients is recommended for both elderly and intermediate- and high-risk young patients with bulky disease.[6] NCCN is less firm, and mainly restricts its recommendation to residual disease (partial remission or PET-positivity, *Online Supplementary Table S1*). These rec-

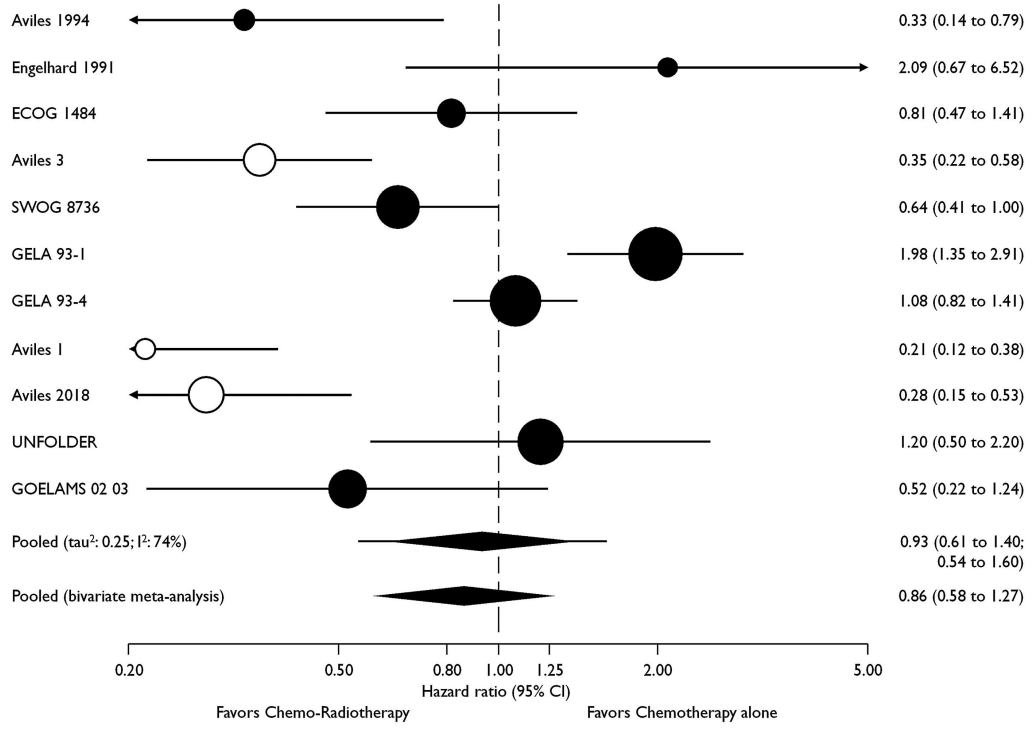

Figure 3. Effect of consolidation radiotherapy on overall survival. Circles are proportional to trial size *i.e.*, number of patients; retracted trials are displayed with hollow circles. CI: Confidence Interval.

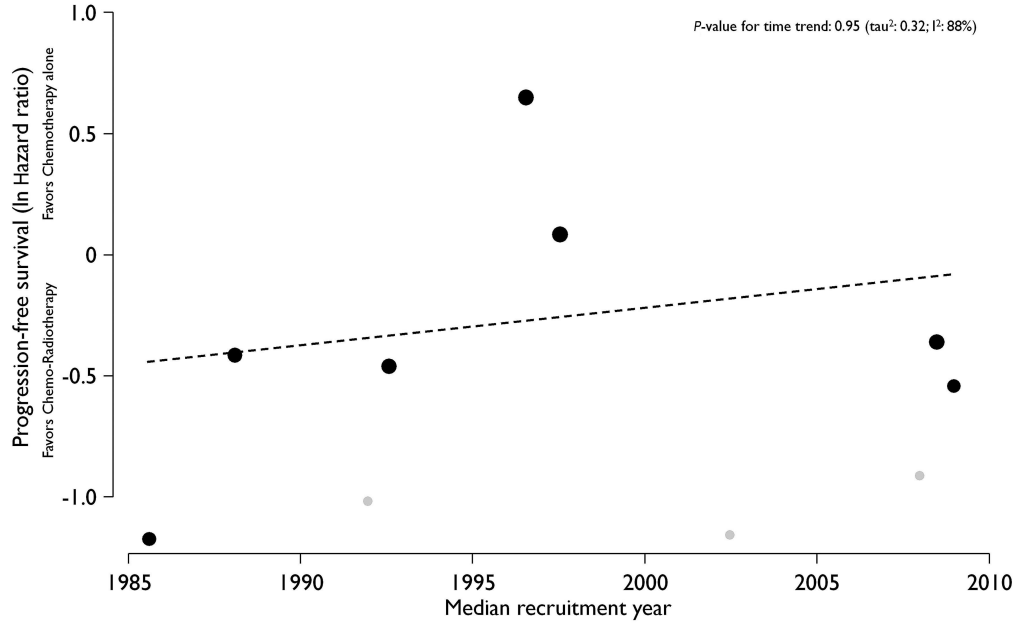

Figure 4. Time trend plot on the effect of consolidation radiotherapy. Circles are proportional to weight in analysis; dashed line shows the fitted linear regression; retracted trials are in grey. ln: natural logarithm.

ommendations are not fully supported by the results of this meta-analysis, especially by the results of the stratified analysis provided in Figure 5. The International Lymphoma Radiation Oncology Group (ILROG) has recently updated its guidelines, albeit in the relapsed and refractory setting.[39] The trials analyzed in our meta-analysis did not specifically include patients with extranodal DLBCL for which both ESMO[40] and ILROG[41] have published separate guidelines. Specifically, consolidative mediastinal radiotherapy is currently recommended in responding primary mediastinal B-cell lymphoma (PMBL) patients after treatment with standard-dose chemoimmunotherapy.[40] However, extrapolation of the data of our meta-analysis on DLBCL not otherwise specified (NOS) to and from entities such as primary mediastinal lymphoma, primary central nervous system (CNS) or testicular lymphoma is discouraged. The safe omission of whole brain radiotherapy for CNS lymphomas is conceptually controversial.[42,43] As the role of adjuvant mediastinal radiotherapy in PMBL patients with complete remission after chemotherapy is unclear and a large number of patients are cured by chemotherapy alone with DA-EPOCH-R,[44] it is important to note that accrual in IELSG-37 (clinicaltrials gov. Identifier: NCT01599559) has recently been completed; this potentially practice changing randomized trial with a non-inferiority design has evaluated the role of consolidation radiotherapy in PET-negative patients.

Our meta-analysis provides further evidence that patients with a complete morphologic remission after chemotherapy or initial bulky disease are unlikely to particularly profit from consolidation radiotherapy.[25,38] PET has become an integral part of the treatment of DLBCL patients, although the prognostic value of interim PET is limited,[45,46] and a PET-based escalation of chemotherapy was unable to improve the outcome.[47] None of the trials that we included in our meta-analysis used a truly PET-guided treatment approach. This was applied in limited stage DLBCL in a retrospective[32] and also a prospective,[30] albeit non-randomized trial. In order not to add also radiotherapy to the recent painful flaws in clinical DLBCL research,[3,4] our meta-analysis should be taken into account when a new trial is planned. We provide evidence on patients that we should rather not selectively irradiate, but we still do not know how to use consolidation radiotherapy. Besides its wide and established use in localized disease,[5] we see the rationale use of radiotherapy in DLBCL patients analogous to the current situation in Hodgkin's disease, *e.g.*, for insufficient responses to chemo-immunotherapy. Considering retrospective trials,[38,48] radiotherapy could be restricted to PET-positive rests. Among other unanswered questions, this would be practice changing. Ideally, this hypothesis needs corroboration in two separate prospective trials to randomly apply radiotherapy in trial 1 for patients with PET-negative, and trial 2 for patients with PET-positive rests. The first trial would be a non-inferiority trial to proof whether it is safe to not irradiate patients perceived

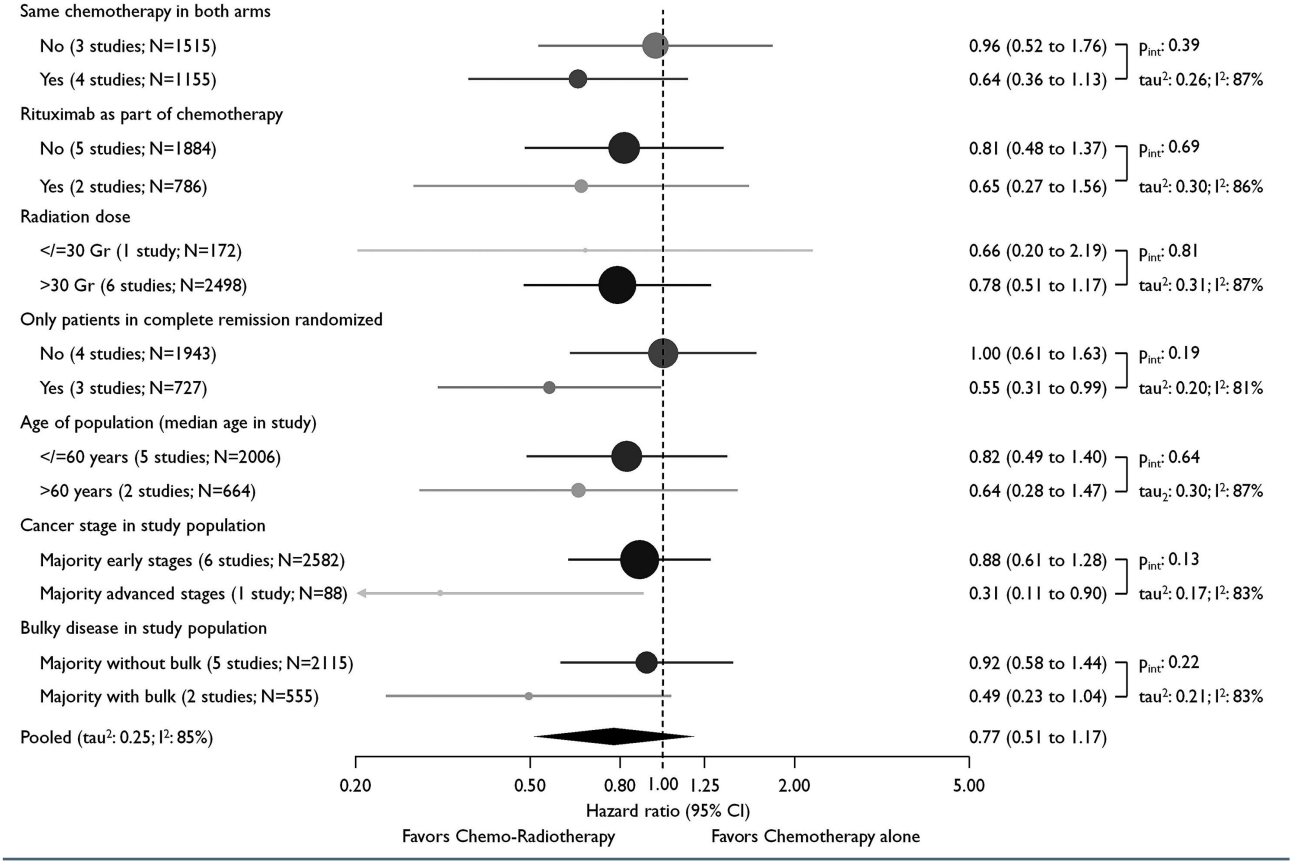

Figure 5. Stratified progression free survival analysis on the effect of consolidation radiotherapy. Circles are proportional to stratum size *i.e.*, overall number of patients in stratum; color of circles reflects number of trials in stratum *i.e.*, from black (seven trials) to light grey (one trial); age, stage, and bulky disease are characteristics of the study population and cannot be interpreted on the individual participant level (ecological fallacy). CI: Confidence Interval.

to be cancer-free. Trial 2 would be a superiority design testing whether radiotherapy is able to improve the outcome residual DLBCL after chemo-immunotherapy. Assuming a 2-year PFS, an appropriate and pragmatic endpoint in DLBCL[49,50] of 80%, an alpha of 0.025 for the non-inferiority (one-sided) and 0.05 (two-sided) for the superiority trial, a power of 80% and enrolment over 5 years, we calculated the following sample size: trial 1 (failure rate of 24% [HR 1.23]), would require 1,916 overall or 384 patients per year; trial 2 (and a HR of 0.75 or an improvement of the 2-year PFS to 85%) would need 1,098 patients or 220 patients per year. Assuming an end-of-therapy PET-positivity of 25-30%,[45] 4,000 or 5,000 patients respectively have to be screened. Clearly, such numbers need a global and fully committed academic effort. However, otherwise the important question on the role of consolidation radiotherapy in DLBCL, which with the current data, regularly gives rise to unsatisfactory and futile discussions at lymphoma boards, will never be answered convincingly. Based on this meta-analysis and other data,[21] we favor a superiority trial that first allocates a role of consolidation radiotherapy in DLBCL. Then, one may also test the use of smaller irradiation volumes according to the concept of involved node versus involved site radiotherapy using modern techniques (intensity modulated radiotherapy [IMRT]) to reduce doses to organs at risk.[31,51] New trials could also approach unanswered questions on the role of consolidation radiotherapy in other subpopulations like patients with interim PET positive disease, or in limited stage disease of high risk histologies such as double hit lymphomas although the prognosis of the later may be better than previously perceived.[52]

Disclosures

No conflicts of interest to disclose.

Contributions

MDB performed research, analyzed data and wrote parts of the paper; ST analyzed data, contributed vital material and wrote parts of the paper; AEB and SJ performed research and analyzed data; CI analyzed data; TL contributed vital material; UN had the idea, designed research, analyzed data, contributed vital material, and wrote the paper.

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